Management of Diabetic Peripheral Neuropathy

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Neuropathies are among the most common of all the long-term complications of diabetes, affecting up to 50% of patients.[1–5] There are many subgroups of neuropathies; readers are referred to recent reviews for discussion of the autonomic neuropathies[6] and the mononeuropathies.[7] This article will focus on the most common of all the peripheral neuropathies: the somatic neuropathies affecting the lower extremities. Detailed discussions of all aspects of these neuropathies were recently published as a technical review[5] and will be included in a forthcoming American Diabetes Association statement.

In the past, a lack of awareness and inappropriate management of diabetic peripheral neuropathy (DPN) has led to much unnecessary morbidity and substantial health care costs. At least half of all foot ulcers, the end stage of such neuropathy, should be preventable by appropriate management and patient education. However, lack of time and inappropriate or inadequate information may lead to suboptimal care.

Diabetic somatic neuropathies do represent a paradox: at one extreme there are patients with severe neuropathic pain who on examination may have only a minimal deficit, whereas at the other extreme are patients with insensate feet who are asymptomatic and may first present with foot ulcers.

This review will provide an overview of DPN and a detailed guide to the management of pain in patients with significant symptomatology.

DEFINITIONS

Members of an International Consensus Meeting on the outpatient diagnosis and management DPN agreed on a simple definition of diabetic neuropathy as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[8] This group also agreed that neuropathy cannot be diagnosed without a careful clinical examination and that absence of symptoms must never be equated with absence of neuropathy. The importance of excluding nondiabetic causes was emphasized in the Rochester Diabetic Neuropathy Study, in which up to 10% of peripheral neuropathy in diabetes was deemed to be of nondiabetic causation.[1]

For day-to-day clinical practice, DPN is a clinical diagnosis. It is generally agreed that DPN should not be diagnosed on the basis of one symptom, sign, or test alone; a minimum of two abnormalities (i.e., abnormal symptoms and signs) is recommended.[5]

IN BRIEF

Diabetic peripheral neuropathy affects up to 50% of older type 2 diabetic patients. Whereas some patients may have extremely painful symptoms, others with a more marked neuropathic deficit may be asymptomatic. Diagnosis requires careful examination of the lower limbs. Management involves establishing that the neuropathy is caused by diabetes instead of more sinister causes and aiming for optimal glycemic control. Medications, usually tricyclic drugs or anticonvulsant agents, may be required. Patients with peripheral neuropathy must be considered at risk of insensate foot ulceration and must receive preventive education and podiatric care.

EPIDEMIOLOGY

DPN is by far the most common of all the diabetic neuropathies and may be divided into the following two main types: acute sensory neuropathy and chronic sensorimotor neuropathy. Acute sensory neuropathy is a distinct variety of the symmetrical polyneuropathies with an acute or subacute onset characterized by severe sensory symptoms, usually with few if any clinical signs. It is usually precipitated by an episode of glycemic instability (such as ketoacidosis or even after the institution of insulin), and its natural history is one of gradual improvement of symptoms with establishment of stable glycemic control and appropriate symptomatic treatments.

Chronic sensorimotor neuropathy is by far the most common form of DPN. It is usually of insidious onset and may be present at the diagnosis of type 2 diabetes in up to 10% of patients. Whereas up to 50% of patients with chronic DPN may be asymptomatic, 10–20% may experience troublesome symptoms sufficient to warrant specific therapy. Sensorimotor neuropathy is often accompanied by autonomic dysfunction. Its late sequelae, which include foot ulceration, Charcot neuroarthropathy, and occasionally amputation, should in many cases be preventable. The prevalence of chronic DPN increases with both age and duration of diabetes, and this diagnosis is more common in those whose glycemic control has been suboptimal in previous years.

CLINICAL FEATURES OF DPN

Acute Sensory Neuropathy

Many of the symptoms of acute sensory and chronic sensorimotor neuropathy are similar, although there are clear differences in the mode of onset, accompanying signs, and prognosis. These are summarized in Table 1. Table 2 offers a list of typical symptoms, both painful and nonpainful. All painful neuropathic symptoms tend to be prone to nocturnal exacerbation. Clinical examination of patients with presumed acute sensory neuropathy may be relatively normal, with allodynia (a painful sensation induced by nonnoxious stimulus) on sensory testing, a relatively normal motor exam, and occasionally reduced ankle reflexes.

In the management of this condition, achieving stable blood glucose control is most important. Stability may well be the key feature, because blood glucose flux (as assessed, for example, by the *M* value, a measure of glycemic excursions from the mean) is associated with pain.[9]

Additionally, however, most patients will require medication after neuropathic pain, and these medications are discussed in detail below in the section on management of chronic DPN. Suffice it to say that the approach is similar, although the dosage and number of medications required may be higher, in acute sensory neuropathy. The natural history of this acute neuropathy is very different from the much more common chronic DPN; its onset is acute or subacute, but the severe symptoms typically resolve in < 12 months.[10,11]

Chronic Sensorimotor Neuropathy

Painful neuropathy can be one of the most distressing and debilitating of all the complications of diabetes. The rest of this review will discuss the approach to patients presenting with chronic DPN and will focus on available treatments with brief comment on those that may soon be available.

As noted above, many patients are asymptomatic, and the neurological deficit may be discovered by chance during a routine neurological exam. Because chronic DPN is a length-dependent process, the sensory manifestations are most pronounced in the lower limbs, although, in more severe cases, the fingers and hands may also be involved. The symptoms, outlined in Table 2, tend to be peculiar to the individual patient but constant during the history of neuropathy in that individual. Patients often find it very difficult to describe the symptoms because they are different from other types of pain the patients have previously experienced.

Table 2. Typical Neuropathic Symptoms

Painful	Nonpainful
Burning pain	Asleep
Knife-like	"Dead"
Electrical sensations	Numbness
Squeezing	Tingling
Constricting	Prickling
Hurting	
Freezing	
Throbbing	
Allodynia	

Although not mentioned in older texts, unsteadiness is increasingly being recognized as a manifestation of chronic DPN resulting from disturbed propriaception and probably abnormal muscle sensory function. Many patients will have a combination of both positive (painful) and negative (nonpainful) symptoms.

Clinical examination of patients with chronic DPN usually reveals a symmetrical sensory loss to all modalities in a stocking distribution. This may well extend into the mid-calf level and may also affect the upper limbs in more severe cases. Ankle reflexes are usually reduced or absent, and knee reflexes may also be reduced in some cases.

In the clinical assessment of patients, a number of simple symptom/screening questionnaires are

Table 1. Contrasts Between Acute Sensory and Chronic Sensorimotor Neuropathies

	Acute Sensory	Chronic Sensorimotor
Mode of onset	Relatively rapid	Gradual, insidious
Symptoms	Severe burning pain, aching; weight loss usual	Burning pain, paresthesiae numbness; weight loss usual
Symptom severity	+++	0 to ++
Signs	Mild sensory in some; motor unusual	Stocking and glove sensory loss; absent ankle reflexes
Other diabetic complications	Unusual	Increased prevalence
Electrophysiological investigations	May be normal or minor abnormalities	Abnormalities unusual in motor and sensory nerves
Natural history	Complete recovery with 12 months	Symptoms may persist intermittently for years; at risk of foot ulceration

available to record symptom quality and severity. Among these is the Michigan Neuropathy Screening Instrument, which is a brief 15-item questionnaire.[12] It is also increasingly recognized that both symptoms and deficits may have an adverse effect on quality of life in diabetic neuropathy,[13] and specific questionnaires have been developed for the assessment of the impact of neuropathy on quality of life. Similarly, composite scores have been used to assess clinical signs, and one that is increasingly used is a modified Neuropathy Disability Score (NDS).[14] The NDS, shown in Figure 1, can be easily performed in the clinic setting and takes only a minute or two to complete. The maximum deficit score is 10, which would indicate complete loss of sensation to all sensory modalities and absent reflexes. In a longitudinal European community-based study, an NDS of ≥ 6 was equated with an increased risk of insensate foot ulceration.[14]

A number of simple devices may be used for clinical screening; the most widely used is the Semmes-Weinstein monofilament.[15] This filament assesses pressure perception when gentle pressure is applied sufficient to buckle the nylon filament. A number of cross-sectional and longitudinal studies have assessed the sensitivity of the 10-g monofilament and have shown it to be a useful tool to identify patients at risk of foot ulceration.[5,15] Of the simple quantitative sensory testing instruments that are used in clinical practice, the most common is the bioesthesiometer (Biomedical Instruments, Newbury, Ohio). This assesses in a semiquantitative manner the perception of vibration and has similarly been shown to be a useful predictor of foot ulcer risk.[16]

Neuropathy Disability Score (NDS)

		Right	Left
Vibration Perception Threshold 128-Hz tuning fork; apex of big toe: normal = can distinguish vibrating/not vibrating	Normal = 0 Abnormal = 1		
Temperature Perception on Dorsum of the Foot Use tuning fork with beaker of ice/warm water			
Pin-Prick Apply pin proximal to big toe nail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp/not sharp			
Achilles Reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS Total out of 10		

Figure 1. The Modified Neuropathy Disability Score

MANAGEMENT

Is It DPN?

The management approach to patients considered to have DPN is provided in Table 3. First, it must be remembered that there are numerous causes of peripheral neuropathy, of which diabetes is probably the most common. However, exclusion of other causes, particularly malignant disease and toxic causes, is of paramount importance. Exclusion of such potentially serious conditions as malignant disease (e.g., small-cell carcinoma presenting as a paraneoplastic syndrome), toxic causes (e.g., alcohol), and infections (diseases such as HIV) is essential.

In most cases, further investigation, such as detailed quantitative sensory testing in electrophysiology, which would require referral to a neurologist, is not essential. Abnormal electrophysiology simply confirms the presence of a neuropathy but does not indicate the underlying cause.

Initial Therapy and Counseling

Once a diagnosis is established, giving patients a full explanation of their condition, allaying their fears and misconceptions, and informing them that the pain may resolve in time can be extremely reassuring. Simple physical treatments, such as the use of a bed cradle to lift the bed clothes off of hyperaesthetic skin, can be beneficial. Advice on suitable footwear may also be provided. In patients with relatively mild pain, simple analgesics or anti-inflammatory agents may be sufficient to treat the discomfort.

Metabolic Control

The most effective method of achieving stable normoglycemia is pancreas or islet cell transplantation. However, this is not practical in most cases because it is mainly available to patients with end-stage diabetic nephropathy who have combined pancreas and renal transplants or in special cases of young people with type 1 diabetes.

Although there have been no randomized, controlled trials of intensive insulin therapy in the management of diabetic neuropathy, data from a number of observational studies suggest that stable glycemic control is of the greatest import. A recent study using continuous glucose monitoring confirmed that painful symptoms were associated with erratic blood glucose control.[9] Having said this, there is no evidence that patients whose diabetes has been well controlled on oral hypoglycemic agents will benefit in terms of pain relief by transferring to insulin.

Pharmacological Management

A large number of therapeutic agents have been proposed for the management

Table 3. Initial Management of Symptomatic Neuropathy

1. Exclude nondiabetic causes:
   - Malignant disease (e.g., bronchogenic carcinoma)
   - Metabolic
   - Toxic (e.g., alcohol)
   - Infective (e.g., HIV infection)
   - Iatrogenic (e.g., isoniazid, vinca alkaloids)
   - Medication-related (chemotherapy, HIV treatment)
2. Provide explanation, support, and information on practical measures, e.g., bed cradle to lift bedclothes off of hyperaesthetic skin
3. Assess level of blood glucose control and blood glucose profiles
4. Aim for optimal, stable control
5. Consider pharmacological therapy

of painful symptoms. These are shown in Table 4 and discussed below with a critique of the evidence supporting their use. Although there is only limited evidence to support the use of nonsteroidal and anti-inflammatory drugs in DPN, some would advocate their use for the management of patients with mild symptoms. Such agents must be used with caution in neuropathic diabetic patients because many will have a renal impairment, which often constitutes a contraindication to the use of nonsteroidal drugs.

Tricyclic agents. The use of tricyclic drugs in the management of neuropathic pain is supported by several randomized, controlled studies.[5,17,18] Although these drugs remain the first-line treatment for symptomatic neuropathy in many centers, their use is restricted because of the frequency and severity of side effects. Thus, some of the newer anticonvulsants are increasingly being used because of their superior side effect profile.

The mechanism of action of the tricyclic agents is not clear but may occur through inhibition of reuptake of norepinephrine and serotonin but also through effects on sodium channels and the *N*-methyl-D-aspartate (NMDA) receptors.[19] Although these agents are most useful in the management of neuropathic pain, it is, once again, their side effect profile that limits their use. Side effects, which are typically predictable and related to anticholinergic actions, include dry mouth, blurred vision, cardiac arrhythmias, sedation, urinary retention, constipation, and postural hypotension. Although nocturnal administration helps reduce the sedative side effects, up to about one-third of all patients cannot tolerate these agents. Amitriptyline and imipramine are most commonly used, although desipramine has fewer anticholinergic side effects and is less sedative.

Selective serotonin reuptake inhibitors. Trials of selective serotonin reuptake inhibitors (SSRIs) as treatment for diabetic neuropathy have been generally disappointing. Such agents work by the inhibition of presynaptic reuptake of serotonin but not norepinephrine. There is some evidence to support the use of paroxetine and citalopram in dosages of up to 40 mg/day from small controlled studies.

Anticonvulsants. These agents have been used in the management of neuropathic pain for many years, but only limited evidence exists for the efficacy of phenytoin and carbamazepine.[5]

Gabapentin is now widely used for neuropathic symptoms. This agent is structurally similar to the neurotransmitter γ-aminobutyric acid and was introduced some years ago as an anticonvulsant for complex partial seizures. The efficacy of gabapentin has been confirmed in two placebo-controlled clinical trials.[5]

The side effect profile may again be troublesome, but appears to be less so than that of the tricyclics. Reported effects include sedation, dizziness, headache, pedal edema, and weight gain. It should be noted that the average dose required for pain relief in clinical trials was ~ 1.8 g/day. Slow dose titration may reduce the incidence of side effects, but it has been suggested that many patients

Table 4. Oral Symptomatic Therapy of Painful Neuropathy

Drug Class	Drug	Daily Dose (mg)	Side Effects
Tricyclics	Amitriptyline	25–150	++++
	Imipramine	25–150	++++
SSRIs	Paroxitene	40	+++
	Citalopram	40	+++
Anticonvulsants	Gabapentin	900–1,800	++
	Pregabalin	160–600	++
	Lamotrigine	200–400	++
	Carbamazepine	up to 800	+++
Antiarrhythmics*	Mexilitene	up to 450	+++
Opioids	Tramadol	50–400	+++
	Oxycodone CR†	10–60	++++

All medications in this table have demonstrated efficacy in randomized, controlled studies. *Mexilitene should be used with caution and with regular electrocardiogram monitoring; †Oxycodone controlled release (CR) may be useful as an add-on therapy in severe symptomatic neuropathy.

are not being treated with a sufficiently high dosage.

A newer drug, pregabalin, which is a central nervous system–active compound and an analog of the neurotransmitter γ-aminobutyric acid, has recently been introduced. Preliminary evidence suggests that this agent may be a useful addition to the anticonvulsants that are helpful in the management of neuropathic pain.[20]

A number of other anticonvulsant agents have confirmed efficacy in randomized, controlled trials. These include lamotrogine[21] and sodium valproate.[22]

Local anesthetic arrhythmic agents. Lidocaine results in sodium channel blockage, dampening both peripheral nociceptor sensitization and ultimately central nervous system hyperexcitability. Although early studies suggested that intravenous lidocaine administration might be beneficial in relieving neuropathic pain, the potential side effects and the need for intravenous administration was problematic. The oral analog of lidocaine, mexiletine, has been reported to be of benefit in some studies,[5,23] but it is not widely used because of side effects and the need for regular electrocardiogram monitoring with its use.

There are now very preliminary data to suggest efficacy from the use of a 5% lidocaine patch in diabetic polyneuropathy. In an open-label study, the use of a maximum of four patches of 5% lidocaine per day was associated with relief of neuropathic symptoms without serious adverse effects.[24]

NMDA antagonists. This is a relatively new class of drugs and includes dextromethorphan and memantine. Preliminary studies of both agents suggest some efficacy in painful diabetic neuropathy, although further studies are required.[25]

Opioid analgesics. Opioids have not traditionally been used in the management of diabetic neuropathic pain, but recent trials of two agents do suggest efficacy. First, tramadol, which is an opioid-like, centrally acting synthetic narcotic analgesic, has been confirmed to be efficacious in a randomized, controlled trial, and a follow-up study suggests that it can be used safely for up to 6 months of sustained pain relief.[26,27] More recently, two studies have confirmed the efficacy of controlled-release oxycodone.[28,29]

The side effects of both drugs are predictable and include somnolence, nausea, and constipation; addiction is also problematic. It may be that opioids such as tramadol and oxycodone may be considered as add-on therapies for patients failing to respond to nonopioid medications in the first instance.

Topical and Physical Treatments

Capsaicin. This alkaloid, which is found in red pepper, depletes tissue of substance P and reduces chemically induced pain. Although several controlled studies combined in meta-analyses seem to provide some evidence of efficacy in diabetic neuropathic pain, it may be best reserved for those with localized discomfort rather than those with widespread generalized neuropathic pain.[30]

Topical nitrate. Some recent data suggest that impaired nitric oxide (NO) synthesis plays a role in the pathogenesis of diabetic neuropathy, and in experimental models it has been shown that impaired neuronal NO generation induces hyperalgesia.[31,32] This was followed by a recent controlled study that suggested that local application to the feet of isosorbide dinitrate spray was effective in relieving overall pain and burning discomfort of DPN.[33] If this is confirmed in larger randomized studies, this could provide a very useful alternative and local treatment for the relief of neuropathic symptoms. A subsequent retrospective review on the data from 18 patients with painful neuropathy treated with glyceryl trynitrate patches reported benefit from this method of applying the topical nitrate.[34]

Acupuncture. A number of masked studies support the use of acupuncture. In the most recently published report, benefits of acupuncture lasted for up to 6 months and reduced the use of other analgesics.[35] There is, however, a need for controlled studies to confirm these observations.

Other physical therapies. Many other physical therapies have been proposed. Controlled evidence has been provided for the use of percutaneous nerve stimulation,[36] static magnetic field therapy,[37] low-intensive laser therapy,[38] and monochromatic infrared light.[39] These therapies have mainly been described in small single-center studies and require confirmation in larger studies. Electrical spinal cord stimulation has been used to treat several chronic painful conditions, including phantom limb pain, vascular disease, and severe neuropathy. Although anecdotal evidence has been presented to support this, this treatment is invasive, expensive, and needs to be confirmed in randomized trials.[40]

New Potential Therapies Now in Clinical Trials

Two treatments that might be useful in opposing some of the pathogenetic factors that are thought to lead to neuropathy are now in clinical trials.

α-lipoic-acid. This free radical scavenger antioxidant has been shown to be efficacious in the management of painful neuropathies when administered parenterally.[41] A large 4-year, multicenter study to confirm the efficacy of this agent in diabetic neuropathy is in progress and should be completed in 2005.

Protein kinase C inhibition. Elevated protein kinase C activity is thought to play a substantial role in the etiology of diabetic microvascular complications. Studies have been conducted using a protein kinase C-β inhibitor (LY333531). A prelim- inary study suggested the possibility of this agent improving positive symptoms of allodynia and prickling pain. Large, phase III, multicenter clinical trials are in progress.[42]

FOOT CARE IN NEUROPATHIC PATIENTS

Most of the above discussion has related to the management of patients with symptomatic diabetic neuropathy.

However, as noted at the start of this article, a substantial number of neuropathic patients may be completely asymptomatic, and these, along with those who have painful neuropathy, are all at risk of insensitive foot injury. The importance of DPN in the etiopathogenesis of foot ulceration has been confirmed in numerous studies and was the subject of a recent review.[43]

It must be remembered that the neuropathic diabetic foot does not ulcerate spontaneously. Rather, it is the combination of neuropathy with other extrinsic factors (e.g., ill-fitting footwear or a foreign body in shoe) or intrinsic factors (e.g., high foot pressures or a plantar callus that results in ulceration). Thus, all patients with neuropathic deficit must be considered as being at risk of foot ulceration and require more frequent review, education in routine foot care, and regular podiatric assessments.

CONCLUSIONS

DPN, which may be asymptomatic in up to 50% of cases, is one of the most important complications of diabetes. All diabetic patients, regardless of their type of diabetes, duration of diabetes, or age, require careful clinical examination of the lower extremities and feet at least once a year.

Until recently, in the management of neuropathic pain, there have been few well-designed, placebo-controlled studies. However, in recent years, a number of well-designed clinical trials have confirmed the efficacy of a number of therapies that are outlined above. Unfortunately, it is not possible to predict which therapy might be of greatest benefit to a particular patient. The tricyclic and anticonvulsant agents remain first-line drugs for the management of painful symptoms, although some new classes of drugs are showing promise. Patients who fail to respond to the medications listed in this review might be considered for referral to a pain clinic or a neurologist.

Any patient with diabetic neuropathy should be considered to be at potential risk of foot ulceration or injury and should receive preventive education and referral to a podiatrist as necessary.

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