

# ADA Releases Diabetic Neuropathies Statement

The latest statement is based on two recent technical reviews.

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**T**he American Diabetes Association (ADA) has released a statement on diabetic neuropathies that defines and classifies the diabetic neuropathies, discusses epidemiology and management of the condition and provides recommendations for screening and treatment.<sup>1</sup> The statement is based on two recent technical reviews.<sup>2,3</sup>

Lead author Andrew J.M. Boulton, MD, FRCP, and colleagues wrote:<sup>1</sup> “The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system that present with clinical manifestations. They may be focal or diffuse.” Dr. Boulton is from the department of medicine, Manchester Royal Infirmary, Manchester, UK.

Coauthors of the statement include Arthur I. Vinik, MD, PhD, Strelitz Diabetes Institute, Eastern Virginia Medical School, Norfolk, Va, and Associate Medical Editor of *Diabetic Microvascular Complications Today*, Joseph C. Arezzo, PhD, department of neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY; Vera Brill, MD, department of medicine (neurology), University Health Network, University of Toronto; and Eva L. Feldman, MD, PhD, department of neurology, University of Michigan.

## MOST COMMON NEUROPATHIES

The statement explains that the most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and autonomic neuropathies. The authors outline five reasons for early recognition and appropriate management of neuropathy in diabetic patients:

- Nondiabetic neuropathies may be present in diabetic patients.
- A number of treatment options exist for symptomatic diabetic neuropathy.
- About 50% of patients with diabetes will develop neuropathy, and about 25% of those patients will experience no pain at all. Because >80% of amputations follow a foot ulcer or injury, early recognition of at-risk patients, providing education and appropriate care may reduce ulcerations and amputation.

- Autonomic neuropathy may involve every system in the body.

- Autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy is present.

The ADA statement said that an international definition of DPN is “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.” Dr. Boulton and colleagues emphasized that the diagnosis cannot be made without careful clinical examination of the lower limbs.

The diagnostic criteria of neuropathy include the sensory neuropathies, focal and multifocal neuropathies and autonomic neuropathies. Sensory neuropathy can either be acute or chronic. Acute sensory neuropathy is rare and usually follows a period of poor metabolic control or a sudden change in glycemic control. Chronic sensorimotor DPN is the most common presentation of neuropathy in diabetes. According to the ADA statement, up to 50% of patients may experience symptoms, which most frequently include burning pain, electrical or stabbing sensations, parasthesiae, hyperesthesiae and deep aching pain.

The diagnosis of DPN can only be made following a careful clinical examination. All patients with diabetes should be screened annually for DPN by examining pinprick, temperature and vibration detection threshold (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal halluces and ankle reflexes. Dr. Boulton and coauthors wrote that the feet should be examined for ulcers, calluses and deformities, and footwear should be inspected.

Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy (CIDP), occur more frequently in diabetes and should be ruled out.

Mononeuropathies may have sudden onset and can occur as a result of involvement of the media, ulnar, radial and common peroneal nerves. The ADA statement said that cranial neuropathies are extremely rare. Diabetic amyotrophy typically occurs in older type 2 diabetic patients. The statement noted that if unusually severe, predominant-

ly motor neuropathy and progressive polyneuropathy develops in diabetic patients, chronic inflammatory demyelinating polyneuropathy (CIDP) and spinal stenosis should be considered.

Diabetic autonomic neuropathy (DAN) results in significant morbidity and can even be fatal in some patients. Cardiovascular autonomic neuropathy (CAN) is the most prominent focus of autonomic dysfunction, according to the statement, because of its life-threatening consequences.

**CARDIOVASCULAR DISORDERS**

CAN is the most studied and clinically important form of DAN, and it can be indicated by resting tachycardia, orthostasis or other disturbances in the autonomic nervous system. CAN has caused sudden death and silent myocardial ischemia in diabetic patients. Because patient history and a

physical exam are ineffective for early detection of CAN, noninvasive tests that have proven effective are required (R-R variation, Valsalva maneuver and postural blood pressure testing). At the time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes, patients should be screened for CAN, the ADA statement said.

Gastrointestinal and genitourinary disturbances can occur in patients with DAN. Evaluations should be performed.

A minimum of one manifestation of DPN is present in at least 20% of the adult diabetic population, according to the ADA statement. It is associated with a number of both modifiable and nonmodifiable risk factors, including the degree of hyperglycemia, lipid and blood pressure indices, diabetes duration and height. Risk factors for DAN include diabetes duration, age and long-term glycemic control.

Among type 1 diabetic patients, the Diabetes Control

**TABLE 1. TREATMENT OF DIABETIC NEUROPATHY BASED ON PUTATIVE PATHOGENETIC MECHANISMS**

Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway <sup>i</sup>	Aldose reductase inhibitors Sorbinil Tolrestat Ponalrestat Zopolrestat  Zenarestat Lidorestat Fidarestat  AS-3201  Epalrestat	Nerve sorbitol <sup>h</sup>	Withdrawn (AE)
			Withdrawn (AE)
			Ineffective
			Withdrawn
			(marginal effects)
			Withdrawn (AE)
			Withdrawn (AE)
			Effective in RCTs, trials ongoing
Myo-inositol <sup>i</sup> Oxidative stress <sup>h</sup>	Myo-inositol alpha-Lipoic acid	Nerve myo-inositol <sup>h</sup> Oxygen free radicals <sup>i</sup>	Effective in RCTs, trials ongoing
			Marketed in Japan
Nerve hypoxia <sup>i</sup>	Vasodilators ACE inhibitors Prostaglandin analogs phVEGF <sub>165</sub> gene transfer	NBF <sup>h</sup>	Effective in one RCT
			Effective in one RCT
			RCTs ongoing
Protein kinase C <sup>h</sup>	Protein kinase C-beta inhibitor (ruboxistaurin)	Angiogenesis <sup>h</sup> NBF <sup>h</sup>	RCTs ongoing
			RCTs ongoing
C-peptide <sup>i</sup>	C-peptide	NBF <sup>h</sup>	Studies ongoing
Neurotrophism <sup>i</sup>	Nerve growth factor BDNF	Nerve regeneration, growth <sup>h</sup>	Ineffective
			Ineffective
LCFA metabolism <sup>i</sup>	Acetyl-L-carnitine	LCFA accumulation <sup>i</sup>	Ineffective
GLA synthesis <sup>i</sup>	gamma-Linolenic acid	EFA metabolism <sup>h</sup>	Withdrawn
NEG <sup>h</sup>	Aminoguanidine	AGE accumulation <sup>i</sup>	Withdrawn

AE adverse event; AGE advanced glycation end product; BDNF brain-derived neurotrophic factor; EFA essential fatty acid; LCFA long chain fatty acid; NBF nerve blood flow; NEG nonenzymatic glycation; RCT randomized clinical trial

and Complications Trial has shown that the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control. According to the statement, data for type 2 diabetic patients is much less strong but still suggest that optimal blood glucose control helps prevent DPN and autonomic neuropathy. While there have been no definitively positive prevention studies of other risk factor medications for DPN, the improvement of lipid and blood pressure levels, the avoidance of cigarette smoking and/or excess alcohol consumption are recommended.

**MULTIFACTORIAL PATHOGENESIS**

The pathogenesis of diabetic neuropathy is multifactorial, as demonstrated by conceptual animal model studies. However, work based on these concepts has been limited in patients; a summary of drugs that are being/have been studied in clinical trials are in Table 1.

The first step in treating symptomatic DPN is stable and optimal glycemic control. According to the statement, observational studies suggest that neuropathic symptoms improve with optimization of control and the avoidance of extreme blood glucose fluctuations. Pharmacological treatments are available for painful symptoms, although only two are specifically licensed for the management of painful DPN (Table 2).

Some agents may be used in combination for severe pain. All patients with DPN, whether or not they have symptoms, are at an increased risk of foot ulceration and should be considered for referral to a podiatrist and given foot care education.

In summary, the authors of the ADA statement said that all diabetic patients should maintain aggressive control of blood glucose, HbA1c, blood pressure and lipids with drug therapy and lifestyle changes.

**SCREENING**

With regard to screening: All patients with diabetes should be screened at diagnosis of type 2 diabetes and 5 years after type 1 diabetes diagnosis for chronic sensorimotor DPN. There should be annual examinations of sensory function in feet, and ankle reflexes should be checked.

**TABLE 2. ORAL SYMPTOMATIC RELIEF OF PAINFUL NEUROPATHY**

Drug class	Drug	Daily dose (mg)	NNT	NNH	Side effects
Tricyclics	Amitriptyline	25-150	2.4	2.7	++++
	Imipramine	25-150	2.4	2.7	++++
SSRIs	Paroxetine	40	ND	ND	+++
	Citalopram	40	ND	ND	+++
Anticonvulsants	Gabapentin	900-1,800	3.7	2.7	++
	Pregabalin	150-600	3.3	3.7	++
	Carbamazepine	200-400	3.3	1.9	+++
Opioids	Topiramate	up to 400	3.0	9.0	++
	Tramadol	50-400	3.4	7.8	+++
	Oxycodone CR	10-60	ND	ND	++++

Data are median (range) unless otherwise indicated. ND, not determined; NNH, number needed to treat to harm one patient; NNT, number needed to treat to achieve pain relief in one patient; SSRI, selective serotonin reuptake inhibitor.

One or more of the following can assess sensory function:

- pinprick,
- temperature, or
- vibration detection threshold (128-Hz tuning fork) or pressure sensation (10-g monofilament).

A history of neuropathic symptoms should be elicited and a careful clinical examination of feet and lower limbs should be performed. At each diabetes care visit, the feet should be examined for ulcers, calluses and deformities, and footwear should be inspected. Whether symptomatic or not, all DPN patients require foot care education and podiatric referral consideration.

For autonomic neuropathy, expert consensus says screening should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Heart rate variability should be used for screening, as it is the most standardized test. A history and an exam for signs of autonomic dysfunction should comprise screening. A negative screen should be repeated annually; if positive, appropriate diagnostic tests and treatments should be started. ■

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3. Boulton AJM, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies (Technical Review). *Diabetes Care*. 2004;27:1458-1486.