ABSTRACT

Neuropathy is a common diabetic microvascular complication, which can be associated with significant positive symptoms for the patient, such as numbness, pricking, aching pain, burning pain, lancinating pain, or allodynia, and in advanced cases, may eventually lead to amputation. Currently, no treatments have been approved to prevent or slow the progression of neuropathy. Strict glycemic control has historically been the only method for decreasing a patient's likelihood of developing neuropathy, but many patients find this level of glycemic control difficult to achieve. Therapies that act on the pathogenesis of neuropathy are therefore being investigated. Trials are ongoing to determine the efficacy of aldose reductase inhibitors, protein kinase Cβ inhibitors, antioxidants, and antiglycation agents, all of which have shown promise in slowing or stopping the progression of diabetic peripheral neuropathy. Medical management of diabetic neuropathic symptoms has traditionally involved analgesics, antidepressants, and antiepileptic drugs, but often the side effects associated with these agents are substantial, and many patients fail to respond. New symptomatic therapies are therefore being sought. The symptomatic treatments may address painful symptoms over the short term; however they do not address the underlying etiology of neuropathy. This article will review emerging therapies targeting the progression of neuropathy as well as those designed to provide symptomatic relief.

cutaneous insulin pump so that hemoglobin A1c values are kept between 6.5 and 7.5) by either means is limited by cost, patient compliance, and in some cases the increased risk of symptomatic hypoglycemia. Intensive insulin therapy also carries with it a high probability of weight gain. Further, in advanced cases of DPN, several years of strict glycemic control may be needed before any beneficial effects on nerve dysfunction are seen.

The incidence of DPN is linked to the duration of the diabetes. Patients with type 1 diabetes usually acquire DPN some time after they have been diagnosed. In this group, improved glycemic control may have a favorable effect on DPN. However, a substantial number of patients with type 1 diabetes have nerve conduction study changes even at the time of diagnosis indicating hyperglycemia causes early alterations in nerve function. In contrast, many patients with type 2 diabetes may already have some degree of clinical DPN at the time they are diagnosed, in spite of the fact that they have experienced no symptoms. In addition, patients with impaired glucose tolerance who have not yet been diagnosed with overt type 2 diabetes mellitus also have been shown to have changes in nerve conduction parameters, and patients in this group may even be found to have clinical DPN.

Even careful glycemic control after diagnosis may be inadequate to delay or prevent the progression of DPN, since some patients present with neuropathy even when metabolic control appears satisfactory. Axonal atrophy, demyelination, nerve fiber loss, and disordered nerve fiber repair have been seen to develop in the early stages of diabetes. As 90% to 95% of patients have type 2 diabetes, and another 41 million people in the United States are estimated to be prediabetic with blood sugar levels of 100 to 110 mg/dL, the potential scope of the problem of DPN is considerable.

Other than attempts to achieve optimal glycemic control and better control of lipid levels and blood pressure, there are no specific approved treatments to prevent or slow the progression of DPN, although modalities that address pain symptoms are available. This article will discuss newer therapies directed toward symptom control, as well as specific emerging therapies to control the pathogenesis of DPN (Table 1).

**Symptomatic Therapies**

In addition to encouraging vigorous glucose control in patients with diabetes to prevent progression of DPN, it is important to treat positive neuropathic sensory symptoms, such as numbness, pricking, aching pain, burning pain, lancinating pain, or allodynia. Painful symptoms are experienced by more than half of those diagnosed with DPN. These patients may describe their pain as burning, tingling, lancinating, or “electrical sensation” type discomfort (known as superficial or dysesthetic pain), or less commonly as aching, tender, or knife-like pain (known as nerve trunk pain). Many other patients experience a loss of feeling or sensation, symptoms often described as a deadness, numbness, tingling, or prickly sensation in their extremities. In some cases, the skin becomes uncomfortably sensitive to touch, even light touch. Other patients lose the ability to feel sensations.

The symptoms experienced are highly variable from case to case of DPN, but most often involve the lower limbs. When such symptoms become chronic, they may impede work and activities of daily living. Sleep deprivation and depression commonly result from nightly exacerbations of symptoms. Over time, numbness and loss of sensation may affect the patient's sensory abilities, such as the ability to determine whether shoes fit properly, or the ability to discriminate water temperature while bathing, possibly leading to injury. The lack of sensation is the leading cause for the negative sequelae of ulceration, infection, loss of toes, and amputation.

In 1985, in a review of drug therapy of neuropathic pain, Maciewicz et al wrote that “the medical management of neuropathic pain is disappointing.” Neuropathic pain responds poorly to most traditional approaches to pain. In the past, analgesics, tricyclic antidepressants (TCAs), antiepileptic drugs, and opioids have been used in attempting to control the painful symptoms of DPN. The major problem with most agents historically used is the regular and predictable occurrence of side effects at the doses required to treat pain, especially the sedation and anticholinergic effects seen with TCAs. Additionally, there is great variability in the responses between patients to the various agents, and even some variability within a single patient over time. Furthermore, few if any of these treatments address symptoms such as numbness or tingly sensations. Though there have been advances since Maciewicz made his somewhat bleak assessment, the control of positive neuropathic symptoms continues to be challenging for the physician and patient. The goal of research in this area is to design agents that provide effective symptom relief without intolerable side effects.
Nonsteroidal Anti-inflammatory Drugs  
Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen are typically recommended upon diagnosis of DPN. These agents may help mild symptoms. Prescription NSAIDs may be recommended for more severe symptoms. Patients taking NSAIDs for long periods of time or in large doses may develop gastrointestinal bleeding, and in individuals at risk of renal dysfunction, these agents may impair renal function by inhibiting the synthesis of prostaglandin.

Antiepileptic Agents  
Anticonvulsant medications (or antiepileptic drugs [AEDs]) have been used in the management of neuropathic pain for over 30 years, and can be useful in DPN. They are effective in several types of diabetic neuropathic pain, and may help, in particular, lancinating pain. Their efficacy may be due to similarities of the pathophysiologic and biochemical mechanisms between epilepsy and neuropathic pain. Several newer AEDs have shown efficacy as analgesics in painful DPN, and are discussed below.

Gabapentin. This drug is thought to have an effect on the α-2-β type of Ca++ channels by which it may exert its inhibitory effect on pain. Backonja et al studied the use of gabapentin as therapy for pain symptoms in 165 patients diagnosed with painful DPN. In this study, most patients (80%) were titrated from 900 to 3600 mg per day administered in 3 divided doses. Gabapentin separated from placebo in terms of pain relief at a dosage level of 1800 mg per day (during the second week of the study). This effect was also maintained at higher doses and for the length of the study (8 weeks). The study concluded that the data showed gabapentin monotherapy was efficacious for the treatment of pain associated with DPN.

Gorson et al also compared gabapentin with placebo in a randomized, double-blind, placebo-controlled cross-over study of patients with diabetes who had a diagnosis of painful, symmetrical sensorimotor DPN by clinical examination (n = 40; all but one had type 2 diabetes). Efficacy of gabapentin in this smaller trial was limited compared with the Backonja trial, but the dosage used was considerably lower, 900 mg per day versus 1800 mg per day, which suggests higher dosages are more effective for neuropathic pain control.

Oxcarbazepine. This agent is approved as treatment for partial seizures (monotherapy for adults and adjunctive therapy for adults and children), and it has also shown promise as a treatment for painful DPN. Beydoun et al studied the efficacy of this agent in an open-label monotherapy trial that included 30 patients with a diagnosis of diabetes (type 1 or 2) and pain attributed to DPN. Patients were titrated from an initial dosage of 150 mg once daily of oxcarbazepine to a dosage of 1200 mg once daily or the highest tolerated dose over a period of 4 weeks, with the active treatment phase of the study running for a total of 8 weeks. The investigators concluded oxcarbazepine was safe and efficacious for the treatment of painful DPN.

Pregabalin. The AED pregabalin is a gamma aminobutyric acid (GABA) analog, and like gabapentin, has no agonistic effect on GABA receptors. This agent was found to be effective both in preclinical studies in neuropathic pain, and also in a randomized, placebo-controlled trial. In this study, which compared 3 different oral doses of pregabalin (75 mg, 300 mg, and 600 mg per day) with placebo in patients with DPN (n = 337), pregabalin showed efficacy in those patients who received 300 mg or more daily.

Lamotrigine. This agent was initially approved by the US Food and Drug Administration as add-on therapy for partial complex seizures. This agent has also been studied in patients with painful DPN. Eisenberg et al conducted an 8-week, randomized, double-blind, placebo-controlled trial of lamotrigine as monotherapy for patients with painful DPN (n = 59). In this study, patients in the active treatment group were slowly titrated from lamotrigine 200 mg once daily to a dosage of 400 mg once daily by the end of the study. The mean daily pain score in the lamotrigine group was significantly lower than that seen with placebo (P < 0.001). Efficacy and tolerability of lamotrigine were similar to that seen with gabapentin in painful DPN.

Topiramate. This drug, introduced for the treatment of seizures in 1997, also has been studied as monotherapy for painful DPN. Edwards et al studied this agent in a double-blind, placebo-controlled study of 26 patients, and found that topiramate reduced painful DPN. Four other randomized, double-blind, placebo-controlled trials of topiramate in painful DPN have been conducted, but the results of only one have been published. That study reported topiramate showed efficacy over placebo in painful DPN. However, cognitive changes may have been severe enough to lead to unmasking in this study. Alternatively, the doses used in some of the studies may have been insufficient to control the painful symptoms.
Zonisamide. The AED zonisamide has a mechanism of action that suggests it may be able to control symptoms of neuropathic pain. It has been studied for its use in thermal hyperalgesia and mechanical alldynia in the chronic constriction injury model of neuropathic pain in rats, and the data suggested that this agent may be useful in some types of neuropathic pain. Further study, including clinical trials, will be necessary to determine if this agent has efficacy in painful DPN.

**Narcotic Analgesics — Opioids**

Typically, neuropathic pain does not respond well to traditional nociceptive pain treatments, including opioid analgesics, which carry with them a risk of severe adverse effects and the possibility of dependency issues. These agents act in the central nervous system to reduce pain perception. Few trials have evaluated the long-term safety and efficacy of opioids in neuropathic pain.

**Other Pharmacological Treatments**

Various other treatments are currently being researched for the treatment of the painful symptoms of DPN. Emerging treatments include N-methyl-D-aspartate (NMDA) receptor antagonists, new-generation antidepressants, and topical treatments.

**Nonpharmacological Devices**

Because of the adverse effects seen with many of the traditional pharmacological therapies used in the pain symptoms of DPN, various alternative device-related treatments have been studied in hopes of lessening the burden on these patients. If a successful therapy is identified, it is also possible that it could be used in conjunction with pharmacological treatment, since there would be no drug interaction when using a device.

**Specific Therapies**

**Targeting Pathogenic Mechanisms**

Many therapies have been used to treat the positive symptoms of DPN, resulting in varying levels of symptom relief. But the agents described above do not address the underlying pathogenesis of DPN, and therefore have no effect on the progression of the disease. Therapies that influence the progression of neuropathy are being sought, but are mainly investigational at this time. The majority of these treatments have no effect on positive symptoms, but rather are intended to slow or stop the loss of nerve fibers seen in DPN. One investigational agent, ruboxistaurin, shows promise in that it provides symptom relief while at the same time, it acts to slow or stop the progressive loss of nerve fibers (Table 2). Because the etiology of DPN is likely multifactorial, several different lines of research are actively seeking agents to prevent or reverse this diabetic microvascular complication based on current understanding of the different pathways involved (Figure). Specific therapies currently being investigated may be classified as aldose reductase inhibitors, protein kinase C (PKC) β inhibitors, antioxidants, and antiglycation products.

**Aldose Reductase Inhibitors**

When a diabetic patient is in a hyperglycemic state, the elevated glucose levels activate the aldose reductase enzyme. High glucose levels are thought to lead to increased sorbitol and fructose levels in peripheral nerves, and the various metabolic imbalances that follow ultimately lead to nerve cell dysfunction and damage. Thus, considerable research efforts have gone into developing aldose reductase inhibitors that work by blocking this rate-limiting enzyme in the polyol pathway. These compounds are divided into 2 general classes: those containing a carboxylic acid moiety and those having a cyclic imide represented by a spirohydantoin or related ring system.

Results from animal studies show aldose reductase inhibitors have a positive inhibitory effect on DPN. Yagihashi et al studied mice that were transgenic for human aldose reductase, demonstrating that the use of aldose reductase inhibitors had several positive results on neuropathy: it prevented the accumulation of sorbitol, improved nerve conduction velocities, and decreased nerve fiber atrophy. Kihara et al found that zenarestat appeared to restore endoneurial blood flow in rats with streptozotocin-induced diabetes, providing further evidence of the efficacy of aldose reductase inhibitors. Data from a study by Sima et al of sorbinil in patients with DPN showed that the sorbinil-treated group had a significant decrease in nerve sorbitol content over placebo ($P < .001$). These patients also had an increase in the percentage of regenerating myelinated nerve fibers ($P = .04$) along with other neural improvements, showing the efficacy of treatment with this aldose reductase inhibitor. The aldose reductase inhibitor epalrestat has shown positive results in clini-
Fidarestat. Hotta et al evaluated the efficacy of fidarestat in a double-blind, placebo-controlled study of patients with DPN. Patients (n = 279) were randomized to receive either placebo or 1 mg fidarestat per day for a total of 52 weeks. This study used electrophysiological measurements of nerve function as well as assessment of subjective symptoms to evaluate efficacy. The results showed fidarestat demonstrated significant improvement compared with placebo in 5 of 8 electrophysiological measures, including improvement in F-wave minimum latency and median nerve F-wave conduction velocity ($P < 0.001$, and $P < 0.001$, respectively). The fidarestat 1 mg per day group also showed improvement in subjective symptoms such as

### Table 1. Emerging Treatments for Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational therapies targeting pathogenic mechanisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldose reductase inhibitors</td>
<td>Block rate-limiting aldose reductase enzyme in polyol pathway</td>
<td>Fidarestat, AS-3201, zenarestat</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Counteract oxidative stress due to ROS accumulation from glucose metabolism</td>
<td>α-Lipoic acid, vitamins A, C, and E, taurine</td>
</tr>
<tr>
<td>Antiglycation agents</td>
<td>Prevent formation of AGEs by reacting non-protein-bound dicarbonyl intermediates. More studies needed to evaluate efficacy in human diabetic neuropathy</td>
<td>Aminoguanidine</td>
</tr>
<tr>
<td>PKC β Inhibitors</td>
<td>Block microvascular-regulating PKC β-enzyme activation in PKC pathway. Normal flux of PKC pathway needed to regulate endoneurial blood flow, preserve nerve function</td>
<td>Ruboxistaurin mesylate (LY333431)</td>
</tr>
<tr>
<td>Symptomatic therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Effective in managing lancinating pain. Efficacy may be due to similar pathophysiologic, biochemical mechanisms of epilepsy, neuropathic pain</td>
<td>Gabapentin, oxcarbazepine, pregabalin, lamotrigine, topiramate, zonisamide</td>
</tr>
<tr>
<td>Narcotic analgesics — opioids</td>
<td>Act in CNS to reduce pain perception. More trials needed to study long-term safety, efficacy in neuropathy</td>
<td>Oxycodone, tramadol</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>Have analgesic properties, but serious adverse effects due to high affinity. Studies of nonselective, less toxic NMDA receptor antagonists under way</td>
<td>Memantine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>New-generation antidepressants may be effective in managing neuropathic pain, without side effects of TCAs. Low affinity for muscarinic cholinergic receptors $\alpha_1$-adrenergic receptors</td>
<td>Duloxetine, bupropion, venlafaxine</td>
</tr>
<tr>
<td>Topical treatments</td>
<td>Topical application may involve vasodilation properties, depletion of substance P from afferent nerves. More studies needed to confirm findings</td>
<td>Capsaicin cream, isosorbide dinitrate spray</td>
</tr>
<tr>
<td>Nonpharmacological devices</td>
<td>Alternative methods may provide pain relief. Unknown mechanisms. May be used in conjunction with pharmacological therapy</td>
<td>Magnet therapy, low-intensity laser therapy, monochromatic near-infrared photo energy therapy</td>
</tr>
</tbody>
</table>

ROS = reactive oxygen species; AGE = advanced glycation end products; PKC = protein kinase C; CNS = central nervous system; NMDA = N-methyl-D-aspartate; TCA = tricyclic antidepressant.
numbness, sensation of rigidity, paresthesia, and hypoesthesia. In contrast to the treatment group, the placebo group showed no improvement on any measure and deterioration in median nerve F-wave conduction velocity over the course of the study. The study concluded that fidarestat may have efficacy in delaying the progressive deterioration of nerve function resulting from DPN.

AS-3201. An aldose reductase inhibitor known as AS-3201 has demonstrated selective, reversible potent inhibition of the aldose reductase enzyme system in preclinical rat studies.47,48 This agent is currently being studied in phase II trials under way in the United States and Canada.49 The AS-3201 Study Group recently sought to determine whether AS-3201 penetrates the sural nerve. In a double-blind, placebo-controlled study of 101 patients with diabetes (type 1: n = 10; type 2: n = 91) diagnosed with mild-to-moderate DPN, patients underwent a battery of tests, including nerve conduction studies, vibration perception threshold tests, and the Toronto Clinical Neuropathy Score in order to determine baseline values. Patients were randomized to placebo, AS-3201 5 mg per day, or AS-3201 20 mg per day, and received treatment for 12 weeks. The data showed that sensory nerve conduction velocities improved by 1 to 2 m/s from baseline in the 20-mg treatment group, and that signs of neuropathy (as assessed by the Toronto Clinical Neuropathy Score) also tended to improve in the 20-mg treatment group. Data on nerve sorbitol concentration obtained by sural nerve biopsy revealed that AS-3201 does penetrate human sural nerve and inhibits sorbitol and fructose accumulation dose-dependently. Further clinical studies are needed to confirm the improved nerve function and clinical measures observed in this trial.48,50

ANALYZING ALDOSE REDUCTASE INHIBITORS: ZENARESTAT REVISITED

Development of the investigational drug zenarestat was suspended in October 2000 because data from phase III clinical trials showed renal function changes (dose-dependent elevations in creatinine levels) in some patients.51 However, recently a new study analyzed data from the phase III zenarestat study (which included patients with mild-to-moderate DPN) to determine baseline and natural progression of DPN over 12 months.51 This study found that, in this patient population, measures such as vibration quantitative sensory testing, neuropathy rating scores, and monofilament examination were insensitive to changes over the study period, while nerve conduction studies and assessments of cool thermal thresholds were useful in showing the effects of treatment or a decline in nerve function at 12 months. These data may be useful in designing future trials of aldose reductase inhibitors. Past studies have also shown that not all aldose reductase inhibitor compounds will penetrate human peripheral nerve.27,32 Furthermore, nerve assays for sorbitol and fructose levels require laboratory analytic methods that are adequately sensitive to detect nanomole concentration levels, as patients with DPN and viable nerve have been shown to have a baseline accumulation of sorbitol in the range of 0.034 to 0.300 nmol/mg in sural nerve.52 It is equally important in clinical trials of aldose reductase inhibitors that study patients be representative of the target population, as patients without a confirmed diagnosis of DPN or patients with very advanced DPN might make pharmacodynamic evaluation difficult or inconclusive.51,52 New compounds that act as aldose reductase inhibitors are currently being screened for their potential use in DPN.

PKC β INHIBITORS

There is evidence that hyperglycemia increases the bioavailability of diacylglycerol, which in turn activates PKC β, the enzyme that regulates microvascular functions.42 Also, elevated glucose levels can activate PKC through the reactive oxygen intermediate pathway as well as through the advanced glycation end product pathway. Dysfunction in the PKC pathway leads to impairment of endoneurial blood flow and initiates other abnormal biochemical mechanisms that are believed to contribute to damage in nerves.24 Thus, it is believed that agents that act to inhibit PKC β might be useful in treating DPN.

Ruboxistaurin Mesylate

Ruboxistaurin mesylate is a specific PKC β inhibitor currently in clinical trials that seek to determine its efficacy in the 3 major diabetic microvascular complications: DPN, diabetic retinopathy, and diabetic nephropathy. In a preclinical study, Cotter et al demonstrated that ruboxistaurin (LY333531) increased neural blood flow and nearly corrected nerve conduction velocity in rats with streptozotocin-induced diabetes.53 Four clinical trials have studied ruboxistaurin in DPN.
Litchy et al performed a double-blind, placebo-controlled, phase II clinical trial of ruboxistaurin in DPN. In this study, patients with type 1 or 2 diabetes who had DPN (n = 205) were randomized 1 of 3 treatment groups (32 mg ruboxistaurin, 64 mg ruboxistaurin, or placebo). The data showed that patients in the 32-mg ruboxistaurin treatment group had improved neurological examinations compared with baseline, and this group also had improved electrophysiologic and quantitative sensory tests. Both doses were found to be effective in patients with milder DPN of shorter duration.

In a second phase II clinical trial of ruboxistaurin, Skljarevski et al sought to determine the efficacy of ruboxistaurin for symptoms of DPN. Patients with type 1 or type 2 diabetes (n = 205) were identified for inclusion in the study by abnormal vibration detection threshold screening, and the Neuropathy Total Symptom Score-6 (NTSS-6) was used to determine which patients had clinically significant symptoms. The NTSS-6 is a measure of frequency and intensity of numbness, pricking, aching pain, burning pain, lancinating pain, and allodynia. Those patients who met the entry criteria were randomized to receive either 32 mg ruboxistaurin once daily, 64 mg ruboxistaurin mesylate once daily, or placebo for up to 58 weeks. At 12 months, the data showed a statistically significant improvement in the NTSS-6 in patients in the 64-mg ruboxistaurin group (P = .015). The data also showed a trend towards improvement between placebo and the 32-mg ruboxistaurin group after 12 months (P = .065). Patients in the 32-mg ruboxistaurin mesylate group also showed clinically significant improvement over patients in the placebo group in the other instruments used to evaluate nerve function in this study, the Neuropathy Impairment Score of Lower Limbs (NIS(LL)) and the NIS(LL) + 4 electrophysiology attributes (P = .049 and P = .046, respectively).

Four phase III studies of ruboxistaurin in DPN are ongoing. Additionally, studies of this agent in diabetic macular edema are underway.

**Antioxidants**

Evidence exists to suggest that during hyperglycemia, the metabolism of glucose leads to generation and accumulation of reactive oxygen species (free radicals) that have a direct neurotoxic effect. This oxidative stress affects endothelial cell function and vascular activity, and contributes to impaired blood flow and oxygenation in peripheral nerve cells, ultimately resulting in DPN. Antioxidants have therefore been studied in DPN. In an animal study involving α-lipoic acid, Nagamatsu et al showed that treatment with α-lipoic acid reduced oxidative stress in diabetic peripheral nerves, and led to electrophysio-

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**Table 2. Therapeutic Uses of Emerging Treatments for DPN**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Delay/reverse DPN progression</th>
<th>Symptom management</th>
<th>Treats underlying microvascular damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldose reductase inhibitors</td>
<td>Fidarestat</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>α-Lipoic acid</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PKC β inhibitors</td>
<td>Ruboxistaurin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Topiramate</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Opioids</td>
<td>Gabapentin</td>
<td>?</td>
<td>Yes (pain only)</td>
<td>?</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>Oxycodone</td>
<td>No</td>
<td>Yes (pain only)</td>
<td>No</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Memantine</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Topical treatments</td>
<td>SNRIs</td>
<td>No</td>
<td>Yes (pain only)</td>
<td>No</td>
</tr>
<tr>
<td>Nonpharmacological devices</td>
<td>Capsaicin</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Magnet therapy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*DPN* = diabetic peripheral neuropathy; *PKC* = protein kinase C; *NMDA* = N-methyl-D-aspartate; *SNRIs* = serotonin-norepinephrine reuptake inhibitors.
logical improvement. The use of oral \(\alpha\)-lipoic acid in DPN has recently been studied in clinical trials.

**\(\alpha\)-Lipoic Acid**

Ziegler et al recently performed a meta-analysis of clinical trials of \(\alpha\)-lipoic acid in order to determine the efficacy and safety of an intravenous dosage of 600 mg daily for 3 weeks in diabetic patients with symptomatic DPN \((n = 1258)\). To be included in the meta-analysis, trials had to be randomized, double-blind, and placebo-controlled. The 4 trials that were identified were the Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) I and ALADIN III studies, the Symptomatic Diabetic Neuropathy (SYDNEY) study, and the Neurological Assessment of Thiocystic Acid in Neuropathy (NATHAN) II study. Using combined data from these 4 studies, the meta-analysis found that the \(\alpha\)-lipoic acid vs placebo responder rates after 3 weeks of treatment were significantly different (**\(\alpha\)-lipoic acid 52.7%, placebo 36.9%, \(P <0.05\)). The group treated with \(\alpha\)-lipoic acid showed total Symptom Score improvement (decreased pain, burning, and numbness) over placebo from day 8. The pinprick and touch-pressure sensation components of the Neuropathic Impairment Score of the lower limbs were also improved in the \(\alpha\)-lipoic acid treatment group after 3 weeks. Rates of adverse events with \(\alpha\)-lipoic acid were similar to placebo. This meta-analysis noted the very rapid improvement of neuropathic symptoms and deficits, and suggested that the mechanisms underlying this improvement might be mediated by the antioxidant effects and improved blood flow caused by \(\alpha\)-lipoic acid. Further trials will be necessary to determine the effect of \(\alpha\)-lipoic acid treatment in DPN over the long term.

**Vitamins C, E, and A**

There is limited evidence to suggest that the increased intake of dietary antioxidants (vitamins C, E, and A) may reduce oxidative stress, and theoretically have a beneficial effect on neuropathy in people with diabetes. Vitamin C is hypothesized to reduce cellular levels of reactive oxygen species and decreases the production of nitric oxide—similar to the actions of \(\alpha\)-lipoic acid. Vitamin C decreases plasma free radicals and increases cellular reduced glutathione levels, and improves nitric oxide-mediated vasodilation. Further, controlled studies of vitamins C, E, and A will be necessary to determine if they have true efficacy in DPN.

**Antiglycation Agents**

There is a body of evidence that under hyperglycemic conditions, sugar-derived advanced glycation end products (AGEs) that form inside and outside cells are involved in sensory nerve fiber damage via several different pathways.

**Aminoguanidine**

The compound aminoguanidine prevents the formation of AGEs, chiefly by reacting with non-protein-bound dicarbonyl intermediates. In preclinical rat studies, treatment with aminoguanidine ameliorated the decreases in: motor and sensory nerve conduction velocities, nerve action-potential amplitudes, and peripheral nerve blood flow normally seen with diabetes. However, another study in baboons did not show these same protective effects in early diabetes. Inhibition of AGE formation and a slowing of the progression of microvascular complications with aminoguanidine treatment have been reported in phase III trials in optimally treated patients with type 1 diabetes who had nephropathy and retinopathy. However, some side effects related to aminoguanidine have introduced reservations about this intervention.

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**Figure. Pathogenic Targets of Investigational Therapies for DPN**

![Pathogenic Targets of Investigational Therapies for DPN](image)

DPN = diabetic peripheral neuropathy; AGEs = advanced glycation end products; ROS = reactive oxygen species; DAG = diacylglycerol; PKC = protein kinase C; VEGF = vascular endothelial growth factor; TGF-\(\beta\) = transforming growth factor-beta; NF-\(\kappa\)B = nuclear factor-kappa B; TCA = tricarboxylic acid; NADH = nicotinamide adenine dinucleotide hydrogen; F6P = fructose-6-phosphate; PAI-1 = plasminogen activator inhibitor-1.
To date, no clinical studies have demonstrated the efficacy of any antiglycation agent in human DPN, but research continues into AGE inhibitors, including several novel compounds.\textsuperscript{70}

**CONCLUSION**

A substantial number of treatments are emerging that have the potential to slow or reverse the progression of DPN by working on the specific pathways involved in the pathogenesis of the disease. Some experts suggest that, ultimately, some type of combination therapy that blocks multiple pathway components might possibly provide effective treatment for those patients who have DPN.\textsuperscript{71} Simultaneously, new agents and treatments are being researched to better treat the painful symptoms that often accompany DPN. These recent therapeutic advances are providing new hope for patients who must face this challenging microvascular complication of diabetes.

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