Are You Overlooking Diabetic Neuropathy?

The increasing prevalence of diabetes may make this condition more common, but treating the associated pain remains a challenge. Here are the new rules for handling it in a clinical setting.

By Nathan Hall, Associate Editor

Diabetes may fall outside the practicing scope of neurology, but clinicians are likely to hear this condition mentioned quite often when taking a patient history. Data from the National Diabetes Information Clearinghouse show that the number of Americans diagnosed with diabetes mellitus went from 5.8 million in 1980 to 14.7 million in 2004. This number is expected to increase in the coming years as more of the general population ages and as more people become overweight.

The growing prevalence of diabetes will mean different things to different subspecialties. The vascular care community will likely think of the raised stroke risk, and the dementia care experts will likely continue to explore the possible link with memory and cognition. But general neurologists and pain management specialists alike may see an increase in diabetic peripheral neuropathic pain, a condition with an unknown pathogenesis and, until very recently, no definitive way to treat it.

This is not to say physicians are bereft of treatment options. In 2004 the FDA approved two medications for this condition—duloxetine (Cymbalta) and pregabalin (Lyrica)—and there are other off-label treat-

ments known to be effective for pain ranging from topical painkillers to anticonvulsants. While studies have shown some benefit to be had from many of these in mitigating diabetic neuropathic pain, the average clinician had no way of knowing how effective the options for this condition were without doing a thorough literature review.

In June 2005, 11 pain management experts convened in New Orleans to review the existing data and create strategies to address the pain associated with diabetic neuropathy. The committee analyzed the results of a literature review spanning 10 years to summarize the prevalence of diabetic peripheral neuropathy and diabetic peripheral neuropathic pain and the comorbidities associated with the condition, including quality-of-life effects and safety issues. To strengthen the clinical value of their recommendations, the committee members also shared their own real-world clinical experiences in managing diabetic peripheral neuropathic pain (DPNP). The consensus recommendations appeared in *Mayo Clin Proc. 2006;81(4,suppl)* and in *J Fam Pract. 2006;55(6):1-20* for the benefit of primary care practitioners, pain specialists, general neurologists and anyone else interested in helping a population with few apparent options.

Prevalence at a Glance

According to the National Diabetes Information Clearinghouse (part of the National Institutes of Health), in 2005 there were an estimated 20.8 million people in the United States with diabetes mellitus, including 6.2 million who have not yet received a diagnosis. Up to two-thirds of those with a diabetes diagnosis will also develop some diabetic peripheral neuropathy, and the most common neuropathy is diabetic peripheral neuropathy. Eleven percent of these patients will experience diabetic peripheral pain; most patients with diabetic peripheral neuropathy will only experience a lack of sensation, and why some feel pain instead of nothing remains a mystery.

To make the presentations more mysterious, diabetes-associated neuropathies take many different forms. These are often classified as generalized symmetrical polyneuropathies and focal or multifocal neuropathies. Diabetic peripheral neuropathy would fall under the symmetrical category along with acute sensory neuropathy and autonomic neuropathy but is differentiated during a clinical exam. When it comes to specifically diagnosing diabetic neuropathic pain, it's important to consider several conditions with similar presentations such as claudication, morton neuroma, Charcot neuroarthropathy and vitamin B12 deficiency (the guidelines offer a full table of other possibilities and their differentiating features). These also include other sources of neuropathy and non-neuropathic conditions, including malignant disease, toxic causes and infections.

By the time the patient presents to a neurologist, though, he or she will likely already have a diagnosis and some stories about why the most obvious treatment choices were unsuccessful. B. Eliot Cole, MD, one of the guidelines' authors, says that primary care physicians and family doctors care for most patients with diabetic peripheral neuropathic pain. "Usually, by the time the pain management specialist sees the refractory patient, he or she will have failed a few trials," he says.

Top Tier for Treatment

The DPNP guidelines are the first standardized rules for treating this condition. Co-author David Fishbain, MD says that before these recommendations, "physicians just handled the condition in a way the literature indicated that they should."

Another of the guidelines' authors, Charles Argoff, MD, says evidence-based guidelines provide practitioners with the best guidance based on the available data for treating this condition, including how to evaluate the clinical trial data of some treatments compared to the FDA-approved ones. "The strength of evidence required for a drug to be FDA approved today is far greater than what it was 20 years ago; thus, when choosing an agent, the neurologist must take this into account," he says. "With newly approved agents such as duloxetine and pregabalin, as well as established agents for which there is reasonable evidence of efficacy, neurologists must realize just how many options there are for their patients."

To create the guidelines, the authors reviewed the existing literature and found, according to Dr. Fishbain, many studies of neuropathic pain but relatively few that specifically looked at diabetic peripheral neuropathic pain. Nevertheless, they found enough to create the recommendations for first- and second-tier treatments for this condition. Those considered to be first-tier treatments have two or more randomized controlled trials confirming their efficacy for use in diabetic peripheral neuropathy; the second tier consists of treatments with one successful randomized control trial for this specific condition and favorable results in one or more trials with other painful neuropathies. The guidelines also include topical treatments that have proven effective in alleviating the pain and other agents that have shown efficacy in other forms of painful neuropathy or in less well-controlled or open-label trials with diabetic peripheral neuropathic pain.

The consensus recommendations classify treatment options as follows:

First Tier: duloxetine, oxycodone CR, pregabalin and tricyclic antidepressants

Second Tier: carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine ER

Topical: capsaicin, lidocaine

Other: bupropion, citalopram, methadone, paroxetine, phenytoin, topiramate

Of course, there are many other factors to weigh when selecting a treatment such as comorbidities, drug interactions, adverse

A Look into the Pain Relief Pipeline

All chronic pain conditions will have their share of refractory cases in which no medical intervention seems to work and patients who wonder if the adverse effects outweigh the pain relief. Seventy-seven percent of the respondents in the Voices of Chronic Pain Survey from the American Pain Foundation said they are looking for new options to treat their pain; only 14 percent reported being satisfied with their current medications. The study did not specify how many of these were diabetic neuropathy patients, but it's a safe bet that a sizeable number of them are looking for a more effective treatment.

At present there are only two treatments specifically FDA-approved for DPNP, and now that the patents have expired on the tricyclics these aren't likely to be submitted to the FDA for consideration. But there are some new prospects in development, including:

- Dextromethorphan and quinidine sulfate (Neurodex), from Avanir Pharmaceuticals. The manufacturer initiated the three-month multi-center phase III trial for this treatment in pain relief for adult patients with distal symmetrical diabetic neuropathy with daily pain in the lower extremities.
- SB-509 from Sangamo BioSciences. This treatment recently yielded positive results in a phase I trial and attempts to treat the condition by up-regulating the expression of the gene encoding vascular endothelial growth factor in patients.
- TRO19622 from Trophos SA. This treatment successfully completed a phase I trial for ALS and the manufacturer will soon initiate a phase II trial to explore its efficacy in diabetic peripheral neuropathic pain.
- Alpha lipoic acid, an antioxidant, showed promise in a European study *(Diabetes Care 1999;22:1296-1301)*. However, it was administered intravenously in this trial, so there is no evidence to support the use of over-the counter oral supplements of this substance.

event profiles and sometimes cost. As Dr. Fishbain says, "Physicians should understand the circumstances and limitations, but the fact that there are now first-tier treatments is an improvement." The two FDA-approved treatments for this condition are in the first tier for reasons that go beyond their clinical data. "When choosing an analgesic, one looks for an agent that is effective, has a favorable side effect profile and is not so costly that its use may be prohibitive," says Dr. Argoff. "These two agents fit this description."

This distinction is also important, Dr. Argoff says, when differentiating duloxetine from other antidepressants such as the tricyclics. "While the tricyclics have been shown in general to be effective for the treatment of various types of neuropathic pain, and while their cost is generally reasonable, their side effects—including anticholinergic effects, weight gain, and cardiovascular issues—make them difficult to use," he says.

Dr. Cole adds that while the data for tricyclics are favorable, this drug class does not have FDA approval for DPNP and will likely never get it because all are available generically. He also says that some of these may have contraindications; for example, amitriptyline should not be used on patients aged 65 years and over. "We're not endorsing all tricyclics be used," he says.

Another first-tier treatment, oxycodone CR, is approved for treating pain but not specifically for diabetic peripheral neuropathic pain. It earned its place in the recommendations by proving effective for controlling pain in two randomized controlled trials specifically for this condition, although there were high rates of adverse effects. Since this agent is relatively controversial due to the potential for addiction, the guidelines recommend evaluating the patient for warning signs of possible abuse and discussing the pros and cons of using an opioid analgesic. If it is decided to be the best possible treatment, it may still prove useful to get an opioid agreement signed by the patient and the physician that specifies the risks and responsibilities.

In addition to the recommendations above, the guidelines note that many patients use and perceive benefit from complementary approaches, although there are no good data that these are effective. Since some of these have little or no risk and low cost but no proven efficacy while others have high costs, high risks and no evidence (such as spinal cord stimulation), it is best to review the risks, costs and evidence with patients and try to discourage them from the more potentially harmful options. Traditional Chinese acupuncture falls somewhere between the two extremes, as it has shown some slight benefit of analgesic efficacy in studies and has minimal but not insignificant risks.

After a therapy is started, the guidelines recommend asking the patient at each visit if the pain is improved and, if so, to what degree, if the nature has been changed; if their physical or social function has changed; and if they have any adverse effects from the treatment. The patient should ultimately be asked if he or she is satisfied with the treatment. If the answer is no, he or she should be offered the option to add another agent but also told that increased risk may come with more potential adverse effects.

Patients who do not respond to first-line treatments or find the adverse effects unacceptable may need to have their regimen modified. In this situation, the guidelines recommend the following steps:

- Switch to another first-line agent with a different mechanism of action.
- Change to a second-line agent with a different mechanism of action.
- Add a different first or second agent using the principles of rational polypharmacy.

The primary goal of treating diabetic neuropathic pain is to

Table 1. Factors to Consider in Choosing First-Tier Agents

The first-tier agents are duloxetine, oxycodone controlled release (CR), pregabalin and tricyclic antidepressants (TCAs).

Factor	Avoid	Recommended
Medical Comorbidities:		
Glaucoma	TCAs	Any other first-tier agent[1]
Orthostatic phenomena	TCAs	Any other first-tier agent
Cardiac or electrocardiographic abnormality	TCAs	Any other first-tier agent
Hypertension	TCAs	Any other first-tier agent
Renal insuffiency		Any first-tier agent[2]
Hepatic insuffiency	Duloxetine	Any other first-tier agent
Falls or balance issues	Pregabalin, TCAs	Any other first-tier agent
Psychiatric Comorbidities:		
Depression[3]	Oxycodone CR, pregabalin	Duloxetine, TCAs
Anxiety	Oxycodone CR	Any other first-tier agent
Suicidal ideation	TCAs, oxycodone CR	Duloxetine, pregabalin
Somatic Issues:		
Sleep		Any first-tier agent
Erectile dysfunction	All first-tier agents	Second-tier agent venlafaxine
Other Factors:		
Cost	Duloxetine, pregabalin	TCAs, generic oxycodone CR
Drug interactions	Duloxetine, TCAs[4]	Oxycodone CR, pregabalin
Weight gain	TCAs, pregabalin	Duloxetine, oxycodone CR
Edema	Pregabalin	Any other first-tier agent

1. Duloxetine is contraindicated only for patients with uncontrolled narrow-angle glaucoma and may be appropriate for other patients with glaucoma.
2. Dosage adjustment of oxycodone CR and pregabalin is recommended for patients with a creatinine clearance of 60ml/min. Duloxetine is not recommended for patients with a creatinine clearance less than 30ml/min.
3. Before initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk of bipolar disorder.
4. Consult prescribing information for individual agents concerning specific drug-drug interactions and contraindications.

Source: Argoff, CE, Backonja M, Belgrade MJ, Bennett GJ, Clark MR, Cole BE, Fishbain DA, Irving GA, McCarberg BH, McLean MJ. Consensus guidelines: treatment planning and options. Mayo Clin Proc April 2006;81(4, suppl):S12-S25.

achieve zero pain; however, the guidelines caution, "be realistic." Taking a real-world approach, though, does not mean the physician should be any less aggressive when pursuing this goal. Rather, remember that few patients will achieve 100 percent pain relief and some may need therapy with multiple agents. The secondary goal is to restore or improve the functional measures in the quality of life, which is important but not a substitute for pain relief.

A Patient Partner

One point the guidelines put a great deal of emphasis on is the need to make patients partners with their physicians when managing their disease. This is true not only for diabetes as a whole but also for diabetic peripheral neuropathic pain. Glycemic control remains very important, and if not achieved, advanced diabetes-related problems can develop over time, including diabetic peripheral neuropathy. This, in turn, can lead to several quality-of-life issues and safety concerns.

To this end, the guidelines emphasize the need for the physician to establish a good relationship with the patient. A large part of this is making the patient understand that pain is not a punishment for not complying with the pharmacological regimen or diet. Physicians should also look for "catastrophizing," a cognitive factor that can raise the risk of disability, and measure this with the Pain Catastrophizing Scale. Patients should also be educated about proper foot care, including to wash their feet twice daily and check for redness, blistering, skin breakdown, or change in sensation.

Exactly how involved the neurologist or pain expert is in managing diabetes varies widely, depending on referral patterns/practices and how interested he or she is in "treating" a patient, according to Dr. Argoff. "Enormous opportunities exist for a neurologist to become involved in the overall management of their patient, though I suspect that most of us would want to focus on the neurological management issues and not get involved with the general management of the patient's diabetes," he says.

Whatever role the neurologist has in the patient's treatment program, he or she may be the one who gives the patient some hope. Dr. Cole says there are a number of studies underway that are searching for the still-unknown pathogenesis behind diabetic peripheral neuropathic pain, and these may lead to treatments that specifically treat this condition in the coming decade. For those intractable patients who present to a neurologist after failing the first-tier treatments prescribed by a GP, it may be best to tell them, "It's not as grim as you thought." **PN**