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The role of physical activity and psychological coping strategies in the management of painful diabetic neuropathy – A systematic review of the literature.

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## Abstract

Background: Diabetes is rising in prevalence; painful diabetic neuropathy (PDN) is one complication of diabetes. PDN is primarily managed with medication but analgesic failure is common and people remain in pain and distress. It is unclear whether pain management strategies are appropriate for PDN.

Objectives: To establish the effectiveness of physical activity and psychological coping strategies for PDN.

Design: Systematic literature review.

Data sources: Ten online databases.

Eligibility criteria (participants and interventions): Controlled trials reporting specific results for PDN, investigating, (a) physical activity or (b) psychological coping strategies and measuring pain as an outcome. The search was restricted to published research with no restriction on language or date of publication.

Study appraisal methods: Methodological quality and risk of bias assessed with Cochrane Collaboration and NICE checklist for randomised controlled trials.

Results: Of 1306 titles identified, four studies met the inclusion criteria. Two trials investigated physical activity and two investigated psychological coping interventions. Studies showed pain measures improved or did not worsen compared to controls, but methodological quality was moderate and results need cautious interpretation.

Limitations: The studies were of small sample size and used a diverse range of outcome measures. There is high risk of bias from lack of blinding and attrition at follow up.

Conclusions and implications of key findings: The research literature in this area is sparse and inconsistent, despite the pressing clinical challenge of PDN. Firm conclusions cannot be drawn from the studies included. Further high quality research is required to match treatment provision to patient requirements.

Abstract word count 253

Key words: diabetes, pain, physical activity, psychological coping, systematic literature review.

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## Introduction

Diabetes Mellitus (DM) is an increasingly common endocrine disorder, the prevalence of which is rising due to rising levels of obesity, decreasing physical activity and an ageing population [1]. As management strategies for DM have improved there has been a decrease in the mortality due to DM, and an increase in the morbidity associated with potential complications [2,3]. Diabetes has been highlighted as the ninth leading cause of years lived with disability [4].

Painful diabetic neuropathy (PDN) is a significant complication of DM and is thought to be caused, at least in part, by pathological microvascular changes to the small nerve fibres particularly within the feet and hands [5]. These changes lead to a burning pain in a 'glove and stocking' distribution that is spontaneous and unpredictable; the pain is not related to physical activity and is often worse at night [6]. PDN is linked with significant impact on physical function and mobility [7] and is associated with negative effect on mood state and quality of life over and above the impact of diabetes alone [8]. PDN affects 16-23% of people with DM [9,10], that is, approximately 600,000 people in the UK.

The management of PDN is primarily pharmacological and there are published guidelines for the medical management of neuropathic pain in general [11,12] and of PDN specifically [13,14]. However, these recommendations do not always agree, which leads to clinical uncertainty [15] compounded by the fact that successful pharmacological management is achieved in less than half of patients with PDN [16]. The recent National Institute for Health and Care Excellence (NICE) update [12] has removed specific advice on which medications should be considered first line therapy.

Multidisciplinary pain management programmes have an established evidence base for management of other persistent pain conditions [17–19]. Programmes incorporate various forms of physical activity and a range of psychological models (for example

Cognitive Behavioural Therapy (CBT) or Acceptance and Commitment Therapy), but have physical reactivation and psychological coping as their key tenets [20].

In the context of pain management, physical activity is not aimed at curing the pain problem but at increasing the person's ability to cope [20]. The physical aspect aims to help people establish a baseline for functional movements and use principles of graded exposure and pacing [21] to gradually increase levels of physical capacity. A recent study [22] of people with PDN (n=2576) identified 'general activity' and 'walking ability' as the most important functions to be improved through treatment of their PDN. These patient expectations are well within the remit of physiotherapy, but there is a lack of evidence for any specific form of physical activity in the management of PDN.

Psychological coping includes the use of cognitive and behavioural interventions to help people challenge maladaptive thoughts in order to manage a persistent pain problem. The use of these strategies specifically for the management of neuropathic pain, have been examined in a previous systematic review [27]. No firm conclusions were possible and it was subsequently criticised for the breadth of interventions (CBT, hypnosis, cognitive restructuring etc.) and pathologies (Phantom limb pain, Spinal cord injury etc.) that were included in the selection process [28].

It may appear plausible to transfer effective management strategies for musculoskeletal pain, to the population who experience neuropathic pain. However, it has been suggested inappropriate to consider all people with persistent pain as a homogenous population, and that greater efforts to target specific treatments to particular sub-groups are required [23,24]. One sub-grouping would be the proposed dominant pain mechanism. Daniel et al. [25] highlighted differences between people with predominantly nociceptive versus neuropathic pain. They found pain-aggravating factors differed, with neuropathic pain greater influenced by environmental temperature and life stress. They found participant beliefs about causes and pain mechanisms differed, with

neuropathic pain seen as due to nerve damage from a disease process. Martin et al. [26] investigated patient understanding of neuropathic pain and highlighted a number of factors relevant to pain rehabilitation: the patient accepting the presence (or not) of psychological influences on pain and the acceptability (or not) of psychologically based treatment options. These data and those of Daniel et al. [25], suggest participant beliefs about aggravating factors, causes and mechanisms of pain may need to be taken into account in a manner specific to neuropathic pain, when designing therapeutic interventions.

Physiotherapists are increasingly expected to deliver a blend of physical rehabilitation and psychological pain coping strategies, as psychologically informed physiotherapy [17]. Around 50% of people who experience PDN have other musculoskeletal causes of pain, which may bring them into contact with physiotherapists [22]. Furthermore, as the prevalence of diabetes and PDN increase, patients in physiotherapy are increasingly likely to have PDN either as a co-morbidity, or potentially as a reason for referral. Guidance documents for PDN recommend specialist assessment when pharmacology fails [12], but do not detail what this assessment and potential treatment should consist of.

The physical and psychological coping strategies taught within existing pain management programmes may be appropriate for helping patients to manage the persistent pain of PDN, however the evidence base for these are unknown.

Objectives.

This systematic review had three objectives: to establish the evidence for 1) physical activity and 2) psychological coping strategies, in the management of PDN; and 3) identify gaps in evidence to inform future research priorities in the management of PDN.

## Methods

### Protocol and registration

The review protocol was registered with PROSPERO (CRD42013006365) [27], and is reported in accordance with PRISMA recommendations [28].

### Eligibility criteria

Studies were required to meet the following inclusion criteria: (1) a study population with clear diagnosis of painful neuropathy, secondary to diabetes (PDN) and results reported specifically for PDN, where other neuropathic pain pathologies were included in the trial; (2) human subjects, 18yrs+; (3) intervention that was either a) physical activity or b) therapeutic interventions delivered under an overarching psychological framework; (4) pain outcome measures (5) controlled methodology; (6) original peer-reviewed research. No exclusion was made based upon language or date of publication.

### Information sources

Ten electronic databases were searched: the Cochrane Library, Physiotherapy Evidence Database (PEDro), Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine (AMED), Embase, SportDiscus, Web of Science, BioMed Central and PsychINFO.

### Search

To ensure a specific and sensitive search strategy was developed, existing high quality reviews, published by Cochrane and known to the authors, were initially scoped for physical activity search terms [29,30]. These terms were further developed to incorporate terms for physical activity targeting neural tissue, as this form of activity may have direct relevance to the population with PDN. This review uses the term psychological coping to include any strategy used in pain management programmes that



aims to help the patient live with persistent pain. Existing systematic reviews of cognitive, behavioural and acceptance based psychological interventions were used as the basis for developing psychological coping search terms [19,29]. The full search strategy can be found in supplementary information Table 1.

This search was applied via EBSCO to Medline, AMED, EMBASE, CINAHL, SportDiscus and PsychINFO. A simplified search strategy was used for PEDro, Cochrane Library, BioMed Central and Web of Science. These searches were conducted (by B.D.) in the week beginning 18<sup>th</sup> November 2013 and repeated 2<sup>nd</sup> July 2014 to ensure the results were up-to-date.

#### Study selection

From the studies retrieved, duplicates were removed and the titles judged against the eligibility criteria. Studies that clearly did not meet eligibility criteria were excluded. Abstracts for all remaining studies were then reviewed and judged against the eligibility criteria. The full texts of studies that could not be clearly excluded were obtained. These full texts were judged against eligibility criteria to select the final included studies. In the case of uncertainty, discussions were had within the research team to reach a consensus, and authors were contacted for additional information where this was appropriate.

#### Data collection process and data items

The principal data extracted from the selected studies included: evidence of diagnostic criteria for PDN, nature of intervention (type of physical activity, type of psychological coping therapy), demographics of the control and intervention arm, duration of follow up, pain outcome measures and, if available, quality of life measures as secondary outcomes, results, attrition rates and noted adverse effects. Prior to commencing the review, scoping of the literature, indicated that relevant studies investigating physical activity and psychological coping strategies incorporated a broad

range of complex heterogeneous interventions. On this basis it was decided 'a priori', that quantitative synthesis of study results would be inappropriate, rather a narrative synthesis would be presented to outline preliminary size and direction of intervention effects [30].

#### Critical Appraisal and Risk of bias in individual studies

Risk of bias was assessed using the Cochrane Collaboration tool [31] and methodological quality was further assessed using the NICE critical appraisal tool for randomised studies [32]. This process ensured that each study was assessed consistently, which limited reviewer bias in the assessment of quality. The lead author conducted this process and a second review was performed by FC for studies involving physical activity and by JGG for studies involving psychological interventions. The individual appraisals were discussed and a consensus reached.

## Results

### Study selection

After duplicates were removed, 1306 potential studies remained. After consideration against the eligibility criteria four articles were retained for full review, two studies focused on physical activity and two focused on psychological interventions. The outline of the screening process is summarised in Figure A – Study selection.

### Study characteristics (see Table 2)

One quasi-experimental trial of Tai Chi [33] and one randomised controlled trial investigating aerobic physical exercise [34] were selected. There were two randomised controlled trials of psychological interventions, CBT and Mindfulness relaxation [35,36]. Studies included participants diagnosed with Type 1 and Type 2 diabetes, although the majority had Type 2. Sample sizes ranged from 19-87, with only two studies reporting a sample size calculation [33,36]. The intervention arms were compared with treatment as

usual [33–35] or a control arm of diabetes self-care education providing equivalent contact time with a health professional as the intervention arm [36].

#### Risk of bias and quality appraisal

A summary of the Cochrane bias appraisal can be found in Table 3, the NICE checklist is available in the supplementary information Table 4.

Two studies of physical activity met the eligibility criteria. Ahn et al. [33] conducted a quasi-experimental study investigating the effects of Tai Chi. Tai Chi had previously been shown to increase peripheral vasodilation and have a potential beneficial effect on HbA1c levels (a measure of blood glucose control) [33]. The first thirty participants consented were allocated Tai Chi, and their outcomes compared to the next block of twenty-nine control participants. A sample size calculation was conducted based on the ability to detect change in HbA1c, and the target sample was recruited. Although not true randomisation there were no significant differences between study arms at baseline. The authors used a robust range of outcome measures but they did not state if the assessors were blind to treatment allocation. The study suffered from a high drop-out rate (~30%) in both study arms and the management of missing data was not discussed, so results are at risk of attrition bias.

One study investigated structured aerobic exercise. Dixit et al. [34] stratified the severity of the neuropathy using the Michigan Diabetic Neuropathy Score and then randomised participants into study arms. There were clear protocols for minimising allocation and detection bias, through blinding of researchers to the trial arm of participants. Anthropometrics were shown to be similar between trial arms at baseline, but other characteristics were not analysed. Clear details of the intervention were provided, and the control arm received weekly physician appointments. Such frequency may not represent true ‘treatment as usual’. No sample size calculation was conducted, however the researchers assessed 335 potential participants and recruited only 87,

suggesting difficulties in recruitment from their population. There was significant loss to follow up (~22%) in both arms of the trial, no details were provided of how missing data were managed so the results are at risk of attrition bias.

Two studies met the criteria for psychological coping strategies. Otis et al. [35] conducted a pilot trial of CBT in a US military veterans population. The CBT programme reflected the curriculum of pain management programmes as advised by the British Pain Society [20]. Participants were randomised to a trial arm and the arms were demonstrated to be comparable at baseline. The CBT intervention was clearly outlined and was compared against usual treatment within primary care. The study used the West Haven Yale Multidimensional Pain Inventory as their primary outcome measure, which has not been validated for neuropathic pain. It was not clear that outcome assessors were fully blind to the treatment arm. The authors took repeated measures (pre-, post-course and at four months), and used appropriate statistical analysis to account for repeated measures (Hierarchical Linear Model), but caution should be applied due to the small sample size (n=19) and high attrition in the treatment arm (3 of 11, 27%).

Teixeira [36] studied the effect of mindfulness relaxation on PDN. Mindfulness relaxation aims to help people live with their pain, rather than fighting against it [37]. Participants were randomly allocated to a trial arm by drawing from concealed numbers. The outcome measures used for pain (Neuropathic Pain Scale) and quality of life (NeuroQoL) were validated for neuropathic pain. Previous studies informed a sample size calculation, however the target was not achieved allowing the possibility of type II error. Further to this, analysis was not carried out to investigate differences between study arms for participant characteristics at baseline and there was no mention of blinding of outcome assessors thus detection bias was a potential issue. There was minimal loss to follow up but management of missing data was not described.

Overall, these studies defined their participant eligibility criteria, used appropriate outcome measures for pain and quality of life in persistent pain states, and described the interventions clearly. They were all of small sample size, experiencing difficulty recruiting participants, or retaining participants within the studies. In half the studies appropriate steps had been taken to blind researchers, but for the interventions studied it was difficult to achieve true blinding of participants. The main concerns with all the identified studies were high attrition rates and the lack of clear intention to treat analysis; this allows results to be inflated in favour of the interventions.

#### Results of individual studies

Detailed results can be found in Table 2 – Synopsis of selected studies. Here, we give a narrative account and include raw mean scores, as they are important and can be suggestive of effect size in some of these low-N studies.

Ahn et al. [33] used the Short Form-36 (SF36) questionnaire that includes a bodily pain subscale. There were no differences between the Tai Chi arm and the control arm at baseline; in contrast, the Tai Chi arm's bodily pain was significantly different to the control arm's after the 12 week intervention period ( $p = 0.009$ ). In the Tai Chi arm, mean bodily pain improved from 67.50 (SD 28.50) to 79.37 (19.98), while the control arm mean worsened from 71.71 (19.91) to 60.36 (24.49). No adverse effects were noted for participation in the Tai Chi arm.

Dixit et al. [34] demonstrated a statistical difference in the pain subscale of the NeuroQoL in favour of the aerobic exercise arm ( $p=0.03$ ), although this appears to be due to the control arm worsening in their pain rating mean 1.65 (SD1.75) to 1.73 (1.69), whereas the intervention arm demonstrated minimal change 1.60 (1.76) to 1.61 (1.29),

Otis et al. [35] used the West Haven Yale Multi-dimensional Pain Inventory, which includes pain severity and pain interference subscales. Hierarchical Linear Modelling was used to account for repeated measures with analysis only reported for variation between

baseline and 4-month follow-up. Examination of regression coefficients showed that participants in the CBT arm improved with treatment, whereas those in the control arm did not. In terms of raw scores, the CBT arm improved in pain severity from baseline mean 3.92 (SD 1.35) to 2.79 (1.21) at the end of treatment phase, which was maintained at four-month follow up, 2.83 (1.27). The control arm pain severity showed less change, being 3.75 (0.85) at baseline, 3.83 (0.67) at end of treatment and 3.71 (0.91) at four-month follow up. Similarly, mean pain interference improved in the CBT arm from 3.80 (1.62) to 2.29 (1.71) at the end of treatment phase and decreased slightly to 2.45 (1.54) at follow up. The pain interference scores for the control arm were unchanged, from 3.32 (1.94) to 3.30 (1.70) at follow up. The authors calculated change scores (baseline to follow up) for both of these variables, and confirmed that the change scores were significantly different in both groups (both  $p < 0.05$ ).

Teixeira [36] proposed mindfulness relaxation would lead to decreased pain. The results demonstrated no statistically significant differences in pain between intervention and control arms. Numbers in this study were low ( $N = 10$  in each group), resulting in low statistical power to detect a significant difference. Thus, it would be productive to examine raw mean scores to understand the data better. However, pre-treatment mean scores were not reported in this study, so this was not possible.

Three studies included outcome measures of quality of life. Ahn et al. [33] demonstrated significant improvements in three SF36 subscales for the intervention arm compared to the control arm at follow up: physical role, emotional role and social function (all  $p \leq 0.006$ ). Dixit et al. [34] found the NeuroQOL total score significantly improved in the intervention arm, compared to a slight decrease in the control arm ( $p < 0.001$ ). Teixeira [36] also used the NeuroQOL but found no significant change following the intervention.

## Synthesis of results

The effects of physical activity on pain are inconclusive in the studies included, whilst there were significant improvements in pain following Tai Chi, the impact of aerobic exercise appears to be due to pain worsening in the control arm, rather than improving in the intervention arm. Physical activity appears to improve measures of physical, social and emotional life quality. There appeared to be barriers to recruitment and retention in the studies of physical activity, which are particularly of relevance given the lifestyle factors that can contribute to the development of Type 2 diabetes. CBT appeared to benefit participants, improving both pain and pain interference, but participants dropped out early in the course. CBT appeared to benefit participants, improving both pain and pain interference. However, caution needs to be used when considering the clinical and scientific importance of these findings due to the high participant attrition rate within this study that may introduce sources of bias.

## Discussion

This systematic review aimed to examine the evidence for physical activity and psychological coping strategies in the management of PDN. Only two studies of physical activity and two studies of psychological coping were identified. The literature was small, heterogeneous and with persistent methodological limitations. Physical activity appeared to improve overall physical and mental wellbeing, but the impact on pain experience was inconclusive in the two studies. In the one study that recorded adverse effects [33], none were noted beyond transient pain increases or hypoglycaemia. Mindfulness relaxation did not have a significant effect on pain or quality of life. CBT was reported to improve both pain and pain interference, but in a small pilot study where risk of bias may have been raised due to high participant dropout.

The studies that investigated a form of physical activity, Ahn et al. [33] demonstrated Tai Chi improved the SF36 bodily pain domain, yet Dixit et al. [34]

demonstrated the aerobic exercise arm remained unchanged. It should be noted that the data in Dixit et al. [34] showed improvement in quality of life, despite the pain scores remaining unchanged. The improvement in quality of life is mirrored by Ahn et al. [33] - there is some improvement in life quality with physical activity. It maybe the interplay between physical health, mental health and pain is sufficiently complex that certainty of the effect of these interventions on the persons' pain experience cannot be established from these two studies.

Significant limitations of the research selected were low rates of recruitment and retention within physical activity studies. The attrition rates (23-33%) do not reflect other studies of pain rehabilitation, for instance a Cochrane review of exercise for fibromyalgia syndrome found attrition rates between 0-18% [38]. While fibromyalgia has a range of symptoms, it does not affect multiple bodily systems in the same manner as diabetes. A recent systematic review [39] of exercise in diabetes that included 12 studies found attrition rates 0-18% in 10 of their included trials. The high rates of attrition found in this review, possibly reflect the difficulties of increasing and maintaining physical activity, experienced by people with diabetes and pain. Strategies for health behaviour change would need to be considered in the development of any clinical service.

The psychological coping interventions studied were CBT [35] and Mindfulness relaxation therapy [36]. There is insufficient evidence to make recommendations on psychological therapies for PDN from these studies. While the results from the pilot study carried out by Otis et al [35] appear encouraging, the high dropout rate limits the quality and validity of the findings. As highlighted previously patients have varying explanations for neuropathic pain, and varying levels of acceptance that psychological processes are relevant to their pain experiences [26]. Guidance from the British Pain Society stresses that engagement with multidisciplinary pain programmes cannot be coerced [20] and assessment must be made of the person's readiness to adopt alternative physical and



psychological behaviours. Otis et al. [38] note that dropout occurred by session three of eleven, we suggest a possible explanation that participants were not sufficiently engaged in CBT to stay the course. An important consideration in future trials of non-pharmacological interventions for PDN is to explore reasons for refusal to participate and drop out. This would help to inform the clinical acceptability of such interventions to a wider range of people with PDN.

This review has raised an important question: why were so few research studies found investigating non-pharmacological management strategies for PDN? The prevalence of PDN is increasing; it impacts on day-to-day functions; it is distressing; patients want their walking ability to be improved [22]; the available analgesics are not sufficient to ameliorate this impact and are costly - yet there is a paucity of research available. We chose to limit the search to PDN specifically, rather than neuropathic pain generally due to the co-morbidities that are present in the diabetic population. We used broad search terms for physical activity and psychological coping to ensure all potential studies using these interventions were included. We specified controlled methodologies, which led to five studies being excluded from the final selection, but choose to look for the most robust level of evidence for the effectiveness of these interventions. We contend that this review highlights an area of persistent pain that is underrepresented in pain rehabilitation research and potentially a population who are underrepresented in clinical rehabilitation services.

#### Further research

Further high quality research is required to understand whether physical activity and/or psychological coping interventions are of benefit and acceptable to the population with PDN. Such research must utilise outcome measures sensitive to change in neuropathic pain, and include measures of functional ability, specifically measures of mobility, as well as pain experience and pain related quality of life [40].

## Conclusions

A cornerstone of pain management programmes aims to assist people to improve their physical capacity. The two studies investigating physical activity contain significant methodological bias, most notably high levels of participants lost to follow up.

The other cornerstone of pain management is psychological coping, yet the paucity of the studies retrieved does not allow firm conclusions to be made on the best psychological strategies to help people to cope with their persistent pain.

The lack of research found in this review highlights the need for further high quality non-pharmacological research and improved management of this painful, distressing and costly condition.

Conflict of interest: none declared

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Table 1 – Search strategy

1. PAIN explode all trees (MeSH)
2. DIABETES explode all trees (MeSH)
3. Neuropath\* or Polyneuropath\*
4. 1 AND 2 AND 3
5. PSYCHOTHERAPY explode tree1 (MeSH)
6. COGNITIVE THERAPY single term (MeSH)
7. BEHAVIOUR THERAPY explode tree 1 (MeSH)
8. BIOFEEDBACK (PSYCHOLOGY) single term (MeSH)
9. ((behaviour\* next therapy) or (behaviour\* next therapies))
10. ((cognitive next therapy) or (cognitive next therapies))
11. (relax\* near technique\*)
12. ((relax\* near therapy) or (relax\* near therapies))
13. meditat\*
14. psychotherap\*
15. (psychological next treatment)
16. ((psychological next therapy) or (psychological next therapies))
17. (group next therapy)
18. (self-regulation next training)
19. (coping next skill\*)
20. (pain-related next thought\*)
21. (behavior\* near rehabilitat\*)
22. (psychoeducation\* next group)
23. (psychoeducation\* next groups)
24. (psycho-education\* next group)
25. (psycho-education\* next groups)
26. (mind and (body next relaxation next technique\*))
27. MIND-BODY AND RELAXATION TECHNIQUES explode tree 1 (MeSH)

28. Mindfulness
29. Mindfulness-based stress reduction or MBSR
30. Mindfulness-based cognitive therapy or MBCT
31. Acceptance-based or acceptance based
32. Acceptance and commitment
33. 5 OR 6 through 32
34. ((exercise\* or resistance or strength or flexibility or endurance) near (train\* or program\*))
35. ((resistance or aerobic\* or endurance\*) near exercise\*)
36. (interval training or sport\* or movement therap\*)
37. stretching.mp
38. (dance therap\* or exercise\* or "Tai Ji" or "Tai Chi" or "Tai-Ji" or "Tai-Chi" or walking or yoga)
39. graded near (activit\* or exercise\* or program\*)
40. physical\* near (active\* or therap\* or exercise\*)
41. exp kinesiotherapy/
42. (nerve or neural) near (glid\* or slid\*)
43. (nerve or neural) near (exercise\* or therap\* or treatment\* or mobilization\*)
44. (nerve or neural) near (tension or mechanic\* or dynamic\*)
45. 34 OR 35 through 44
46. 5 AND (33 OR 45)



1 Table 2 – Synopsis of selected studies

Authors	Ahn et al. [36]	Dixit et al. [37]	Otis et al. [38]	Teixeira [39]
Research objective	Physical activity	Physical activity	Psychological coping	Psychological coping
Study design	Quasi-experimental controlled trial	Single blind, RCT	Single blind, RCT	Open label, RCT
Participant characteristics Mean age (standard deviation) Gender Type of DM Duration of DM Duration of PDN Location of treatment	Intervention (n=20): 66 (6.4) years, 12 male, all Type 2, DM duration - 12 (8.8) years. PDN duration not stated. Control (n=19): 62.7 (7.5) years, 8 male, all Type 2, DM duration - 13 (10) years. PDN duration not stated. Korean University Hospital outpatient clinic.	Intervention (n=40): 54.4 (1.2) years, 22 male, all Type 2 DM type, DM duration 65.5(1.9) months, PDN duration not stated. Control (n=47): 59.4(1.1) years, 31 males, all Type 2 DM, DM duration 82.1(1.6) months, PDN duration not stated. Tertiary care centre, India.	Intervention: 62 (11) years, all male, all type 2 DM, DM and PDN duration not stated. Control: 63 (11.6) years, all male, all type 2, DM and PDN duration not stated. US veterans medical centre.	All participants (n=20): 74 (10.8) years, 5 male, all type 2, DM duration - 12.6 (9.4) years, PDN duration – 7.7 (6.6) years. Community medical practice and retirement communities, USA.
Sample size	n=59	n=87	n=19	n=22
PDN diagnostic criteria	10g monofilament assessment, NTSS	Physician assessment. Other causes for neuropathy excluded	Medical records screened for primary complaint of neuropathic pain in hands or feet	Self-referred, no medical screening
Intervention	Tai Chi (40 minutes Tai Chi movement, with 15 minutes Qigong warm up and cool down), 2x1 hour per week, 12 weeks, plus routine education on diabetes management	Aerobic treadmill exercise at 40-60% of HRR, 5-6 days per week, accumulating 150-360 mins/week exercise, at RPE 6-20. 8 weeks. Advice on foot care and hypoglycaemia	Individual CBT, 1-hour session, x11 sessions. Content included: cycle of pain, pain mechanisms, relaxation, identification and challenge negative thoughts, pacing, sleep strategies.	Mindfulness relaxation. 1 hour session then audio CD for home practice.

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Authors	Ahn et al. [36]	Dixit et al. [37]	Otis et al. [38]	Teixeira [39]
Control arm	Routine education on diabetes management	Weekly physician appointments with diet and foot care advice	Treatment as usual, offered CBT after completion of 4 month follow up.	Nutritional advice (1hour) and asked to keep a food diary for 4 weeks
Outcomes	SF36 (Korean)	NeuroQoL	WHYMPI	NPS NeuroQoL
Main findings	SF36: Bodily pain subscale Tai Chi arm: mean 67.5(SD28.5) to 79.37(19.98), Control arm: 71.71 (19.9) to 60.36(24.49) (p=0.009).  Quality of life SF36 subscales: physical function Tai Chi arm improved mean difference 4.75(16.58), control - 5.78(11.69), p=0.028. Role physical Tai Chi 17.25(28.64), control -4.02(14.20), p=0.006. Role emotional Tai Chi 17.5(24.78), control - 7.36(20.73), p=0.002. Social function Tai Chi 10.89(30.29), control -18.28(18.85), p=0.001. All other SF36 subscales were	NeuroQoL Pain subscale exercise arm: 1.6(1.76) (CI 2.12 – 1.08) to 1.61(1.29) (CI 2.08 – 1.14), control arm: 1.65(1.75) (CI 2.17 – 1.14) to 1.73(1.69) (CI 2.28 – 1.18), p=0.03.  Quality of life NeuroQoL total score improved in exercise arm: 32.85(1.32) (CI 33.28 – 32.42) to 24.14(1.12) (CI 24.82 – 24), control arm: 33.55(1.37) (CI 33.95 – 33.15) to 34.16(1.37) (CI 34.61 – 33.71), p<0.001.	HLM: Pain severity CBT group decreased B=-0.54, (CI -0.9 to -0.99). Control arm were unchanged (B=0.00). Pain interference slope B=-0.77 (CI -0.24 to -1.30), compared to control arm B=-0.09 (CI 0.3 to -0.48)  Between arm pre-post (4/12): pain severity decreased mean 1.08 (0.79), Control arm unchanged, mean 0(0.51), p<0.1.  Pain interference declined CBT mean 1.35 (SD 1.22), control arm increased mean 0.22 (SD 0.73), p<0.5.	Hypothesis (Mindfulness leads to decreased pain): no significant difference in pain intensity or pain unpleasantness.  Hypothesis (Mindfulness leads to quality of life improvement): no significant difference in overall, symptom related or pain quality of life.

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	not significantly different $p > 0.1$ .			
Adverse effects/events	Reported: None noted	Not reported	Not reported	Not reported
CI – confidence interval, CBT – Cognitive behavioural therapy, DM – Diabetes mellitus, HLM – Hierarchical linear modelling, HRR – Heart rate reserve, NPS - Neuropathic pain scale, NTSS - Neuropathy total symptom score, PDN – Painful diabetic neuropathy, RCT – randomised controlled trial, RPE – rate of perceived exertion, SD – Standard deviation, WHYMPI - West Haven Yale Multidimensional Pain Inventory				

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6 Table 3 – Cochrane risk of bias summary

	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ahn et al. [36]	+	-	-	?	-	+	?
Dixit et al. [37]	+	-	-	+	-	+	-
Otis et al. [38]	+	-	?	?	-	?	?
Teixeira [39]	+	?	-	?	?	+	?
- The method described contains a high risk of bias, + The method described contains a low risk of bias, ? The risk of bias cannot be ascertained from the described method, Higgins et al 2011							

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8 Figure A – Study selection

