

# Treatment of Diabetic Peripheral Neuropathy

Nada M. Farhat, PharmD, and Krista L. Yezback, MSN, NP

## ABSTRACT

Peripheral neuropathy is a common complication among patients with diabetes. Although several treatment options have been studied for diabetic peripheral neuropathy, the most optimal regimen or combination of agents has yet to be determined. Based on current data and recommendations, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, and gamma-aminobutyric acid analogs are recommended first-line agents, whereas opioids and topical treatments are second-line options.

**Keywords:** diabetes, diabetic peripheral neuropathy, pain, painful diabetic neuropathy, pain management

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The prevalence of diabetes and related costs are expected to at least double in the next 2 decades, resulting in an increased number of related complications.<sup>1</sup> One of the most common diabetes-related complications is neuropathy, currently affecting at least 20% of adults with diabetes,<sup>2</sup> and eventually it will affect about half of all adult patients with diabetes.<sup>3</sup> Given the prevalence of diabetic peripheral neuropathy (DPN), nurse practitioners should be familiar with potential treatment options for this complication. Furthermore, DPN also has a significant impact on patient quality of life, morbidity, and mortality. In fact, DPN and related complications have an estimated annual cost between 4.6 and 13.7 billion dollars, using up to 27% of the direct medical costs of diabetes.<sup>4</sup>

## CLASSIFICATION

There are several types of diabetic neuropathy that can be further categorized by diffuse or focal neuropathy. Diffuse neuropathies are more common and progressive and include DPN and diabetic autonomic neuropathy.<sup>5</sup> Focal neuropathies such as mononeuropathy, radiculopathy, and cranial neuropathy are far less common and are usually self-limiting.<sup>5</sup> This article focuses on the treatment of the most common type of neuropathy, DPN, which is

also known as distal symmetric sensory or sensorimotor polyneuropathy. Specifically, painful diabetic neuropathy is addressed.

## PATHOPHYSIOLOGY

Both metabolic and vascular causes may be responsible for the development of DPN. Hyperglycemia is a major contributor in both type 1 and type 2 diabetes, and prolonged hyperglycemia can eventually lead to several manifestations of cellular damage. Other factors such as dyslipidemia, impaired insulin signaling, and metabolic syndrome may also be underlying mechanisms responsible for the development of DPN.<sup>3</sup>

## CLINICAL PRESENTATION

DPN is characterized by nerve damage in the feet and/or hands. Patients typically experience a burning sensation, tingling-like feeling of “pins and needles,” and/or an “electrical” pain in their feet but sometimes may experience just simple numbness.<sup>6</sup> Additionally, patients also describe a feeling of “wearing socks or gloves.” They may have hyperalgesia or allodynia, especially in their feet, with pain triggered by the slightest activity such as their feet touching a bedsheet. These hallmark symptoms aid in the diagnosis of DPN. Other typical symptoms include weakness in the muscles of feet and legs,

complaints of decreased dexterity, and feeling unsteady with standing or ambulation.<sup>7</sup>

Early symptoms such as pain, burning, and tingling are caused by small fiber involvement, whereas numbness and loss of protective sensation are caused by the involvement of large fibers.<sup>8</sup> When patients develop loss of protective sensation, this is usually an indication of distal sensorimotor polyneuropathy.

The lack of symptoms does not rule out neuropathy because a careful history and physical examination are essential. Early detection and prevention of complications with DPN are crucial, given that an estimated 50% of patients living with DPN may be asymptomatic.<sup>8</sup> The loss of sensory sensation may perpetuate the development of further complications because of open wounds on a patient's foot, for example, that may go unnoticed.

## DIAGNOSIS

A thorough history and physical examination can aid the health care provider with DPN screening and diagnosis. The American Diabetes Association is the leading professional resource that recommends "all patients should be assessed for DPN starting at diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes, and at least annually thereafter."<sup>8</sup> If neuropathy is present, a foot examination, which includes a visual, circulatory, and sensory assessment, should be performed at every office visit.<sup>7</sup>

## Objective Findings

During a bilateral foot examination, a provider should first inspect the patient's skin integrity for the presence of cracks, calluses, or ulcers and then evaluate the quality of pedal pulses, assess the temperature of the feet, and identify any bone and muscle deformities.<sup>8</sup> Additionally, a neurologic evaluation may be performed to assess a patient's ability of sensory perception, primarily with a 10-g monofilament test.

Monofilament testing will detect the loss of sensory perception in the patient's feet. Testing at many locations on the soles of the feet will help measure the degree of sensory loss. Semmes-Weinstein monofilament testing is among the safest and least expensive methods of DPN screening.<sup>9</sup> The tool is made of nylon, is user-friendly, and is recommended

as a valid tool for testing a patient's sensory perception.<sup>10</sup> Monofilament testing only assesses large fiber neuropathy and can mislead the provider from mild neuropathy caused by small fiber deficits.<sup>11</sup> In addition to monofilament testing, vibration perception with a 128-Hz tuning fork and ankle reflex testing may also be used to test for large fiber function.<sup>8</sup>

## Subjective Findings

Patients should be assessed for the presence of pain in their hands and/or feet, pain intensity, pain distribution, and the psychological and functional impact of pain. The assessment includes an 11-point pain scale, with 0 defined as no pain and 10 being the worst pain imaginable.<sup>12</sup> Quantifying a patient's pain perception will assist the provider in monitoring changes over time, as well as the effectiveness of certain interventions.

## Other Etiologies

Because neuropathic pain is subjective, the diagnosis of DPN is by exclusion when other causes of painful neuropathies are ruled out.<sup>8</sup> Nutritional deficiencies, chemical exposures, medications, or pressure on nerves can also cause neuropathy.<sup>13</sup> If the patient's skin integrity is altered and/or deformities are noted, an appropriate referral is warranted to address these issues. A weak or absent peripheral pulse would indicate a circulatory etiology and should be investigated further.

## TREATMENT

Optimization of glycemic control plays an important role in the progression of neuropathy. In patients with type 1 diabetes, optimization of glycemic control has been shown to effectively prevent or delay the development of neuropathy.<sup>8</sup> Unfortunately, the role of intensive glycemic control in patients with type 2 diabetes is less clear; however, there are data showing optimal glucose control may potentially slow the progression of neuropathy in these patients.<sup>8</sup>

Although several medications have been implicated for the treatment of DPN, there is limited clinical evidence to determine which agent is most effective, and there is no specific treatment to target the underlying nerve damage. Currently, the United

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