

DPN: The Forgotten Complication and New Therapeutic Approaches

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes, estimated to affect 50% of patients—approximately 4 million people in the United States alone.¹⁻⁶ Its prevalence increases with the patient's age, duration of diabetes, and poor glycemic control.⁷⁻¹⁰

Many patients who have DPN do not experience symptoms. For the almost 30% who do suffer from chronic, painful symptoms, however, their quality of life (QOL) is reduced and they experience considerably negative consequences on their social and psychological well-being. DPN substantially increases health care costs as well.¹¹⁻¹⁸

DPN is often referred to as the forgotten complication because, despite how commonly it occurs, it is the chronic diabetes complication that is least often addressed by health care providers.¹⁹ Results of the 2005 American Diabetes Association (ADA) National Survey found that only one in four patients surveyed who experience symptoms of DPN have been diagnosed with the condition.²⁰ This is partly because many practitioners have had very little success with its treatment as well as a lack of awareness of available treatment strategies. A wide range of treatments are available for neuropathic pain, however, many patients remain in adequately treatment. The prescribing pattern suggests that no one treatment addresses all factors.

Foot complications are the greatest burden of all serious chronic complications among patients with diabetes. As many as 40% to 60% of lower extremity amputations (LEAs) are related to DPN, and more than 50,000 LEAs are performed each year in this country.^{21,22} Approximately 15% of patients with diabetes will develop a foot ulcer and one in six will need to have an amputation. Additionally, half of those patients who develop an ulcer will have one on the opposite foot within 3 years.²³⁻²⁵ Short of ulceration and amputation, DPN limits mobility, impairs sleep, and seriously effects overall quality of life. It is a progressive disease that may actually begin before any alteration in sensation is detected.

Diabetes-related foot complications represent a significant economic burden to society. LEAs are often associated with long-term hospitalization, as well as rehabilitation services, prosthetics, social services, and home care. The direct cost of a single LEA is estimated at \$30,000 to \$60,000. Indirect costs come from loss of employment, productivity and quality of life, all combining for an estimated \$4 million annually for care of the diabetic foot in the United States.^{26,27}

SIGNS AND SYMPTOMS OF DPN

Early symptoms of DPN may be subtle and can easily be overlooked if providers do not specifically question patients about them. The clinical features of neuropathy can vary immensely and patients may present to a wide spectrum of specialities, from dermatology to podiatry or from urology to cardiology, for example.^{28,29} Neuropathies are characterized by a progressive loss of nerve fibers, which may affect both

principle divisions of the peripheral nervous system. Distal symmetrical sensorimotor polyneuropathy is the most common form of DPN. Signs and symptoms may progress from distal to proximal over time.

Signs include diminished vibratory perception, decreased knee and ankle reflexes, reduced protective sensation (eg, pressure, hot and cold, pain), and a diminished ability to sense the position of one's toes and feet. Symptoms can be numbness, loss of feeling, prickling, tingling, aching pain, burning pain, lancinating pain, and unusual sensitivity or tenderness when feet are touched (ie, allodynia).^{28,29} It is important to note that not all patients with DPN will have pain and numbness. Additionally, some patients will have loss of normal sensation as a result of nerve damage and hypofunction and will not be aware of their disability until injury and ulceration have occurred.

Symptoms produced by DPN can be considered positive and negative.³⁰ The positive symptoms include spontaneous pain, dysesthesias (C-fibers/unpleasant), parasthesias (A-fibers/not unpleasant). Negative symptoms include loss/impairment of sensory quality, numbness, dry skin, erectile dysfunction, incontinence, and gait instability and fall risk. DPN symptoms have an impact on functioning, activities of daily living, and QOL. QOL is a unique, individual experience and is described as how an individual patient perceives and reacts to his/her health status. Psychosocial morbidity can include depression, anxiety, anger, and loss of self-esteem. Societal consequences associated with diminished QOL are social isolation, strained relationships with family and friends, and effects on intimacy and normal sexual activity.³¹

The majority of symptomatic DPN patients are insensate, with 36% experiencing sensory loss, 18% experience pain, and 46% are asymptomatic.¹⁸ The clinical impact of positive and negative DPN symptoms are illustrated in Figure (slide 15).

The effort to optimize foot care for patients with diabetes led to the ADA's Consensus Statement on Foot Care, which recommends that the cutaneous pressure threshold be measured at least once a year among diabetes patients. "The goal of this recommendation is to reduce the risk of ulceration, infection, and amputation due to sensory loss that can occur through progressive neuropathy," according to the ADA.^{32,33}

CLINICAL ASSESSMENT AND DIAGNOSTIC TESTS FOR DPN

A number of simple symptom screening questionnaires are available to record neuropathy symptom quality and severity. The Michigan Neuropathy Screening Instrument is a brief 15-item questionnaire.³⁴ It is increasingly recognized that both symptoms and deficits have an adverse effect on QOL in diabetic neuropathy,³⁵ and specific questionnaires have been developed for the assessment of the impact of neuropathy on QOL. Similarly, composite scores have been used to assess clinical signs, and one that is increasingly used is a modified Neuropathy Disability Score (NDS).³⁵ The NDS can be easily performed in the clinic setting and takes only a minute or two to complete. The maximum deficit score is 10, which would indicate complete loss of sensation to all sensory modalities and absent reflexes. In a longitudinal European community-based study, an NDS of ≥ 6 was equated with an increased risk of insensate foot ulceration.³⁶

Whatever methodology is used, it should be noted that the neurological exam of the lower limbs is the most important aspect in the clinical diagnosis.

The results of sensory examination are commonly abnormal in patients with DPN pain.³⁷ A broken tongue depressor is an easy, low-tech way to test for sharp sensation, although more specific commercial sterile examination pins and nylon monofilaments are available. Vibratory sensation is assessed by placing a 128-Hz tuning fork over the bony surface of the malleolus or first distal phalanx.³⁷ The threshold to vibratory sensation is usually elevated in the feet compared with that in the knees. Data from one study suggest that the predictive value of testing with a 128-Hz tuning fork in the diagnosis of DPN pain is similar to that of national and international scoring systems.³⁸ Temperature sensation may be assessed with a cool tuning fork or with test tubes that contain warm or cold water.¹⁸ Like the thresholds to vibratory sensation, altered thresholds to thermal sensation have been well documented in patients with DPN pain, and their elevation has been associated with progression of neuropathy.^{28,39}

Because the diagnosis of DPNP is usually evident based on results of the bedside examination, further neurologic testing is unnecessary in most patients.^{18,40} Other diagnostic tests, however, may be helpful in patients with atypical clinical presentations or in the research setting. Several methods to assess peripheral nerve function are available.

Diagnostic Tests for DPNP

- **Nerve conduction studies (NCS) and electromyography (EMG).** These two tests have long been considered the gold standard for the assessment of peripheral neuropathy. They measure the speed and amplitude of sensory and motor conduction, and the test is objective, parametric, and noninvasive. DPN pain may affect predominantly small nerve fibers, and these tests are insensitive in acute and small-fiber neuropathy. Therefore NCS and EMG may yield normal results or show only minor abnormalities, but NCS may be useful to differentiate DPN pain from other neuropathies.^{18,29,41} Abnormal NCS results frequently indicate more severe involvement, a less benign course, and a less favorable diagnosis. The progressive loss of distal axons is the pathologic hallmark of peripheral neuropathies. This loss is reflected in NCS by prolonged distal latencies, reduction in evoked potential amplitudes, and secondary slowing of conduction velocity. NCS/EMG has a >50% false-negative for tarsal tunnel syndrome.

- **Quantitative sensory tests (QSTs).** QSTs are used mostly for research purposes, although they may also be applied in the clinical setting. QSTs detect sensory thresholds for vibration, heat, and pain, and are useful in tracking the progression of neuropathy in large cohorts and the efficacy of treatment endpoints in multicenter clinical trials.^{18,41,42}

- **Skin biopsy/intraepidermal nerve fiber density (IENFD).** Skin biopsy is a newer technique that measures density of intraepidermal nerve fiber at various sites in the leg. The loss of nerve fibers is associated with increased neuropathic pain. Although this is an invasive test requiring a 3-mm skin biopsy specimen, it enables a direct study of small nerve fibers—thinly myelinated and unmyelinated nerve fibers. Skin biopsy is the most sensitive measure of neuropathic changes. In diagnosing small fiber neuropathy IENF has a sensitivity of 88.4% and a specificity of 95% to 97%. Significant inverse correlations between the density of nerve fibers and the severity of neuropathy have been documented.⁴³ Moreover, changes in nerve fiber density over time correlates with decreased neuropathic pain.⁴⁴ Skin

specimens are routinely obtained by punch biopsy at the foot, calf, and/or thigh, under local anesthesia. The IENFD at the calf-foot/ankle is routinely compared to that at the thigh to help differentiate between distal neuropathy and neuronopathy or multifocal neuropathy. Patients with small fiber neuropathy exhibit a reduction in epidermal nerve fiber density or structural abnormalities that are indicative of neuropathy. (image: Caption/Skin biopsy)

This image demonstrates skin with normal nerve fiber density (Epidermal Nerve Fiber Density). Arrow points to the small nerve fiber in the epidermal layer of skin, arrowhead points to the basement membrane that separates the dermis from the epidermis.

Skin with low normal nerve fibers, consistent with small fiber neuropathy. The arrow points to the basement membrane of the epidermis. Slide 19)

Other diagnostic tools used to detect DPN include the 5.07-g Semmes-Weinstein Monofilament; a biothesiometer, a calibrated tuning fork, Disk-Criminator for 2-Point Spacing (AliMed, Dedham, MA), and the Neurometer CPT (Neurotron, Denver) which tests A-beta, A-delta, and C fibers. The Pressure Specified Sensory Device offers the earliest detection of pathology of A-beta skin surface and touch fibers, and the Neuropad (correlates with IENFD, $P=.04$) is also used.

ETIOLOGY OF DIABETIC NEUROPATHY

The etiology of diabetic neuropathy is multifactorial and involves many different pathways. Persistent hyperglycemia leads to microvascular disease via several mechanisms. Although animal and cell studies have provided a conceptual framework for the cause and thus potential treatments of DPN, there is limited translational work in patients, therefore much debate continues.²⁸ Longitudinal data support that the duration and severity of exposure to hyperglycemia are related to the severity of neuropathy. Small nerve fiber involvement may be the earliest detectable sign of neuropathy.²⁸

(Figure – Pathophysiology HYPERGLYCEMIA (23))

Other Pathogenetic Mechanisms in the Development of DPN

Polyol pathway. In animal models of diabetes an association between increased flux through the polyol pathway and a reduction in nerve conduction velocity have been shown. This is not as clear in humans, however. In an early study, sorbitol and fructose levels were increased in only one-third of the sural nerve biopsies studied and could not be related to clinical, neurophysiological, or pathological severity of neuropathy. Linear regression analysis has demonstrated a significant inverse correlation between nerve sorbitol and myelinated fiber density.⁴⁵

Sorbitol concentration. Excess sorbitol within the nerve causes it to retain water and nerve edema/compression.

Myoinositol. Myoinositol deficiency has been proposed to play a role in the pathogenesis of DPN, there is little evidence to support this contention. In a sural nerve biopsy study, myoinositol levels did not vary

among patients with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes .46 Myoinositol helps nerves conduct electricity, and regulates potassium, sodium, and calcium.

Glycation. Hyperglycemia results in the formation of advanced glycation end products (AGEs), which in turn act on specific receptors (RAGEs), inducing monocytes and endothelial cells to increase the production of cytokines and adhesion molecules.⁴⁷ Human sural nerve specimens demonstrate normal furosine, an early reversible glycation product, but significantly elevated pentosidine levels in both cytoskeletal and myelin protein.⁴⁸ Enhanced staining for carboxymethyllysine in the perineurium, endothelial cells, and pericytes of endoneurial microvessels, as well as myelinated and unmyelinated fibers, has been shown to correlate with a reduction in myelinated fiber density in peripheral nerves from diabetic individuals compared with control patients.⁴⁹ Pyrraline, an AGE, is also increased in postmortem samples of optic nerves from diabetic patients.⁵⁰

Oxidative stress. An increasing body of data supports the role of oxidative stress in the pathogenesis of DPN in animal models,⁵¹ and treatment benefits have been observed with alpha-lipoic acid . One study showed improvement in the neuropathy impairment score after intravenous therapy,⁵² and this result has been replicated in other studies.

Vascular factors. There is direct evidence from large-vessel revascularization studies that improving tissue blood flow may improve DPN. Increasingly, evidence suggests that conventional risk factors for macrovascular disease (such as deranged lipids) are also important in the pathogenesis and progression of human DPN.⁵³

Growth factors. Neurotrophins promote the survival of specific neuronal populations by inducing morphological differentiation, enhancing nerve regeneration, stimulating neurotransmitter expression, and altering the physiological characteristics of neurons. Diabetic nerves are deficient in folate, B6, and B12.⁵⁴

Insulin-like growth factors (IGF). IGF-1 and IGF-1 receptor mRNA levels have not been shown to differ in the sural nerve of diabetic patients compared with control individuals.⁵⁵

C-peptide. Impaired insulin/C-peptide action has emerged as a prominent pathogenetic factor. Preclinical studies have demonstrated a range of actions that include effects on sodium/potassium-ATPase activity, endothelial nitric oxide synthase, expression of neurotrophic factors, regulation of molecular species underlying the degeneration of the nodal apparatus in type 1 diabetic nerves, as well as DNA binding of transcription factors and modulation of apoptotic phenomena.^{56,57}

Vascular endothelial growth factor (VEGF). VEGF was originally discovered as an endothelial-specific growth factor with a predominant role in angiogenesis. Recent observations, however, indicate that VEGF also has direct effects on neurons and glial cells, stimulating their growth, survival, and axonal outgrowth.⁵⁸ Thus, with its potential for a dual impact on both the vasculature and neurons, it could represent an important therapeutic intervention in DPN.

Immune mechanisms. Studies suggest that sera from type 2 diabetic patients with neuropathy contains an autoimmune immunoglobulin that induces complement-independent, calcium-dependent

apoptosis in neuronal cells.⁵⁹ The expression of these cytotoxic factors has been related to the severity of neuropathy and the type of neuronal cell killed.⁶⁰ Thus, it has been suggested that such toxic factors may contribute to DPN by acting in concert with hyperglycemia to damage sensory/autonomic neurons.⁶⁰

Diabetes is associated with endothelial dysfunction. The endothelium is a biologically active organ that is adversely affected by deranged nitric oxide pathways. Damage to the endothelium is multifactorial, stemming from hyperglycemia, insulin resistance, and the production/metabolism of free fatty acid.

CLASSIFICATION OF NEUROPATHY

The ADA has classified diabetic neuropathies into two main categories: generalized symmetric polyneuropathies and focal/multifocal neuropathy.²⁹ The first category includes acute sensorimotor, chronic sensorimotor, and autonomic neuropathy. The second includes cranial, truncal, focal limb, proximal (amyotrophy), and coexisting chronic inflammatory demyelinating polyradiculoneuritis. This article focuses on sensorimotor neuropathy, which is the most common type of neuropathy, affecting 30% to 50% of all diabetic patients.²⁹ It is most often involved in diabetic foot problems.

Characteristics of large-fiber, distal, symmetric diabetic neuropathies are weakness, wasting, impaired vibration detection, loss of position sense, loss of reflexes, and interference with activities of daily living.⁶¹ Small-fiber neuropathy is associated with pain, autonomic and thermal impairment but patients have normal strength and reflexes. Small-fiber neuropathy is electrophysiologically silent and produces symptoms that lead to morbidity and mortality. Small-fiber neuropathy presents as C-fiber type pain, with superficial allodynia. Patients also have early hyperesthesia, hyperalgesia, impaired neurovascular function, as well as late hypoesthesia and hypoalgesia.^{61,62}

Sensorimotor neuropathy develops progressively, initially involving more distal parts. The main symptoms are numbness of the legs and feet, muscular cramps, pins and needles, shooting, deep aching, and burning pain. Pain is exacerbated at night, and symptoms may be absent or present either in the early or late stages. Clinical signs of sensorimotor neuropathy are reduced or absent sensation to pain, touch, cold, hot, and vibration. The patient often will have reduced or absent ankle reflexes, muscle weakness, small muscle atrophy, and prominence of the metatarsal heads.²⁹

Diagnosis of sensorimotor neuropathy should be based on clinical symptoms and signs, quantitative sensory testing, electrophysiology, and sural nerve biopsies. Not all methods will be necessary on a daily clinical basis, and simple tests can often identify the at-risk patient.²⁹

THERAPEUTIC OPTIONS FOR DPN

In painful DPN, the acute phase typically occurs in people with an intermediate duration of diabetes.²⁹ The first line of therapy is tight glucose control with as near normoglycemia as possible and simple analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen). Simple analgesics, however, are typically not effective. Often, neuropathic pain requires treatment with off-label therapies. Some typically used medications include antidepressants, anticonvulsants, and antiarrhythmics.^{28,29}

Oral Symptomatic Therapy

Tricyclic antidepressants (TCAs) such as amitriptyline, imipramine, desipramine, and nortriptyline. 63-66

Serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as paroxetine, citalopram, and duloxetine).67,68

Anticonvulsants. Commonly used antiepileptic drugs (AEDs) include gabapentin, pregabalin, carbamazepine, lamotrigine, and newer AEDs such as topiramate.69-71

Opioids. Commonly used are tramadol and oxycodone CR.72-75

Other pharmacologic treatments used are lidocaine (transdermal and intravenous), the antiarrhythmic agent mexiletine, and alpha-2 adrenergic agonists.

The best efficacy evidence has been reported for 20-amine TCAs and there is some evidence for the use of SSRI/SSNRIs and atypical antidepressants.⁷⁶ Current palliative treatments only target painful or positive symptoms (Figure 36). Studies indicate that 25% of patients with painful DPN are not treated at all, while 53.9% are treated with opioids, 39.7% NSAIDs, 21.1% SSRIs, 11.3% TCAs and 11.1% anticonvulsants.⁷⁷

Topical treatments have been used in DPN patients, such as topical nitrate and capsaicin, both of which have some evidence of efficacy.^{78,79}

FDA approved agents

Currently, the agents approved by the US Food and Drug Administration (FDA) for the treatment of painful DPN are pregabalin (Lyrica, Pfizer)⁸⁰ and duloxetine (Cymbalta, Eli Lilly).⁸¹

Pregabalin. Indications for pregabalin are DPN, fibromyalgia, postherpetic neuralgia, and use as an adjunctive seizure medication. For DPN, the approved dosage is 50 mg three times a day increasing to 100 mg three times a day within 1 week. Side effects include dizziness, drowsiness, dry mouth, edema. Drug interactions include alcohol and sedating agents which may increase the sedative effect of pregabalin.⁸²

Pregabalin selectively binds to the alpha2-delta subunit of calcium channels. In this way it modulates calcium influx in hyperexcited neurons and reduces neurotransmitter release. ⁸³ Its pharmacologic effect requires binding at this site, however, the clinical significance of these observations in humans is currently unknown.

In a trial of 146 patients randomized to receive placebo (n=70) or pregabalin 300 mg/day (n=76), Rosenstock et al⁸⁴ found that pregabalin produced significant improvements versus placebo for mean pain scores ($P < .0001$) and mean sleep interference scores ($P < .0001$), as well as other measures. They found that pain relief and improved sleep began during week 1 and remained significant throughout the 8-week study ($P < 0.01$). More than 50% of patients had a reduction in pain.⁸⁴

Duloxetine. Duloxetine is indicated for the treatment of depression, generalized anxiety disorder, DPN, and fibromyalgia. According to the manufacturer's Web site,⁸⁵ treatment should begin at 30 mg once

daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is no evidence that doses >60 mg/day confer additional benefit, even in patients who do not respond to a 60-mg dose, and [higher doses are associated with a higher rate of adverse reactions](#). Duloxetine can cause hepatotoxicity in the form of transaminase elevations. It may also be a factor in causing more severe liver injury, but there are no cases in the NDA database that clearly demonstrate this. Use of duloxetine in the presence of ethanol may potentiate the deleterious effect of ethanol on the liver. Drug interactions are cited for diet agents, monoamine oxidase inhibitors, the chemotherapy drug procarbazine, SSRIs, St. John's Wort, thioridazine, tryptophan, and venlafaxine.

Duloxetine, as a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine, is thought to inhibit pain via descending pain pathways. In a 12-week multicenter double-blind trial of 457 patients, Goldstein et al⁸⁶ found that duloxetine 60 and 120 mg/day demonstrated statistically significant greater improvement compared with placebo on the 24-hour average pain score. Improvements were seen beginning 1 week after randomization and continuing through the 12-week trial. Additionally, they reported that duloxetine separated from placebo on nearly all the secondary measures including health-related outcome measures. Significantly more patients in all three active-treatment groups achieved a 50% reduction in the 24-hour Average Pain Score compared with placebo.

New Therapeutic Approaches

New therapeutic approaches for DPN that have been investigated include aldose reductase inhibitors, antioxidants (eg, alpha-lipoic acid), nerve growth factors, and gamma-linolenic acid. All of these have proved largely ineffective with the exception of alpha-lipoic acid.⁸⁷

To prevent and improve symptoms of DPN, the most important factor is diabetes control. The DCCT has shown definitively that in type 1 diabetes, the risk of DPN can be reduced with improved blood glucose control. Although the data are less strong for type 2 diabetes, DCCT results and epidemiologic studies, including those in type 2 diabetes, strongly suggest that optimal blood glucose control helps prevent DPN.²⁹

Potential Disease-State-Modifying Therapies

In addition to tight glucose control, certain therapies may also have potential disease-state modifying properties. One example is alpha-lipoic acid, as mentioned previously, and another is the combination of L-methylfolate, methylcobalamin, and pyridoxal 5'-phosphate such as is found in Metanx (Pamlab)—a medical food.

According to the FDA, a medical food is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.”⁸⁸

Medical foods have an active ingredient that is present in or derived from food, is an oral dosage, and addresses distinct nutritional requirements of patients diagnosed with specific diseases or conditions. The

efficacy and dosing of medical foods must be proven in peer-reviewed scientific literature and they are administered under the care of a physician.

New therapeutic approaches to DPN. Treatments that appear to improve nerve hypoxia are being researched. Currently under study are vascular endothelial growth factor (VEGF) agents, VEGF zinc finger proteins, ruboxistaurin, benfotiamine, and pyridoxamine.⁸⁹ Angiotensin converting enzyme inhibitors have shown some potential in this capacity.

Vitamin B. A Cochrane database review of vitamin B for DPN found 13 studies of 741 patients.⁹⁰ Although two studies revealed no short-term pain reduction, one showed improved vibration detection. According to Ang et al, at higher doses, vitamin B improved paresthesias, pain, temperature sensitivity, vibration, and numbness. Data on vitamin B is still limited, however.

METANX

The active ingredients in Metanx are 2.8 mg of L-methylfolate, 2 mg of methylcobalamin, and 25 mg of pyridoxal 5'-phosphate.

L-methylfolate. This is the active form of folate necessary for neural function, it works with methylB12 to activate protein, it is important in DNA/RNA synthesis, and it increase nitric oxide synthesis (Figure NO synthesis slide 51).

Methylcobalamin. This is the neurologically active form of B12, it is the methyl donor in DNA metabolism, which is needed to up-regulate gene transcription for peripheral nerve repair and regeneration. Additionally, methylcobalamin enhances protein metabolism in Schwann cells.

Pyridoxal 5'-phosphate. This is the active form of B6, which is necessary for neural function, and it may inhibit the effects of AGEs.

Proposed Mechanism of Action

Patients with diabetes have been shown to have a reduction in nerve fiber density. In fact, nerve fiber density is reduced even during prediabetes, among individuals with impaired glucose tolerance. As the disease progresses and patients develop overt DPN and its associated symptoms, the density of the peripheral nerves continue to regress. Therefore, nerve fiber density is correlated to diabetes duration.⁹¹

Although peripheral nerves have the ability to repair and regenerate themselves, they need adequate blood flow to facilitate this action.⁹² Improved blood flow allows essential nutrients and oxygen to be delivered to the nerves so they can perform their normal functions, such as protein synthesis and myelinogenesis—the development of the protective myelin sheaths around nerve fibers.

The ingredients in Metanx help the body to create an environment conducive to the ability of peripheral nerves to regain their ability to perform their normal functions. The ingredients in Metanx help restore endoneurial blood flow and therefore kick start normal physiological functions that have been suppressed due to the diabetic state. Evidence shows that improvement in the nerve environment leads to an increase

in nerve fiber density, a reduction in burning pain, and most importantly, a restoration of sensory perception.⁹³ Because patients have improved sensory perception, they are steadier on their feet and can more easily avoid the development of late DPN complications and subsequent ulceration.

In this way, Metanx provides a different therapeutic option. The most commonly used agents target pain and are palliative in nature, however, the natural history of DPN continues to progress. It is believed that Metanx—as a neurotrophic agent—creates a potentially disease modifying environment.

Correlative Data

Correlative data for Metanx exist in the form of a subjective visual analog score (VAS) study as isolated therapy, subjective VAS study combined with palliative agent, using quantitative sensory testing (QST), and IENFD testing.

Jacobs presented data from a 20-week randomized controlled study of 97 patients at the 2008 New Cardiovascular Horizons meeting showing that Metanx reduced painful DPN.⁹³ In this investigation, the average absolute pain reduction after 20 weeks in the Metanx study group was 1.73 versus 0.44 in the active acetaminophen group ($P < .008$) (* compare with abstract? 1.58 vs 0.42). Compared with baseline, after 10 weeks the study group demonstrated a reduction in VAS of 32.92% compared with an 11.57% reduction ($P < .01$) in the active control group. Compared with baseline, after 20 weeks the study group demonstrated a reduction in VAS of 35.28% versus 11.73% in the control group ($P < .01$). (figures from abstract)

Also presented at the NCVH meeting, Jacobs revealed data that looked at Metanx supplementation to pregabalin among partial-responders for management of DPN pain.⁹⁴ Results from this 20-week, open trial of 24 patients showed the average absolute pain reduction at study's end to be 3.0 among Metanx-treated patients compared with 0.25 in the active control group (pregabalin alone) ($P < .001$). After 20 weeks, the Metanx group experienced greater pain relief compared with the active control group, an 87.5% vs. 25.0% reduction in neuropathic pain scale, respectively ($P = .005$). (figures from abstract)

Restoration of Cutaneous Sensorium

In a study presented by Walker et al,⁹⁵ at the Diabetic Foot Global Conference in 2009, 16 consecutive DPN patients with established sensory loss were quantified using the Pressure Specified Sensory Device (PSSD). Study outcomes were measured at baseline, 6 months, and 1 year after Metanx treatment for eight outcome measurements (great toe pulp and medial heel bilaterally, one-point and two-point static measured in gm/mm² using PSSD). (figures from abstract)

Compared with baseline (figures) after 6 months and 1 year of the study agent, the average absolute change in 2-point discrimination was -21.8 gm/mm² ($P = .006$) and -38.7 gm/mm² ($P < .001$) at the great toe, respectively. Compared with baseline, after 6 months and 1 year of Metanx, the average absolute change in 2-point discrimination was -30.3 gm/mm² ($P < .001$) and -41.9 gm/mm² ($P < .001$) at the medial heel, respectively.

At the same meeting, Jacobs96 also reported on the pharmacological management of diabetic small fiber neuropathy using Metanx as a neurotrophic agent. This study looked at 11 symptomatic DPN patients . Patients underwent IENFD testing performed by obtaining two 30-mm skin punch biopsies 4 cm proximal to the lateral malleolous between the peroneal tendons and the Achilles tendons. A total of 22 biopsies were performed. Metanx administered twice daily for 6 months was associated with a 97% increase in IENF density (P=.004). (figures from abstract, clonical case outcome)

Metanx: Indication and Dosage

Metanx is an orally administered prescription medical food for the dietary management of endothelial dysfunction in patients with DPN. Metanx is a potential disease-state modifying neurotrophic agent. The recommended dosage is 1 tablet twice daily.

An ongoing randomized, double-blind, placebo-controlled clinical trial is further studying the effects of Metanx in 216 patients with DPN. The primary endpoint is to determine if Metanx improves VPT in DPN patients. The principle investigators are Vivian Fonseca, MD, Tulane Medical; Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center; Lawrence Lavery, DPM, Texas A&M University Health Sciences Center; Cyrus Desouza, MD, Omaha VA Medical Center; Douglas Denham, MD, DgD Research, Inc.; and Fernando Ovalle, MD, University of Alabama School of Medicine. The expected completion date is February 2010.

SUMMARY

Most patients with DPN experience loss of protective sensation, and the etiology of DPN may primarily be microvascular insufficiency. A progressive disease, the pain associated with DPN can be mild to moderate or severe with such symptoms as burning, shooting, and stabbing pains, and increased sensitivity. This can lead to sensory loss and reduced thermal sensation. Sensory loss is a significant predictor of the complications associated with DPN like ulceration, foot deformity, and nontraumatic amputation.

Reduced epidermal nerve fiber density precedes the diagnosis of diabetes and is more prevalent in DPN patients compared with diabetes patients who do not have neuropathy and patients with impaired glucose tolerance. Therapeutic options for the treatment of DPN should be based on individual patient factors. It is important that clinicians focus on disease-modifying, neurotrophic agents in order to manipulate the underlying pathophysiology of DPN. Metanx offers patients the option of nutritional management jat increases nitric oxide synthesus potentially improving blood flow to peripheral nerves. It works by regenerating BH4, a cofactor for eNOS— the endothelial isoform of nitric oxide synthase—to convert argininine into nitric oxide. Nitric oxide is diffused into the smooth muscles cells, which then dilate and blood flow is improved. Enhanced blood flow allows nutrients and oxygen to reach the nerves and therefore nerve repair can commence. Nerve repair includes production of the myelin sheath, which protects and insulates nerve fibers.

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