Diabetic Neuropathic Pain Requires Perseverance

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Most patients with diabetic peripheral neuropathic pain will experience significant relief and improved quality of life when treated with tricyclic antidepressants, duloxetine, controlled-release oxycodone, pregabalin, or a combination of these agents, according to new treatment guidelines issued by the American Society of Pain Educators.

Treatment strategies should begin with these drugs, which have already been proved effective in the disorder, and take into account physical and psychiatric comorbidities, adverse event profiles, and cost, according to the guidelines (Mayo Clin. Proc. 2006;81[4 Suppl]:S12-25).

Almost all patients with diabetic peripheral neuropathic pain (DPNP) will improve if they and their physicians are patient and persistent, said Dr. B. Eliot Cole, executive director of the American Society of Pain Educators and chairman of the panel that created the guidelines.

Problems arise when both parties become frustrated over nonresponsiveness to initial therapies, Dr. Cole said. Overcoming this attitude will go a long way toward improving treatment outcomes. Since the approval of several agents specifically for treatment of DPNP, and with the judicious use of older agents, DPNP is far from being the untreatable problem many believe it to be, he said in an interview.

If the first treatment doesn't work, another probably will. It is also important to instill realistic expectations, noted Dr. Cole. "Of course our goal is always 100% freedom from pain, but the reality is that most patients probably won't experience that. We can, however, put together plans that are easy to follow and have low side effects, which significantly increase compliance and the chances of pain control."

Undertreatment is probably the biggest obstacle to success, he said. "The majority of diabetics with pain are taking over-the-counter nonsteroidal anti-inflammatories as their primary form of treatment. Many physicians might not know that those drugs are totally ineffective for DPNP."

Even those who receive prescriptions appear to be undertreated, according to a 2004 study cited in the guidelines. Of 55,686 DPNP patients, 53% were getting only a short-acting opioid and 40% an NSAID. Other commonly prescribed drugs included benzodiazepines and SSRIs (J. Pain 2004;5:143-9), neither of which are effective for neuropathic pain, said Dr. Cole.

In constructing the guidelines, the committee reviewed 120 drug studies published in 1995-2005. The studies included those specific to DPNP as well as studies of other neuropathic pain conditions.

Duloxetine, controlled-release oxycodone, pregabalin, and tricyclic antidepressants, having the strongest evidence of efficacy, are the committee's first-tier drug treatment choices, each having more than two positive randomized, controlled trials specific for DPNP, according to the new guidelines.

Duloxetine and pregabalin are the only drugs approved for DPNP. With duloxetine, more than 50% of patients can expect at least a 50% decrease in pain. Its effects are rapid, usually occurring within 1 week. Advantages include once-daily dosing and antidepressant efficacy.

The guidelines go on to note that pregabalin, especially at its higher doses, can decrease pain by 70% or greater in at least 30% of patients, and by 50% in at least 50% of patients. Patients should notice its effects within 1 week. Side effects of somnolence and dizziness can be bothersome, however.

The tricyclics amitriptyline and desipramine are also effective, although they are not tolerated as well as duloxetine, according to the guidelines. In two DPNP trials, controlled-release oxycodone significantly reduced all measures of pain. However, it's important to evaluate each patient's potential for abuse before prescribing the drug.

Second-tier agents—with one randomized, controlled trial for DPNP and at least one trial in another painful neuropathy—include carbamazepine, gabapentin, lamotrigine, tramadol, and extended-release venlafaxine.

The guidelines committee also reviewed the evidence for topical treatments (capsaicin and lidocaine) and the evidence for bupropion, citalopram, methadone, paroxetine, phenytoin, and topiramate, none of which have been studied for treating DPNP. However, each has at least one randomized, controlled trial in other painful neuropathies.

To reap maximum benefit, first-tier agents should be aggressively dosed, but physicians shouldn't waste a lot of time waiting for results, according to the guidelines. "First-tier agents should be titrated to maximum tolerated dose. A reduction in pain of at least 50% from baseline should be expected if the agent is effective for that patient." If there are no significant results by 3 weeks, a modification of therapy is warranted.

Once therapy is initiated, patients should undergo regular follow-up. "Patients must be asked at each visit whether their pain is improved and, if so, to what degree. …If they are not satisfied with the treatment effect, they should be offered the option to add therapy, along with an explanation that they may receive more relief at the expense of more potential adverse events," according to the guidelines.

When adding an agent, it's best to prescribe a drug that has a different method of action rather than just adding another similar drug, Dr. Cole said. "We're looking for the synergistic effect, not the additive effect. We hope 1 plus 1 will equal 3."

The guidelines will be a valuable resource not only for neurologists, but also for family physicians, internists, and psychiatrists, all of whom are called upon to treat DPNP in a busy clinical practice—a venue that makes it tough to give these patients the time and attention they need, he said.

"Pregabalin and duloxetine are very easy to work with," Dr. Cole said. "They have one starting dose; you follow an easy progression of titration, and within 2-4 weeks, you know if it's going to be effective. It doesn't take 6 months to know if you're on the right track, and that's very helpful for a busy clinician."

Dr. Cole receives honoraria from Eli Lilly & Co. and Endo Pharmaceuticals. ■

Prescribing Recommendations for DPNP Drugs

Comorbidity	Recommended	Avoid
Medical		
Cardiac or EKG abnormality	Any other first-tier agent	TCAs*
Falls/balance problems	Any other first-tier agent	Pregabalin, TCAs*
Glaucoma	Any other first-tier agent	TCAs*
Hepatic insufficiency	Any other first-tier agent	Duloxetine
Hypertension	Any other first-tier agent	TCAs*
Orthostatic phenomenon	Any other first-tier agent	TCAs*
Psychiatric		
Anxiety	Any other first-tier agent	Oxycodone CR
Depression	Duloxetine, TCAs*	Oxycodone CR, pregabalin
Suicidal ideation	Duloxetine, pregabalin	TCAs*, oxycodone CR
Somatic		
Erectile dysfunction	Venlafaxine	All first-tier agents
Other Issues		
Affordability	TCAs, generic oxycodone CR	Duloxetine, pregabalin
Drug interactions	Oxycodone CR, pregabalin	Duloxetine, TCAs*
Edema	Any other first-tier agent	Pregabalin
Weight gain	Duloxetine, oxycodone CR	TCAs*, pregabalin

*Tricyclic antidepressants.

Source: Consensus Guidelines for the Treatment of Diabetic Peripheral Neuropathic Pain (Mayo Clin. Proc. 2006;81[4 Suppl.]:S12-25)

Guidelines Advise Monitoring Diabetics for Chronic Kidney Disease

BY SARAH PRESSMAN LOVINGER
Contributing Writer

CHICAGO — Guidelines developed for the first time by the Kidney Disease Outcomes Quality Initiative provide detailed information on how to improve clinical outcomes in patients who have both diabetes and chronic kidney disease, Dr. Robert Nelson said at a meeting on clinical nephrology sponsored by the National Kidney Foundation.

The guidelines emphasize tight control of glucose, blood pressure, and lipids, along with frequent monitoring of urinary protein in patients with this dual condition. Dr. Nelson of the National Institutes of Health in Phoenix offered a preview of the guidelines, which will be published in the American Journal of Kidney Diseases this fall.

The Kidney Disease Outcomes Quality Initiative guidelines recommend that people with type 1 diabetes undergo screening for diabetic kidney disease 5 years after diagnosis, and then annually. In type 2 diabetics, annual screening should begin at diagnosis.

Primary care physicians can easily follow these guidelines by obtaining spot urine samples for an albumin/creatinine ratio—at least two samples within 3 months, Dr. Nelson noted.

If the urine albumin/creatinine ratio exceeds 300 mg/g, a number that is consistent with macroalbuminuria, then the physician can diagnose diabetic kidney disease without doing a renal biopsy.

In addition, patients with microalbuminuria who also have retinopathy are considered to have diabetic kidney disease.

Clues to the diagnosis of nondiabetic kidney disease in diabetic patients include lack of diabetic nephropathy, a rapid decrease in glomerular filtration rate, and sudden onset of nephropathy.

Solid research evidence shows that the cornerstone of managing patients with diabetic kidney disease is maintaining a target hemoglobin A_{1c} of 7% or below, Dr. Nelson said, citing the Diabetes Control and Complications Trial (N. Engl. J. Med. 1993;329:977-86).

Physicians must also manage hypertension aggressively in patients with diabetic kidney disease. Both ACE inhibitors and angiotensin-receptor blockers (ARBs), often given with a diuretic, can help patients achieve the goal blood pressure of 130/80 mm Hg or lower.

"We believe that the efficacy of ACE inhibitors and ARBs are similar," Dr. Nelson said.

Achieving the blood pressure goal is a very important preventive measure, and clinicians can use additional classes of antihypertensive medication as needed to meet this goal. ■