# Pharmaceuticals for the Treatment of Painful Diabetic Neuropathy

*What drugs your patient takes may influence this process.*

## Objectives

1) Recognize key features present during the complex process of the pathogenesis of painful diabetic neuropathy.

2) Appreciate the clinical data relative to pharmaceuticals and their use in the treatment of painful diabetic neuropathy as found in the literature.

3) Appreciate the clinical data regarding investigational pharmaceuticals' effects on painful diabetic neuropathy.

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### Introduction

The American Diabetes Association has reported that presently there are 23.6 million people in the United States, or 8% of the population who have diabetes.[1] Further, the total prevalence of diabetes has been reported to have increased by 13.5% since 2005.[1] Diabetic peripheral neuropathy is a heterogeneous neurodegenerative complication of type-1 and type-2 diabetes mellitus that can affect almost every tissue of the body and is associated with significant morbidity and mortality. It falls within the broad category of generalized symmetrical polyneuropathies and focal or multifocal neuropathies, and is also known as chronic sensorimotor distal polyneuropathy.[2] Backonja states that approximately 45% of diabetic patients will experience neuropathy during the course of the disease.[3,4] Moreover, the American Diabetes Association estimates that about 60% to 70% of people with diabetes have mild to severe forms of nervous system damage resulting in impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and other nerve problems.[1] The incidence of diabetic neuropathy appears to depend principally on the duration of disease and the degree of glycemic control.[4-6]

Painful diabetic peripheral neuropathy affects a minority of patients and is often chronic, severe, and debilitating. Backonja asserts that 4% to 5% of all diabetic patients will have painful neuropathy.[3] Pain is a common component of sensory peripheral neuropathy and occurs primarily as a consequence of damage to small unmyelinated C fibers.[7]

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Neuropathic pain results from either primary lesions or dysfunction in the peripheral or central nervous system.[4] This pain encompasses a variety of sensory, motor, and autonomic symptoms.[4,8] Neuropathic pain is defined as spontaneous pain and hypersensitivity to painful stimuli in association with damage to the nervous system.[8]

Additionally, Attal and Bouhassira declare that neuropathic pain is described as usually spontaneous, continuous, burning, paroxysmal, and evoked by various mechanical or thermal stimuli.[9] Podiatric physicians should realize that neuropathic pain is only a symptom of neurological dysfunction and not a disease itself.[4] Currently, the only treatment that addresses the underlying cause of painful diabetic neuropathy is improved control of blood glucose levels.[4] In the absence of a curative therapy for painful diabetic neuropathy, podiatric physicians must rely on pharmacological or non-pharmacological modalities or a combination of both to control their patients' symptoms.[4]

### Peripheral Neuropathic Pain

Treatment of diabetic peripheral neuropathic pain is often challenging because this pain is generally non-responsive to conventional analgesic, non-steroidal anti-inflammatory drugs, and acetaminophen. Therefore, the primary intention of this article is to answer the question: "What are the possible pharmacologic treatment options available that the podiatric clinician can utilize for patients experiencing pain associated with diabetic peripheral neuropathies?"

In order to answer this crucial question, a foundation must be placed first describing the pathogenesis and characteristics of painful diabetic neuropathy as a basis for understanding medication selection. Secondly, the pharmacologic properties of medications used to treat painful diabetic neuropathy are described as a narrative and presented graphically in a table format. This table will offer comparisons of these medications, including dosages, frequencies, and adverse effects to assist the podiatric physician with selection of the most appropriate agent for each individual patient.

Finally, the literature will be explored and findings of current investigational medication agents for the treatment of painful diabetic neuropathy will be presented.

### Pathophysiology of Painful Diabetic Neuropathy

The excruciating, refractory pain that can accompany sensorimotor neuropathy is recognized as diabetic neuropathy.[4] The pathophysiology of diabetic peripheral neuropathy remains incompletely understood, although it is clear that it is related to the length of time nerves are exposed to hyperglycemia. Some evidence suggests that stable glycemic control is very important in controlling the progression of diabetic neuropathy. As diabetic neuropathy progresses, neuronal dysfunction correlates with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia.[4,10-13] Cameron, et al.[14] and Sheetz and King[15] identified hemodynamic abnormalities, hypoperfusion, and neuronal ischemia as well-established characteristics of diabetic neuropathy. Different neuropathies may have different and overlapping mechanisms involved with their pathogenesis. Duby, et al. identified and summarized the variety of interdependent pathologic pathways of diabetic neuropathy to include micro-vascular dysfunction, oxidative stress or protein kinase C, advance glycation end products, and polyol pathway.[10]

The predominant pathologic change observed in the microvascular system of a diabetic patient with neuropathy is a physiologic shift favoring vasoconstriction, evidenced by blunted vasodilation and elevated vasoconstrictor activity.[10,14] Increase in oxidative stress may be related to the development of neuropathy. Accordingly, the foremost hypothesis is known as "oxidative stress" and is described by Baynes and Thorpe.[16] Diabetes mellitus promotes elevated intracellular concentrations of glucose that can prompt a variety of pathologic processes. Glucose can react with reactive oxygen species to form carbonyls that can further react with proteins or lipids to produce glycol-oxidation or lipoxidation compounds.[10,16]

This increase in extracellular osmotic stress results in the accumulation of protein kinase C and a decrease in antioxidant defenses in the cell. The increased protein kinase C leads to vascular damage resulting from increased permeability. Overactivation of the hexosamine pathway induces oxidative stress through the generation of hydrogen peroxide.

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### TABLE 1
### Key Elements of Painful Diabetic Peripheral Neuropathy for Successful Management

- Establish the diagnosis of diabetes mellitus or impaired glucose tolerance over 200 mg/dL for diabetes mellitus
- Understanding the key elements of diagnosis of painful diabetic peripheral neuropathy
- Establish the presence of neuropathy—a positive answer to the question: "Do your feet burn,hurt, or tingle?"
- Validate all positive answers with questionnaires with Neuropathic Pain Questionnaire or Brief Pain Inventory for DPN
- Screening for the development and progression of diabetic neuropathy to prevent complications
- Use simple handheld screening devices like 10-g monofilament, 128-Hz tuning fork
- Realize each type of diabetic neuropathy has its own prognosis, clinical course and requirements for management
- Rule out non-diabetic causes of neuropathy or pain—(Metastic disease, Infection, or toxic substances)
- Use recent guidelines and establish evidence-base medicine for rational pharmacologic interventions
- Set realistic goals and reasonable expectations and develop a rapport with the patient to insure compliance
- Non-pharmacological treatments may be used to augment successful treatment and avoidance of complications

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Clinical trials that have been conducted to show the principle role of oxidation stress as it relates to the pathologic process of diabetic neuropathy have yielded disappointing results.[10]

Another described hypothesis for the pathogenesis of diabetic neuropathy is centered on a reduction in nerve blood flow as a result of the increase in advanced glycation end products disrupting excellular protein interactions.[10,16] In normal aging, non-enzymatic glycosylation of proteins and lipids occurs at a slow rate. Advanced glycated end-products (AGEs) are formed from incorporation of glucose into proteins, an irreversible chemical response. This leads to the production of oxidative radicals such as superoxide and hydrogen peroxide.

In diabetics, there are higher levels of AGEs and reactive oxidants. Increased inflammatory responses, vascular permeability and procoagulant activity may occur in collagen, basement membranes, arteries and endothelial cell surfaces.[17] This results in macrovascular and microvascular occlusion and ischemia of nerve endings.

### The Polyol Pathway Hypothesis

The polyol pathway hypothesis is described as hyperglycemia that causes an increase in aldoreductase activity that converts intracellular glucose to sorbitol. This accumulation of intercellular sorbitol causes tissue damage secondary to edema, cell membrane breakdown, and oxidative stress on the vasa nervorum. The increased turnover of the co-factors nicotinamide adenine dinucleotide phosphate and nicotinamide adenine dinucleotide is due to the high rate of flux of glucose through the polyol pathway; this increase is pathogenic.[4]

### Immune System

Finally, the patient's immune system may play a role in the pathogenesis of certain diabetic neuropathies. The specific organs under immune mediated attack are the nerves or the vasa nervora. This idea of immune-mediated attack has been explored in diabetic patients with chronic inflammatory demyelinating polyneuropathy and proximal diabetic neuropathy.[18,19] Dyck, et al. have suggested that the vasculitic abnormalities associated with diabetic sensorimotor polyneuropathy and proximal diabetic neuropathy may be the result of immune-mediated damage.[20]

### Management of Painful Diabetic Neuropathy

Despite years of research on diabetic neuropathy, no treatment has emerged that prevents or reverses its development or progression.[4] The initial step in the management of painful diabetic peripheral neuropathy is to exclude other causes. At present, the only treatment that addresses the underlying cause of painful diabetic neuropathy is improved control of blood glucose levels. This is the most important long-term treatment for diabetic polyneuropathy.[4] The podiatric physician should counsel patients to strive to achieve and maintain excellent diabetic control, with a glycosylated hemoglobin level less than 7%.

Successful management of diabetic peripheral neuropathies rests on certain principles summarized in Table 1. The podiatric clinician should realize that each type of diabetic neuropathy has its own prognosis, clinical course and requirements for management. It must be acknowledged that for painful diabetic neuropathies, recent guidelines have been established, utilizing evidence-based medicine for more rational pharmacological interventions.

### Pharmacological Suggested Treatments

Painful diabetic peripheral neuropathy co-morbidities include sleep disturbances, depression, and interference with activities of daily living. The first task in patient management of painful diabetic peripheral neuropathy is patient rapport and education. Berger, et al. have reported numerous studies that indicate that many patients with painful diabetic neuropathy are either not treated or are receiving inadequate or incorrect treatment.[21]

It is frequently impossible to eliminate all pain, and realistic goals of modification of pain and improvement of functionality must be advanced as obtainable and desirable goals. Therefore, podiatric physicians who consider pharmacologic interventions for pain management should consider treatment of the co-morbidities such as depression and anxiety.[4]

Many studies have been conducted to identify pharmacologic agents that are successful in treating diabetic peripheral neuropathic pain. Pharmacologically, the classes of drugs with the best proven efficacy include antidepressants, anticonvulsants, and opioids. The most data is available on duloxetine, oxycodone controlled release, pregabalin, and tricyclic antidepressants. A table was constructed to present medications used to treat neuropathic pain syndromes and include opioid analgesics, anti-depressants, anti-convulsants, anti-hyperalgesics, and topical agents, with their dosing frequency as well as common side-effects (Table 2).

### Opioid Analgesics

The use of narcotic analgesics, particularly opioid agonists, for the treatment of neuropathic pain is controversial and not widely accepted.[4,22,23] Two randomized, controlled studies for diabetic, painful, peripheral neuropathy found opioids were effective but have significant high rates of adverse effects to include constipation, dry mouth, sedation, and dizziness. Gimble, et al.[22] studied the efficacy of controlled-release oxycodone therapy for six weeks in 159 diabetic patients with painful neuropathy from multiple centers. The therapy was found to be effective as measured by overall average daily pain intensity. Watson, et al.[23] also found a clinically significant benefit of controlled-release oxycodone in the treatment of painful diabetic neuropathy.

Opioids may be the best choice to treat moderate to severe pain in elderly patients because this age group may not tolerate other available agents and their associated side-effects. Given the potential for abuse and diversion, the podiatric physician should consider and employ the use of a narcotic contract. The purpose of a narcotic contract is to standardize and provide documentation of chronic pain management. Elements or rules of a narcotic contract may include behaviors that must be adhered to by the patient with outline consequences. Some of these behaviors include using one pharmacy, keeping all appointments with the providing physician, taking the narcotic medications exactly as prescribed, not selling or sharing prescriptions. A drug screen may be performed from time-to-time without notice. Examples of narcotic contracts are available on the Internet.

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### Antidepressants

Tricyclic antidepressants have been the most prescribed drug class for the treatment of diabetic sensorimotor neuropathy.[4,24] The podiatric physician's choice of tricyclic antidepressant should be based chiefly on individual patient tolerance and risk of adverse reactions.[10] This class of medications has long been a standard of treatment for chronic pain because it provides a secondary benefit of treating depression, which may accompany chronic pain. Antidepressants with mixed receptor or noradrenergic activity seem to have the greatest analgesic effect in patients with neuropathic pain. Serotonergic and adrenergic re-uptake blockade antidepressants, as a group, are more effective in treating neuropathic pain than selected serotonin re-uptake inhibitors.[10] The efficacy of tricyclic antidepressants in the treatment of neuropathic pain seems to be independent of their antidepressant effect.[4,10]

Two major disadvantages limit the use of tricyclic antidepressants for the treatment of painful diabetic neuropathy. The first is that the effective dose must be titrated over a long period; secondly, as a therapeutic class, antidepressants have a narrow therapeutic window; thus patients may experience intolerable adverse effects beyond a certain dose. The severity of adverse effects associated with tricyclic antidepressants is attributed to their relative affinities for muscarinic, histamine, and alpha-1 receptors.[10]

Despite the wide use and demonstrated efficiency of tricyclic antidepressants in the treatment of painful diabetic neuropathy, they are not approved by the U.S. Food and Drug Administration (FDA) for this indication.[4,10] Podiatric physicians may consider the use of tertiary amine tricyclic antidepressants as second or third line agents in geriatric patients and use them with caution in geriatric patients because of their associated adverse drug effects.[4,10]

Duloxetine (Cymbalta®–Eli Lilly) is a balanced and selected serotonin-norepinephrine re-uptake inhibitor, which is FDA approved for the treatment of painful diabetic neuropathy at doses of 60 and 120 mg. per day based on two randomized, double blind, placebo-controlled studies. Higher dosages do not provide any great benefit.[25] In clinical studies, patients have reported the following adverse effects when taking duloxetine: constipation, decreased appetite, dizziness, dry mouth, fatigue, increased sweating, loss of strength or energy, and sleepiness. The most common adverse effect was mild to moderate nausea, which usually subsided within one to two weeks.[4] Safety for patients who are over 65 years of age, with comorbid hypertension, GERD, erectile dysfunction and hyperlipidemia/hyperchosterolemia was established, but it is contra-indicated in patients with narrow angle glaucomas and patients taking MAO inhibitors. The drug is metabolized through the cytochrome P450 2D6 and 1A2 enzyme systems with no clinically significant drug interactions reported.[4,25]

### Anti-convulsant Agents

Anti-convulsant agents have been used in the management of neuropathic pain for many years, but there is limited evidence to support the efficiency of phenytoin and carbamazepine. The described principal mechanism of action of anticonvulsants include sodium channel blockade, potentiation of gamma-aminobutytic acid activity, calcium channel blockade, and antagonism of glutamate at N-methyl-D-aspartate receptors.[26]

Carbamazepine and lamotrigine have been used, as well as other anticonvulsants, and have some efficacy in reducing neuropathic symptoms, which have not been validated in randomized, controlled, double-blind, placebo-controlled studies. The focus of this section overview will be on gabapentin and pregabalin.

Gabapentin is widely used for neuropathic symptoms, and its efficacy has been confirmed. In a randomized, double-blind study, Morello, et al.[27] demonstrated equal effectiveness of gabapentin and amitriptylline for painful diabetic neuropathy. Backonja, et al.[28] conducted an eight-week multicenter, randomized, double-blind, placebo controlled trial to assess the effectiveness of gabapentin in 165 patients with painful diabetic neuropathy. They found that gabapentin was significantly superior to placebo in pain control, and significantly reduced interference with sleep. Dizziness and somnolence were the most common adverse events reported.[26,28] One notable disadvantage of using gabapentin

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## TABLE 2
## Medications Used to Treat Painful Diabetic Neuropathy

| MEDICATION | DAILY DOSAGE (MG) | ADVERSE EFFECTS |
|---|---|---|
| Oxycodone | 40 -160 | Sedation, dizziness, nausea/vomiting, dry mouth, constipation |
| Amitriptyline | 75-150 | Dry mouth, sedation, dizziness, confusion, orthostatic hypotension |
| Duloxetine | 60-120 | Constipation, decrease appetite, dizziness, dry mouth, fatigue |
| Desipramine | 75-200 | Dry mouth, sedation, dizziness, confusion, orthostatic hypotension |
| Imipramine | 50-100 | Dry mouth, sedation, dizziness, confusion, orthostatic hypotension |
| Citalopram | 20-60 | Dry mouth, constipation, dizziness, sedation, insomnia, diarrhea |
| Paroxetine | 20-60 | Dry mouth, constipation, dizziness, sedation, insomnia, diarrhea |
| Gabapentin | 1,800-3,600 | Sedation, dizziness, ataxia, nystagmus, leukopenia, constipation |
| Pregabalin | 150-300 | Dizziness, ataxia, somnolence, increase appetite, swelling, dry mouth |
| Oxcarbazepine | 1,200-2,400 | Sedation, dizziness, ataxia, nystagmus, tremor, hyponatremia |
| Topiramate | 400 | Diarrhea, loss of appetite, somnolence, reduce body weight |
| Capsaicin | Apply to affected area four times a day | Burning, itching, stinging, cough |

that may complicate diabetes management is weight gain after long-term use, as reported by DeToledo, et al.[29]

Pregabalin has received approval by the U.S. Food and Drug Administration for the treatment of post-herpetic neuropathy and diabetic peripheral neuropathy. Pregabalin is a derivative of delta-aminobutyric acid that does not act on either delta-aminobutyric acid A or delta-aminobutyric acid B receptors.[30] It has a unique mechanism of action and a favorable adverse effect profile. It attaches to over-firing nerve cells. As pregabalin binds pre-synaptically to the alpha-2-delta subunit of the voltage-gated calcium channel, it modulates the influx of calcium in hyper-excited neurons. This reduces the flow of calcium into the axon during depolarization or firing of the neuron, thereby reducing neurotransmitter release from that neuron.

This modulation reduces the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide. It is thought to help reduce the pain signals that cause the symptoms of diabetic nerve pain. The absorption of pregabalin is rapid and extensive, with the drug having bio-availability of at least 90%.[30]

It is a Schedule 5 controlled substance with a mild potential for abuse. Studies in doses of 75, 150, 300, 600 mg. daily have shown efficacy at the 300 and 600 mg. dosages in three randomized, double blind, placebo controlled studies.[31-33] Weight gain, especially at higher doses, as well as dizziness, somnolence and peripheral edema, have been reported.

A variety of anticonvulsants have been explored as adjunctive analgesics for painful diabetic neuropathy; however, the clinical evidence supporting their efficacy is limited. Carbamazepine and, more recently, oxcarbazepine have shown efficacy in treating diabetic peripheral neuropathic pain, but they do not have FDA-approved indications for this condition. Podiatric physicians who decide to initiate lamotrigine as an adjunctive agent because the patient may present with depression, or is intolerant or non-responsive to first line agents, must be mindful that lamotrigine has serious potential dermatological complications including Stevens-Johnson syndrome. Another point of interest is the use of topiramate as monotherapy reduced pain and body weight more effectively than placebo in diabetic patients with painful neuropathy. The reduction in body weight is a potential benefit for the diabetic population. Finally, Vinik[26] stated that topiramate may be one of the few antiepileptic agents to show potential for altering the basic biological nerve dysfunction in diabetic neuropathy.

### Anti-hyperalgesics

The use of dextromethorphan for painful diabetic peripheral neuropathy has received limited clinical investigation. The drug is a partial antagonist of N-methyl-D-aspartate receptor that has been implicated in the mediation of neuropathic pain in animal models.[10] Its analgesic effect and effectiveness remain unclear because the dose needed to produce sufficient analgesia remains undefined. A review by Criner and Perdun[34] suggests that there is a need for well-controlled trials to evaluate dextromethorphan, because there are insufficient safety and efficacy data to justify its use for the treatment of painful diabetic peripheral neuropathy. The available literature indicates that extremely high average daily doses are required for pain relief and a variety of associated adverse effects result from its use.[10]

Finally, ketamine, a dissociative anesthetic, has been used by pain specialists in some cases of neuropathic pain. However, even with low, sub-anesthetic doses, the psychotomimetic side effects may limit its utility and safety.

### Topical Agents

The topical agent capsaicin applied multiple times per day has been shown to be effective in the treatment of painful diabetic peripheral neuropathy.[35] The therapeutic activity of capsaicin is based on its ability to deplete the pain neurotransmitter substance P from sensory nerve endings with continuous application. Tandan, et al. concluded that topical capsaicin therapy for 22 weeks reduced pain in patients with diabetic neuropathy.[36] Patients should be instructed to use the lower strength concentration four times a day before attempting to use the higher strength concentration.

Many patients may experience an intense burning sensation that may persist for several weeks into their treatment. Unfortunately, the effectiveness of capsaicin depends on a regimen of multiple applications, at least four times a day. This is difficult for some patients to follow and results in a high degree of patient non-adherence to capsaicin therapy.[4,35]

Furthermore, many patients with allodynia or burning pain are reluctant to use this product because it must be applied to the affected area and induces a sensation of warmth.[36]

Finally, patients should be advised to wash their hands thoroughly after using capsaicin and avoid contact with their eyes and mucous membranes.

Zeigler, et al. found that transdermal clonidine provided no benefit over placebo for painful diabetic neuropathy.[37] The most common adverse effects encountered by patients in the study group were dry mouth, drowsiness, and orthostatic hypotension. A fundamental disadvantage encountered by these investigators was a dose-dependent effect on blood pressure, which limits its adequate dose titration.[37] Currently, however, a multicenter, randomized, double blind, parallel group study comparing the efficacy and safety of clonidine 0.1% topical gel with placebo is being explored at the University of Alabama at Birmingham. Topical local anesthetics are also used commonly and lidocaine (5%) is available. The topical lidocaine patch is approved for post-herpetic pain. Up to three patches per day can be applied at once for up to 12 hours in a 24-hour period.

### Investigational Agents

A number of investigations have been and are currently being conducted for the treatment of painful diabetic peripheral neuropathy. Treatments that alter protein kinase C activity affect nerve sodium-potassium ATPase activity, but the mechanism involved is not well understood. Joy, et al.[38] reviewed current clinical data regarding the pharmacologic actions of ruboxistaurin mesylate, an inhibitor of protein kinase C-beta, and its potential to help reduce the development and progression of diabetic microvascular complications.

Vinik, et al. report on the treatment of symptomatic diabetic peripheral neuropathy with the protein kinase C beta-inhibitor ruboxistaurin mesylate during a one-year, randomized, placebo-controlled, double-blind clinical trial.[39]

Their methods were that patients were enrolled in a multi-national, ran-

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domized, Phase II, ruboxistaurin mesylate double-blind, placebo-controlled parallel-group trial comparing 32 mg. daily or 64 mg. daily with placebo for one year.[39] Two hundred and five patients were assessed: 66 were assigned to the 32 mg. per day ruboxistaurin mesylate group, 71 to the ruboxistaurin mesylate 64 mg. per day group, and 68 to the placebo group. The primary end point was the change in vibration detection threshold.

Secondary end-point measures included effects of ruboxistaurin mesylate versus placebo on Neuropathy Total Symptom Score-6 (NTSS-6), neurologic examination, electro-physiologic nerve conduction studies, neuropathy impairment score, clinical global impressions, and safety. Among the 83 patients with significant symptoms at baseline, there was a reduction from baseline at 12 months in the NTSS-6 total score in the 32 mg. per day ruboxistaurin mesylate and 64 mg. per day (P = 0.015) groups compared with placebo.[39] Ruboxistaurin mesylate appeared to be well-tolerated in the patients with diabetic peripheral neuropathy who participated in this study.[39]

More recently, Casellini, et al. using the Norfolk Quality-of-Life Questionnaire for Diabetic Neuropathy [QOL-DN], evaluating endothelium-dependent and C fiber-mediated SkBF, sensory symptoms, neurological deficits, nerve fiber morphometry, quantitative sensory and autonomic function testing, nerve conduction studies, and adverse events were evaluated for 20 placebo and 20 ruboxistaurin-treated (32 mg/day) diabetic peripheral neuropathy patients (aged > or =18 years; with type-1 or type-2 diabetes and A1C < or =11%) during a randomized, double-masked, single-site, six-month study.

Significant improvements from baseline within the ruboxistaurin group were also observed for the Neuropathy Total Symptom Score.[40] In this cohort of diabetic peripheral neuropathy patients, ruboxistaurin enhanced SkBF at the distal calf, reduced sensory symptoms (NTSS-6), improved measures of Norfolk QOL-DN, and was well-tolerated.[4]

Carisbamate is a novel drug with neuro-modulator activity that is currently under development for the treatment of epilepsy, diabetic neuropathy, and neuralgia. The compound possessed a promising pharmacological profile in tests in vivo, and demonstrated broad anti-convulsant activity in pre-clinical studies. The preliminary evaluations of carisbamate in humans indicated complete absorption, extensive metabolism, and carbamate ester hydrolysis. The most frequently reported side-effects associated with carisbamate are dizziness, headache, somnolence and nausea. In clinical trials, carisbamate did not display any significant interactions with commonly used anti-epileptic drugs such as carbamazepine, valproate and lamotrigine.

The purpose of a Johnson and Johnson randomized, double-blind, placebo-controlled, crossover, parallel-group, multicenter study that finished in May of 2008 was to evaluate the safety, effectiveness, and tolerability of 200 mg. of RWJ-333369 (Carisbamate) given twice daily by mouth compared with placebo in the treatment of diabetic peripheral neuropathy. The study hypothesis was that 200 mg. of RWJ-333369 given twice daily by mouth for four weeks will be more effective than placebo in reducing pain due to DPN, as measured by average daily DPN pain scores.[41] It is hoped that once these results are published, they will offer validity to another medication that may help patients with painful diabetic peripheral neuropathy.

### Conclusion

Painful diabetic neuropathy is a chronic disorder that compromises the patient's quality of life. Currently, the only treatment that addresses the underlying cause of painful diabetic neuropathy is improved control of blood glucose levels. In the absence of a curative therapy for painful diabetic neuropathy, the only agents presently FDA-approved for this indication are pregabalin and duloxetine. Other agents may be employed to treat diabetic painful neuropathy symptoms even in the absence of FDA approval. ■

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Continuing Medical Education

## EXAMINATION


***See instructions and answer sheet on pages 228-230.***


**1) According to this review, the patho-physiology of diabetic peripheral neuropathy remains incompletely understood, although it is clear that it is related to the length of time nerves are _____?**

- **A) Exposed to hypokalemia**
- **B) Exposed to hypoglycemia**
- **C) Exposed to hyperglycemia**
- **D) Exposed to hyponaturemia**

**2) Dyck, et al. have suggested the vascular abnormalities associated with diabetic sensorimotor polyneuropathy and proximal diabetic neuropathy may be the result of _____.**

- **A) infection and sepsis**
- **B) immune-mediated damage**
- **C) injury**
- **D) ulceration**

**3) Pharmacologically, the classes of drugs with the best proven efficacy for the treatment of diabetic peripheral neuropathic pain include _____.**

- **A) antidepressants**
- **B) anticonvulsants**
- **C) opioids**
- **D) all of the above**

**4) Two randomized controlled studies _____ evaluating opioids in painful diabetic peripheral neuropathy concluded that it was effective but had high rates of adverse effects.**

- **A) Said, et al. and Llewelyn, et al.**
- **B) Cameron, et al. and Britland, et al.**
- **C) Gimble, et al. and Watson, et al.**
- **D) Wesranmo, et al. and Said, et al.**

**5) Two major disadvantages limiting the use of tricyclic anti-depressants are that they: 1)are titrated over a long period and 2) as a class have _____?**

- **A) a narrow therapeutic window**
- **B) a large cost to affect ratio**
- **C) many incidences of allergic reactions**
- **D) few advantages**

**6) Adverse effects reported by patients using duloxetine include:**

- **A) moderate nausea**
- **B) increased sweating**
- **C) loss of strength or energy**
- **D) all of the above are adverse effects**


*Continued on page 142*

Continuing Medical Education

# EXAMINATION

(cont'd)

7) One notable disadvantage of using gabapentin impacting diabetes mellitus reported by DeToledo, et al is?
- A) interference with sleep
- B) increase in platelet aggregation
- C) weight gain after long-term use
- D) an increase in somnolence

8) Pregabalin, an alpha 2-delta ligand, is FDA approved for both _____ and _____.
- A) hypertension and drug abuse
- B) weight control and alcohol abuse
- C) painful diabetic neuropathy and post herpetic neuralgia
- D) diabetes mellitus and somnolence

9) Lamotrigine has serious potential dermatological complications that include _____.
- A) Acne
- B) Stevens-Johnson syndrome
- C) Alopecia
- D) Itching

10) Another point of interest with the use of topiramate as monotherapy is that it _____ more effectively than a placebo in diabetic patients with painful neuropathy.
- A) increases pain and body mass
- B) increases sedation and decreases memory
- C) increases body mass and increases sedation
- D) reduces pain and body weight.

11) _____is a partial antagonist of N-methyl-D-aspartate receptors that has been implicated in the mediation of neuropathic pain in animal models.
- A) Dextromethorphan
- B) Ampicillin
- C) Calciferol
- D) Cyclosporin

12) Backonja states that approximately _____ of diabetic patients will experience neuropathy during the course of the disease.
- A) 25%
- B) 15%
- C) 45%
- D) 95%

13) Currently, the only treatment that addresses the underlying cause of painful diabetic neuropathy is:
- A) improved pharmacological agents
- B) improved control of blood glucose levels
- C) improved adherence to exercise
- D) improved diet

14) The therapeutic activity of _____is based on its ability to deplete the pain neurotransmitter substance P from sensory nerve endings with continuous application.
- A) duloxetine
- B) amitriptyline
- C) capsaicin
- D) nitroglycerin

15) Zeigler, et al. found that _____provided no benefit over placebo for painful diabetic neuropathy.
- A) transdermal verapamil
- B) transdermal nifedipine
- C) transdermal scopolamine
- D) transdermal clonidine

16) Duloxetine (Cymbalta®–Eli Lilly) is contra-indicated in patients with_____.
- A) Hypertension and those with GERD
- B) narrow angle glaucomas and those taking MAO inhibitors
- C) erectile dysfunction and hyperlipidemia/ hyperchosterolemia.
- D) Diabetic neuropathy and pain

17) Joy, et al. reviewed current clinical data regarding the pharmacologic actions of ruboxistaurin mesylate, an inhibitor of _____ ?
- A) protein kinase C-delta
- B) protein kinase D-alpha
- C) protein kinase C-beta
- D) protein kinase E-gamma

18) As pregabalin binds presynaptically to the alpha-2-delta subunit of the voltage-gated calcium channel, it modulates the _____in hyper-excited neurons.
- A) influx of calcium
- B) influx of sodium
- C) influx of potassium
- D) influx of magnesium

19) The topical lidocaine patch is approved for _____.
- A) Sedation
- B) Cold and Flu symptoms
- C) Post-herpetic pain
- D) Seizures

20) The most frequently reported side-effect(s) associated with carisbamate (is) are_____?
- A) dizziness
- B) headache
- C) somnolence and nausea
- D) All the above

**SEE INSTRUCTIONS AND ANSWER SHEET ON PAGES 228-230.**