Review

Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature

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ABSTRACT

Aims: Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes mellitus. A systematic literature review was conducted to provide an overview of published literature in the last 10-years on the epidemiology, humanistic burden and economic burden of PDPN in Europe.

Methods: A search was performed according to pre-defined strategy and review criteria in Embase, Pubmed, and conference proceedings databases from 2003 till December 2012. In total, 30 publications written in English covering the relevant patient population and topics of interest.

Results: European prevalence ranges from 6% to 34% in diabetes mellitus patients. PDPN has a significant humanistic and economic impact. Patients are limited in their general functioning and their ability to sleep and often experience anxiety and depression. Not surprisingly, PDPN is associated with reduced Health-Related-Quality-of-Life (HRQoL). PDPN patients incur high health care costs due to hospitalizations and outpatient visits. In addition, the painful symptoms cause impaired work productivity. Studies suggest both humanistic and economic burden increase with higher pain severity.

Conclusions: The burden from PDPN appears to be higher with increasing pain severity. More severe pain leads to a higher impairment in daily functioning, sleep and HRQoL. Higher pain intensity also leads to increasing healthcare costs and work productivity losses.

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1. Introduction

Diabetic polyneuropathy (DPN) is one of the most common complications of diabetes and the most common form of neuropathy in the developed world [1]. Clinical manifestations of DPN include painful diabetic neuropathy (PDPN), troublesome autonomic features such as orthostatic hypotension [2], cardiac autonomic neuropathy (a clinical condition which can result in sudden death) [3], other conditions caused by non-cardiac autonomic neuropathy (such as gastro-paresis and erectile dysfunction) [3], and insensitivity to trauma (which can result in ulceration, infections, and lower extremity amputations) [2].

PDPN develops as a result of damage to or dysfunction of the system that signals pain [4]. Patients suffering with PDPN describe symptoms as burning, aching, shooting, and stabbing; usually with nocturnal exacerbations [1,5]. PDPN is often present in arms, hands, legs, and feet. It can affect the ability of patients to perform daily activities, their sleep, their work, how they feel, and therefore reduce the enjoyment of life for these patients [6]. Health related quality of Life (HRQoL), sleep and mood are frequently impaired in patients with PDPN [6,7]. Generally, pain reduction (as a result of treatment) is related to improvement in QoL [8,9].

The only intervention that has been shown to reduce the risk of development of neuropathy in diabetes patients is intensive glycaemic control [1,10]. Apart from suboptimal glycaemic control, patients with longer diabetes duration, of older age, hypertensive, with cardiovascular disease or who smoke are more likely to develop diabetic neuropathy [1].

In Europe, duloxetine is recommended as the first-line treatment option for PDPN, by the European Federation of Neurological Societies (EFNS) [9] and the National Institute for Health and Clinical Excellence (NICE) [4]. Pregabalin, gabapentin, amitriptyline, other tricyclic antidepressants (TCAs), tramadol, topical lidocaine, strong opioids and a combination of these drugs are advised as second-line and third-line treatments; the choice of drug(s) is made on an individual patient basis. Large studies are required to better define patient responder profiles for specific drug treatments [9].

Although a wide range of treatment options are available, an unmet need among PDPN patients still exists since neuropathic pain is often difficult to treat due to the resistance to many medications or due to their associated adverse effects. Many people require treatment with more than one drug, but the correct choice of drugs and the optimal sequence for their use is so far unknown [4]. The use of multiple drugs (polypharmacy) may also increase the risk of additional adverse events and incorrect use of medication [11].

Due to their pain, PDPN patients are expected to incur higher health care costs compared to the general population and diabetes patients without PDPN as they take pain reducing medication and are likely to visit health care professionals more frequently. In addition, the absence from work or reduced functionality at work can result in additional costs for society.

The objective of this literature review was to collect and discuss European data regarding the epidemiology, humanistic and economic burden associated with PDPN in order to provide a complete overview from a European perspective of the evidence published in the last 10 years. The research questions to be answered by the review are ‘What is the prevalence and incidence of PDPN?’, ‘What are the identified risk factors and patient subgroups in PDPN?’, ‘How are PDPN patients affected in their general functioning, sleep, anxiety, depression and overall HRQoL?’ and ‘What is the resource use associated with PDPN, including direct and indirect costs?’

2. Literature review process

2.1. Search strategy

A systematic literature search was performed to obtain available European literature on epidemiology, and the humanistic and economic burden associated with PDPN. In addition, the search included publications on PDPN management to provide background information regarding current treatment patterns. Before commencing the search, a protocol was developed following the PRISMA statement [12].

Embase and PubMed were searched for relevant publications from January 2003 to December 13th 2012. Websites of European Health Technology Assessment (HTA) organizations and conference proceedings from the International Association for the Study of Pain (IASP) were searched from January 2010 to December 13th 2012. These last two sources were searched for the last 3 years only, as it is expected that abstracts of high quality are highly likely to be published in peer reviewed journals during this period. Disease terms for PDPN were combined with search terms for the topics of interest, such as epidemiology, prevalence, incidence, humanistic burden, quality of life, comorbidities, anxiety, depression, healthcare cost, budget impact, resource use,
work disability, guidelines, treatment pattern, and standard of care.

Publications were included in the review if they contained all of the following criteria (1) concerned PDPN patients; (2) contained data for epidemiology, humanistic burden or economic burden; (3) had a European scope; (4) were written in the English language; and (5) were full-texts or conference abstracts of original studies.

For studies reporting costs in currencies other than Euros, the amounts were converted to Euros using the conversion rate of March 2013 [13]. Euro and the original currency (in brackets) are reported in the text.

2.2. Search results

A total of 1694 citations were obtained via Embase and PubMed and 185 via other databases. After removing duplicates, 1485 titles and abstracts were screened, and 238 full texts were assessed for eligibility (Fig. 1). Main reasons for exclusion: articles not addressing PDPN, not describing one of the relevant topics, not an original study or with no European scope. The search resulted in the inclusion of 33 publications covering 30 different studies. Table 1 provides an overview of included studies and key characteristics.

Thirteen articles reported on epidemiology [14–26], 10 on humanistic burden [27–36] and three on economic burden [37–39]. Seven studies provided data for both humanistic burden and epidemiology (n = 3) [40–42] or economic burden (n = 4) [43–46]. Most epidemiology and humanistic burden studies were performed in the UK (n = 5) [14,16,18,40,41] and n = 7 [27,28,33,35,40,41,44], respectively. Economic burden studies were performed in Spain (n = 3) [38,43,45], UK (n = 2) [37,44] and Europe (n = 2) [39,46]. The majority of included studies were cross-sectional by design (n = 15) [14–16,19,21,22,24,27,28,34,35,39,40,42,46]; the remainder were retrospective database studies (n = 9) [17,18,20,23,25,26,37,38,41], cohort studies (n = 6) [29–33,36] and economic evaluations (n = 3) [43–45].

Included studies used a range of different methods to determine whether patients met the PDPN criteria (see Table 1). Seven studies based their criteria on completed questionnaires [14,15,24–26,33,40], most frequently used questionnaire was the Michigan Neuropathy Screening Instrument (MNSI). Other studies included patients based on medical record status [17,18,20,23,27,41], clinical examination [16,19,21,22,40], physician diagnosis [15,42,46] or International Classification of Diseases (ICD) codes [28,37,38]. Eleven studies did not report the methods or criteria they applied [29–32,34–36,39] or it was not relevant for the study design (i.e., economic model) [43–45].

3. Epidemiology

PDPN is a common comorbidity among diabetes patients; the reported prevalence of PDPN in Europe ranged from 0.7% to 34% in overall, type1 or type 2 diabetes mellitus patients (see Table 2). Excluding outliers, the prevalence range was found to be 5.8–34% [14–16,19–22,24,26,40]. The incidence rate of PDPN was reported to be 0.72 per 1000 persons per year for the Netherlands [17], and 0.64–0.69 per 1000 persons per year in the UK [18,41].

Identified risk factors for PDPN were older age, female gender, type 2 diabetes mellitus, and longer duration of diabetes [14,16,19,21,22,24,25,40]. None of the included studies investigated risk factors as the main study objective.

The literature review identified few studies focusing on PDPN subgroups. One German cross-sectional study by Baron

![Fig. 1 – PRISMA flow.](image-url)
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Topic</th>
<th>Country</th>
<th>N</th>
<th>Study design</th>
<th>Sponsor</th>
<th>Method to determine PDPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott 2011[14]</td>
<td>Epidemiology</td>
<td>UK</td>
<td>15,692</td>
<td>Observational–Cross-sectional</td>
<td>Department of health</td>
<td>Questionnaire (NDS)</td>
</tr>
<tr>
<td>Daousi 2004[16]</td>
<td>Epidemiology</td>
<td>UK</td>
<td>694</td>
<td>Observational–Cross-sectional</td>
<td>No sponsor disclosed</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Dieleman 2008[17]</td>
<td>Epidemiology</td>
<td>The Netherlands</td>
<td>362,693</td>
<td>Observational–Database</td>
<td>Pfizer</td>
<td>Medical records</td>
</tr>
<tr>
<td>Hall 2008[18]</td>
<td>Epidemiology</td>
<td>UK</td>
<td>2.9 million</td>
<td>Observational–Cross-sectional</td>
<td>Pfizer</td>
<td>Medical records</td>
</tr>
<tr>
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<td>No sponsor disclosed</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Rubino 2007[20]</td>
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<td>Observational–Database</td>
<td>Eli Lilly and company</td>
<td>Medical records</td>
</tr>
<tr>
<td>Truini 2011[21]</td>
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<td>No sponsor disclosed</td>
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<td>Epidemiology</td>
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<td>1111</td>
<td>Observational–Cross-sectional</td>
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<td>Clinical examination</td>
</tr>
<tr>
<td>Van Kollenburg 2012[23]</td>
<td>Epidemiology</td>
<td>The Netherlands</td>
<td>497</td>
<td>Observational–Database</td>
<td>No sponsor disclosed</td>
<td>Medical records</td>
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<td>Wu 2007[24]</td>
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<td>France</td>
<td>14,352 (households)</td>
<td>Observational–Cross-sectional</td>
<td>Eli Lilly and company and Boehringer Ingelheim</td>
<td>Questionnaire (MNSI)</td>
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<td>Ziegler 2009a[25]</td>
<td>Epidemiology</td>
<td>Germany</td>
<td>393</td>
<td>Observational–Database</td>
<td>Research institute</td>
<td>Questionnaire (MNSI)</td>
</tr>
<tr>
<td>Ziegler 2009b[26]</td>
<td>Epidemiology</td>
<td>Germany</td>
<td>393</td>
<td>Observational–Database</td>
<td>Research institute</td>
<td>Questionnaire (MNSI)</td>
</tr>
<tr>
<td>Davies 2006[40]</td>
<td>Epidemiology humanistic burden</td>
<td>UK</td>
<td>385</td>
<td>Observational–Cross-sectional</td>
<td>Pfizer</td>
<td>Questionnaire (DNSS) and clinical examination</td>
</tr>
<tr>
<td>Hall 2006[41]</td>
<td>Epidemiology humanistic burden</td>
<td>UK</td>
<td>&gt;6.8 million</td>
<td>Observational–Database</td>
<td>Pfizer</td>
<td>Medical records</td>
</tr>
<tr>
<td>Baron 2009[42]</td>
<td>Epidemiology humanistic burden</td>
<td>Germany</td>
<td>1623</td>
<td>Observational–Cross-sectional</td>
<td>Pfizer</td>
<td>Physician diagnosis</td>
</tr>
<tr>
<td>Cash 2012[27]</td>
<td>Humanistic burden</td>
<td>UK</td>
<td>300</td>
<td>Observational–Cross-sectional</td>
<td>No sponsor disclosed</td>
<td>Medical records</td>
</tr>
<tr>
<td>Currie 2006[28]</td>
<td>Humanistic burden</td>
<td>UK</td>
<td>1298</td>
<td>Observational–Cross-sectional</td>
<td>Eli Lilly and Company</td>
<td>ICD codes</td>
</tr>
<tr>
<td>D’Amato 2012[29]</td>
<td>Humanistic burden</td>
<td>Italy</td>
<td>33</td>
<td>Observational–Cohort</td>
<td>No sponsor disclosed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Schneider 2011a[30]</td>
<td>Humanistic burden</td>
<td>Germany</td>
<td>2576</td>
<td>Observational–Cohort</td>
<td>No sponsor disclosed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Schneider 2011b[31]</td>
<td>Humanistic burden</td>
<td>Germany</td>
<td>2576</td>
<td>Observational–Cohort</td>
<td>No sponsor disclosed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Spallone 2012[32]</td>
<td>Humanistic burden</td>
<td>Italy</td>
<td>105</td>
<td>Observational–Cohort</td>
<td>No sponsor disclosed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tahrani 2011[33]</td>
<td>Humanistic burden</td>
<td>UK</td>
<td>204</td>
<td>Observational–Cohort</td>
<td>Research institute</td>
<td>Questionnaire (MSNI)</td>
</tr>
<tr>
<td>Taylor-Stokes 2012a[34]</td>
<td>Humanistic burden</td>
<td>Europe</td>
<td>634</td>
<td>Observational–Cohort</td>
<td>Pfizer</td>
<td>Not reported</td>
</tr>
<tr>
<td>Thomas 2012[35]</td>
<td>Humanistic burden</td>
<td>NA (UK)</td>
<td>113</td>
<td>Observational–Cross-sectional</td>
<td>No sponsor disclosed</td>
<td>Not reported</td>
</tr>
<tr>
<td>Vileikyte 2009[36]</td>
<td>Humanistic burden</td>
<td>US and UK</td>
<td>495</td>
<td>Observational–Cohort</td>
<td>Patient organization</td>
<td>Not reported</td>
</tr>
<tr>
<td>De Salas-Cansado 2012[43]</td>
<td>Humanistic burden economic burden</td>
<td>Spain</td>
<td>189</td>
<td>Economic evaluation</td>
<td>Pfizer</td>
<td>NA (model)</td>
</tr>
</tbody>
</table>
et al. 2009 stratified PDPN patients according to different neuropathy sensory symptoms [42]. Based on patient-reported pain symptoms (i.e., burning, allodynia, thermal pressure, pricking, pain attacks, and numbness), five different sensory/neuropathy profiles were developed showing remarkable differences in the expression of symptoms. For instance, the prominent features of the first profile are moderate to strong spontaneous burning pain in combination with slight to moderate dynamic mechanical allodynia (DMA), while the dominant symptoms of the second profile are severe and clinically relevant pain attacks. The study did not investigate how these different profiles influence quality of life or treatment effects. Whether patients with various symptom profiles are likely to respond differently to different pain treatments, and how this information can be used to develop optimal treatment pathways, requires further investigation.

Pain severity can also be used to divide PDPN patients into subgroups; a commonly used classification is a division into mild, moderate, and severe. This division is based on the measurement of pain scores, using instruments such as the Numeric Rating Scale (NRS), Brief Pain Inventory (BPI), Toronto Clinical Scoring System (TCSS), or The Neuropathy Total Symptom Score-6 (NTSS-6) scores [28,37,40,47,48]. For NRS [47] and BPI [48] scores range from 0 to 10, where 0 is no pain and 10 is worst imaginable pain. For NTSS-6, PDPN symptom severities can be classified as none (0), mild (>0 and ≤3.3), moderate (>3.3 and ≤7.64) and severe (>7.64 and ≤10) [28].

Studies reported 15.7–36.4% of patients to have mild symptoms; 13.8–57.1% to have moderate pain; and 10–35% to have severe pain (as measured with the instruments described above) [24,30,40,46]. None of the included studies investigated how these subgroups could be helpful for determining treatment patterns; however, the following sections will outline that higher pain severity is associated with a higher disease burden and higher economic burden.

4. Humanistic burden

The pain experienced by PDPN patients can considerably affect their daily life by reducing the ability to walk and/or perform general everyday activities. The pain and associated impairment of daily living also affect the mood of patients and how they value the quality of their life. Concomitant medication use is high in these patients; a patient survey shows 43% of PDPN patients received prescription medications for sleep disturbance, anxiety and/or depression [46].

The interference of pain with general activity, mood, walking, work, relationships, sleep, and enjoyment of life is measured with the BPI interference score; where 0 is no interference and 10 is complete interference [46]. On this scale, PDPN patients score 4.8 for overall pain interference; with subscales for walking ability and general activity being most affected [30,31,46]. The scores on the subscales for sleep, mood and enjoyment of life are almost as equally highly impaired as walking and general activity, only the subscale ‘relationships’ is less affected by PDPN [46]. The BPI score measured in PDPN patients is comparable to osteoarthritis (OA); a baseline BPI score of 5.1 was found in OA patients [49].
Table 2 – Reported PDPN prevalence and incidence.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence/incidence rate</th>
<th>Diagnosis method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Kollenburg 2012 [23]</td>
<td>Prevalence PDPN: 0.7% from the studied diabetic patients in the nursing home had PDPN and 0.7% had possible PDPN.</td>
<td>PDPN diagnosis based on medical record</td>
</tr>
<tr>
<td>Abbott 2011 [14]</td>
<td>The overall prevalence of painful neuropathy symptoms in this cohort was 34% of the diabetic population.</td>
<td>PDPN diagnosis based on NSS score ≥5 and NDS score ≥3</td>
</tr>
<tr>
<td>La Cesa/Truini 2011 [19,21]</td>
<td>Prevalence PDPN: 18% of the diabetic patients had neuropathic pain (50% of total diabetic study population)</td>
<td>PDPN diagnosis based on DN4 questionnaire</td>
</tr>
<tr>
<td>Bouhassira 2011 [15]</td>
<td>Prevalence PDPN: 20.8% in the diabetic study population.</td>
<td>PDPN diagnosis method not reported</td>
</tr>
<tr>
<td>Ziegler 2009a [25]</td>
<td>Prevalence PDPN: 13.3% of diabetic patients</td>
<td>PDPN diagnosis based on MNSI questionnaire</td>
</tr>
<tr>
<td>Van Acker 2009 [22]</td>
<td>Prevalence PDPN: 14% (over all), 17.9% in diabetes type 1 patients; 5.8% diabetes type 2 patients.</td>
<td>Neuropen and DN4 were used to assess PDPN</td>
</tr>
<tr>
<td>Wu 2007 [24]</td>
<td>Prevalence PDPN in diabetic patients: 8%</td>
<td>PDPN diagnosis based on MNSI score &gt;7</td>
</tr>
<tr>
<td>Rubino 2007 [20]</td>
<td>Prevalence PDPN Approximately 50% of the DPN patients experienced pain. (The proportion of patients with diabetes diagnosed with PDPN ranged from 9.6% to 23.1%)</td>
<td>PDPN diagnosis method not reported</td>
</tr>
<tr>
<td>Davies 2006 [40]</td>
<td>Prevalence PDPN: 26.4% of patients with type 2 diabetes</td>
<td>PDPN diagnosis based on the Toronto clinical scoring system</td>
</tr>
<tr>
<td>Daousi 2004 [16]</td>
<td>Prevalence PDPN: 16.2% in diabetes patients compared with 4.9% in the age and sex-matched control group.</td>
<td>PDPN diagnosis based on a Pain symptom score ≥3, NSS score ≥5 and NDS score ≥3</td>
</tr>
<tr>
<td>Dieleman 2008 [17]</td>
<td>Incidence PDPN: 0.72 per 1000 persons per year</td>
<td>PDPN diagnosis based on medical record of patients</td>
</tr>
<tr>
<td>Hall 2006 [41]</td>
<td>Incidence PDPN: 15.3 per 100,000 person years</td>
<td>PDPN diagnosis based on medical record of patients</td>
</tr>
<tr>
<td>Hall 2008 [18]</td>
<td>Incidence PDPN: 27.2 per 100,000 person years</td>
<td>PDPN diagnosis based on medical record of patients</td>
</tr>
</tbody>
</table>

The impact of PDPN on daily living, measured with disease specific instruments, also show that PDPN patients have impaired functioning. Patients score 2.51 with the Neuro-Qol activities of daily living scale; where 1 is no interference and 5 is high interference [36]. On the Sheehan disability scale, PDPN patients show a mean value of 15, on a scale from 0 (unimpaired) to 30 (highly impaired) [30]. In comparison, a recent study in epilepsy patients found a mean score of 13.9 on the Sheehan disability scale [50].

Due to nocturnal pain, PDPN is often associated with sleep disturbance; it has been reported that 72–96% of patients are moderately to severely affected in their sleep [35,42]. PDPN patients showed significantly worse scores on The Medical Outcomes Study-Sleep Scale (MOS-SS), particularly in the items of ‘sleep adequacy’ and ‘awaken short of breath’ or ‘with headache’, compared to both diabetes patients without neuropathy and diabetes patients with any other form of neuropathy [29,32]. Cash et al. 2012 reported sleep interruption to be significantly correlated with PDPN severity in a linear regression analysis (p < 0.001) [27].

The continuous pain, interference with patients’ daily lives and uncertainty about successful treatment are associated with symptoms of anxiety and/or depression. Studies measuring this with the Hospital Anxiety and Depression Scale (HADS) or the Patient Health Questionnaire 9 (PHQ-9) found that 24.5–72.1% of PDPN patients had symptoms of depression and/or anxiety [27,30,36,42]. The study by Hall et al. 2006 found that 21.6% of PDPN patients had a diagnosis of depression in their medical record [41].

Higher pain severity is found to be significantly correlated with higher interference of daily living and sleep [27,34]. SF-36 scores (in brackets) for physical functioning decrease with increasing severity: no symptoms (74.93), mild symptoms (48.07), moderate symptoms (45.04), and severe symptoms (23.81) [28]. Recent published mean SF-36 physical functioning scores were 60.8 for epilepsy patients and 62.3 for asthma patients [51].

Furthermore, the negative impact of PDPN on the daily lives of patients is reflected in poor HRQoL and low observed utility values in PDPN patients. PDPN patients had significantly worse QoL (measured by NeuroQol) compared with diabetes mellitus patients with no pain and those with non-neuropathic pain [46].

Comparative to daily activities and sleep, a significant relationship exists between pain severity and QoL. This relationship has been shown by measurements with both disease-specific (NeuroQol) [28,40] and different generic HRQoL instruments (EQ-5D, SF-36) [28,46,48]. Mean EQ-5D health state valuations were 0.81, 0.59–0.63, 0.43–0.52, and 0.20–0.25 for no, mild, moderate, and severe pain, respectively (Fig. 2) [28,46].

5. Economic burden

Several studies have been identified showing that PDPN patients induce high health care costs and have impaired productivity.

A European study reported 76% of patients visited their physician at least once in the past 4 weeks [46]. Telephone consultations in the previous 4 weeks were reported by 25% of patients, and slightly less than half of the patients (43%) reported having been evaluated by a pain specialist [46]. In a UK study, the number of GP contacts per 6 weeks ranged from
0.63 to 1.40 and annual inpatient days ranged from 2.58 to 6.36 [37].

The resource use of PDPN patients results in mean annual per patient UK health care costs of €2,963 (£2,511); 41% of these costs accounted for inpatient care [37]. These annual costs are comparable to those found in a Spanish national health system (NHS) database study, presenting mean annual costs of €2,476 per patient when pregabalin or gabapentin was added to usual care [38]. Modeled healthcare costs from the Spanish NHS perspective found similar costs per year of €2,441 when patients were treated with usual care (which could include antidepressants, opioids, anticonvulsants other than pregabalin, and/or any analgesics according to the physician’s medical practice) or pregabalin plus usual care; with medical visits accounting for 34% of healthcare costs [43].

Drug costs accounted for 30–32% of healthcare costs in the included studies [37,43]. Per patient drug costs can vary widely depending on the choice of medication. Costs of generic antidepressants are low compared to the newer branded medications, though the evidence base for anti-depressants within the PDPN population is less substantiated [4].

None of the studies reviewed compared resource use or health care costs with other diseases, and therefore do not indicate whether PDPN patients use more resources compared to, for example, non-PDPN diabetes patients. Studies found higher resource use and direct costs when the pain severity of the PDPN patients increased [37,46]. Annual healthcare costs ranged from €1,902 to €3,795 (£1,612 - £3,217) per patient for different levels of pain severity (Fig. 2). General linear modeling indicated that the PDPN severity score NTSS-6 (classified as none/mild/moderate/severe) was a significant predictor of both annual health resource costs and yearly prescribed drug costs. On average, each 1-point increase in NTSS-6 score predicted a 6% increase in primary and secondary care costs and a 3% increase in log transformed drug costs. The same study showed that gender, age, type of diabetes, duration of diabetes and BMI were not significant predictors for health care use and costs [37].

PDPN is significantly associated with disruptions in employment status and work productivity losses. In a UK cross-sectional study approximately 35% of the PDPN patients reported some level of disruption due to pain; 59% of the working patients reported being less productive at work at least some of the time. Pain severity was also significantly associated with interruption in employment. While only 14% of patients with mild pain reported pain-related work
disruptions, the figures more than doubled for moderate pain patients (38%) and more than tripled for severe pain patients (48%) [46].

Disturbance in employment status resulted in European productivity losses of €10,484 per patient per year [39]. Productivity losses were similar among the included European countries and were primarily driven by presenteeism (impairment while working) [39]. Also, annual lost productivity cost increased with pain severity. Estimated annual productivity losses based on several European countries were €5,646, €10,552, and €16,597 for mild, moderate, and severe PDPN, respectively [Fig. 2].

The literature review did not identify any evidence regarding total budget implications of PDPN for European countries from either a health care or societal perspective.

6. Discussion

European prevalence of PDPN ranges from 5.8% to 34% in patients with diabetes. The reported prevalence of PDPN in Europe in all identified studies ranged from 0.7% to 34% in diabetes mellitus patients. The value 0.7% is assumed to be an outlier, since the study was conducted in nursing homes. The majority of the included population was ≥75 years of age; therefore, the study sample is not comparable to the general diabetes population [23].

None of the studies investigated risk factors as the main study objective. Large risk factor studies have been conducted, but these results were published before 2003 and therefore not included in our search results. An example of a large risk factor study is the European diabetes research project (Eurodiab study), where it was discovered that suboptimal glycaemic control is a major determinant for developing diabetic peripheral neuropathy [1]. Furthermore, there is a possibility that not all relevant risk factors have been investigated yet; Van Acker et al. (2009) suggested that body height might influence the development of PDPN [22].

The studies identified in the literature review show that PDPN is burdensome from both humanistic and economic perspectives. PDPN patients are limited in their general daily functioning and their ability to sleep. Furthermore, the pain and limitations on daily activities and functioning are associated with symptoms of anxiety and depression in many patients. Not surprisingly, PDPN patients experience a low overall HRQoL as a result of their symptoms. PDPN patients induce high health care costs due to hospitalizations and outpatient visits. In addition, the painful symptoms cause impaired work productivity.

Intervention studies (e.g., clinical trials) were excluded in this literature review. Therefore, in the studies included in this literature review patients could be receiving (neuropathic) pain medication. Unfortunately it is not always clearly specified in the included studies. As a result, the reported humanistic burden in the included studies could be on average underestimating the real-life burden of PDPN patients which would not receive (neuropathic) pain medication.

The burden from PDPN appears to be higher with increasing pain severity. Increased pain intensity leads to a higher impairment in daily functioning, sleep and HRQoL. This relationship also applies to healthcare costs and productivity losses related to PDPN; more severe pain leads to higher costs from healthcare and societal perspectives.

Compared to diabetes patients with other complications and comorbidities such as heart disease, COPD, and stroke, PDPN patients have the lowest EQ-5D utility value (0.63, 0.65, 0.56 vs. 0.41) [46,52]. Compared to other chronic diseases such as asthma, Parkinson’s disease, and depression the utilities from PDPN patients are lowest (0.89, 0.67, and 0.47 vs. 0.41, respectively) [46,53–55].

The low utility values for PDPN patients can be explained by the large influence of pain on EQ-5D scores. This is reflected in the EQ-5D UK value sets. When EQ-5D index values are determined, pain/discomfort has larger influence on the values than mobility, self-care, usual activities, and anxiety/depression [56].

Due to PDPN being a chronic condition and the impact of PDPN on patients daily life, patients place a high value on obtaining relief from painful symptoms [46]. Patients with higher pain severity have a relative lower QoL and this relationship between pain severity and utilities appears to be non-linear [48,57,58]. Therefore it is expected that reducing pain in patients with more severe symptoms results in a larger QoL gain. Hoffman et al. 2010 reported patients in the “severe-to-moderate” pain group had a greater mean improvement in the health status score than those in the “moderate-to-no/mild” pain group after treatment. It is suggested that patients whose pain is not reduced with treatment to a mild level of severity can still experience clinically important changes in health status [48].

Data regarding economic burden of PDPN, such as resource use and real-life costs, was rather limited. Identified publications mainly concerned direct health care costs in the UK and Spain [37,38] or resource use and productivity losses at a European level [39,46]. None of the studies compared the results for PDPN patients directly to non-PDPN patients or to the general population. In addition, no publication was found estimating the total economic burden of PDPN for a European country. Future research for these evidence gaps would provide valuable information about the economic burden of PDPN.

The key strength of this review is its broad scope including European epidemiology, humanistic burden, and economic studies. The search was not restricted to Embase and PubMed databases, but also included websites of European HTA organizations and conference proceedings from the IASP to ensure relevant evidence not included in peer reviewed journals was obtained.

The literature review has some limitations. All studies included in the review contained data concerning PDPN patients, however, there is variation between studies on how PDPN was defined and assessed. For instance, epidemiology studies evaluate the percentage of PDPN patients within the diabetes population based on questionnaire results [14,15,24–26,40], the description of symptoms in medical records [18,23,41] or clinical examination [25,26,40]. PDPN severity was determined by different questionnaires (e.g., BPI and NTSS-6) and cut-off points, which may affect the comparability of the results.

Furthermore, the review did not identify any studies comparing the humanistic burden of PDPN patients to the general population. Therefore, no qualitative data is available to
show to what extent these patients suffer compared to healthy people. However, as PDPN patients have significantly worse HRQoL compared to diabetes patients with no pain and non-neuropathic pain [40], it can be assumed that PDPN patients value their HRQoL much lower than the general population. None of the identified economic burden studies compared the costs and productivity losses of PDPN patients to diabetes mellitus patients or the general population. Therefore this review is unable to provide direct evidence that PDPN patients incur more healthcare and societal costs compared to these populations. On the other hand, PDPN patients with mild pain symptoms have a lower economic burden compared to patients with moderate to severe pain symptoms. This finding suggests diabetes mellitus patients without (painful) neuropathy to have a lower economic burden compared to subjects with PDPN.

In conclusion, European data show that PDPN patients experience lower HRQoL due to the pain and its impact on daily functioning in life, the quality and quantity of sleep, and anxiety/depression levels. In addition, the review found that increasing severity of painful symptoms is related to larger impairment of HRQoL. Healthcare costs and impaired productivity increase as well with more severe symptoms. Reducing painful symptoms by treatment in PDPN patients will lead to improvements in quality of life.

Conflicts of interest statement

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Disclosure

All authors had complete access to all data and had final control over the content, review and submission of the manuscript.

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