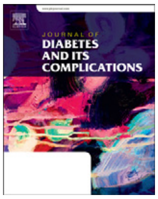
Journal of Diabetes and Its Complications 29 (2015) 1112–1118

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM



# Patient reported outcomes for diabetic peripheral neuropathy

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## ARTICLE INFO

*Article history:*
Received 14 July 2015
Received in revised form 19 August 2015
Accepted 20 August 2015
Available online 22 August 2015

*Keywords:*
Diabetes
Neuropathy
Patient-reported outcome
Quality of life
Treatment

## ABSTRACT

*Objective:* Multiple patient-reported outcomes (PROs) have been used to assess symptoms among patients with Diabetic Peripheral Neuropathy (DPN). However, there is little consistent application of measures in clinical or research settings. Our goal was to identify and compare patient reported outcome measures (PROs) specifically evaluated in neuropathy populations.

*Methods:* Literature search, summary, and qualitative comparison of PROs validated in neuropathy populations.

*Results:* We identified 12 studies of PROs evaluated in neuropathy populations that included DPN patients. Two assessed sleep quality, 5 assessed painful symptoms, and 5 assessed quality of life. The number of items per measure ranged from one to 97, and the number of domains ranged from one to 18. All had adequate internal consistency (Chronbach's Alpha > 0.70). There was mild to moderate standardization of domains across measures and only a few instruments used common comparators. The spectrum of DPN symptoms addressed included: sensory symptoms, autonomic symptoms, and function, beliefs, role participation, sleep quality, and perceptions of illness.

*Conclusions:* There remains a need for a gold standard for DPN symptom assessment. Few existing instruments are adequately validated and the domains assessed are inconsistent. Current instrument selection should depend on the clinical and social context of the assessment.

## 1. Introduction

Diabetic peripheral neuropathy (DPN) affects 30% to 50% of all adults with diabetes and costs the U.S. an estimated $5 to 14 billion in health care expenditures each year (daCosta, Cappelleri, & Joshi, 2011; Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003). Between 11% and 26% of patients with DPN have painful symptoms such as pain, tingling, numbness, and burning sensations (Argoff, Cole, Fishbain, & Irving, 2006; daCosta et al., 2011). DPN patients with painful symptoms have lower quality of life and incur higher health care costs compared to DPN patients without painful symptoms. (Argoff et al., 2006; daCosta et al., 2011; Zelman, Brandenburg, & Gore, 2006)

Painful symptoms are generally under treated in clinical settings (Argoff et al., 2006; daCosta et al., 2011). This is partly because pain is a subjective experience that varies between individuals and is affected by many social, cultural, economic and psychological factors (Argoff et al., 2006; Cintron & Morrison, 2006; Green, Anderson, Baker, et al., 2003; Treede, Jensen, Campbell, et al., 2008). Medical treatment for DPN symptoms requires careful adjustment of different medications to maximize symptom relief and minimize side effect burden (Bril, England, Franklin, et al., 2011). Although accurate monitoring of symptoms is a critical component of care, there is currently no gold standard for DPN symptom assessment.

In the absence of a gold standard, DPN symptoms are usually assessed using a range of patient-reported outcome measures (PROs) that quantify discomfort, sleep disturbance, and quality of life (Cruccu, Sommer, Anand, et al., 2010; Hogg, Peach, Price, Thompson, & Hinchliffe, 2012). However, few commonly used measures capture the complex symptomatology (such as tingling, itching, burning, and temperature sensitivity) that characterizes DPN (daCosta et al., 2011). For example, studies assessing the impact of DPN symptoms have used instruments ranging from simple pain scales to global health status (daCosta et al., 2011). In addition, cultural differences affect perceptions of, and communications about, pain and quality of life, and not all PROs have been suitably validated among the

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Conflicts of interest: None of the authors report any conflicts of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2015.08.015
1056-8727/

diverse population of patients with DPN (Cintron & Morrison, 2006; Green et al., 2003). Contextually and culturally validated tools for DPN symptom assessment are needed to advance clinical practice and research.

In this article, we identify patient reported measures that have been evaluated within populations with DPN to identify measures potentially suitable for use clinical and research purposes. Our goal was to identify one or more valid measures that could be used consistently across multiple research and/or clinical settings to accurately describe and quantify DPN symptoms from the patient's perspective.

## 2. Methods

### 2.1. Search strategy

Given our goal of identifying instruments that could capture the complex nature of DPN symptoms, we sought articles that had been formally evaluated within DPN populations. We searched Pubmed, PsycInfo and Embase for English-language articles describing validation studies for patient reported outcomes in DPN populations from the beginning of the database to September, 2013. Our search included three primary sets of terms: "Diabetic Peripheral Neuropathy" and derivations thereof; terms reflecting common symptoms measured in randomized clinical trials of DPN treatments; and indicators of validation metrics (Fig. 1). We included studies reporting initial validation of patient-reported DPN outcome measures that contained elements from all three sets of search terms. Review articles were used to identify possible additional articles but were not included in the analysis. We also examined references from DPN studies to identify potentially relevant articles that were not identified in our search of the literature. Although our focus was on assessing quality of life in individuals with painful neuropathy, not all references were specific about whether study populations focused on those with painful DPN versus nonspecific DPN.

### 2.1.1. Study selection

Two authors [CB, AA] screened each abstract independently to evaluate whether patients with DPN were included, the paper included PROs, and studies assessed reliability and validity testing. Studies including patients with DPN as well as those with other neuropathic conditions (e.g., post hepatic neuralgia) were included in the review. When we found studies that applied previously validated measures, we selected only the primary validation study for review. One study evaluated a PRO that did not specifically fit into one of the three domains of interest, but that was highly specific to patients with DPN (the Patient Interpretation of Neuropathy [PIN] questionnaire) and included questions about the degree to which patients worry about the consequences of DPN such as foot amputation (Vileikyte, Gonzalez, Leventhal, et al., 2006). This study was grouped with those focused on patient quality of life/lived experience. A final qualifying article from June, 2015 was identified after initial review. We excluded studies that were solely focused on diagnosing DPN rather than assessing or evaluating patient reported outcomes related to DPN.

### 2.1.2. Data extraction and appraisal

From each paper, we extracted information on the measurement of painful symptoms, sleep, and/or quality of life; the demographics and sample size of the validation population; and metrics related to reliability and validity. We used standards developed by the Mayo/FDA Patient Reported Outcomes Consensus Meeting Group to evaluate the overall reliability and validity reported in published studies (Frost, Reeve, Liepa, Stauffer, & Hays, 2007). To assess reliability, we extracted statistics related to internal consistency (Cronbach's alpha) and test–retest reliability (Interclass correlation or ICC). We used a standard threshold of 0.70 to assess reliability, indicating that metrics with a Cronbach's alpha and/or ICC of 0.70 or higher were considered to be adequately reliable.

We also examined all articles for common metrics used to evaluate validity, including content, criterion, construct, convergent, and discriminant validity as well as responsiveness. We only evaluated criterion validity for PROs where there was an objective method of measurement for comparison (e.g., patient reported painful symptoms versus mechanically and thermally evoked pain).

## 3. Results

Our search identified 299 articles (Fig. 1). Of these, 33 were considered relevant to DPN and underwent abstract review. Of these, 19 focused on measuring symptoms or impact of DPN symptoms

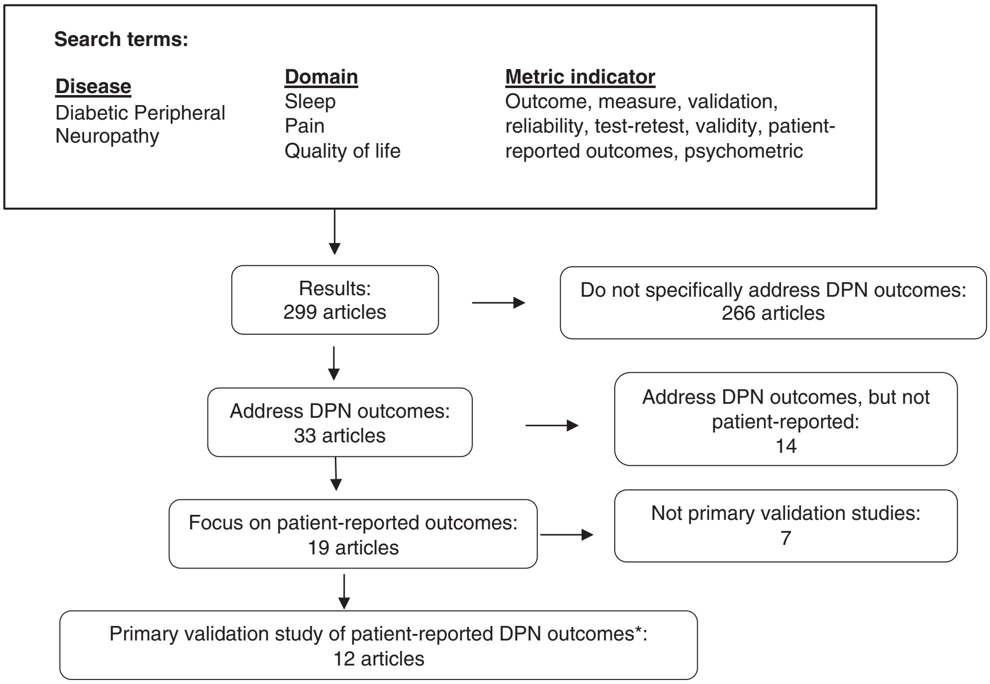

**Fig. 1.** Results of search and article review process.