

Peripheral Neuropathy: Pathogenic Mechanisms and Alternative Therapies

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Abstract

Peripheral neuropathy (PN), associated with diabetes, neurotoxic chemotherapy, human immunodeficiency virus (HIV)/antiretroviral drugs, alcoholism, nutrient deficiencies, heavy metal toxicity, and other etiologies, results in significant morbidity. Conventional pain medications primarily mask symptoms and have significant side effects and addiction profiles. However, a widening body of research indicates alternative medicine may offer significant benefit to this patient population. Alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methylcobalamin, and topical capsaicin are among the most well-researched alternative options for the treatment of PN. Other potential nutrient or botanical therapies include vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6 fatty acids, L-arginine, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, and St. John's wort. In the realm of physical medicine, acupuncture, magnetic therapy, and yoga have been found to provide benefit. New cutting-edge conventional therapies, including dual-action peptides, may also hold promise. (*Altern Med Rev* 2006;11(4):294-329)

Introduction

Prevalence

Peripheral neuropathy (PN) – characterized by pain, numbness, and tingling in the extremities and slow nerve conduction – affects a significant percentage of the U. S. population and can be extremely debilitating. A 1999-2000 report, National Health and Nutrition Examination Survey (NHANES), of 2,873 men and women ages 40 or older (419 with diabetes), found a PN prevalence of 14.8 percent.¹ PN was defined as at least one insensitive area on the foot with

monofilament testing; it was also assessed by self-reported symptoms. The incidence of PN was significantly higher (62%) in the subset with diabetes. The incidence of PN also increased significantly with age. NHANES found 8.1 percent of the 40-49 year age group had PN, compared to 34.7 percent of individuals over age 80.

Etiological Factors

Peripheral neuropathy manifests as axonal degeneration. Diagnosis of PN involves a complete evaluation to determine the extent of the neurological deficit as well as a complete history and physical examination to determine the possible etiology. Despite thorough history and physical exam, etiology remains a mystery in approximately 50 percent of cases.²

Peripheral neuropathy can be the result of genetics, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications.

Among chronic diseases, diabetes mellitus is the most common cause of PN. Mechanisms involved in diabetes-associated PN are discussed in depth in a later section. Other endocrinological abnormalities that can result in neuropathy include hypothyroidism and acromegaly.³ The neuropathy associated with hypothyroidism commonly manifests as carpal tunnel syndrome. Other manifestations resemble diabetic neuropathy, with tingling paresthesias in a stocking-glove distribution. PN of acromegaly (excess growth hormone) includes carpal tunnel syndrome and sensorimotor polyneuropathy. Human immu-

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nodeficiency virus (HIV) also results in PN, usually involving distal, nonpainful paresthesias, decreased ankle reflexes, and abnormal pain and temperature perception.⁴ Amyloidosis is another chronic disease resulting in PN.

Environmental neurotoxins that can cause peripheral neuropathy include exposure to mold in water-damaged buildings,⁵ solvents such as n-hexane and methyl n-butyl ketone,⁶ and heavy metals, including thallium,⁷ arsenic,⁷ lead,⁸ mercury,⁹ and germanium.¹⁰

Peripheral neuropathy is common among chronic alcohol abusers, with prevalence as low as nine percent and as high as 50 percent. Alcohol-associated PN is related to a combination of factors, including malnutrition, nutrient deficiencies (thiamine in particular), and direct neurotoxicity of alcohol.¹¹

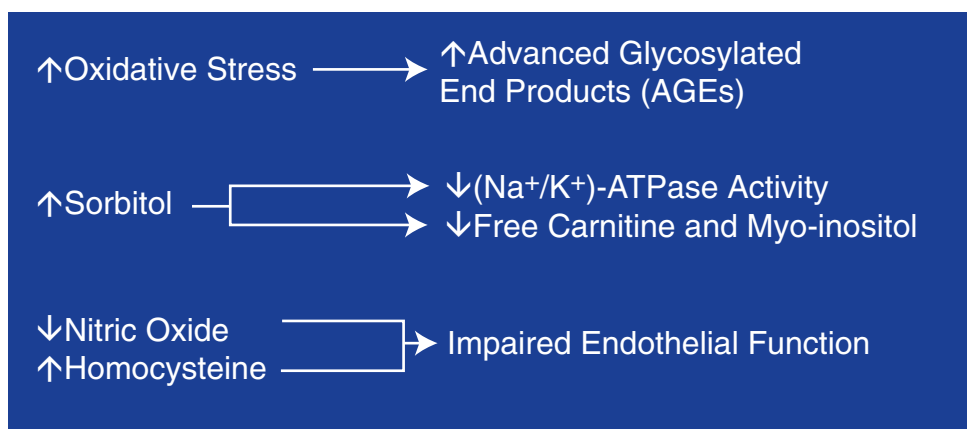
Medications that commonly result in PN include the chemotherapy drugs cisplatin, suramin, paclitaxel, and docetaxel,¹² as well as cholesterol-lowering statin drugs,¹³ HIV antiretroviral drugs, and thalidomide.¹²

Pathogenesis of Peripheral Neuropathy

Diabetic Peripheral Neuropathy

PN affects 30 percent of hospitalized and 20 percent of non-hospitalized individuals with diabetes.¹⁴ The mechanisms underlying PN depend on etiology. Diabetes, being the most common etiological factor, is also the most studied in terms of pathogenesis. While conventional theory holds that prolonged hyperglycemia results in the complications associated with diabetes, including neuropathy, a recent study found PN can manifest even in individuals with abnormal glucose tolerance, a pre-diabetic condition. The study found that in a group with chronic idiopathic polyneuropathy, subjects were twice as likely to have abnormal glucose tolerance than age-matched controls from the general population.¹⁵

Figure 1. Pathophysiological Factors in Diabetic Peripheral Neuropathy

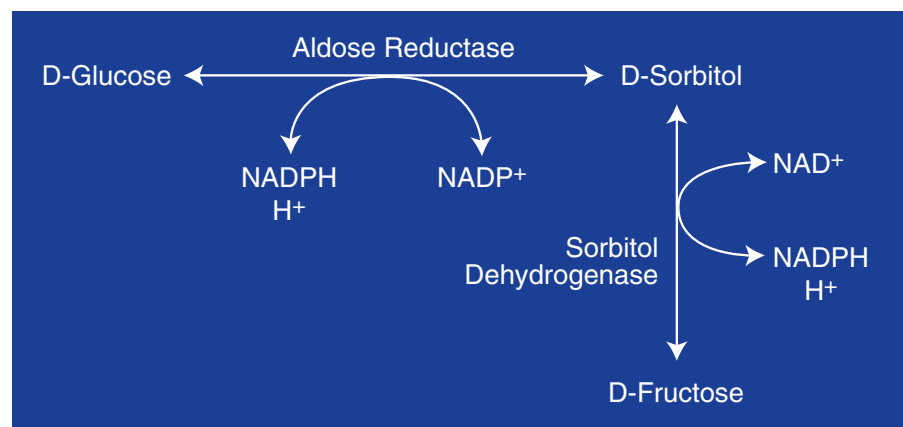


The pathophysiology of diabetic neuropathy (summarized in Figure 1) includes increased oxidative stress yielding advanced glycosylated end products (AGEs), polyol accumulation, decreased nitric oxide/impaired endothelial function,¹⁶ impaired $(\text{Na}^+/\text{K}^+)\text{-ATPase}$ activity,¹⁷ and homocysteinemia.¹⁸ Not only are nerve cells more likely to be destroyed in a hyperglycemic environment, but repair mechanisms are also defective. Reduced levels of neurotrophic agents, including nerve growth factor and insulin-like growth factor, have been noted in experimental diabetes.¹⁹

Oxidative Stress/Protein Glycosylation

Diabetes results in increased products of oxidation. In hyperglycemia, glucose combines with protein, yielding glycosylated proteins, which can become damaged by free radicals and combine with fats, yielding AGEs that damage sensitive tissues. In addition, glycosylation of antioxidant enzymes can render the defense system less efficient.

Significant evidence points to increased oxidative stress in diabetic PN, either because of enhanced production of reactive oxygen species (ROS) or defective scavenging of free radicals. A study compared markers of oxidative stress in 189 people with diabetes (105 with PN, 22 with PN plus cardiac autonomic neuropathy [CAN], and 22 with no PN or CAN) with 85 controls.¹⁴ Markers of oxidative stress included plasma 8-iso-prostaglandin F_{2a} , superoxide anion generation, and lag time to peroxidation

Figure 2. The Sorbitol Pathway

by peroxynitrite. Subjects with PN or PN plus CAN demonstrated significant elevations of all three markers, as well as significant decreases in the protective antioxidant vitamins C and E.

The effect of pro-oxidants has been examined in experimental diabetic neuropathy. In one study, rats exposed to two pro-oxidant interventions – either the drug primaquine or a vitamin E-deficient diet – demonstrated decreased nerve conduction velocity (NCV), nerve growth factor in the sciatic nerve, and neuropeptides compared to diabetic rats not exposed to additional oxidative stress.²⁰

Sytze van Dam provides a review of the pathophysiology of oxidative stress in PN, including a summary of additional *in vitro* and animal research.²¹

Polyol Accumulation

Glucose is able to passively diffuse without insulin into certain types of cells, including nerve cells. Once inside the cell, glucose is converted to sorbitol and other polyols by the enzyme aldose reductase (Figure 2). Because polyols do not passively diffuse out of cells, they concentrate within cells such as neurons, creating an osmotic gradient that allows excess sodium and water to follow.²²

It is now believed that, in addition to osmotic effects, polyol-pathway linked metabolic changes are involved. Fructose is also a byproduct of polyol-pathway activation via the sorbitol dehydrogenase-driven conversion of sorbitol to fructose. High fructose levels result in increased AGE precursors,²³ another source of oxidative stress.

Accumulation of sorbitol and fructose in nerve cells has been shown to decrease (Na⁺/K⁺)-ATPase activity.²² In addition, free carnitine and myo-inositol content in the caudal nerves of diabetic rats were significantly decreased with polyol accumulation.²⁴ Providing the rats with an aldose reductase inhibitor decreased the depletion of both myo-inositol and carnitine in caudal nerves²⁴ and preserved (Na⁺/K⁺)-ATPase activity in the sciatic nerve,²² adding further evidence that metabolic derangements are

associated with polyol-pathway hyperactivity.

Nitric Oxide Deficiency/Impaired Endothelial Function: The Arginine Connection

Vascular factors have also been implicated in the pathogenesis of diabetic PN. Nerve blood flow is diminished in experimental diabetic neuropathy, and numerous studies indicate it may be mediated by alterations in nitric oxide metabolism. One such study examined nerve blood flow and nitric oxide synthase (NOS) activity in the microvasculature serving peripheral nerves in diabetic rats.²⁵ Hyperglycemia resulted in a significant diminution of nerve blood flow compared to controls. N-nitro-L-arginine, an inhibitor of NOS, also resulted in decreased nerve blood flow. L-arginine reversed the effects of NOS inhibition and restored blood flow to the nerves.

An animal study also found disruptions in neuronal nitric oxide synthase (nNOS) in experimental diabetes. Decreased nNOS expression was associated with increased neuropathic pain.²⁶

Nitric oxide plays an important role in controlling (Na⁺/K⁺)-ATPase activity,²⁷ a diminution of which has been implicated in the pathogenesis of PN.¹⁷ Experimental analysis revealed hyperglycemia results in an excess of endothelial superoxide radicals that result in reduced stimulation of NO on (Na⁺/K⁺)-ATPase activity; this effect is inhibited by L-arginine.²⁷ Another animal study, however, did not find a relationship between altered NO activity and the development of sensory PN.²⁸

Erectile dysfunction (ED) in diabetic men correlates with reduced NO activity and resultant endothelial dysfunction. A study of 60 men with diabetes (30 with ED) found a further correlation with peripheral neuropathy. Heat/pain perception was abnormal in 40 percent of diabetics with ED but in only 10 percent of diabetics without ED, while warmth perception was abnormal in 50 percent of those with ED compared to 30 percent without ED.²⁹ These results indicate a probable connection between abnormal NO activity and neuropathy in a clinical setting.

A Connection Between Increased Polyol Activity and Decreased NO Activity?

The interrelationships between the various pathogenetic aspects of diabetic PN are poorly understood. An animal study attempted to elucidate a possible connection between aldose reductase activity (enhanced polyol pathway activity) and decreased NO activity. The researchers found NO to be an important mediator of nerve (Na^+/K^+)-ATPase and aldose reductase activity on NCV. NADPH is a cofactor for both NOS and aldose reductase. Therefore, the authors theorize that hyperglycemia increases activity of aldose reductase, subsequently decreasing NOS activity via cofactor competition.¹⁷

Hyperhomocysteinemia

Diabetes and its complications are associated with elevated homocysteine levels. A group of 65 subjects with type 2 diabetes were divided into two groups, those with neuropathy ($n=43$) and those without neuropathy ($n=22$). The frequency of hyperhomocysteinemia ($\geq 15 \mu\text{mol/L}$) was significantly higher in the group with neuropathy (13/43) compared to those without neuropathy (1/22). Of the three vitamin cofactors for homocysteine metabolism (vitamins B6 and B12 and folate), plasma vitamin B12 levels demonstrated a downward trend in the neuropathy group, whereas there were no differences in vitamin B6 or folate levels between the two groups.¹⁸

Hyperhomocysteinemia is associated with impairment of endothelial function, providing a mechanism for its possible involvement in diabetic complications, including neuropathy. Researchers propose a synergistic effect between AGEs and homocysteine, resulting in endothelial damage. In a

group of 75 type 1 diabetics, those with hyperhomocysteinemia had significantly higher plasma thrombomodulin levels (a sign of endothelial damage; 62.2 ng/mL versus 38.2 ng/mL) and higher prevalence of neuropathy (57% versus 41%).³⁰

Not all studies have found a correlation between high homocysteine levels and diabetic neuropathy. In a study of 629 people (266 with normal glucose tolerance, 167 with impaired glucose tolerance, and 162 with type 2 diabetes) no definitive correlation was found between hyperhomocysteinemia and PN.³¹

Alcohol-related Neuropathy

Neuropathy associated with chronic liver disease/alcoholism appears to be associated with direct toxic effects of alcohol, malnutrition, thiamine deficiency, and genetics. Ammendola et al found the strongest correlation was between incidence of axonal neuropathy (most commonly of the sural nerve) and total lifetime dose of ethanol, compared to other parameters examined (malnutrition and family history of alcoholism).¹¹ Other B-vitamin deficiencies, including folate deficiency, have also been associated with cases of alcohol-related neuropathy.³²

Thyroid/Pituitary Neuropathies

Mucinous deposits in soft tissue resulting in nerve compression and carpal tunnel-like symptoms have been implicated in neuropathy associated with hyperthyroidism.³ Neuropathy associated with excess growth hormone or acromegaly has been associated with subperineurial-tissue proliferation and diminished myelinated and unmyelinated fibers.³

AIDS-associated Neuropathy

Peripheral neuropathy affects as many as one-third of individuals with acquired immunodeficiency syndrome (AIDS), most commonly manifested as distal, symmetrical polyneuropathy. A study of 251 HIV-positive individuals found the incidence of neuropathy was significantly correlated with extent of immune deficiency (reflected in low CD4 counts) and malnutrition (decreased weight, hemoglobin, and serum albumin).⁴

Table 1. Cancer Chemotherapeutic Agents Associated with Peripheral Neuropathy

Cisplatin and its analogs
5-Fluorouracil
5-Azacytidine
Vinca alkaloids (vincristine, vinblastine, etc.)
Taxoids (paclitaxel, docetaxel)
Cytarabine
Etoposide
Gemcitabine
Hexamethylmelamine
Ifosphamide
Misonidazole
Suramin
VM-26

PN associated with AIDS resembles PN caused by vitamin B12 deficiency. Kiebertz et al report a prevalence of vitamin B12 deficiency (20%) in HIV-infected patients with PN.³³ Others have reported no association between vitamin B12 deficiency and AIDS-related PN.^{4,34}

Other proposed mechanisms (aside from antiretroviral drugs, addressed below) for the high incidence of PN in AIDS include increased oxidative stress and inflammatory cytokine production, and impaired repair mechanisms caused by decreased S-adenosylmethionine.³⁵

Drug-induced Neuropathy

Factors that render peripheral nerves susceptible to drug toxicity include a leaky blood-peripheral nerve barrier (compared to the blood-brain barrier) and genetics.¹²

Antiretroviral Agents

Antiretroviral drugs used to treat individuals with HIV are implicated in PN. One study of 147 HIV-positive adults found exposure to didanosine (ddI) or stavudine (d4T) significantly increased the risk of developing PN (odds ratio of 3.21 and 7.66, respectively);³⁶ zalcitabine (ddC) can also cause neuropathies.¹² It is believed the neuropathies occur in part because of drug-induced mitochondrial defects. In a rabbit model, ddC resulted in demyelination via

Schwann cell mitochondrial toxicity.³⁷ High lactic acid levels are associated with the use of antiretroviral drugs and may be used to differentiate drug-induced versus AIDS-related neuropathy in people with HIV.³⁸

Cancer Chemotherapeutic Agents

Numerous cancer chemotherapy drugs are associated with neurotoxicity and PN (Table 1).

High cumulative doses of cisplatin result in incidence of PN as high as 70-100 percent, with more conventional lower doses resulting in a PN rate of 12 percent. Impaired DNA repair mechanisms are believed to be the cause of PN in this population.¹²

Taxoids such as paclitaxel and docetaxel result in peripheral neuropathy, particularly at high doses. The mechanism is unknown but large arrays of disordered microtubules, a major effect on tumor cells, may be a cause of neurotoxicity.¹² Vinca alkaloids may exert neurotoxic effects by inhibiting microtubular assembly.¹²

Lipid-lowering Drugs

PN is one of the less common side effects of the class of cholesterol-lowering drugs that inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase – the so-called statin drugs.¹² A case-control study using automated databases found a significant increase in neuropathy in people taking lipid-lowering drugs as a whole (odds ratio: 1.27); statins (odds ratio: 1.22), and fibrates (another class of lipid-lowering drugs; odds ratio: 1.54).¹³

Potential mechanisms include interruption of cholesterol synthesis, resulting in disruption of cholesterol-rich neuronal membranes, or inhibition of coenzyme Q10 synthesis (also inhibited by HMG CoA reductase), resulting in neuron mitochondrial damage.³⁹

A suspected case of diabetic neuropathy in a patient with type 1 diabetes on a statin drug completely resolved when the statin drug was withdrawn – indicating the neuropathy was from statin use, not diabetes.³⁹ On the other hand, statin drugs may actually restore normal nerve function in diabetic neuropathy. In a study of mice with type 2 diabetes and neuropathy, the statin drug rosuvastatin restored nerve function and vascularity, at least in part by restoring nNOS, which improved microcirculation.⁴⁰

Conventional Treatment of PN

Treatment of peripheral neuropathy depends, in part at least, on the cause of the neuropathy. In the case of drug-induced neuropathy, removing the offending agent or decreasing the dose can result in resolution of the symptoms. In other cases, such as in the case of alcohol-related neuropathy, correcting a deficiency (in this case B vitamins, particularly thiamine) is essential. Initially, it is often necessary to provide thiamine intravenously.

Because of the prevalence of PN in diabetes, much of the research has focused on diabetic neuropathy. Conventional treatments include antidepressants (tricyclics – TCAs and serotonin selective reuptake inhibitors – SSRIs), anticonvulsants, antiarrhythmics (sodium-channel blockers; mexiletine), N-methyl-D-aspartate (NMDA) receptor antagonists, five-percent lidocaine patches, opioid and non-opioid analgesics,⁴¹ and aldose reductase inhibitors (such as sorbinil⁴² or zenarestat⁴³).

A review of placebo-controlled and comparative studies examined the efficacy and safety of several classes of drugs for neuropathy, including SSRIs, TCAs, NMDA-receptor antagonists, sodium-channel blockers, narcotic analgesics (tramadol, oxycodone), and first- and second-generation anticonvulsants (e.g., carbamazepine, sodium valproate, and gabapentin).⁴⁴ The authors concluded that gabapentin showed the greatest efficacy with the fewest side effects and potential drug interactions. Other anticonvulsants in early stages of testing for PN include pregabalin (better absorbed than gabapentin)⁴⁵ and lacosamide.⁴⁶

Alternative Treatments for Peripheral Neuropathy

alpha-Lipoic Acid

Clinical Effects of Alpha-lipoic Acid (ALA) for Diabetic Peripheral Neuropathy

ALA, among the most well-researched nutrients for peripheral neuropathy, has been used as a treatment for PN in Europe for decades. Three large-scale, double-blind, placebo-controlled trials – the Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) studies – have examined various routes of administration, dosages, and neurological effects of ALA. The first ALADIN study (n=328 type 2 diabetics) found

three weeks of intravenous (I.V.) ALA at 600 or 1,200 mg daily was superior to placebo for reducing symptoms of neuropathy measured by several pain-score questionnaires; the 600-mg dose yielded slightly better results with fewer side effects.⁴⁷

ALADIN II examined nerve conduction parameters as well as Neuropathic Disability Score (NDS) in a two-year trial of 65 patients with type 1 or 2 diabetes. Patients were assigned to one of three treatment groups: 600 mg ALA twice daily, 600 mg ALA once daily plus placebo once daily, or double placebo. After receiving the treatments I.V. for five days, subjects were placed on oral administration of the respective treatments. ALA resulted in significant improvement in some nerve conduction parameters but not in NDS compared to placebo.⁴⁸

In the seven-month ALADIN III trial, 509 PN subjects with type 2 diabetes received 600 mg I.V. ALA daily for three weeks, followed by 600 mg orally three times daily for six months; 600 mg I.V. ALA daily for three weeks, followed by placebo three times daily for six months; or double placebo. While no significant differences were noted in subjective symptom evaluation among the groups, treatment with ALA was associated with improvement in nerve function.⁴⁹

In the randomized, double-blind, placebo-controlled Symptomatic Diabetic Neuropathy (SYDNEY) trial, 120 type 2 diabetic patients with PN were administered 600 mg I.V. ALA (n=60) or placebo (n=60), five days/week for a total of 14 treatments. At the end of the trial, the ALA group reported significant improvement in overall symptoms, including lancinating and burning pain, numbness, and tingling compared to the placebo group; improvement in one nerve conduction parameter was also reported.⁵⁰

A meta-analysis of four placebo-controlled trials (n=1,258) – ALADIN I and III, SYDNEY, and a fourth unpublished trial (Neurological Assessment of Thioctic Acid; NATHAN II), all with the same protocol of 600 mg ALA administered I.V. for three weeks – found a continuous daily improvement in symptom scores beginning on the eighth day of treatment.⁵¹

Several smaller studies confirm the potential benefit of ALA for diabetic peripheral neuropathy. Like the first ALADIN study, one small study lasted only three weeks. Type 2 diabetics with symptomatic

PN were given 600 mg ALA (n=12) or placebo (n=12) orally three times daily. Even with the study's short duration, burning pain and NDS improved significantly in the ALA group compared to placebo.⁵² A smaller oral dose was also found effective in an uncontrolled study of 26 type 2 diabetics with PN. An oral daily dose of 600 mg ALA for three months resulted in reversal from symptomatic to asymptomatic neuropathy; five patients had no signs of neuropathy based on symptom evaluation or NCV.⁵³

A small study of 10 subjects with diabetic PN found 600 mg I.V. ALA for three weeks resulted in improved nerve function as well as decreased symptom scores. In this study, nerve microcirculation was examined by measuring capillary blood cell velocity (CBV). In normal healthy volunteers, cooling of one hand results in a decrease in CBV in the contralateral hand. In this small sample of 10 subjects no such reaction occurred. However, after three weeks of ALA treatment, response to cooling was observed with significant reduction in CBV. In addition, there was a significant reduction in neuropathy symptom scores.⁵⁴ In another small study of diabetics with PN, some of these same researchers further confirmed that one of the mechanisms of action of ALA involves improved microcirculation to the nerves, and that this effect occurs acutely, even after one I.V. infusion of ALA.⁵⁵

A Russian study found ALA was most effective in patients with mild neurological symptoms and a short history of diabetes.⁵⁶ ALA has also been found to be effective for diabetics with cardiac autonomic neuropathy⁵⁷ at an oral dose of 800 mg daily for four months, and for diabetic mononeuropathy of the cranial nerves⁵⁸ at a dose of 600 mg I.V. for 10 days followed by 600 mg/day orally for 60 days.

Mechanisms of Action of ALA for the Treatment of Diabetic PN

A clinical study was conducted to determine the effect of ALA on nitric oxide production in 16 individuals with diabetic neuropathy. Prior to ALA supplementation total plasma concentrations of nitrates and nitrites – a reflection of NO production – were two-fold lower in diabetic subjects than in healthy volunteers. ALA supplementation – 600 mg I.V. five days/week and 600 mg orally on weekends for three weeks, followed by 600 mg ALA orally for

the remaining 20 days – resulted in normalization of NO metabolite levels as well as improvement in clinical symptoms and electrophysiological signs of neuropathy.⁵⁹ Theoretically, increased NO production would result in increased circulation to the neurons.

Several *in vitro* and animal studies have helped elucidate the mechanisms of action of ALA for diabetic PN. In an *in vitro* study, sciatic nerve was incubated in glucose, resulting in a four-fold increase in lipid peroxidation. Addition of ALA as the R(+) form, the S(-) form, or the racemic mixture resulted in significant reductions in lipid peroxidation as measured by TBARS. There were no differences in effectiveness of the various forms of ALA.⁶⁰ Another *in vitro* study confirmed ALA's effect on decreasing lipid peroxidation in a high-glucose environment. In addition, ALA was found to decrease protein glycosylation (measured by glycosylated hemoglobin) and increase (Na⁺/K⁺)-ATPase activity.⁶¹ The effect of ALA on lipid peroxidation was confirmed in a study of people with diabetic PN. A daily dose of 600 mg ALA for 70 days resulted in significant reductions in serum lipid peroxides that had been elevated compared to non-diabetic controls.⁶²

Several studies examining the mechanism of ALA have been conducted on streptozotocin-diabetic rats with neuropathy. ALA was found to increase glucose uptake by nerve cells,⁶³ nerve myo-inositol,^{63,64} glutathione levels,^{64,65} (Na⁺/K⁺)-ATPase activity,⁶⁴ and nerve blood flow,⁶⁵ and normalize NAD:NADH ratios.⁶⁴

Acetyl-L-Carnitine (ALC)/L-Carnitine ALC for Treatment of Peripheral Neuropathy Associated with HIV

Infection with HIV has been associated with a secondary deficiency of the amino acid L-carnitine. This deficiency may be due to malabsorption and other gastrointestinal disturbances, renal loss, shifts in metabolism,⁶⁶ and use of antiretroviral drugs.⁶⁷

Antiretroviral drugs are a major cause of peripheral neuropathy in HIV-positive individuals, potentially due to a drug-induced deficiency of L-carnitine or ALC. As mentioned previously, severe axonal peripheral neuropathy can occur in subjects treated with the nucleoside analogues ddI, ddC and d4T (d-drugs), probably due to their action of

reducing mitochondrial DNA content. In a non-randomized study, serum L-carnitine and ALC levels in 12 HIV-positive individuals, with axonal peripheral neuropathy on various combinations of ddI, ddC, and d4T, were compared to 21 subjects on ddI or zidovudine (AZT) without neuropathy, 10 HIV-negative subjects with axonal or demyelinating autoimmune neuropathies, and 13 healthy individuals, the latter three groups serving as controls. Subjects with PN on antiretroviral d-drugs had significantly lower ALC levels compared to the control groups; there were no significant differences in L-carnitine levels among the groups.⁶⁸

Another larger study did not support these findings. Free carnitine, ALC, and total carnitine were measured in a group of 232 HIV-positive individuals with PN. Although there were a significant number in the study group with lower total and free carnitine levels compared to healthy controls, there were no significant differences in ALC levels. There were also no significant differences between exposure to antiretrovirals or extent of neuropathy and carnitine levels.⁶⁹

Although ALC deficiency in HIV-positive individuals with PN associated with d-drug antiretrovirals remains an open question, preliminary evidence points to a potential therapeutic effect of ALC in this population. In a study of 21 HIV-positive subjects with PN, 1,500 mg oral ALC twice daily for up to 33 months resulted in improved symptoms of neuropathy in 76 percent of subjects. In addition, periodic skin biopsies examining histological innervation found improvements beginning after six months of treatment.⁷⁰

Another small, short-term study examined the effect of 500 mg or 1 g ALC administered I.V. or intramuscularly (I.M.) daily for three weeks to HIV-positive individuals. Pain intensity was measured before and after treatment, and 10 subjects reported symptom improvement, five reported no change, and one reported a worsening of symptoms.⁷¹ Larger, long-term, placebo-controlled studies are indicated to determine the possible benefit of ALC for PN associated with HIV.

Potential mechanisms of action of ALC may include counteracting the drug-induced mitochondrial damage by direct antioxidant effects, promotion

of free fatty acid transport across the mitochondrial membrane improving cellular energy metabolism, correcting a deficiency, or enhancing the response to nerve growth factor.⁷⁰

ALC for the Treatment of Cancer Chemotherapy-induced Neuropathy

As mentioned previously, cancer chemotherapy drugs, including the taxanes (paclitaxel, docetaxel), platinum drugs (cisplatin, oxaliplatin, carboplatin), and vinca alkaloids (vincristine, vinblastine) are associated with significant neurotoxicity, particularly if prescribed in high doses. The associated peripheral neuropathy can be disabling and can persist for years after discontinuation of the drug. Other cancer chemotherapeutic agents with potential neurotoxicity are listed above in Table 1.

Acetyl-L-carnitine has been tested in clinical and animal studies for the treatment of chemotherapy-induced peripheral neuropathy. In one study, 26 patients with cisplatin- or paclitaxel-induced PN were given I.V. infusions of 1 g ALC daily for 10-20 days. The severity of PN was assessed by the World Health Organization (WHO) Toxicity Grading List at baseline and at the end of treatment. All five cisplatin-treated patients experienced at least one grade improvement in neuropathy symptoms, while eight of 12 patients in the paclitaxel group and eight of 10 in the combination paclitaxel/cisplatin group experienced at least one grade improvement in symptoms.⁷²

Oral doses of ALC have also been found effective for chemotherapy-induced PN, although improvement may take longer than with I.V. or I.M. routes of administration. Twenty-five patients with paclitaxel- or cisplatin-induced PN of grade 3 or greater during chemotherapy or grade 2 or greater persisting for at least three months post-chemotherapy, based on National Cancer Institute Common Toxicity Criteria (NCI-CTC), were given 1 g ALC three times daily for eight weeks. Sensory symptoms improved in 15 of 25 patients (1 grade in nine; 2 grades in six); motor symptoms improved in 11 of 14 reporting motor neuron dysfunction. Symptomatic relief persisted long after discontinuation of ALC – for an average of 13 months in 12 of 13 surviving patients. In addition, significant improvement was noted in sensory nerve action potentials and sensory NCV in 21 and

22 subjects, respectively. The one patient in the study who experienced a worsening of symptoms was also receiving the drug vinorelbine.⁷³

Several animal studies support the use of ALC for chemotherapy-induced PN and help elucidate possible mechanisms for its benefit. In one study, nerve conduction velocity was compared in rats given cisplatin or cisplatin plus ALC and in another group of rats given paclitaxel or paclitaxel plus ALC. The decreases in NCV were significantly less in groups supplemented with ALC. In addition, ALC did not interfere with antitumor effects of the drugs.⁷⁴ Another animal study found ALC prevented paclitaxel-induced neuropathy – an effect that lasted three weeks after discontinuation of ALC. In a separate arm, ALC provided an analgesic effect for rats with already established neuropathy.⁷⁵ Further animal studies have found acetyl-L-carnitine is protective against the neurotoxicity of oxaliplatin,⁷⁶ cisplatin,⁷⁷ and vincristine,⁷⁷ without interfering with their antitumor effects.^{76,77}

Although the pathogenesis of neurotoxicity associated with cancer chemotherapy drugs is largely unknown, cisplatin appears to affect nerve growth factor (NGF). One research group found cisplatin reduced circulating levels of NGF in rats, levels of which seemed to reflect the extent of neurological damage.⁷⁸ In an animal model, ALC modulated cisplatin-induced decreases in NGF,⁷⁴ and *in vitro* ALC potentiated the effect of NGF,⁷⁴ providing a potential mechanism for ALC's benefit for chemotherapy-induced PN.

ALC/L-Carnitine for the Treatment of Diabetic Peripheral Neuropathy

Clinical studies point to a possible L-carnitine and/or ALC deficiency in diabetic PN. In a clinical investigation, 24 type 2 diabetics with complications were compared to 15 type 2 diabetics without complications. Serum free and total carnitine levels were found to be significantly lower in individuals with diabetic complications, including PN; there were no differences in ALC levels.⁷⁹

Another study compared L-carnitine and ALC levels in peripheral nerves of 11 people with diabetic PN to levels in nerves from 13 people with ischemic non-diabetic neuropathy and 11 normal

controls. Although both groups with PN demonstrated decreased L-carnitine and ALC compared to controls, the differences did not reach statistical significance, leading the authors to speculate that carnitine deficiency may be one, but not the primary, factor in diabetic PN.⁸⁰

In a double-blind, placebo-controlled, multicenter trial, 333 subjects with diabetic neuropathy were given ALC or placebo for one year. ALC at a dose of 1,000 mg was administered I.M. for the first 10 days followed by an oral dose of 2,000 mg daily for the remaining 355 days. Nerve conduction velocities, amplitudes, and pain symptoms using a visual analog scale (VAS) were assessed at baseline and at six and 12 months. At 12 months, NCV, amplitude, and VAS pain scores were significantly better in the ALC group compared to placebo; pain scores were reduced from baseline by 39 percent in the ALC group and eight percent in the placebo group.⁸¹

Another larger study consisted of two multicenter, parallel, double-blind, placebo-controlled trials using the same protocol – 500 mg or 1,000 mg oral ALC or placebo three times daily for one year. One study consisted of centers in the United States and Canada (UCS) while the other study was conducted in centers in the United States, Canada, and Europe (UCES), with a total of 1,346 subjects. Results of the two studies were analyzed individually and as pooled cohorts. Vibrational sensation was significantly improved in the fingers at both 500- and 1,000-mg dosages of ALC three times daily, but in the toes only in the 1,000-mg dosage in the UCS group. In the UCES group, the only improvement in vibrational sense occurred in the toes with the dosage of 1,000 mg ALC three times daily. In the pooled cohorts of UCS and UCES, greater improvement in clinical symptoms was noted in both ALC groups compared to placebo. In the 27 percent of subjects who reported pain at baseline, 1,000 mg ALC three times daily resulted in significant improvements in pain in the UCS and pooled cohorts, but not in the UCES. When analyzed by subgroup it was determined the UCES had more subjects with type 1 diabetes and longer duration of neuropathy compared to the UCS. ALC appeared to work more effectively in patients with type 2 diabetes and a shorter duration of neuropathy.⁸²

In a study of 51 children with type 1 diabetes, L-carnitine was supplemented at a dose of 2 g/m²/day for two months. NCV and neurological exams were performed at baseline and at the end of treatment. Children with abnormal NCV but normal neurological exams exhibited improvement in nerve conduction velocity, whereas those with abnormal neurological exams exhibited no such improvement. Autonomic neuropathy measured by sympathetic skin response was improved in both groups.⁸³ Animal studies found acetyl-L-carnitine may benefit cardiac autonomic neuropathy⁸⁴ and gastrointestinal autonomic neuropathy.⁸⁵

Animal studies have confirmed the clinical affects of ALC for diabetic PN and helped determine potential mechanisms of action. In a study of diabetic rats given either ALC or sorbinil (an aldose reductase inhibitor drug), both were associated with improvements in NCV, decreases in malondialdehyde of sciatic nerve (a sign of reduced lipid peroxidation), and normalized myo-inositol content; sorbinil, but not ALC, reduced nerve sorbitol levels.⁸⁶ Another study found similar results, with ALC increasing nerve myo-inositol and free carnitine levels without affecting sorbitol accumulation.²⁴ Another study found deficiencies of ALC in diabetic rats resulted in decreased (Na⁺/K⁺)-ATPase activity and myo-inositol levels.⁸⁷

Another esterified form of L-carnitine, propionyl-L-carnitine (esterified with propionic acid instead of acetic acid as in the case of ALC), also improved nerve conduction and sciatic nerve blood flow in streptozotocin-diabetic rats.⁸⁸

Vitamin E

Vitamin E for the Treatment of Diabetic Peripheral Neuropathy

Oxidative stress appears to play a significant role in peripheral neuropathy, particularly in the case of PN due to diabetes. In a double-blind, placebo-controlled trial, 21 type 2 diabetics with PN were given either 900 mg vitamin E (n=11) or placebo (n=10) for six months. Electrophysiological parameters of nerve function, examined at baseline and at the end of the study, found significant improvement in two of 12 parameters – median motor NCV and tibial motor nerve distal latency – in the vitamin E group compared to placebo.⁸⁹

In an animal study of streptozotocin-diabetic rats, depletion of vitamin E resulted in a depletion of reduced glutathione in nerves of diabetic and normal rats and an induction or aggravation of abnormalities in nerve conduction, particularly in sensory nerves.⁹⁰

Vitamin E for the Prevention and Treatment of Chemotherapy-induced Peripheral Neuropathy

Cisplatin might induce a vitamin E deficiency that may be a cause of the neurotoxicity associated with this chemotherapy drug. Plasma vitamin E levels were found to be low in five patients who had developed severe neuropathy following cisplatin treatment. Two and four cycles of cisplatin also were found to significantly decrease plasma vitamin E levels in another group of five patients in whom vitamin E levels were measured at baseline and after cisplatin treatment.⁹¹

In a study evaluating the effect of vitamin E on attenuation of cisplatin neurotoxicity, 13 patients received cisplatin plus 300 mg vitamin E daily; 14 received cisplatin alone. Vitamin E was administered orally prior to onset of chemotherapy and continued for three months after cisplatin was concluded. The incidence (30.7% versus 85.7%) and severity of neurotoxicity were significantly less in the group receiving vitamin E. Evaluation of vitamin E in a preclinical animal study found it did not interfere with the tumor inhibition or tumor growth delay of cisplatin.⁹²

In two studies by the same researchers, patients on cisplatin or carboplatin, plus other chemotherapy drugs as the type of cancer indicated, were divided into two groups – one receiving chemotherapy plus 300 mg vitamin E twice daily, the other chemotherapy only. Vitamin E was supplemented at commencement of chemotherapy and for three months after chemotherapy was completed. In one trial 30 patients completed the study (14 in the vitamin E-plus-chemotherapy group and 16 in the chemotherapy-only group);⁹³ while in the second trial 31 patients completed the trial (16 in the vitamin E-plus-chemotherapy group and 15 in the chemotherapy-only group).⁹⁴ The extent of PN was evaluated in both studies by Neurological Symptom Score, Neurological Disability Score, and electrophysiological studies of nerve conduction and amplitudes of action potentials.

Significant differences in incidence of neurotoxicity were seen in both studies when comparing the vitamin E-plus-chemotherapy groups to the chemotherapy-only groups (3/14 versus 11/16 in one study;⁹³ 4/16 versus 11/15 in the second study⁹⁴).

In an identical study by the same researchers, the effect of vitamin E (300 mg twice daily) for prevention of paclitaxel-induced PN was examined. Thirty-two subjects (16 in each group) received either vitamin E-plus-chemotherapy or chemotherapy alone. The incidence of neurotoxicity was three of 16 in the vitamin E group and 10 of 16 in the chemotherapy-only group.⁹⁵

Vitamin E for the Treatment of Other Types of Peripheral Neuropathy

Vitamin E deficiency is associated with significant neurological pathology, including PN. Therefore, a vitamin E deficiency should always be ruled out in cases of PN of unknown origin. In a case report, a 22-year-old man experienced severe demyelinating neuropathy. The only abnormality on laboratory examination was a significant deficiency of vitamin E with fasting serum total tocopherol level on high-performance liquid chromatography (HPLC) measuring 0.3 mg/L (normal 6.0-19.0 mg/L). The patient was started on 1,200 mg vitamin E daily in divided doses and followed for four years. Supplementation resulted in improvement but not complete resolution of nerve conduction abnormalities. Because all other fat-soluble vitamins were normal, broad-spectrum fat malabsorption was ruled out. The authors mentioned an isolated vitamin E deficiency could have been caused by a mutation in the autosomal recessive alpha-tocopherol transfer protein gene.⁹⁶

Gastrectomy can also result in a vitamin E deficiency, which can in turn result in neuropathy. In a study of 11 postgastrectomy patients with vitamin E deficiency (10 with neurological complications), subjects were given 150-300 mg vitamin E daily, resulting in improvement of neurological symptoms in nine of 10 subjects.⁹⁷

Glutathione

Glutathione (GSH) for the Treatment of Oxaliplatin-induced Peripheral Neuropathy

Fifty-two patients with advanced colorectal cancer on oxaliplatin chemotherapy were randomized to receive an I.V. infusion of glutathione or saline (26 in each group) before each oxaliplatin cycle; 12 patients dropped out (seven in the placebo arm and five in the GSH arm). After eight cycles, nine patients experienced clinical signs of neuropathy in the GSH group compared to 15 in the placebo group. When severity of neuropathy was assessed by NCI-CTC, 11 of 19 in the placebo arm and two of 21 in the GSH arm had moderate-to-severe PN.⁹⁸

The authors of the above study discussed glutathione's possible mechanism in reducing neurotoxicity of platinum-based drugs. Reactive oxygen species generated by platinum drugs result in neuronal cell death. GSH, as an ROS scavenger, may prevent such damage.⁹⁸ The theory is supported by an *in vitro* study in which cisplatin induced apoptosis of mouse neurons, which was then prevented by preincubation with N-acetylcysteine, a precursor to GSH.⁹⁹

Glutathione and ALA for the Treatment of Diabetic Peripheral Neuropathy

Because of the connection between oxidative stress and diabetic neuropathy, a preliminary animal study examined the effect of GSH or ALA in the prevention and treatment of diabetic PN. In streptozotocin-diabetic rats, intraperitoneal ALA but not GSH partially reversed the decreased sciatic nerve blood flow initiated by diabetes. Interestingly, ALA but not GSH increased RBC GSH levels. Elevated levels of malondialdehyde (a sign of oxidative stress) were partially reversed by ALA and GSH; nerve conduction velocity was not affected by ALA or GSH.¹⁰⁰

Thiamine/Benfotiamine

A vitamin B1 (thiamine) deficiency, which can be due to various underlying causes, is known to be a factor in peripheral neuropathy. For example, gastrectomy is associated with thiamine deficiency and resultant PN. A study comparing 17 postgastrectomy PN patients with 11 subjects with thiamine-deficiency neuropathy due to dietary imbalances found the clinical presentation was identical.¹⁰¹

Benfotiamine is the most extensively studied form of thiamine for treatment of PN. Several clinical trials in healthy adults have demonstrated the superior absorption and bioavailability of this lipid-soluble thiamine analogue compared to several water-soluble thiamine salts.¹⁰²⁻¹⁰⁴ In addition, because of the lipophilic nature of benfotiamine, it may be more readily transported across cell membranes, including neurons.

Benfotiamine/Thiamine for the Treatment of Diabetic Peripheral Neuropathy

In a double-blind, randomized, placebo-controlled pilot study, 40 subjects (20 in each group) with diabetic PN were given two 50-mg tablets of benfotiamine four times daily (400 mg total daily dose) or placebo for three weeks. Assessment was via neuropathy symptom and vibration sensation scores from both physician and patient. A statistically significant improvement in the neuropathy score was reported in the treatment group compared to placebo. The most significant improvement reported was decrease in pain, although, there was no significant improvement in vibration perception measured by the tuning fork test.¹⁰⁵

Several studies have investigated the effect of benfotiamine in combination with other B vitamins in the treatment of diabetic neuropathy. In one study, 30 subjects received Milgamma® (50 mg benfotiamine and 250 mcg B12 as cyanocobalamin per tablet) at a dose of two tablets four times daily for three weeks (total daily dose: 400 mg benfotiamine and 2,000 mcg cyanocobalamin), followed by one tablet three times daily for nine weeks. The second group of 15 subjects received a B-complex vitamin supplement at a dose of two tablets three times daily for the entire three months. Changes in pain severity and vibration perception thresholds were measured at baseline and at the end of the study. All Milgamma-treated patients experienced significant relief in neuropathic pain and dramatic improvement in vibration perception thresholds, while subjects receiving a B-complex vitamin experienced only slight, non-statistically significant improvement.¹⁰⁶

In a second six-week trial, 36 subjects with diabetic PN were divided into three groups of 12 each receiving: (1) Milgamma-N® (40 mg benfotiamine,

90 mg pyridoxine, and 250 mcg cyanocobalamin per capsule) at a dose of two capsules four times daily (320 mg benfotiamine, 720 mg pyridoxine, and 2,000 mcg cyanocobalamin daily); (2) Milgamma-N at a lower dose of one capsule three times daily (120 mg benfotiamine, 270 mg pyridoxine, and 750 mcg cyanocobalamin daily); or (3) 50 mg benfotiamine three times daily. Neuropathy was assessed via pain and vibration sensation at baseline and after three and six weeks. Patients in all three groups reported beneficial therapeutic effects, even at three weeks, with the most significant improvement reported by patients receiving the highest-dose benfotiamine.¹⁰⁷

A double-blind, randomized, placebo-controlled, 12-week study examined the effectiveness of another benfotiamine combination containing both vitamins B6 and B12 in 24 diabetic subjects with PN. A statistically significant improvement in NCV in the peroneal nerve was observed in the treatment group compared to placebo.¹⁰⁸

Animal studies also confirm the benefit of benfotiamine for neuropathy in a rat model of diabetic PN.^{109,110} One study comparing the effect of water-soluble thiamine with lipid-soluble benfotiamine found benfotiamine superior in preventing functional nerve damage and preventing formation of AGEs – a cause of diabetic PN.¹¹⁰

At least two *in vitro* studies confirm the effect of thiamine and benfotiamine on AGEs. Two studies found benfotiamine^{111,112} and one study found thiamine¹¹² reduced the formation of AGEs in glucose-incubated cells. Other *in vitro* studies have found benfotiamine or thiamine decreased glucose-induced apoptosis of endothelial cells¹¹³ and decreased polyol accumulation by inhibition of aldose reductase expression.¹¹⁴

Benfotiamine for the Treatment of Alcohol-related Peripheral Neuropathy

Chronic alcoholics commonly develop a thiamine deficiency, resulting in peripheral neuropathy and other health problems. A deficiency of vitamin B1 in this population can be due to inadequate dietary intake, reduced capacity for hepatic storage, inhibition of intestinal transport and absorption, or decreased formation of the active coenzyme form. An animal study found chronic alcohol consumption by rats

resulted in a significant depletion in thiamine diphosphate (TDP) – the active coenzyme form of thiamine. Supplementation with benfotiamine significantly increased levels of TDP and total thiamine compared to supplementation with thiamine HCl.¹¹⁵

An eight-week, randomized, multicenter, placebo-controlled, double-blind study compared the effect of benfotiamine alone to a benfotiamine complex (Milgamma-N) or placebo in 84 alcoholic patients. Benfotiamine was given in a daily oral dose of 320 mg (two 40-mg tablets four times daily) during weeks 1-4, followed by 40 mg three times daily (120 mg total daily dose) during weeks 5-8. A second group received Milgamma-N (providing a total daily dose of 320 mg benfotiamine, 720 mg pyridoxine, and 2,000 mcg cyanocobalamin) during weeks 1-4 and a total daily dose of 120 mg benfotiamine, 270 mg pyridoxine, and 750 mcg cyanocobalamin during weeks 5-8; a third group received placebo.¹¹⁶

Parameters measured included vibration perception in the great toe, ankle, and tibia; neural pain intensity; motor function and paralysis; sensory function; and overall neuropathy score and clinical assessment. Although benfotiamine therapy was superior to Milgamma-N or placebo for all parameters, results reached statistical significance only for motor function, paralysis, and overall neuropathy score. Why the benfotiamine-alone group had better results than the Milgamma-N group, despite the fact that the benfotiamine dosage was equivalent, is not completely understood. The authors hypothesized vitamins B6 and B12 might have competed with the effects of vitamin B1 in the Milgamma-N group. On the other hand, in the case of diabetic neuropathy, the positive effects of the combination may be due to the fact that deficiencies of vitamins B1, B6, and B12 are all implicated in its possible pathogenesis; whereas, alcoholic neuropathy is associated with only vitamin B1 deficiency.

A small Russian study also found benefit of benfotiamine for alcoholic neuropathy. Fourteen chronic alcoholic men with polyneuropathy were given 450 mg benfotiamine daily for two weeks, followed by 300 mg daily for an additional four weeks; regression of neuropathy symptoms was observed. A more in-depth report of the results is not possible because only the abstract is in English.¹¹⁷

Methylcobalamin for the Treatment of Peripheral Neuropathy

Vitamin B12 Deficiency Neuropathy

Vitamin B12 deficiency has been associated with significant neurological pathology, including peripheral neuropathy. Testing serum metabolites such as methylmalonic acid and homocysteine can help clinically identify individuals at risk for a deficiency-associated neurological syndrome.¹¹⁸ One of the mechanisms believed to be at play in vitamin B12 deficiency neuropathy is hypomethylation in the central nervous system. Inhibition of the B12-dependent enzyme methionine synthase results in a fall in the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine;¹¹⁹ the resultant deficiency in SAM impairs methylation reactions in the myelin sheath. The methylation of homocysteine to methionine requires both methylcobalamin (an active form of vitamin B12) and the active form of folic acid (5-methyltetrahydrofolate).¹²⁰ An animal model of B12 deficiency neuropathy, however, does not support the hypomethylation theory.¹²¹

Animal studies help elucidate some of the potential mechanisms involved in vitamin B12-associated neuropathies. Rats rendered B12 deficient by total gastrectomy were found to have elevated levels of the neurotoxic cytokine tumor necrosis factor-alpha (TNF- α) and decreased levels of neurotrophic epidermal growth factor and the neurotrophic cytokine interleukin-6. Levels of these cytokines and growth factors were normalized by the administration of cobalamin.¹²²

In an experimental animal model of acrylamide-induced neuropathy, an ultra-high dose of methylcobalamin was found to stimulate nerve regeneration by up-regulating gene transcription. In a comparison of three groups, rats were given intraperitoneal methylcobalamin at a dose of 500 mcg/kg or 50 mcg/kg body weight, while a third group received saline. Only the high-dose methylcobalamin group experienced regeneration of motor neurons.¹²³

Methylcobalamin for the Treatment of Diabetic Peripheral Neuropathy

In a four-month, double-blind, placebo-controlled trial of type 1 and 2 diabetics with neuropathy, 21 subjects were given oral methylcobalamin at a dose of 500 mcg three times daily (the authors presumably erroneously reported this dosage in mgs), while 22 subjects received placebo. Significant improvements were reported for somatic and autonomic symptoms in the treatment group compared to placebo.¹²⁴

A smaller study examined the effect of intrathecal injections of methylcobalamin in 11 subjects with type 2 diabetes. The study design was variable in that several patients had different dosage schedules. Each subject received 2,500 mcg methylcobalamin via injection with one or two more injections occurring at one-month intervals. In addition, five subjects took 1,500 mcg/day oral methylcobalamin for one month; one subject got 500 mcg/day I.V. methylcobalamin for one month; and three subjects received an additional injection one year after completion of the initial course. Subjects reportedly began to feel effects from several hours to several days after the initial injection – primarily involving a decrease in heaviness of the lower limbs and improved sensation. Benefits lasted from several months to four years. No changes in NCV were noted.¹²⁵

Another study of 72 patients with diabetic PN found the combination of methylcobalamin and prostaglandin E1 was superior to either substance alone.¹²⁶ A review of several clinical trials of the use of methylcobalamin alone or vitamin B12 (form not specified) combined with other B vitamins found overall symptomatic relief of neuropathy symptoms was more pronounced than electrophysiological findings.¹²⁷

In a study of 20 type 2 diabetics compared to 20 age-matched controls, serum vitamin B12 levels were significantly lower in the diabetic group. Supplementation of 1,500 mcg/day methylcobalamin for two months resulted in improved vibratory perception thresholds and heart rate variability (a sign of improvement in signs of autonomic neuropathy) in the diabetic group.¹²⁸

Supplementation of vitamin B12 may benefit diabetic PN by correcting a deficiency. While diabetes itself can result in vitamin B12 deficiency,

metformin, an oral antihyperglycemic agent used to treat type 2 diabetes, may also cause vitamin B12 deficiency.¹²⁹

In streptozotocin-diabetic rats, methylcobalamin resulted in decreased demyelination and protection of nerve fiber density and size. The rats were administered I.M. methylcobalamin at a very high daily dose of 500 mcg/kg body weight for 16 weeks.¹³⁰

Methylcobalamin for the Treatment of Neuropathy Associated with Renal Failure

Uremia is associated with peripheral neuropathy and is characterized by motor and sensory neuropathy that begins distally and ascends as the condition worsens. In a study of nine patients on renal dialysis due to chronic glomerulonephritis, diabetes, or renal tuberculosis (six with uremic neuropathy; three with diabetic/uremic neuropathy), subjects were given 500 mcg methylcobalamin I.V. three times weekly for six months. Due to poor renal excretion, serum vitamin B12 reached extremely high levels during the course of the study (mean, 72,000 pg/mL). Significant decrease in pain scores was experienced by six of nine subjects; NCV increased significantly.¹³¹

Methylcobalamin has also been found to benefit uremics with autonomic neuropathy. In a group of eight dialysis patients with abnormal beat-to-beat heart rate variability, 1,500 mcg methylcobalamin daily for six months resulted in improvement of this sign of autonomic neuropathy – from variability of 3.3 beats/minute at the beginning of the study to 5.8 beats/minute after six months.¹³²

Vitamin B12 deficiency has been reported in patients with renal failure, providing one potential cause for neuropathy in this population.¹³² In addition, accumulation of neurotoxic compounds is a likely cause, since dialysis or renal transplant can ameliorate the condition.¹³³

Cyanide may be one of the neurotoxic metabolites involved, as researchers have found a relationship between the severity of neuropathy as measured by vibrational sensation and tobacco smoking (a significant source of cyanide).¹³³ Uremic patients were also found to have high levels of cyanide as measured by accumulation of thiocyanate, a detoxification product of cyanide. Another method of detoxifying cyanide is to utilize the pool of free cyanide to

synthesize cyanocobalamin (a form of vitamin B12). These researchers found that administration of methylcobalamin resulted in increased cyanocobalamin and decreased levels of thiocyanate (a reflection of free cyanide levels). They theorized methylcobalamin was providing the cobalamin substrate for utilization of cyanide in cyanocobalamin synthesis. These same researchers had previously noted improved vibrational thresholds in this population of individuals when supplemented with methylcobalamin.¹³³

Vitamin B12 Status in HIV-associated Neuropathy

Peripheral neuropathy was diagnosed in 34 of 49 HIV patients (69%) referred to a neurology clinic for examination of vitamin B12 status. Abnormal B12 status, defined by a serum level less than 150 pmol/L or a Schilling test reflecting less than eight-percent absorption, was found in 29 percent of patients with PN compared to 20 percent in the group as a whole. Eighty percent of subjects with abnormal vitamin B12 status had progressed to AIDS. Five of eight patients who received parenteral vitamin B12 therapy experienced clinical improvement in neuropathy symptoms within one week of treatment.³³

Another study examining 20 subjects with early-stage HIV infection found a five-percent incidence of PN, but it was not associated with impaired vitamin B12 metabolism.³⁴ Neuropathies in this population are often associated with antiretroviral drugs (see above).

Folate for the Treatment of Peripheral Neuropathy

In addition to folic acid's involvement in vitamin B12 metabolism, a folate deficiency can result in PN, independent of vitamin B12 status. In a series of 20 subjects with abnormal neurological findings, 10 subjects fit the diagnostic criteria for peripheral neuropathy. The only abnormality detected was a low serum, RBC, or cerebral spinal fluid (CSF) folate level.¹³⁴

In a Japanese study of 343 patients with various neurological diseases, primarily axonal neuropathy, 36 subjects (10.5%) demonstrated low serum folate levels. Supplementation with high-dose folate (15 mg/day) resulted in improvement in neurological symptoms in 24 of 36 subjects (67%).¹³⁵

A folate deficiency may contribute to the pathogenesis of alcoholic peripheral neuropathy. In a study of 46 hospitalized alcoholics with PN, eight percent demonstrated low plasma folate levels two weeks after alcohol abstinence. When functional folate status was evaluated using the formiminoglutamic acid (FiGlu) excretion test or the deoxyuridine suppression (dU) test, 50 percent of this population was found to be deficient.¹³⁶

PN can be caused by several medications associated with folate deficiency, including sulfasalazine, methotrexate, antituberculosis drugs, anticonvulsants, and oral contraceptives.¹³⁷ In a study of 51 epileptic patients newly placed on anticonvulsants and followed for five years, no clinical signs of neuropathy were noted, although 18 percent of the group taking phenytoin (and none in another group on carbamazepine) showed signs of slowed nerve conduction or decreased action potentials. Clinical and electrophysiological signs of neuropathy were noted in six patients on chronic barbiturate therapy and in 10 patients on chronic phenytoin.¹³⁸

Patients on longer-term anticonvulsant therapy appear to be more likely to exhibit signs of neuropathy. In 29 epileptics on long-term therapy, all but three showed abnormalities in electrophysiological measurements of nerve function. Sensory nerve action potentials were reduced or absent in 76 percent of patients; all subjects had low serum and CSF folate levels. These 19 patients were treated with either folic acid (n=10) or folic acid (n=9) for one month with significant reversal of nerve abnormalities; a greater effect was noted in the folic acid group. The researchers theorized that folic acid was able to raise levels of folate in the CSF slightly more than folic acid.¹³⁹

Pyridoxine and Peripheral Neuropathy

Vitamin B6 deficiency may be associated with the development of peripheral neuropathy. In addition, in the form of pyridoxine HCl, high doses of B6 have been implicated as a cause of PN.

Pyridoxine Deficiency Neuropathy

Vitamin B6 deficiency PN has been studied in an experimental rat model. Morphometric analysis demonstrated decreased nerve fiber density and increased axon-to-myelin ratio, indicative of peripheral neuropathy.¹⁴⁰

Medications, particularly isoniazid for tuberculosis, can result in pyridoxine-deficiency neuropathy that can be prevented by simultaneous supplementation with vitamin B6.¹⁴¹ Isoniazid appears to inhibit the activity of vitamin B6.¹⁴² PN associated with isoniazid therapy typically manifests as burning feet and can be reversed within a few weeks by 250 mg pyridoxine daily.¹⁴³

A study of patients with carpal tunnel syndrome (CTS), some with concomitant PN, found patients with PN (but not CTS without PN) demonstrated abnormalities of pyridoxine metabolism as measured by erythrocyte glutamine oxaloacetic acid transaminase (EGOT) activity.¹⁴⁴

PN associated with vitamin B6 deficiency is seen in patients with uremia. In a study of 66 dialysis patients, 12 experienced PN with a significant negative correlation between pyridoxal 5' phosphate (P5P; the active form of vitamin B6) levels and PN symptoms. Supplementation of 30 mg vitamin B6 daily for one month resulted in increased levels of P5P and improvement in sensory abnormalities in eight of 12 patients.¹⁴⁵

Pyridoxine in the Treatment of Diabetic Peripheral Neuropathy

Pyridoxine may have application for the treatment of diabetic neuropathy, although studies have been limited and results equivocal. A study of 50 patients (24 males and 26 females) with significant diabetic neuropathy found significantly lower levels of P5P in this population compared to age- and gender-matched controls with diabetes but without neuropathy.¹⁴⁶ On the other hand, another study examining various vitamin levels in type 2 diabetics with or without neuropathy found no correlation between vitamin B6 levels and neuropathy. In fact, this study found no correlation between neuropathy and levels of any vitamins tested – vitamins A or E, beta carotene, vitamins B1, B2, B6, B12, or folate.¹⁴⁷

Despite possible low levels of P5P in individuals with diabetic neuropathy, intervention studies have been disappointing. In one double-blind, controlled study 16 subjects received 25 mg pyridoxine daily while 14 subjects were given placebo. After three months, symptoms and neurological signs were assessed. There were no significant differences between

pyridoxine and placebo groups, with nine patients in each group demonstrating significant improvements. However, 16 of 30 subjects were initially low in P5P and of the 18 patients who experienced improvement, 12 were low in P5P (eight in the pyridoxine group and four in the placebo group).¹⁴⁸

Another double-blind study found no statistically significant difference between pyridoxine HCl supplementation or placebo for diabetic PN. Eighteen diabetic subjects with neuropathy were randomly assigned to 50 mg pyridoxine HCl three times daily for four months or placebo. Six of nine in the B6 group and four of nine in the placebo group experienced significant relief of symptoms. Only one patient had low P5P levels at the beginning of the study.¹⁴⁹

It is possible that vitamin B6 will provide therapeutic value for the treatment of PN primarily in cases where a deficiency is evident. In addition, magnesium and riboflavin are needed for conversion of pyridoxine to active P5P in the liver. Diabetics are frequently deficient in magnesium; thus, supplementing with active P5P might have resulted in improved outcomes.

In a study of 200 diabetic patients with peripheral neuropathy, 100 were randomly assigned to 50 mg pyridoxine and 25 mg thiamine daily, while 100 subjects were assigned to 1 mg of each vitamin for four weeks. Severity of PN symptoms decreased in 48.9 percent of subjects on higher-dose pyridoxine/thiamine, compared to only 11.4 percent of subjects on 1 mg of each. Only thiamine levels were tested in this study and low levels were found to correlate with intensity of neuropathy symptoms. Therefore, the effect of pyridoxine in this study is difficult to assess.¹⁵⁰

An *in vitro* study helps to illuminate a possible mechanism for pyridoxine in the prevention of diabetic PN. Both pyridoxine and its intermediate metabolite pyridoxamine were found to inhibit free radical formation, lipid peroxidation, and protein glycosylation, and protect (Na⁺/K⁺)-ATPase activity – all mechanisms involved in diabetic PN – in RBCs exposed to high glucose concentrations.¹⁵¹

High-dose Pyridoxine May Cause Peripheral Neuropathy

During the 1980s and early 1990s a rash of case reports of peripheral neuropathy associated with high-dose pyridoxine appeared in the scientific literature. In most cases the dosages ranged from 1-5 g daily. In one prospective study, 1 or 3 g pyridoxine was given to five healthy volunteers, resulting in symptomatic and electrophysiological changes in all subjects; those receiving the higher dose experienced earlier symptoms.¹⁵²

Animal studies continue to examine neurological abnormalities induced by pyridoxine. For instance, 1,200 or 600 mg/kg/day (a very high dose) to rats for 6-10 days results in necrosis of sensory neurons, especially affecting large diameter neurons.¹⁵³

Why there was a plethora of pyridoxine-toxicity reports 15-20 years ago, with a dearth of reports in recent years, remains a mystery. In addition, a mechanism of pyridoxine's potential toxicity has not been offered. One study found a mere 25 mg pyridoxine daily for 10 days resulted in a decrease in folate levels in eight healthy volunteers, with no change in vitamin B12 levels.¹⁵⁴ Is it possible high-dose vitamin B6 supplementation causes neuropathies because it negatively impacts levels of other B vitamins? The conventional wisdom that suggests the importance of taking the full range of B-complex vitamins may have application in this situation.

Biotin for the Treatment of Peripheral Neuropathy

The B vitamin biotin has application for the treatment of uremic neuropathy. It is hypothesized that renal failure and subsequent metabolic imbalances result in impaired formation by the intestinal flora and absorption of biotin. In a small study, nine patients on dialysis suffering from PN were supplemented with a large dose of biotin – 10 mg daily in three divided doses – for 1-4 years. Marked improvements in paresthesia, restless legs, and difficulty walking were noted in all patients within three months. One patient who had been unable to walk for three months improved significantly after six months of treatment, and at the time the study was submitted had been walking 2 km/day for two years.¹⁵⁵

After using biotin successfully in dialysis patients, these same researchers began using it for patients with diabetic PN. In a case series, three subjects with severe diabetic neuropathy were supplemented with 10 mg biotin via I.M. injection daily for six weeks, followed by three times weekly for another six weeks; oral administration of 5 mg daily continued. Objective symptom improvement was noted within 4-8 weeks in all three patients. NCV was only slightly improved or not at all.¹⁵⁶

The Application of Myo-inositol for Diabetic Peripheral Neuropathy

Myo-inositol is an important constituent of the phospholipids that make up nerve cell membranes. Because low nerve myo-inositol levels have been observed in the pathogenesis of diabetic neuropathy, the potential for supplementation has been explored. In an animal model of experimental diabetic neuropathy, nerve myo-inositol levels were diminished, with subsequent decreases in (Na⁺/K⁺)-ATPase activity and NCV (by 25-30%), axonal atrophy, and demyelination; dietary myo-inositol prevented these signs of nerve degeneration.¹⁵⁷ In another animal model, experimental diabetes induced a decrease in motor NCV. Supplementation of 500 mg myo-inositol/rat/day partially prevented this decrease, while supplementation with an analogue of myo-inositol – D-myo-inositol-1,2,6-trisphosphate – at a dose of 24 mg/rat/day completely prevented a reduction in nerve conduction velocity.¹⁵⁸

Sural nerve biopsies were conducted on 30 male subjects – 10 with type 1 diabetes (five with clinical signs of diabetic neuropathy), 10 with impaired glucose tolerance, and 10 with normal glucose tolerance. Nerve myo-inositol levels were significantly lower in diabetics with neuropathy. Also, in subjects with normal or impaired glucose tolerance, high nerve myo-inositol levels were associated with nerve regeneration as illustrated by increased nerve fiber density.¹⁵⁹

Despite myo-inositol's potential to prevent or reverse the signs and symptoms of diabetic PN, clinical evidence has been limited. In a small, double-blind, placebo-controlled, crossover trial, seven subjects with clinical signs of neuropathy (n=3) or subclinical neurophysiological signs (n=4) were

supplemented with 500 mg myo-inositol or placebo twice daily for 14 days and crossed over to the other group. Each group was on placebo for two 14-day intervals and myo-inositol for one 14-day interval. Action potentials in the median, sural, and popliteal nerves increased in amplitude by 76-, 160-, and 40-percent, respectively, during myo-inositol supplementation. No significant differences were noted in NCV during either myo-inositol or placebo supplementation.¹⁶⁰

In a double-blind study, 28 diabetics with early, subclinical neuropathy were supplemented with 2 g myo-inositol or placebo three times daily for two months. No significant changes were noted in NCV, vibratory perception, or amplitude of action potentials in either group after two months. Although blood and muscle tissue levels of myo-inositol were not found to be low, nerve myo-inositol levels were not evaluated.¹⁶¹

L-Glutamine for the Treatment of Chemotherapy-induced Peripheral Neuropathy

Paclitaxel is a chemotherapeutic agent associated with PN. Neurological exams were conducted before and after paclitaxel (average interval between before-and-after evaluations was 32 days) in 12 patients supplemented with the amino acid glutamine and 33 patients who did not receive glutamine. L-glutamine was supplemented orally at a dose of 10 g three times daily for four days, beginning 24 hours after a high-dose paclitaxel cycle. Only eight percent of patients in the glutamine group experienced moderate-to-severe pain in the fingers and toes compared to 40 percent in the no-glutamine group. Signs of PN in the form of decreased vibrational sense, motor weakness, ataxic gait, and sensory deficits were significantly less prevalent in the glutamine group.¹⁶²

Taurine for the Potential Treatment of Diabetic Peripheral Neuropathy

Several animal studies indicate the amino acid taurine may provide some benefit for prevention or treatment of PN due to diabetes. Taurine is deficient in diabetes, particularly in the Schwann cells and vascular endothelium of nerves.¹⁶³ Taurine may

act as an osmolytic agent and inhibitory neurotransmitter, resulting in modulation of pain perception. Theoretically, as high glucose results in sorbitol accumulation within the cell, taurine is depleted in the peripheral nerves, resulting in excitability and pain. One study of streptozotocin-diabetic rats found taurine levels decreased by 31 percent and myo-inositol levels by 37 percent. When sorbitol accumulation was decreased by an aldose reductase inhibitor, taurine levels increased by 22 percent.¹⁶⁴ In another animal study, diabetes resulted in abnormal calcium-ion signaling. Taurine repletion resulted in normalization of intracellular calcium concentrations, with resultant diminution of pain.¹⁶⁵ Other animal studies found taurine decreased diabetes-induced nerve conduction and nerve blood flow deficits,^{166,167} and increased nerve growth factor and nerve ascorbate levels,¹⁶³ at least in part via antioxidant mechanisms. Clinical studies are indicated to determine whether taurine can provide benefit to individuals with diabetic PN.

The Application of N-acetylcysteine (NAC) for Peripheral Neuropathy

The amino acid NAC may have application in the prevention or treatment of neuropathy. NAC is a potent antioxidant and helps to enhance glutathione levels.

Application of NAC for Diabetic Peripheral Neuropathy

Oral administration of NAC to streptozotocin-diabetic rats resulted in prevention of diabetes-induced deficits. Motor nerve conduction velocity was significantly decreased by diabetes; NAC reduced the decrease in NCV and inhibited atrophy of myelinated fibers.¹⁶⁸ In another study, experimentally-induced diabetes for two months in rats resulted in 20-percent reduction in NCV and 48-percent reduction in endoneurial blood flow; both were largely corrected by NAC supplementation.¹⁶⁹ Clinical studies are warranted to determine NAC's application for treatment of diabetic PN.

Table 2. Summary of Nutrients for the Treatment of Chemotherapy-induced Peripheral Neuropathy

Nutrient Intervention	Chemotherapy	Trial	Route of Administration	Daily Dosage Range
Acetyl-L-carnitine	Cisplatin, paclitaxel, or both	Uncontrolled; n=26; 10-20 days	I.V.	1,000 mg
	Cisplatin or paclitaxel	Uncontrolled; n=25; 8 weeks	Oral	3,000 mg
Vitamin E or nothing	Cisplatin	Controlled; n=27; 3 months	Oral	300 mg
	Cisplatin or carbaplatin	Two controlled trials; n=30/31; 3 months	Oral	600 mg
Glutathione or saline	Oxaliplatin	RCT; n=40 completers	I.V.	Dosage not specified
L-Glutamine or nothing	Paclitaxel	Controlled; n=45 (12 glutamine; 33 no glutamine)	Oral	30 g for 4 days after each chemo treatment
N-acetylcysteine or placebo	Oxaliplatin	RCT; n=14; 12 cycles of chemotherapy	Oral	1,200 mg

To benefit the clinician, only positive clinical studies have been included in this table.
RCT=randomized, controlled trial

NAC for the Treatment of Chemotherapy-induced Peripheral Neuropathy

A mechanism of cisplatin chemotherapy-induced PN was elucidated in an *in vitro* mouse model. Apoptosis of neurons was induced by cisplatin, but preincubation with NAC completely blocked apoptosis; incubation with vitamin E partially blocked apoptosis.⁹⁹

A small pilot study was conducted to determine the effect of NAC on oxaliplatin-induced neuropathy. Fourteen stage III colon cancer patients were randomly assigned to 1,200 mg oral NAC or placebo daily. Neurological evaluations were conducted at baseline and after four, eight, and 12 cycles of chemotherapy. After four cycles, two of five in the NAC group and seven of nine in the placebo group experienced neuropathy; after eight cycles no one in the NAC group experienced neuropathy compared to five of nine in the placebo group. Only one in the NAC

group, but eight of nine in the placebo group, experienced neuropathy after 12 cycles.¹⁷⁰

Table 2 summarizes the potential nutrients for prevention and treatment of chemotherapy-induced neuropathy.

Minerals for the Treatment of Diabetic Peripheral Neuropathy

Magnesium

Plasma magnesium levels have been found to be significantly lower in diabetic subjects compared to controls.^{171,172} Despite the fact magnesium may be the most common mineral deficiency in diabetes, its clinical significance for peripheral neuropathy is unknown. An animal study found oral magnesium supplementation to diabetic rats resulted in decreased pain measured by thermal pain thresholds.¹⁷³

Table 3. Summary of Nutrients for the Treatment of Diabetic Peripheral Neuropathy

Intervention	Clinical Trials	Routes of Administration	Daily Dosage Range
alpha-Lipoic acid or placebo	RCT; n=328; 3 weeks	I.V.	600-1,200 mg
	RCT; n=65; 2 years	I.V. for 5 days followed by oral	600-1,200 mg
	RCT; n=509; 7 months	I.V. for 3 weeks followed by oral	600 mg (I.V.); 1,800 mg (oral)
	RCT; n=120; 5 days/week for 14 treatments	I.V.	600 mg
	Small RCT; n=24; 3 weeks	Oral	1,800 mg
alpha-Lipoic acid	Small uncontrolled; n=26; 3 months	Oral	600 mg
Acetyl-L-carnitine or placebo	RCT; n=333; 1 year	I.M. for 10 days followed by oral	1,000 mg (I.M.); 2,000 mg (oral)
	2 multicenter RTCs; n=1,346; 1 year	Oral	1,500-3,000 mg
Vitamin E or placebo	Small RCT; n=21; 6 months	Oral	900 mg
Benfotiamine or placebo	RCT; n=40; 3 weeks	Oral	400 mg
Benfotiamine plus cyanocobalamin (Milgamma) or B-complex	Comparative trial; n=30 Milgamma; n=15 B-complex; 3 months	Oral	400 mg benfotiamine and 2,000 mcg cyanocobalamin (3 weeks), followed by 150 mg benfotiamine and 750 mcg cyanocobalamin (9 weeks)
Benfotiamine, pyridoxine, and cyanocobalamin versus benfotiamine alone	Open trial; n=36 (12/group); 6 weeks	Oral	320 or 120 mg benfotiamine, 720 or 270 mg pyridoxine, and 2,000 or 750 mcg cyanocobalamin versus 150 mg benfotiamine
Methylcobalamin or placebo	RCT; n=43; 4 months	Oral	1,500 mcg
Methylcobalamin or nothing	Matched controls; n=40; 2 months	Oral	1,500 mcg
Zinc sulfate or placebo	RTC; n=30	Oral	660 mg (267 mg elemental zinc)

To benefit the clinician, only positive clinical studies have been included in this table.
 RCT=randomized, controlled trial

Zinc

A clinical study examined the effect of zinc for parameters of blood sugar control and peripheral neuropathy in 50 subjects. Thirty diabetics with PN were supplemented with 660 mg zinc sulfate (267 mg elemental zinc) daily or placebo (equal number in each group) for six weeks and compared to a group of 20 healthy controls. Serum zinc levels were significantly lower at the beginning of the study in both groups with diabetes compared to controls. NCV in the median and peroneal nerves significantly increased in the group supplemented with zinc. In addition, significant improvements in fasting and post-prandial blood sugar were noted in the zinc group compared to the diabetics taking placebo.¹⁷⁴

Chromium

A chromium deficiency, seen in particular in patients on total parenteral nutrition, can cause a peripheral neuropathy associated with impaired glucose tolerance.^{175,176} Infusion of as little as 250 mcg chromium daily for three weeks reversed abnormal nerve conduction.¹⁷⁶

Table 3 summarizes the most promising nutrient treatment options for diabetic PN.

Essential Fatty Acids for Peripheral Neuropathy

Gamma-linolenic Acid (GLA) for the Treatment of Diabetic Peripheral Neuropathy

Diabetics appear to have impaired conversion of linoleic acid to GLA, apparently due to faulty desaturase enzyme activity.¹⁷⁷ Because metabolites of GLA are essential for nerve membrane structure and blood flow, a deficiency could contribute to the development of neuropathy.

Clinical studies of GLA for PN have been limited to two, in which evening primrose oil (EPO) was used. In a preliminary, double-blind study, 22 patients with diabetic neuropathy were assigned to 360 mg GLA (n=12) or placebo (n=10) for six months. Subjects on GLA exhibited significantly better neuropathy scores, NCV, and action potentials compared to placebo.¹⁷⁸

In a subsequent, multicenter, double-blind, placebo-controlled trial, 84 subjects with mild diabetic neuropathy were given 480 mg GLA from EPO (n=44) or placebo (n=40) daily for one year. Thirteen of 16 parameters of neurological function, including NCV, improved in the GLA group, while the placebo group deteriorated.¹⁷⁹ While the results of these two studies appear promising, one of the centers involved in the multicenter study was determined by the General Medical Council in Great Britain to have used fraudulent research techniques by falsifying results. This center raised suspicions when a clear benefit of EPO was reported, while the other centers found little or no difference between EPO and placebo.^{180,181}

Animal studies lend some support for use of GLA and elucidate its potential mechanisms in diabetic PN. In a study of streptozotocin-diabetic rats, diabetes resulted in decreased NCV, abnormal fatty acid phospholipid composition, and decreased (Na⁺/K⁺)-ATPase activity. Supplementation of diabetic rats with 260 mg GLA daily, either at onset of diabetes for 12 weeks (preventive group) or after six weeks of diabetes for six weeks (reversal group), resulted in restoration of normal NCV in both the prevention and reversal groups and partial normalization of (Na⁺/K⁺)-ATPase activity in the prevention group.¹⁸²

Another animal study found GLA may improve NCV and neuronal blood flow in diabetic PN. It compared the effect of GLA from EPO with GLA in a triglyceride form not found in EPO and found they were equally effective at improving NCV and blood flow; sunflower oil with no GLA had no effect.¹⁸³

GLA and ALA in the Treatment of Diabetic Peripheral Neuropathy

One study examined the effects of EPO or ALA on NCV, nerve blood flow, and lipid parameters in streptozotocin-diabetic rats. While both EPO and ALA improved neuronal blood flow and NCV, ALA also improved signs of dyslipidemia, while EPO resulted in increased dyslipidemia.¹⁸⁴ In another animal study, a conjugate of ALA plus GLA worked better than either substance alone in improving NCV and neuronal circulation.¹⁸⁵

Omega-3 Fatty Acids in the Treatment of Peripheral Neuropathy

Similar to omega-6 fatty acids such as GLA, omega-3 fatty acids are also essential for healthy nerve cell membranes and blood flow. A clinical study of 21 type 2 diabetics with symptoms and signs of neuropathy found 1,800 mg eicosapentaenoic acid (EPA) daily for 48 weeks significantly decreased symptoms of coldness and numbness and improved vibrational perception; improvement in vibratory threshold plateaued at 12 weeks. Circulation, measured in the dorsal pedis artery, and lipid profiles also significantly improved.¹⁸⁶

A study in diabetic rats found fish oil, compared to olive oil, increased NCV, improved (Na⁺/K⁺)-ATPase activity, and prevented histological signs of nerve degeneration such as demyelination and axonal degeneration.¹⁸⁷

The omega-3 fatty acid, docosahexaenoic acid (DHA), was isolated in phospholipid liposomes and fed to diabetic rats at a dose of 60 mg/kg body weight. Eight weeks of diabetes led to significant decreases in NCV, nerve blood flow, and (Na⁺/K⁺)-ATPase activity in sciatic nerve and RBCs. DHA completely prevented the decreases in blood flow and NCV; it improved (Na⁺/K⁺)-ATPase activity in RBCs but not sciatic nerve. These researchers hypothesized that DHA might work better than a combination of DHA and EPA because EPA might interfere with the beneficial effects of omega-6 fatty acids.¹⁸⁸ Since this study did not compare the two, this is merely conjecture.

A Topical Flavonoid-Vitamin Complex for the Treatment of Peripheral Neuropathy

A topical compound called QR-333 was studied in a double-blind trial of 34 individuals with neuropathy due to type 1 or 2 diabetes. The compound, consisting of quercetin, ascorbyl palmitate, and vitamin D3, was formulated because the flavonoid quercetin is an aldose reductase inhibitor, vitamin C in a fat-soluble form could enhance its free radical scavenging effects in the lipophilic environment of neural tissue, and a synthetic analogue of vitamin D3 has been shown *in vitro* to enhance nerve growth factor. Twenty-three subjects received the active cream

while 11 received placebo three times daily for four weeks. Reduction in total symptom score was statistically significant for the treatment group compared to placebo, with particular improvement in numbness, irritation from socks or bedding, and jolting pain. It should be noted, however, there was also a trend toward improvement in the placebo group. Since the placebo group was smaller than the treatment group, statistical significance would have been more difficult to achieve.¹⁸⁹

Herbal Treatments for Peripheral Neuropathy

St. John's Wort for the Treatment of Peripheral Neuropathy

Because tricyclic antidepressant medications are used for PN, a study was conducted to determine whether St. John's wort (*Hypericum perforatum*) would have a similar effect. In a randomized, double-blind, placebo-controlled, crossover study, 54 patients (49 completed, including 18 diabetics and 29 non-diabetics) were given three tablets of St. John's wort containing 900 mcg hypericin/tablet (equivalent to 300 mg of a 0.3-percent hypericin extract per tablet) or placebo daily for five weeks, then crossed over to the other treatment. Four pain symptoms were evaluated – constant pain, lancinating pain events, touch-evoked pain, and pressure-induced pain. A trend toward improved overall pain scores was noted, although no significant differences were achieved with any individual pain index. Nine individuals in the treatment group and two in the placebo group experienced moderate to complete pain relief.¹⁹⁰ The dosage used in this study is the lowest dosage typically recommended for the treatment of depression. When using conventional treatments such as gabapentin, higher-end dosages are typically required for treatment of neuropathy. Therefore, a study employing double the dosage used in this study is recommended.

Topical Capsaicin Cream for the Treatment of Peripheral Neuropathy

Numerous studies have evaluated the effect of capsaicin cream for the treatment of peripheral neuropathy. Capsaicin is an active principal of the herb *Capsicum officinalis* and is believed to stimulate

afferent C-fibers (fibers in the mechano-heat class). The initial stimulation of C-fibers results in burning and irritation that stimulates release of substance P (a pain-relieving neuropeptide) and other neuropeptides. Repeated exposures result in a diminution of the initial burning and irritation and a long-lasting analgesic effect.¹⁹¹

Capsaicin for the Treatment of Diabetic Peripheral Neuropathy

The majority of studies of capsaicin cream for PN have been conducted in individuals with diabetes. In a large, multicenter, double-blind, placebo-controlled trial conducted by The Capsaicin Study Group, 277 subjects entered the study, 252 continued for at least two weeks, and 219 completed the eight-week trial. Subjects applied 0.075-percent capsaicin cream (n=100 completers) or placebo cream (n=119 completers) four times daily and were evaluated at two-week intervals for eight weeks. Pain was assessed via physician assessment as well as patient-driven VAS. Statistically significant improvements were noted in physician global assessment (69.5% versus 53.4%), pain intensity (38.1% versus 27.4%), and degree of pain relief (58.4% versus 45.3%) in the capsaicin versus placebo groups, respectively; statistically significant differences started during the fourth week.¹⁹² Effect on daily activities was also assessed, and statistically significant improvements in walking, working, sleep, and participation in recreational activities were noted in the capsaicin group compared to placebo.¹⁹³

In a smaller double-blind study, 54 (49 completers) subjects with type 1 or 2 diabetes and moderate-to-severe pain that interfered with sleep or daily activities applied 0.075-percent capsaicin cream (n=28; 24 completers) or placebo cream (n=26; 25 completers) to painful areas four times daily for eight weeks (same protocol as the previous study). Pain was measured via VAS, physician global assessment, and effect on interference with daily activities. After eight weeks, 89.5 percent of the capsaicin group and 50 percent in the placebo group experienced improvement; the average decrease in pain intensity was 49.1 percent in the capsaicin group and 16.5 percent in the placebo group – statistically significant differences. The differences in pain assessment after two

weeks were similar in both groups, indicating a need for continued use of capsaicin in order to experience pain relief.¹⁹⁴

Another study using the same protocol as the above studies was conducted on 22 diabetics with PN (11 in each group). Decrease in pain intensity via VAS was 16 percent in the capsaicin group and 4.1 percent in the placebo group. In an open-label continuation of the study (average follow-up 22 weeks), 50 percent of subjects experienced improvement or complete amelioration of pain, 25 percent remained unchanged, and 25 percent worsened.¹⁹⁵ Sensory function was tested in this same group of individuals and there were no differences between active or placebo in regard to sensations of vibration, warmth, or cold.¹⁹⁶

Another eight-week, double-blind study compared the effects of capsaicin cream to amitriptyline capsules in 235 patients with diabetic neuropathy. Subjects on capsaicin cream were given placebo capsules and subjects in the amitriptyline group received placebo cream. Equal and statistically significant improvements in pain were noted in both groups. While no systemic side effects were reported in the capsaicin group, most on amitriptyline experienced at least one side effect, most commonly sleepiness, but also neuromuscular or cardiovascular side effects.¹⁹⁷

To determine the mechanism of action of capsaicin, a study was conducted on 13 subjects with diabetic PN who used 0.05-percent capsaicin for eight weeks. Cream was applied to one foot while the other foot served as a control. In addition to pain scores and vibrational and thermal thresholds, serum levels of substance P were measured. Significant improvements in total pain score and heat thresholds were noted in the treatment foot compared to the untreated foot, indicating very localized effects. Substance P levels increased initially during the first four weeks of the study, but declined to baseline by the end of the study, calling into question the long-term effect of capsaicin on substance P.¹⁹⁸

The primary side effect reported by patients in the various capsaicin studies was burning at the site of application, sometimes resulting in dropout. In order to address the issue of topical irritation and to examine the effect of higher-concentration capsaicin, a study examined the use of highly concentrated

Table 4. Summary of Topical Treatments for Diabetic Peripheral Neuropathy

Intervention	Frequency and Length of Trial	Trial Type	Number in Trial
QR-333 (quercetin, ascorbyl palmitate, and vitamin D3) or placebo cream	3 times daily for 4 weeks	RCT	n=34 (23 active; 11 placebo)
Capsaicin (0.075-percent capsaicin) or placebo cream	4 times daily for 8 weeks	RCT	n=219 completers
	4 times daily for 8 weeks	RCT	n=49 completers
	4 times daily for 8 weeks/22 weeks	RCT (8 weeks); open label (average of 22 weeks)	n=22
Capsaicin or placebo cream versus amitriptyline or placebo capsules	8 weeks	RCT	n=235

To better support the clinician, only positive clinical studies are included in this table.
RCT=randomized, controlled trial

capsaicin (5-10%) in addition to regional anesthesia in 10 patients with intractable pain (three with neuropathy – diabetic, HIV-associated, idiopathic). Although two applications of the cream resulted in pain relief (significant in nine of 10), I.V. fentanyl had to be used to counteract the breakthrough burning associated with such a high concentration of capsaicin. Analgesic effects lasted from less than a week to more than 50 weeks. This treatment may provide relief for chronic, intractable pain and reduce dependence on opioids.¹⁹⁹

Studies on topical treatments for diabetic PN are summarized in Table 4.

Capsaicin for the Treatment of HIV-associated Peripheral Neuropathy

In a double-blind study, 26 patients with HIV-related PN were given either 0.075-percent capsaicin cream (n=15) or identical placebo cream (n=11) and asked to apply the cream and record pain scores four

times daily for four weeks. Dropout rate was high – 10 in the capsaicin group (five because of localized burning) and two in the placebo group. No statistically significant differences were noted between treatment and placebo groups in regard to any aspect of pain or quality of life during the course of the study.²⁰⁰ Due to the depletion of subjects – only five remained in the capsaicin group – this result is not surprising.

Acupuncture for the Treatment of Peripheral Neuropathy

Several studies have examined the effect of acupuncture for the treatment of various types of PN – diabetic, HIV-associated, chemotherapy-induced, and mixed etiologies. Some studies have been difficult to fully analyze as they are in foreign languages with just the abstract available in English.

One study involved 17 patients with chronic PN of unspecified etiologies. Subjects were treated with electroacupuncture twice weekly for four weeks.

Table 5. Summary of Treatments for HIV-associated Peripheral Neuropathy

Intervention	Trial	Routes of Administration	Daily Dosage Range
Acetyl-L-carnitine	Uncontrolled; n=21; up to 33 months	Oral	3,000 mg
	Uncontrolled; n=16; 3 weeks	I.V. or I.M.	500 or 1,000 mg
Vitamin B12	Uncontrolled; n=8	I.V.	Dosage not specified
Capsaicin or placebo cream	RTC; n=26; 4 weeks	Topical	4 times daily
Acupuncture	Small, uncontrolled; n=7; 30 days	Electroacupuncture	20 minutes daily
	Case series; n=21; 5 weeks	Standard acupuncture	30-45 minutes, twice weekly

To better support the clinician, only positive clinical studies are included in this table.
 RTC=randomized, controlled trial

VAS was used to assess intensity of continuous and intermittent pain and duration and number of attacks. Two weeks after the series of treatments, average continuous pain score was decreased by 32.9 percent and pain intensity by 59 percent; average number of attacks decreased from 4.2 to 2.2 per day. Three months after treatments were discontinued, pain intensity was still decreased by 44 percent.²⁰¹

Acupuncture for the Treatment of HIV-associated Peripheral Neuropathy

Several studies have examined the effect of acupuncture for neuropathy associated with HIV infection. In a large-scale, placebo-controlled, multicenter, 14-week study of 250 patients, standard acupuncture, amitriptyline, or both were compared to placebo, control points, or both. Neither acupuncture nor drug therapy was significantly more effective than placebo.²⁰²

In a very small, uncontrolled trial, seven HIV patients with antiretroviral-induced neuropathy were treated with electroacupuncture 20 minutes daily for 30 days. Muscle-stimulated nerve amplitudes and physical strength increased with general improvement in functional activity.²⁰³

In a case series, 21 subjects with HIV-associated PN received 30- to 45-minute acupuncture treatments twice weekly for five weeks. A significant reduction in pain, assessed by the Pain Rating Scale and Subjective Peripheral Neuropathy Screen, was noted post-treatment compared to pre-treatment for total overall pain score as well as symptoms of numbness, pins and needles, and pain (aching, burning).²⁰⁴

Table 5 summarizes the most promising treatments for HIV-associated PN.

Acupuncture for the Treatment of Chemotherapy-induced Neuropathy

Dose reduction or early termination of treatment with neurotoxic chemotherapy drugs is often necessitated due to significant PN. A pilot study of five cases demonstrated encouraging results with the use of acupuncture to correct qi, blood, and yang deficiencies in this population.²⁰⁵

Acupuncture for the Treatment of Diabetic Peripheral Neuropathy

In a study of 90 subjects with diabetic PN, 30 received wrist-ankle acupuncture, 30 received whole-body acupuncture, and 30 received conventional

Table 6. Physical Medicine for the Treatment of Diabetic Peripheral Neuropathy

Intervention	Trial	Description of Therapy
Acupuncture	Controlled; n=90	Wrist-ankle acupuncture (n=30); whole-body acupuncture (n=30); conventional medicine/control group (n=30)
	Uncontrolled; n=44	Six courses of acupuncture for a 10-week period
	Case series; n=68	Not specified in abstract (article in Chinese)
Magnets or placebo	RCT; n=375; 4 months	Magnetic insoles or non-magnetized insoles (placebo)
Yoga or no yoga	Controlled; n=40; 40 days	30-40 minutes of yoga daily

To better support the clinician, only positive clinical studies are included in this table.
RCT=randomized, controlled trial

medical treatment (control group). Both acupuncture groups experienced significantly better results than the conventional medical/control group.²⁰⁶

Forty-four individuals with diabetic PN were treated with six courses of acupuncture for a 10-week period. Thirty-four (77%) experienced significant symptom improvement, with seven subjects reporting complete elimination of symptoms. Patients were followed for 18-52 weeks and only eight individuals required additional treatment. Standard medications were used by 63 percent of subjects at the beginning of the trial and 67 percent of these patients were able to decrease or discontinue medications during the follow-up period.²⁰⁷

In a series of 68 cases of diabetic PN treated with acupuncture, 43 individuals experienced marked improvement, 20 experienced some improvement, and five exhibited no improvement; overall significant improvement in NCV was observed. The article, being in Chinese, was only available in English as an abstract; therefore, the number and frequency of treatments and specifically what symptoms were improved is unknown.²⁰⁸

Magnets for the Treatment of Peripheral Neuropathy

It is hypothesized that electromagnetic fields may benefit PN by polarization of neurons that may be firing ectopically, resulting in neuropathy.²⁰⁹ Pulsed magnetic field therapy (strength of 20 gauss and frequency of 30 Hz) was used to treat 24 subjects with PN of various etiologies – diabetes, chronic inflammatory demyelinating polyneuropathy, mercury poisoning, pernicious anemia, paraneoplastic syndrome, tarsal tunnel syndrome, and idiopathic sensory neuropathy. The most symptomatic foot in each subject received treatment, while the contralateral foot served as a control. Subjects were evaluated after nine one-hour consecutive treatments (weekends off) using VAS and Patient's Global Assessment of Change. Average pain scores decreased by 21 percent at the end of nine treatments and by 49 percent at a 30-day follow-up assessment; all 24 subjects completed the study but only 15 were available for follow-up. The treatment was even more effective for more severe pain. Of 19 subjects with moderate-to-severe pain, a 28-percent reduction in pain score was experienced

at the end of treatment compared to baseline; a 39-percent reduction was observed between baseline and the end of the 30-day follow-up period.²⁰⁹

A large, multicenter (48 centers), double-blind, placebo-controlled trial was conducted on 375 individuals with diabetic PN. Subjects wore either multipolar, static, 450 G magnetic insoles or placebo (unmagnetized) insoles in their shoes for four months. VAS was used to assess numbness and tingling, burning, and quality of life, with significant decreases in burning, numbness and tingling, and foot pain on exercise reported during the third and fourth months of the study compared to baseline in the magnetic-insole group compared to placebo.²¹⁰

Yoga for the Treatment of Diabetic Neuropathy

In a controlled trial, 20 subjects with type 2 diabetes and mild-to-moderate neuropathy were treated with 30-40 minutes of yoga daily for 40 days. A group of 20 subjects matched for age and severity of disease serving as a control did not engage in yoga but were prescribed light exercise such as walking. NCV, assessed in the median nerve for both right and left hands, improved slightly in the yoga group (from 52.81 to 53.87 in the right hand and 52.46 to 54.75 in the left hand). NCV in the control group continued to deteriorate.²¹¹

Table 6 summarizes physical medicine treatments for diabetic PN.

Cutting-Edge Conventional Treatments for Peripheral Neuropathy

Some cutting-edge conventional approaches to PN are on the horizon – treatments that potentially do more than just mask symptoms. Several small, “dual-action” peptides have been shown to have neurotrophic activity – C-peptide and islet neogenesis-associated protein peptide (both from pancreatic proteins), and derivatives of erythropoietin.²¹²

Recent recognition that C-peptide, originally thought to be inert and merely a marker for endogenous insulin production, improves sensory neural deficits, microvascular blood flow, and renal filtration in diabetes has stimulated research on its potential for diabetic neuropathy.²¹² C-peptide has been found to stimulate (Na⁺/K⁺)-ATPase activity²¹³ and endothelial

nitric oxide synthase for improved circulation.²¹⁴ In an animal model of type 1 diabetes, C-peptide for 4-7 months resulted in a dose-dependent prevention of signs of neuropathy, including effects on NCV, nerve fiber number, nerve regeneration, and overall neuropathy score.²¹⁵ In a phase II trial of 49 type 1 diabetics with subclinical PN, subcutaneous administration of C-peptide or placebo for three months resulted in significant (80%) improvement in NCV in the C-peptide group compared to placebo.²¹⁶

Islet neogenesis-associated protein peptide (INGAP) is a pancreatic peptide that has been found to enhance formation of new pancreatic islet cells and reverse hyperglycemia in type-1 diabetic animals.²¹² A preliminary study indicates it may hold promise for treatment of neuropathy associated with diabetes. Two-week administration of INGAP to streptozotocin-diabetic rats with neuropathy resulted in improved thermal detection, enhanced nerve growth in dorsal root ganglia, and activation of signaling pathways involved in nerve regeneration.²¹⁷

In addition to its involvement in hematopoiesis, erythropoietin receptors have been found in neurons.²¹² Erythropoietin appears to directly prevent axonal degeneration – the gross pathology seen in peripheral neuropathies of various etiologies, including diabetes and HIV. Researchers found nitric oxide signals erythropoietin secretion from Schwann cells in response to neuronal injury. Administration of exogenous erythropoietin to animals with axonal neuropathy prevented axon degeneration and reduced behavior associated with neuropathic pain.²¹⁸ Animal studies of diabetes-induced²¹⁹ or cisplatin chemotherapy-induced²²⁰ neuropathy found erythropoietin significantly attenuated nerve degeneration associated with these two types of neuropathy. An *in vitro* study demonstrated erythropoietin's protection of neurons against the neurotoxic effects of antiretroviral agents; thus it may have potential for HIV-associated neuropathy.²²¹

Preliminary research from the University of Utah and Tufts University has found netrins, a family of proteins involved in vascular and nerve growth, may provide promise for the treatment of diabetic PN. In a phase II trial, netrins injected into diabetic mice resulted in both blood vessel and nerve growth.²²²

Conclusion

Peripheral neuropathy presents with considerable morbidity and can result in significant decreases in quality of life. While conventional medicine can offer some relief, the potential side effects or addictive nature of many of the medications render long-term use undesirable. Such treatments, furthermore, merely mask the symptoms and do not address the underlying pathologies. Alternative therapies, on the other hand, are typically without side effects and address nutrient deficiencies, oxidative stress, and other etiological factors associated with the development of PN.

Alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methylcobalamin, and topical capsaicin are among the most well-researched alternative options for the treatment of PN. Other potential nutrient or botanical therapies include vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6 fatty acids, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, St. John's wort, and topical capsaicin. In the realm of physical medicine, acupuncture, magnetic therapy, and yoga have been found to provide benefit.

A questionnaire-based study examined the use of alternative treatments for PN in 180 consecutive outpatients at St. Elizabeth's Medical Center in Boston, MA. Seventy-seven patients (43%) reported using alternative therapies; 37 of 77 (48%) employed more than one type of alternative treatment. Seventeen (27%) of the respondents reported improvement in neuropathy symptoms with unconventional approaches. The treatments most often employed were "megavitamins" (35%), magnets (30%), acupuncture (30%), herbal remedies (22%), and chiropractic manipulation (21%). Those who used alternative approaches were more likely to be younger, college educated, and suffering from diabetes compared to those who did not use unconventional approaches.²²³

The use of well-researched nutrients, physical medicine, and the possible addition of new cutting-edge treatments should decrease the morbidity associated with peripheral neuropathy and the side effects associated with the commonly prescribed conventional pain-relieving treatments in current favor.

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