New ADA Guidance Charts Success, Failure in Diabetic Neuropathy
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Notably missing from the first US guidelines to address diabetic neuropathy in more than a decade is any recommendation for disease-modifying treatments, since none are currently approved by the US Food and Drug Administration (FDA).

Indeed, many candidate drugs for diabetic neuropathy have failed in trials, and one of the new guideline authors believes novel end points — particularly measures of small-nerve fiber damage and repair — that could better assess a potential drug's efficacy need to be employed in clinical studies.

Coauthor Rayaz A Malik, MBChB, FRCP, PhD, of Weill Cornell Medicine-Qatar, Doha and New York, told Medscape Medical News, "As a clinician, I'm frustrated that current drugs have no benefit for the underlying nerve damage. We have witnessed failure after failure of clinical trials of disease-modifying drugs, because the end points are not fit for that purpose."

Such assessments of small-nerve fiber damage should also be used for earlier diagnosis of diabetic neuropathy, says Dr Malik.

"Although about 20% of patients have painful neuropathy and can present to their doctor, the majority have painless neuropathy, which is silent and is diagnosed only when it is too late and the patient has already developed a foot ulcer," he continued.

"Given that the 5-year mortality of a patient with a foot ulcer is worse than most cancers, there is a need to identify early neuropathy. Yet currently advocated tests, like the monofilament, identify only patients with advanced neuropathy. Why do we have robust methods for detecting early retinopathy and nephropathy, but not neuropathy?"

Published in the January issue of Diabetes Care, the new ADA position statement revises ADA's last neuropathy guideline, published in 2004.

The new document covers prevention and management of distal symmetric polyneuropathy (DSPN), diabetic autonomic neuropathies including cardiovascular autonomic neuropathy (CAN), as well as less common forms of neuropathy.

The aim is to provide state-of-the-art information for clinical management of the condition but to also acknowledge the current lack of disease-modifying drugs.

Most Patients Don't Need Sophisticated Testing or Opioids

Lead author of the new guidelines, Rodica Pop-Busui, MD, PhD, of the University of Michigan, Ann Arbor, told Medscape Medical News that there are two key clinical messages in the new document: the first is that electrophysiologic testing or referral to a neurologist is rarely needed for diagnosing neuropathy and the second is that opioids for the pain of diabetic neuropathy should be considered only as a very last resort and not as first- or second-line therapy.

"The purpose of the document is to provide clinicians with evidence-based tools to understand how to diagnose, monitor, and manage some of the aspects related to diabetic neuropathy….It provides a tool to help them confidently diagnose neuropathy on their own and avoid expensive unnecessary tests or referrals," Dr Pop-Busui said.

The statement also covers neuropathy prevention, including glycemic control and lifestyle modification. Assessment for DSPN, the document advises, should be undertaken at diagnosis of type 2 diabetes, 5 years after diagnosis of type 1 diabetes, in those with prediabetes and symptoms of peripheral neuropathy, and every year thereafter.

Modalities for assessment should include careful history and either temperature or pinprick sensation to assess small-fiber function, along with tuning fork for vibration sensation, and 10-g monofilament testing for ulceration risk.

Electrophysiologic testing or referral to a neurologist is rarely necessary, except in atypical situations.
"There were several neurologists on the writing group, in addition to endocrinologists. We reached the same conclusion — that referral is not needed for typical cases of diabetic neuropathy — and we have provided a stepwise approach to get an idea of whether a patient has typical symptoms and signs," Dr Pop-Busui noted.

For treating neuropathic pain, the document advises the FDA-approved pregabalin or duloxetine as first-line treatment and various nonapproved agents, including gabapentin or tricyclic antidepressants, as second-line. Due to the high risks of addiction and other complications, opioids are advised only for patients with severe pain who don't respond to other medications, and referral to specialized pain clinics is advised in such cases.

Recommendations are also provided for assessment of cardiovascular, gastrointestinal, and urogenital autonomic neuropathies in patients with microvascular and neuropathic complications.

Included are considerations for excluding other conditions or drug effects that could be mimicking the symptoms, use of short-term metoclopramide for treatment of gastroparesis, assessment of patient-specific neuropathy-related end points, such as falls and mobility, and assessment of less common neuropathies.

"Hopefully readers will find this document very useful. We tried to make it very easy to read, with pearls that are all evidence-based….We want to give them the tools to be able to see a complicated patient with diabetic neuropathy relatively easily in their office," Dr Pop-Busui explained.

**Why Aren't There Any Drugs to Treat Neuropathy?**

In the document's final section "Neuropathy Clinical End Points for Research and Clinical Trials," the authors point out that "multiple clinical trials for these conditions have failed."

They cite as contributing factors "a lack of agreement and uniformity in the use of the most sensitive DSPN measures that capture the natural history of the disease and detect repair in the specific nerve-fiber populations, as well as the inclusion of appropriate patient populations."

For DSPN drug trials in particular, the statement recommends the use of validated clinical instruments for assessing symptoms and disability, along with advice to "consider" using electrophysiology and measures of small-fiber damage and repair, such as intraepidermal nerve-fiber density or corneal confocal microscopy.

Dr Malik has long maintained that one of the main impediments to better neuropathy treatment in both clinical practice and research has been the focus on measures of symptoms and large-fiber dysfunction, rather than assessment of small-fiber damage and repair that occurs earlier and could therefore serve as a more appropriate target for early intervention and for the development of drugs to treat neuropathy.

"I honestly believe there are many drugs that have failed because of this. If you test small fibers they repair sooner than large fibers. If you do a clinical trial lasting only 1 or 2 years you actually might not see the benefit of that drug because you're not looking at the small fibers….Big Pharma has invested huge amounts of money in disease-modifying drugs, but they've all failed," Dr Malik asserted.

He blames advisors to the FDA for not "moving away from symptoms, signs, and neurophysiology" and for not allowing small-fiber assessment to be at least a secondary end point in drug trials "to give disease-modifying therapies a fighting chance."

He believes that many promising drugs like the aldose reductase inhibitors, nerve growth factor, C-peptide, and the novel investigational peptide ARA 290 (Araim Pharmaceuticals) could well be approved for DSPN if small-fiber evaluation were included as an end point.

However, Dr Pop-Busui pointed out, other candidate drugs have failed due to toxicity — notably the aldose-reductase inhibitors — although one of those (epalrestat) is currently licensed for DSPN in some countries in Asia.

Also, she noted that there has been difficulty in identifying an appropriate animal model for human diabetic neuropathy.
"We are working very hard to try to identify the right targets that can be developed into more successful phase 2 and phase 3 trials….This is a very complex question," she said.

What's the Best Tool for Research and Clinical Practice?

Dr Malik has conducted extensive research demonstrating the utility of corneal confocal microscopy, a tool originating from ophthalmology that has been shown to predict the development of peripheral neuropathy in patients with diabetes and even prediabetes.

Corneal confocal microscopy could serve both clinically and as a surrogate end point in clinical trials as a noninvasive alternative to skin biopsy for the assessment of early small-fiber damage and repair. This is the type of tool needed for drug development, he believes.

"No drug company is going to invest in a 5-year clinical trial. What you need is something that will give you a signal that nerves are beginning to repair within 12 months, which then allows you to continue and show that other tests like [quantitative sensory testing] and neurophysiology also improve," he explained.

"The monofilament and neurological examination are very good at picking up advanced neuropathy and identifying the high-risk foot but are terrible at detecting early neuropathy and indeed nerve repair," he added.

But such tools still play an important role in clinical practice, Dr Pop-Busui stressed.

"Some tools may be ancient but in fact provide extremely important information. These tools can be carried in a physician's pocket and used in a few minutes. Yes, we are using technology in many aspects of diabetes management, but in diabetic neuropathy, the clinical exam is very important."

And she pointed out that use of tools such as corneal confocal microscopy at this point is unlikely to change clinical practice.

"We don't have preventive treatments, so we wouldn't do anything different. We would still treat their glucose and other risk factors. We don't have other pathogenic treatments as we talk right now."

For the current document, she said, "The task given to us was to help physicians and patients to have the best effective care of the complication with all the information critically evaluated. In medicine things change all the time. If the evidence changes, we will update the document."

FDA Still Working on Development Programs for Agents for DSPN

Both Drs Pop-Busui and Malik participated in a February 2013 FDA public workshop, "Clinical Development Programs for Disease-Modifying Agents for Peripheral Neuropathy."

In response to a Medscape Medical News query about the outcome of that meeting and the status of the end-points issue, an FDA spokeswoman responded: "The FDA has taken into account the information discussed at the 2013 public workshop and the comments received as we continue to work with industry on clinical development programs for disease-modifying products for the management of peripheral neuropathy. We will provide updates on this topic as appropriate."

The guidelines authors have no relevant financial relationships.

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