PAIN MEDICINE
Volume 9 • Number 6 • 2008

REVIEW ARTICLE

Painful Diabetic Neuropathy: Epidemiology, Natural History, Early Diagnosis, and Treatment Options

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ABSTRACT

Objective. To facilitate the clinician’s understanding of the basis and treatment of painful diabetic neuropathy (PDN).

Background. PDN is one of several clinical syndromes in patients with diabetic peripheral neuropathy (DPN) and presents a major challenge for optimal management.

Methods. A systematic review of the literature was undertaken for articles specific to PDN, using Medline databases between 1966 and 2007.

Results. The epidemiology of PDN has not been well established and on the basis of available data the prevalence of pain is 10% to 20% in patients with diabetes and from 40% to 50% in those with diabetic neuropathy. It has a significant impact on the quality of life and health care costs. Pathophysiologic mechanisms underlying PDN are similar to other neuropathic pain disorders and are broadly characterized as peripheral and central sensitization. The natural course of PDN is variable, with many patients experiencing spontaneous improvement and resolution of pain. Hyperglycemia-induced pathways result in nerve dysfunction and damage, which lead to hyperexcitable peripheral and central pathways of pain. Glycemic control may prevent or partially reverse DPN and modulate PDN. Quantifying neuropathic pain is difficult, especially for clinical trials, although this has improved recently with the development of neuropathic pain-specific tools, such as the Neuropathic Pain Questionnaire and the Neuropathic Pain Symptom Inventory. Current therapeutic options are limited to symptomatic treatment and are similar to other types of neuropathic pain.

Conclusions. A better understanding of the peripheral and central mechanisms resulting in PDN is likely to promote the development of more targeted and effective treatment.

Key Words. Neuropathic Pain; Diabetic Neuropathy; Symptomatic Therapy; Pain Assessment; Mechanisms

Disclosure Information: An earlier version of this article was written with the editorial assistance of IMPRINT Publication Science, which is supported by an unrestricted grant from GlaxoSmithKline. The authors received no honoraria and GSK were not privy to any review of the material before submission.

Dr. Backonja has received honoraria, consulting fees, or grant/research support from Endo Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson, NeurogesX, Inc., Novartis Pharmaceuticals, Pfizer Inc., Purdue Pharma LP, Wyeth, and XenoPort. Dr. Malik has received honoraria or consulting fees from AstraZeneca Pharmaceuticals, Takeda Pharmaceuticals, and Pharma Inc. and grant/research support from AstraZeneca. Dr. Veves is a member of the Advisory Panel of GlaxoSmithKline.

Overview

Diabetes is one of the leading causes of peripheral neuropathy, a heterogeneous group of disorders that can affect neuronal function throughout the body [1,2]. Peripheral neuropathies manifest with painful or painless symptoms and many patients experience both. Furthermore, diabetes may not necessarily be the cause of the neuropathy in all diabetic patients. Indeed other causes such as hereditary, inflammatory, and other metabolic neuropathies may coexist and should be actively excluded [1]. Once diagnosed correctly, painful diabetic neuropathy (PDN) presents a unique challenge in patient management and should be considered a syndrome clinically distinct from diabetic peripheral neuropathy (DPN) [3]. PDN can have debilitating consequences with a significant impact on quality of life (QOL) and costs of management [4,5]. Current therapies that reduce pain in PDN do not prevent progression of DPN. This review was designed to facilitate the clinician’s understanding of PDN as one syndrome of DPN by surveying the epidemiology, pathophysiology, natural history, assessment, and management of PDN. Furthermore, to provide insights into the pathophysiology of neuropathic pain, the symptoms, signs, and pathologic abnormalities associated with impaired glucose tolerance (IGT) will be discussed. Assessment tools for recognizing neuropathic pain and current therapeutic options will be considered.

Methods

Medline database (1966–2007) searches were performed to provide a comprehensive, systematic review of the literature regarding PDN. Terms combined with PDN were IGT (impaired glucose tolerance) and FGT (fasting glucose test), neuropathology, pathogenesis, pathophysiology, epidemiology, natural history, assessment, and management of PDN. Furthermore, to provide insights into the pathophysiology of neuropathic pain, the symptoms, signs, and pathologic abnormalities associated with impaired glucose tolerance (IGT) will be discussed. Assessment tools for recognizing neuropathic pain and current therapeutic options will be considered.

Results

Epidemiology of PDN

The epidemiology of PDN has not been extensively studied. Historically, epidemiologic studies of DPN have not differentiated between patients with and without pain, but have included pain as one of several inclusion criteria. Also, most studies do not indicate whether patients with neuropathic pain resulting from an etiology other than diabetes have been excluded. In the literature, the prevalence of PDN ranges from 10% to 20% of patients with diabetes and from 40% to 50% of those with diabetic neuropathies [3–5]. A detailed evaluation of PDN was undertaken in a European multicenter study of 1,171 patients with type 1 and type 2 diabetes and served to illustrate the complex nature of PDN [6]. Ziegler et al. reported significantly lower pain in both the lower (11.6% [75/647] vs 32.1% [168/524]) and upper (7.1% vs 16.6%) extremities in patients with type 1 (mean duration, 10 years) compared with type 2 diabetes, respectively. However, there was no correction for age (the mean age of patients with type 2 diabetes was 21 years greater than the mean age of those with type 1 diabetes) or comorbidities. Peripheral neuropathy was defined by the presence of at least two of the following three characteristics: (1) pain, paresthesias, or numbness of ≥10 mm on a 0- to 100-mm visual analog scale (VAS); (2) absent tendon reflexes; or (3) abnormal malleolar vibration perception threshold assessed by a tuning fork. The study did not indicate whether an attempt was made to distinguish between PDN and pain of a different origin. Of note, the percentage of patients with type 2 diabetes reported to have lower-limb pain was greater (32.1%) than the percentage of patients with type 2 diabetes reported to have neuropathy (23.9%), suggesting either that not all of the pain was PDN or that the criteria for determining peripheral neuropathy did not identify all cases.

Symptomatic neuropathies have been recognized in individuals with IGT and newly diagnosed diabetes. Sumner et al. [7] performed oral glucose tolerance tests in 73 of 97 patients who were referred to three neuromuscular clinics with neuropathy of unknown origin. Test results were abnormal for 41 (56%) individuals, with 15 and 26 meeting the criteria for diabetes and IGT, respectively [7]. The prevalence of neuropathic pain did not differ significantly between patients with IGT (76.9%) and patients with diabetes (93.3%, P = 0.1). Electrophysiologic studies (sural nerve amplitude and conduction velocity and deep peroneal amplitude) and skin biopsy to determine intraepidermal nerve fiber (IENF) density indicated a less severe neuropathy in individuals with IGT, which predominantly affected small fibers.
**Pathophysiology**

Although considerable data are available regarding the molecular processes leading to cellular damage in the nervous system as a result of hyperglycemia, the mechanisms specific to pain in diabetic neuropathy have not been identified. Neurophysiologic and pathologic parameters do not distinguish between patients with painful and painless neuropathy [8]. To determine neuropathologic changes, studies of PDN have included patients with DPN without pain and a control group without neuropathies. Results from studies comparing morphometric parameters between diabetic patients with and without painful neuropathy have been inconclusive [8–10]. In three studies, there was no significant difference in the degree of myelinated nerve fiber loss, although there was a trend toward more active degeneration of unmyelinated fibers in patients with PDN. In an early study, peripheral small and large nerve fiber function did not differ between patients with PDN and patients with painless DPN [11]. More recently, in 191 diabetic patients with and without painful neuropathy, patients with pain detected a cold stimulus at a lower temperature (−3.7°C) compared to those without pain (−0.6°C), but there were no differences for the heat pain tests, suggestive of an effect on A-delta fibers as opposed to C fibers [12]. However, the same group have also demonstrated more severe loss of IENF in those with neuropathic pain but with little or no objective sign of neuropathy, suggesting that IENF damage may only partially explain pain and that different mechanisms may underpin the genesis of pain at various stages of neuropathy [13].

**Mechanisms of Pain**

The current understanding of general mechanisms of neuropathic pain may provide insights into the abnormalities leading to pain in diabetic neuropathy. Damage to peripheral nerves results in hyperexcitability in primary afferent nociceptors (peripheral sensitization) that leads to hyperexcitability in central neurons (central sensitization) and generation of spontaneous impulses within the axon as well as the dorsal root ganglion of these peripheral nerves [14]. When the nerve is able to repair itself, the sensitization resolves; however, in chronic disease such as diabetes with ongoing damage, continued sensitization and altered processes in nociceptors lead to further generation of spontaneous symptoms. Sensitization is characterized by a lowered activation threshold, increased response to a given stimulus, and abnormal spontaneous activity [14–16].

In animal studies, damaged peripheral nerves become hyperexcitable, mechanosensitive, and epinephrine-sensitive [15]. Several studies have confirmed the role of epinephrine sensitivity and sympathetically mediated pain in PDN [15,17,18]. Abnormal electrical connections exist in experimental animal models of chronic peripheral nerve damage that may result in ephaptic transmission or “cross-talking,” a transfer of impulses from one axon to another [19]. Ephaptic transmission may occur between sensory and sympathetic fibers contributing to sympathetically mediated pain. Increased sympathetic activity has been shown in patients with PDN by Tsigos et al. [17], who evaluated circulating levels of norepinephrine and found that patients with PDN had concentrations equivalent to control subjects without diabetes and higher than those in diabetic patients with or without painless neuropathy. In a study using norepinephrine spillover assessment and positron emission tomography, patients with PDN were shown to have evidence of regionally selective sympathetic denervation in their feet [20]. Furthermore, a recent study has shown impaired sympathetically mediated vasoconstriction in patients with PDN, suggestive of inappropriate local blood flow regulation in these patients [21].

Alteration to damaged axons causes sodium channels to accumulate at the injury site and along the length of the axon, promoting ectopic electrical impulses and hyperexcitability [22]. These phenomena contribute to the increased bursts of electrical impulses to the dorsal horn, altering the gating mechanism and substance P expression. The role of ectopic discharge and increased sodium channels in PDN is consistent with the established efficacy of membrane stabilizers (anticonvulsants and tricyclic antidepressants) in relieving neuropathic pain.

Changes occur in the dorsal root ganglia in models of chronic neuropathic pain and include coupling of sympathetic and afferent neurons and abnormal release of substance P from A fibers [14,23]. With injury to peripheral nerves, sympathetic nerve fibers of local vasculature sprout basket-like terminals around large primary afferent neurons [16]. Substance P, normally found only in C fibers, is released by the larger A fibers of the dorsal column and produces signals interpreted as mechanical allodynia [21].

Hyperexcitability of the peripheral nerves results in central hyperexcitability, and persistent
nerve stimulation activates N-methyl-D-aspartate (NMDA) receptors located postsynaptically in the dorsal horn, with subsequent glutamate release \[14,22\]. Glutamate is an excitatory neurotransmitter that causes neuronal membrane depolarization, allowing stimuli to produce much larger postsynaptic potentials than usual—a process known as synaptic potentiation. Long-term synaptic potentiation has been shown in various pain states \[24,25\]. An important, and perhaps predominant, role of central mechanisms modulated principally at the level of the spinal cord has thus been suggested recently \[26\]. Although a recent magnetic resonance imaging study demonstrated a progressive reduction in cervical spine cord area at C2/C3, which correlated with neuropathic severity, it did not find a difference between those with and without painful neuropathy \[27\].

Natural History
The pain associated with diabetic neuropathies can be severe and sometimes intractable. Studies have reported two possible types, an acute remitting \[28\] and a chronic PDN \[29\]. Archer et al. \[28\] studied nine patients with persistent lower-limb pain with nocturnal exacerbation and significant weight loss, which resolved in all but one patient. A follow-up study of 36 patients with PDN showed no change in pain scores, but a worsening median nerve motor conduction velocity over 4.7 years \[29\]. Although data regarding the natural history of PDN are limited, clinicians should be aware that pain symptoms can improve and completely resolve while progression of neuropathy continues; diminution of pain can mean worsening of sensory function \[29\].

Benbow et al. \[30\] prospectively studied the natural history of painful symptoms, small-fiber function, and peripheral vascular disease (PVD) in 50 patients who were followed for an average of 3.6 years (3.0–4.1). Comparisons between baseline and end-of-study small-fiber function tests indicated significant deterioration in patients without PVD (thermal thresholds and weighted pinprick thresholds, \(P < 0.0001\) each test). For patients with PVD at baseline, nerve function deterioration was less, with an increase in thermal threshold reaching statistical significance \(P < 0.05\). In contrast, pain symptoms measured by a 10-cm VAS significantly improved within each patient group, and seven patients \(21\%\) were pain-free at the final evaluation. For these seven patients, there was a tendency toward a shorter history of pain before study entry compared with the other participants, but this difference did not reach statistical significance. These findings were supported in a survey of 105 respondents with PDN, of whom \(72\%, 12\%\), and \(15\%\) reported worsening, improvement, and no change, respectively, in symptoms since the onset of PDN \[4\]. The mean age at diagnosis of diabetes was 49.6 years, and the mean age at PDN onset was 56.7 years. Pain was reported in 20 of 26 patients evaluated for idiopathic neuropathy who were subsequently diagnosed with IGT, suggesting that PDN can be an early manifestation of altered glucose metabolism \[7\].

Early Diagnosis and Intervention
With evidence that neuropathy is associated with IGT, diabetes screening and early evaluation of nerve function have added significance in the prevention of PDN \[7\]. While standard measures of neuropathy such as nerve conduction studies and vibration detection thresholds can be used to detect abnormalities in large-fiber function, several methods have been investigated for use in the clinical evaluation of small-fiber dysfunction and damage. Measurement of nerve-axon reflex-related vasodilation is an objective measure directly related to function of C-nociceptive fibers \[31\]. IENF density measurement from skin biopsy can be used to evaluate small-fiber involvement in diabetic neuropathy and has been shown to detect changes in patients with IGT and other neuropathies \[32\]. Although as noted previously the interpretation of skin biopsy findings may be complex as the loss of IENF does not necessarily explain pain in all cases \[13\].

As neuropathies including PDN can be the presenting symptom of IGT and diabetes, clinically distinguishing neuropathic pain from non-neuropathic pain could indicate individuals who should be evaluated for IGT or diabetes. Furthermore, lifestyle intervention by improving glycemic control, blood pressure, and lipid profile has been shown to improve both painful neuropathic symptoms and IENF density, suggesting that early identification and appropriate intervention may be of significant clinical benefit \[33\].

Neuropathic Pain Assessment
Pain is a symptom that is difficult to classify, but for a complete diagnosis and to judge the benefits of treatment, the scoring of severity is necessary. Many different scores have been developed or adapted. Although the McGill Pain Questionnaire has been used frequently, it has not been rigorously evaluated for use in neuropathic pain disor-
ders. Recently, scores specific for DPN have been introduced and include the Brief Pain Inventory (BPI) short form for DPN [34]. The BPI is a patient-completed numeric rating scale that assesses the severity of pain and its impact on daily functioning on a seven-item pain interference scale. The Neuropathic Pain Questionnaire (NPQ) has also been developed to provide a general assessment of neuropathic pain and discriminate between neuropathic and non-neuropathic pain [35]. Originally, 32 items were evaluated using discriminant analysis to determine the items that successfully distinguished between neuropathic and non-neuropathic pain. The analysis indicated 12 necessary items, which were shown to differentiate neuropathic pain with 74.7% sensitivity and 77.6% specificity [35]. A short form of the NPQ has been validated (Figure 1) using stepwise discriminant analysis on three items from the original NPQ, which when used clinically, demonstrate preserved ability to differentiate neuropathic from non-neuropathic pain. The three items are tingling pain, numbness, and increased pain due to touch [36]. An additional diagnostic tool, the pain diagnostic questionnaire (DN4), has also been developed recently and compares pain syndromes associated with nervous or somatic lesions [37]. Follow-up assessment of pain in PDN can also be undertaken using either the NPQ or the other recently developed tool, the Neuropathic Pain Symptom Inventory (NPSI), which is a self-questionnaire designed to evaluate different symptoms of neuropathic pain [38]. The NPSI includes 10 descriptors that allow for the discrimination and quantification of clinically relevant aspects of neuropathic pain. It is suggested that this pain questionnaire may be able to (1) characterize subgroups of neuropathic pain patients, and (2) verify differential responses to pharmacologic or other treatment interventions. The Neuropathic Pain Scale has been designed specifically to monitor effects of therapy on neuropathic pain [39].

**Treatment Options**

Treatment options for PDN are limited, but the first step for all patients is to maintain glucose concentrations within the normal range. Glycemic control is important in individuals with diabetes to prevent progression of neuropathy, and intensive glucose lowering therapy reduces the risk of developing diabetic neuropathy [40–43]. Furthermore, a recent study has highlighted the importance of fluctuations in glucose concentrations as they may adversely affect neuropathic pain [44]. Pain scores from daily diaries of 10 diabetic patients with neuropathic pain and 10 without neuropathic pain showed an association between pain and greater mean glucose concentrations, greater deviations of glucose concentrations from a set point, and more glycemic excursions [44]. The beneficial effect of improving glycemic control on painful symptoms is limited to small studies. In a case series of nine patients with unrelenting acute PDN, Archer et al. reported that improved glucose control with insulin improved severity of symptoms [28]. In another group of nine patients with PDN, Boulton et al. used continuous subcutaneous insulin infusion and reported a significant improvement in pain scores measured on a 10-cm horizontal graphic rating scale [45].

The ideal therapy should be directed at preventing or arresting the progressive loss of nerve function and improving symptoms with minimal side effects. However, once pain develops, current treatment options are not specific for the underlying cause of nerve damage and are aimed often only at partially alleviating the symptoms due to significant adverse effects. Furthermore, despite the increasing evidence base for the rational treatment of painful neuropathy, a recent study using the general practice research database demonstrated that, of 16,690 patients with diabetic neuropathy and postherpetic neuralgia, approximately 16.6% were on tricyclic antidepressants, 11.0% were on second-generation antidepressants, 12.2% on antiepileptics, and surprisingly 43.1% were taking nonsteroidal anti-inflammatory drugs [46]. Furthermore, the average daily doses were considerably lower than those recommended for neuropathic pain.

**Antidepressants**

In recent years, drugs originally targeting very different disorders have emerged as valuable treatments of PDN. Serotonin and norepinephrine, together with endogenous opioids and γ-aminobutyric acid, are neurotransmitters that form the network of inhibitory neurons, which modulate actions of the nociceptive pathways. Centers in the brain and brainstem activate the body’s natural inhibitory system for pain (descending inhibitory pathways) which synapse in the dorsal horn of the spinal cord. Presynaptic re-uptake inhibition of serotonin and norepinephrine by serotonin–norepinephrine inhibitors (SNRIs) increases the levels of these amines in the synaptic clefts and can be assumed to enhance pain
NEUROPATHIC PAIN QUESTIONNAIRE—Short Form

In order to assess and treat your pain problem, we need to thoroughly understand just exactly what type of pain you have, and how it may or may not change over time. You may have only one site of pain, or you may have more than one.

Please name the site of pain which is most severe or disturbing for you (arm, foot, etc):

For all the following questions, please rate your pain at the site you just listed.
Please use the space below to describe your pain in your own words as well:

Please use the items below to rate your pain as it usually feels. Indicate a number that represents your pain on each scale. For example, if you have no tingling pain, you would rate the first item “0.” If you have the worst tingling pain imaginable, you would rate it “100.” If neither of those fits your pain because it is in between, choose a number that fits your pain.

1Sf. Tingling Pain

Please rate your usual pain: __________

2Sf. Numbness

Please rate your usual pain: __________

We are also interested in learning what circumstances cause changes in your pain. Please write the number that indicates the amount you experience each of the following:

3Sf. Increased pain due to touch

Please rate your usual pain: __________

Canonical Discriminant Function Coefficients and Structure Coefficients

<table>
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<th>Item</th>
<th>Canonical Discriminant Function Coefficient</th>
<th>Structure Coefficient</th>
</tr>
</thead>
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<td>1Sf. Tingling Pain</td>
<td>.015</td>
<td>.828</td>
</tr>
<tr>
<td>2Sf. Numbness</td>
<td>.017</td>
<td>.819</td>
</tr>
<tr>
<td>3Sf. Increased Pain due to Touch</td>
<td>.011</td>
<td>.569</td>
</tr>
<tr>
<td>Constant</td>
<td></td>
<td>−1.302</td>
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</tbody>
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TOTAL DISCRIMINANT FUNCTION SCORE: =

Check one of the following boxes:

Discriminant Function Score Below 0: Predicts Non-Neuropathic Pain
Discriminant Function Score at or Above 0: Predicts Neuropathic Pain

Figure 1 Neuropathic pain questionnaire—short form.
suppression induced by the descending inhibitory pathways. Thus, diffuse noxious inhibitory control by inhibition of presynaptic reuptake of serotonin and norepinephrine has been suggested as a key mechanism of how antidepressants relieve pain. Current knowledge suggests that both reuptake mechanisms play a role, as tricyclic antidepressants with balanced reuptake inhibition tend to work better than noradrenergic tricyclic antidepressants [47]. In addition, SNRIs are more efficacious than selective serotonin reuptake inhibitors (SSRIs) [47]. Thus, it can be deduced that the noradrenergic mechanism appears to be more important. However, the mechanism of action of tricyclic antidepressants in neuropathic pain is probably multimodal with contribution of monoamine reuptake inhibition and blockade of NMDA receptors as well as sodium channels [48]. Unfortunately, most studies with tricyclic antidepressant have enrolled a small number of patients with still fewer completing the treatment regimens. Antidepressants commonly prescribed for PDN include amitriptyline [49–51], imipramine [52,53], and desipramine [54,55], yet for amitriptyline, the most extensively prescribed tricyclic antidepressant, fewer than 150 patients with PDN have been studied in controlled trials [49–51]. Both amitriptyline and imipramine are prescribed at a dosage between 25 and 150 mg daily and the usefulness of these agents has been confirmed in several systematic reviews [56,57]. The major problem remains the frequency of predictable side effects, which include drowsiness and lethargy, and the anticholinergic side effects, particularly dry mouth and postural hypotension. Furthermore, as there were significant differences in defining patients with PDN and the outcome measures used in each of these trials, comparisons cannot be made between studies to determine which drug may have been most beneficial. Other small studies have also shown efficacy in patients with PDN using the SSRIs paroxetine [58] and citalopram [59].

The only drug from this class of medication to receive Food and Drug Administration (FDA) approval [60] for PDN is duloxetine and this is based on several multicenter, parallel, double-blind, randomized, placebo-controlled trials demonstrating efficacy in patients with PDN. Duloxetine is the first relatively balanced serotonin and norepinephrine reuptake inhibitor for three indications—major depressive disorder, diabetic painful neuropathy, and female stress urinary incontinence—and has been shown to be safe and well tolerated with few reported side effects apart from nausea and somnolence [61]. In 348 type 1 and type 2 diabetic patients with painful neuropathy, duloxetine 60 mg once and twice daily over 12 weeks significantly improved the weekly mean score of 24-hour average pain evaluated on an 11-point Likert scale compared with placebo [62]. Similarly, in 457 patients with PDN assigned to duloxetine 20 mg/day (20 mg QD), 60 mg/day (60 mg QD), 120 mg/day (60 mg BID), or placebo, duloxetine 60 and 120 mg/day demonstrated statistically significant greater improvement than placebo on the 24-hour average pain score within 1 week of randomization and continued through the 12-week trial with less than 20% discontinuing due to adverse events [63]. The most recent data is derived from a double-blind study of patients with PDN but without comorbid depression assigned to duloxetine 60 mg once and twice daily, or placebo for 12 weeks. Duloxetine 60 mg QD and 60 mg BID demonstrated an improvement in the 24-hour average pain severity score and all secondary measures for pain (except allodynia) within 1 week of commencing treatment. This was associated with an improvement in both the Clinical Global Impression of Severity and Patient’s Global Impression of Improvement [64]. All the previous studies were of short duration, and in order to assess both longer-term efficacy and safety, several of these trials were converted to open-label studies. Thus, in a follow-up open-label study, the long-term safety of duloxetine at a fixed dose of 60 mg twice daily (BID) (N = 161) was compared with 76 patients randomized to routine care, which consisted primarily of treatment with gabapentin, amitriptyline, or venlafaxine over 52 weeks [65]. There were no significant differences in the 36-item Short-Form Health Survey subscales or in the EuroQol 5-Dimension Questionnaire between groups, but a higher percentage of routine care-treated patients experienced one or more serious adverse events. In a 28-week, open-label study, 449 patients with DPN were randomized (3:1) to receive duloxetine 60 mg twice daily (BID) (N = 334) or duloxetine 120 mg once daily (QD) (N = 115) with a comprehensive safety and efficacy evaluation. Patients in both groups demonstrated a significant improvement in the Brief Pain Inventory and Clinical Global Impression of Severity scales with 63.8% and 62.6% of patients completing the 60 mg BID and 120 mg QD dosage, respectively. Heart rate increased slightly in both groups (P < 0.02) and was not associated with significant QTc prolongation. While systolic blood pressure was unaffected, diastolic blood
pressure decreased slightly in the 120 mg QD group (P = 0.04) [66].

To define potential adverse metabolic effects of duloxetine, data were pooled from three similarly designed clinical trials of 1,024 patients with PDN randomized to 60 mg duloxetine QD, 60 mg BID, or placebo for 12 weeks and then in 867 patients re-randomized to 60 mg duloxetine BID or routine care for an additional 52 weeks [67]. Whilst short-term duloxetine treatment resulted in mean weight loss (−1.03 kg; P < 0.001 vs placebo), a slight, nonsignificant weight gain was seen in both duloxetine and routine care groups with longer treatment. Duloxetine treatment increased fasting plasma glucose in both short- (0.50 mmol/L) and long-term (0.67 mmol/L) studies, with a greater increase in HbA1c relative to routine care (0.52% vs 0.19%) in long-term studies. Lipid parameters changed slightly. Overall, these metabolic changes did not appear to impact on the improvement in pain severity and nerve conduction. Most recently, to provide data relevant to the practicing clinician when prescribing duloxetine, the impact of baseline characteristics was evaluated using data from three pooled placebo-controlled studies, which showed no effect of age, type of diabetes, duration of diabetes, duration or severity of diabetic neuropathy, and baseline HbA1c levels [68]. Of note, duloxetine was most effective in the subgroup with the most pain. Other SNRIs have less robust evidence to support their use but include venlafaxine, which has been shown to be efficacious in patients with acute insulin neuritis [69] and chronic DPN [70].

Anticonvulsants

Although anticonvulsants have been used in the management of neuropathic pain for many years [71], several recent reviews, including a Cochrane review, have found limited evidence for efficacy with this class of drugs in PDN [72,73]. For carbamazepine, “there was insufficient data for an NNT to be calculated” for its efficacy in PDN [74]. However, in a recent multicentre, placebo-controlled 16-week trial, of 146 patients with DPN randomized to oxcarbazepine (a ketodervative of carbamazepine) compared with placebo, demonstrated significantly larger decreases and a greater proportion of patients with >50% reduction in the VAS score, together with significant improvements in the global assessment of therapeutic effect and sleep disturbance [75]. However, in a larger trial, with 347 patients randomized to oxcarbazepine or placebo, no significant change in mean VAS score was observed from baseline to the last week of the study, although the overall mean weekly VAS scores did improve significantly [76]. Similarly, in 141 patients randomized to oxcarbazepine or placebo, there was no change in mean VAS score from baseline to the last week of a 16-week study [77]. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid and was introduced some years ago as an anticonvulsant for complex partial seizures but is now widely used for painful neuropathy. It acts as a ligand for the auxiliary-associated protein alpha2delta subunit of voltage-gated calcium channels, resulting in a reduction in neurotransmitter release. The first study to evaluate the efficacy of gabapentin in patients with diabetic painful neuropathy was a double-blind, placebo-controlled, 8-week trial, which randomized 165 patients to gabapentin (titrated from 900 to 3600 mg/day or maximum tolerated dosage) or placebo [78]. Gabapentin significantly improved the mean daily pain score and QOL (Short Form-36 Quality of Life Questionnaire and Profile of Mood States) and was associated with significantly more dizziness (24% vs 4.9%) and somnolence (23% vs 6%). In a recent Cochrane review, seven studies of patients with diabetic neuropathy treated with gabapentin were analyzed and demonstrated a favorable number needed to treat for effective pain relief of 2.9 (95% CI 2.2–4.3) [79]. Furthermore, in a recent review of all the trials of gabapentin for neuropathic pain, it was concluded that dosages of 1,800–3,600 mg/day of this agent were effective; the side-effect profile also seems superior to that of the tricyclic drugs [80]. Pregabalin is a higher-potency and higher-effective analog of gabapentin and is the only other agent apart from duloxetine to receive FDA approval for the treatment of PDN. Evidence of its efficacy is derived from three pivotal clinical trials in diabetic painful neuropathy [81]. In 146 patients with PDN randomized to receive placebo (N = 70) or pregabalin 300 mg/day (N = 76), pregabalin showed a significant improvement in the mean pain scores, mean sleep interference, mood disturbance, and tension–anxiety during week 1, which remained significant throughout the study, but was associated with dizziness and somnolence compared with placebo [82]. In a larger study, 338 patients with PDN were randomized to receive pregabalin 300 or 600 mg or placebo three times daily for 5 weeks and improvements were seen in weekly pain score, sleep interference score, patient global impression of change, clinical global
impression of change, Short-Form McGill Pain Questionnaire, overall pain, and sleep disturbance within 1 week, which were sustained for the duration of the study, but again there was a significantly higher incidence of dizziness and somnolence [83]. In the last of these trials, 246 patients with PDN were randomized to pregabalin 150 or 600 mg/day or placebo. The most effective dose was 600 mg/day, which significantly decreased mean pain score; increased the proportion of patients who had a >50% decrease from baseline pain; and significantly reduced sleep interference, past week and present pain intensity, sensory and affective pain scores, and bodily pain [84].

Lamotrigine, an antiepileptic agent with at least two antinoceptive properties was assessed recently in two replicate randomized, double-blind, placebo-controlled studies enrolling 360 diabetic patients with painful neuropathy receiving lamotrigine 200, 300, or 400 mg daily or placebo over 19 weeks. Compared with placebo, lamotrigine 200 mg had no effect and the 300 and 400 mg dose were inconsistently effective for reduction in pain [85].

**Opioid Analgesics**

The use of opioids for neuropathic pain remains controversial, as studies have generally been small, have yielded equivocal results, and have not established the long-term risk–benefit ratio. A recent Cochrane analysis has demonstrated opioid efficacy for spontaneous neuropathic pain in general with a modest but highly significant reduction in the VAS score of 13 points, on a scale from zero to 100, compared with placebo. However, the most common adverse events were nausea (33% vs 9%), constipation (33% vs 10%), drowsiness (29% vs 12%), dizziness (21% vs 6% control), and vomiting (15% vs 3%) [86]. Furthermore, in a recent analysis of the efficacy of mu-opioids in reducing spontaneous neuropathic pain, a significant attenuation of dynamic mechanical and cold-induced allodynia was demonstrated with no effect on static allodynia or the threshold for mechanical or heat allodynia [87]. Thus, it is not surprising that tramadol, a mu-opioid agonist, demonstrated efficacy in a multicenter, double-blind, placebo-controlled, parallel-group study in 131 patients with PDN over 42 days. A significant improvement occurred in pain and physical and social functioning, but with no benefit on sleep, even though somnolence, nausea, constipation, and headache were significant side effects [88]. These benefits were maintained in a 6-month open extension following the 6-week double-blind randomized trial [89]. Compared with morphine, oxycodone has a higher oral bioavailability and is about twice as potent but with a lower incidence of intolerable typical opiate side effects. In a placebo-controlled study of 36 patients with DPN, continued release oxycodone was shown to have a significant impact on mean daily pain (both steady pain and brief pain) as well as on total pain and disability [90]. Recently, in 36 patients with PDN, gabapentin and morphine combined achieved a greater reduction in the total score on the Short-Form McGill Pain Questionnaire at lower doses of each drug than either as a single agent, although constipation, sedation, and dry mouth were frequent adverse effects [91].

**Antiarrhythmics**

Mexilitine is a class 1B antiarrhythmic agent and a structural analog of lignocaine. Its efficacy has been evaluated in several randomized, placebo-controlled trials in patients with PDN [92–94]. The drug decreased mean VAS pain ratings in all studies that used this measure, although in only two studies was this effect significantly greater than the often substantial responses seen with placebo. The dosage used in trials (up to 450 mg/day) is lower than that usually used for the treatment of cardiac arrhythmias; however, regular ECG monitoring is necessary and the long-term use of mexilitine cannot be recommended.

**NMDA Receptor Antagonists**

These agents include ketamine and dextromethorphan and both have demonstrated efficacy predominantly in reducing postoperative pain and analgesic consumption [95]. In a small study of 13 patients with PDN, dextromethorphan demonstrated a reduction in pain by 24% relative to placebo [96]. In a crossover trial of 19 patients with DPN, comparing dextromethorphan with memantine and placebo, no statistically significant response for pain reduction was found, although in 10 patients who responded to dextromethorphan, there was a significant dose–response effect on pain intensity [97]. Most recently, a combination of dextromethorphan with quinidine in 36 patients with PDN demonstrated a significant impact on pain intensity rating scale, pain relief rating scale, and patients’ diary assessments of sleep and pain intensity [98].
Topical and Physical Treatment

Topical Nitrate
Twenty-two diabetic patients were randomized to the local application to the feet of isosorbide dinitrate spray or placebo and showed a significant reduction in overall pain and burning discomfort over 4 weeks [99]. Similarly, glyceryl trinitrate patches were applied in 18 patients with PDN, and again 44% reported a reduction in pain [100].

Capsaicin
Several controlled studies combined in a meta-analysis provide some evidence that the topical application of capsaicin has efficacy in diabetic neuropathic pain [101]. However, of major clinical concern, topical capsaicin application has been shown to produce complete or nearly complete denervation of the epidermis in both control subjects and people with diabetes and the presence of neuropathy was associated with a significant reduction in regeneration [102].

Acupuncture
A number of un-masked studies support the use of acupuncture. In the most recent published report, benefits of acupuncture lasted for up to 6 months and were associated with a reduction in the use of other analgesics [103]. The conduct of potential blinded studies of acupuncture is problematic and, although a placebo response is possible with acupuncture, this should not detract from its use, which is generally without side effects.

Other Physical Therapies
Although many other physical therapies have been proposed, controlled evidence has only been provided for the use of percutaneous nerve stimulation [104] and, most recently, static magnetic field therapy [105]. A case series of patients with severe painful neuropathy unresponsive to conventional therapy has also demonstrated efficacy when using an implanted spinal cord stimulator [106]. Surgical decompression at the site of anatomic narrowing has also been vigorously promoted recently as an alternative treatment for patients with symptomatic diabetic neuropathy [107]. However, a systematic review of the literature has shown only Class IV studies concerning the utility of this therapeutic approach and, accordingly, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has reported that this treatment is considered unproven (Level U) until prospective randomized controlled trials with standard definitions and outcome measures are undertaken [108].

Dual Action Therapy
The antioxidant alpha-lipoic acid (ALA) is the only agent that has provided evidence of potential efficacy for both neuropathic symptoms and modifying the natural history of DPN [109–111].

In the most recent multicenter, randomized, double-blind, placebo-controlled trial, 181 diabetic patients received once-daily oral doses of 600 mg (N = 45), 1,200 mg (N = 47), 1,800 mg (N = 46) ALA or placebo (N = 43) for 5 weeks. The mean total symptom score (TSS) and proportion of patients achieving a >50% reduction in TSS, as well as the occurrence of stabbing and burning pain, were significantly lower in those on ALA. Although, the neuropathy impairment score improved, this was not significant and the highest dose was associated with an increased incidence of nausea, vomiting, and vertigo [112].

Increasing data from a number of larger randomized trials has led to FDA approval of pregabalin and duloxetine and allowed formulation of consensus-based assessment and treatment guidelines for PDN [2,113,114] (Table 1). Finally, drug selection should consider medical and psychiatric comorbidities, potential adverse effects, and drug interaction in an individual patient, and many patients may require rational multidrug therapy [115].

Table 1  Pharmacologic options with evidence from randomized clinical trials for efficacy in symptomatic treatment of DPNP (modified from Argoff et al. [113] with permission)

<table>
<thead>
<tr>
<th>Pharmacological Option</th>
<th>Evidence from Randomized Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-tier agents</td>
<td>(positive results from two or more randomized clinical trials)</td>
</tr>
<tr>
<td>○ duloxetine (SNRI)</td>
<td>○ pregabalin (alpha2delta calcium channel modulator)</td>
</tr>
<tr>
<td>○ oxycodone CR (opioid)</td>
<td>○ TCAs (antidepressants)</td>
</tr>
<tr>
<td>Of these, duloxetine and pregabalin have FDA approval for treatment of DPNP.</td>
<td></td>
</tr>
<tr>
<td>Second-tier agents</td>
<td>(evidence of efficacy from a single trial in patients with PDN and evidence from studies of other painful neuropathies)</td>
</tr>
<tr>
<td>○ gabapentin (alpha2delta calcium channel modulator)</td>
<td>○ venlafaxine (SNRI)</td>
</tr>
<tr>
<td>○ tramadol (opioid)</td>
<td>Carbamazepine and lamotrigine may also be considered.</td>
</tr>
<tr>
<td>Topical therapies</td>
<td>(based on mechanism of action, may be appropriate early in treatment and for specific individuals)</td>
</tr>
<tr>
<td>○ capsaicin</td>
<td>○ lidocaine 5% patch</td>
</tr>
<tr>
<td>Some patients may require therapy with multiple agents. Multidrug decisions should be based on mechanism of action and adverse event profiles.</td>
<td></td>
</tr>
</tbody>
</table>

SNRI = serotonin-norepinephrine inhibitor; TCAs = tricyclic antidepressants; FDA = Food and Drug Administration; DPNP = diabetic peripheral neuropathic pain; DPN = diabetic peripheral neuropathy.
Conclusions

Painful diabetic neuropathy is a common, difficult-to-manage complication of diabetes. Signs and symptoms consistent with PDN have been identified in patients with IGT and new-onset diabetes, indicating that early detection and intervention are important. Both peripheral and central mechanisms have been proposed to play a role in the genesis of the painful symptoms. Despite the evaluation of many pharmacologic and nonpharmacologic therapies, there are presently only two FDA-approved treatments of PDN.

Acknowledgments

We wish to thank the staff of IMPRINT Publication Science, New York for their editorial support in the initial preparation and styling of this article.

References

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