

New AAN Guidelines on Painful Diabetic Neuropathy

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April 11, 2011 (Honolulu, Hawaii) — The American Academy of Neurology has released new guidelines on the treatment of painful diabetic neuropathy (PDN).

The document provides evidence-based guidance on use of a range of pharmacologic agents, including anticonvulsants, antidepressants, opioids, and others, as well as nonpharmacologic treatments, such as transcutaneous electrical nerve stimulation (TENS) and magnetic field treatment.



Dr. Vera Brill

“We were pleased to see so many of the pain treatments had high-quality studies that support their use,” said Vera Brill, MD, from the University of Toronto, Ontario, Canada, lead author of the guidelines. “Still, it is important that more research be done to show how well these treatments can be tolerated over time, since diabetic nerve pain is a chronic condition that affects a person’s quality of life and ability to function.”

The guidelines are published online April 11 in *Neurology* and were presented here at the American Academy of Neurology 63rd Annual Meeting. They were developed in collaboration with the American Association of Neuromuscular and Electrodiagnostic

Medicine and the American Academy of Physical Medicine and Rehabilitation; the document will appear in the April issues of their respective journals, *Muscle and Nerve* and *PM&R*.

Unreported, Untreated

It is estimated that PDN affects 16% of the more than 25 million people who have diabetes in the United States, the authors point out. The condition is “often unreported and more often untreated, with an estimated 2 out of 5 cases not receiving care,” Dr. Brill noted.

“As we emphasize the use of evidence-based guidelines to treat different disorders, it becomes clear that this field is very confusing because of the volume of literature,” Dr. Brill told a press briefing here. “So the guidelines have been developed and will provide a framework for physicians to use when treating their patients. Physicians can understand what the evidence is for the treatments they’ll use; when there is evidence, when there isn’t, or when the evidence is negative.”

The process started in 2007, with more than 2200 papers on PDN; of these, 463 were deemed relevant to the guidelines. Author teams reviewed these papers and identified 79 considered “highly pertinent” to the guideline. Each of these reports was rated by teams of 2 with regard to class of evidence for effectiveness, and disagreements were arbitrated by a third member.

The only drug to earn a “Strong Evidence, Level A” rating was pregabalin, but several drugs and nonpharmacologic interventions met criteria for “Moderate Evidence, Level B” endorsement.

That only 1 drug met this level of evidence was a bit of a surprise, Dr. Brill noted. “One of the big factors that moved a study from class I to class II is that you needed at least 80% of the people in the study to complete the study,” Dr. Brill said, and 2 class I studies were required for a Level A recommendation.

“I can tell you there was discussion internally about the rules because of the way it fell out, but it would be a little strange to be changing your rules for guidelines because of the findings in 1 guideline process,” she said. “The others are Level B mostly because they didn’t get 80% completing their studies.”

The level of evidence is not driven by the effect size of the drug, she noted. “So pregabalin has a small effect on pain, but the studies were class I, and you could say people tolerated the treatment and stayed in” the pregabalin studies, Dr. Brill added. “So you can’t make assumptions and change the rules because of what you’re finding.”

They also provide the recommended doses of agents considered useful in the document.

Strong Evidence (Level A)

- ◆ Pregabalin should be offered “if clinically appropriate.”

Moderate Evidence (Level B)

- ◆ Anticonvulsants gabapentin and sodium valproate should be considered for PDN treatment. The authors note though that because valproate is potentially teratogenic, it should be avoided in diabetic women of child-bearing age, and due to its potential adverse effects of weight gain and worsening of glycemic control, “this drug is unlikely to be the first treatment choice for PDN.”
- ◆ Anticonvulsants oxcarbazepine, lamotrigine, and lacosamide should probably not be considered.
- ◆ Antidepressants amitriptyline, venlafaxine, and duloxetine should be considered; however, “data are insufficient to recommend one of these agents over the others,” they note.
- ◆ Opioids dextromethorphan, morphine sulphate, tramadol, and oxycodone should be considered for the treatment of PDN, they note. Again data were insufficient to recommend one of these over the others.

They note that the use of opioids for chronic nonmalignant pain has “gained credence over the last decade due to the studies reviewed in this article.” Both tramadol and dextromethorphan were associated with substantial adverse events, including sedation with both agents and nausea and constipation with tramadol. The use of these agents can also be associated with development of novel pain syndromes, such as rebound headache, the authors note, and long-term use can lead to tolerance and frequent escalation of dose.

- ◆ For other pharmacologic interventions, they recommend that capsaicin cream and isosorbide dinitrate spray be considered to manage PDN, although they note that many patients can be intolerant to the adverse effects of capsaicin, which include burning pain on contact with warm or hot water or in hot weather.
- ◆ Clonidine, pentoxifylline, and mexiletine, on the other hand, should “probably not” be considered for use.
- ◆ For nonpharmacologic treatments, they recommend that use of TENS be considered but “probably not” electromagnetic field treatment, low-intensity laser treatment, or Reiki therapy.

Weak Evidence (Level C)

- ◆ They found weak evidence that adding venlafaxine to gabapentin may provide a better response and that the Lidoderm patch may be considered to treat PDN.

Insufficient Evidence (Level U)

- ◆ The authors found insufficient evidence to “support or refute” use of the anticonvulsant topiramate; the antidepressants desipramine, imipramine, and fluoxetine; or the combination of nortriptyline and fluphenazine.
- ◆ Similarly, there was insufficient evidence either way on the use of vitamins and α -lipoic acid or the combination of amitriptyline with electrotherapy for treatment of this condition.

Placebo Effect

In their summary document, the authors point out as “notable” that the placebo effect varied from 0% to 50% pain reduction in the studies reviewed for this guideline.

“The panel recognizes that PDN is a chronic disease and that there are no data on the efficacy of the chronic use of any treatment, as most trials have durations of 2 to 20 weeks,” they write. “It is important to note that the evidence is limited, the degree of effectiveness can be minor, the side effects can be intolerable, the impact of improving physical function is limited, and the cost is high, particularly for novel agents.”

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