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Review Article

Psychosocial Factors in Painful Diabetic Neuropathy: A Systematic Review of Treatment Trials and Survey Studies

Kitty Kioskli, MSc,* Whitney Scott, PhD,*,† Kirsty Winkley, PhD,‡ Stavros Kylakos, MSc,§ and Lance M. McCracken, PhD*,†,¶

*Health Psychology Section, Psychology Department, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK; †Guy's and St Thomas' NHS Foundation Trust, London, UK; ‡Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, King's College London, London, UK; §Department of Computer Science, City, University of London, London, UK; ¶Department of Psychology, Uppsala University, Uppsala, Sweden

Correspondence to: Lance M. McCracken, PhD, Psychology Department, Uppsala University, PO Box 1225, 751 42 Uppsala, Sweden. Tel: +46-18-471-21-23; E-mail: lance.mccracken@kcl.ac.uk.

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Abstract

Objective. Diabetes mellitus is associated with a number of complications that can adversely impact patients' quality of life. A common and often painful complication is painful diabetic neuropathy. The aims of this study were to systematically review and summarize evidence from studies of psychological treatments and psychosocial factors related to painful diabetic neuropathy and assess the methodological quality of these studies. **Methods.** Electronic databases, related reviews, and associated reference lists were searched. Summaries of participants' data relating to the efficacy of psychological treatments and/or to associations between psychosocial factors and outcomes in painful diabetic neuropathy were extracted from the included studies. The methodological quality of included studies was assessed using two standardized quality assessment tools. **Results.** From 2,921 potentially relevant titles identified, 27 studies were included in this systematic review. The evidence suggests that depression, anxiety, sleep, and quality of life are the most studied variables in relation to pain outcomes in painful diabetic neuropathy and are consistently associated with pain intensity. The magnitude of the associations ranged from small to large. **Conclusions.** Research into psychosocial factors in painful diabetic neuropathy is unexpectedly limited. The available evidence is inconsistent and leaves a number of questions unanswered, particularly with respect to causal associations between variables. The evidence reviewed indicates that depression, anxiety, low quality of life, and poor sleep are associated with pain in painful diabetic neuropathy. The disproportionate lack of research into psychological treatments for painful diabetic neuropathy represents a significant opportunity for future research.

Key Words: Painful Diabetic Neuropathy; Psychological Interventions; Psychosocial Factors; Systematic Review

Introduction

Diabetes mellitus (DM) is highly prevalent and a significant public health problem [1]. Common complications of DM include cerebrovascular and cardiac diseases, kidney failure, stroke, foot ulcer, blindness, and amputation [2,3]. Another frequent complication of DM is painful diabetic neuropathy (PDN), which affects 25–30% of people with DM [3–5].

PDN diagnosis is a clinical one and is based on the patient's description of pain, which is often described as a prickling, burning, deep aching, or sharp sensation, similar to an electric shock [6]. Subjective report of these painful symptoms can be used to screen for possible PDN; however, definitive diagnosis requires the presence of objective PDN signs (e.g., decreased ankle reflex) and findings confirming nerve dysfunction, such as using nerve conduction or through skin biopsy. Although these objective indicators are required to confirm PDN diagnosis, for practical reasons, some studies rely on self-reported neuropathic pain symptoms for people with diabetes as an indicator of possible PDN [4].

PDN primarily involves the toes, feet, and legs and is associated with significant interference with mobility, sleep, mood, social interactions, and overall quality of life (QOL) [7–9]. PDN appears to significantly impact mental health, including anxiety and depression [10,11], which in turn contributes to poorer outcomes overall [12]. Essentially, PDN is a chronic disease associated with long-term suffering and disability for many people [13,14].

At present, most treatments for neuropathic pain are pharmacological [15–17]. The American Diabetes Association (ADA), recommends optimization of glucose control to achieve the prevention or delay of PDN, as well as pregabalin or duloxetine as pharmacological options for pain management [18]. However, no single treatment has proven effective enough for pain relief or prevention [19]. Findings are similar in the broader neuropathic pain literature. A systematic review of published and unpublished studies from 174 randomized controlled clinical trials (RCTs) [20] and a meta-analysis of 229 RCTs [21] examined the medical management of neuropathic pain. The meta-analysis found that outcomes from trials were modest, including a number needed to treat (NNT; $\geq$50% relief) of 6.4 (95% confidence interval [CI] = 5.2–8.4) for duloxetine, 7.7 (95% CI = 6.5–9.4) for pregabalin, 7.7 (95% CI = 6.5–9.4) for gabapentin, and 10.6 (95% CI = 7.4–19.0) for capsaicin patches. According to these results, even when PDN is treated with medication, many people continue to experience significant pain. These results suggest a need for new or additional treatments, potentially including nonpharmacological interventions.

Within the broader chronic pain literature, there is good evidence supporting psychological treatments, such as cognitive behavioral therapy (CBT), for chronic pain [22–24]. However, it appears that there are limited published studies of psychological treatments for people with diabetic neuropathies [25,26] and only one literature review examining physical and psychological interventions for people with PDN [8]. This earlier review searched the literature up to July 2014 and identified only two psychological intervention studies. An updated review on this important topic appears due. Also, it is unknown which psychosocial factors might impact outcomes in people with PDN from a wider range of study designs. A wider view of psychosocial factors could prove fruitful, as it could lead to treatment developments that have not yet been conceived.

The purpose of this study was to synthesize and evaluate the evidence from trials of psychological treatments for PDN and other research into psychosocial factors in relation to PDN outcomes. From this we intended to 1) identify current psychological interventions for individuals who suffer from PDN and examine their effectiveness, 2) identify potentially modifiable psychosocial factors that might influence clinical outcomes associated to PDN, and 3) assess the methodological quality of the included studies.

Methods

Registration

This systematic review protocol is registered with PROSPERO (registration number CRD42017060339) and may be accessed online at:https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017060339.

The current review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [27] and established guidelines for narrative synthesis [28].

Search Strategy

We searched the following electronic databases from 1946 to August 10, 2018: Medline, Embase, PsycINFO, Cinahl, Web of Science, ISRCTN registry, ClinicalTrials.gov registry, and EU Clinical Trials registry. Also, the reference lists of all included papers and related published reviews [29] were screened to identify any additional eligible studies. The PICOS framework was used to develop the search strategy explicitly for the treatment trials. Our target population was patients suffering from neuropathic pain due to diabetes. Included interventions were any study involving psychological treatments. In addition to treatment trials, observational studies examining relationships between psychosocial factors and relevant outcome variables were also sought. All comparators were eligible. The selected outcomes were physical and emotional functioning, pain experience, pain-related interference with functioning, or QOL (Table 1).

Furthermore, the MeSH and free-text terms were divided into three groups—PDN, psychological interventions, and psychosocial factors—including all study designs, in order to identify both observational studies and RCTs (Supplementary Data). Particularly, the boolean operator "OR" was used to enable identification of either relevant RCTs *or* observational designs measuring psychosocial factors in relation to pain outcomes in PDN.

Table 1. PICOS Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults (minimum age 18 years) & clear diagnosis of PDN	Children, adolescents (under 18 years), & neuropathic pain due to other causes
Intervention	Any psychological treatment addressing psychosocial factors *or* studies measuring psychosocial factors for PDN and allowing the examination of these in relation to pain outcomes	Interventions that are only educational
Control	All comparators are eligible for this systematic review	–
Outcomes	Physical functioning Emotional functioning Pain experience Pain related interference Symptoms and adverse effects Quality of life	–
Study design	Any	Reviews
Publication type	Published full-text articles	Unpublished dissertations and articles, editorials, letters/ uncompleted trials
Language	English	Non-English articles

– = not applicable; PDN = painful diabetic neuropathy.

Inclusion and Exclusion Criteria

We included any study involving psychological treatments incorporating any of the outcomes specified: physical or emotional functioning, pain experience, pain-related interference, or QOL in individuals with PDN. Also, we included studies designed to investigate the association between psychosocial factors, for instance, emotional responses, thoughts, beliefs, cognitive factors, or other behavioral patterns, and the designated pain outcomes. Studies examining potentially modifiable social processes, such as perceived quality of social support, in relation to pain outcomes were also included. Studies were excluded if they were not written in English or were not published as a full-text article. Additionally, studies that only investigated pain prevalence, and not the association between pain outcomes and psychosocial factors, were not eligible. Studies that assessed only unmodifiable sociodemographics (e.g., ethnicity) in relation to pain outcomes were excluded. Studies were also excluded if they were solely educational interventions (meaning primarily focused on enhancing knowledge or providing information, rather than more active processes of psychological or behavioral change). Participants within the included studies were adults, aged 18 years and older (at the time of their entry into the study), with a stated diagnosis of PDN. Studies of participants who suffered from neuropathic pain due to causes other than diabetes were not included.

Screening of Studies

After running searches in each electronic database, the predefined inclusion criteria were applied independently by two reviewers (KK, SK) in order to screen all potentially relevant titles and abstracts. After screening titles and abstracts for eligibility, the remaining potentially eligible full-text articles were reviewed for selection. Disagreements regarding eligibility were discussed, where required, so that a consensus was reached. Disagreements that could not be resolved through discussion were settled by input from a third reviewer (LM, KW, or WS).

Data Extraction

The data extraction tool included the following: publication date, authors, country, journal, study design, types of interventions or psychosocial factors investigated, pain and related outcomes, participants' characteristics, study setting, study inclusion and exclusion criteria, recruitment method, reported medications, duration of PDN, outcome measures used, and statistical analyses. The data were extracted from the eligible studies by three reviewers (KK, SK, or WS). KK extracted data from all studies, whereas SK and WS each independently extracted data from approximately half of the studies. If the reviewers failed to reach a consensus on the extracted data, a third opinion was provided by another member of the research team (LM or KW).

Quality Assessment

The methodological quality of the included studies was evaluated using the Downs and Black quality assessment tool [30] for observational studies or the Cochrane risk of bias tool for RCTs [31], depending on the design of the study.

The Downs and Black quality assessment tool [30] has been identified as appropriate for quality assessment in systematic reviews. It was applied to nonrandomized trials and other observational studies. The checklist was modified minimally to meet the needs of the current systematic review. The methodological quality tool contained 27 items. The component ratings are divided as follows: A: Reporting, Score 0–10 (eight questions); B: External Validity, Score 0–3 (three questions); C: Internal Validity–Bias, Score 0–7 (seven questions); D: Internal Validity–Confounding, Score 0–7 (seven questions).

The Cochrane risk of bias tool [31] is a widely used tool for assessing bias and flaws in the conduct, design, analysis, and reporting of RCTs and is better suited to this than the Downs and Black tool [30]. This risk of bias assessment tool includes selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

The checklists were administered by three independent reviewers (KK, SK, or WS) and cross-checked for

consistency. Again, KK assessed all the studies, and SK and WS each assessed half of the studies. Any disagreements were resolved by a third reviewer (LM or KW).

Data Analysis and Data Synthesis

Most studies investigated associations between more than one psychosocial variable and pain outcomes. The reported results are organized according to the specific psychosocial factors and pain outcomes included in the studies. The magnitude of relations from correlational methods was reported in terms of the correlation coefficient *r* when available.

Cohen's *d* was calculated by the first author (KK) to reflect effect sizes for between-group comparisons, based on the means and SDs reported in each study. For variables that were assessed by more than one measure, a Cohen's *d* was calculated for each measure, and the final effect size reported for the variable was the mean of the Cohen's d of all measures [32,33]. The calculated *d*s are interpreted, according to Cohen, as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$).

Ninety-five percent confidence intervals were calculated for Cohen's *d* and correlation coefficient *r* (for studies that reported a within-group correlation coefficient). For Cohen's *d*, the 95% CI was calculated by first identifying the t-value and then using the "ci.smd" function of the MBESS package in R [34]. The t-value was calculated as follows [35]:

$$t = Cohen's\ d\ \times \sqrt{\frac{Sample\ Size\ 1 \times\ Sample\ Size\ 2}{Sample\ Size\ 1 + Sample\ Size\ 2}}$$

. For the correlation coefficient *r*, the 95% CI was calculated by first transforming the *r* to z', calculating the standard error for z', the 95% CI for z', and then transforming it back to values for *r*. The correlation coefficient *r* was transformed to z' with the following formula [36]:

$$z' = 0.5 \times [ln(1 + r) - ln(1 - r).]$$

The standard error for z' was calculated by:

$$SE = \frac{1}{\sqrt{Sample\ Size - 3.}}$$

The lower and upper bounds of the 95% CI for z' were found as follows:

$$Lower\ Bound = z' - 1.96\ \times SE;$$

$$Upper\ Bound = z' + 1.96\ \times SE.$$

Finally, the lower and upper bound values were transformed back to *r* values using the equation originally used to transform *r* to z'.

Results

Study Selection

The detailed selection process for included studies can be found in Figure 1. Each database was searched individually, and the total number of hits was 2,922; 2,226 articles remained after deduplication. After applying the predefined inclusion and exclusion criteria to the titles and abstracts, 41 articles remained for full-text review by the two reviewers. The manual search of the reference lists revealed seven more studies that did not appear during the electronic searches. At the end of the screening and selection process, 27 studies (29 published papers) met criteria and were included in this systematic review.

General Study Characteristics

The 27 studies found eligible for this systematic review were published between 1998 [37] and 2018 [38]. The majority of the studies (17/27) were cross-sectional [3,6,9–12,38–52]. Two studies were described as case–control [37,53], three as prospective cohort designs [4,14,54], and three were RCTs [25,26,55].

Most of the studies recruited participants from the United States (10 studies, 37%), the UK (six studies, 22%), and the Netherlands (two studies, 8%). The remaining studies (nine studies, 33%), recruited participants from a range of countries across Europe, Asia, and North and South America. The mean ages ±SDs of participants reported in the studies ranged from 45.9 ± 15 to 74.6 ± 10.8 years. Twenty-six out of the 27 studies included both male and female participants, while one included only male participants [26]. Detailed information regarding study characteristics can be found in Table 2 and the Supplementary Data.

Clinical Characteristics of the Studies

Regarding the participants' clinical characteristics, 40.9% to 88.3% of the participants were taking medications for PDN. The most common medication types reported within the studies were tricyclic antidepressants (33.5%), nonsteroidal anti-inflammatory drugs (26.8%), anticonvulsants (26.1%), and opioids (13.6%) [9–12,37,40,42–45,47–50]. Approximately 60% of the included studies did not report participants' use of pain medication.

Comorbid conditions were typically reported by 80% of participants in the included studies. The most commonly reported conditions were congestive heart failure, hypertension, nephropathy, foot ulcer, dyslipidemia, retinopathy, and fibromyalgia [3,9–12,37,38,40,42–45,47,48]. Fifty percent of the studies did not report participants' comorbidities.

PDN duration was not consistently reported. However, 11 studies included reports of participants' time since PDN diagnosis [4,6,12,14,25,39,42,43,45,46,48]. From the studies providing data, the PDN duration ranged from 2.4 to 7.8 years. Forty-four percent (12/27) of the studies did not report time since diagnosis (Table 2).

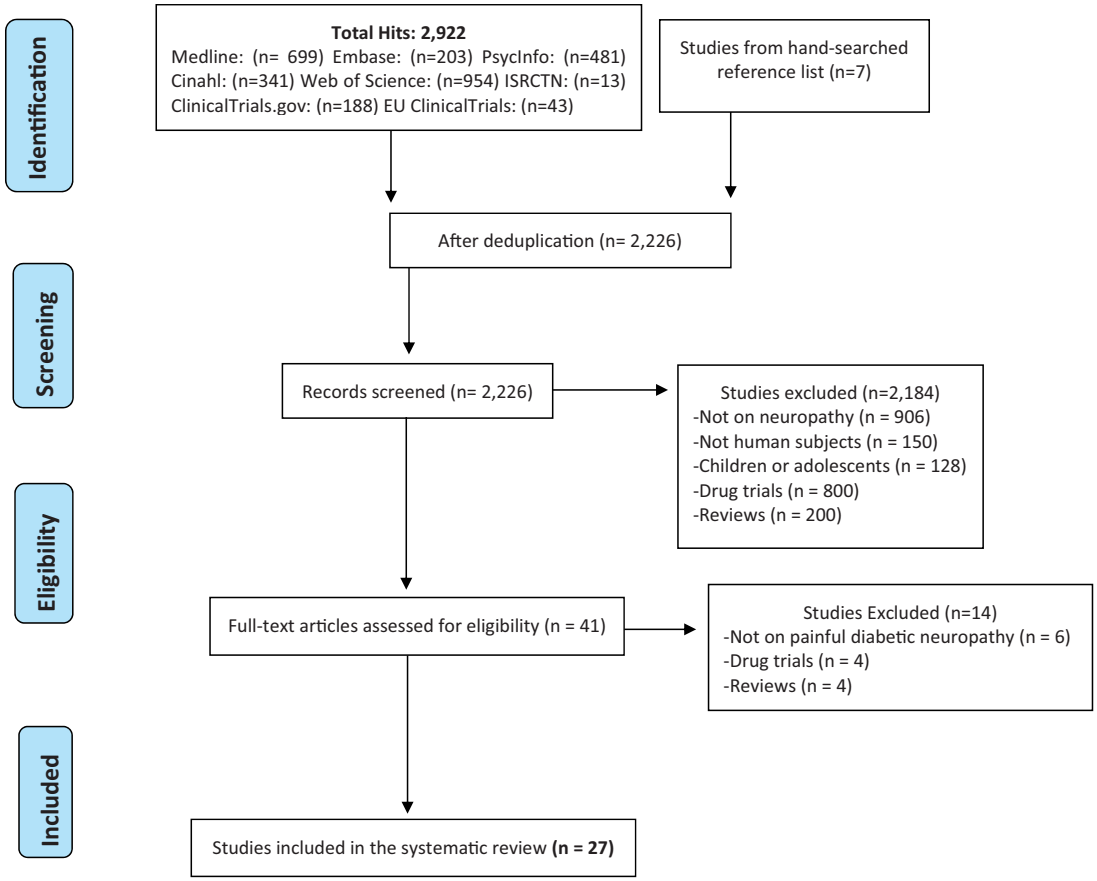

Figure 1. Flowchart: Selection process.

Treatment Outcomes

Three out of the 27 studies were RCTs of psychological treatments for patients suffering from diabetic neuropathies (Table 3) [25,26,55].

Teixeira conducted a pilot trial of mindfulness meditation for PDN [25]. The intervention group (n = 10) received training in mindfulness, and the control group (n = 10) received an "attention-placebo" treatment for four weeks. The results indicated a small effect in the mindfulness group compared with the control on QOL. It was also found that pain and poor sleep were positively correlated in the full sample.

Pfmmater conducted a study of thermal biofeedback for PDN [55]. The experimental group (n = 10) received six sessions of thermal biofeedback, and the control group (n = 11) six sessions with a therapist talking about nonstressful topics. Overall, this study did not produce any statistically significant effects between the experimental and control groups, or any other consistent associations. Notably, 11 out of the 21 participants withdrew from the study.

Lastly, Otis et al. investigated CBT for PDN (n = 11) compared with treatment as usual (TAU) (n = 8) [26]. Results indicated that participants in the CBT group improved on pain severity and interference compared with the TAU group at four-month follow-up, but there was no improvement on depressive symptoms for either group. Results suggested large between-group effects in pain severity and interference, both at post-treatment and follow-up. For depression, medium and small between-group effects were observed at post-treatment and follow-up, respectively.

Depression and Pain Outcomes

Eight cross-sectional studies [3,10,12,43,45,48–50] investigated the role of depression in relation to pain in PDN (Table 4). Two studies investigated the association between depression and pain outcomes and reported large positive effect sizes [3,41]; one reported medium [48], and another small (Table 4) [10].

One study found that depression and pain severity are positively but weakly associated. This was a cross-sectional study that did a group comparison in three regions (Asia, Latin America, Middle East) [43].

Three studies investigated depression in relation to pain, but data (means and SDs) were not available to compute the effect sizes. One study [45] reported that participants with chronic pain with neuropathic characteristics had higher depression scores than participants without neuropathic pain. One study [49] reported a significant difference in depression between participants

Table 2. Studies' general characteristics

Study	Design	Location	Recruitment Sites	Sample Size (N) per Group	Mean Age, y	Male/Female, %	PDN Duration
AL-Mahmood et al. (2018) [51]	Cross-Sectional	Malaysia	Medical Outpatient Department Clinic of Hospital (MOPD) clinic of hospital Tegku Ampaun Afzan (HTAA)	T: 90	65	60/40	–
Benbow et al. (1998) [37]	Case–control	UK	Adult hospital, diabetic clinic	T: 116, PDN: 41, DM: 38, C: 37	55.6	70/30	–
Bouhassira et al. (2013) [45]	Cross-sectional	France	Hospital departments, private practice	T: 766, PDN: 156, T1DM: 297, T2DM: 469	48.3	55/45	At least 1 y at 57.4% of the participants
Currie et al. (2006) [40]	Cross-sectional	UK	Hospital Trust	T: 1125, T1DM: 236, T2DM: 889	64	56/44	–
Dobrota et al. (2014) [3]	Cross-sectional	Croatia	Clinical hospital, university clinic for diabetes	T: 160, PDN: 80, DM: 80	62.4	52/48	–
Galer et al. (2000) [4]	Prospective cohort	USA	Advertisements, newsletters, letters to physicians	T: 105	62.9	50/50	(diagnosed at 56.7 y of age)[SC]
Geelen et al. (2016, 2017) [9, 11]	Cross-sectional	Netherlands	Informative letter to regional hospital	T: 154	65.7	62/38	–
Gore et al. (2005, 2006) [12, 41]	Cross-sectional	USA	Primary care	T: 255	61.3	49/51	6.4 y
Hoffman et al. (2009) [43]	Cross-sectional	Asia, Latin America, Middle East	Investigational centers	T: 401	57.3	38/62	2.73 y
Jacovides et al. (2014) [47]	Cross-sectional	South Africa	Public and private outpatient clinics	T: 961, PDN: 291, DM: 670	55.9	51/49	–
Kulkantrakorn et al. (2013) [6]	Cross-sectional	Thailand	Internal medicine and neurology clinic at a university hospital	T: 33	60.5	46/54	4 y
Levterova et al. (2018) [38]	Cross-sectional	Bulgaria	University hospital "Kaspela," Plovdiv	T: 37	58.3	57/43	–
Lewko et al. (2007) [53]	Case–control	Poland	Endocrinology, Diabetes and Internal Medicine clinics at the Medical University of Bialystok	T: 59, PDN: 22, DM: 37	61.3	18/32	–
Mai et al. (2015) [14]	Prospective-observational	Canada	The Canadian Neuropathic Pain Database	T: 60	57.1	57/43	4.9 y
Otis et al. (2013) [26]	Single-blind, RCT	USA	Advertisements in the Dept. of Veterans Affairs medical center	T: 19, CBT: 11, C: 8	63	100/0	–
Pfmmater (2012) [55]	RCT	USA	Databases/advertisements/posters	T: 21, BF: 10, C: 11	59.3	53/47	–
Sadosky et al. (2013) [46]	Cross-sectional	USA	Community-based physician practices	T: 112	61.1	47/53	5.9 y
Selvarajah et al. (2014) [48]	Cross-sectional	UK	Multidisciplinary outpatient service	T: 142	61.2	57/43	8.4 y
Teixeira (2010) [25]	Open label, RCT	USA	Medical practices and retirement communities	T: 20	74.6	25/75	7.76 y

(continued)

Table 2. continued

Study	Design	Location	Recruitment Sites	Sample Size (N) per Group	Mean Age, y	Male/Female, %	PDN Duration
Themistocleous et al. (2016) [49]	Cross-sectional	UK	Primary care practices, diabetes clinics, teaching hospitals, neurology clinics, advertisements	T: 191, No PDN: 80, Mild PDN: 41, Moderate/Severe PDN: 70	67.23	45/55	–
Tölle et al. (2006) [42]	Cross-sectional	France, Germany, Italy, Netherlands, Spain, UK	Community-based practices	T: 140	65.6	58/42	3–6 m: 14% 7–12 m: 22% 13–35 m: 43% ≥36 m: 61% [SC]
Van Acker et al. (2009) [44]	Cross-sectional	Belgium	Outpatients diabetes clinics	T: 1111, PDN: 478, T1DM: 344, T2DM: 767	T1DM: 45.9, T2DM: 63.6	T1DM: 54/46 T2DM: 57/43	–
Vileikyte et al. (2005) [10]	Cross-sectional	UK, USA	–	T: 484	61.86	70/30	–
Vileikyte et al. (2009) [54]	Prospective cohort	UK, USA	–	T: 495	61.24	71/29	–
Wickramasinghe et al. (2016) [50]	Cross-sectional	Sri Lanka	Diabetic clinic	T: 235	56	35/65	–
Zelman et al. (2005) [39]	Cross-sectional	USA	Primary care	T: 255	61.3	45/51	6.4 y
Zelman et al. (2006) [52]	Cross-sectional	USA	Primary care	T: 255	61.3	45/51	6.4 y

Location: At the time, the location is provided to the lowest level reported (i.e., city). Recruitment sites: Where the recruitment site is not reported, recruitment methods are. Sample size: Sample sizes are provided in groups where given by the authors. Mean age: Where the mean age is not reported, the alternative is. Only totals are reported. Male/female: Only totals are reported. Where the % doesn't add up to 100, it means that there are missing data. PDN duration: Most values are given as mean ± SD. SC: Galer provides the mean age when PDN was diagnosed for the sample; Tolle presents the duration of PDN in ranges of months and percentage of total sample falling within each range (special case).

– = not reported; BF = biofeedback; C = control group; CBT = cognitive behavioural therapy; DM = diabetes mellitus; PDN = painful diabetic neuropathy; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; T = total.

Table 3. Outcomes associated with RCTs of psychological interventions

Study	Intervention outcome/ Psychosocial variable	Comparison	Cohen's *d* (95% CI)	Correlation *r* (95% CI)	Magnitude Interpretation	*P* Value
Otis et al. (2013) [26]	CBT (post-treatment) - Depression	Between-group	0.68 (–0.19 to 1.55)	–	Medium	>0.05
	CBT (follow-up) - Depression	Between-group	0.47 (–0.39 to 1.33)	–	Small	>0.05
	CBT (post-treatment) - Pain Interference	Between-group	0.91 (0.02 to 1.8)	–	Large	>0.05
	CBT (follow-up) - Pain Interference	Between-group	0.85 (–0.03 to 1.74)	–	Large	>0.05
	CBT (post-treatment) - Pain Severity	Between-group	0.88 (–0.01 to 1.77)	–	Large	>0.05
	CBT (follow-up) - Pain Severity	Between-group	0.83 (–0.05 to 1.71)	–	Large	>0.05
Teixeira (2010) [25]	Mindfulness - QOL	Between-group	–0.16 (–1.1 to 0.78)	–	Small	>0.05
	QoL and Sleep	Whole sample	–	0.53 (0.048 to 0.813)	Large	<0.05
Pfmmater (2012) [55]	TB - Pain Severity/ Control (Session 1)	Whole sample	–	–0.42 (–0.721 to 0.014)	Large	>0.05
	TB - Pain Severity/ Control (Session 4)	Whole sample	–	–0.62 (–0.830 to –0.257)	Large	<0.05
	TB - Pain Severity/ Control (Session 6)	Whole sample	–	–0.65 (–0.845 to – 0.303)	Large	<0.01

– = not applicable; CI = confidence interval; Correlation *r* = correlation coefficient; QOL = Quality Of Life; RCT = randomized controlled trial; TB: thermal biofeedback.

suffering from moderate/severe neuropathic pain and participants with no/mild neuropathic pain; one study [50] found that depression among DPN participants was higher than in those without DPN.

Anxiety and Pain Outcomes

Five cross-sectional studies investigated anxiety in relation to pain severity and pain interference (Table 4) [12,43,45,48,49]. One study [48] investigated the association between anxiety and pain in patients with confirmed PDN differing in pain intensity and found a medium effect size, and one study [12] found a large effect size between patients with mild and severe PDN. However, contrary to this, another study [43] demonstrated an overall weak and negative effect size between anxiety and pain severity. This appeared to be due to unexpectedly high anxiety reported in some of their low-pain participants; otherwise the trend was for those reporting severe pain to also report higher anxiety.

Two further studies also investigated anxiety in relation to pain outcomes, but data were not available to compute the effect sizes. One study [45] reported that participants with chronic pain and neuropathic characteristics had higher anxiety scores compared with those without neuropathic pain, and one study [49] investigated pain-related anxiety and found that participants with moderate/severe neuropathy reported significantly higher scores compared with participants with mild/no neuropathy.

Sleep and Pain Outcomes

Seven cross-sectional studies examined the association between sleep and pain in PDN (Table 4) [12,43,45,47,48,50,52]. Two studies reported large effect sizes. In the first study, participants were grouped according to pain severity, and a strong association between pain severity and sleep impairment was found [12]. These findings were supported by a more recent study that reported a large effect between pain and sleep interference [47]. One study found a medium effect when comparing individuals with PDN and the general US population, whereas another study [43] found a small effect between sleep and pain.

Three studies also investigated the relation between sleep disturbances and pain, but data were not available to compute the effect sizes. One study [45] reported that participants with neuropathic pain had more sleep disturbance than participants without neuropathic pain. One study [49] showed significantly greater sleep impairment in participants with moderate/severe neuropathy relative to those with mild/no neuropathy. One study [50] concluded that 43.7% of the total sample had sleep disturbances due to their neuropathic symptoms.

Catastrophic Thinking and Pain Outcomes

Two cross-sectional studies [48,49] and one prospective cohort [14] examined pain catastrophizing (Table 4). It is worth noting that there are three dimensions within catastrophizing: rumination, magnification, and helplessness [56]. One study showed that helplessness and rumination are strongly associated with the experience of pain in

Table 4. Associations between depression, anxiety, QOL, sleep, and pain outcomes for studies reporting sufficient data to compute effect sizes

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI)or β if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Depression										
Dobrota et al. (2014) [3]	Between-group	Cross-sectional	Univariate	Presence of Pain (VAS, LANSS)	BDI	1.07 (0.73 to 1.4)	–	Large	<0.001	–
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	HADS-D	0.99 (0.66 to 1.32)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-D	0.02 (–0.51 to 0.55)	–	Weak	N/R	1/3
Selvarajah et al. (2014) [48]	Within-group	Cross-sectional	Multivariate (reported *r* is univariate)	Pain Intensity (NPS)	HADS-D	–	0.33 (0.161 to 0.480)	Medium	<0.01	–
Vileikyte et al. (2005) [10]	Within-group	Cross-sectional	Multivariate	Pain Severity (NeuroQoL)	HADS-D	–	Pain predicting depression $\beta = -0.27$ (0.185 to 0.351)	Small	<0.001	–
Vileikyte et al. (2009) [54]	Baseline/follow-up	Longitudinal (change in pain predicting follow-up depression)	Multivariate	Pain Severity (NeuroQoL)	HADS-D	–	Pain intensity predicting depression $\beta =$ –0.04 (–0.146 to 0.067) Pain disability predicting depression β =0.16 (0.054 to 0.262)	Weak	< 0.05 <0.01	–
Anxiety										
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	HADS-A	0.97 (0.64 to 1.29)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-A	–0.15 (–0.68 to 0.18)	–	Weak	N/R	2/3
Selvarajah et al. (2014) [48]	Within-group	Cross-sectional	Multivariate (reported *r* is from univariate analysis)	Pain Intensity (NPS)	HADS-A	–	0.45 (0.295 to 0.582)	Medium	<0.01	–
Pain/Diabetes-Related Fears										
Geelen et al. (2017) [11]	Within-group	Cross-sectional	Multivariate	Pain Severity and Disability (VAS, PDI)	HFS, TSK, PASS-20, FES-I, TSF, BFNE	–	0.78† (0.695 to 0.839) 0.73† (0.635 to 0.796)	Large	N/R	3/11

(continued)

Table 4. continued

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI)or *β* if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Quality of Life										
Dobrota et al. (2014) [3]	Between-group	Cross-sectional	Univariate	Pain Presence (VAS, LANSS)	SF-36	–1.12 (–1.45 to –0.78)	–	Large	<0.001	–
Geelen et al. (2017) [11]	Within-group	Cross-sectional	Multivariate (reported *r* is from univariate analysis)	Pain Severity and Disability (VAS, PDI)	QOL-DN	–	0.49 (0.348 to 0.610)	Large	<0.01	–
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	EQ-5D	–1.96 (–2.34 to –1.58)	–	Large	<0.01	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	EQ-5D VAS	–0.12 (–0.64 to 0.41)	–	Small	<0.05	–
Jacovides et al. (2014) [47]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	EQ-5D	–0.95 (–1.1 to –0.81)	–	Large	N/R	–
Levterova et al. (2018) [38]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	SF-36v2	–0.5 (–2.13 to 1.13)	–	Medium	N/R	4/8
Lewko et al. (2007) [53]	Within-group	Cross-sectional case–control	Univariate	Presence of diabetic peripheral neuropathy (assessment of neuropathy unclear)	SF-36v2, AIS	–	0.48 (0.256 to 0.656)	Large	<0.05	–
Sadosky et al. (2013) [46]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI-SF)	SF-12v2	–1.49 (–2.11 to – 0.86)	–	Large	<0.001	–
Zelman et al. (2005) [39]	Between-group	Cross-sectional	Univariate	Severity (BPI, VRS)	EQ-5D	–15.69 (–17.44 to – 13.89)	–	Large	<0.001	–
Zelman et al. (2005) [39]	Between-group	Cross-sectional	Univariate	Severity (BPI, VRS)	SF-12v2	–1.09 (–1.42 to 0.76)	–	Large	<0.001	–
Sleep										
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	MOS	1.46 (1.11 to 1.8)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	MOS	0.31 (–0.22 to 0.84)	–	Small	<0.05	–
Jacovides et al. (2014) [47]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	DSIS	1.12 (0.98 to 1.27)	–	Large	N/R	–

(continued)

Table 4. continued

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI)or *β* if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Zelman et al. (2006) [52]	Between-group (Cohen's *d*)/ within-group (*β*)	Cross-sectional	Multivariate	Severity (BPI-DN)	MOS	0.47 (0.33 to 0.61)	Pain predicting sleep problems: $\beta = 0.30$ (0.184 to 0.408)	Medium	<0.001	–

Only groups of absolute interest are reported in this table. *P* values: In instances where an effect size is calculated for a number of different subscales with different *P* values, a proportion of significance is reported as the number of comparisons of the total comparisons that reported a significant difference. For papers that had three or more groups based on pain severity, a comparison was undertaken between the groups with the least severe symptoms and the most severe symptoms.

– = not applicable; AIS = Acceptance of Illness Scale; BDI = Beck Depression Inventory; BFNE = Brief Fear of Negative Evaluation Scale; CI = confidence interval; DN4 = Douleur Neuropathique 4; DSIS = Daily Sleep Interference Scale; EQ-5D = EuroQOL; FES-I = Falls Efficacy Scale-International; HADS = Hospital Anxiety and Depression scale; HFS = Hypoglycaemia Fear Survey; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; mBPI = modified Brief Pain Inventory; MOS = Medical Outcomes Study–Sleep scale; MPQ = McGill Pain Questionnaire; NDS = Neuropathy Disability Score; NPS = Neuropathic Pain Scale; NeuroQol = Neuropathy and Foot Ulcer–specific Quality of Life Instrument; N/R = not reported; PASS-20 = Pain Anxiety Symptom Scale; PDI = Pain Disability Index; QOL-DN = Norfolk Quality of Life Questionnaire; *r* = correlation coefficient effect size or otherwise explained in the comments; SF-12v2 = Short Form Health Survey Version 2; SF-36 = Short Form Health Survey; TSF = Tampa Scale of Fear of Fatigue; TSK = Tampa Scale of Kinesiophobia; VAS = visual analog scale; VRS = verbal rating scale.

*When both univariate and multivariate analyses were reported in the same paper, we extracted univariate data, given differences in multivariate models across studies that limit their interpretability. For cases in which only a multivariate model was reported, those data were extracted.

†The effect size reported was not originally calculated by the author of the study but by the first author of this systematic review.

diabetic neuropathy [48]. In another study, participants with moderate/severe PDN scored significantly higher on catastrophizing than those with no/mild PDN [49]. Finally, in one study catastrophizing did not predict outcome, possibly because the sample size was relatively small (n = 60) [14]. None of the studies described provided adequate data to compute effect sizes.

Other Psychosocial Variables and Pain Outcomes

One study investigated the association between acceptance of illness and QOL, finding a large effect size (Table 4) [53]. One study, of prospective cohort design, investigated depression as an outcome variable at 18 months and found that this was predicted by increased pain from baseline to nine months [54]. Another study investigated the association between acceptance of pain and anxiety and depression. The results demonstrated that lower acceptance scores were strongly associated with higher levels of depressive symptoms and anxiety. However, the data were insufficient to calculate an effect size [48].

One study investigated the role of a number of different fears, including fear of movement (kinesiophobia), fear of fatigue, fear of hypoglycemia, fear of pain, fear of falling, and fear of negative evaluation in relation to QOL. This study found medium to large correlations between QoL and these fear-related variables (range: $r = 0.39$–0.71). This study also found medium to large correlations between fear-related variables and disability (range: $r = 0.28$–0.66) [9].

Pain and Quality of Life

Most of the studies included in this review (20/27) aimed to capture the perceived impact of PDN on QOL (Table 4). These studies were mainly cross-sectional and mostly concluded that pain is associated with reduced QOL. The factors framed as predictors of QOL, or independent variables, include presence of pain, pain intensity, and pain severity. However, it is also possible to conceive QOL as a potential contributory psychosocial factor in relation to other pain-related outcomes. Indeed, common QOL measures often incorporate items assessing psychological functioning, such as depression and anxiety, as well as usual daily activities (EQ-5D-5L) [57].

Eight studies provided sufficient data to calculate effect sizes, reflecting mostly large associations between QOL and pain. Six studies found large effects in comparisons between groups with severe vs mild PDN [11,39,45,46]. One study found a medium and negative effect between pain severity and QOL [38]. And another study found a small effect between pain severity and QOL [43]. Twelve additional studies reported negative associations between QOL and pain but did not provide enough information to calculate effect sizes [4,6,14,37,39,42,44,45,48–51].

Table 5. Methodological quality of observational studies [30]

Study	Component Score: A	Component Score: B	Component Score: C	Component Score: D	Overall Score
AL-Mahmood et al. (2018) [51]	5	2	3	2	92.3% (12/13)
Benbow et al. (1998) [37]	4	1	0	1	46.2% (6/13)
Bouhassira et al. (2013) [45]	5	2	3	2	92.3% (12/13)
Currie et al. (2006) [40]	6	0	3	2	84.7% (11/13)
Dobrota et al. (2014) [3]	5	2	3	2	92.3% (12/13)
Galer et al. (2000) [4]	5	2	2	1	71.4% (10/14)
Geelen et al. (2016; 2017) [9, 11]	4	1	3	0	66.7% (8/12)
Gore et al. (2005; 2006) [12, 41]	6	0	2	0	57.1% (8/14)
Hoffman et al. (2009) [43]	6	0	3	2	84.7% (11/13)
Jacovides et al. (2014) [47]	5	0	2	0	50% (7/14)
Kulkantrakorn et al. (2013) [6]	4	0	0	1	38.5% (5/13)
Levterova et al. (2018) [38]	5	2	3	2	92.3% (12/13)
Lewko et al. (2007) [53]	3	0	1	1	38.5% (5/13)
Mai et al. (2015) [14]	4	0	2	2	57.1% (8/14)
Sadosky et al. (2013) [26]	5	0	3	0	61.5% (8/13)
Selvarajah et al. (2014) [48]	5	1	3	1	77% (10/13)
Themistocleous et al. (2016) [49]	5	0	3	0	61.5% (8/13)
Tölle et al. (2006) [42]	5	0	1	0	46.2% (6/13)
Van Acker et al. (2009) [44]	5	2	3	2	92.3% (12/13)
Vileikyte et al. (2009) [54]	5	1	3	2	78.6% (11/14)
Vileikyte et al. (2005) [10]	5	1	3	2	84.7% (11/13)
Wickramasinghe et al. (2016) [50]	5	1	3	1	77% (10/13)
Zelman et al. (2005) [39]	6	0	2	0	57.1% (8/14)
Zelman et al. (2006) [52]	6	0	2	0	57.1% (8/14)

Component Score A: Reporting, score range 0–7; Component Score B: External Validity, score range 0–2; Component Score C: Internal Validity–Bias, score range 0–3; Component Score D: Internal Validity–Confounding (selection bias), score range 0–2.

Table 6. Methodological quality of the RCTs (Cochrane risk of bias assessment tool)

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding (Performance and Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Otis et al. (2013) [26]	+	?	+	+	+	?
Pfmmater (2012) [55]	?	−	?	−	−	−
Teixeira (2010) [25]	+	?	?	?	−	−

\+ Low risk of bias.

? Unclear risk of bias. High risk of bias.

− RCT = randomized controlled trial.

Quality Assessment

The inter-rater reliability (IRR) in assessing the quality of the 27 included studies was good, at 87.5% agreement between the two raters. There were some minor disagreements, mainly regarding the internal validity of the studies, but these were solved without consulting another member of the research team.

Overall, the methodological quality score, using the Downs and Black quality assessment tool [30], was high in 14 studies [3,4,9,10,12,38,40,43–45,48,50,51,54], medium in four studies [14,39,46,49], and low in five studies [6,37,42,47,53].

The three RCTs were assessed with the Cochrane risk of bias tool, which showed that one study had low risk of bias

Figure 2. Quality of randomized controlled trials: Cochrane's risk of bias assessment tool.

[26], one study had unclear risk of bias [25], and one study had high risk of bias [55]. The studies were more likely to have low risk of bias for random sequence generation and high risk of bias for potential for selective reporting and "other" bias. More details on the quality assessment of the studies can be found in Tables 5 and 6 and Figure 2.

Discussion

This systematic review was specifically focused on evidence for the role of psychosocial factors and related treatments in relation to outcomes in PDN. The relevant literature was heterogeneous and included few randomized controlled trial designs. The search revealed 27 studies (29 papers). These provide limited evidence of mixed quality for benefits from psychological interventions and some high-quality evidence for associations between depression, anxiety, sleep, and QOL, typically in relation to pain in PDN. There was less evidence for other outcomes, such as physical, social, or emotional functioning. The results of this review identify a need for the further investigation of psychosocial processes in PDN, in relation to a wider set of clinical outcomes guided by a clear theoretical model and for theory-driven treatment development evaluated in larger RCTs.

The identification of only three small RCTs in the review limits the conclusions that can be drawn about the potential efficacy of psychosocial treatment for PDN. These were very small in size, included three distinctly different types of treatment, and produced inconsistent results. The limited number of RCTs of psychological treatments for PDN contrasts with the larger number of reasonably higher-quality RCTs for chronic pain in general, estimated at 35 RCTs [22], and in conditions such as fibromyalgia, for which there are currently around 29 RCTs of CBT [24]. Notably, the lack of trials identified in the current review is consistent with a review of RCTs of psychological treatments for neuropathic pain (not restricted to PDN) [29]. Unfortunately, the current evidence from these studies is not sufficient to support specific recommendations regarding effective psychological treatment for PDN.

The current results provide limited clues regarding the types of psychosocial factors that might influence outcome in PDN and almost exclusively include psychological factors and not social ones. With the exception of fear of negative evaluation, a clear social factor [9], and a study of changing social perception [54], none of the commonly studied social factors (e.g., social support, spousal responses) often found to relate to chronic pain were featured in the available evidence here.

This review found evidence of a mostly consistent positive association between depression and the presence, intensity, or severity of pain in people with PDN, with effects ranging from small to large. This is consistent with a large body of findings in the wider chronic pain literature that consistently links depression and chronic pain outcomes related to depressive symptoms with diabetes [58–62]. Within the current review, the majority of the studies were cross-sectional, which precludes statements about the direction of association between these variables. Drawing on the wider literature, it is likely that there is a bi-directional association between pain and depression. Current results are also consistent with results from a meta-analysis of 27 studies investigating depression in diabetic patients that also showed a significant correlation between depression and complications of diabetes [63].

Another key finding arising from this review was the positive association ranging from medium to large effects between anxiety and pain severity or intensity. Only one of five studies found an inconsistent effect. This overall result is consistent with the broader chronic pain literature, where anxiety is found to either contribute to, or reflect effects of, poor functioning and health [64]. Anxiety and depression are often highly correlated when measured simultaneously in the same sample, and the degree to which the present findings for these variables reflect significantly distinct processes and targets for change is unclear [65,66].

Some of the most frequently studied variables in the context of chronic general or musculoskeletal pain include catastrophizing and acceptance [66,67]. Here, in contrast, only three studies included catastrophizing, and two studies examined some form of acceptance. Overall, these studies did not provide a clear basis for inferring the size of the association or the potential utility of either of these variables for guiding treatment development for PDN. Only one study (two papers) investigated the relationship between pain-related fears and pain. This study showed a large positive association between various fears, including fears of pain, hyperglycemia, falling, and fatigue with increased neuropathic disability, reduced QOL, and pain intensity. This was, as far as we are aware, the first study aiming to specify pain-related fears in a PDN population. That there is only one study of fear in relation to PDN may appear surprising, as the Fear-Avoidance Model is otherwise a widely applied and

productive model of disability in chronic pain in general [68–70]. All of these anxiety-related variables overlap to a degree conceptually and in their measurement. This again can point to the need for conceptual clarity in the choice of variables we investigate.

Evidence of medium to large associations was also found between pain and sleep disruption in the present systematic review, based on three studies. This may be a potentially useful relation, as poor sleep appears common in individuals with neuropathic pain in general and with PDN in particular [52,71]. Poor sleep in the context of chronic pain appears potentially modifiable [72,73] and is a target that could guide treatment development.

The majority of the studies reviewed included QOL. Predominantly, these studies focused on the impact of disease, designed to document the impact of PDN on QOL. Most studies found large associations between pain and poor QOL. This is not surprising, and in fact both direct adverse impacts of PDN on QOL and indirect impacts from depression and anxiety in the context of PDN are well documented [74–77]. The reason that, in a sense, we have turned QOL around and conceived it as a potential influence on other outcomes in PDN, is that we feel that components of QOL, particularly the more behavioral components, such as social and physical activities, are essentially directly modifiable. We know from general chronic pain studies that it is possible to take a direct approach to improving daily activities, for example, and achieve both improvements in these activities and in such outcomes as pain, depression, and other symptoms at the same time [78].

It is notable that there were three additional studies of biofeedback identified during the literature search [79–81]. However, the reported treatment outcomes were physiological, for example, temperature reduction, rather than reports of pain intensity, pain-related functioning, or psychological distress, so these studies were excluded from this systematic review. Thus, future studies exploring biofeedback in this context might benefit from including measures of pain and functioning as outcomes.

Overall, setting aside QOL as a direct treatment target, the available evidence reveals that few modifiable psychosocial factors have been studied in the literature of PDN. Also, when they are studied, they are generally examined in relation to pain as an outcome and not in relation to a wider range of outcomes, such as physical, social, or emotional functioning. In this systematic review, variables like anxiety, depression, and QOL are treated as both outcomes and correlates of outcome. Few studies have examined correlations with these variables, except for pain, pain severity, pain interference, and acceptance of pain. Most of the studies include anxiety and depression as potential independent variables. Only six studies, all cross-sectional, have examined such otherwise frequently studied variables as catastrophizing, fear, or acceptance. What seems to be entirely missing are studies of conventional variables such as beliefs or coping [29] or other facets of psychological flexibility [66]. Hence, the results, as they stand, do not identify specific psychosocial factors or treatment methods that ought to be targeted or applied in PDN, nor do they appear to provide clear guidance for treatment development, other than to highlight the potential role of emotional functioning, sleep, and perhaps a direct approach to daily functioning. The very limited number of studies of psychological treatments or psychosocial factors in PDN compared with other chronic pain conditions, particularly in the context of the clear treatment needs in PDN, raises questions as to why this is the case and what might be the barriers to psychological studies in this population.

Several limitations of this systematic review need to be considered. Our defined population was explicitly adults; therefore, the results of this review cannot be generalized to children and adolescents. We used broad search terms for PDN, psychosocial factors, and psychological interventions to identify all the eligible studies; however, given the broad nature of the search, it is possible that we may have missed studies. We calculated effect sizes based on the given means and SDs, but not all studies provided sufficient data for effect sizes. We collapsed multiple between-group analyses into dichotomous comparisons to enable comparison across studies to minimize paired comparisons; however, this may have eliminated a more subtle understanding of the association between psychosocial factors an pain outcomes.

Future research is encouraged to examine a wider array of theoretically based psychosocial factors than currently done and to more deeply pursue the utility of such current theoretical models as the Fear-Avoidance Model and the Psychological Flexibility Model. Naturally, studies from either of these models can incorporate the role of emotional functioning, and ought to do so, as this domain is the one that is most clearly highlighted here as relevant, and it appears that the Psychological Flexibility Model can address sleep [72,82].

There appears to be a clear potential for nonpharmacological, particularly psychological, treatments for PDN. The current review does not, however, clarify specific psychological processes to target, and certainly not comprehensively. The absence of fully powered, high-quality studies of psychological treatment for PDN found here is notable. Future trials may explore questions around nonparticipation and dropout and ways to enhance access and acceptability in addition to the core questions of effectiveness. It is recommended that future treatments aim not only to treat pain but also to improve other aspects of the condition, such as emotional and physical functioning, and participation in life in general. The challenge here then seems to be the identification of a model of treatment processes with the potential to produce these general results.

Authors' Contributions

KK, the first author, responsible for the work as a whole, contributed to the design of the project, searched the selected databases, screened the titles, selected the eligible articles, did the data extraction and methodological quality check, interpreted the results, and produced the first draft of the manuscript. LM contributed to the conception and research plan, to the final selection of the articles, critically revised the manuscript, and approved the final version. KW contributed to the design of the study, contributed to the final selection of the articles, critically evaluated the manuscript, and approved the final version. WS acted as the second reviewer of the research and contributed to the data extraction and methodological quality check. SK acted as a third reviewer and contributed to the search of the databases, screening of the titles and abstracts, selection of the eligible articles, data extraction, and quality assessment. All authors contributed to critically revising the manuscript and approved the final submitted version. None of the authors declares a conflict of interest or any financial or other relationship that might lead to any conflict.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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