

The Management of Diabetic Neuropathy and

Glycemic Control in Long-Term Care Facilities

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Release date: January 15, 2009

Expiration date: January 14, 2011

Estimated time to complete: 1.75 hours

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This CME activity is supported by an
educational grant from Pfizer Inc.,
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A CME/CPE/CE Activity

The Management of Diabetic Neuropathy and Glycemic Control in Long-Term Care Facilities

A Multisupported CME Monograph

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Statement of Need

One of the most frequent microvascular complications of type 2 diabetes is diabetic neuropathy, which affects sensory, autonomic, and motor neurons of the peripheral nervous system. Diabetic neuropathy is estimated to be present in half of the people living with diabetes mellitus, can affect nearly every tissue or organ in the body, and can lead to pain, morbidity, and mortality. While the challenge of treating diabetic neuropathy may be daunting, research shows that by controlling hyperglycemia and implementing lifestyle modifications and aggressive pharmacotherapies, diabetic neuropathy may be effectively managed. Furthermore, research shows that clinicians who forge trusting relationships with patients and empower them through education and support have a better chance at producing positive outcomes.

Recent significant increases in the incidence and prevalence of diabetes make understanding the high prevalence of chronic diabetic neuropathy and its associated pain essential for clinicians. This educational activity provides clinicians with the tools and knowledge necessary to diagnose and treat diabetic neuropathy, including tools to assess disease severity, tips on diagnosis, information on patient education and empowerment, and recent clinical trial data on pharmacotherapies.

Target Audience

This activity is designed for medical directors, directors of nursing, primary care physicians, physician assistants, nurse practitioners, nurses, and pharmacists who treat diabetes and neuropathic pain in the elderly population, with a particular focus on long-term care.

Learning Objectives

Upon completion of this education-based activity, participants should be able to:

1. Describe the definition of diabetic peripheral neuropathy, and how to exclude disorders that mimic it
2. List the complications of diabetic neuropathy, and utilize a management plan for preventing its complications
3. Review the importance of tight glycemic control as it pertains to the development of diabetic neuropathy
4. Initiate pain management with efficient pharmacotherapy, and implement tight diabetes control to slow disease progress
5. Devise strategies for improving communication gaps between elderly long-term care patients with type 2 diabetes and healthcare providers

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The Management of Diabetic Neuropathy and Glycemic Control in Long-Term Care Facilities

Introduction

The prevalence of diabetes mellitus is estimated at 180 million, and the World Health Organization projects that prevalence will double from that level by the year 2030.¹ Approximately half of the patients with diabetes mellitus will develop a preventable but devastating complication called *diabetic peripheral neuropathy* (DPN).²

This educational activity recaps the epidemiology, classification, diagnosis, and pathology of diabetic neuropathy and summarizes the optimal pharmacological and nonpharmacological methods of treatment.

Defining the Challenge

Definition and Prevalence

DPN is often defined as “the presence of symptoms or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes.”³ There are several challenges to using this definition. Clinicians detect peripheral nerve dysfunction based on patients’ presenting symptoms and/or physical examination.⁴ Most often, symptom- and/or physical examination-based scales are used, but these may lack sensitivity.^{4,5} Some experts advocate using a large panel of different tests together to maximize sensitivity, and scales may be supplemented by electrodiagnostic studies such as nerve conduction studies, electromyography (which is sensitive for large-diameter sensory and motor fiber dysfunction), autonomic testing, and epidermal nerve fiber density testing (which is sensitive for small fiber dysfunction).⁶

A second challenge comes from the “exclusion of other causes.”³ Diabetes mellitus can affect sensory nerves, motor nerves, and autonomic nerves. Distal symmetric polyneuropathy typically leads to both small and large nerve fiber damage. Frequently, combinations of nerves are affected in what is termed *polyneuropathy*.⁷

Classification systems have been proposed based upon the types and patterns of peripheral nerves involved.³ For every one of these sites of pathology, there will be a list of potential causes. A detailed description of all the causes of every type of peripheral nerve dysfunction that can be seen in a patient with diabetes mellitus is beyond the scope of this monograph. However, there are certain patterns of neuropathy that are highly unlikely to be related to diabetes mellitus. The most common presentation of DPN (and its differential diagnoses) is presented later in this monograph.

The challenges of the definition of DPN, as the challenge of ascertainment bias, make the true prevalence of DPN difficult to know. Dyck and colleagues attempted to determine the extent of diabetic neuropathies in a community-based study of 380 patients with clinically recognized diabetes mellitus.⁸ Of these patients, 102 had insulin-dependent diabetes mellitus

(IDDM), and 278 had non-insulin-dependent diabetes mellitus (NIDDM). Two-thirds of the IDDM patients had some type of neuropathy; of these patients, 54% had polyneuropathy, 22% had asymptomatic carpal tunnel syndrome, 11% had symptomatic carpal tunnel syndrome, 7% had visceral autonomic neuropathy, and 3% had other neuropathies. Patients with NIDDM had similar rates of neuropathies: polyneuropathy (45%), asymptomatic carpal tunnel syndrome (29%), symptomatic carpal tunnel syndrome (6%), visceral autonomic neuropathy (5%), and other neuropathies (3%).

DPN Presentation Is Typically Sensory and Insidious in Onset

Chronic sensorimotor polyneuropathy is the most common form of DPN.³ Up to 50% of the patients with this type of neuropathy experience painful symptoms such as burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain. From 10% to 20% have symptoms severe enough to require treatment.⁹ In most patients, the pain is worse at nighttime.³

DPN presentation is mainly sensory and insidious in onset.³ Symptoms begin in the toes and the feet and gradually extend proximally.¹⁰ Later, the fingers and hands may become affected, again with proximal spread. Usually, when extensive, the anterior abdominal wall may be involved, and sensory loss gradually spreads laterally around the trunk. Patients may lose their ability to feel, identify, or manipulate smaller objects.¹¹ They can gradually lose the capacity to ascertain temperature or sense painful or threatening stimuli. The loss of innervation can lead to atrophy of essential pedal muscles, resulting in deformities (eg, hammer toes) that leave patients vulnerable to ulceration.^{11,12} Sensorimotor neuropathy is the main risk factor for developing diabetic foot ulcers, which are the predominant risk factor for lower-extremity amputations in diabetes patients.

Motor involvement is less frequent than sensory involvement.¹⁰ However, when severe, this neuropathy causes weakness of distal leg muscles.

Autonomic Neuropathies

The autonomic nervous system may become widely involved itself in diabetic neuropathy.¹¹ Diabetic autonomic neuropathy can develop in patients with type 1 or type 2 diabetes. While autonomic neuropathy can occur at any stage of diabetes, those over age 40 years who have had the disease for more than 25 years and have difficulty controlling their blood sugar run the highest risk.¹³

Most patients have symptoms that are not severe, but some have significant morbidity and even mortality, especially with *cardiovascular autonomic neuropathy* (CAN).³ Symptoms of autonomic neuropathy range from cardiac (ie,

early fatigue, weakness with exercise, and postural hypotension) to gastrointestinal (ie, gastroparesis, erratic glucose control, abdominal pain, early satiety, nausea, vomiting, constipation, and diarrhea). Other symptoms include sexual, bladder, and sudomotor dysfunction.

Cardiovascular Autonomic Neuropathy

CAN affects both the sympathetic and parasympathetic innervation of the heart and coronary vessels.¹¹ Primary symptoms of CAN are orthostatic hypotension and decreased heart rate variability, and CAN may contribute to left ventricular dysfunction, silent or asymptomatic myocardial infarction, and exercise intolerance.^{11,14} There is evidence that the disease process may begin early in the course of diabetes but remains asymptomatic until later stages.^{11,14}

Gastrointestinal Autonomic Neuropathy

Diabetic autonomic neuropathy can affect the entire gastrointestinal system. Symptoms range from mild discomfort to disabling impairment of daily activities. Gastroesophageal dysfunction manifests as gastroesophageal reflux disease in roughly 30% of diabetes patients.¹⁵ Delayed gastric emptying and gastric retention, which are present in one-fourth of patients with diabetes, can result in early satiety, bloating, epigastric pain (heartburn), nausea, vomiting, and anorexia.¹⁶ Gastroparesis can also complicate pharmacotherapy by delaying the absorption of glucose or antidiabetic medication.

Focal Neuropathies

Diabetic mononeuropathy has an acute onset, usually is asymmetric, and involves the cranial, truncal, and peripheral

nerves.¹⁷ The neuropathy generally resolves spontaneously in 3 to 12 months, but in rare cases may last for years.

Cranial Neuropathies

Cranial neuropathies are rare, and include the III, IV, VI, and VII cranial nerves.³ Cranial neuropathy affects the nerves connected with the brain that control sight, eye movement, hearing, and taste.¹⁸ Most often, cranial neuropathy affects the nerves that control the eye muscles. Neuropathy starts with pain on one side of the face near the affected eye. Later, the eye muscle becomes paralyzed, resulting in double vision. Nevertheless, symptoms of this type of neuropathy usually resolve within 2 or 3 months.

Truncal Neuropathies

Truncal neuropathy usually presents subacutely with painful paresthesia in variable size patches in the trunk, either unilaterally or bilaterally.¹⁹ Associated involvement of motor nerve fibers can lead to bulging of the abdominal wall in the paresthetic areas. Clinicians should check for a patch of sensory abnormality in the region of the symptoms.

Proximal Neuropathies

Proximal neuropathies may develop in long-standing diabetics with poor metabolic control and may lead to weight loss.²⁰ A prominent feature is pain that is often severe and located in the hips and thighs.^{20,21} Proximal neuropathy causes weakness in the legs and often leaves patients unable to emerge from a sitting to a standing position without aid. The length of the recovery period varies, depending on the type of nerve damage.

Figure 1 Patient Case: Vivian

Case Study: Vivian is a 77-year-old white female who was diagnosed with type 2 diabetes 15 years ago. She is using metformin and glimepiride for glucose control. Vivian is also currently taking an angiotensin-converting enzyme inhibitor for her blood pressure and aspirin 81 mg/day. She has never smoked.

- Body mass index: 27.3 kg/m²
- Blood pressure: 138/85 mm Hg
- Total cholesterol: 212 mg/dL
- Low-density lipoprotein-cholesterol (LDL-C): 132.6 mg/dL
- High-density lipoprotein-cholesterol (HDL-C): 46.2 mg/dL
- Triglycerides: 202.4 mg/dL
- Serum creatinine: 1.58 mg/dL
- Fasting plasma glucose: 156.7 mg/dL
- A1C 7.3%

- Vivian complains of experiencing “pins and needles” in the soles of her feet for 2 years
- She rates her pain during the day at 7 out of 10 and at night at 9 out of 10
- She reports recent depression, primarily due to a feeling of helplessness about her symptoms



Early Detection of DPN Is Critical

Boulton and colleagues offer the following reasons to emphasize the importance of early detection and management of DPN³:

- Nondiabetic neuropathies may occur in diabetics, thereby confusing the diagnostic process
- A number of treatment options exist for symptomatic DPN
- Up to half of DPN may be asymptomatic, leading to injuries the patient does not perceive, and contributing to amputations for complications of diabetes
- Autonomic neuropathies may involve multiple organ systems
- Morbidity and mortality increase with autonomic neuropathy, particularly if CAN is present

Diagnosing chronic DPN requires clinicians to exclude nondiabetic causes.³ Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy, vitamin B₁₂ deficiency, hypothyroidism, and uremia, occur in more frequency in diabetics than in the general population and require ruling out. The differential diagnosis includes various forms of hereditary neuropathy, as well as numerous causes of acquired neuropathy.²²

The diagnosis of DPN is made on the basis of a careful clinical examination and, when indicated, electrodiagnostic studies.³ The combination of using more than one test has a > 87% sensitivity in detecting DPN.

Table 1 lists the procedures clinicians should perform for all of their diabetic patients on an annual basis.³

Diagnosing Diabetic Neuropathy

Diagnosing diabetic neuropathy requires clinicians to perform a thorough physical examination, elicit patient history, and use clinical judgment; it does not necessarily hinge on any particular neurologic test or finding.¹⁷ Some patients such as Vivian (Figure 1) present with severe pain but only minimal neurologic deficits, while others present with foot ulcers but have no pain or neurologic symptoms.

A complete medical evaluation enables clinicians to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care.⁴

Table 2 lists the factors clinicians should consider when evaluating patients presenting with symptoms of diabetic neuropathy.¹⁷

Differential Diagnoses

No single test can definitely diagnose diabetic neuropathy, and clinical judgment must play a role.⁵ Good commu-

Table 1
Annual Screening for DPN³

- Examination of pinprick and temperature sensitivity – touch the patient's feet with a clean safety pin and with the cold metal of a tuning fork, then ask if they can appreciate these sensations as sharp and cold. Touch them more proximally to determine if there is a subjective difference in the intensity of the sensation proximally vs. distally.
- Vibration perception using a 128-Hz tuning fork – perform test at the great toes
- A 10-g Semmes-Weinstein monofilament pressure test at the distal hallux – as shown in the accompanying figure



Photo courtesy of the American College of Physicians

- Ankle reflex testing – between ages 50 and 65 years, ankle reflexes may normally be reduced; above age 65 years, the reflexes may normally be absent
- The feet should be examined for ulcers, calluses, and deformities, and clinicians should check the footwear of the patients

nication skills are important when assessing patients presenting with symptoms of diabetic neuropathy. Patient descriptions of burning, tingling, or pain would suggest diabetic neuropathy. However, clinicians should understand that there are other potential causes of diabetic neuropathy that must be excluded before a diagnosis of diabetic neuropathy is made. Conditions with symptoms resembling diabetic neuropathy that must be excluded include malignant disease, toxic causes, and infections, particularly human immunodeficiency virus. The patient's history may suggest other diagnoses as well, such as postherpetic neuralgia. Other pain syndromes that may mimic diabetic peripheral neuropathic pain include tarsal tunnel syndrome, osteoarthritis, idiopathic distal small fiber neuropathy, and erythromelalgia.

Diagnostic Tests

Several diagnostic tests can be used to determine the presence and type of diabetic neuropathy.¹⁷ Clinicians should review patients' symptoms to determine if neuropathy is present and to what extent. It is important to remem-

Table 2
Considerations for Evaluation of Diabetic Neuropathy¹⁷

History	<ul style="list-style-type: none"> • Screen for symptoms of diabetic neuropathy • Review diabetes history, disease management, daily glycemic records, and previous A1C levels • Identify any family history of diabetes or neuropathy • Review medication history (including use of over-the-counter products and herbal or homeopathic products) and environmental exposures • Review for other causes of neuropathy, including vitamin B₁₂ deficiency, alcoholism, toxic exposures, medications, cancers, and autoimmune disease
Physical Examination	<ul style="list-style-type: none"> • Vital signs and pain index • Supine and standing blood pressure for postural hypotension • Cardiovascular examination to look for arrhythmias, absent or diminished pulses, edema, or delayed capillary refilling • Cutaneous examination to look for extremity hair loss, skin or nail changes (including callus), and pretrophic (red) areas, especially between toes • Neurologic examination using the 5.07 Semmes-Weinstein nylon filament test (10-g monofilament test) • Inspection of feet for asymmetry, loss of arch height, or hammer toes • Evaluation of all positive screening findings
Annual Diabetes Evaluation	<ul style="list-style-type: none"> • Evaluation for neuropathy • Sensorimotor examination and evaluation of cranial nerves, muscle strength, and range of motion <ul style="list-style-type: none"> – Document distribution, intensity, and type of sensory or motor deficits – Evaluate small nerve fibers with temperature, light touch, or pinprick testing – Test large nerve fibers by vibratory sensation, position sense, muscle strength, sharp-dull discrimination, and 2-point discrimination • Autonomic examination, including orthostatic blood pressure measurements <ul style="list-style-type: none"> – Consider heart rate variability tests and electrocardiography if sensory neuropathy is present or symptoms warrant further evaluation – Consider heart rate variability tests in the patient who has had type 1 diabetes for 10 years or type 2 diabetes for 5 years – Consider cardiac stress testing before the patient starts an exercise program

ber that all other potential causes of, for example, muscle weakness and numbness, be ruled out before making a diagnosis of diabetic neuropathy.

All patients with diabetes should receive an annual foot examination in which the foot is assessed for skin sensation using a monofilament (Semmes-Weinstein 5.07 [10-g]), skin integrity (calluses and sores, especially between toes), bone deformities or deformities in the foot's structure or biomechanics, and vibration perception.^{3,4,17} Ankle reflexes should also be tested. Quantitative sensory testing (responses to pressure, vibration, and temperature) can be used to determine loss of sensation or sensitivity of nerves.

Tools Clinicians Can Use to Measure Pain

Clinicians also have a variety of tools to assess pain, including the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Scale (NPS), Neuropathic Pain Questionnaire (NPQ), and the Brief Pain Inventory for Diabetic Peripheral Neuropathy.⁵ Other tools also used to measure neuropathic pain include the Neuropathic Pain Symptoms Inventory and the Neuropathic Pain Diagnostic Questionnaire (DN4).^{23,24}

Based on existing data, the LANSS has the most empirical support as a measure that distinguishes patients with and without neuropathic pain.⁵ The NPS has the most empirical support as a measure of treatment outcome. The LANSS includes 7 items (5 symptom items and 2 examination items).²⁵ Usually, the examination items are done by a clinician, but the modified version (the self-report LANSS [S-LANSS]) allows patients to use the scale themselves. The purpose of the LANSS is to assess whether the pain that is experienced is predominantly due to nerve damage or not. Both the LANSS and S-LANSS are scored out of 24; a score of 12 or more strongly suggests neuropathic pain. Clinicians can access the S-LANSS at: <http://www.neurocentre.com/slanss/slanss.pdf>.

To validate the LANSS, Bennett and colleagues asked 200 patients with chronic pain to complete the S-LANSS unaided.²⁶ A researcher then administered the S-LANSS scale and the NPS in interview format. The S-LANSS scale correctly identified 75% of pain types when self-completed and 80% when used in interview format.

The NPS is designed to assess distinct pain qualities associated with neuropathic pain.²⁷ The NPS is a 10-item questionnaire that has 2 global pain domains (intensity and unpleasantness), 8 pain qualities (sharp, hot, dull, cold, sensitive, deep, surface, and itchy pain), and is able to differentiate patients from different diagnostic groups.

Like the LANSS and NPS, the NPQ also distinguishes neuropathic pain patients from nonneuropathic pain patients.²⁸ The NPQ consists of 12 items that include 10 related to sensations or sensory responses, and 2 related to

affect. The NPQ demonstrated a 67% sensitivity and 74% specificity compared to clinical diagnosis in the validation sample. The short form of the NPQ maintained similar discriminative properties with only 3 items (numbness, tingling pain, and pain increase in response to touch).²⁹

The Brief Pain Inventory for Diabetic Peripheral Neuropathy assesses the severity of pain, its impact on daily functioning, and other aspects of pain.⁵ It includes 11 items (a 4-item pain severity scale and a 7-item pain interference scale). The pain severity scale uses *worst pain*, *least pain*, *average pain*, and *pain now*, with worst pain being most predictive of mild, moderate, and severe pain.

The DN4, which was developed in France, consists of 7 items related to symptoms and 3 related to clinical examination.²⁴ A total score of 4 out of 10 or more suggests neuropathic pain.

Risk Factors

The primary risk factor for diabetic neuropathy is hyperglycemia.⁴ The length of time a patient has diabetes also increases the risk of neuropathy, but the association between duration and prevalence may depend in part upon patient age, which itself is a risk factor.³⁰

Nerve damage in diabetic neuropathy is likely due to a combination of factors²¹:

- Metabolic factors (high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin)
- Neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to nerves
- Autoimmune factors that cause inflammation in nerves
- Mechanical injury to nerves, such as carpal tunnel syndrome
- Inherited traits that increase susceptibility to nerve disease
- Lifestyle factors, such as smoking or alcohol use

Consequences of DPN Can Be Severe

Diabetic neuropathies can lead to a series of serious complications, including death.^{3,31} Among the most serious complications is amputation of a limb.³² Because nerve damage caused by DPN affects a patient's ability to feel, cuts and sores may go unnoticed and become infected or ulcerated. Because diabetes reduces blood flow to feet, the risk of infection is high. Infections that cause tissue death (ie, gangrene) may require amputation of a toe, foot, or limb. Another complication associated with diabetic neuropathies includes Charcot joint, which ensues after a joint (usually in the foot) deteriorates.

Other conditions that may accompany diabetic neuropathies include sexual dysfunction, urinary tract infections, urinary incontinence, hypoglycemia unawareness, low

blood pressure, digestive problems, increased or decreased perspiration, and social isolation.³²

Diabetic Neuropathy Imposes Barriers to Quality of Life

Like most chronic pain syndromes, diabetic neuropathy impacts patients' quality of life (QOL). A 1998 study found that QOL was significantly more impaired in patients with diabetic neuropathy who registered higher degrees of impairment measures such as emotional reactions, energy, pain, physical mobility, and sleep compared to diabetic patients without neuropathy.³³ Another study of 105 patients with painful diabetic neuropathy reported high levels of interference with sleep and enjoyment of life, and moderate interference with mobility, employment, and recreational and social activities.³⁴

Diabetic Neuropathy Is Preventable

The Diabetes Control and Complications Trial (DCCT) demonstrated that tight control of glycemia may result in a greater than 60% reduction in the risk of developing clinical neuropathy in patients with type 1 diabetes.^{3,35} A follow-up study to DCCT, Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), demonstrated a lower prevalence of neuropathy in the intensively treated group when assessed either by questionnaire (1.8% vs 4.7%; $P < 0.0001$) or examination (17.8% vs 28.0%; $P < 0.0001$).³⁶

The UK Prospective Diabetes Study (UKPDS) 33 obtained similar findings in patients with type 2 diabetes, reporting significant reductions in microvascular and neuropathic complications with intensive glucose-lowering therapy.³⁷

Both the DCCT and UKPDS demonstrated that long-term intensive glucose control improved measures of autonomic function in both DPN and diabetic autonomic neuropathy.^{35,37} Acute sensory neuropathy has a strong association with blood glucose levels maintaining euglycemia, and often results in the resolution of painful symptoms.³

Controlling Blood Glucose, Blood Pressure, and Cholesterol Reduces Risk of Diabetic Neuropathy

Several studies also confirm how intensive therapy combining tight control of blood glucose, blood pressure, and cholesterol can benefit diabetic neuropathy. In the Steno-2 study published in 2008, Gæde and colleagues randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy over a mean treatment period of 7.8 years.³⁸ Intensive combined therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio [HR] 0.43; 95% confidence interval [CI], 0.19–0.94; $P = 0.04$) and a lower risk of cardiovascular events (HR 0.41; 95% CI, 0.25–0.67; $P < 0.001$). Intensive therapy also reduced the relative risk of autonomic neuropathy to 0.53

($P = 0.004$), but the relative risk of peripheral neuropathy was 0.97 ($P = 0.89$).

Another 2008 study conducted by the Action in Diabetes and Vascular Disease (ADVANCE) Collaborative Group revealed that intensive glucose and blood pressure control significantly reduced microvascular events.³⁹ However, the effect was primarily due to a reduction in nephropathy; new or worsening neuropathy was unchanged by intensive treatment (2353 with intensive treatment vs 2311 with standard treatment). Stratton and colleagues showed that the incidence of clinical complications was significantly tied to glycemic control.⁴⁰ In their 2000 study (UKPDS 35) in nearly 4600 patients, the authors concluded that each 1% reduction in updated mean A1C was associated with risk reductions of 21% for any endpoint related to diabetes (95% CI, 17-24; $P < 0.0001$), 21% for deaths related to diabetes (95% CI, 15-27; $P < 0.0001$), 14% for myocardial infarction (95% CI, 8-21; $P < 0.0001$), and 37% for microvascular complications (95% CI, 33-41; $P < 0.0001$).

Tight Glycemic Control Is Key When Managing the Elderly

Approximately 1 in 5 nursing home residents has diabetes.⁴¹ Of these patients, 90% have shown signs of coronary artery disease, stroke, and/or peripheral vascular disease. Elderly patients suffer from higher rates of all complications of diabetes, including autonomic neuropathy, nephropathy, retinopathy, erectile dysfunction, and foot ulcers.⁴²

Suh and colleagues compared the prevalence of type 2 diabetes mellitus in the U.S. elderly population between 1988 to 1994 and 1999 to 2004, and assessed glycemic control and comorbid conditions in this population.⁴³ After adjusting for patient characteristics, including duration of diabetes mellitus, patients with nephropathy or renal insufficiency were 40% less likely to achieve their A1C goal compared to those without. Approximately half of the elderly population diagnosed with type 2 diabetes had an A1C of 7% or higher.

Although many elderly diabetics do not maintain glycemic control, they are unaware of the problem because common symptoms of hyperglycemia might be absent.⁴⁴ Symptoms may include nonspecific lethargy, functional decline, weakness, and confusion.

Maintaining glycemic control in elderly patients offers several benefits and should be a high treatment priority.⁴⁴ Although tight glycemic control offers several benefits, including prevention of acute complications of hyperglycemia (ie, dehydration, mental status changes, and infection risk) and faster wound healing, clinicians should keep in mind the greater susceptibility elderly patients have to the adverse effects of hypoglycemia.

What A1C Goals Should Patients Pursue?

When patients achieve their A1C goals, patient outcomes have been shown to generally improve. The UKPDS 35

Table 3
ADA Recommendations for A1C Goal¹

The ADA encourages patients not to alter their course of treatment and continues to advise patients to strive for an A1C of < 7%:

- A level of approximately 7% has been shown to dramatically reduce complications of diabetes

ADA guidelines also state that "Less stringent A1C goals may be appropriate for patients with...":

- History of severe hypoglycemia
- Limited life expectancies
- Children
- Comorbid conditions
- Longstanding diabetes
- Minimal or stable microvascular complications

demonstrated that reducing A1C levels by 1% led to a 21% reduction in the risk of diabetes-related complications and deaths.⁴⁰ While the American Diabetes Association (ADA) recommends an A1C target of < 7%, the potential advantages and drawbacks of intensifying a treatment regimen to achieve the target should be considered for each individual patient, as outlined in Table 3.⁴

Clinicians should also realize that the ADA's recommendation has not changed following the recent announcement of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study that reported deaths in patients with type 2 diabetes receiving intensive glycemic therapy.⁴⁵

Diabetes Care: Improving but Still Falling Short of the Mark

Despite the results of the DCCT trial,³⁵ nearly 30% of commercial managed care patients have poor glycemic control (A1C > 9.5%).⁴⁶ Fortunately, according to a new analysis of National Health and Nutrition Examination Survey (NHANES) data published in 2008, glycemic control has improved during the current decade. The predictive margin for having A1C < 7.0% has increased from 37.0% in 1999-2000 to 49.7% in 2001-2002, and still higher to 55.7% between 2003 and 2004.⁴⁷ Clearly there is still work to be done to optimize prevention of DPN.

Pathophysiology

How Does Diabetes Mellitus Cause Nerve Damage?

Although the pathophysiology of diabetic neuropathy is unclear, most experts believe that hyperglycemia is the cause of the nerve damage in DPN.⁴⁸ Hyperglycemia causes increased levels of intracellular glucose in nerves, leading

to saturation of the normal glycolytic pathway.⁴⁹ Nevertheless, different neuropathies may have different (and perhaps overlapping) mechanisms; for example, with focal or asymmetrical diabetic neuropathy syndromes, vascular injury or autoimmunity may play more important roles. Other factors thought to play a role include activation of the polyol pathway, advanced glycation end products, increases in oxidative stress, altered gene expression with altered cellular phenotypes, changes in cell physiology relating to endoskeletal structure or cellular transport, reduction in neurotrophins, and nerve ischemia.

Managing Diabetic Neuropathy Requires Treating the Underlying Disease

Treatment of Neuropathic Pain in Type 2 Diabetes

Optimal management of diabetic neuropathies requires that clinicians understand that long-term control of blood sugars and reduction of cardiovascular risk factors is the cornerstone of treatment, both for diabetes and for diabetic neuropathy.³ Clinicians who properly treat the underlying diabetes have a better chance of reducing neuropathy and its accompanying symptoms, as opposed to regimens that simply address the neuropathy symptoms. Figure 2 presents the ADA and American Association of Clinical Endocrinologists/International Diabetes Federation–recommended goals for patients with type 2 diabetes who are at risk for diabetic neuropathy.^{4,50-52}

Nonpharmacological Treatment Options

Lifestyle Modifications

Diet and exercise have been shown to promote cutaneous reinnervation and improve pain in diabetic neuropathy patients.^{23,53} Patients should be counseled on the benefits of weight loss, tobacco cessation, and the effects of alcohol on diabetic neuropathy.

The Importance of Foot Care

Once a patient has diabetic neuropathy, foot care becomes crucial for preventing ulceration, infection, and amputation.³² At each visit, the physician should examine the patient's feet to detect evidence of neuropathy or early lesions, as well as skin breaks, red or callused areas, decreased pedal pulses, delayed capillary refilling, bony deformities, and protective sensation.¹⁷

Table 4 provides instructions clinicians should provide patients to foster effective foot care.^{5,17}

Pharmacological Treatment Options

The classes of drugs with the best proven efficacy are antidepressants, anticonvulsants, and opioids.¹⁰ Duloxetine, a serotonin noradrenaline reuptake inhibitor (SNRI), and pre-

Figure 2 Treatment Goals^{*4,50-52}

- A1C
 - ADA recommends < 7% in general, < 6% for selected individuals
 - American Association of Clinical Endocrinologists/International Diabetes Federation recommend \leq 6.5%
- Blood pressure
 - < 130/80 mm Hg
- Cholesterol
 - LDL-C: < 100 mg/dL (< 70 mg/dL in very high-risk patients)
 - HDL-C: > 40 mg/dL in men and > 50 mg/dL in women
 - Non-HDL-C: < 130 mg/dL (< 100 mg/dL in high-risk patients)
 - Triglycerides: < 150 mg/dL

* Physicians need to use clinical judgment in the management of blood sugar, hypertension, and serum lipids in frail, nursing home patients, recognizing the significant risks associated with hypoglycemia and hypotension, and the limited data available documenting benefit of aggressive risk factor control in the frail elderly with short life expectancies.

Table 4 Instructions to Give Patients for Proper Foot Care^{5,17}

- Inspect feet daily for dry or cracking skin, fissures, plantar callus formation, and signs of infection between the toes and around the toenails
- Avoid using topical ointments to damaged areas
- Break in new shoes slowly because new shoes frequently cause ulceration
- Avoid walking barefoot and cutting nails incorrectly, and exposing feet to hot objects or chemicals

gabalin are specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of painful DPN. All other agents must be considered “off-label,” although other considerations, including cost, intolerance of approved agents, comorbidities, and efficacy, may dictate their use.

Antidepressants

Duloxetine has been studied in 2 randomized, double-blind, placebo-controlled trials for relief of pain in patients with painful diabetic neuropathy,^{54,55} and is approved by the FDA at total dosages of 60 mg/day.⁵⁶

The first study, published in 2005, was a 12-week, multi-center, double-blind study in which 457 patients experiencing pain due to polyneuropathy caused by type 1 or type 2 diabetes mellitus were randomly assigned to treatment with duloxetine 20 mg/day, 60 mg/day, or 60 mg BID or placebo.⁵⁴ Duloxetine 60 and 120 mg/day demonstrated statistically significant greater improvement on the 24-hour average pain score compared to placebo. Duloxetine also

proved more efficacious than placebo on almost all secondary measures (ie, worst pain severity and mood). Patients in the 120-mg/day treatment arm experienced a statistically significant improvement in Short Form-36 mental ($P \leq 0.01$) and general health perception domains ($P \leq 0.001$) as well.

All doses of duloxetine were well tolerated, with no significant changes in concentrations of A1C, LDL-C, HDL-C, or triglycerides.⁵⁴ Adverse events included somnolence and constipation with the 60-mg/day dose, and nausea, somnolence, dizziness, constipation, dry mouth, sweating, decreased appetite, anorexia, and weakness with the 120-mg/day dose.

In another trial, patients with diabetic neuropathy were randomly assigned to receive either placebo ($n = 116$), duloxetine 60 mg/day ($n = 116$), or duloxetine 60 mg BID ($n = 116$).⁵⁵ The patients treated with duloxetine 60 mg daily had marked improvements in 24-hour average pain score, 24-hour worst pain severity score, and night pain score ($P < 0.001$). Patients treated with duloxetine 60 mg BID also had improvements in 24-hour average pain score ($P < 0.001$), 24-hour worst pain severity score ($P < 0.01$), and night pain score ($P < 0.001$).

Another antidepressant, venlafaxine, has yielded efficacy in alleviating pain in diabetic neuropathy when used in higher doses (150–225 mg/day).⁵⁷ In a randomized, placebo-controlled trial, venlafaxine extended-release (ER) at 2 doses (75 mg/day or 150–225 mg/day) was compared to placebo for the treatment of painful diabetic neuropathy. Rowbotham and colleagues concluded that the higher dose of venlafaxine ER significantly reduced pain intensity compared to placebo and venlafaxine ER 75 mg/day at week 6. The most common adverse events in the venlafaxine groups were nausea ($> 10\%$) and somnolence ($> 10\%$). Dyspepsia, insomnia, and sweating also occurred in 10% of the patients treated with venlafaxine ER 150–225 mg/day. Impotence was reported in 6% of the men receiving venlafaxine ER 75 mg/day and in 5% of the men receiving venlafaxine ER 150–225 mg/day.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are widely used to treat neuropathic pain but are not FDA-approved for this purpose and have a significant adverse-effect profile.⁵⁸ TCAs include amitriptyline, desipramine, clomipramine, and nortriptyline. TCAs have yielded significant pain relief in patients with DPN, although clinical trials of these agents have typically included small patient populations.⁵⁹ Randomized, double-blind, crossover, placebo-controlled studies of amitriptyline and desipramine demonstrated that 67% of the patients receiving amitriptyline ($P \leq 0.001$) experienced good to excellent pain relief, while 63% ($P < 0.05$) of the patients receiving desipramine experienced moderate or greater pain relief.

The side-effect profile of TCAs includes anticholinergic and muscarinic side effects, contraindicating all (especially amitriptyline) in the elderly and those with cardiovascular

pathology.⁵⁸ There is little efficacy difference between amitriptyline and desipramine (which has the lowest side-effect profile in this group), as Max and colleagues demonstrated in a small crossover study in 20 patients.⁶⁰ The lower cost and demonstrated efficacy must be weighed against the significant side-effect profile including sudden cardiac death at higher doses.⁵⁸

Anticonvulsants

Pregabalin is FDA-approved for painful diabetic neuropathy and postherpetic neuralgia.⁵⁸ As an anticonvulsant, it is approved for the treatment of partial seizures. It is a Schedule V controlled substance with a mild potential for abuse.⁵⁶

Studied in doses of 75, 150, 300, and 600 mg daily, pregabalin has yielded efficacy at the higher 2 doses in 3 randomized, double-blind, placebo-controlled studies.^{61–63} There may be a tendency for weight gain, especially at higher doses.^{61,63} Furthermore, a study conducted by Lesser et al reported significant incidences of dizziness, somnolence, and peripheral edema in both the 300- and 600-mg groups.⁶¹

The efficacy of gabapentin is comparable to amitriptyline at doses of 1565 mg/day compared to 59 mg/day.⁶⁴

Lidocaine Patches

Lidocaine patches may be useful if the pain of diabetic neuropathy is very focal. One to 3 patches can be applied to intact skin over the painful area, 12 hours on and 12 hours off.⁶⁵

Capsaicin Cream

Capsaicin cream depletes substance P, the major neurotransmitter used in conveying messages about pain into the central nervous system.⁶⁶ This can be applied over the painful area 3–4 times daily.⁶⁷ Gloves should be worn if this is used, and care taken to avoid contact with the eyes. Clinicians should note that many patients are unable to tolerate the intense increase in pain that occurs over the first few days that capsaicin cream is applied (until substance P is depleted).

Education and Effective Patient-Clinician Communication Is Critical for Treatment Success

Therapeutic patient education is a patient-centered approach directed toward patient needs, resources, and values.⁶⁸ Education enables patients to improve their knowledge and skills with both their illness and treatment. It brings a better QOL, a greater therapeutic compliance, and a reduction in complications.

Patient education means more than conveying information about the patient's disease.⁶⁹ Education focuses on bolstering self-management, because patients who "take control" of their disease are not only better able to cope with the challenges of living with a chronic disease,⁶⁹ but also to adhere to medication regimens and modify their lifestyles as necessary.⁶⁸ Clinicians' roles include providing information

patients need to set priorities and solve problems, assisting and supporting the implementation of lifestyle changes by identifying reasonable modifications they can make, and providing emotional support and encouragement.⁶⁸

One way clinicians can hone both their communication skills and be effective patient educators is by employing motivational interviewing.⁶⁸ Optimal outcomes for diabetic neuropathy patients often depend on their willingness to modify longstanding behaviors and adhere to complex medication schedules. Many patients have difficulty accomplishing these tasks, which leads to poorer outcomes.

The purpose of motivational interviewing is to explore the reasons patients do not adhere to their treatment regimen in a nonjudgmental manner, and then have the patients consider another point of view and become actors in their own decision-making.⁷⁰ This requires clinicians to hone their communication skills, not only their interviewing techniques, but also their ability to listen to patients. Golay and colleagues list the 4 requirements necessary to conduct effective motivational interviewing⁷⁰:

- Ask open-ended questions instead of closed ones
- Validate patients' efforts, personal efficacy, and self-esteem
- During therapeutic education, make use of reflective listening with empathic reformulations and paraphrasing, which reflect patients' legitimate feelings
- Summarize the interview's various stages to allow patients to follow the progress of the explanations of their ambivalence

Vég and colleagues demonstrated the therapeutic importance of using these techniques (especially asking open-ended questions) in a study of 183 patients with type 2 diabetes.⁶⁹ The authors investigated whether they could determine patients' diabetes self-management habits by asking 3 open-ended questions: "What is your role in your diabetes management?"; "What is your goal with your diabetes management?"; and "What kind of support do you need for your diabetes management?" The authors separated patients into 3 groups – Disease Manager, Compliant, and Disheartened – based on the patients' answers to the

3 open-ended questions. Disease managers believed in taking a proactive role in their diabetes management and either had limited support needs or were happy with the support they received. Compliant patients tended to follow their clinicians' treatment recommendations and expressed a greater need for support. Disheartened patients tended to explain why their treatments were not working and described a passive role for themselves in treating their disease. At the end of 24 months, Disease Manager patients reduced their A1C levels by -0.28. Compliant patients reduced their A1C by -0.18 after 6 months, but did not reduce their levels significantly after then. Disheartened patients did not reduce their A1C by statistically significant amounts.

Another approach clinicians can use with their patients is cognitive-behavioral techniques, which are focused on identifying the triggers that lead to negative behaviors.⁷⁰ The key to cognitive-behavioral techniques is formulating a functional analysis (such as the one shown in Figure 3) that displays a hypothetical trigger, negative thoughts, emotions, behavior, and consequences of the behavior for a diabetic patient who does not adhere to proper dieting habits.

The functional analysis of this food binge described in Figure 3 enables clinicians to illustrate to patients how a trigger (in this case, frustration at work) leads to negative consequences.⁷⁰ By analyzing the flow from trigger to consequence, patients can attain a better understanding of the underlying mechanisms responsible for their behaviors. Figure 4 displays how the "vicious cycle" can become a "virtuous circle" with a cognitive-behavioral approach.

Figure 3
Functional Analysis of Reasons for Poor Adherence to Dieting in Diabetic Patients⁷⁰

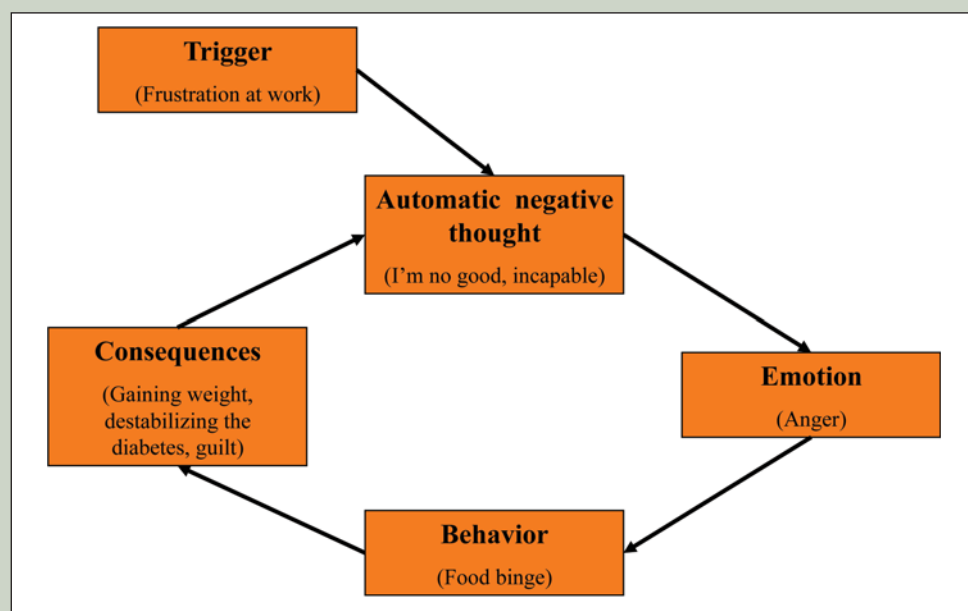


Figure 4
The "Virtuous Circle" Made Possible Through Cognitive-Behavioral Techniques⁷⁰

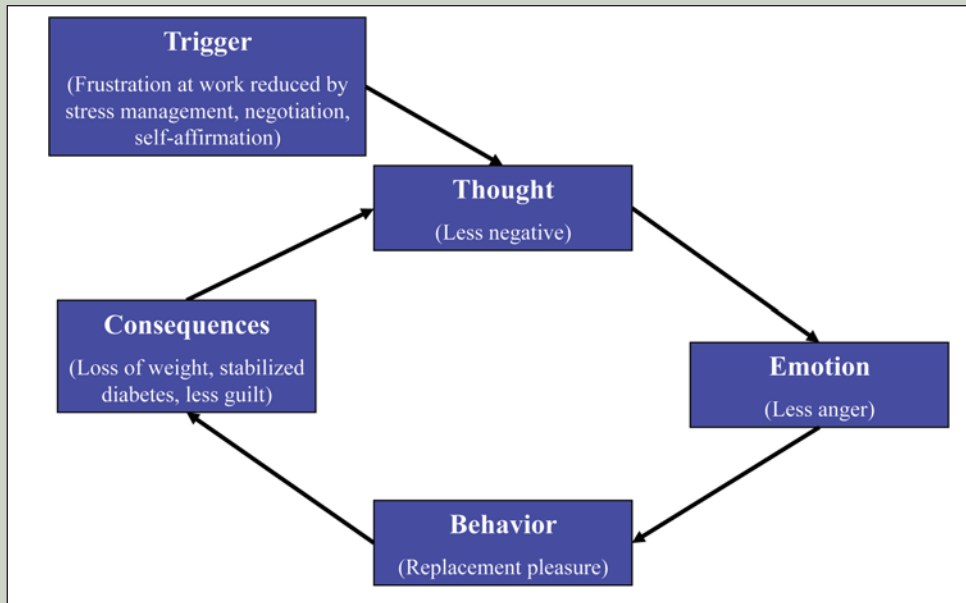
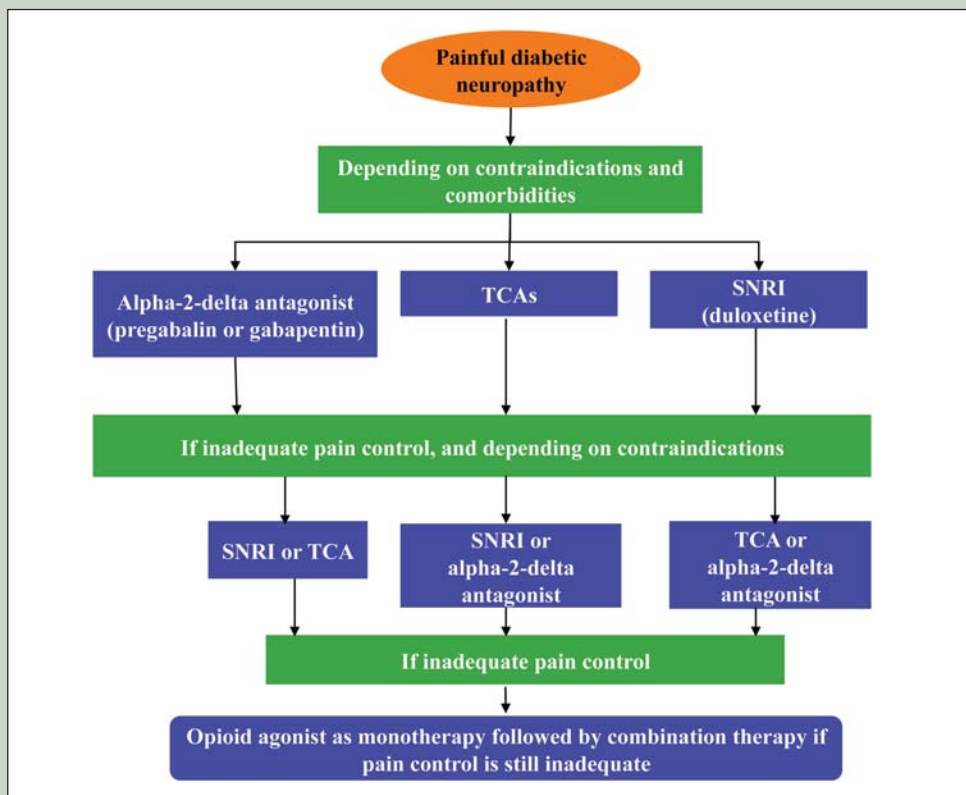


Figure 5
Algorithm for the Treatment of Painful Diabetic Neuropathy²³



Treatment Algorithm

Clinicians should formulate treatment regimens based on pathogenetic mechanisms,¹⁰ and strive to manage the pain symptoms associated with diabetic neuropathies while counseling patients to mitigate risk factors such as smoking, lack of physical activity, or a high-fat, high-calorie diet.²³ Clinicians should also screen for the development and progression of diabetic neuropathy to reduce the risk of complications.¹⁰

Each type of diabetic neuropathy has its own prognosis, clinical course, and requirements for management. Clinicians should set realistic goals and reasonable expectations while developing a rapport with the patients, all of which are crucial in ensuring patient compliance with the therapeutic regimen.⁵⁸ Developing a treatment plan for diabetic neuropathy includes discussion and negotiation between the patient and physician regarding the goals for therapy. Clinicians should explain that complete relief of pain may not be achieved.

Despite limitations in the available data concerning currently available agents that are effective in reducing pain due to diabetic neuropathy, a consensus panel has issued a treatment algorithm for neuropathic pain, as shown in Figure 5.²³ The algorithm recommends initiating treatment with either an alpha-2-delta agonist (ie, pregabalin or

Figure 1 Continued Patient Follow-up: Vivian

- After all other etiologies for neuropathy were ruled out, Vivian was diagnosed with DPN
- Vivian's diabetes regimen will be intensified with the addition of an oral glucose-lowering agent and an additional blood pressure-lowering medication. She will also be started on a statin.
- Vivian is also referred to a registered dietitian to reinforce her understanding of dietary changes that can help control her blood glucose, blood pressure, and cholesterol
- Because she reported depression in her presentation, she is prescribed duloxetine. The use of TCAs is avoided because of her history of angina and her age (> 65 y/o).
- The importance of foot care and frequent self- and physician examination of the feet is emphasized because she has high risk factors for complications potentially leading to amputation
- Information on local and national resources is made available
- Vivian is given a referral to a psychological counselor for her depression



gabapentin), a TCA, or an SNRI (ie, duloxetine). These options are evaluated on the basis of the contraindications and comorbidities of individual patients.

Clinicians should realize this algorithm in Figure 5 has the following limitations²³:

- The underlying pain mechanisms in diabetic neuropathy have not been delineated
- Lack of direct head-to-head comparative trials
- Need for standardized study endpoints
- Need for further long-term efficacy and safety data
- Need for investigation of the efficacy and safety of different combination therapies

Conclusion

Diabetic neuropathy is a common and diverse complication that adversely affects the QOL and life expectancy of diabetes patients. Controlling hyperglycemia is crucial. Clinicians tasked with managing diabetic neuropathy patients must know how to properly diagnose the condition while considering differential diagnoses. Understanding current, rational, and evidence-based recommendations is necessary for treating DPN. Finally, in order to have a successful outcome, clinicians must counsel patients on various lifestyle modifications and forge partnerships with patients based on honest setting of goals and realistic expectations.

Thank you for participating in this activity. To take the evaluation and posttest and receive your credit, please go to:
<http://www.totalmeded.com/diabeticneuropathy>.

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