Epidemiology, Public Health Burden, and Treatment of Diabetic Peripheral Neuropathic Pain: A Review

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A B S T R A C T

Objective. The literature examining the epidemiology, quality of life burden, cost, and treatment of diabetic peripheral neuropathy pain (DPNP) in U.S. adults was reviewed.

Design. A comprehensive computerized literature review of DPNP was conducted using MEDLINE and other databases, which were searched from 1995 through August 2004 using the Medical Subject Headings diabetic neuropathies and pain combined with relevant terms. A supplementary MEDLINE search of clinical trials of pharmacological treatments for DPNP was conducted through July 2005.

Results. The search resulted in 321 articles. Several epidemiological studies assessed diabetic peripheral neuropathy among patients with diabetes and reported prevalence rates of 26–47%. No estimates of DPNP prevalence were reported, although one study (N = 2,405) reported that 26.8% of participants with diabetes experienced either pain or tingling. Randomized clinical trials have been conducted of several medications and classes of medication in patients with DPNP, and the U.S. Food and Drug Administration has approved two drugs for DPNP. Several published studies reported that DPNP impairs quality of life. Estimates of the costs of DPNP in the United States were limited. One study estimated average annual pain medication costs of $1,004 per DPNP patient.

Conclusions. This review of DPNP identifies gaps in the literature and highlights the need for further study. The establishment of a consistent definition and diagnostic code for DPNP would improve ability to collect data and understand the impact of DPNP on patients and the health care system. Well-designed, prospective studies are needed to better define the epidemiology and public health burden of DPNP.

Key Words. Diabetic Neuropathy; Pain; Epidemiology; Burden of Illness; Cost; Treatment; Quality of Life

Introduction

Diabetes is one of the most common and costly diseases in the United States [1]. Diabetic neuropathies are a family of nerve disorders caused by diabetes that can be classified as peripheral, autonomic, proximal, and focal [2], with peripheral neuropathy being the most prevalent [2,3].

Diagnosis of diabetic peripheral neuropathy is dependent on a variety of factors, including the presence of a characteristic pattern of signs and symptoms. Upon examination, many people with diabetes have signs of neuropathy, such as reduced nerve conduction velocity, but no symptoms. If the appropriate clinical tests are not performed and the patient is asymptomatic, diagnosis may be delayed until the patient begins to experience symptoms, such as paresthesias, dysesthesias, and neuropathic pain. Pain related to diabetic peripheral neuropathy, which can be termed diabetic peripheral neuropathy pain (DPNP), further
impairs quality of life in patients who are faced with the treatment challenges and other complications of diabetes.

Neuropathic pain is defined by the International Association for the Study of Pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” [4]. Peripheral neuropathic pain occurs when a lesion or dysfunction affects the peripheral nervous system [4]. While numerous studies have been conducted of diabetic neuropathy (which affects as many as 50% of those with diabetes) [5], fewer have specifically focused on patients with painful diabetic neuropathy. When pain has been described, it is often in combination with other symptoms or outcomes (e.g., ulcers, amputations). It is difficult therefore to adequately evaluate the burden and impact of DPNP.

This report presents results of a review of the literature regarding the epidemiology, treatment, quality of life burden, and cost of DPNP in adults in the United States. Specifically, this review attempts to answer the following research questions:

1. What are the prevalence and incidence of DPNP?
2. What are the evidence-based pharmacological treatment options for patients with DPNP?
3. What is the quality of life burden associated with DPNP?
4. What is the cost of illness associated with DPNP?

Methods

Literature Search
The overall strategy included a comprehensive literature search for DPNP combined with terms relevant to the topics of quality of life, epidemiology, cost, and treatment. The literature review was focused on the most recent and relevant data, with studies published between 1995 and August 2004 identified by a computerized search using MEDLINE, EMBASE, International Pharmaceutical Abstracts, Current Contents, EconLit, and Cochrane Library. Within MEDLINE, search terms included National Library of Medicine Medical Subject Headings (MeSH terms) for diabetic neuropathies and pain combined with those for quality of life, epidemiology, economics, cost, treatment, morbidity, mortality, and comorbidity. To broaden the search and ensure that articles focusing on diabetic neuropathy but containing information about DPNP were not overlooked, further searches combining the MeSH term for diabetic neuropathies (without reference to pain) and key words related to the topics of interest also were conducted. For example, the MeSH term for diabetic neuropathies was included with key words related to epidemiology such as prevalence, incidence, risk, and population. Title and abstract fields in all journals indexed in MEDLINE were searched.

If no relevant data were located within the publication date limits of the search (i.e., since 1995), the search period was extended. Key articles published before 1995 were identified among reference lists, and other articles known to the authors also were included. Additional searches were conducted using national and international organizations with resources available over the Internet, including the following:

- Agency for Healthcare Research and Quality (AHRQ), http://www.ahrq.gov/
- American Academy of Neurology (AAN), http://www.aan.com/professionals/
- American Diabetes Association (ADA), http://www.diabetes.org/home.jsp
- American Pain Society (APS), http://www.ampainsoc.org/
- Centers for Disease Control and Prevention (CDC), http://www.cdc.gov/
- International Association for the Study of Pain (IASP), http://www.iasp-pain.org/
- National Institutes of Health (NIH), http://www.nih.gov/

Clinical trial data published through July 2005 for agents indicated for DPNP were gathered in a supplementary search of MEDLINE.

Inclusion/Exclusion Criteria
Articles were included in this report if they described epidemiology or economic studies, or if they included treatment guidelines, randomized clinical trials (RCT) of pharmacological treatments, standardized or validated instruments for the collection of patient-reported outcomes, prevalence-based cost-of-illness estimates, or total direct and/or indirect costs associated with DPNP. Editorials, commentaries, case studies, case series, discussion papers, and letters were excluded from this study. Also excluded were articles describing studies conducted using nonhuman subjects, children and adolescents, populations outside the United States, local samples rather than national or regional level data, studies with fewer than 30
subjects, and studies of nonpharmacological treatments.

Results

The MEDLINE search for diabetic neuropathies and pain resulted in 232 articles, and the search for diabetic neuropathic pain in EMBASE, International Pharmaceutical Abstracts, Current Contents, EconLit, and the Cochrane Library resulted in 118 EMBASE records. No additional unique records from International Pharmaceutical Abstracts, Current Contents, EconLit, or the Cochrane Library were found. Of the 350 articles located through this initial search, 321 were relevant to the research questions and fell into the following categories: epidemiology, 9; treatment, 298; quality of life burden, 13; cost, 1.

Epidemiology: Prevalence and Incidence

Diabetes, diabetic peripheral neuropathy, and DPNP result in substantial public health burden in the United States. The 2005 estimated total U.S. prevalence of diabetes (diagnosed and undiagnosed) was 7.0%, and the estimated prevalence among individuals aged 60 years or older in the United States was 20.9% [1]. The estimated incidence of diabetes in 2005 in the United States among people aged 20 years or older was 1.5 million. The U.S. prevalence and incidence rates for DPNP were not reported in the literature; however, estimates of the prevalence of diabetic peripheral neuropathy among adults with diabetes ranged from 26% [6] to 47% [7]. The wide range in prevalence rates likely was due to differences in the case definitions and sensitivity of the method used to detect diabetic peripheral neuropathy, as well as the specific demographics of the study populations.

For example, the studies reporting prevalence rates of 26% and 47% both involved a neurological assessment of participants, but the study reporting the higher prevalence also used nerve conduction testing, which likely provided a more sensitive diagnostic criterion for DPNP than a neurological examination alone. The studies reporting prevalence were conducted during the time period from 1984 to 2000, although no single study spanned more than 4 years. Prevalence results included both painful and nonpainful diabetic peripheral neuropathy. Prevalence rates were reported for all diagnosed diabetics, and also for patients with non-insulin-dependent diabetes mellitus (NIDDM) or insulin-dependent diabetes mellitus (IDDM), and in one case, for NIDDM by gender.

Two of the studies assessing the prevalence of diabetic neuropathy were analyses of national health survey data [8,9], and three were cross-sectional analyses of population-based studies of patients with diabetes [6,7,10]. See Table 1 for a summary of the results of these epidemiological studies.

An analysis of 1989 National Health Interview Survey Diabetes Supplement data revealed a prevalence rate of 30.2% for symptoms of sensory neuropathy (defined as any numbness, pain or tingling, or decreased ability to feel hot and cold in the past 3 months) among an adult diabetic population (N = 2,405) [8]. The symptom of “pain or tingling” was reported by 26.8% of these diabetic respondents [8]. Although this number did not represent a prevalence rate for DPNP, it provided an estimate of an upper limit of DPNP prevalence.

Several prevalence studies of diabetic peripheral neuropathy include references to pain but give no specific data on DPNP. An analysis of 1999–2000 National Health and Nutrition Examinations Survey data estimated that the prevalence of lower extremity peripheral neuropathy (defined as numbness, loss of feeling, or pain or tingling in feet in the last 3 months) in a population of 2,873 men and women aged 40 years and older was 28.5% among diagnosed diabetics and 14.8% in the overall population [9]. The Rochester Diabetic Neuropathy Study, a longitudinal, population-based study (N = 380) initiated in 1986, found an overall prevalence of diabetic polyneuropathy of 47.3% among diabetics based on assessments by a neurologist and nerve conduction testing. The San Luis Valley Diabetes Study, a population-based case–control study of NIDDM conducted from 1984 to 1986, found an age-adjusted prevalence of distal symmetric sensory neuropathy of 3.9% among controls (n = 488), 11.2% among those with impaired glucose tolerance (n = 89), and 25.8% among participants with NIDDM (n = 279) [6]. Finally, a cross-sectional analysis of baseline data from the Pittsburgh Epidemiology of Diabetes Complications Study found a neuropathy prevalence rate of 34% among a population of 400 patients aged 18 years and older with IDDM [10].

The magnitude of the disease burden from DPNP remains inadequately estimated due to the absence of population-based studies employing standardized and validated assessments compared with background frequency. Importantly, few studies examined the incidence or prevalence of
pain vs nonpainful symptoms in patients with diabetic neuropathy; knowledge of the epidemiology of DPNP is therefore limited [5].

**Treatment**

Currently, DPNP can be treated only symptomatically; however, prevention of diabetic neuropathy and other microvascular complications of diabetes through intensive glycemic control has been well documented in the literature and demonstrated through a prospective study [11].

Diabetic peripheral neuropathy pain has been treated with a variety of medications, alone and in combination, with varying degrees of success. Many patients require medications from more than one class (e.g., anticonvulsants, opioids, tricyclic antidepressants [TCAs]) and may require concomitant use of multiple pharmacological and nonpharmacological therapies [12]. By one estimate, most therapies for DPNP result in a 30–50% reduction in pain, but this level of improvement is often disappointing to patients [13].

The utilization rates of current therapies have been reported. A cross-sectional, community-based survey of 255 patients with DPNP recruited through the offices of endocrinologists, neurologists, anesthesiologists, and primary care physicians found that a majority (79.2%) of patients had taken at least one and more than half (52.1%) had taken at least two medications for DPNP during the preceding week [14]. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most commonly used medications, with 46.7% reporting their use, although there is little evidence to support the efficacy of NSAIDs in DPNP, and NSAIDs have a high potential for renal impairment in patients with diabetic neuropathy [15]. Other frequently used medications were short- and long-acting opioids (43.1%), anticonvulsants (27.1%), second-generation antidepressants (18%), and TCAs (11.4%) [14]. These utilization rates are summarized in Table 2.

The only existing treatment guideline that is relevant to DPNP was developed for neuropathic

### Table 1 Epidemiological studies examining prevalence of diabetic neuropathy

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Population</th>
<th>Period of Data Collection</th>
<th>Basis of Diagnosis</th>
<th>Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gregg et al. 2004 [9]</td>
<td>National Health and Nutrition Examination Survey</td>
<td>1999–2000</td>
<td>Diabetic peripheral neuropathy diagnosed by symptoms (numbness, loss of feeling, or pain or tingling in feet in the last 3 months) and ≥1 insensate areas based on monofilament testing</td>
<td>Peripheral neuropathy—28.5% among diagnosed diabetics</td>
</tr>
<tr>
<td>Dyck et al. 1993 [7]</td>
<td>Rochester Diabetic Neuropathy Study</td>
<td>1986</td>
<td>Diabetic polyneuropathy diagnosed by symptoms and electrophysiological testing</td>
<td>All diabetics—47.3%</td>
</tr>
<tr>
<td>Harris et al. 1993 [8]</td>
<td>National Health Interview Survey, N = 2,405 Adult diabetics</td>
<td>1989</td>
<td>Sensory neuropathy diagnosed by symptoms (numbness, pain or tingling, or decreased ability to feel hot and cold in the past 3 months)</td>
<td>IDDM—54%</td>
</tr>
<tr>
<td>Maser et al. 1989 [10]</td>
<td>Pittsburgh Epidemiology of Diabetes Complications Study, N = 400 (first 400 subjects seen at baseline) Adults with IDDM</td>
<td>1984–88</td>
<td>Diabetic neuropathy diagnosed by presence of 2 of 3 of the following: abnormal sensory or motor signs, symptoms, decreased tendon reflexes</td>
<td>IDDM—34%</td>
</tr>
</tbody>
</table>

IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus.
pain by members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain (2003) [16]. This guideline was developed prior to U.S. Food and Drug Administration (FDA) approval of any medication for DPNP. Five medications or classes of medications (gabapentin, the 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and TCAs) were recommended as first-line treatments for patients with neuropathic pain based on positive efficacy data from at least two, placebo-controlled RCTs. Recommendations for second-line medications were based on positive results from a single RCT or inconsistent results from multiple RCTs [16].

Because of the results of recent clinical trials, these guidelines must now be supplemented by consideration of other medications. We will discuss treatment options for DPNP in three different categories that are based, in part, on the approach used in the neuropathic pain guideline:

1. Medications or classes of medications with replicated evidence of efficacy (at least two positive, placebo-controlled RCTs) in patients with DPNP.
2. Medications with evidence of efficacy (at least one positive placebo-controlled RCT) in DPNP and supportive evidence from another placebo-controlled RCT in a closely related condition.
3. Other noteworthy medications, including those with a single positive placebo-controlled RCT and those with inconsistent results from multiple RCTs.

### Medications with Replicated Evidence of Efficacy in DPNP

Four medications or classes of medications have replicated evidence of efficacy in patients with DPNP: duloxetine, opioid analgesics, pregabalin and gabapentin, and TCAs. Only two of these medications, duloxetine and pregabalin, are approved by the FDA for the treatment of DPNP. Because both of these approvals occurred in 2004, there is still relatively limited clinical experience with these agents in the community.

The efficacy of duloxetine in the treatment of DPNP was established in three double-blind, placebo-controlled RCTs that included a total of 1,139 patients [17–19]. The FDA-approved dosage of duloxetine 60 mg daily demonstrated rapid onset of action (within the first week of treatment) and sustained pain relief, with significantly greater improvement than placebo in improving the primary efficacy endpoint, the weekly mean score of 24-hours average pain severity, as well as other secondary outcomes measures, such as the Patient’s Global Impression of Improvement (PGII). The data from these three trials were pooled, and patients who completed the study were analyzed with respect to changes in functional outcome measures, including the Medical Outcomes Study Short Form 36 (SF-36), the EuroQol 5D (EQ-5D), and the Brief Pain Inventory interference scale. Treatment with duloxetine was associated with significant improvement in functional status as measured by each of these instruments [20].

Table 2 Reported use of pharmaceutical treatment for diabetic peripheral neuropathy pain during preceding week

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Utilization Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>46.7</td>
</tr>
<tr>
<td>Short- and long-acting opioids</td>
<td>43.1</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>27.1</td>
</tr>
<tr>
<td>Second-generation antidepressants</td>
<td>18.0</td>
</tr>
<tr>
<td>TCAs</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Source: Gore et al. 2004 [14].
NSAIDs = nonsteroidal anti-inflammatory drugs; TCAs = tricyclic antidepressants.

The efficacy of pregabalin in DPNP has been established in three published double-blind, placebo-controlled RCTs that included a total of 730 patients [21–23]. In these trials, pregabalin demonstrated early and sustained improvement in pain and a beneficial effect on sleep with dosages ranging from 150 mg to 600 mg daily. In addition, significantly greater percentages of patients reported improvement on the Patient Global Impression of Change (PGIC) with pregabalin treatment than placebo. Pooled analyses of the data from these three published clinical trials of pregabalin in DPNP, a published trial that included patients with either postherpetic neuralgia (PHN) or DPNP [24], two unpublished DPNP trials, and two published [25,26] and two unpublished PHN trials found significantly greater improvement with pregabalin treatment vs placebo on several scales of the SF-36, including vitality, mental health, social functioning, and emotional role limitations [27].

In an RCT (N = 165) with dosages titrated from 900 mg to 3,600 mg daily as tolerated, gabapentin significantly reduced DPNP compared with placebo, and also was associated with significant improvements in sleep, mood, and quality of life measures [28]. However, a small crossover trial (N = 40) of 900 mg daily of gabapentin in DPNP...
found benefit for only one of four pain outcome measures [29], and gabapentin was not different from placebo in a large unpublished trial in DPNP [30].

The two medications approved by the FDA for the treatment of DPNP, duloxetine and pregabalin, have different mechanisms of action. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor and is thought to reduce pain by augmenting serotonin and norepinephrine activity in descending pain inhibitory pathways that originate in the midbrain and terminate in the spinal cord [31]. Duloxetine has no in vitro affinity for opioid, glutamate, and gamma-aminobutyric acid (GABA) receptors and no significant affinity for dopaminergic, adrenergic, cholinergic, and histaminergic receptors [32].

Although gabapentin and pregabalin are closely related to GABA, neither compound appears to exert its pharmacological activity through direct interaction with GABA receptors. Both drugs act at the alpha2-delta subunit of voltage-gated calcium channels to reduce transmitter release, and binding activity of both drugs correlates with decreased calcium channel function and decreased release of several neurotransmitters, including glutamate, norepinephrine, and substance P [33]. The results of recent studies of mutant mice with decreased alpha2-delta binding affinity demonstrate that binding to this calcium channel subunit is required for the actions of pregabalin and gabapentin on neurotransmitter release and that this provides the mechanism of their analgesic effects in rodent pain models [33].

Two other classes of medications have demonstrated consistent relief of pain in patients with diabetic neuropathy. Because of the lack of careful study, the efficacy of opioid analgesics in the treatment of neuropathic pain had remained controversial until recently. In the past several years, however, the results of a number of RCTs have established that opioid analgesics are efficacious in patients with DPNP [34,35]. In addition, opioid analgesics also have demonstrated efficacy in patients with various other neuropathic pain conditions [16,36].

Tricyclic antidepressants have been considered first-line agents for the treatment of neuropathic pain for many years based on the results of numerous RCTs in patients with diabetic neuropathy, PHN, and other neuropathic pain syndromes [37–39]. The TCAs amitriptyline, clomipramine, desipramine, and imipramine have all demonstrated efficacy in patients with DPNP, but use of secondary amine TCAs has been emphasized because of their generally greater tolerability compared with tertiary amine TCAs [16,40].

Medications with Evidence of Efficacy in DPNP and Closely Related Conditions

Tramadol is a weak mu opioid agonist that also inhibits the reuptake of serotonin and norepinephrine. It has demonstrated efficacy in RCTs of 131 patients with DPNP [41] and 45 patients with diverse painful polyneuropathies, including those with painful diabetic neuropathy [42].

Venlafaxine, a selective norepinephrine and serotonin reuptake inhibitor, has also demonstrated efficacy in an RCT of 244 patients with DPNP, in which patients administered 150–225 mg daily but not 75 mg daily reported significantly reduced pain compared with those administered placebo [43]. Venlafaxine also demonstrated efficacy in an RCT of 40 patients with diverse painful polyneuropathies, including painful diabetic neuropathy [44].

Other Noteworthy Medications

A large number of medications with a single positive placebo-controlled RCT in patients with DPNP, inconsistent results from multiple RCTs, or other noteworthy characteristics warrant consideration in the treatment of DPNP. Although it is beyond the scope of this article to review all of these, we will discuss three groups of such medications:

- Anticonvulsant drugs other than pregabalin and gabapentin.
- Selective serotonin reuptake inhibitors (SSRIs).
- The topical treatments capsaicin and lidocaine patch 5%.

The results of RCTs of the anticonvulsants carbamazepine and phenytoin show some evidence of a beneficial effect for patients with DPNP, but these results are primarily from trials that were conducted 30 or more years ago that do not meet current methodological standards [16,45]. Two recent studies conducted by the same investigators reported evidence of the efficacy of sodium valproate in 108 patients with DPNP [46,47]. Of the second-generation anticonvulsants, RCTs have been conducted examining lamotrigine, oxcarbazepine, topiramate, and zonisamide for the treatment of DPNP. Lamot...
rigide demonstrated efficacy in one clinical trial of 59 patients with DPNP [48], but results of intention-to-treat analyses were negative in two recent large trials of DPNP [49]. For oxcarbazepine, one positive and several unpublished trials [50] have been accompanied by an announcement that its development as a potential treatment for neuropathic pain has been discontinued. For topiramate, three negative trials [51] contrast with one positive trial [52], and for zonisamide, a small pilot study found greater pain reduction with zonisamide than placebo but the differences were not statistically significant [53].

The mechanism of action for SSRIs involves the selective inhibition of serotonin reuptake. Placebo-controlled RCTs of SSRIs in patients with DPNP are limited to single positive trials of citalopram (N = 15) [54] and paroxetine (N = 19) [55] and a negative trial of fluoxetine (N = 46) [56]. Although SSRIs may be better tolerated than TCAs, they are less effective as analgesics in the treatment of painful diabetic neuropathy and other chronic neuropathic pain syndromes [13,16].

Topical treatments generally have fewer side-effects and drug interactions than treatment with the oral medications discussed above. Among the topical treatments that have been investigated in patients with painful diabetic neuropathy, two have recently received attention. A meta-analysis of RCTs of capsaicin, which included studies of DPNP, concluded that topical capsaicin has relatively limited efficacy overall but that it may benefit some patients who are unresponsive to other treatments [57]. The 5% lidocaine patch has demonstrated efficacy in double-blind, randomized, vehicle-controlled clinical trials in patients with PHN [58,59], for which it is approved by the FDA, and diverse peripheral neuropathic pain syndromes [60]. Although a placebo-controlled trial has not been conducted in patients with painful diabetic neuropathy, the results of an open-label study considered together with these RCTs suggest that the lidocaine patch 5% is well tolerated and deserves further study for the treatment of DPNP [61].

The RCTs discussed in this section have typically compared a single medication with placebo to evaluate efficacy in patients with DPNP. In clinical practice, however, the treatment of patients with DPNP often involves the combination of two or more of the medications discussed above. Until recently, there was no evidence base for such combination therapy. However, the results of a recent RCT that compared the combination of morphine and gabapentin with each of these drugs alone and with placebo in 57 patients with either DPNP or PHN demonstrated that combination treatment can be more efficacious than treatment with a single medication or placebo [62].

**Burden: Quality of Life**

Five published studies reported that DPNP has a negative impact on both quality of life and functional status. Specific domains of health-related quality of life affected by DPNP included patient-reported interference with general activity, mood, mobility, work, social relations, sleep, leisure activities, and enjoyment of life [63–65]. The five studies are described below. For a summary of the quality of life study results, see Table 3.

In a cross-sectional, community-based survey of 255 DPNP patients, study participants reported that pain substantially interfered with walking ability, normal work, sleep, and enjoyment of life as measured by the Modified Brief Pain Inventory-Diabetic Peripheral Neuropathy (mBPI-DPN) [65]. DPNP patients also indicated significant impairment in both physical and mental functioning on the Medical Outcomes Study Short Form 12 Version 2 (SF-12) questionnaire compared with patients with diabetes without diabetic neuropathy [64]. DPNP patients reported moderate to severe levels of anxiety (35%) and depression (28%) as measured by the Hospital Anxiety and Depression Scale (HADS) [64,65]. Increasing levels of mBPI-DPN scores for average and worst pain severity from “mild” (ratings of 0–3) to “moderate” (ratings of 4–6) to “severe” (ratings of 7–10) corresponded to lower EQ-5D utility scores and lower levels of physical and mental functioning. Increasing pain levels as indicated by mBPI-DPN scores also corresponded to higher levels of anxiety and depression symptoms and sleep problems [64,65].

In a survey of 105 patients with painful diabetic polyneuropathy exploring the nature and scope of pain problems in persons with diabetic neuropathy, the reported average pain intensity in the last week was 5.75 (on a 0–10 scale, with 0 = “no pain” and 10 = “the worst pain imaginable”); least and worst pain in the last week were 3.56 and 6.89, respectively [63]. The majority of patients (53%) reported that they experience pain on a constant, daily basis, and in 52% of patients, the pain was...
worse at night. Patients completed the Neuropathic Pain Scale (NPS), a validated 10-item questionnaire used to quantify the different qualities of neuropathic pain, each on a 0–10 scale [63]. Pain qualities with mean scores on the NPS ≥5 are summarized in Table 3, along with the percentages of persons reporting “substantial” (defined as score ≥5) interference on activities assessed with the mBPI-DPN.

A prospective study of 331 diabetic veterans found that diabetic neuropathic pain reduced quality of life among diabetic individuals over time, as measured by the SF-36. SF-36 scores of individuals with diabetes were collected during two surveys conducted several years apart (the mean time between the two surveys was 3.1 years). Increases over time in neuropathic pain, numbness, burning, tingling, formication (sensation of insects crawling on or under the skin), and tactile sensitivity assessed with a microfilament were significantly associated with decreases in several SF-36 domains, indicating increased functional impairment [66].

**Cost of Illness**

Cost of illness studies usually estimate either the direct costs associated with an illness, including medical and drug costs, or the indirect costs associated with lost productivity resulting from morbidity or premature mortality [67]. Studies that estimate costs may be further categorized as offering prevalence-based or incidence-based cost estimates. The prevalence-based model measures all costs due to an illness occurring within a given time period, usually a single year, regardless of the

### Table 3 Quality of life burden associated with diabetic peripheral neuropathy pain (DPNP)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Instruments</th>
<th>Results</th>
</tr>
</thead>
</table>
| Gore et al. 2004 [64] | 255 patients with diabetic neuropathic pain recruited from endocrinologist, neurologist, anesthesiologist, and primary care physician offices | mBPI-DPN, SF-12v2, HADS, MOS-S | mBPI-DPN—Percentage with substantial interference (score ≥5):  
- General activity: 48.0%  
- Mood: 43.4%  
- Mobility: 57.0%  
- Normal work: 56.6%  
- Relations: 36.1%  
- Sleep: 57.1%  
- Enjoyment of life: 58.2%  
- Self care: 35.1%  
- Recreational activities: 56.1%  
- Social activities: 50.5%  
NPS—Pain qualities with mean scores ≥5:  
- Intensity  
- Sharp  
- Unpleasant  
- Deep  
- Surface  |
| Gore et al. 2004 [65] | 255 patients with diabetic neuropathic pain recruited from endocrinologist, neurologist, anesthesiologist, and primary care physician offices | EQ-5D Global overall health rating | EQ-5D—Global mean score 0.5  
- Mean score 56.4 |
| Galer et al. 2000 [63] | 105 patients with painful diabetic polyneuropathy | mBPI-DPN, NPS | mBPI-DPN—Percentage with substantial interference (score ≥5):  
- General activity: 48.0%  
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- Social activities: 50.5%  
NPS—Pain qualities with mean scores ≥5:  
- Intensity  
- Sharp  
- Unpleasant  
- Deep  
- Surface  |

**EQ-SD** = EuroQol-5D; 0–1 scale, 0 = worst health imaginable, 1 = perfect health.  
**Global overall health rating scale;** 1–100, 0 = worst possible health, 100 = perfect health.  
**mBPI-DPN** = Modified Brief Pain Index-Diabetic Peripheral Neuropathy; 0–10 scale, 0 = “no pain” and 10 = “pain as bad as you can imagine.”  
**MOS-S** = Medical Outcomes Study Sleep Scale; 0–100 scale.  
**NPS** = Neuropathic Pain Scale; 0–10 rating of 10 pain qualities.  
**SF-12v2** = Medical Outcomes Study Short Form 12 Version 2; Physical Health Component Score (PCS) and Mental Health Component Score (MCS); 0–100 scale, with lower scores indicating greater impairment.
time of disease onset. The incidence-based model quantifies the total lifetime costs of new cases of an illness with onset in the base year [68].

**Direct Cost Estimates of DPNP**

Prevalence-based estimates of the direct cost of DPNP in the United States were limited; only three studies were identified. Each of these studies estimated pharmaceutical costs for treating DPNP.

A retrospective cohort study used patient-level administrative claims data from 2002 for individuals diagnosed with diabetes and diabetic neuropathy [69]. The types of providers prescribing pain medication, along with the type of medication and its annual costs, were compiled to give a picture of the utilization and costs of pain medications from a third-party payer perspective. The average cost of pain medications among patients with DPNP was $1,004 per year. Average annual costs for monotherapy were $327; for multiple therapies, the average annual costs were $1,588. The average daily cost per patient ranged from $2.35 (antidepressants) to $7.74 (long-acting narcotics) [69]. Table 4 provides a breakdown of annual costs per patient by specific medications.

A second prevalence-based cost study estimated the total annual drug treatment costs to U.S. payers for treating symptomatic DPNP [70] at $237 million (2001 USD), given that 14% of patients with diabetic peripheral neuropathy would experience mild to severe pain (based on the results of the Rochester Diabetic Neuropathy Study), and all of those experiencing pain would receive pharmacotherapy (e.g., a TCA, amitriptyline) at a mean weekly cost of $5.90 per patient [70]. As this estimate was based solely on the costs of treatment with amitriptyline, one of the least expensive medications that may be prescribed for DPNP, it was likely an underestimate of pharmaceutical costs for treatment of DPNP in general. If the model included other, more expensive pharmaceutical treatments and combination therapies likely to be used by patients with DPNP (e.g., anticonvulsants, newer antidepressants), the cost would likely increase substantially. This study focused on the direct costs of serious complications resulting from diabetic peripheral neuropathy such as foot ulcers and amputation; no medical costs (e.g., physician visits, neurological tests) were attributed to DPNP in this model [70].

Incidence-based estimates of direct costs of DPNP in the United States also are limited. Two studies identified pharmaceutical costs associated with the symptom of DPNP [70,71]. The results of these studies are summarized in Table 4.

The first study presented a cost-of-illness model of the health care costs of diabetic peripheral neuropathy that generated an incidence-based estimate of annual pharmaceutical costs per patient for DPNP of $306.80 (2001 USD) to treat with amitriptyline (unspecified dosage) [70]. This finding is similar to that of a study using different methods performed by Able and colleagues [69]. Through a retrospective database analysis, Able and colleagues arrived at an estimate of $327 (2002 USD) for the average annual costs for pain medication monotherapy for a person with DPNP [69].

### Table 4  Direct costs per patient associated with diabetic peripheral neuropathic pain

<table>
<thead>
<tr>
<th>Source</th>
<th>Year of Data</th>
<th>Costs Included</th>
<th>Annual Direct Cost Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gabapentin: $979</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amitriptyline: $559</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TCAs: $159</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SSRIs: $683</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Short-acting narcotics: $174</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydrocodones: $115</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxycodones: $151</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-acting narcotics: $1,021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tramadol: $398</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxycodone Controlled Release: $1,722</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-narcotic analgesics: $368</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cox-2 inhibitors: $556</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Cox-2 NSAIDs: $194</td>
</tr>
<tr>
<td>Bizzacco et al. 2000 [71]</td>
<td>Not specified</td>
<td>Medication, mean costs</td>
<td>Gabapentin: $964</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amitriptyline: $226</td>
</tr>
<tr>
<td>Gordois et al. 2003 [70]</td>
<td>2001</td>
<td>Medication, mean costs</td>
<td>Amitriptyline: $306.80</td>
</tr>
</tbody>
</table>

TCAs = tricyclic antidepressants.
SSRIs = selective serotonin reuptake inhibitors.
NSAIDs = nonsteroidal anti-inflammatory drugs.
In the second study, the annual cost per patient for gabapentin and amitriptyline was estimated [71]. These estimates were derived from a clinical decision model estimating the cost and quality-adjusted life-years associated with gabapentin and amitriptyline for the management of DPNP from the perspective of an unspecified managed care organization over a 3-month time period. Probabilities were obtained from multicenter RCTs. The estimates generated were $954 for gabapentin 3,600 mg per day and $226 for amitriptyline 100 mg per day [71].

**Indirect Cost Estimates of DPNP**

One study examined both indirect and direct costs of DPNP treatment from a societal perspective [72]. The study population consisted of 233 U.S. patients participating in a 52-week randomized trial of duloxetine vs routine treatment for DPNP. Patients’ medical services and drugs (direct costs), as well as productivity losses (indirect costs), were measured for 50 weeks. The primary efficacy measure was the SF-36 bodily pain (BP) domain. From a societal perspective, duloxetine was cost-effective compared with routine treatment of DPNP. Total cost savings with duloxetine were $2,754 (2002 USD) compared with routine treatment over the period of data collection. The incremental cost-effectiveness ratio was –$429/1 unit of SF-36 BP [72].

A major limitation in comparing these studies is that the types of costs used to estimate the economic burden of DPNP vary across studies, including, for example, drug costs [70] vs clinical consultations and procedures [71].

**Discussion**

Peripheral diabetic neuropathy is one of a family of nerve disorders caused by complications of diabetes [2]. Peripheral neuropathy is the most common of the diabetic neuropathies and the most frequently studied.

Diagnosis of diabetic peripheral neuropathy is dependent on the presence of a characteristic pattern of signs and symptoms. Upon examination, many people with diabetes have signs of neuropathy, but no symptoms. In these cases, diagnosis may be delayed until the patient begins to experience symptoms, including DPNP.

Current treatment patterns as assessed by community surveys suggest that clinical practice does not conform to evidence-based treatment recommendations [16]. Although NSAIDs are not recommended as treatment for neuropathic pain, pharmaceutical utilization rates in a DPNP population showed that NSAIDs were used by 46.7% of patients, making them the most commonly used medications for DPNP [14]. Gabapentin was recommended as a first-line medication for the treatment of neuropathic pain [16]; however, only 26% of patients reported using gabapentin for neuropathic pain [14]. Slightly more than half of the patient population (52.1%) had taken at least two medications for DPNP during the preceding week, which may indicate the need for multiple medications to achieve pain relief [14].

Most epidemiological studies focusing on diabetic peripheral neuropathy did not report the epidemiology of DPNP specifically. Due to the various case definitions for diabetic peripheral neuropathy used in the epidemiology studies, prevalence rates ranged from 25.8% [9] to 47.3% [8]. A few studies [6–8] provided data describing the prevalence of symptomatic diabetic peripheral neuropathy; however, the studies did not provide the frequency of painful symptoms separately from nonpainful symptoms. The lack of DPNP-specific epidemiology data made it difficult to analyze long-term trends in DPNP and to draw comparisons with data from other chronic pain populations.

Well-designed prospective studies of the impact of DPNP on quality of life are needed to fully understand the burden of personal suffering and social costs caused by this chronic complication of diabetes. The available research indicated that DPNP imposes a substantial burden in terms of pain, impaired functional status and sleep, and increased levels of anxiety and depression. The burden of painful diabetic neuropathy specifically vs diabetic neuropathy in general has not received a great deal of attention in the literature. Often DPNP appears as part of a study assessing the burden of several complications of diabetes.

Several gaps exist in the literature describing the cost associated with DPNP. The studies that exist use varying types of cost estimates (e.g., drug cost vs clinical consultations), making it difficult to accurately quantify the economic burden and conduct comparisons across studies. The levels of specific medical resources required to treat DPNP might inform the types of costs included in an economic analysis, but these data were not identified for DPNP. Patients with DPNP often try several different types of therapies, and may combine or switch therapies. The use of combination therapy and frequent switching of medications...
would have an impact on medical and drug costs; however, no studies describing the cost implications of combination therapy or of switching therapies were identified. There are indirect costs associated with DPNP, but such costs have been identified only in one study published in the literature [72], and this study does not report indirect costs separately.

This systematic review of DPNP identified the limitations of the existing literature, highlighting the need for further study. The use of consistent case definitions and a diagnostic code for collecting data would vastly improve our understanding of the impact of DPNP on patients and the health care system. This review also highlighted the variety of practice patterns and minimal treatment guidelines currently available for patients with DPNP. Well-designed, prospective studies are needed to compare treatment options alone and in combination, as well as to evaluate the quality of life burden and costs associated with DPNP.

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