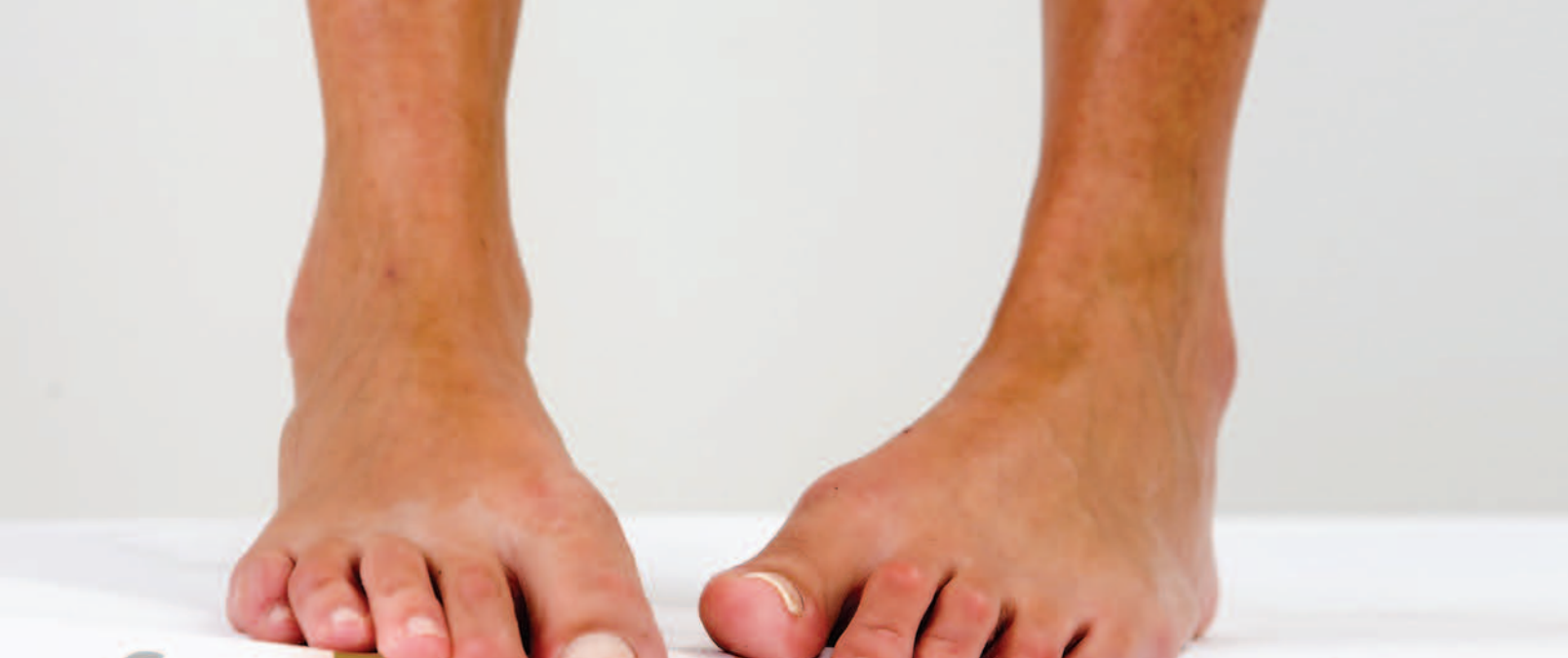

Six Burning Questions

Diabetic neuropathies are the most common types of neuropathies worldwide. Although there has been significant progress in understanding the clinical aspects of these conditions, many questions remain unanswered or difficult to answer in terms of causation, risk factors and genetic susceptibility, effective treatments and restoration of nerve functions, and pain management. The major handicap in studying diabetic neuropathies is the lack of a suitable animal model that addresses both acute and chronic events leading to diabetic neuropathy. Unfortunately and despite numerous drug trials, other than strict glycemic control, which is often difficult to maintain, there are no other treatments to slow the progression or delay the development of diabetic neuropathy. This article attempts, in a limited and selected fashion, to highlight a few unanswered or controversial questions regarding diabetic neuropathies.

1. What are the risk factors for the development and progression of diabetic peripheral neuropathies?

The duration of diabetes and degree of metabolic control are the two major predictors of the development of neuropathy and determinant of its severity. Other factors, such as patient's age, height and presence of proliferative retinopathy, nephropathy and cardiovascular diseases, also have been implicated (Table 1).[1] Longer duration of diabetes also increases the possibility of developing more than one form of diabetic neuropathy. This factor is exemplified by a threefold increase in the prevalence of sympathetic and parasympathetic neuropathies in patients with diabetic neuropathy 10 years after the initial diagnosis of neuropathy.[2]

The role of excessive alcohol consumption as an independent risk factor for the development of diabetic neuropathy also has been emphasized,[3] but the role of smoking is less clear. Smoking is not only a major dose-dependent risk factor for atherosclerosis and cardiovascular diseases but also may serve as an independent risk factor for cardiovascular autonomic dysfunction[4] and peripheral neuropathy.[1,5,6] Smoking and agents contained in nicotine induce an increase in insulin resistance, an abnormal state in which an impairment of cellular insulin signaling results in an overt resistance to the physiologic effects of insulin in terms of disposal of glucose and suppression of gluconeogenesis. This state leads to a combination of hyperinsulinemia and hyperglycemia, endothelial cell dysfunction, and hypertension and microvascular complications.[7] It is not clear whether cessation of smoking results in the improvement or slower progression of these complications, but it is prudent that patients be encouraged to do so.

Genetic factors also may play a role in individual susceptibility to diabetic neuropathy. APOE genotype has been proposed as a risk factor for the severity of neuropathy in patients who have diabetes.[8] Having an E3/4 and 4/4 APOE genotype is the equivalent of having 15 extra years of age or diabetes

Much is known about this common condition, but key questions remain unanswered, particularly regarding its pathogenesis and treatment.

About Diabetic Neuropathy

By Yadollah Harati, MD

duration. The APOE-4, however, does not function as susceptibility gene for the development of diabetic neuropathy in type II diabetes.[9] APOE genotype may influence the severity of neuropathy by several mechanisms, including acceleration of atherosclerosis, impairment of cytoskeletal stabilization, changes in cell adhesion, or use of growth factors.[10] This possible risk factor requires further longitudinal studies with large numbers of patients who have diabetes in different stages of disease to establish its potential clinical use.

Aldose reductase gene (AKR1B1) polymorphisms also have been implicated in the rate of decline in neuropathic function in diabetes and the early development of neuropathy and albuminuria in type II diabetes.[11,12] Aldose reductase is the rate-limiting enzyme of the polyol pathway of glucose metabolism expressed in many tissues and is implicated in the pathogenesis of diabetic microvascular complications. It catalyzes the NADPH-dependent reduction of glucose to sorbitol, which leads to intracellular accumulation of sorbitol and various metabolic imbalances, including enhanced oxidative stress. A recent longitudinal genetic association study of a cohort of 262 adolescent patients with type I diabetes followed for a median of seven years revealed that the rate of decline in quantitative sensory and autonomic testing was strongly associated with AKR1B1 polymorphism.[13] Further and larger studies regarding different neuropathy subtypes and aldose reductase genes are required to clarify the role of aldose reductase gene polymorphism as a predictor for the development and severity of neuropathy and its use in clinical practice.

The presence of the D allele of the angiotensin I converting enzyme (ACE) is reported to be associated with increased risk of peripheral neuropathy in women with type II diabetes but not in men.[14] The role of angiotensin II, which is pro-inflammatory and pro-oxidant, in the development of vascular complications of type II diabetes has been implicated in several studies. By catalyzing the conversion of angiotensin I to angiotensin II, ACE facilitates this process. ACE inhibitors are shown to be effective in delaying the progression of microvascular complications, including nephropathy and retinopathy, and improving nerve conduction velocity, temperature discrimination threshold and vibration perception in patients who have diabetes.[15] The D allele of the ACE gene has also been associated with higher ACE activity and macrovascular and microvascular complications and progression of nephropathy. Exactly why there should be a gender difference in the ACE genotype in determining the risk of neuropathy is not clear; however, modulation of ACE activity by estrogens at the level of transcription resulting in a relatively higher ACE level may play a role.[16] If female carriers of the D allele of ACE are at greater risk for diabetic neuropathy, an earlier treatment with ACE inhibitors or angiotensin receptor blockers may reduce the risk of neuropathy.

Although familial clustering for diabetic nephropathy and

Table 1. Risk Factors for Diabetic Neuropathy

- Poor glycemic control
- Longer duration of diabetes
- Older age
- Male sex
- Height
- Alcohol
- Hypertension
- Nicotine use
- Hyperlipidemia
- APOE genotype
- Aldose reductase gene hyperactivity
- Angiotensin-converting enzyme genotype

retinopathy has been demonstrated, such a familial clustering has not been observed in diabetic neuropathy.[17,18]

2. Can a unified hypothesis for the pathogenesis of diabetic neuropathy be formulated?

Several mechanisms for the pathogenesis of diabetic neuropathy have been proposed, but none has achieved general acceptance. In general, they are divided into two major subgroups: (1) abnormalities that suggest a metabolic etiology and (2) abnormalities that suggest a vascular etiology (Table 2). For several of these hypotheses there is strong experimental support, but the precise detail of each mechanism and—more importantly—their possible interrelationships remain unanswered.

Among these abnormalities, the formation of advanced glycation end products (AGEs) may serve as a unifying bridge between the two major hypotheses and explain many of the diabetic complications. AGEs are formed as a result of irreversible binding of high levels of glucose-and possibly fructose-to various proteins both intracellularly and extracellularly (glycated proteins). This is a relatively slow process that results in alteration of proteins physicochemical properties and their interaction with other molecules. The accumulation of glycated proteins in areas such as endothelial cells basement membrane or elastic lamina leads to vascular dysfunction. In patients who have diabetes and aged normal individuals there is an abundance of accumulated glycated proteins in the inner elastic layers of arteries. Binding of glucose to proteins also occurs with DNA and various crucial enzymes, such as antioxidants, matrix metalloproteinases and their tissue inhibitors, transforming growth factor-β, and extracellular signal-regulated kinases, among others. Bindng leads to ineffectiveness, deficiency, or dysfunction of these enzymes. Formation of AGE in the peripheral nerves and intra-axonal structures further interferes with axonal transport and nerve function. The intensity of AGE accumulation in the microvessels, endoneurium, and perineurium of nerve biopsies of patients who have diabetic neuropathy has been shown to correlate with the severity of axonal loss.[19]

The glycated proteins, especially elastin and collagen, also bind to transition metals, which accumulate within the subendothelium and prevent access of endothelium-derived relaxing factor to smooth muscles. Reversal of this binding by administration of transition metal chelators (i.e., desferrioxamine and trientin) in diabetic rats results in improved nerve function.[20] Impaired blood vessel relaxation leads to reduced nerve blood flow and nerve hypoxia or other nutritional deficiencies[21] and, ultimately, nerve degeneration. Reduced nerve perfusion and oxygenation in human diabetic neuropathy has been demonstrated.

The accumulation of AGEs in the vessel wall also results in increasing macrophage recognition and uptake, stimulation of macrophage-derived and other growth factors, and increased vessel wall low-density lipoproteins, which lead to smooth muscle proliferation, atherogenesis, and further nerve hypoxia. Binding of glucose to the proteins of antioxidant enzymes, such as glutathione, catalase, and superoxide dismutase, results in further damage by rendering these enzymes ineffective in removing harmful free radical species. The excess free radical species damage cellular proteins, mitochondria, nuclear and mitochondrial DNA, and membranes. The interaction between AGEs, their receptor, and their primary effectors (activated NF-kappa B and interleukin-6) is also of interest because receptor AGE and its effectors have been co-localized in the sural nerve microvessels of patients who have diabetes.[22] Receptor AGE is thought to play a role in internalization and clearance of AGE.

If the accumulation of AGE is responsible for the initiation of cascades of metabolic, physiologic and structural abnormalities in various tissues, including the peripheral nerve, would the inhibition of AGE formation prevent or ameliorate these complications? The answer to this question is far from clear. Although some agents effectively inhibit formation of AGE (including aminoguanidine, 2,3-diaminophenazone, tenilsetam and pyridoxamine) and in experimental animals cause improvement of vascular and nerve conduction abnormalities, their effect in human complications (*e.g.*, nephropathy) has been disappointing and they have not been tested in human diabetic neuropathy.

Regardless of how vascular abnormalities begin in diabetes, a substantial body of data implicates the dysfunction of nerves' blood vessels in the development of metabolic, functional, and structural nerve abnormalities. Patients who have diabetic neuropathy and reduced nerve oxygen tension and impaired nerve blood flow fail to raise nerve conduction velocities immediately after exercise, which suggests poor blood flow.[23] Patients who

Table 2. Proposed Abnormalities Implicated in the Pathogenesis of Diabetic Neuropathy

Abnormalities Suggesting Vascular Etiology:

- Advanced glycation of vessel wall
- Basement membrane thickening and reduplication
- Endothelial cell swelling and pericyte degeneration
- Occlusive platelet thrombi
- Closed capillaries
- Multifocal ischemic proximal nerve lesions
- Epineurial vessel atherosclerosis
- Increased oxygen free radical activities
- Reduced endothelial nitric oxide activity
- Nerve hypoxia

Abnormalities Suggesting Metabolic Etiology:

- Accumulation of sorbitol
- Reduction in the rate of synthesis and transport of intra-axonal proteins
- Reduction in nerve sodium-potassium-ATPase
- Enhanced protein kinase C activity
- Reduced amino acid incorporation into dorsal root ganglion
- Reduced incorporation into myelin of glycolipids and amino acids
- Reduced nerve l-carnitine level
- Abnormal inositol lipid metabolism
- Impaired essential fatty acid and prostaglandin metabolism
- Excessive glycogen accumulation
- Increased nonenzymatic peripheral nerve protein glycation
- Increased oxygen free radical activity
- Increased diacylglycerol -protein kinase C-beta signal transduction
- Nerve hypoxia

Other Abnormalities:

- Increased nerve edema
- Increased blood-nerve permeability
- Impaired endogenous neurotrophic or vascular growth factors
- Insulin deficiency

have diabetes and lower limb vascular insufficiency tend to have a more severe neuropathy than patients without ischemia.[24] Although these and other observations strongly suggest that a microvascular-induced nerve ischemia hypoxia can serve as an all-encompassing explanation for the pathogenesis of diabetic neuropathy, many unanswered questions remain. The structural microvascular and electrophysiologic abnormalities seen in diabetic neuropathy are late occurrence, and the earliest adverse effects of hyperglycemia are generally metabolic and result from direct exposure of nerve to glucose, where, unlike in other tissues, its uptake and transfer do not require insulin. The initial metabolic phase, which is potentially amenable to therapeutic intervention, is progressively replaced by a structural phase that becomes increasingly unresponsive to such interventions.

3. Is it "diabetic neuropathy" or "neuropathy in a diabetic patient"?

This question has become increasingly relevant because there has been an alarming worldwide rise in the prevalence of diabetes mellitus in recent years, with further increases predicted for the next decades. This rise is attributed to increased obesity, especially among younger individuals. Currently, diabetes affects approximately 20.8 million people in the United States,[25] and it is predicted that approximately 220 million people worldwide will be afflicted by the year 2010. Earlier observations and more recent population-based cohort studies have shown that 66 percent of patients who have type I diabetes and 59 percent of patients who have type II diabetes develop objective neuropathy.[26] These results, when applied to the US population with diabetes, suggest that as many as 11 million people in this country may have some degree of one or more diabetic peripheral neuropathies. Because diabetes is such a common disorder, however, it may coincide with other conditions that cause peripheral neuropathies.

The mere association of neuropathic symptoms with diabetes is not sufficient for diagnosis of diabetic neuropathy, and other causes of peripheral neuropathy always must be excluded. This approach is particularly relevant when the neuropathy is rapidly progressive, there is prominent motor abnormality or cranial nerve involvement, or there are disproportionate large fiber abnormalities. If there is involvement of the entire lower limbs without neuropathy of the distal upper limbs, it is unlikely that the process would be related to diabetic neuropathy and other causes should be investigated.

It has been estimated that approximately one third of patients who have diabetes have a neuropathy unrelated to diabetes.[20] In The Rochester Diabetic Neuropathy Study,[26] 10 percent of patients who have diabetes and distal sensory neuropathy had other possible causes of neuropathy. Gorson and

Table 3. The Rochester Diabetic Neuropathy Study

	Type I (%)	Type II (%)
Polyneuropathy	54	45
Asymptomatic carpal tunnel syndrome	22	29
Symptomatic carpal tunnel syndrome	11	6
Visceral autonomic neuropathy	7	5
Other variants	3	3

Ropper[27] recently showed that this number is significantly higher, because 55 percent of their 103 consecutive patients with diabetes and distal sensory neuropathy had apparent additional causes for neuropathy. Chronic alcohol use, neurotoxic medications, low serum vitamin B12 or B6, hypertriglyceridemia, and monoclonal proteins and paraproteinemia were the frequent findings. Patients who had additional causes for neuropathy more often had sensory symptoms and findings in the hands, and their neuropathy was more severe. In agreement with previous studies, nine percent of Gorson and Ropper patients had electrophysiologic features of demyelination and six percent had conduction blocks.[28]

It is possible that an immune-mediated neuropathy be an additional cause for neuropathy, responding to the appropriate treatment and necessitating further diagnostic evaluation. Similarly, with the high prevalence of diabetes it is likely that patients with diabetic neuropathy and chronic immune-mediated demyelinating polyneuropathy would be encountered in the neurology practice. Such a coincidence has led to the exaggerated conclusion that diabetic neuropathy itself is an immune-mediated disorder. Considering the current prevalence of diabetes in the United States and the crude overall estimates of prevalence of chronic immune-mediated demyelinating polyneuropathy at 0.81 to 1.9 per 100,000 population,[29-31] approximately 1600 to 3800 patients are expected to have both conditions. These numbers would be even significantly higher for patients in the 70- to 79-year-old age group or male patients if the respective prevalences of 6.7 and 9.5 per 100,000 population for chronic immune-mediated demyelinating polyneuropathy in these groups are considered.[31] A clear answer to the question of immune-mediated diabetic neuropathy must await prospective studies in which a comprehensive and systematic evaluation of large numbers of patients is performed.

4. Does glucose modulate pain perception in diabetic neuropathy?

This important question has received scant attention despite the clinical observations that pain intensity in diabetic neuropathy fluctuates diurnally and in response to meals and that such variations may influence pain management or pain evaluation in drug trials. Research has suggested that, at least in experimental animals, glucose or serum insulin level plays an important mediating factor in the painful symptoms[32,33] and there may be a direct hyperalgesic effect of hyperglycemia on the dorsal root ganglia.[34] In humans, the idea that glucose may be an important contributing factor in painful diabetic neuropathy has been suggested in several clinical studies. In a randomized, single-blind study, Morley and coworkers[35] demonstrated in nondiabetic humans that a 50g infusion of glucose resulted in increased pain detection and reduced tolerance thresholds to electric stimuli. Patients who had hyperglycemic type II diabetes were shown to be hyperalgesic when compared with nondiabetic control patients.[35] Research also has shown that recovery from painful diabetic neuropathy is more likely to occur if patients are maintained in good diabetic control, which is particularly true if the onset of painful symptoms is acute or subacute but is less evident when the onset is insidious and is followed by sensory loss.

Because infusion of glucose in healthy subjects results in a marked stimulation of insulin secretion, it is difficult to attribute the hyperalgesic effects of glucose infusion observed by Morley and colleagues solely to hyperglycemia alone. In contrast to the study by Morley and colleagues, infusion of glucose in eight healthy young adults had no effect on heat-induced pain threshold in another double-blind study[36] and in a small study of five patients who had type I diabetes. Thye-Ronn and colleagues[37] also demonstrated no effect of short-term hyperglycemia in ten patients who had nonneuropathic type I diabetes after the infusion of glucose on the heat-pain threshold but not on pressure-pain threshold. These studies and others[38] raised some doubt as to the reported effect of hyperglycemia on increased pain perception. It is known that glucose or sucrose administered orally to neonates provides effective analgesia for painful procedures. This effect can be decreased by opioid receptors antagonists.

Whether there is a direct enhancing effect of glucose on the opioid receptors or an indirect effect via the release of endogenous opioids after the oral glucose administration remains to be investigated. In one study that used an in vitro expression system for mu-opioid receptors, no direct interaction between these receptors and glucose could be demonstrated.[39] In another study, three to four weeks' consumption of 32 percent sucrose in rats resulted in an increased morphine antinociceptive effect.[40]

These conflicting studies indicate that the suggested relation between hyperglycemia and pain perception, the glucose and diverse functions of opioid receptors, and the effects of pharmacologic agents on these interrelationships are far from clear but worthy of further investigation.

5. Types I and II diabetes have different pathogenesis. Is there a difference between neuropathy of types I and II diabetes?

Type I diabetes is a multifactorial autoimmune disease that results in severe insulin deficiency that is influenced by environmental and genetic factors. Type II diabetes is a nonimmune disorder with varying degrees of insulin resistance and impaired insulin secretion usually associated with obesity. Despite the differences in causation of both types of diabetes, it has traditionally been assumed that the neuropathy of types I and II diabetes is the consequence of hyperglycemia and the same pathogenetic factors.

Although this assumption is to a large extent true, there are structural and electrophysiologic differences between these two types of neuropathies, at least in experimental animals. In obese, hyperglycemic BBZ rats, which have no insulin deficiency and serve as a model for diabetes with insulin resistance (type II), a slowly progressive nerve conduction deficit, severe reduction in Na + /K ± ATPase activity, moderate myelinated fiber atrophy, and relatively severe segmental demyelination and Wallerian degeneration are observed. On the other hand, in type I diabetic BB/WOR rats with acute onset of hyperglycemia caused by an immune-mediated destruction of insulin producing cells, there is axonal swelling in paranodal regions, distal to proximal axonal atrophy, excessive myelin wrinkling, and impaired axonal regeneration.[41] Insulin deficiency and C-peptide impairment that occur in human type I diabetes and only in advanced type II diabetes play an important role in the abnormal protein interactions, perturbation of gene regulatory mechanisms, and impaired neurotrophic factors, which collectively contribute to the development of diabetic complications, including neuropathy.[42]

These observations suggest that there should be some appreciable differences between the two types of diabetes in terms of type, severity or progression of neuropathy. Population-based studies, however, have demonstrated modest differences only in the degree of the severity of neuropathy between the two types of diabetes. The Rochester Diabetic Neuropathy Study,[26] which prospectively studied 380 of 870 patients who had diabetes in Rochester, Minnesota, revealed that 278 patients (73.2 percent) had type II diabetes, whereas 102 patients (26.8 percent) had type I diabetes. Fifty-nine percent of patients who had type II and 66 percent of patients who had type I had some forms of neuropathy (Table 3).

Symptomatic degrees of polyneuropathy occurred with similar frequency in types I and II diabetes (15 percent versus 13 percent), but more severe stages of neuropathy with distal sensory and autonomic dysfunction occurred more frequently in type I (six percent) than II (one percent) diabetes.

6. Is there an effective therapeutic measure for eradication of pain in diabetic neuropathy?

Only approximately 10 percent of all diabetic neuropathies are painful; however, the distressing nature of symptoms and difficulties in their treatment have given rise to the false impression that diabetic neuropathy is usually a painful condition. Persons who have diabetes with painless neuropathies are rarely referred to neurologists and often are cared for by their primary care physicians or endocrinologists. Pain control in diabetic neuropathy is often difficult and disappointing, with the best agents available providing only 30 percent more pain relief above placebo and eradication of pain remaining a longing for patients and physicians alike.

Persistent pain exerts a substantial impact on the quality and enjoyment of life and causes significant disturbances in sleep. Because there is a possible effect of hyperglycemia in reducing the pain threshold, a better control of blood glucose and prevention of wide fluctuation of blood glucose level may aid in alleviating the pain. Arriving at an appropriate drug and dosage may require several attempts and must strike a balance between pain relief and side effects. Some patients with similar painful symptoms respond to one class of drug, whereas others respond to a different group of medications. This difference should be emphasized to patients before initiating treatment. Genetic differences in pain-mediating pathways may explain this phenomenon.

Patients should be told about the possibility of spontaneous resolution of pain because a simple reassurance that pain is not permanent is usually sufficient to ensure cooperation in coping with the pain. Patients who are seen by neurologists already have tried simple analgesics, but the use of nonsteroidal anti-inflammatory drugs should be discouraged because of their potential nephrotoxicity. To avoid early and unacceptable side effects, the principle of "start low, go slow" in initiating drug therapy should be followed for all classes of drugs, especially tricyclic antidepressants. Many treatment failures can be attributed to insufficient dosing or intolerance caused by rapid dose escalations. Drugs from several different pharmacologic classes have been shown to be safe and effective in alleviating neuropathic pain, but none has caused elimination of pain. These drugs include tricyclic antidepressants, anticonvulsants, sodium-channel blockers, opioids and non-narcotic analgesics, and topical agents. In practice, combinations of these drugs often are used; however, no data from clinical trials provide guidance regarding which combination to choose.

To compare efficacy among the different agents, the number needed to treat (NNT) is given whenever possible. The NNT is an estimate of the total number of patients who must be treated to obtain one patient with at least 50 percent pain relief.[43] In other words, the lower the NNT value, the more effective the drug. Tricyclics, which reduce pain independent from their effect on mood, have an NNT between 2 and 3. Most studies have shown that doses of tricyclics of 75 to 150mg (less for elderly patients) are required for pain suppression. At such high dosage levels, sedation, confusion, anticholinergic effects (*e.g.*, constipation, dry mouth, urinary retention) and orthostatic hypotension are common side effects, particularly in elderly patients and patients who have clinical or nonapparent diabetic autonomic neuropathy.

In such cases, if a patient seems to respond to amitriptyline, a trial of nortriptyline may be worthwhile, due to its lower propensity to cause orthostatic hypotension. Because of the weaker serotonergic activity of nortriptyline, however, it may be less effective for pain relief. Venlafaxine, with an NNT of 5 to 6.9, is an inhibitor of norepinephrine and serotonin reuptake with fewer side effects than tricyclics. At a dose of 150 to 225mg/day, it is less effective than imipramin (NNT of 1.3-3.0).[44] Duloxetin, a newly introduced dual reuptake inhibitor of 5-HT and norepinephrine, has a moderate effect on pain (60-120mg/day) with an NNT of 5.2.[45] The most frequent side effects include nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite. Other antidepressants are either ineffective or have minimal effect.

Anticonvulsants are considered second-line agents but are frequently given to all patients who have diabetic neuropathies, even patients who have painless sensory symptoms, a practice that should be discouraged. There is also a misunderstanding among some patients who have diabetic neuropathy that these agents treat the neuropathy itself. They should be appropriately educated that these agents are designed to modulate the pain without favorably influencing the course of the underlying neuropathy. The efficacy of carbamazepine (1000-1600mg/day) is equivalent to tricyclic antidepressants (NNT of 3), but intolerable side effects limit its use. Its analog, oxcarbazepine, at a dose of 1200mg or more daily, may be modestly effective.[46]

Gabapentin, with an unknown mechanism of action, is used for many types of pain, but a median effective dose ranges from 900 to 1600mg/day; even 3600mg is needed for effective pain relief in diabetic neuropathy. Its NNT is 4. At a high dose there may be unacceptable side effects, including dizziness, sedation, confusion, mild gastrointestinal symptoms, gait problems, weight gain, and increased pedal edema. The latter two side effects may pose particular problems—diagnostically and therapeutically—among older patients who have diabetes. Pregabalin, which is structurally similar to gabapentin, has been shown in several trials to be consistently effective, with an average NNT of 3.9. The side-effect profile is essentially the same as gabapentin. Topiramate had a marginal effect with NNT of 7.4. This drug also decreases insulin resistance, lowers blood pressure, and has a favorable impact on lipid metabolism. Lamotrigine, which acts by blocking sodium channels and inhibiting the presynaptic release of glutamate, results in moderate (NNT of 4) pain relief at 200 to 400mg/day. A recent study showed even fewer and inconsistent beneficial effects, however.[47]

In patients who have not responded to tricyclics or anticon-

1. Tesfaye S, Stevens LK, Stephenson JM, et al.and the EURODIAB IDDM Study Group. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia. 1996;39(11):1377-1384. CrossRef

2. Dyck PJ, Davies JL, Wilson DM, et al.. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. Diabetes Care. 1999;22(9):1479-1486. MEDLINE | CrossRef

3. Swade TF, Emanuele NV. Alcohol and diabetes. Compr Ther. 1997;23(2):135-140. MEDLINE

4. Anan F, Takahashi N, Shinohara T, et al.. Smoking is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients. Eur J Clin Invest. 2006;36(7):459-465. MEDLINE | CrossRef

5. Mitchell BD, Hawthorne VM, Vinik AI. Cigarette smoking and neuropathy in diabetic patients. Diabetes Care. 1990;13(4):434-437. MEDLINE

6. Sands ML, Shetterly SM, Franklin GM, et al.. Incidence of distal symmetric (sensory) neuropathy in NIDDM: the San Luis Valley Diabetes Study. Diabetes Care. 1997;20(3):322-329. MEDLINE

7. Groop PH, Forsblom C, Thomas MC, et al.. Mechanisms of disease: Pathway-selective insulin resistance and microvascular complications of diabetes. Nat Clin Pract Endocrinol Metab. 2005;1:100-110. MEDLINE | CrossRef

8. Bedlack RS, Edelman D, Gibbs JW, et al.. APOE genotype is a risk factor for neuropathy severity in diabetic patients. Neurology. 2003;60(6):1022-1024.

9. Zhou Z, Hoke A, Cornblath DR, et al.. APOE epsilon4 is not a susceptibility gene in idiopathic or diabetic sensory neuropathy. Neurology. 2005;64(1):139-141.

10. Bedlack RS, Strittmatter WJ, Morgenlander JC. Apolipoprotein E and neuromuscular disease: a critical review of the literature. Arch Neurol. 2000;57(11):1561-1565. MEDLINE | CrossRef

11. Sivenius K, Pihlajamaki J, Partanen J, et al.. Aldose reductase gene polymorphisms and peripheral nerve function in patients with type 2 diabetes. Diabetes Care. 2004;27(8):2021-2026. MEDLINE | CrossRef

12. Sivenius K, Niskanen L, Voutilainen-Kaumisto R, et al.. Aldose reductase gene polymorphisms and susceptibility to microvascular complications in type 2 diabetes. Diabet Med. 2004;21(12):1325-1333. MEDLINE | CrossRef

13. Thamotharampillai K, Chan AK, Bennetts B, et al.. Decline in neurophysiological function after 7 years in an adolescent diabetic cohort and the role of aldose reductase gene polymorphisms. Diabetes Care. 2006;29(9):2053-2057. MEDLINE | CrossRef

14. Stephens JW, Dhamrait SS, Acharya J, et al.. A common variant in the ACE gene is associated with peripheral neuropathy in women with type 2 diabetes mellitus. J Diabetes Complications. 2006;20(5):317-321. Abstract | Full Text | Full-Text PDF (127 KB) | MEDLINE | CrossRef

15. Malik RA. Can diabetic neuropathy be prevented by angiotensin-converting enzyme inhibitors?. Ann Med. 2000;32(1):1-5. MEDLINE | CrossRef

16. Sanada M, Higashi Y, Nakagawa K, et al. Relationship between the angiotensin-converting enzyme genotype and the forearm vasodilator response to estrogen replacement therapy in postmenopausal women.

17. Seaqist ER, Goetz FC, Rich S, et al.. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med. 1989;320(18):1161-1165. MEDLINE

18. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 1997;46(11):1829-1839. MEDLINE

19. Misur I, Zarkovic K, Barada A, et al.. Advanced glycation endproducts in peripheral nerve in type 2 diabetes with neuropathy. Acta Diabetol. 2004;41(4):158-166. MEDLINE | CrossRef

20. Lozeron P, Nahum L, Lacroix C, et al.. Symptomatic diabetic and non-diabetic neuropathies in a series of 100 diabetic patients. J Neurol. 2002;249(5):569-575. MEDLINE | CrossRef

21. Eaton JW, Qian M. Molecular bases of cellular iron toxicity. Free Radic Biol Med. 2002;32(9):833-840. MEDLINE | CrossRef

22. Bierhaus A, Haslbeck KM, Humpert PM, et al.. Loss of pain perception in diabetes is dependent on a receptor of the immunoglobulin superfamily. J Clin Invest. 2004;114(12):1741-1751. MEDLINE | CrossRef

23. Tesfaye S, Harris ND, Wilson RM, et al.. Exercise-induced conduction velocity increment: a marker of impaired peripheral nerve blood flow in diabetic neuropathy. Diabetologia. 1992;35(2):155-159. CrossRef

24. Ram Z, Sadeh M, Walden R, et al.. Vascular insufficiency quantitatively aggravates diabetic neuropathy. Arch Neurol. 1991;48(12):1239-1242. MEDLINE

25. National Diabetes Information Clearinghouse. National Diabetes Statistics. NIH Publication No. 06-3892.2005.

26. Dyck PJ, Kratz KM, Karnes JL, et al.. The prevalence by staged severity of various types of diabetic neuropa-

vulsants, tramadol may provide significant pain relief. This drug has at least two complementary modes of action: (1) low affinity (one-tenth of codeine) binding to mu-opioid receptors and (2) inhibition of reuptake of synaptic norepinephrine and serotonin. This combined mode of action makes it desirable for the treatment of painful diabetic neuropathy. In clinical trials, doses of 200 to 400mg/day have proved effective with an NNT of 3.4. The drug is generally well tolerated, but transient nausea and constipation occur in approximately 20 percent of patients.[48] Tramadol has been reported to have little potential for abuse but should not be used in patients with a history of substance abuse.

Mexiletin, the oral analog of lidocaine, is generally ineffective, and gastrointestinal side effects make its use problematic. High-dose dextromethorphan, a low-affinity NMDA antagonist, provides partial pain relief but is associated with significant sedation and ataxia. The use of narcotics in painful diabetic neuropathy is generally discouraged because of the potential for drug dependency and their modest effect on neuropathic pain. In severe cases that are refractory to other treatments, however, narcotics may be used under guidelines established for chronic narcotic drug use.

Topical use of capsaicin-containing creams in the treatment of painful diabetic neuropathy may be modestly and temporarily effective, but most patients find the initial irritation after topical application too unpleasant and discomforting to continue the treatment.

Alpha-lipoic acid, an antioxidant with hypoglycemic effects, has been shown to be effective in an oral dose of 600mg once daily for reducing stabbing and burning pain.[49] The drug has an overall favorable safety profile. The effect of drug is usually evident within one to two weeks after treatment.

Nonpharmacologic approaches, such as transcutaneous nerve stimulation, high-frequency muscle stimulation, frequency-modulated electromagnetic nerve stimulation, monochromatic infrared energy and biofeedback, and psychological support have been tried with minimum sustained benefit.

The use of surgical decompression of multiple peripheral nerves as an alternative approach to treatment of painful diabetic neuropathy is a contentious issue that cannot be supported, despite public interest and promotional statements by the proponents of this procedure. No prospectively conducted randomized controlled trials using standard definitions for neuropathy and outcome measures have been conducted to allow recommending this procedure.[50]

Summary

Despite several novel analgesic drugs, the pharmacologic or nonpharmacologic treatment of chronic painful diabetic neuropathy remains a challenge, and the current state of treatment remains unsatisfactory and far from being able to eradicate pain. Ultimately, an effective treatment may include a combination of pain relief and improvement and slowing the progression of the underlying diabetic neuropathy. **PN**

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thy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993;43(4):817-824. MEDLINE

27. Gorson KC, Ropper AH. Additional causes for distal sensory polyneuropathy in diabetic patients. J Neurol Neurosurg Psychiatry. 2006;77(3):354-358. MEDLINE | CrossRef

28. Abu-Shakra SR, Cornblath DR, Avila OL, et al.. Conduction block in diabetic neuropathy. Muscle Nerve. 1991;14(9):858-862. CrossRef

29. Kusumi M, Nakashima K, Nakayama H, et al.. Epidemiology of inflammatory neurological and inflammatory neuromuscular diseases in Tottori Prefecture, Japan. Psychiatry Clin Neurosci. 1995;49(3):169-174. MEDLINE | CrossRef

30. Lunn MP, Manji H, Choudhary PP, et al.. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. J Neurol Neurosurg Psychiatry. 1999;66(5):677-680. MEDLINE

31. McLeod JG, Pollard JD, Macaskill P, et al.. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales. Australia. Ann Neurol. 1999;46(6):910-913.

32. Lee JH, Cox DJ, Mook DG, et al.. Effect of hyperglycemia on pain threshold in alloxan-diabetic rats. Pain. 1990;40(1):105-107. Abstract | Full-Text PDF (291 KB) | MEDLINE | CrossRef

33. Holder MD, Bolger GT. Chronic sweet intake lowers pain thresholds without changing brain mu- or delta-opiate receptors. Behav Neural Biol. 1988;50(3):335-343. MEDLINE | CrossRef

34. Dobrestov M, Hastings SL, Stimers JR, et al.. Mechanical hyperalgesia in rats with chronic perfusion of lumbar dorsal root ganglion with hyperglycemic solution. J Neurosci Methods. 2001;110(1-2):9-15. MEDLINE | CrossRef

35. Morley GK, Mooradian AD, Levine AS, et al.. Mechanism of pain in diabetic peripheral neuropathy. Effect of glucose on pain perception in humans. Am J Med. 1984;77(1):79-82. MEDLINE | CrossRef

36. Chan AW, MacFarlane IA, Bowsher DR, et al.. Does acute hyperglycaemia influence heat pain thresholds?. J Neurol Neurosurg Psychiatry. 1988;51(5):688-690. MEDLINE

37. Thye-Ronn P, Sindrup SH, Arendt-Nielsen L, et al.. Effect of short-term hyperglycemia per se on nociceptive and non-nociceptive thresholds. Pain. 1994;56(1):43-49. Abstract | Full-Text PDF (758 KB) | MEDLINE | CrossRef

38. Chan AW, MacFarlane IA, Bowsher DR. Short term fluctuations in blood glucose concentrations do not alter pain perception in diabetic-patients with and without painful peripheral neuropathy. Diabetes Res. 1990;14(1):15-19. MEDLINE

39. Kracke GR, Uthoff KA, Tobias JD. Sugar solution analgesia: the effects of glucose on expressed mu opioid receptors. Anesth Analg. 2005;101(1):64-68. MEDLINE | CrossRef

40. D'Anci KE, Kanarek RB, Marks-Kaufman R. Beyond sweet taste: saccharin, sucrose, and polycose differ in their effects upon morphine-induced analgesia. Pharmacol Biochem Behav. 1997;56(3):341-345. MEDLINE | CrossRef

41. Sima AA, Zhang W, XU G, et al.. A comparison of diabetic polyneuropathy in type II diabetic BBZDR/Wor rats and in type I diabetic BB/Wor rats. Diabetologia. 2002;43(6):786-793. CrossRef

42. Sima AA. Pathological mechanisms involved in diabetic neuropathy: can we slow the process?. Curr Opin Investig Drugs. 2006;7(4):324-337. MEDLINE

43. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology. 2000;55(7):915-920. MEDLINE

44. Sindrup SH, Bach FW, Madsen C, et al.. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003;60(8):1284-1289.

45. Wernicke JF, Pritchett YL, D'Souza DN, et al.. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006;67(8):1411-1420. CrossRef

46. Grosskopf J, Mazzola J, Wan Y, et al.. A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. Acta Neurol Scand. 2006;114(3):177-180. MEDLINE | CrossRef

47. Vinik AI, Tuchman M, Safirstein B, et al.. Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. Pain. 2006;Dec 8 [Epub ahead of print].

48. Harati Y, Gooch C, Swenson M, et al.. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology. 1998;50(6):1842-1846. MEDLINE

49. Ziegler D, Ametov A, Barinov A, et al.. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care. 2006;29(11):2365-2370. MEDLINE | CrossRef

50. Chaudry V, Stevens JC, Kincaid J, et al.. Practice Advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2006;66(12):1805-1808. CrossRef