CHAPTER **41**

OVERVIEW ON THE TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY

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Diabetes mellitus is a serious condition affecting 9.3% of the American population for a total of 29.1 million people. As podiatrists, we work closely in the care of these patients and they represent a large percentage of our patient population. According to the Centers for Disease Control and Prevention, 60-70% of diabetics have some degree of nervous system damage ranging from mild to severe, and greater than 60% of nontraumatic lower limb amputations occur in the diabetic population. Our role as healthcare professionals is to recognize these at risk patients by being able to diagnose diabetic peripheral neuropathy (DPN) and treat it according to the recommended guidelines (1). Many treatment options are available and target different aspects of the problem, the underlying mechanism, the symptoms and quality of life, and the overall progression (2, 3).

Neuropathy has many etiologies including diabetes, alcoholism, vitamin deficiency, human immunodeficiency virus (HIV), hypoglycemia, hypothyroidism, chronic liver disease, carcinoma, sepsis, medications, and many others (4). An Italian study on chronic symmetric symptomatic polyneuropathy of the elderly identified diabetes as the most common independent associated factor and was present in 43.7% of their neuropathic sample (5,6). here are many types of diabetic neuropathies, which are separated in three broad categories: rapidly reversible, generalized symmetrical, and focal and multifactorial neuropathies. The type of diabetic neuropathy that we see and treat most commonly in our offices is the chronic sensorimotor neuropathy affecting small and large fibers, which is a type of symmetrical polyneuropathy. It has a stocking and glove distribution and causes sensory and motor symptoms such as pain, hyperesthesia, paresthesia, numbness, burning, and loss of balance and proprioception (2).

Dellon also identified that neuropathic symptoms could be caused by nerve compressions. Peripheral nerves in diabetics are more susceptible to compression due to their larger size and stiffness secondary to edema, binding of advanced glycosylation products, and inability to restore membranes at compression sites. This condition should be promptly identified, with its correlation to a positive Tinel's sign, in order to give the appropriate treatment of surgical decompression (7-9).

To have an accurate diagnosis of DPN, the first step is a thorough history and physical including identification of other risk factors for nerve damage such as medications, history of back injuries, or exposure to toxic substances. The physical examination should include deep tendon reflexes evaluation, vibratory sensation with 128 Hertz tuning fork, 2 point discrimination with 10 gram monofilament, temperature, and pinprick perception. Combination of more than one test has a sensitivity of greater than 87% in detecting DPN (2, 10). The Michigan Neuropathy Screening Instrument Form is a scoring algorithm that includes a questionnaire administered to patients and a lower extremity examination. It has been studied in the type 1 diabetic population and is considered a comparable tool with gold standard diagnostic testing (11). Nerve conduction velocity measures the conduction speed of large myelinated fibers and is a good tool in the diagnosis of peripheral neuropathy, however the results will typically remain normal when only small fibers are involved. To quantify the degree of small fibers that are affected, a 3 mm punch biopsy can be performed (4).

Our three goals in the treatment of diabetic neuropathy should be addressing the causative mechanism, relieving the symptoms, and preventing its progression (2). The Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications observational study demonstrated that intensive blood glucose control prevents and delays the progression of distal symmetrical polyneuropathy and cardiovascular autonomic neuropathy in a type 1 diabetic population (12). A prospective study performed by Tesfaye et al with a mean follow up of 7.3 years identified potentially modifiable risk factors for diabetic neuropathy. They determined that high LDL cholesterol and triglycerides, hypertension, smoking, a high body mass index, a high von Willebrand factor, and urinary albumin excretion rate were significant risk factors for diabetic neuropathy. They also emphasized that cardiovascular disease doubled the risk of neuropathy (13). Some of these risk factors are modifiable and should be addressed with a multidisciplinary approach.

Another strategy is the use of antioxidants. Chronic hyperglycemia seen in diabetics is responsible for oxidative stress and neuroinflammation, which leads to the development and progression of diabetic neuropathy (14). There are many trials on antioxidants in the literature, most of which have insufficient evidence to support or refute their usefulness. Alpha-lipoic acid has been approved by the Food and Drug Administration (FDA) for therapeutic

use as it was shown to relieve sensory and functional deficits in diabetic neuropathy with 600 mg/day intravenously over 3 weeks (14-16). Vitamin B and one of its derivatives, benfotiamine, have been studied in 13 trials and showed an improvement in vibration perception compared to placebo, but pain relief was less effective than alpha-lipoic acid (17). There is promising ongoing research showing that a deficiency in nerve growth factor and calcitonin gene-related peptide causes small fiber degeneration (2, 18). Further research is still in process on other types of growth factors, such as vascular endothelial growth factor, human hepatocyte growth factor, and islet neogenesis-associated protein (2).

There are three main classes of medications that are used for the control of symptoms of DPN and improvement in quality of life: anticonvulsants, antidepressants, and opioids. Some topical agents and adjunctive treatments are also available. Pregabalin (Lyrica) and Gabapentin (Neurontin) are the two main anticonvulsants that are recommended in the treatment of DPN by the American Association of Neurology (AAN) (19). Pregabalin is proven to significantly relieve pain while improving social functioning, mental health, vitality, and sleep with total daily dosing of 300 to 600 mg (19). It is the only anticonvulsant that is approved by the FDA and the European Medicines Agency (EMA) specifically for the treatment of diabetic neuropathy (20).

Pregabalin also has anxiolytic properties (20, 21). The dose titration can be done more rapidly than Gabapentin, thus the effects are visible faster (22). Possible side effects include dizziness, somnolence, peripheral edema, headaches, and weight gain (3). Pregabalin undergoes renal excretion, therefore the dose should be adjusted for patients with renal impairment in correlation with their creatinine clearance. It is also suggested that a supplemental dose should be given after hemodialysis in patients with end-stage renal disease in order to keep a steady state plasma concentration (23).

Gabapentin (Neurontin) significantly improves mental health, sleep, vitality, and has a small effect on pain with a dose from 900 to 3600 mg/day (19). Common side effects include somnolence, dizziness, confusion, ataxia, and weight gain (3). A study by DeToledo et al showed that more than 50% of their study group treated with Gabapentin gained 5% or more of their baseline body weight (24). Gabapentin is excreted by the kidneys so the dose should be adjusted for renal patients according to their creatinine clearance. Since hemodialysis decreases gabapentin concentration, a post hemodialysis dose should be given. Other anticonvulsants have been studied and used for DPN including sodium valproate (Depakote), but the evidence to support it as a first line treatment is insufficient (25).

Duloxetine (Cymbalta), Venlafaxine (Effexor), and Amitryptyline (Elavil) are the three main antidepressants recommended by many medical associations including the AAN (19). Duloxetine is the only antidepressant that has been approved for the treatment of diabetic neuropathy by the FDA and the EMA (20). This serotonin norepinephrine reuptake inhibitor (SNRI) has been proven to decrease pain and improve quality of life with a total daily dose of 60-120 mg (19). This medication has the advantage of requiring only a once-daily dose. It should be avoided in patients with insomnia as it is associated with increased wake and reduced total sleep time, however there is evidence that it improves central nervous system arousal and performance on sensory motor tasks during the daytime (25). It is a good option for a patient with other comorbidities such as depression or generalized anxiety disorder (20, 26). Common side effects are nausea, somnolence, dizziness, and anorexia (3). In some instances, it can cause duloxetine-induced liver injury, a mechanism that still remains unknown. It should be avoided in patient with hepatic disease and monitoring with liver function tests should be performed during treatment (27).

Venlafaxine (Effexor) is another SNRI that has been shown to relieve pain and improve mental health and vitality with a dosage of 75-225mg/day (19). The titration period is longer than duloxetine and takes approximatively 2-4 weeks. It is not recommended for cardiac patients as it has shown some effects on cardiac conduction and blood pressure (28). If the medication needs to be discontinued, it needs to be slowly tapered as it is known to produce serious withdrawal symptoms (20)

Amitriptyline (Elavil) is a tricyclic antidepressant that has been shown to significantly reduce pain with a total daily dose of 25-100 mg (19) and is available for a very low cost. It is a good choice of medication if the patient has concomitant depressive symptoms. It requires a long titration, of 6-8 weeks, to have some effects (20). It should be used with caution in patients with glaucoma, cardiovascular disease, orthostatic hypotension, and seizure disorder. Side effects include unsteadiness, falls, and weight gain. It can also cause somnolence, dizziness, dry mouth and tachycardia (3). Its use should be avoided in the elderly population due to predisposition to falls, and in those with cardiac disease (20, 22).

Dextromethorphan, morphine sulfate, tramadol, and oxycodone can be used to control neuropathic pain, but should not be first line agents. They should only be used for a short period of time or for acute symptoms as they can cause tolerance, addiction, nausea, constipation, somnolence, and rebound headaches (19).

Capsaicin, a substance present in chili peppers, is considered a good adjunct treatment for DPN in a 0.075% gel applied 3 to 4 times a day for 8 weeks. It has been shown to cause a depletion of axonal substance P, therefore causing desensitization of the skin due to decreased transmission

of painful signals to the brain (29). Its application causes degeneration of intraepidermal nerve fibers after only 3 days (30). The recommended length of treatment is restricted to 8 weeks (31). The most common adverse effect is burning sensations, erythema, and itching on initial treatment.

Meier et al evaluated the efficacy of 5% lidocaine patches for neuropathic pain symptoms with a randomized, double-blind, placebo-controlled study and concluded that it was effective as an add-on therapy in reducing the ongoing pain and allodynia with few side effects (32).

The literature has many research studies on adjunctive therapies for DPN including electrostimulation, cannabis, magnets, spiritual healing or Reiki, acupuncture, and more (19).

The only ones that have been shown to improve symptoms are electrostimulation and cannabis while the effectiveness of magnets still remains unclear in the literature (19,33). Electrostimulation can be used percutaneously or transcutaneously, and significantly improves well-being, sleep, decreases pain, improves physical activity, and decreases the need for oral analgesic medications (34). Cannabis is also another option for patients who cannot tolerate the typical oral agents or had inadequate symptom relief with them (35). Wilsey et al conducted a double-blind, placebo-controlled crossover study that consisted of evaluating vaporized cannabis for treatment of neuropathic pain on subjects that failed traditional treatment. Patients with underlying mental illness, substance abuse, or cardiopulmonary disease were excluded. They showed that a low dose (1.25% tetrahydrocannabinol [THC]) was an effective analgesic with few psychological side effects (36).

Some measures have to be taken to prevent progression of the disease by educating patients on DPN. As podiatrists, this includes preventing, correcting, or accommodating lower extremity deformities with orthotics, shoewear, braces, or surgery. Low impact activities like Tai Chi, yoga, pilates, and high intensity strength training help to improve coordination and balance. Regular follow-up with all healthcare professionnals is also essential (9).

In conclusion, there are multiple factors that have to be taken into account in the treatment of DPN. After a proper evaluation and diagnosis, the patient needs to see the appropriate group of health care professionals in order to maintain good metabolic control and decrease risk factors. The symptoms and quality of life of the patient should be initially addressed with first-line agents such as Pregabalin, Gabapentin, Duloxetine and Amitriptyline. The medication should be chosen keeping in mind the possible side effects and the comorbidities of the patient. If it remains ineffective, the next step is to change the treatment to another first line agent from a different class. Combination of first-line agents can be considered or second-line agents such as venlafaxine, opioids, complementary therapies, or topicals added to first-line agents for better pain control (19, 20). If certain cases do not respond to therapy, we must rethink our diagnosis and not hesitate to refer to a neurologist or pain specialist.

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014.
2. Vinik A, Ullal J, Parson HK, Casellini CM. Diabetic neuropathies: clinical manifestations and current treatment options. Nature Clin Pract 2006;2:269-81.
3. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. Endocrin Metab Clin North Am 2013;42:747-87.
4. Overview of polyneuropathy. 2014. URL: http://www.uptodate.com/contents/overview-of-polyneuropathy.
5. Italian General Practitioner Study Group (IGPSG). Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. Neurol 1995;45:1832-6.
6. Beghi E, Monticelli L,Italian General Practitioner Study Group. 1998. Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation of risk factors for polyneuropathy in two Italian Communities. J Clin Epidem 1998;51:697-702.
7. Dellon AL. Susceptibility of Nerve in Diabetes to Compression: Implications for Pain Treatment. Plast Recon Surg 2014;134(4 Suppl 2):142S-50.
8. Dellon AL. Diabetic neuropathy: review of a surgical approach to restore sensation, relieve pain, and prevent ulceration and amputation. Foot Ankle International/American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society 2004;25:749-55.
9. Valdivia JMV, Dellon AL, Weinand ME,Maloney CT Jr. Surgical treatment of peripheral neuropathy: outcomes from 100 consecutive decompressions. J Am Podiatr Med Assoc 2005;95:451- 4.
10. Rendell ML. Quantitative measurement of cutaneous perception in diabetic neuropathy. Muscle Nerve 1996;19:406-7.
11. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, et al. Use of the Michigan neuropathy screening instrument as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the diabetes control and complications trial/epidemiology of diabetes interventions and complications. Diabetic Med 2012;29:937-44.
12. Pop-Busui R, Herman WH, Feldman EL, Low PA, Martin CL, Cleary PA, et al. 2010. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diabet Rep 2010;10: 276-82.
13. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. New Eng J Med 2005;352:341-50.
14. Sandireddy R, Yerra VG, Areti A, Kcomirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Intl J Endocr 2014; 4:674-87.
15. Tesfaye S, Vileikyte L, Rayman G, Sindrup S, Perkins B, Baconja M, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. diabetes/metabolism research and reviews 2011. E-pub ahead of print.
16. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis. Diabet Med 2004;21:114-21.

17. Ang CD, Alviar M, Dans AL, Bautista-Velez G, Villaruz-Sulit M, Tan JJ, et al. Vitamin B for treating disorders of the peripheral nerves. Cochrane Collaboration. 2008.
18. Pittenger G, Vinik A. Nerve Growth Factor and Diabetic Neuropathy. Experimental Diabet Res 2003;4:271-85.
19. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the american academy of neurology, the American association of neuromuscular and electrodiagnostic medicine, and the American academy of physical medicine and rehabilitation. Neurology 2011;76:1758-65.
20. Ziegler D, Fonsec V. From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy. J Diabet Compl 2014; doi:10.1016/j.jdiacomp.2014.08.008.
21. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic Management of Neuropathic Pain: Evidence-Based Recommendations. Pain 2007;132:237-51.
22. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmac 2003;43:277-83.
23. DeToledo JC, Toledo C, DeCerce J, Ramsay RE. Changes in body weight with chronic, high-dose gabapentin therapy. Therap Drug Mon 1997;19:394-6.
24. Dipender G, Derry S, Wiffen PJ, Moore RA. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. Cochrane Reviews 2011;10:CD009183.
25. Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S et al. Randomized placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain. Diabet Care 2012;35:2451-58.
26. Khan AY, Macaluso M. Duloxetine for the treatment of generalized anxiety disorder: a review.Neuropsych Dis Treat 2009;5:23-31.
27. Seung-Gul K, Park YM, Lee HJ, Yoon B. Duloxetine-induced liver injury in patients with major depressive disorder. Psychiat Invest 2011;8:269-71.
28. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa NL, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin 2010;85:(3 Suppl):S3-14.
29. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004;328:991.
30. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. Pain 1999;81:135-45.
31. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004;328:991.
32. Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 2003;106:151-58.
33. Pittler J, Max H, Ernst E. Complementary therapies for neuropathic and neuralgic pain: systematic review. Clin J Pain 2008;24:731-3.
34. Hamza MA, White PF, Craig WF, Ghoname ES, Ahmed HE, Proctor TJ, et al. Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. Diabet Care 2000;23:365-70.
35. Grant I. Medicinal cannabis and painful sensory neuropathy. Virtual Mentor 2013;15:466-9.
36. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14:136-48.