Diabetic Neuropathies

A statement by the American Diabetes Association

ANDREW J.M. BOULTON, MD, FRCP[1,2]
ARTHUR I. VINIK, MD, PHD[3]
JOSEPH C. AREZZO, PHD[4]
VERA BRIL, MD[5]
EVA L. FELDMAN, MD, PHD[6]
ROY FREEMAN, MB, CHB[7]
RAYAZ A. MALIK, PHD, MRCP[1]
RAELENE E. MASER, PHD[8]
JAY M. SOSENKO, MS, MD[2]
DAN ZIEGLER, MD, FRCP[9]

The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system that present with diverse clinical manifestations. They may be focal or diffuse. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and the autonomic neuropathies. DPN is a diagnosis of exclusion. The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons. *1*) Nondiabetic neuropathies may be present in patients with diabetes. *2*) A number of treatment options exist for symptomatic diabetic neuropathy. *3*) Up to 50% of DPN may be asymptomatic, and patients are at risk of insensate injury to their feet. As >80% of amputations follow a foot ulcer or injury, early recognition of at-risk individuals, provision of education, and appropriate foot care may result in a reduced incidence of ulceration and consequently amputation. *4*) Autonomic neuropathy may involve every system in the body. *5*) Autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy (CAN) is present. Treatment should be directed at underlying pathogenesis. Effective symptomatic treatments are available for the manifestations of DPN and autonomic neuropathy.

This statement is based on two recent technical reviews (1,2), to which the reader is referred for detailed discussion and relevant references to the literature.

DEFINITIONS AND CLASSIFICATION

— An internationally agreed simple definition of DPN for clinical practice is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (3). However, the diagnosis cannot be made without a careful clinical examination of the lower limbs, as absence of symptoms should never be assumed to indicate an absence of signs. This definition conveys the important message that not all patients with peripheral nerve dysfunction have a neuropathy caused by diabetes. Confirmation can be established with quantitative electrophysiology, sensory, and autonomic function testing.

Numerous classifications of the variety of syndromes affecting the peripheral nervous system in diabetes have been proposed in recent years. The classification shown in Table 1 is based on that originally proposed by Thomas (4).

DIAGNOSTIC CRITERIA AND BRIEF CLINICAL ASPECTS

A) Sensory neuropathies: clinical features

1) Acute sensory neuropathy. Acute sensory neuropathy is rare, tends to follow periods of poor metabolic control (e.g., ketoacidosis) or sudden change in glycemic control (e.g., "insulin neuritis"), and is characterized by the acute onset of severe sensory symptoms (as detailed below) with marked nocturnal exacerbation but few neurologic signs on examination of the legs.

2) Chronic sensorimotor DPN. This is the most common presentation of neuropathy in diabetes, and up to 50% of patients may experience symptoms, most frequently burning pain, electrical or stabbing sensations, parasthesiae, hyperasthesiae, and deep aching pain. Neuropathic pain is typically worse at night, and the symptoms are most commonly experienced in the feet and lower limbs, although in some cases the hands may also be affected. As up to half of the patients may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when the patient presents with a painless foot ulcer. Other patients may not volunteer symptoms but on inquiry admit that their feet feel numb or dead. Examination of the lower limb usually reveals sensory loss of vibration, pressure, pain, and temperature perception (mediated by small and large fibers) and absent ankle reflexes. Signs of peripheral autonomic (sympathetic) dysfunction are also frequently seen and include a warm or cold foot, sometimes with distended dorsal foot veins (in the absence of obstructive peripheral vascular disease), dry skin, and the presence of calluses under pressure-bearing areas

3) Diagnosis. The diagnosis of DPN can only be made after a careful clinical examination, and all patients with diabetes

From the [1]Department of Medicine, Manchester Royal Infirmary, Manchester, U.K.; the [2]Division of Endocrinology, Diabetes & Metabolism, University of Miami School of Medicine, Miami, Florida; [3]The Strelitz Diabetes Institute, Eastern Virginia Medical School, Norfolk, Virginia; the [4]Department of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; the [5]Department of Medicine (Neurology), University Health Network, University of Toronto, Toronto, Canada; the [6]Department of Neurology, University of Michigan, Ann Arbor, Michigan; the [7]Department of Neurology, Harvard University, Boston, Massachusetts; the [8]Department of Medical Technology, University of Delaware, Newark, Delaware; and the [9]German Diabetes Clinic, German Diabetes Center, Leibniz Institute at the Heinrich Heine University, Düsseldorf, Germany.

Address correspondence and reprint requests to (somatic) Prof. A.J.M. Boulton, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, U.K. E-mail: aboulton@med.miami.edu. Or (autonomic) Dr. Aaron Vinik, Director, Strelitz Diabetes Research Institute, 855 W. Brambleton Ave., Norfolk, VA 23510. E-mail: vinikai@evms.edu.

Abbreviations: CAN, cardiovascular autonomic neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; DAN, diabetic autonomic neuropathy; DPN, distal symmetric polyneuropathy; HRV, heart rate variability.

Table 1—*Classification of diabetic neuropathy*

Generalized symmetric polyneuropathies
• Acute sensory
• Chronic sensorimotor
• Autonomic
Focal and multifocal neuropathies
• Cranial
• Truncal
• Focal limb
• Proximal motor (amyotrophy)
• Coexisting CIDP

Adapted from Thomas (4). Note: Clinicians should be alert for treatable neuropathies (CIDP, monoclonal gammopathy, vitamin B_{12} deficiency, etc.) occurring in patients with diabetes.

should be screened annually for DPN by examining pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal halluces, and ankle reflexes. Combinations of more than one test have >87% sensitivity in detecting DPN. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers. Indeed, longitudinal studies have shown that a simple clinical examination is a good predictor of future foot ulcer risk (5). The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected. Different scoring systems have been developed for monitoring progression or response to intervention in clinical trials.

Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy (CIDP), B_{12} deficiency, hypothyroidism, and uremia, occur more frequently in diabetes and should be ruled out. The practitioner may wish to refer the more complex patient, or those in whom diagnosis needs confirmation, to a neurologist for specialized examination and testing.

The diagnosis of chronic DPN is therefore a clinical one and involves the exclusion of nondiabetic causes: investigations should be ordered as dictated by clinical findings and might typically include serum B_{12}, thyroid function, blood urea nitrogen, and serum creatinine. A combination of typical symptomatology and distal sensory loss with absent reflexes, or the signs in the absence of symptoms, is highly suggestive of DPN.

B) Focal and multifocal neuropathies

Mononeuropathies may have a sudden onset and can occur as a result of involvement of the median (5.8% of all diabetic neuropathies), ulnar (2.1%), radial (0.6%), and common peroneal nerves. Cranial neuropathies are extremely rare (0.05%); involve primarily cranial nerves III, IV, VI, and VII; and are thought to occur due to a microvascular "infarct," which, in the majority, resolves spontaneously over several months. Electrophysiological studies show a reduction in both nerve conduction and amplitude suggestive of underlying demyelination and axonal degeneration. In contrast, up to one-third of patients with diabetes have an entrapment. Common nerves involved are the ulnar, median, peroneal, and medial plantar nerves. Spinal stenosis is also common in people with diabetes and needs to be distinguished from the proximal neuropathies and amyotrophy. Electrophysiological studies are most helpful in identifying blocks in conduction at the entrapment sites. Entrapments may require decompression, but initial management should be expectant with strong reassurance to the patient for recovery (6).

Diabetic amyotrophy typically occurs in older patients with type 2 diabetes, and in some cases, an immune-mediated epineurial microvasculitis has been demonstrated in nerve biopsies. Clinical features of amyotrophy include severe neuropathic pain and uni- or bilateral muscle weakness and atrophy in the proximal thigh muscles. When an unusually severe, predominantly motor neuropathy and progressive polyneuropathy develops in diabetic patients, one must consider CIDP and spinal stenosis. The diagnosis of CIDP is often overlooked and the patient simply labeled as having diabetic neuropathy: progressive symmetric or asymmetric motor deficits, progressive sensory neuropathy in spite of optimal glycemic control together with typical electrophysiological findings, and an unusually high cerebro-spinal fluid protein level all suggest the possibility of an underlying treatable demyelinating neuropathy (7). As immunomodulatory therapy with combinations of corticosteroids, plasmapheresis, and intravenous immune globulin can produce a relatively rapid and substantial improvement in neurological deficits and electrophysiology in some cases of CIDP, referral to a neurologist is indicated if this diagnosis is suspected.

C) Autonomic neuropathy (8–14)

Diabetic autonomic neuropathy (DAN) results in significant morbidity and may lead to mortality in some patients with diabetes. The most common dysautonomic features are listed in Table 2, together with their associated symptoms and management. The symptoms of autonomic dysfunction should be elicited carefully during the history, particularly since many of these symptoms are potentially treatable.

Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure. CAN is the most prominent focus of autonomic dysfunction because of the life-threatening consequences of this complication and the availability of direct tests of cardiovascular autonomic function. However, neuropathies involving other organ systems should also be considered in the optimal care of patients with diabetes.

Cardiovascular

CAN is the most studied and clinically important form of DAN. The reported prevalence of CAN varies widely depending on the cohort studied and the methods of assessment. The presence of autonomic neuropathy may limit an individual's exercise capacity and increase the risk of an adverse cardiovascular event during exercise. CAN may be indicated by resting tachycardia (>100 bpm), orthostasis (a fall in systolic blood pressure >20 mmHg upon standing) without an appropriate heart rate response, or other disturbances in autonomic nervous system function involving the skin, pupils, gastrointestinal, or genitourinary systems. Sudden death and silent myocardial ischemia have been attributed to CAN in diabetes. Resting and stress thallium myocardial scintigraphy is an appropriate noninvasive test for the presence and extent of macrovascular coronary artery disease in these individuals. Hypotension and hypertension after vigorous exercise are more likely to develop in patients with autonomic neuropathy, particularly when starting an exercise program. Be-

Table 2—*Treatment of diabetic neuropathy based on the putative pathogenetic mechanisms*

Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (AE)
	Lidorestat		Withdrawn (AE)
	Fidarestat		Effective in RCTs, trials ongoing
	AS-3201		Effective in RCTs, trials ongoing
	Epalrestat		Marketed in Japan
Myo-inositol ↓	*Myo*-inositol	Nerve *myo*-inositol ↑	Equivocal
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in RCTs, trials ongoing
Nerve hypoxia ↑	Vasodilators	NBF ↑	
	ACE inhibitors		Effective in one RCT
	Prostaglandin analogs		Effective in one RCT
	phVEGF$_{165}$ gene transfer	Angiogenesis ↑	RCTs ongoing
Protein kinase C ↑	Protein kinase C-β inhibitor (ruboxistaurin)	NBF ↑	RCTs ongoing
C-peptide ↓	C-peptide	NBF ↑	Studies ongoing
Neurotrophism ↓	Nerve growth factor (NGF)	Nerve regeneration, growth ↑	Ineffective
	BDNF	Nerve regeneration, growth ↑	Ineffective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
GLA synthesis ↓	γ-Linolenic acid (GLA)	EFA metabolism ↑	Withdrawn
NEG ↑	Aminoguanidine	AGE accumulation ↓	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.

cause these individuals may have difficulty with thermoregulation, they should be advised to avoid exercise in hot or cold environments and to be vigilant about adequate hydration.

Observational studies have consistently documented an increased risk of mortality in subjects with autonomic neuropathy, although these associations may be related in part to the presence of other comorbid complications. A recent meta-analysis of published data demonstrated that reduced cardiovascular autonomic function, as measured by heart rate variability (HRV), was strongly (i.e., relative risk is doubled) associated with increased risk of silent myocardial ischemia and mortality (1).

A patient's history and physical examination are ineffective for early detection of CAN, and therefore noninvasive tests that have demonstrated efficacy are required. Proceedings from a consensus conference in 1992 recommended that three tests (R-R variation, Valsalva maneuver, and postural blood pressure testing) be used for longitudinal testing of the cardiovascular autonomic system (Table 5). Other forms of autonomic neuropathy can be evaluated with specialized tests, but these are less standardized and less available than commonly used tests of cardiovascular autonomic function, which quantify loss of HRV. The ability to interpret serial HRV testing requires accurate, precise, and reproducible procedures that use established physiologic maneuvers. The battery of three recommended tests for assessing CAN is readily performed in the average clinic, hospital, or diagnostic center with the use of available technology (Table 5).

At time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes (unless an individual has symptoms suggestive of autonomic dysfunction earlier), patients should be screened for CAN. Screening should comprise a history and an examination for signs of autonomic dysfunction. Tests for HRV, including expiration-to-inspiration ratio and response to the Valsalva maneuver and standing, may be indicated. Early measurement of HRV can serve as a baseline from which interval tests can be compared. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions. HRV testing may also facilitate differential diagnosis and the attribution of symptoms (e.g., erectile dysfunction, dyspepsia, dizziness) to autonomic dysfunction. Finally, knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies, such as ACE inhibitors and β-blockers, that are proven to be effective for patients with CAN.

Orthostatic measurement of blood pressure should be performed in people with diabetes and hypotension when clinically indicated.

Cardiovascular system and exercise. Cardiac autonomic function testing should be performed when planning an exercise program for individuals with diabetes about to embark on a moderate- to high-intensity exercise program, especially those at high risk for underlying cardiovascular disease (15).

Gastrointestinal

Gastrointestinal disturbances (e.g., esophageal enteropathy, gastroparesis,

Table 3—*Oral symptomatic therapy of painful neuropathy*

Drug class	Drug	Daily dose (mg)	NNT	NNH	Side effects
Tricyclics	Amitriptyline	25–150	2.4 (2.0–3.0)	2.7 (2.1–3.9)	++++
	Imipramine	25–150	2.4 (2.0–3.0)	2.7 (2.1–3.9)	++++
SSRIs	Paroxetine	40	ND	ND	+++
	Citalopram	40	ND	ND	+++
Anticonvulsants	Gabapentin	900–1,800	3.7 (2.4–8.3)	2.7 (2.2–3.4)	++
	Pregabalin	150–600	3.3 (2.3–5.9)	3.7	++
	Carbamazepine	200–400	3.3 (2.0–9.4)	1.9 (1.4–2.8)	+++
	Topiramate	Up to 400	3.0 (2.3–4.5)	9.0	++
Opioids	Tramadol	50–400	3.4 (2.3–6.4)	7.8	+++
	Oxycodone CR	10–60	ND	ND	++++

Data are median (range) unless otherwise indicated. See refs. 2, 19, and 20. 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.

constipation, diarrhea, fecal incontinence) are common, and any section of the gastrointestinal tract may be affected. Gastroparesis should be suspected in individuals with erratic glucose control. Upper-gastrointestinal symptoms should lead to consideration of all possible causes, including autonomic dysfunction. Evaluation of gastric emptying should be done if symptoms are suggestive. Barium studies or referral for endoscopy may be required. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea. Endoscopy may be required to rule out other causes.

Genitourinary

DAN is also associated with genitourinary tract disturbances, including bladder and/or sexual dysfunction. Evaluation of bladder dysfunction should be performed in individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder. In men, DAN may cause loss of penile erection and/or retrograde ejaculation. A complete work-up for impotence in men should include history (medical and sexual); psychological evaluation; hormone levels; measurement of nocturnal penile tumescence; tests to assess penile, pelvic, and spinal nerve function; cardiovascular autonomic function tests; and measurement of penile and brachial blood pressure.

EPIDEMIOLOGY

DPN

DPN is a common disorder. Although estimates vary, it appears that at least one manifestation of DPN is present in at least 20% of adult diabetic patients. DPN has been associated with a number of modifiable and nonmodifiable risk factors, including the degree of hyperglycemia, lipid and blood pressure indexes, diabetes duration, and height. DPN has been less consistently associated with cigarette smoking and alcohol consumption.

DAN

Prevalence data for DAN range from 1.6 to 90% depending on tests used, populations examined, and type and stage of disease. Risk factors for the development of DAN include diabetes duration, age, and long-term poor glycemic control. DAN may cosegregate with factors predisposing to macrovascular events such as raised blood pressure and dyslipidemia. Thus, in addition to good glycemic control, lipid modulation and blood pressure control may be beneficial in the prevention of DAN. There are no true population-based studies using radioisotopic techniques that quantify gastric emptying in diabetic patients, but cross-sectional studies have indicated that ~50% of outpatients with long-standing diabetes have delayed gastric emptying and up to 76% of diabetic outpatients indicate that they have one or more gastrointestinal symptom, the most common of which is constipation. Both upper- and lower-gastrointestinal symptoms occur more frequently in individuals with diabetes than in control subjects, but the symptoms are nonspecific and occur in the general population (12,13). Specific symptoms such as bloating after meals, vomiting of previously ingested food, and alternating constipation and explosive diarrhea should lead to further evaluation (Table 4).

Genitourinary bladder dysfunction has been shown in 43–87% of individuals with type 1 diabetes. Diabetic women have a fivefold higher risk of unrecognized voiding difficulty compared with nondiabetic women. The history and physical are generally noncontributory, and the patient should be referred to a urologist for urodynamic studies.

The prevalence of erectile dysfunction in diabetic men ranges from 27 to 75% (14).

MANAGEMENT

A) Prevention

The DCCT (Diabetes Control and Complications Trial) has shown definitively that in type 1 diabetic patients, the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control. Although data from a small number of trials are much less strong for type 2 diabetic patients, DCCT data and data from epidemiologic studies (including studies of type 2 patients) strongly suggest that optimal blood glucose control helps to prevent DPN and autonomic neuropathy in both type 1 and type 2 diabetic patients. There have been no definitely positive prevention studies of other risk factor modifications for DPN, but the improvement of lipid and blood pressure indexes, and the avoidance of cigarette smoking and excess alcohol consumption, are already recommended for the prevention of other complications of diabetes.

B) Pathogenetic treatments (16–19)

Recent experimental studies suggest a multifactorial pathogenesis of diabetic

Table 4—*Treatment of autonomic neuropathy*

Symptoms	Tests	Treatments
Cardiac		
Exercise intolerance, early fatigue and weakness with exercise	HRV, multigated angiography (MUGA) thallium scan, 123I metaiodobenzlyguanidine (MIBG) scan	Graded supervised exercise, ACE inhibitors, β-blockers
Postural hypotension, dizziness, lightheadedness, weakness, fatigue, syncope	HRV, measure blood pressure standing and supine, measure catecholamines	Mechanical measures, clonidine, midodrine, octreotide
Gastrointestinal		
Gastroparesis, erratic glucose control	Gastric emptying study, barium study	Frequent small meals, prokinetic agents (metoclpramide, domperidone, erythromycin)
Abdominal pain or discomfort, early satiety, nausea, vomiting, belching, bloating	Endoscopy, manometry, electrogastrogram	Antibiotics, antiemetics (phenergan, compazine, tigan, scopolamine), bulking agents, tricyclic antidepressants, pancreatic extracts, pyloric Botox, gastric pacing, enteral feeding
Constipation	Endoscopy	High-fiber diet and bulking agents, osmotic laxatives, lubricating agents and prokinetic agents used cautiously
Diarrhea, often nocturnal alternating with constipation and incontinence		Trials of soluble fiber, gluten and lactose restriction, anticholinergic agents, cholestyramine, antibiotics, clonidine, somatostatin, pancreatic enzyme supplements
Sexual dysfunction		
Erectile dysfunction	History and physical examination, HRV, penile-brachial pressure index, nocturnal penile tumescence	Sex therapy, psychological counseling, sildenafil, vardenafil, tadalafil, prostaglandin E1 injection, device or prosthesis
Vaginal dryness		Vaginal lubricants
Bladder dysfunction		
Frequency, urgency, nocturia, urinary retention, incontinence	Cystometrogram, postvoiding sonography	Bethanechol, intermittent catheterization
Sudomotor (sweating) dysfunction		
Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Quantitative sudomotor axon reflex, sweat test, skin blood flow	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor		
Visual blurring, impaired adaptation to ambient light, impaired visceral sensation	Pupillometry, HRV	Care with driving at night, recognition of unusual presentations of myocardial infarction

neuropathy. Studies in animal models and cultured cells provide a conceptual framework for the cause and treatment of diabetic neuropathy. However, limited translational work in diabetic patients continues to generate much debate and controversy over the cause(s) of human diabetic neuropathy, and to date we have no effective long-term treatment. A summary of the drugs that have/are being studied in clinical trials is provided in Table 2 (19).

C) Symptomatic treatments

1) DPN (2,3,20–22). The first step in management of patients with DPN should be to aim for stable and optimal glycemic control. Although controlled trial evidence is lacking, several observational studies suggest that neuropathic symptoms improve not only with optimization of control but also with the avoidance of extreme blood glucose fluctuations. Many patients will require pharmacological treatment for painful symptoms: several agents have efficacy confirmed in published randomized controlled trials, although with the exception of Duloxetine and Pregabalin, none of the others is specifically licensed for the management of painful DPN (Table 3). An algorithm for the management of symptomatic DPN is provided in Fig. 1.

Although a detailed discussion of all these agents is provided in the recent technical review (2), some comment will be made on the more commonly used agents.

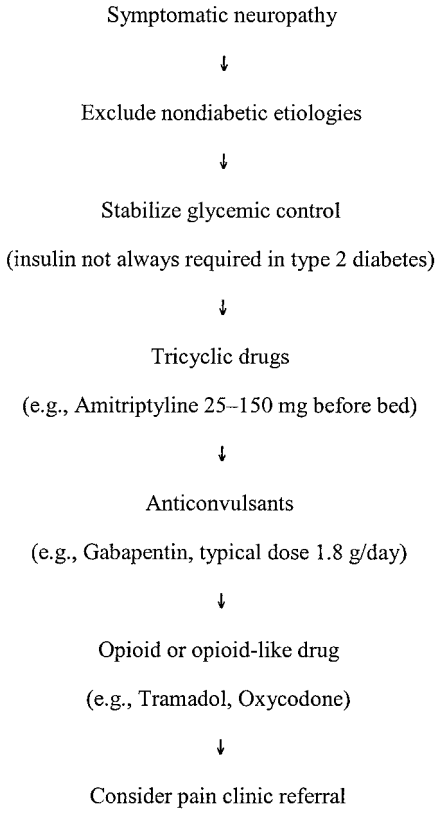

Figure 1—*Algorithm for management of symptomatic DPN (1). Note that nonpharmacological, topical, or physical therapies might be useful at any stage. These include acupuncture, capsaicin, glyceryl trinitrate spray/patches, etc. (2).*

Table 5—*Diagnostic tests of CAN*

- Resting heart rate
  >100 bpm is abnormal.
- Beat-to-beat HRV*
  With the patient at rest and supine (not having had coffee or a hypoglycemic episode the night before), heart rate is monitored by ECG or autonomic instrument while the patient breathes in and out at six breaths per minute, paced by a metronome or similar device. A difference in heart rate of >15 bpm is normal, <10 bpm is abnormal. The lowest normal value for the expiration-to-inspiration ratio of the R-R interval is 1.17 in people 20–24 years of age. There is a decline in the value with age†.
- Heart rate response to standing*
  During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing. Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio is >1.03.
- Heart rate response to the Valsalva maneuver*
  The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R to shortest R-R should be >1.2.
- Systolic blood pressure response to standing
  Systolic blood pressure is measured in the supine subject. The patient stands, and the systolic blood pressure is measured after 2 min. Normal response is a fall of <10 mmHg, borderline is a fall of 10–29 mmHg, and abnormal is a fall of >30 mmHg with symptoms.
- Diastolic blood pressure response to isometric exercise
  The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min. The normal response for diastolic blood pressure is a rise of >16 mmHg in the other arm.
- ECG QT/QTc intervals
  The QTc should be <440 ms.
- Spectral analysis
  Very-low-frequency peak ↓ (sympathetic dysfunction)
  Low-frequency peak ↓ (sympathetic dysfunction)
  High-frequency peak ↓ (parasympathetic dysfunction)
  Low-frequency–to–high-frequency ratio ↓ (sympathetic imbalance)
- Neurovascular flow
  Using noninvasive laser Doppler measures of peripheral sympathetic responses to nociception.

From Vinik A, Erbas T, Pfeifer M, Feldman E, Stevens M, Russell J: Diabetic autonomic neuropathy, 2004. In *The Diabetes Mellitus Manual: A Primary Care Companion to Ellenberg and Rifkin's 6th Edition*. Inzucchi SE, Ed. New York, McGraw Hill, 2004, p. 351. *These can now be performed quickly (<15 min) in the practitioner's office using stand-alone devices that are operator friendly. †Lowest normal value of expiration-to-inspiration ratio: age 20–24 years, 1.17; 25–29, 1.15; 30–34, 1.13; 35–39, 1.12; 40–44, 1.10; 45–49, 1.08; 50–54, 1.07; 55–59, 1.06; 60–64, 1.04; 65–69, 1.03; and 70–75, 1.02. ECG, electrocardiogram.

Tricyclic drugs. The usefulness of the tricyclic drugs, such as Amitriptyline and Imipramine, has been confirmed in several randomized controlled trials. Although inexpensive and generally efficacious in the management of neuropathic pain, side effects, particularly anticholinergic (dry mouth, urinary retention, etc.), can be troublesome and limit their use in many patients. The central side effects, such as fatigue and drowsiness, are also common, so it is advised to start at 25 mg before bed and gradually increase the dose, if necessary, to a maximum of 150 mg.

Anticonvulsants. Gabapentin is now the most commonly prescribed anticonvulsant that has been proven to be efficacious in the treatment of neuropathic pain. As most patients require at least 1.8 g/day for relief of symptoms, it is advisable to start at 300 mg at bedtime and then increase over days to the dosage that achieves symptomatic relief. This gradual titration of drug dosage until the therapeutic effect is realized is advisable, as it is felt that this may lessen the severity of side effects that may be experienced if the drug is introduced at a high dose on day 1. The structurally related compound Pregabalin has recently been confirmed to be useful in painful diabetic neuropathy in a randomized controlled trial (20). In contrast to Gabapentin, which is usually given in three daily doses, Pregabalin is effective when given twice daily. As noted in Table 4, all of these agents are prone to side effects, typically central in nature such as drowsiness. Finally, Topiramate, another anticonvulsant used in complex partial seizures, was recently shown to be efficacious in the management of neuropathic pain (21).

Other agents. The 5-hydroxytryptamine and Norepinephrine reuptake inhibitor Duloxetine has recently been approved by the Food and Drug Administration for the treatment of neuropathic pain. However, at the time this statement was being prepared, the evidence of efficacy of this agent was only published in abstract form (22).

In cases of severe pain, certain agents may be used in combination (e.g., an antidepressant and an anticonvulsant) or combined with a topical or nonpharmacological treatment (2) (Fig. 1). All patients with DPN, whether symptomatic or not, are at increased risk of foot ulceration (2) and should be considered for podiatric referral and foot care education.

2) Autonomic neuropathy. Treatment approaches to the management of autonomic neuropathy are summarized in Table 4.

RECOMMENDATIONS FOR SCREENING FOR AND TREATMENT OF DIABETIC NEUROPATHY

A. Tight glycemic control

For all diabetic patients, maintain aggressive control of blood glucose, HbA_{1c}, blood pressure, and lipids with pharmacological therapy and/or lifestyle changes

B. Screening

1) Chronic sensorimotor DPN. All patients with diabetes should be screened for DPN at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually by examining sensory function in the feet and checking ankle reflexes. One or more of the following can be used to assess sensory function: pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), or pressure sensation (using a 10-g monofilament pressure sensation at the distal halluces). Any history of neuropathic symptoms should be elicited, and a careful clinical examination of the feet and lower limbs should be performed. The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected at each diabetes care visit. All patients with DPN, whether symptomatic or not, require foot care education and consideration for podiatric referral.

2) Autonomic neuropathy. Based on expert consensus and clinical experience (level E), screening should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Screening might comprise a history and an examination for signs of autonomic dysfunction. Tests for HRV, including expiration-to-inspiration ratio and response to the Valsalva maneuver and standing, may be indicated. If screening is negative, this should be repeated annually; if positive, appropriate diagnostic tests and symptomatic treatments should be instituted (Tables 4 and 5).

References

1. Vinik AI, Maser RE, Mitchell BD, Freeman R: Diabetic autonomic neuropathy (Technical Review). *Diabetes Care* 26:1553–1579, 2003
2. Boulton AJM, Malik RA, Arezzo JC, Sosenko JM: Diabetic somatic neuropathies (Technical Review). *Diabetes Care* 27: 1458–1486, 2004
3. Boulton AJM, Gries FA, Jervell JA: Guidelines for the diagnosis and outpatient management diabetic peripheral neuropathy. *Diabet Med* 15:508–514, 1998
4. Thomas PK: Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. *Diabetes* 46 (Suppl. 2):S54–S57, 1997
5. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, Hann AW, Hussein A, Jackson N, Johnson KE, Ryder CH, Torkington R, Van Ross ER, Whalley AM, Widdows P, Williamson S, Boulton AJM: The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 19: 377–384, 2002
6. Vinik A, Mehrabyan A, Colen L, Boulton AJM: Focal entrapment neuropathies in diabetes (Review). *Diabetes Care* 27: 1783–1788, 2004
7. Ayyar DR, Sharma KR: Chronic demyelinating polyradiculoneuropathy in diabetes. *Curr Diab Rep* 4:409–412, 2004
8. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D: Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 291:2978–2984, 2004
9. Boulton AJM, Selam JL, Sweeney M, Ziegler D: Sildenafil citrate for the treatment of erectile dysfunction in men with type II diabetes mellitus. *Diabetologia* 44: 1296–1301, 2001
10. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT: Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 25:2159–2164, 2002
11. Goldstein I, Young J, Fischer J, Bangerter K, Segerson T, Taylor T, the Vardenafil Diabetes Study Group: Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes. *Diabetes Care* 26:777–783, 2003
12. Maleki D, Loche R, Camilleri M: Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 160:2808–2816, 2000
13. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M: Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 161: 1989–1996, 2001
14. Bacon CG, Hu FB, Giovannucci E, Glasser DB, Mittleman MA, Rimm EB: Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. *Diabetes Care* 25:1458–1463, 2002
15. Zinman B, Ruderman N, Campaigne BN, Devlin JT, Schneider SH: Physical activity/exercise in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S58–S62, 2004
16. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA: Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabet Med* 21:114–121, 2004
17. Ekberg K, Brismar T, Johansson BL, Jonsson B, Lindstrom P, Wahren J: Amelioration of sensory nerve dysfunction by C-peptide in patients with type 1 diabetes. *Diabetes* 52:536–541, 2003
18. Simovic D, Isner JM, Ropper AH, Pieczek A, Weinberg DH: Improvement in chronic ischemic neuropathy after intramuscular phVEGF165 gene transfer in patients with critical limb ischemia. *Arch Neurol* 58:761–768, 2001
19. Vinik A, Mehrabyan A: Diabetic neuropathies. *Med Clin N Am* 88:947–999, 2004
20. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U: Pregabalin for the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled trial. *Pain* 110: 628–638, 2004
21. Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, Vinik AI, the CAPSS-141 Study Group: Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 63:865–873, 2004
22. Wernicke J, Rosen AS, Lu Y, Iyengar S, Lee TC: Superiority of Duloxetine over placebo in the treatment of diabetic neuropathic pain demonostrated in two studies (Abstract). *Diabetes* 53 (Suppl. 2):A24, 2004