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ORIGINAL RESEARCH

A Conceptual Model of Patient Experiences of Painful Diabetic Peripheral Neuropathy to Support Clinical Outcomes Assessment

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Introduction: Painful diabetic peripheral neuropathy (pDPN) is associated with nerve damage caused by diabetes mellitus (Type 1 or Type 2) and affects approximately 30% of the diabetes population globally. Many patients are unsatisfied with analgesic treatments for pDPN.

Methods: To support research using treatment outcomes that are meaningful and relevant to patients, this study explored patient-focused concepts including the symptoms and quality of life (QOL) impacts of pDPN based on a targeted literature review (TLR) of qualitative studies and qualitative concept elicitation interviews (n = 25) with people with pDPN. Findings were harmonized in a conceptual model characterizing the patient experience of pDPN.

Results: The TLR included eight studies and the US Food and Drug Administration's Voice of the Patient report on neuropathic pain associated with peripheral neuropathy. The TLR and qualitative interviews identified 57 unique concepts of interest to patients, divided into ten domains. Harmonized findings showed that people with pDPN described highly impactful experiences of pain and co-occurring symptoms of numbness, tingling, and muscle weakness. pDPN impacted four areas of QoL including physical, social, emotional and cognitive functioning.

Discussion: Findings highlight the burden of living with pDPN. The resulting evidence-based conceptual model of pDPN provides more detailed insight into key pDPN symptoms and their impacts on QoL compared to previous models, and may help to inform the selection of clinical outcome assessments for clinical trials of treatment for the condition to ensure the meaningfulness of novel therapies to patients.

Keywords: diabetes mellitus, chronic pain, neuropathy, patient experience, qualitative interviews, literature review

Introduction

Diabetic peripheral neuropathy (DPN) is a condition caused by nerve damage due to type 1 or type 2 diabetes mellitus. Chronic hyperglycemia leads to oxidative stress, inflammation, and microvascular damage, resulting in nerve fiber degeneration and impaired function.[1] Metabolism plays a significant role in the development and progression of DPN. Metabolic dysregulation, particularly mitochondrial dysfunction, is a key factor in DPN pathogenesis.[2] Metabolic syndrome factors such as central obesity, hypertriglyceridemia, decreased HDL cholesterol, and insulin resistance are strongly associated with the development of DPN.[3]

As the most common form of distal sensory polyneuropathy (DSP), DPN affects the longest nerve fibers first. Typically, it starts in the toes and feet and progresses upward below the knees and then to the hands. DPN is often progressive and bothersome, leading to clinical complications and impairments in functioning.[4–6] DPN is frequently accompanied by pain, leading to a condition called painful DPN (pDPN), and is a very common sequelae of diabetes, affecting approximately 2.3 million Americans and 30% of the diabetes population globally.[6,7] Risk factors for DPN and pDPN are glycemic control, increased age, and diabetes duration.[1] Although men may have a higher prevalence of DPN

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and women are more frequently affected by pDPN, existing data on gender differences remain inconsistent.[8] People with pDPN experience considerable burden from the condition, including significant limitations in capacity for a range of physical activities; reductions in ability to participate in family, social, work, and recreational life; and impacts on mental well-being.[9–11]

Background: Conceptual Models

Various treatments have been used for pDPN, and new treatments are being developed.[12] Pain medications for pDPN include gabapentinoids, serotonin and norepinephrine reuptake inhibitors, sodium channel blockers, and topical capsaicin with US Food and Drug Administration (FDA) approved medications including pregabalin, duloxetine, tapentadol, and capsacin 8% patch. Recommended nonpharmacologic therapies include high-frequency (10 kilohertz) spinal cord stimulation, exercise, reduced sedentary behavior, and dietary modification.[1,13] However, research suggests that significant percentages of patients with pDPN do not achieve meaningful improvement in outcomes from treatment.[14,15] In the FDA report, *The Voice of the Patient: Neuropathic Pain Associated with Peripheral Neuropathy*, patients expressed a need for broader pain control that would address a wide range of painful sensations associated with peripheral neuropathy, as well as a need for treatments with fewer side effects and long term risks.[16]

To support patient-focused drug development, the US FDA guidance recommends the development of an evidence-based conceptual model of relevant health experiences (eg, signs, symptoms, quality of life (QoL) impacts) that may be linked to the outcomes of treatment.[17] A conceptual model provides a foundation for patient-focused measurements by illustrating the links between a proposed set of clinical outcome assessments (COAs) and the health experiences of patients themselves, thus providing a key form of evidentiary support for a claim that a proposed treatment will produce benefits for patients. From 2020 to 2024, the use of patient-reported outcomes (PROs) in FDA novel drug approvals rose from 18% to 40%, while their impact on reimbursement decisions increased 15% to 55%, underscoring the growing importance of patient perspectives in evaluating the effectiveness of medications.[12] There are few existing conceptual models of pDPN with some limitations. One model focuses holistically on contextual factors that impact pDPN experiences but may not be best positioned to inform drug development as it is not specific to experiences linked to outcomes of treatment.[10] Another focuses more narrowly on pain experiences, but excludes some content prioritized by patients, such as social impacts.[18] To better understand the patient experience of pDPN and address the need for a comprehensive patient-centered model to support clinical outcomes assessment, a multidisciplinary research team developed a conceptual model based on results from a targeted literature review (TLR) of qualitative studies of people with pDPN and qualitative interviews with people with pDPN. Interviews focused on how people with pDPN describe their pain experiences and the symptoms and impacts that are most bothersome for people living with pDPN and most important to improve with treatment.

Materials and Methods

A TLR and qualitative interviews with adults (aged ≥ 18 years) with pDPN were conducted. Patient-focused concepts identified from these efforts were combined into a conceptual model aligned with the FDA's Patient Focused Drug Development Guidance.[17]

Targeted Literature Review

A targeted search of qualitative studies of patient experiences with pDPN was conducted using the PubMed and Embase databases to identify publications for review. The literature search was limited to English language materials published since 2010 reporting studies with an adult population with pDPN. Studies that did not use qualitative methods and provide substantive information about the disease concepts that matter to patients were excluded. The following search terms and operators were used to identify studies about pDPN; "Diabetic peripheral neuropathic pain" OR DPNP OR "painful diabetic neuropathy" OR ("peripheral neuropathy" AND diabetes AND pain) OR "diabetic nerve pain" OR (diabetic neuropathies [MeSH Major Topic] and pain [MeSH Major Topic]). Searches were conducted by combining these with terms and operators developed to identify qualitative studies of concepts that matter to patients; "Patient perspectives" OR "patient perceptions" OR "patient experience" OR qualitative OR interview OR "focus group". The

search was conducted on December 12, 2022 and re-run on October 8th, 2024. No new papers meeting the inclusion criteria were identified at that time.

All bibliographic records for articles, conferences, and other retrieved publications were uploaded into Covidence, a systematic reviewing platform.[19] Two analysts independently reviewed the title and abstract information for each record and applied the inclusion and exclusion criteria. Conflicts between reviewers were discussed and agreement reached on inclusion. Full text review was conducted by a single analyst and comprised a check of the full text to ensure adherence to inclusion and exclusion criteria. A second reviewer checked 30% of full text reviews to confirm proper application of review criteria. However, all the included qualitative studies were subjected to repeated full-text review and data extraction by two analysts during the process of conceptual modeling. Study methods, aims, sample characteristics, and concepts/themes found in the results were extracted from the articles. Data extraction from articles included close examination of quotations to determine if they reflected concepts or themes not discussed in the article. A cross-cutting analysis then assessed the similarities and differences between the concepts or themes reported in each article and developed a comprehensive table of concepts of interest identified by these studies. Three conceptual models were identified from the literature and assessed for similarities and differences, one of which was based on research with both patients with pDPN and patients with another form or neuropathy,[9] and two of which were specific to pDPN.[10,18]

Qualitative Patient Interviews

An interview study was conducted to elicit data about the experiences and impacts of neuropathic pain relevant to patients living with pDPN. The concept elicitation portion of the interview was approximately 20 minutes. The interviews included a cognitive debriefing of several measures of symptoms and impacts related to pDPN. The interviews were conducted via web-conferencing with 25 US-based adults. Recruitment aimed to enroll individuals representing heterogeneous demographic characteristics (eg, age, sex, race, level of education, geographic location). Eligibility was determined by the person's self-report and provision of a clinician confirmation of diagnosis with DPN. Individuals were eligible for the study if they; were a resident of the US, 18 years of age or older, able to provide a physician-confirmed diagnosis of DPN, experienced DPN in their feet or toes, had experienced pain from DPN for at least one year, self-reported moderate to severe pain from DPN (a score of 4 to 9 on a 0–10 scale), were comfortable reading and speaking in English, were able to provide informed consent to participate in the study, and were willing to have their interview audio- or video-recorded and transcribed. Individuals were excluded from participating if they were currently participating in a clinical trial for treatment of DPN or pDPN or self-reported any of the following conditions; lumbar sacral radiculopathy present currently, and, in past month, active sciatica, fibromyalgia, or amputations of lower limbs or toes due to diabetes, or had a disorder that compromised their ability to give informed consent or participate in an interview (eg, untreated schizophrenia or bipolar disorder, stroke, traumatic brain injury, dementia). Employees or family members of Vector Psychometric Group, LLC, Eli Lilly, or any of the collaborators/consultants associated with this project also were ineligible.

A sampling target of 25 participants was selected to ensure saturation of concepts. A 2018 review of concept elicitation studies found that 99% of symptom concepts emerged by the 25th interview across studies.[20] Participants were recruited by a professional research recruiting firm. Interviews lasted 90 minutes total and were recorded and professionally transcribed verbatim. Participants who took part in an interview were compensated for their time. The concept elicitation inquired about participants' experience of pDPN, including symptoms and impacts on functioning and quality of life. Interview questions were open-ended to encourage spontaneous descriptions of experiences. Participants' informed consent included the potential for publication of anonymized responses including direct quotes. The study was approved by Advarra CIRBI, a US-based, fully accredited, independent, centralized institutional review board on May 23, 2023. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices. Interviews were conducted July through September 2023. All participants provided informed consent.

Analysts coded the concept elicitation portion of transcripts for concepts and terminology used by study participants to describe symptoms and impacts of pDPN. The first three transcripts were dually coded, then the remaining transcripts were initially coded by a single researcher and then reviewed by the study lead for agreement. The research team then

organized concepts into hierarchical groups based on alignment with broad domains (eg, symptoms, physical functioning) and observable similarities and differences in concept content. Thematic analysis was used to confirm that concepts represented by codes had been clearly distinguished from each other and appropriately placed in the conceptual hierarchy, and that variations in individual experiences within each code had been accounted for.[21] Saturation analysis was conducted to assess the number of novel concepts identified in each interview.

Conceptual Model Development

To develop a conceptual model of pDPN, an evidence table was created synthesizing concepts identified in the TLR with concepts identified in the patient interviews. This process included comparing the concept terms and definitions (if any) used by article authors with the terms and descriptions used by interview participants and by individuals who were quoted in published articles. Definitions for each concept were developed based on the available content from published studies and interviews, and concepts were organized into a conceptual model, documenting the criteria used to determine placement of each concept. Level of evidence for each concept was assessed based on evidence of replication (ie, documented in multiple published studies and in interviews), prevalence (ie, reported rates of endorsement by patients), and semantic similarity (ie, concepts were described in similar terms by patients across published studies and the interviews). Those concepts that emerged in multiple studies and in interviews, were endorsed by the majority of interview participants, and were described consistently in similar terms across studies and interviews are highlighted in the conceptual model as highest level of evidence. A conceptual model diagram was developed to provide a simplified depiction of the concepts, domains, and relationships documented in the evidence table, in alignment with the FDA's Patient Focused Drug Development Guidance. To comport with the guidance's focus on modeling meaningful aspects of health, contextual and environmental factors unrelated to the direct experience of pDPN symptoms and unlikely to be responsive to a pharmacological intervention specifically addressing pain (eg, concepts related to costs of care or access to healthcare providers) were excluded from the model. The goal is to gather comprehensive and representative input that reflects the patient's condition, treatment experiences, and outcomes. Including environmental factors might dilute the focus on the patient's direct experiences and make it more challenging to identify what is most important to patients in terms of their health and treatment outcomes. The new conceptual model was also compared against existing pDPN models.

Results

Targeted Literature Review

The search retrieved 170 published studies for review, including eight qualitative studies that prospectively analyzed the experiences of adult patients with pDPN and the proceedings from the FDA's Voice of the Patient that focused on patients with neuropathic pain (see Table 1). The eight published studies collected data from individuals in the US, Japan, Netherlands, Turkey, and United Kingdom. A total of 66 concepts were identified comprising six domains: symptoms, physical functioning, psychosocial functioning, cognitive functioning, sexual functioning, and treatment burden. Symptom concepts included numbness, pain (which was commonly described as sharp, burning, aching, cramping, squeezing, and shock-like or shooting), and tingling. Three conceptual models of DPN or pDPN in adults were identified.[9,10,18] Two models, those by Gok Metin et al and Brod et al were specific to pDPN, while one by Hwang et al was a dual model of DPN and another form of neuralgia.

Qualitative Patient Interviews

The interview study included 25 participants of varied age, sex, race or ethnicity, educational background, and employment status (Table 2). All participants self-reported moderate to severe pain from DPN (a score of 4 to 9 on a 0–10 scale). More than half of the sample reported using prescription medication to treat their pain (n = 15, 60%) and most reported using over-the-counter medication (n = 21, 84%). Duration of participants' experiences with pDPN symptoms ranged from one to ten years, with a sample mean of 3.6 years. Participants resided in ten different US states representing all regions of the country. Conceptual saturation was reached in interview 21.

Table 1 Characteristics of Qualitative Studies from Literature Review

Reference	Study Aims	Sample Size	Sample Characteristics
Brod et al[18]	To assess the burden and impact of pDPN on patient's functioning and well-being.	70	Adults with pDPN
Brod et al[22]	To develop and validate the DPNPI measure	25 participants for the CE	Adults with pDPN
Davies et al[23]	To understand the coping strategies those with pDPN to manage their pDPN, and their perspectives on the utility of pain management strategies	23	Adults with pDPN
Gok Metin et al[10]	To explore the effects of pDPN on daily life and the individual experiences of living with pDPN from the perspective of Turkish patients with diabetes	14	Adults with pDPN
Hwang et al[9]	To examine the impacts of neuropathic pain and develop an overarching conceptual model that can be compared to existing measures and explore where gaps lie in current measures.	29	Adults with pDPN and adults with another form of neuropathy
Kanera et al[24]	To obtain more in-depth information on psychological risk factors in persons with pDN.	12	Adults with pDPN
Kirk at al[25]	To assess patients' perspectives of pain experienced through neuropathy and the impact on type 2 diabetes management.	99	Adults with pDPN
Liu et al[26]	To explore the experiences of living with pDN and with a group acupuncture intervention in a sample of low-income, diverse patients.	17	Adults with pDPN
FDA[16]	To hear perspectives from people living with neuropathic pain associated with peripheral neuropathy	37 in person and 54 web participants	Adults with peripheral neuropathy from any cause

Abbreviations: CE, concept elicitation; DPNPI, Diabetic Peripheral Neuropathic Pain Impact; FDA, US Food and Drug Administration; pDPN, painful diabetic peripheral neuropathy; pDN, painful diabetic neuropathy;

Table 2 Qualitative Interview Study Participant Characteristics

Characteristic	Count (N = 25)	Percent (%)
Age		
30–39	1	4%
40-49	6	24%
50-59	10	40%
60-69	8	32%
Sex		
Female	10	40%
Male	12	48%
Prefer not to answer	3	12%
Race		
White	17	68%
African American	4	16%
American Indian/Alaska Native	1	4%
Native Hawaiian/Other Pacific Islander	1	4%
Prefer not to answer	2	8%

(*Continued*)

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Table 2 (Continued).

Characteristic	Count (N = 25)	Percent (%)
Ethnic Background		
Hispanic	5	20%
Non-Hispanic	18	72%
Prefer not to answer	2	8%
Education		
High school or less	6	24%
Some college or technical school	6	24%
Completed college or technical school	8	32%
Attended/Completed graduate or professional school	2	8%
Prefer not to answer	3	12%
Employment Status		
Employed full time or part time	5	20%
Not employed, not looking for work	7	28%
Not employed, disabled/on disability	1	4%
Retired	7	28%
Prefer not to answer	5	20%

All interview participants reported pDPN symptoms in their feet, with some experiencing symptoms in their legs as well. Some participants also noted symptoms in the hands or arms, usually described as numbness or tingling rather than pain. Participants often described the frequency and severity of their symptoms as unpredictable and fluctuating. Participants also commonly reported worsening symptoms at nighttime or following physical activity (eg, walking or standing for long periods). Participants described symptoms with many of the same terms identified in the TLR, including numbness, tingling, burning, sharp, stabbing or electric-shock like pain, aching, tightness, squeezing, and cramping. Nearly all participants (n = 24, 96%) reported that pDPN in the feet or legs interfered with physical function, including any activity or task that required walking or standing, such as household chores, exercise, or running errands. Impacts on emotional well-being, social life and cognitive functioning were also reported by a majority of participants. For example, participants reported avoiding social events with others if the plans involved physical activity and canceling plans or avoiding social interactions while in pain because they were angry or irritated and did not want their mood to affect others. Cognitive effects were most often described as diminished mental acuity due to pain consuming one's thoughts, making it challenging to think and focus normally.

Conceptual Model Development

Overlap between concepts and domains from the TLR and the interview study was found. After combining similar concepts and removing concepts unrelated to the direct experience of pDPN, 57 unique concepts were grouped into ten domains which included three domains related to symptoms (pain, sensory abnormalities, muscle weakness), six domains related to functioning impacts (physical functioning, social functioning, emotional functioning, cognitive functioning, sleep, sexual functioning), and one domain related to treatment burden. The uniform concepts, domains, concept definitions, links between concepts, level of evidence assessment, and supporting quotations and citations are outlined in Table 3 and in the Supplemental Table 1.

Table 3 Evidence Table

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Domain: Pain						
Aching	Aching is commonly described as a continuous or prolonged pain that is unpleasant, but dull or not particularly strong; sometimes described as soreness or stinging		Moderate, Replication across studies but not consistently defined	15 (60%)	Sometimes it can be shooting pain, it can be aching pain, it can be burning (US21)	Hwang et al,[9] Liu et al,[26] Kirk et al[25]
Burning	Burning sensations in the areas affected by neuropathy.	This experience may co-occur or be similar to tingling.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	18 (72%)	Sometimes it's a burning feeling in the very bottom of the foot (US14)	Hwang et al,[9] FDA,[16] Brod et al,[18] Davies et al[23]
Increased sensitivity to pain/ hyperalgesia	Experiences of severe or excessive pain in response to an experience that should normally cause only mild pain or discomfort		Low, Limited evidence is available to describe this concept.	2 (8%)	Or tenderness, if something kind of sharp touch my feet or with the nail clippers and these things, I feel that for example, like a tenderness, which is unusual on my feet and toes. (US13); When the doctor's checking them, when you are getting a pedicure or you are getting your toenails clipped or cared for. Generally, yeah, I think of doctors and healthcare, touching, examining (US21)	Hwang et al[9]
Sharp sudden pain	Sensations of sharp, sudden pain in the areas affected by neuropathy; these sensations are often described using terms like stabbing, shooting, jolts, or electric shock-like pains.	Descriptions of this pain reflected overlapping usage of a variety of terms that describe other sudden sharp pains; assessments should reference a range of terms in order to reliably capture this concept.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	17 (68%)	Yeah, it's painful. I do not want to say, like, debilitating, but it's just, I guess, like, annoying just how, out of nowhere, I could be getting like, sharp pains (US15)	Hwang et al,[9] FDA,[16] Brod et al,[18] Liu et al[26]
Soreness	Insufficient information to determine whether soreness is indistinct from aching.	-	Moderate, Replication across studies but overlaps with ache	2 (8%)	Just a sharp pain that feels like – yeah, I would liken it to an electric shock-like feeling and it's just a shooting pain that's not like other pains that you feel, you know, when something hurts or something's sore. This is just like this jetting, quick jolt of pain and you can tell it's within your nerves (US09)	Hwang et al,[9] FDA[16]
Squeezing/ Cramping	Feelings of cramping, spasms, or tightness in the feet or lower limbs, or sensations of being squeezed or crushed, or that one's feet or lower limbs are being pulled or placed under pressure.	-	Moderate, Replication across studies, some inconsistency in how it is described	4 (16%)	When you get really bad cramps, that's really painful and it does not – it's like you cannot – it's like you are paralyzed (US02)	Hwang et al,[9] FDA,[16] Brod et al,[18] Liu et al[26]
Stinging	Insufficient information to derive a definition.	-	Low, Limited evidence is available to describe this concept.	2 (8%)	Basically, there's the numbness, but on top of it is like aching and some stinging, but mainly just like a toothache (US01)	FDA[16]

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Table 3 (Continued).

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Domain: Sensory Abnormalities						
Increased sensitivity to touch/allodynia	Experiences of discomfort or pain resulting from touch that is not normally painful		Low, Limited evidence is available to describe this concept.	1 (4%)	Sometimes a sheet on my feet can be painful and annoying. It does not like to – I sleep with my feet hanging out of the blankets (US05)	Hwang et al,[9] Davies et al[23]
Itching	Insufficient information to derive a definition.	-	Low, Limited evidence is available to describe this concept.	-	-	Hwang et al,[9] FDA[16]
Numbness	Sensations of numbness or lack of feelings in the toes, feet, or lower limbs.	This concept overlaps significantly with tingling and with pain sensations.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	23 (92%)	I started just getting a lot of numbness and it just kind of progressively got worse (US02)	Hwang et al,[9] Gok Metin et al,[10] FDA[16] Brod et al,[18] Davies et al,[23] Liu et al,[26] Kanera et al[24]
Tingling	Feelings of tingling, prickling, or 'pins and needles'; tingling comprises the sensation of multiple small points of sharp pain in an area of the body, often associated with numbness. Clinical: parasthesia.	Significant overlaps between this concept and concepts of numbness and pain.	Moderate, Replication across studies but significant overlap with other symptoms	20 (80%)	It's a tingling, a tingling sort of sensation. That's the best way I can describe it is a tingling (US03)	Hwang et al,[9] FDA[16] Brod et al[18]
Domain: Muscle Weakness						
Muscle weakness	Weakness or sense of a lack of power in the muscles	Some evidence of overlap with fatigue.	Low, Limited evidence is available to describe this concept.	3 (12%)	Also muscle weakness, it really impacts you (US01)	Gok Metin et al,[10] Brod et al[18]
Domain: Physical Function						
Ability to carry out routine daily activities	Any type of daily functioning that requires standing or walking could be affected by symptoms. For some patients, functions that required sitting upright were also affected, with some individuals reporting that they need to move and stimulate their feet/lower limbs to reduce discomfort. Impairments included inability to carry out certain tasks at all; impaired ability to complete tasks, including need for help; avoidance of tasks when symptoms tend to be worse or because of concerns about exacerbating symptoms; and pacing task completion to mitigate impacts from numbness or pain symptoms.	Impairments of routine daily activities and responsibilities were linked with similar frequency to numbness and pain symptoms, and were also connected to other impacts of pDPN, such as fatigue due to sleep problems or difficulties with balance and coordination.	High, Replication across studies	14 (56%)	I can do anything I want to do, but not for very long. I will finish a job or two around the house and then I will have to sit down a while. (US01); I am able to do certain things like tinker around the house, you know, walk the dog, but still, the numbness is still there (US15)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Kanera et al,[24] Brod et al,[22] Kirk et al[25]

Ability to carry out tasks quickly (productivity)	Ability to carry out tasks at one's usual pace, or to be able to do things quickly without difficulty; carrying out functions at a slower, more methodical pace to minimize discomfort or increase perceived safety during movement.	Impairments of functional speed and productivity were commonly linked to pain and numbness symptoms, as well as issues with balance, concentration, and fatigue	High, Replication across studies	2 (8%)	That's the main thing. I guess that would be – the best answer I could give is it's forced me to slow down and not do things the way that I used to (US09)	Gok Metin et al,[10] Brod et al,[18] Davies et al,[23] Brod et al[22]
Ability to go out into the community	Ability to go out in the community encompasses all aspects of leaving one's home and being able to move around in the immediate community or to travel to other places, including experiences of being housebound or bedridden due to symptoms as well as feelings of reluctance or avoidance of leaving home. These experiences may be temporary (ie, 1–2 days) or long term; when long term, being housebound can have significant impacts on aspects of emotional and psychosocial life	Appears to be an impact that results from the aggregation of symptoms and proximal functional impacts of pDPN. It is unclear whether this is a progressively worsening impact of pDPN or an episodic/intermittent one.	Moderate, Concept is broadly replicated across sources, but differences in how the concept is described and/or lack of detailed evidence of specific meaning create obstacles to matching the concept to COA items in a reliable way.	2 (8%)	It's heavy pain, I am kind of stuck at home (US22)	Gok Metin et al,[10] FDA,[16] Kanera et al,[24] Kirk et al[25]
Ability to stand up from a seated/prone position	Ability to get up from a seated, prone, or other non-standing position into a standing position		Moderate, Concept is broadly replicated across sources but may overlap substantially with the broader concept of standing.	1 (4%)	I have learned I cannot just stand up and just get out of bed quickly (US09)	Gok Metin et al,[10] FDA,[16] Brod et al,[18] Brod et al,[22] Kirk et al[25]
Avoiding activity	Avoidance of activities that are challenging or may result in unwanted results, such as worsened symptoms, falls, or embarrassment	-	Low, Limited evidence is available to describe this concept.	5 (20%)	Walking, bending, heavy lifting. All those things, I try to avoid them (US19)	Davies et al,[23] Liu et al,[26] Kanera et al[24]
Balance	Ability to balance while standing or moving, including while standing or moving on level ground or different uneven surfaces; includes the need to use aids or assistance to maintain balance (eg, holding onto furniture or railings, using a walking stick or walker)	This concept is linked to pain and numbness symptoms, as well as distraction resulting from these symptoms	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	20 (80%)	Somehow, I do not feel balanced and stable, so that's why I always, when I stand somewhere, I hold something. If there's a chair, table, a counter, or even it's a wall, I go and put my back and kind of stand close to the wall and hold it there, my back. And it helps me a lot (US13) When the pain gets worse, then it's harder to balance because it throws you off…I lose balance sometimes because I am walking and I cannot sometimes kind of walk a straight line (US24)	FDA,[16] Brod et al,[18] Liu et al,[26] Kanera et al,[24] Brod et al[22]
Bending	Ability to bend the body while standing, including bending at the waist, stooping, and squatting down.	It is not clear whether these various movements are regarded as similar by people with pDPN or result in similar challenges with functioning or symptoms.	Moderate, Concept endorsed across multiple sources, but not well explained and may overlap with other physical function concepts	1 (4%)	Walking, bending, heavy lifting. All those things, I try to avoid them (US19)	Brod et al,[18] Brod et al[22]

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Table 3 (Continued).

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Daytime fatigue/energy	Feelings of fatigue, tiredness, low energy, or daytime sleepiness	This concept is linked to sleep because poor quality sleep or lack of adequate sleep due to symptoms results in fatigue on subsequent day (s).	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	2 (8%)	Well, when it hits me at night, I do not sleep well. I work. I actually work, so it's not good for me to be tired all day. Then, I think it becomes a vicious cycle of being tired and then I am more susceptible.I am tired and it just – it takes my energy (US07)	Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Kanera et al[24] Brod et al[22]
Difficulty driving	Ability to operate a motor vehicle such as a car due to numbness in the limbs.	This concept is linked to numbness symptoms. It is related to the broader concept of "Ability to go out into the community." Impairments of driving are also linked to concerns about driving while using pain medication.	Low, Limited evidence is available to describe this concept.	2 (8%)	Just kind of doing my daily chores or going out and driving or trying to exercise, and just generally doing really anything. It could be a drag (US25) It's not wise to drive an automobile with the pain medication (US22)	FDA[16]
Falls	Experience of falling due to symptoms attributed to pDPN		Moderate, Concept endorsed across studies.	2 (8%) reported falling	I have fallen before, and I have gotten lucky every time. I have been very, very lucky but yeah, it just seems that sometimes I am very accident-prone, so I have to really watch that (US21)	Gok Metin et al,[10] FDA,[16] Brod et al,[18] Liu et al,[26] Kirk et al[25]
Going up and down stairs	Ability to walk up or down a set of stairs	This concept is linked to numbness and pain symptoms, as well as to fear of falling.	Moderate, Concept is broadly endorsed, may overlap with other physical function concepts	2 (8%)	Well, again, yeah, because I live in a two-story house and, if I come down the stairs, again, having awoken from asleep, I gotta really hold on to the rail and watch my – slow down (US09)	Hwang et al,[9] Gok Metin et al,[10] Brod et al,[22] Kirk et al[25]
Kneeling	Insufficient information to derive a definition.	-	Low, Limited evidence is available to describe this concept.	-	-	Hwang et al[9]
Prolonged/ vigorous physical activity	Ability to engage in exercise or other prolonged/vigorous physical activity, including long walks, cycling, or swimming in which foot and lower limb function is essential.	Ability to undertake prolonged or vigorous physical activity was affected for any activity involving use of the feet/lower limbs. Impacts were linked primarily to pain symptoms, which were often exacerbated by activity. Numbness symptoms could also affect this concept, as could other impacts of pDPN such as problems with balance.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	5 (20%)	I cannot walk for very long distances. It starts to get too achy or too much pain, and I have to sit down and rest my feet. Yeah, it makes things difficult. I am supposed to do physical activity, but it gets to be challenging at times with it. Sometimes the pain just gets so intense, I just have to stop (US14) I try not to do a lot of running, a lot of intense exercises are things I used to do, but if I am playing basketball, I do not really notice it because I am so into the game, that I forget about it, you know, and my mind is completely (US24)	Gok Metin et al,[10] Brod et al,[18] Davies et al,[23] Kanera et al,[24] Brod et al,[22] Kirk et al[25]

Sitting	Ability to sit with feet on the floor for a period of time, as well as ability to get up from a seated position.	This concept is linked to numbness and pain symptoms	Moderate, Replication across studies, some inconsistency in how it is described (ability to sit with feet on floor vs get up from seated position)	17 (68%)	I can do it [sit with feet on floor] a short period of time. You might be seeing me stand up halfway through this interview, though. That's what I will have to do sometimes…it's just longer periods of time that's the problem (US01) I try not to crimp the areas…because that's where I think it agitates any…You know, the condition is if you are sitting where you are crimping at the waist and at the knee, or if you are going to be, so that's why a lot of the times, if I am sitting, I am reclining and I have got my feet up, and even if I lay down on the couch, I will place a pillow or two under my feet so I can prop those areas up (US18)	Gok Metin et al,[10] FDA,[16] Brod et al,[22] Kirk et al[25]
Standing	Being on your feet or getting up on to your feet from a sitting or prone position		High, Replication across studies, substantial rates of endorsement	24 (96%)	I do not want to stand when I am in pain because standing on it, actually, I think increases the pain intensity (US04) If you have numbness in your feet, you cannot stand on them comfortably for any period of time. It's where you have to get off of them, and then even sitting it's uncomfortable, but standing, walking, I would not advise it only because I feel like I may fall. I feel like I may take a misstep or a wrong step (US17)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Kanera et al,[24] Kirk et al[25]
Walking	Ability to walk without support	This concept is linked to numbness and pain symptoms.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	19 (76%)	The problem with this is, when it's numb like that, you cannot feel anything. I mean, I could step on a nail and not feel it, you know, till it's too late, so that's one of the problems with it… I have to be really, really careful (US08) I am still walking, but it's a different type and style of walking. Before, I was a jogger and could do quite a bit. Now, I still try to walk at least a mile a day, but I am not walking because I feel rushed and pressured. There's times when I do it, and I am okay, and there's times I do it, it actually hurts and I get cramps (US02)	Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Liu et al,[26] Kanera et al,[24] Brod et al,[22] Kirk et al[25]
Domain: Social Function						
Ability to participate in social and family relationships	Physical and emotional ability to participate in events, activities, and interactions needed to maintain social and family relationships, and to derive the wanted, needed, or expected level of enjoyment or fulfillment from participation.	This concept is linked to both pain and numbness symptoms. Appears to have both proximal and distal aspects. Understanding could be enhanced by additional research to discern measurable proximal impacts that may be relevant to evaluating treatment benefits.	Moderate, Concept is broadly replicated across sources, but differences in how the concept is described and/or lack of detailed evidence of specific meaning create obstacles to matching the concept to COA items in a reliable way.	4 (16%)	For example, if my family or my friends, they call me and invite me for example, for a small gathering or small parties or go here and there, I refuse to do that, and I say, "Please excuse me. I'm not in a good mood to come." So, I cancel or I do not accept the invitations too many times and try not to go and be at home. It affects my social life, yes (US13)	Hwang et al,[9] Gok Metin et al,[10] Brod et al,[18] Brod et al[22]

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Table 3 (Continued).

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Family roles and relationships	Ability to fulfill family roles and engage in family relationships as desired. Includes capacity to engage in family activities without physical or emotional difficulties; to care for others and to have family relationships unaffected by the symptoms or impacts of pDPN.	Appears to be a distal impact that results from the aggregation of symptoms and proximal functional impacts of pDPN.	Low, Limited evidence is available to describe this concept.	2 (8%)	I may look fine on the outside, but if I am telling you something – I have had a lot of challenges and debates and arguments and hurdles with my relationship (US02)	Gok Metin et al,[10] FDA,[16] Kanera et al,[24] Brod et al[22]
Social and recreational life	Ability to engage in social and recreational activities that are important.	-	High, Replication across studies, substantial rates of endorsement	14 (56%)	Well, put it this way, I ain't doing a bunch of dancing anymore, that's for sure. And, I would say it cuts down some of my social life. I am getting old. I am [age redacted] now, so it's not like, you know, 20 years ago or something, partying every night or something like that. But, you know, I have cut down a lot of my activities going out, that, you know, involves walking or any type of thing like that. I would say I cut that at least in half, you know? (US08) There are times where I would really want to go out and do something and go somewhere with friends, and I have all good intentions of doing that and preparing to do it, but during that time of preparing myself and leaving to go do it, that just does not work out because of pain, being uncomfortable, of not wanting to get out, and then something will happen to me there where I would have to take medication, or I would have to leave. So, with this pain it's not worth it. Sometimes it's not worth it (US17)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Kanera et al,[24] Brod et al[22]
Social isolation	Feelings of isolation or loneliness.	-	Low, Limited evidence for isolation specifically and overlaps with social and recreational life	-	-	Gok Metin et al,[10] Brod et al,[18] Davies et al[23]

Work/ professional life	Ability to work, including impacts on work productivity, ability to complete certain types of work tasks, or complete inability to work.	This concept is broad and may not be universally applicable to all people with pDPN; it is unclear whether any impairments of work are due to aspects of pDPN not otherwise captured by symptom severity or impairments of mobility and cognitive functioning.	High, Replication across studies	4 (16%)	I have got a bachelor's degree in business, and right before I got my total disability, I had gotten my dream job, let us say. It was in management at the (REDACTED) that's like two minutes from my house. I could easily walk there if I had to. It was perfect. I had been waiting for that kind of job for years. Then, I just could not concentrate on my work, and I kept messing up at the register and could not remember stuff. I just finally had to quit because when you start hurting, you really cannot pay attention as well (US01) Well, right now, I am on disability. I work for [company name redacted] and then, I do a lot of – I am a shift supervisor so I do a lot of walking and, you know what? It's just sometimes I feel like my balance is not there, so I kind of took some time off from work – just the loss of coordination (US05)	Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Kanera et al,[24] Brod et al,[22] Kirk et al[25]
Domain: Emotional Function						
Ability to enjoy life	Ability to enjoy life, including the ability to feel as though you are able to have a sense of purpose and meaning in life.	Appears to be a distal impact that results from the aggregation of symptoms and proximal functional impacts of pDPN	Moderate, Concept is broadly replicated across sources, but differences in how the concept is described/lack of detailed evidence of specific meaning create obstacles to matching the concept to COA items in a reliable way.	2 (8%)	Well, it makes life tougher. It makes life not so much fun. Pain takes the joy out of life (US10)	Gok Metin et al,[10] Brod et al,[18] Kanera et al,[24] Brod et al[22]
Acceptance of illness	Acceptance of illness	-	Low, Limited evidence is available to describe this concept.	3 (12%)	You know, there's always that, "Why me?" and, "Why do I have this pain?" but I guess there's always that self-sympathy, but you just have to deal with it and that's all you can do is just accept the facts, which I am not really good at sometimes (US10)	Davies et al,[23] Kanera et al[24]
Anxiety	Anxiety, worry, or feelings of stress about symptoms experienced. Includes long term worry or fears about future worsening and short term anxiety that activity will exacerbate symptoms or that symptoms will disrupt plans	Related to or overlapping with Fear	Moderate, Concept is broadly replicated across sources, but differences in how the concept is described and/or lack of detailed evidence of specific meaning create obstacles to matching the concept to COA items in a reliable way.	4 (16%)	I have more anxiety about it because I feel that it's not – I have it, but it has a mind of its own. If I am having really bad muscle cramps or if I am having all of a sudden shooting pains, I cannot control that or prepare myself (US02)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Liu et al,[26] Kanera et al,[24] Brod et al[22]

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Table 3 (Continued).

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Depression/ sadness	Depression or sadness due to the impacts of living with pDPN	-	Moderate, Concept is broadly replicated, but described differently in different studies	4 (16%)	Emotionally, I feel very bad because I see the other people are – they go outside, for example, for grocery shopping or something. I see them, they look more normal than me, much better than me. They get dressed, wake up, everything. I feel that they look much better than me, and I get a little disappointed and depressed. So, I'd rather be at home and just watch TV or read some magazines or be at home more comfortable for me (US13)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Brod et al,[22] Kirk et al[25]
Embarrassment	Feelings of embarrassment that result from impairments of functioning due to pDPN	Appears to be a distal impact that results from the experience of other impacts of pDPN.	Low, Limited evidence available to describe this concept	1 (4%)	I feel embarrassed, like if I do not talk perfect, or something, and so I just feel like when the pain really kicks in, and it's heavy pain, I am kind of stuck at home (US22)	Kanera et al[24]
Fear	Feelings of fear about potential for increased symptoms/worsening overall health; fears and anxieties about the impacts of pDPN has on quality of life; anxiety or fear about becoming addicted to pain medications; and generalized fear of the future due to uncertainties association with pDPN.	Some fears may be specific to the underlying health condition (ie, diabetes) rather than to neuropathy with pain.	Moderate, Concept is replicated across studies, but described differently and encompasses broad conceptual territory; endorsement rates are relatively low despite broadness of the concept; and it is unclear whether people with pDPN think this concept is relevant to evaluating treatment efficacy.	6 (24%)	It weighs on you because you wonder if it will get worse. You know, is it temporary, you know? As long as it stays within at a certain level, you are okay, but if you are worried about in the future, it becoming really, you know, really numb, then you start to worry about circulatory problems and possible amputation and all kinds of crazy stuff (US03) I have to fight my mind, I have to allow myself to take something. I do not like pain medication. My sister-in-law got very addicted to pain medication from a back injury. Anytime I want to take something, I think of her problems. And I do not know if I have PTSD from it, but I get fearful of being addicted (US04)	Hwang et al,[9] FDA,[16] Brod et al,[18] Davies et al,[23] Kanera et al,[24] Brod et al[22]

Fear of falling	Feelings of fear and anxiety about falling during activity	May be related to experiences with balance problems	Moderate, Concept is broadly replicated across sources and similarly described.	12 (48%)	I am afraid to be on my feet with pain from the feeling of itself of hurting to everything that could go wrong of hurting myself or falling or God knows what to happen to me, that it's best to be safe to sit, and sit in a chair with my feet elevated. So, I do have that fear where when it kicks in, my most comfortable place to be is lay in bed (US04) I have lots of fear of falling. That's why, as I said, I hold something when I am standing. And when I am walking – not walking, just for example, this room to another room or whatever, I try to watch in front of me, for example, if there's a shoe, a piece of shoe or something, is on the floor and I do not see that. It might put me at risk for falling down so I am very careful wherever I walk, what is in front of me. I see very carefully if there's nothing on the floor, that I did not see that. Because I feel not stable, and always I am trying to – when I go in the kitchen or any room, I look at the corners, that if I can hold something. I can do, for example, some – for example, I like to cook or do something, but meanwhile, I try to hold something and stand close to the counter, for example. I can rely on it (US13)	Hwang et al,[9] Brod et al,[18] Davies et al,[23] Kanera et al[24]
Frustration/ Anger	Feelings of anger, frustration, or aggravation that result from symptoms or from the impairments of functioning that result from symptoms.	This concept is linked to irritability.	High, Replication across studies and concept described in similar terms; endorsement rate not consistently reported, but significant in the CE study.	9 (36%)	It's really frustrating…I feel like I cannot accomplish things that I normally would have done in the past, maybe sooner in the day, I guess…Like say, for example…standing there folding laundry or something, maybe it would take me like 15, 20 minutes. Now, it takes me – I have to stop and then come back to it. Or mopping the house – I do not mop the whole house at once anymore. I break it up into, like, two days, just because the house is so big and having to stand, and it does get bothersome… It's just like, "Ugh", like, "What a bummer", you know? Like, "This is my life now." (US15)	Hwang et al,[9] Kanera et al[24]

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Table 3 (Continued).

Uniform Concept	Uniform Concept Definition	Concept Links/Limitations	Level of Evidence/Rationale for Level of Evidence	Interviews n (%) Reporting	Illustrative Quotes from Patient Interview Study	Relevant Citations to Qualitative Studies Reporting the Concept
Irritability	Feelings of irritability, short-temperedness, or impatience, primarily in relation to interactions with other people. This emotional state is different than anger, frustration, or aggravation, which are typically directed at the disease symptoms and impacts themselves.	-	High, Replication across studies and concept described in similar terms; endorsement rate not consistently reported, but significant in the CE study.	15 (60%)	I am always complaining, I am not happy, I am irritated.My girlfriend sometimes does not want to be with me because I am just such a – yeah, such a evil guy, I do not want to say I am not an evil guy, but just sometimes I can be mean…Like, friends call me up and they want to go have fun and hang out. I just buzz them off, so, "Just don't call me", you know?. So, those things I hate doing…I just do not want to talk to anybody. I do not want to do anything. Just, "Whatever. Who cares? I'm tired of all this." Like, "Ooh, why are you bugging me?" (US23)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Brod et al[22]
Self-perception: Self-stigma	Insufficient information to derive a definition.	-	Low, Limited evidence	-	-	Kanera 2019 (p. 93)[24]
Self-perception: Sense of independence	Ability to be independent without the need to rely on other people, or feelings of helplessness or loss of control due to inability to function independently.	This concept may be linked to anxiety and fear of the future.	Moderate	-	-	Hwang et al,[9] Gok Metin et al,[10] Kanera et al[24]
Domain: Sleep						
Ability to fall asleep	Ability to fall asleep	Falling asleep was affected primarily by pain symptoms, which many participants found more noticeable when lying down to sleep. Some people also reported that pDPN symptoms worsened at night following the day's activities.	Moderate, Concept is replicated across some studies and endorsed in interviews	3 (12%)	Sometimes even laying down at night trying to go to sleep, it can affect me. It's either pain or tingling, burning. It's always something different. It's almost like I have restless legs. I just cannot seem to get comfortable (US14)	Hwang et al,[9] Brod et al,[18] Brod et al[22]
Ability to fall back asleep	Ability to fall back asleep after awakening at night	Ability to fall back asleep was affected primarily by pain symptoms	Low, Limited evidence (not endorsed in interviews), not defined in detail and potentially overlaps with ability to fall asleep	-	-	Hwang et al,[9] FDA,[16] Brod et al,[18] Brod et al[22]
Ability to wake up in the morning	Ability to wake up in the morning	This concept may be linked to fatigue that results from poor sleep.	Low, Limited evidence is available to describe this concept.	-	-	Brod et al[18]
Nighttime waking/ability to stay asleep	Experiences of being awakened at night by symptoms.	This concept is linked to pain symptoms.	High, Replication across studies, substantial rates of endorsement	4 (16%)	It does interfere, you know, at nights. It will wake me up when I get these sharp pains (US06)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Liu et al,[26] Brod et al[22]

Restful sleep	Ability to get restful sleep and/or to feel well-rested upon waking	Night waking and discomfort while sleeping contributed to restless sleep that was not refreshing	Low, This concept showed limited replication across studies and appears to overlap other sleep-related concepts.	3 (12%)	Well, when it hits me at night, I do not sleep well (US07)	Brod et al,[18] Brod et al[22]
Sleep interference/ disturbance	Experiences of restless, disturbed sleep due to symptoms	This concept appears to encompass nighttime waking (a form of sleep disturbance)	Moderate, Replication across studies, but broad and some inconsistency in how it is described	6 (24%)	You know, just not been able to have a very, like, straight six or seven hours of sleep, just waking up in the middle of the night. Even sometimes, that numbness or the tingling wakes me up and then I have to move my leg or, you know, take out my blanket or something to be more comfortable (US06)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Davies et al,[23] Liu et al,[26] Brod et al[22]
Domain: Cognitive Function						
Ability to concentrate	Ability to concentrate or focus on what you are doing.	Ability to concentrate was most often disrupted by pain could also be affected by numbness symptoms and fatigue that resulted from sleep disruptions.	High, Replication across studies, substantial rates of endorsement, and concept described in similar terms	13 (52%)	Especially when I am having symptoms, it just does not let me concentrate. I just cannot multitask the way that I used to before (US19) When I have pain and burning and numbness and all that, it's really hard to concentrate (US12)	Hwang et al,[9] Gok Metin et al,[10] FDA,[16] Brod et al,[18] Davies et al,[23] Kanera et al,[24] Brod et al[22]
Ability to think clearly	Ability to think clearly, to feel mentally alert, or to be undistracted by pain or other symptoms.	This concept is linked primarily to pain symptoms.	Low, Limited evidence is available to describe this concept in a way clearly distinct from concentration.	3 (12%)	Sometimes, I do not think too clearly. You know, my thought process is not as sharp as when I do not have pain. You know, pain kind of messes with your – you know, makes you forget things, and sometimes you just say things you do not want to say, and so there's definitely that aspect to it (US10)	Gok Metin et al[10]
Domain: Sexual Function						
Ability to engage in intimate relations	Ability to engage in sexual or intimate activities	Sexual functioning was affected primarily by pain symptoms and hypersensitivity to touch, as well as other impacts of pDPN such as fatigue, depression, and irritability. Some participants noted that sexual functioning is also affected by diabetes, making it difficult to clearly distinguish the origin of impacts experienced.	Moderate, Concept is broadly replicated across sources, but differences in how the concept is described and/or lack of detailed evidence of specific meaning create obstacles to matching the concept to COA items in a reliable way.	14 (56%)	That [sexual desire], at this time, is very, very low, my desire, because I am not – most of the times, I am not in a good mood, and it does not feel good. So, I am very depressed. My desire is very, very low. I do not enjoy it. Yeah, it somehow bothers me and my husband, but what can I do? I am not in a good mood to do those things (US13) Just cannot function properly. I might not have the energy or desires. I might be in too much pain so – because it [sexual function] just is affected quite a bit then (US25)	Gok Metin et al,[10] FDA,[16] Brod et al[18]
Erectile dysfunction	Insufficient information to derive a definition.	-	Low, Limited evidence is available to describe this concept.	2 (8%)	The desire never goes away, although I will tell you, I am [age redacted] years old. But, I do feel this is affecting – there may be some ED issues (US06)	Gok Metin et al[10]

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Table 3 (Continued).

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Impact on partner	Impact from health condition on a partner's sexual life or happiness.	-	Low, Limited evidence available to describe this concept	1 (4%)	Just, it's not an easy thing to talk about, but I will talk about it. Just, like, the girlfriend sometimes – because I am irritated, I just do not want to do it, and she gets kind of mad. So, there's a lot of back and forward arguing, so it's not something that she feels she's happy about. I am not happy about it, so both nobody's happy about it (US23)	Gok Metin et al[10]
Lack of desire/ libido	Ability to feel the desired level of sexual interest in a partner without interference from symptoms or other impacts of pDPN.	This concept is linked to irritability and other negative impacts of neuropathic pain.	Moderate, Concept is broadly endorsed, but experiences could also be treatment-related and may not apply universally.	14 (56%)	That [sexual desire], at this time, is very, very low, my desire, because I am not – most of the times, I am not in a good mood, and it does not feel good. So, I am very depressed. My desire is very, very low. I do not enjoy it. Yeah, it somehow bothers me and my husband, but what can I do? I am not in a good mood to do those things (US13) I might not have the energy or desires. I might be in too much pain so – because it [sexual function] just is affected quite a bit then (US25)	Gok Metin et al,[10] FDA[16]
Domain: Treatment Burden (not included in the conceptual model)						
Treatment burden	Level of burden imposed by treatment for the condition.	This concept may benefit from refinement to determine the relevant aspects of treatment that are burdensome to patients.	Moderate, Limited replication across studies, high rate of endorsement when reported.	25 (100%)	Everything. I have tried from massage. I have tried from exercises, physical therapy, pain relief, pain relievers, better control of my diabetes, which they say is the first thing you can do is better your diabetes. Well, I [audio cuts out] and that does not necessarily work. Then, of course, being seen by the doctor and making sure I have good foot care and kind of just – they do like testing with your feet and electrodes, like sending nerves or something, firing off (US02) I mean, I have changed my diet. I have. Well, I mean, there are so many things that I have done. I am taking, like, over-the-counter pain medication, and also prescription medicine, you know, when it's really bad. That's what I am doing right now (US05)	FDA[16]

Abbreviations: COA, clinical outcomes assessment; pDPN, painful diabetic neuropathy.

A conceptual model diagram was developed to concisely display the relationships between domains and concepts (Figure 1). Treatment burden was excluded from the conceptual model diagram, which focuses on the relationship between pain, other symptoms (sensory abnormalities and muscle weakness), and functioning impacts.

Pain was reported and described by all participants in the qualitative interviews and all of the articles in the TLR. Burning was the most common pain concept across studies and interviews, which was cited in four studies and reported by 72% of interview participants.[9,16,18,23] Meanwhile, aching and sharp, sudden pain were noted by interview participants to be the most bothersome types of pain. Unpredictability of pain was also very bothersome for interview participants and was included in the model along with other cross-cutting themes such as the pain location, severity, consistency, and exacerbating factors. Numbness was the most frequently cited symptom in the literature apart from pain, appearing in seven studies.[9,10,16,18,23,24,26] Ninety-two percent of interview participants reported experiencing numbness, and they described it, along with pain, as one of the most bothersome symptoms.

Findings from the TLR and patient interviews showed that pDPN negatively impacts multiple domains of QoL. The physical functioning impacts with the most citations across studies and endorsement in interviews were walking, standing still, standing up from a seated or prone position, balance, ability to engage in prolonged or vigorous activity, and daytime fatigue.[9,10,16,18,22–26] The physical functioning impacts described as most bothersome by interview participants were walking, standing still, sitting, routine daily tasks, and activities outside the home. The emotional functioning impacts with the highest level of replication, consistency, and endorsement across studies and interviews were irritability and frustration/anger, while fear of falling, fear of condition getting worse, and impact on ability to enjoy life were the most bothersome for interview participants.[9,10,16,18,22] The social functioning impacts with the highest level of evidence across studies and interviews were participation in social life, work, and recreational life.[10,16,18,22–25] The sleep impact with the highest level of evidence was nighttime waking, which was discussed in six studies,[9,10,16,18,22,26] while the

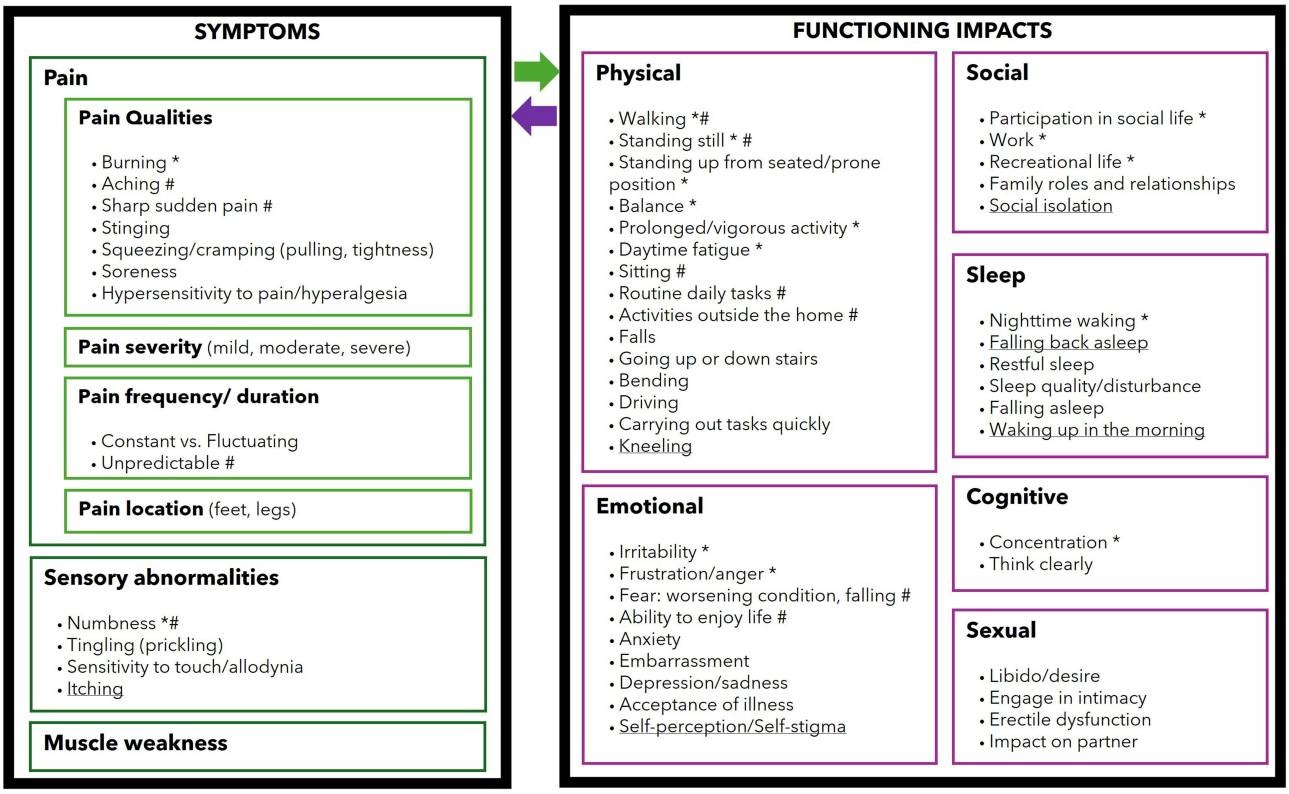

Figure 1 Conceptual model of domains inclusive of symptoms and functioning impacts.
Notes: Overarching concepts were categorized as symptoms or functional impacts, with arrows showing their influence within specific domains. * Concepts with the highest level of evidence based on replication across studies, substantial rates of endorsement, or concept described in similar terms. # Concepts indicated during patient interviews to be most bothersome or most important to improve with treatment. Underlined text indicates concepts identified in published qualitative literature only.

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cognitive impact with the highest level of evidence was concentration.[9,10,16,18,22–24] Impact on sexual desire/function was broadly endorsed in the interviews (56% of participants) and appeared in multiple TLR sources,[10,16,18] however it was unclear whether these experiences were a result of pDPN symptoms or were treatment related.

While most concepts were found in both the TLR and the interviews, there were several concepts included in the model that were only found in the TLR. These included one symptom, itching, which was mentioned in Hwang et al and *Voice of the Patient* but not described in sufficient detail to determine how it fit with or was related to the other symptoms.[9,16] There were also several functioning impacts; kneeling,[9] social isolation,[10,18,23] self-perception/self-stigma,[24] falling back asleep,[9,16,18,22] and ability to wake up in the morning[18] that were mentioned only in the literature and did not arise in interviews.

The new conceptual model diagram includes many of the same functioning impacts as the previous conceptual models designed by Gok Metin et al and Brod et al, however it contains greater detail on symptoms, particularly the different types of pain experiences, that lead to these impacts. The Gok Metin model and Brod models show environmental factors which influence pDPN experiences,[10,18] while the new model designed to support clinical outcomes assessment is more narrowly focused on symptoms and does not include environmental constraints that could affect individuals' access to treatment and/or ability to manage their diabetes. The new model also provides greater detail on social, emotional, cognitive, and sexual functioning impacts than the prior models and includes information on which concepts had the highest level of evidence across studies and which concepts patients identified as most bothersome or important to improve with treatment.

Discussion

This study explored patient experiences of pDPN, a common form of DSP, through a TLR and qualitative interviews. The TLR identified studies describing symptoms and impacts of pDPN that influence patients' experience, while interviews provided insight into the most bothersome symptoms and impacts, focusing on patients' descriptions of pain associated with DPN, and how it impacts their daily lives. Synthesis of data from concept elicitation interviews and a TLR of qualitative studies of experiences of patients with pDPN identified 57 unique concepts of interest to patients, divided into ten domains. Most studies included substantive direct quotation from patients, suggesting that concepts cited across multiple studies are robust and widely applicable to pDPN. Most of these concepts arose in both the interviews and in the data extracted from published studies identified in the TLR. In fact, the qualitative patient interviews did not yield additional symptoms or impacts not already identified through the TLR. However, the interviews addressed some gaps in the literature as they provided further insight into the terms people with pDPN use most commonly to describe their pain experiences and which symptoms and impacts were most bothersome for people living with pDPN and most important to improve with treatment.

A few concepts included in the model describe experiences that, although important to patients, may not be well-suited to assessing health outcomes within a shorter-term clinical trial or other research study. For example, falls are a very serious safety risk, and fear of falling has a significant emotional impact on people with pDPN. While fear of falling is certainly a clinically meaningful concept for assessment, falls likely do not occur sufficiently frequently to be a useful outcome in a short-term clinical trial. Key factors to consider when designing a strategy for outcomes assessment include not just the severity and frequency of symptoms and impacts, the frequency of symptoms and impacts, but also unpredictability of symptoms, the degree to which symptoms necessitate rest during activity (pacing), and the exacerbation of symptoms due to inactivity or at night.

The interview and TLR findings demonstrate the central importance of pain to people with pDPN and its direct impact on functioning and QoL. Pain causes experiences of distress that vary in frequency, unpredictability, severity, and type, with sharp pain and aching being described as most bothersome compared to other pain types such as squeezing/cramping and soreness. Pain experiences differentially burden quality of life by limiting a wide range of activities, causing people to avoid activities they enjoy, and generating considerable physical discomfort and emotional distress. Numbness was identified as the most bothersome sensory experience other than pain and was linked to specific disabilities, such as difficulty with navigating uneven terrain or stairs and problems with balance. The findings suggest that improvement in symptoms as a result of treatment must be sufficient to adequately restore physical functioning, as

difficulty with basic functions such as being able to sit at a desk, do routine tasks around the house, and do activities outside the home were among the most bothersome limitations for participants. It is important to note that self-report suffices as a criteria for initiating analgesic treatment and there is no pathological or neurophysiological test which is sensitive or specific for the symptoms identified in this study.[27,28]

The conceptual model developed based on these findings has been designed to support the selection, modification, or development of clinical outcome assessments for patient-focused drug development. As such, the model builds upon existing qualitative study findings and prior conceptual models of pDPN by providing greater detail on pain experiences, including terms used to describe the different types of pain people with pDPN experience. The model also provides additional detail on the social, emotional, cognitive, and sexual impacts resulting from pDPN symptoms compared with prior models.

Understanding of some concepts in the model could be further improved by targeted additional research with patients. For example, itching was reported in two sources,[9,16] but was not well described, and was not referenced in the interviews. Itching may be related to or an alternative means to describe tingling/prickling. Similarly, although bending was mentioned in multiple publications and in interviews, it was not clear whether this is a distinct concept or an aspect of balance difficulties and fear of falling.

Strengths and Limitations

Conceptual models, as emphasized in the FDA's Patient Focused Drug Development guidance, offer several advantages over traditional models by systematically incorporating patient perspectives to improve the relevance of clinical trial endpoints. The qualitative interview participants had physician confirmed diagnosis of DPN and conceptual saturation was reached. The conceptual model focused on concepts likely to be responsive to a pharmacological treatment targeting pain specifically, harmonizing information from the literature and patient interviews to fully describe the experiences of patients living with pDPN.

This study has some limitations. Due to the limited number of published qualitative studies on the experiences of people with pDPN, evidence from the FDA's Voice of the Patient report was also used to identify potentially relevant outcome concepts. However, only one concept included in the model, driving, is cited in the Voice of the Patient but not cited in any of the other literature. The Voice of the Patient includes direct testimonials from patients, but it is not a scientific study and could be subject to various forms of limitation and bias. DPN is a progressive condition and patient experiences are heterogenous, making it difficult to generalize the small group of studies identified in this review to the entire population of people with pDPN. Some concepts drawn from the literature were not described in sufficient depth to develop detailed definitions or clearly establish relationships with other concepts. Reporting of concepts in the literature could also reflect researchers' priorities rather than the level of importance to patients. Data on rates of endorsement for symptoms and impacts were not consistently included in published studies but are reported for the interview study. The interviews were hybrid concept elicitation and cognitive debriefing interviews, thus the concept elicitation comprised only the first 20 minutes of the interview, and longer discussions may have elicited more or different information from participants. However, the brief concept elicitation focused on aspects of experience that were 'top of mind' for participants and likely to reflect their most spontaneous perspectives on their experiences. The interviews were all conducted in the United States, which may limit their transferability to other cultures and languages. Although recruitment aimed to enroll individuals representing heterogeneous demographic characteristics, the study may be limited in capturing the heterogeneity within the US population including the diverse cultural, geographic, and socioeconomic backgrounds. Data regarding which concepts are most bothersome for patients are drawn only from the interviews, as this was not consistently assessed across the articles included in the literature review. Multifactorial syndromes with diabetes may be associated with more severe pain and activity limitation[29] and were not specifically examined in this study. Further research is needed to continue to better understand the concepts and relationships outlined in this conceptual model. It will also be important to characterize the burden in patients with other forms of DSP beyond pDPN that are highly overlapping and often co-occurring, and for whom unmet need is great because there are few FDA approved therapies.

Conclusion

Findings from the TLR and qualitative patient interviews identified a broad set of symptoms and impacts that matter to patients with pDPN and provided insight into impacts most bothersome to patients and most important to address with treatment. The resulting evidence-based conceptual model of pDPN can guide the selection of COAs for clinical trials, enhancing the understanding of the clinical significance of treatment outcomes. By incorporating the patients' perspective, this model may also improve doctor-patient communications, ensuring that the patient's viewpoint is considered in the treatment process. New therapies addressing the symptoms and impacts highlighted in the model could significantly improve QoL for adult patients with pDPN. Results suggest that assessments need to comprehensively measure pain and its impacts on quality of life and highlight the need for effective therapies to address symptoms of pDPN and mitigate their impact on patients' lives.

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