ABSTRACT

Nonpharmacologic management of diabetic peripheral neuropathy (DPN) includes early, frequent, and conscientious foot examination, provision of proper footwear, and counseling of patients who may be insensate to injury of their feet. In addition, several studies have revealed that both the risk and manifestations of DPN can be reduced with improved blood glucose control. With respect to the pharmacologic management of DPN, treatments generally fall into 2 main categories: those treatments that provide symptomatic relief for the pain, burning, paresthesias, numbness, and tingling that mark this condition, and those that actually influence the natural history of the disease, which is progressive loss of limb function. Because they may affect various important mechanisms of pain signaling, antidepressants, anticonvulsants, and anaesthetics all may be useful in the treatment of DPN. In addition, a number of other pathogenetic treatments are emerging. These include: the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Lastly, a number of non–Food and Drug Administration-approved investigational agents are being evaluated for use in averting or delaying microvascular complications. These include: advanced glycation end-product receptor blockers, aldose reductase inhibitors, α-lipoic acid, poly (ADP-ribose) polymerase inhibitors, and protein kinase C β inhibitors.

roidism, and uremia, respectively. If other conditions have been excluded, a combination of typical symptomatology and distal sensory loss with absent reflexes, or signs in the absence of symptoms, is highly suggestive of DPN. Once the diagnosis has been established, the next step in treatment is to assess the level and stability of glycemic control.

**Establishing and Maintaining Glycemic Control**

The Diabetes Control and Complications Trial (DCCT) has shown definitively that in patients with type 1 diabetes, the risk of DPN can be reduced with improved blood glucose control. Although not as strong for patients with type 2 diabetes, data from a small number of trials and from epidemiologic studies strongly suggest that optimal blood glucose control helps prevent DPN in both type 1 and type 2 diabetes. Thus, patients and clinicians must aim for stable glycemic control, avoiding swings in glycemia and aiming for near-normoglycemia. Insulin is not always needed in type 2 diabetes (normal glycated hemoglobin and blood glucose levels in the range of 70 to 140 mg/dL); such patients are not likely to benefit from insulin therapy. It is important to explain to patients that symptomatic improvement may be delayed after stabilizing control.

In an early study, we treated outpatients with diabetic neuropathy with continuous subcutaneous insulin infusion (CSII) for 4 months. Painful symptoms were scored on a 10-cm horizontal graphic rating scale. Pain scores changed significantly ($P < .1$) from a baseline of 7.2 to 2.2 by study end. In addition, motor conduction velocity (MCV) was measured in the median and peroneal nerves, and vibration perception threshold (VPT) was recorded in the great toes. Improved diabetic control was confirmed by significantly lower mean blood glucose levels, M-values (baseline 85, study end 21.6; $P < .1$), and glycosylated hemoglobin. In addition to the improvement in pain scores, all patients noted symptom relief. Significant improvement also was seen in VPT and MCV after 6 weeks of CSII, which was maintained throughout the 4-month period. However, sensory studies in the median nerve showed no significant changes during the study. The authors concluded that stable, near-normoglycemic control is indicated in all cases of symptomatic diabetic neuropathy.

A later study that also utilized continuous glucose monitoring demonstrated that patients with painful neuropathy have very unstable control, with flux of glycemia. Oyibo et al compared 2 matched groups of patients (those with painful and those with painless DPN) in terms of their mean glucose as well as the mean amplitude of glucose excursions, concluding that patients with painful neuropathy had greater glucose flux, and possibly poorer diabetes control. Thus, it is hypothesized that blood sugar flux from low to high brings on neuropathic pain, perhaps affecting less receptive afferent fibers; however more investigation is needed to support this conclusion. There is some evidence that certain nonsteroidal anti-inflammatory medications (NSAIDs) might help, but extreme caution must be exercised when using nonsteroidal drugs in patients with diabetic neuropathy, as these patients also may have nephropathy and renal disease—both contraindications to the use of NSAIDs.

**Medications Useful for Treating Symptomatic Diabetic Peripheral Neuropathy**

The pathophysiology of the pain that accompanies symptomatic diabetic neuropathy is not well un-
stood, but undoubtedly involves complex pathways and mechanisms that contribute to neuropathic pain signals. For example, pain may result from hyperexcitability of peripheral and central pain pathways mediated by sodium and calcium channels, by excitatory neurotransmitters such as glutamate, and/or reduced inhibition of γ-aminobutyric acid (GABA). Antidepressants, anticonvulsants, and analgesics affect several of these mechanisms of pain signaling and therefore all may be useful in the treatment of DPN (Table 2).

Antidepressants

For the most part, the tricyclic antidepressant drugs, such as imipramine (25 mg to 150 mg at night) and amitriptyline (25 mg to 150 mg at night), remain the first-line agents. This is because they are highly effective, as demonstrated in randomized-controlled trials. For example, in a meta-analysis by McQuay et al, the effectiveness and safety of antidepressants in neuropathic pain was examined via a review of randomized-controlled trials of such parameters as pain relief or decrease in pain intensity (which approximated to more than 50% pain relief); adverse effects also were examined. Twenty-one placebo-controlled treatments in 17 randomized-controlled trials were included, involving 10 antidepressants. In 6 of 13 diabetic neuropathy studies, the odds ratios (ORs) showed significant benefit compared with placebo. The combined OR was 3.6 (95% confidence interval, 2.5–5.2), with a number-needed-to-treat for benefit of 3 (2.4–4). Comparisons of tricyclic antidepressants failed to demonstrate any significant difference between them; they were significantly more effective than benzodiazepines in the 3 comparisons available. Paroxetine and mianserin were less effective than imipramine. In summary, the authors found that, compared with placebo, 30 of 100 patients with neuropathic pain who are given antidepressants will obtain more than 50% pain relief, 30 will have minor adverse reactions, and 4 will have to stop treatment because of major adverse effects. Early symptomatic relief is typical and the efficacy is related to plasma drug levels. Blockade of norepinephrine reuptake at synapses of descending pain control systems is likely to mediate the analgesic effect of these antidepressant drugs. Furthermore, the pain relief effects are rapid.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug†</th>
<th>Daily Dose</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Tricyclics</td>
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<tr>
<td>Imipramine</td>
<td></td>
<td>25 to 150</td>
<td>+++</td>
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<tr>
<td>Amitriptyline</td>
<td></td>
<td>25 to 150</td>
<td>+++</td>
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<tr>
<td>SSRIs</td>
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<tr>
<td>Citalopram</td>
<td></td>
<td>40</td>
<td>+++</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td>40</td>
<td>+++</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>900 to 1800</td>
<td>++</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>200 to 400</td>
<td>++</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Up to 800</td>
<td>+++</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
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<tr>
<td>Mexiletine‡</td>
<td></td>
<td>Up to 450</td>
<td>+++</td>
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<tr>
<td>Opioids</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td>50 to 400</td>
<td>+++</td>
</tr>
<tr>
<td>Oxycodone CR§</td>
<td></td>
<td>10 to 60</td>
<td>+++</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor.

†All medications in the table have demonstrated efficacy in randomized-controlled studies.
‡Mexiletine should be used with caution and with regular electrocardiogram monitoring.
§Oxycodone CR may be useful as an add-on therapy in severe symptomatic neuropathy.
and independent of mood changes (suggesting that their efficacy is not related to treatment of depression). These drugs also are inexpensive; however, the negative side to tricyclic antidepressants is the likelihood of adverse effects—present in up to one third of all patients. In particular, these drugs cause drowsiness and anticholinergic side effects, especially dry mouth. Thus, the clinician may need to consider other agents. (Among other tricyclic antidepressants, desipramine may be better tolerated than amitriptyline.)

Certain selective serotonin reuptake inhibitors, for example, paroxetine but not fluoxetine, also may produce significant pain relief with fewer side effects. In addition, duloxetine, which is a serotonin and norepinephrine reuptake inhibitor (SNRI) newly approved (September 2004) for treatment of painful diabetic neuropathy, also has demonstrated efficacy. Goldstein et al found it to be effective in a 12-week double-blind, randomized clinical trial in 457 patients with painful diabetic neuropathy. In all 3 active treatment groups a greater number of patients achieved 50% reduction in pain scores compared with placebo, and there were no issues with safety or adverse effects.

**ANTICONVULSANTS**

Anticonvulsants have been used in the management of neuropathic pain for many years. For example, carbamazepine may be useful, but adverse effects are common. Gabapentin, although originally introduced as an anticonvulsant for complex partial seizures, is now widely used for neuropathic symptoms. Its efficacy in diabetic neuropathy was proven in a randomized, double-blind, controlled trial of 165 patients with painful diabetic neuropathy. In all 3 active treatment groups a greater number of patients achieved 50% reduction in pain scores compared with placebo, and there were no issues with safety or adverse effects.

**Analgesic Medications**

Tramadol, an opioid-like drug with fewer side effects than opioids, was shown to be effective in a randomized trial by Harati (and also in a 6-month follow-up study) of 117 patients comparing tramadol with placebo. Unfortunately, the predictable side effects that accompany opioid and opioid-like medications were present, including nausea, somnolence, and constipation.

Whereas there are limited data on the use of opioids in painful diabetic neuropathy, 2 recent randomized clinical trials of oxycodone controlled release (CR) demonstrated significant improvement in symptoms and quality of life. The first, a multicenter study by Gimbel et al, examined 159 subjects given 10 to 60 mg per day of oxycodone vs placebo. The mean dose necessary to demonstrate significant relief of symptoms was 37 mg; however, at this range of therapeutic dosages, side effects were exhibited in 96% of patients. In another single-center study by...
Watson et al, 36 subjects ingested oxycodone CR at dosages of 10 to 80 mg/day vs active placebo (benztropine). As with the previous study, significant improvement in symptoms and quality of life were demonstrated in patients taking oxycodone (mean dose 40 mg/day) and typical opioid adverse effects were present in >90% of patients. Thus, oxycodone CR may be useful in resistant cases of painful diabetic neuropathy, but other agents with less adverse effects should be implemented first.

**CARDIAC AGENTS: MEXILETINE AND NITRATE SPRAY**

Mexiletine is a class 1B antiarrhythmic agent that has been used short term for DPN in dosages of up to 450 mg/day, which is lower than the usual dosage for cardiac use. Its efficacy has been confirmed in controlled trials; however, like oxycodone, it is not a first-line therapy nor can it be recommended for long-term use because of potential adverse effects. During use of mexiletine, regular electrocardiogram monitoring is necessary.

Another traditional cardiac medication that has been studied for use in DPN is isosorbide dinitrate (ISDN) spray. The basis for its use is the theory that impaired nitric oxide (NO) generation is involved in the pathogenesis of diabetic neuropathic pain. ISDN is an NO donor with local vasodilating properties, and in a study by Yuen, it was applied locally to the feet to ascertain what effect, if any, it would have on pain. The study was double-blind, randomized, and placebo-controlled with 22 subjects either using ISDN or placebo sprays for 4 weeks, or then exchanging their treatment for a further 4 weeks after a 2-week washout period. ISDN spray reduced overall neuropathic pain ($P = .02$) and burning sensation ($P = .006$). No treatment difference was observed with other sensory modalities (eg, hot/cold sensation, tingling, numbness, hyperesthesia, and jabbing-like sensation). At study completion, 11 patients (50%) reported benefit and wished to continue using the ISDN spray, 4 (18%) preferred the placebo, and the remaining 7 (32%) were undecided. Thus, ISDN spray may represent a new therapeutic approach to neuropathic pain management. (Nitrate patches also may be efficacious.) Other local treatments that have been used with success in some patients include acupuncture and electrical therapy. However, all of these target symptoms rather than altering the natural history of microvascular complications, which is the aim of the therapies considered in the sections that follow.

**TREATMENTS THAT INFLUENCE DISEASE NATURAL HISTORY**

**GLYCEMIC CONTROL**

Hyperglycemia plays a role in both the symptomatology and natural history of DPN. The Rochester Diabetic Neuropathy Study Group conducted a longitudinal study of 264 individuals with diabetes over a span of 7 years. In multivariate analysis, the severity level of neuropathy was associated with the severity level of retinopathy, nephropathy (as measured by 24-hour proteinuria multiplied by duration of diabetes), and mean glycated hemoglobin. This and other studies point to the fact that achieving near-normoglycemia is a vital step in both the prevention and treatment of DPN.

However, a number of other pathogenetic treatments are emerging. These include the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (Table 3). Of the latter group, only irbesartan and losartan are Food and Drug Administration (FDA) approved for the treatment of diabetic complications.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITION**

Clinical trials have demonstrated that ACE inhibitors delay progression of other microvascular complications of diabetes mellitus (DM)—specifically, both diabetic nephropathy and retinopathy—in type 1 and type 2 diabetes. Building upon that concept, Mallik et al investigated the effect of ACE inhibition on diabetic neuropathy. The authors conducted a small, randomized, double-blind, placebo-controlled study over 1 year of 41 normotensive patients with type 1 or type 2 DM and mild neuropathy. Neuropathy symptoms and deficits were evaluated based on VPT, peripheral-nerve electrophysiology, and cardiovascular autonomic function. Peroneal nerve motor function improved after 12 months in the group using ACE inhibitors compared with placebo, regardless of diabetes type. Thus, given the benefit that these drugs provide, it is prudent to administer them to all patients with diabetes, unless they are otherwise contraindicated.

**INVESTIGATIONAL AGENTS FOR DIABETIC MICROVASCULAR COMPLICATIONS**

A number of non–FDA-approved investigational agents also are being evaluated for use in averting or delaying microvascular complications. These include
advanced glycation end-product (AGE) receptor blockers, aldose reductase inhibitors (ARIs), benfotiamine, α-lipoic acid, poly (ADP-ribose) polymerase (PARP) inhibitors, and protein kinase C (PKC) β inhibitors.

**ALDOSE REDUCTASE INHIBITORS**

There are a number of signaling pathways involved in glucose metabolism, and whereas chronic hyperglycemia is key at the beginning of all of these pathways, sustained alteration in cell signaling pathways (such as changes in phospholipids or kinases) induced by the products of glucose metabolism may ultimately lead to microvascular complications. For example, animal models of diabetes consistently demonstrate an association between the alterations in the polyol pathway and nerve conduction velocity—both of which can be improved with ARIs (Figure 1). However, it may not be as clear-cut in human subjects. A meta-analysis of all randomized-controlled trials of ARIs identified 19 trials, testing 4 different ARIs for 4 to 208 weeks. It demonstrated a small but statistically significant reduction in decline of median and peroneal motor nerve conduction velocity, but no benefit in sensory nerves. This was unfortunate because it is mainly loss of sensation—and not motor function—that is cause for grave concern, as it is the latter that leads to ulcer formation and amputation in patients with DPN. Furthermore, trials of ARIs were either flawed (too short-lived to demonstrate a benefit for a con-
tion that takes years to impact; too few patients under study; or intervention were too late), or the drugs themselves were toxic or ineffective. Hence, there is only 1 drug (epalrestat) available in this class for DPN, and it is marketed only in Japan.

**ANTIOXIDANTS: α-Lipoic Acid**

Oxidative stress also may play an important role in diabetic neuropathy—both from a symptom and pathogenetic vantage point. There have been 2 large German trials to date investigating this using the antioxidant α-lipoic acid (ALA). The Alpha Lipoic Acid in Diabetic Neuropathy (ALADIN) study showed that intravenous ALA administered for 3 weeks resulted in significant symptom relief for patients with diabetic neuropathy. Another, the Deutsche Kardiale Autonome Neuropathie (DEKAN) study, utilized oral ALA for 6 months resulting in significant improvement in cardiac autonomic neuropathy tests. One additional investigation, the SYDNEY trial, randomized 120 patients to receive either intravenous ALA or placebo, and again, the patients receiving ALA demonstrated significant improvement in their neuropathic symptoms without side effects. As of this writing, there are 2 large multinational studies in progress—one using intravenous therapy and the other oral therapy; the results of these studies in terms of whether this antioxidant reduces symptoms, or whether it may slow the natural history of progression of loss of nerve fibers, are forthcoming.

**POLY (ADP-RIbose) POLYMERASE (PARP) AND GLYCAtion INHIBITORS**

PARP is a nuclear enzyme toxic to β cells and involved in the development of brain dysfunction in diabetic neuropathy. It has been discovered that PARP inhibition reverses diabetic endothelial dysfunction in diabetic mice, and in general seems to protect against β cell destruction. Once again, a signaling pathway is involved in this, and studies of aminoguanidine, which inhibits the formation of AGEs, thus far has been found to be useful in nephropathy. The usefulness of these types of agents for DPN remains to be seen.

**PROTEIN KINASE C (PKC) β INHIBITION: Ruboxistaurin**

Intracellular hyperglycemia increases intracellular 1,2-diacylglycerol accumulation, and this leads to activation of PKC that may ultimately lead to cellular dysfunction and damage in the nerves (Figure 2). This, in turn, results in numerous pathogenetic consequences (eg, formation of NO and vascular endothelial growth factor. Treatment with the PKC β inhibitor ruboxistaurin might improve nerve function in patients with DPN. Vinik et al conducted a phase 2, 1-year, randomized-controlled trial of ruboxistaurin vs placebo. The authors noted symptomatic improvement at 6 and 12 months (Figure 3), and although phase 3 studies for neuropathy have not been as encouraging, studies are ongoing, and PKC β inhibitors appear to have an impact on other microvascular complications, such as aspects of diabetic retinopathy.

**CONCLUSION**

First-line treatment for diabetes complications includes control of hyperglycemia, body weight, dyslipidemia, and high blood pressure. Treatments for DPN can influence disease natural history and/or provide symptom relief, although treatments that influence pathogenesis are mainly experimental at this point in time. Microvascular therapy may include a range of drugs used off label, including tricyclic antidepressants; FDA-approved treatments for painful DPN include the SNRI duloxetine and the antiepileptic pregabalin. Emerging therapies differentially affect pathogenetic signaling through the aldose reductase, AGE, and PKC β signaling pathways, and clinical trials are suggestive of some use of these drugs in this area. Lastly, the American Diabetes Association published a position statement in 2005 that states that diabetic neuropathy is a diagnosis of exclusion.

Tight glycemic control is the only proven preventative treatment. For patients with type 1 diabetes, screening for DPN should commence after 5 years of disease. For patients with type 2 diabetes, results from the United Kingdom Prospective Diabetes Study showed that 13% of patients at diagnosis have neuropathy of significant enough severity to be at risk of foot ulcers. Therefore, screening annually from the date of diagnosis is advised for all patients with type 2 diabetes.

Clinical history and physical examination of the feet are essential to making an accurate diagnosis, though quantitative sensory testing and electrophysiology should not be used routinely—but only in occa-
Several evidence-based therapies are available for symptomatic neuropathy, and research is ongoing to continue to develop treatment for this potentially devastating complication of DM.

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