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## Systematic review

Charlotte C.M. van Laake-Geelen\*, Rob J.E.M. Smeets, Suzan P.A.B. Quadflieg, Jos Kleijnen and Jeanine A. Verbunt

# The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: a systematic review

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### Abstract

**Background and aims:** Approximately 25% of patients with diabetes mellitus type 2 (DMII) develop painful diabetic neuropathy (PDN). PDN is known to affect both mental and physical wellbeing, resulting in anxiety, depression, low quality of life and physical disability. Pharmacological treatment of PDN aims at pain relief and is often ineffective and/or has many side effects. Rehabilitation treatment modalities that are designed to help the patient deal with PDN related complaints, are mostly focussed on either physical (e.g. exercise therapy) or psychological aspects (e.g. cognitive behavioural therapy, CBT). There is emerging evidence that PDN can be approached from a biopsychosocial perspective, in which physical and psychosocial aspects are integrated. From this biopsychosocial approach it is plausible that integrated treatment modalities such as acceptance commitment therapy (ACT) or exposure *in vivo* (EXP) could

be effective in patients with PDN. The objective of this review was to provide an overview of the current evidence on the effects of rehabilitation treatments that combine exercise therapies with psychological therapies in order to improve physical activity (PA) and quality of life (QoL) in patients with PDN.

**Methods:** Systematic review of the current literature. EMBASE, MEDLINE, Medline In-Process citations and e-Pubs ahead-of-print, Pedro, Web of Science, PsycINFO, CENTRAL, PubMed and Google Scholar were searched. All studies on interventions combining exercise therapy with psychological interventions in patients with PDN, aged >18 years, were included. Outcome measures were PA, QoL. **Results:** The search resulted in 1603 records after removing duplicates. After screening on titles and abstracts, 100 records remained. From these, not one study reported on interventions that combined exercise therapy with psychological interventions. Through a secondary hand search, a total of three reviews were identified that described a total of five studies regarding either physical or psychological interventions in patients with PDN. These studies reported moderate effects of (1) mindfulness meditation on QoL, (2) CBT on pain severity, (3) mindfulness-based stress reduction intervention on function, health-related QoL, pain catastrophizing and depression, (4) aerobic exercise on QoL and (5) Tai Chi on glucose control, balance, neuropathic symptoms, and some dimensions of QoL in patients with PDN. All studies were of a moderate quality, and results should be interpreted with caution.

**Conclusions:** Based on increasing knowledge in the domain of chronic pain, it could be assumed that integrated rehabilitation treatments for patients with PDN are beneficial. There is no literature to support this and more research should be done on integrated biopsychosocial interventions in patients with PDN.

**Implications:** This empty review highlights the importance that more research should be done on integrated biopsychosocial interventions in patients with PDN. Currently, our research group is performing a study on the effects of EXP treatment in patients with PDN.

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**Keywords:** painful diabetic neuropathy; review; rehabilitation intervention; exercise; psychological coping; quality of life.

## 1 Introduction

Approximately 25% of patients with diabetes mellitus type 2 (DMII) develop painful diabetic neuropathy (PDN) [1], characterised by pain, paraesthesia and sensory loss [2–4]. Currently, the treatment of PDN is mainly pharmacological [5]. Side effects occur and/or the effects are often limited [6].

PDN can have far-reaching consequences in daily life [7, 8]. It can lead to sensory loss, the development of pressure ulcers (PU's), balance impairments, an altered gait with potentially an increased risk of falling [9, 10]. This leads to a more sedentary lifestyle [7] with impaired levels of physical activity [11–13], less engagement in social activities, dependency on others, social isolation, depression and as a result decreased quality of life [14–17]. Depression in turn, can amplify diabetic complications related to suboptimal glycaemic control [18]. Furthermore, patients with PDN can suffer from anxiety and fears, such as fear of pain, fear of falling, fear of disturbed glucose regulation, leading to persistence of the consequences of PDN [12, 19–21]. It seems likely that the overall QoL of patients with PDN can be improved when comorbid anxiety and negative emotions are adequately screened, diagnosed and treated [12, 19, 20, 22].

Increasing physical activity in patients with DM is known to have favourable effects on diabetes-related outcomes [23, 24], such as improved blood sugar control, decreased body fat, and an improved body reaction to insulin therapy [25, 26]. Aerobic exercise has shown to improve the QoL in patients with PDN [27]. Unfortunately, dropout rates in physical exercise programmes are high (up to 45%), due to the occurrence of PU's, overuse injuries and lack of motivation [28, 29]. Therefore, an interdisciplinary therapeutic approach that targets physical and emotional factors has been recommended [16, 17, 19, 30, 31].

Since patients with PDN frequently share the comorbidities of depression and fear (and as a consequence disability) with other chronic pain populations [12, 22], it seems apparent to integrate the knowledge obtained in the treatment populations with other pain syndromes into the field of PDN. Within the fear-avoidance-model (FAM) [32], chronic pain is approached from a biopsychosocial perspective. The model states that negative exaggerated or irrational thoughts (catastrophizing) and fears can give rise to avoidance behaviour, which can lead to significant

health consequences such as disuse, disability and depression, further fuelling the vicious cycle of chronic disabling pain [33, 34]. In line with the FAM model, one could hypothesise that a physical intervention or psychological treatment alone will not suffice to restore QoL and participation in daily life, as these treatment address only one (“bio” or “psycho”) component of the model. Research has shown that multidisciplinary rehabilitation interventions that target factors from all biopsychosocial domains, administered by healthcare professionals from different backgrounds, are more effective than physical or psychological interventions alone [35].

The aim of this study was to provide an up-to-date overview of the current evidence on the effects of rehabilitation interventions that combine exercise therapies with psychological therapies in order to improve physical activity (PA) and quality of life (QoL) in patients with PDN.

## 2 Methods

The review protocol was registered with PROSPERO (CRD42018081664).

### 2.1 Eligibility criteria

Studies on interventions combining exercise therapies with psychological therapies in patients with a clear diagnosis of PDN (DM I and II), aged >18 years were included in this systematic review. Primary outcome measures were physical activity and QoL.

### 2.2 Search

Ovid's EMBASE, MEDLINE, Medline In-Process citations and e-Pubs ahead-of-print and PsycINFO and in Pedro, Web of Science, CENTRAL in Wiley and PubMed (for the newest publications), were searched. Google Scholar was searched for on-going research. A full overview of search terms in Embase is provided in Supplementary data 1. Subject headings and truncations were modified per database.

### 2.3 Selection of studies

Primarily, randomised controlled trials (RCT's) were included. In case no RCT's were available other study types were included, in order of preference: cohort studies, case

control, cross over studies, observational studies, single case studies, cross-sectional study and experimental studies. Study selection was performed by two reviewers (CvL and SQ). First, both reviewers selected articles for relevance based on title and abstract. Of all articles that appeared to be relevant, the full text articles were retrieved. Of all duplicates, just one was included. The reference lists of all retrieved articles were hand searched for additional references. Consensus meetings were held to resolve disagreements. If disagreement persisted a third reviewer could be consulted (RS).

## 2.4 Quality assessment

The Cochrane Risk of Bias tool for randomised controlled trials and ROBINS-I for non-randomised studies and interventions was used [36]. The individual results were compared by two reviewers (CvL and SQ) and disagreements were resolved through discussion when needed. A third reviewer (RS) was available if consensus could not be reached.

## 2.5 Data extraction and reporting of data

DATA extraction was performed by two reviewers (CvL and SQ) independently. Due to the expected heterogeneity of the concepts of PA and QoL, a narrative summary of all included studies was given. Information on study characteristics (number of participants, gender, age, type of DM, duration

of PDN), descriptions of the intervention and control arm, duration of follow up and the data on the outcome measures PA and QoL was extracted from the selected articles.

## 3 Results

The search resulted in 1603 records after having removed 23 duplicates. After screening on title and abstract, 100 records remained for full text reading and 1503 articles were excluded. The reasons for exclusion were related to: wrong diagnosis ( $n=1029$ , e.g. chemotherapy induced peripheral neuropathy, non-specific chronic pain, diabetic neuropathy without pain), study design ( $n=224$ , e.g. descriptive reviews), type of intervention ( $n=180$ , e.g. pharmacological), different outcome measures ( $n=47$ , e.g. improvement of balance disorders and uncertain gait). From the 100 remaining potentially relevant studies, 96 full texts could be retrieved. After full text reading, additional articles were excluded because of not fulfilling the criteria as set on diagnosis ( $n=44$ ), study design ( $n=28$ ), type of intervention ( $n=24$ ). By contacting the authors of the non-retrievable studies, we obtained 1 additional study, which was excluded since this article did not fulfil the criteria set for intervention. At the end of our study selection, not one study that answered our research question could be included. Therefore, no quality assessment was performed. Figure 1 illustrates the study selection.

Through hand search of the 100 selected articles, we identified a total of eight articles that reported on the

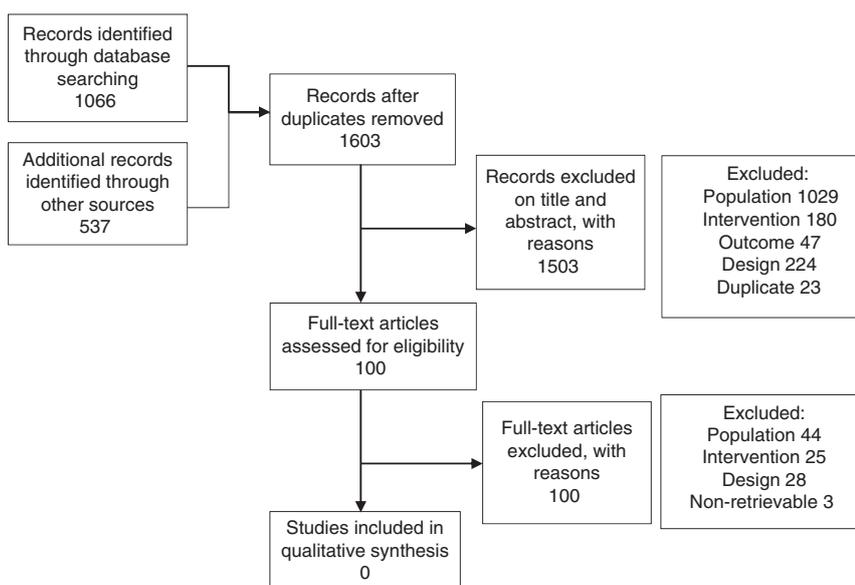


Fig. 1: Flowchart of study selection.

effectiveness of either a physical or a psychological intervention in patients with PDN (5 RCT's, three reviews). The full overview of these articles with its study characteristics and outcomes is presented in Supplementary data 2.

In short, we identified two studies that investigated exercise based treatments for patients with PDN. A RCT by Dixit et al. [37] showed the positive effects of aerobic exercise compared to usual care, with statistically significant improvement on the following domains of the quality of life in neurological disorders (NeuroQoL) scale: QoL total score, pain subscale, reduced feeling/sensation, sensory motor symptoms and restrictions in daily life activities subscales [37, 38]. A pretest–posttest quasi-experimental design by Ahn and Song [39], reported the positive effect of Tai Chi on glucose control, balance, neuropathic symptoms, and the following dimensions of QoL [Short Form 36 Health Survey (SF36)]: bodily pain subscale, physical functioning, role physical, role emotional, social function in diabetic patients with neuropathy compared to no intervention [39]. We identified 3 RCT's that focused on psychologically based treatments. Teixeira investigated the effect of mindfulness meditation on QoL in patients with PDN compared to care as usual and found no effects symptom related quality of life, measured with NeuroQoL and Neuropathic pain scale (NPS) [40]. Otis et al. reported that pain severity and pain interference, measured with the West Haven Yale Multidimensional Pain Inventory (WHYMPI) decreased in the CBT group compared to treatment as usual [41]. Nathan et al. showed that a mindfulness-based stress reduction resulted in significant improvement in function, better health-related quality of life, and reduced pain catastrophizing, and depression compared to those receiving usual care [42]. Results of all studies should be interpreted with caution, as they were of moderate quality.

In 2015, a review was published by Davies et al. [43], which described the studies by Ahn and Song [39], Teixeira [40], Otis et al. [41] and Dixit et al. [37]. Reviews by Rosenberg and Watson [5] and Castelnovo et al. [44], discussed the work of Otis et al. [41].

## 4 Discussion

The aim of this systematic review was to provide an overview of the current literature regarding the effectiveness of treatments that combine exercise therapy with psychological therapy for the improvement of physical activity and QoL of patients with PDN. Although studies in the domain of chronic pain suggest that a multidisciplinary

therapeutic approach based on the biopsychosocial model could be effective in improving physical activity and QoL in patients with PDN, this systematic review of the literature revealed no studies that described or tested treatments that combine exercise therapy with psychological treatment modalities. This so called empty review shows that the biopsychosocial approach in the treatment low levels of physical activity and QoL in patients with PDN is a rather unexplored topic and that studies on the effectiveness of multidisciplinary treatments are needed.

Consequences of PDN can be physical (sensory loss, weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities) [13]. PDN has shown to be associated with catastrophic thinking, increased disability, diminished quality of life, depression and anxiety [12, 22, 45, 46]. A recent study by our group identified specific fears related to diabetes and pain that showed to be important predictors of physical and social activities; e.g. fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation [12]. Negative feelings can enhance pain experience and amplify the risk for diabetic complications, again leading to less physical activity and diminished health related quality of life (QoL), creating a vicious cycle [12, 17, 18, 47]. Research has shown that multidisciplinary rehabilitation interventions that target all factors from the different biopsychosocial domains, administered by healthcare professionals from different backgrounds, are more effective than physical or psychological interventions alone [35].

In this review, we identified five studies that reported on the effectiveness of treatments for PDN that are either psychological treatments or exercise interventions alone [37, 39–42]. The results regarding the effectiveness of psychological treatments are not conclusive. A positive, however not statistically significant effect of mindfulness meditation on QoL was found in patients with PDN compared to care as usual [40]. CBT seems to have positive effects on pain severity [41]. A mindfulness-based stress reduction intervention showed improvement in function, better health-related QoL, and reduced pain catastrophizing and depression [42]. We also found limited evidence for exercise-based treatments. Aerobic exercise showed to have positive effects on peripheral neuropathy symptoms [37]. Beneficial effects of Tai Chi on glucose control, balance, neuropathic symptoms, and some dimensions of QoL were found [39]. However, none of these studies supports or rejects a multidisciplinary and/or biopsychosocial approach for PDN.

A combined physical and cognitive behavioural treatment modality with a potential positive effect is exposure *in vivo* (EXP) [48–51]. EXP aims to decrease pain-related disability by specifically targeting irrational thoughts and fears about pain and its consequences [32, 52, 53]. EXP treatments have shown to be effective in reducing pain-related fear and the perceived harmfulness of physical activity in various chronic pain conditions, such as chronic low back pain [51, 54, 55] and complex regional pain syndrome type I (CRPS-I) [50, 54]. Another combined physical and cognitive behavioural treatment modality is acceptance and commitment therapy (ACT) [56]. ACT includes a combination of acceptance and mindfulness methods along with activation and behaviour change methods. Multidisciplinary ACT has shown to be effective in reducing the burden of chronic pain in various pain conditions [56, 57]. In this review, we have found no articles that discussed EXP or ACT. Currently, our group is conducting a clinical study in single-case-design to test the effectiveness of an EXP treatment that was specifically designed for the needs and risks of patients with PDN (ActiFeeT, NCT03066570).

There are a few limitations of the current study that should be mentioned. For this systematic review, the search was focused on combined treatments (exercise and psychological). Within the set of articles retrieved, we identified eight articles that discussed exercise or psychological therapies alone. It should be noted that this was not our primary research question and therefore the listing may not be complete. We evaluated the option of performing a new search with the or option, but decided not to do this, as this work has already been done by Davies et al. in 2015 [58]. By performing a thorough hand search through all databases, we identified only one article that was published after the review of Davies et al. [43]. We added this article to our results. Furthermore, we could not retrieve the full text of three remaining articles. Based on the abstracts, we did not expect any added value of these articles (wrong diagnosis and/or design).

In conclusion, PDN is a multifactorial disease in which pain, balance disorders, gait disturbance and fear/avoidance behaviour can significantly limit daily life activities QoL. Current care, mostly based on pharmacotherapy, physical training and/or psychological support, seems insufficient to increase physical activity and regain normal daily functioning. Although studies suggest that a multidisciplinary therapeutic approach could be effective in improving daily life functioning and QoL in patients with PDN, this systematic review of the literature revealed no studies that describe or test treatment modalities that combine exercise therapy with psychological treatment. This empty review

highlights the need for studies on the effectiveness of multidisciplinary treatments such as EXP or ACT.

#### Authors' statements

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**Conflict of interest:** None of the authors have any financial or other relationship that might lead to a conflict of interest.

**Informed consent:** Not applicable.

**Ethical approval:** Not applicable.

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