

Novel insights on diagnosis, cause and treatment of diabetic neuropathy: focus on painful diabetic neuropathy

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Abstract: Diabetic neuropathy is common, under or misdiagnosed, and causes substantial morbidity with increased mortality. Defining and developing sensitive diagnostic tests for diabetic neuropathy is not only key to implementing earlier interventions but also to ensure that the most appropriate endpoints are employed in clinical intervention trials. This is critical as many potentially effective therapies may never progress to the clinic, not due to a lack of therapeutic effect, but because the endpoints were not sufficiently sensitive or robust to identify benefit. Apart from improving glycaemic control, there is no licensed treatment for diabetic neuropathy, however, a number of pathogenetic pathways remain under active study. Painful diabetic neuropathy is a cause of considerable morbidity and whilst many pharmacological and nonpharmacological interventions are currently used, only two are approved by the US Food and Drug Administration. We address the important issue of the 'placebo effect' and also consider potential new pharmacological therapies as well as nonpharmacological interventions in the treatment of painful diabetic neuropathy.

Keywords: diabetic neuropathy, diagnosis, painful diabetic neuropathy, nonpharmacological treatment, pharmacological

Introduction

Diabetic neuropathy is extremely distressing and significantly reduces the patients' quality of life [Zelman *et al.* 2006; Mojaddidi *et al.* 2005]. Hyperglycaemia is clearly important in the genesis of nerve damage and recent studies suggest that even minimal perturbations in blood glucose in those with impaired glucose tolerance (IGT) may lead to the development of both small [Green *et al.* 2010; Tavakoli *et al.* 2010] and large [Sahin *et al.* 2009] nerve fibre damage and neuropathic pain [Smith and Singleton, 2008].

Diagnosis of diabetic neuropathy

Several different approaches have been employed to diagnose and evaluate the severity of neuropathic deficits in diabetic neuropathy. The neuropathy disability score and 10 g monofilament have been recommended as screening tools in general practice to detect those at risk of foot ulceration [Abbott *et al.* 2002]. However, data to suggest that the 10 g monofilament may not

be reliable [Booth and Young, 2000] or optimal for identifying those at risk of foot ulcers [Miranda-Palma *et al.* 2005] have been conveniently ignored. A more important point relates to the inappropriate use of the 10 g monofilament to diagnose 'neuropathy' as it will only detect advanced large fibre neuropathy. Hence, a 'normal test' may falsely reassure practitioners when in fact the patient may have mild neuropathy or indeed involvement of the small fibres. Furthermore, because effective intervention must be aimed at a stage when there is a capacity for the nerve to repair, i.e. in the subclinical or mild neuropathy, it is important to reliably quantify small fibre damage. Quantitative sensory testing (QST) including a thermal threshold assessment for cold sensation (A- δ fibres) and warm sensation (c fibres) assesses small fibre dysfunction and therefore can detect early neuropathy, but are highly subjective with low reproducibility [Boulton *et al.* 2004] and hence have shortcomings when employed to define

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therapeutic efficacy in clinical intervention trials [Mojaddidi *et al.* 2005]. Indeed small fibre abnormalities as assessed by intraepidermal nerve fibre (IENF) density and the Quantitative Sudomotor Axon Reflex Test (QSART) and not neurophysiology or QST, improved after lifestyle intervention in patients with IGT neuropathy [Smith *et al.* 2006]. Diabetic patients with minimal neuropathy (normal electrophysiology and quantitative sensory tests) show significant unmyelinated fibre [Malik *et al.* 2005] and IENF damage [Loseth *et al.* 2008; Quattrini *et al.* 2007; Umaphathi *et al.* 2007]. Direct examination of these fibres can be undertaken in sural nerve [Malik *et al.* 2005, 2001] or skin-punch [Smith *et al.* 2005; Sumner *et al.* 2003] biopsies, however, both are invasive procedures. Recently, we have shown that corneal confocal microscopy (CCM), a novel noninvasive technique can detect small fibre neuropathy in diabetic patients by visualizing the subbasal nerve plexus in Bowman's layer of the cornea [Quattrini *et al.* 2007; Hossain *et al.* 2005]. CCM may also be more sensitive than IENF density (IENFD) in detecting early damage [Quattrini *et al.* 2007] and repair after pancreas transplantation [Mehra *et al.* 2007; Boucek *et al.* 2005]. We have also demonstrated a progressive loss of corneal sensation with increasing severity of neuropathy, providing a functional correlate of corneal nerve fibre loss [Tavakoli *et al.* 2007]. With regard to painful neuropathy, more severe IENF loss [Sorensen *et al.* 2006b] and reduction in both IENF and corneal nerve fibre length [Quattrini *et al.* 2007] has been related to symptoms, suggestive of a pathological basis for painful diabetic neuropathy (PDN). As CCM is noninvasive it may be an ideal technique to assess alterations in small nerve fibre pathology in relation to PDN and progression of neuropathic deficits. In our recent study of patients with idiopathic small fibre neuropathy (ISFN) and IGT we have demonstrated significant corneal nerve damage [Tavakoli *et al.* 2010]. We have also shown that CCM as opposed to thermal thresholds can be used to demonstrate small nerve fibre damage in patients with Fabry disease, a condition characterized by painful neuropathy [Tavakoli *et al.* 2009].

A summary of the advantages and limitations of the present techniques to quantify nerve fibre damage in diabetic neuropathy is presented in Table 1.

Treatment of diabetic neuropathy

The ideal therapy should prevent or arrest the progressive loss of nerve function and improve symptoms with minimal side effects. However, current treatment options do not address the underlying cause of nerve damage. Furthermore, recent data highlight the main challenge with future clinical trials assessing improvement in diabetic neuropathy to be the lack of significant worsening of neuropathy in the placebo group [Dyck *et al.* 2007]. At present, apart from improving glycaemic control there is no licensed treatment for diabetic neuropathy. We have not provided a detailed review of all treatments but we have focused on three areas which are still being actively pursued.

Aldose reductase inhibitors

The aldose reductase theory remains viable in experimental diabetic neuropathy [Oates, 2008], however, its translation to man has been disappointing [Schemmel *et al.* 2009; Hamada and Nakamura, 2004]. Some of the aldose reductase inhibitors (ARIs) were withdrawn due to toxicity (Tolrestat, Sorbinil, Zenerastat), others due to a lack of efficacy [Schemmel *et al.* 2009; Chalk *et al.* 2007]. However, it also appears that reliance on nerve sorbitol as a means to assess aldose reductase inhibition may well have led to an underestimation of the doses needed for clinical efficacy and an overestimation of drug safety margins [Oates, 2008]. Furthermore, the choice of clinical endpoints and the magnitude of response required to prove efficacy has been questioned recently [Dyck *et al.* 2007].

Epalrestat, the only ARI in use, is currently only licensed for use in Japan [Ramirez and Borja, 2008; Hotta *et al.* 1996]. In a small study of 39 type 2 diabetic patients Epalrestat prevented progression of peripheral neuropathy, but surprisingly this was related to a reduction in the production of advanced glycation endproducts (AGEs) [Kawai *et al.* 2009], suggesting cross talk between two important pathogenetic pathways of diabetic neuropathy. In a recent study from India, Epalrestat improved motor and sensory nerve conduction velocities (NCVs) and the vibration perception threshold (VPT) [Sharma and Sharma, 2008]. Longer-term benefits have also been demonstrated with Epalrestat in a 3-year trial, reporting improvements in motor NCV, F-wave latency and VPT as well as neuropathic symptoms, particularly in patients with better glycaemic control and less overt microvascular

Table 1. Advantages and disadvantages for different tests of neuropathy.

Method	Advantage	Disadvantage
Clinical/neurological examination Electrophysiology	Simple, easy to use Sensitive, objective	Not sensitive or reproducible Assesses only large fibres Requires special equipment
Quantitative sensory tests (QST)	Evaluates both large and small nerve fibres	Subjective, low reproducibility, requires special equipment
Sympathetic skin response (SSR)	Simple, fast, objective	Semi quantitative, low sensitivity
Quantitative sudomotor axon reflex test (QSART)	Sensitive, objective, reproducible	Requires special equipment, time-consuming
Autonomic testing	Objective, quantitative	Moderate sensitivity, requires special equipment
Nerve/skin biopsy	Quantitative, sensitive	Invasive, problems with wound healing, specialist histological technique to quantify intraepidermal nerve fibre.
Corneal confocal microscopy/Corneal aesthesiometry	Rapid, noninvasive, reiterative and quantitative	Requires special equipment and expertise

complications [Hotta *et al.* 2006]. In 30 diabetic patients with mild to moderate neuropathy, median, tibial and sural NCV and wrist and ankle F-waves improved over 6 months and were associated with increased nodal Na⁺ [Misawa *et al.* 2006]. The only other ARI that remains in clinical trials is Ranirestat (AS-3201), which has been shown to prevent sural nerve accumulation of sorbitol and fructose with an improvement in sural NCV [Bril and Buchanan, 2004]. In a double-blind, placebo-controlled biopsy trial, sensory nerve function improved at 12 weeks, whilst motor NCV and VPT improved at 60 weeks [Bril and Buchanan, 2006]. In one of the largest ARI trials to date, 549 patients randomized to a 52-week, multiple-dose, placebo-controlled, double-blind study demonstrated a significant improvement in summed motor NCV (peroneal, tibial and median) at 12, 24 and 36 weeks and in peroneal NCV at 36 and 52 weeks, but with no improvement in neurological examination, QST or symptoms of neuropathy [Bril *et al.* 2009].

Antioxidants

Oxidative stress and impaired antioxidant defence mechanisms have been implicated as major pathogenic components of diabetic polyneuropathy [Shay *et al.* 2009]. Intravenous alpha-lipoic acid (ALA), an antioxidant and a free-radical scavenger, has been shown to improve symptomatic diabetic neuropathy [Ziegler *et al.* 2004; Evans *et al.* 2002]. The SYmptomatic Diabetic NEuropathy (SYDNEY) trial [Ametov *et al.* 2003] demonstrated an improvement in neuropathic symptoms in patients treated with ALA. A very short (4-week) study in 14 type 2 diabetic patients demonstrated that 400 mg daily ALA over 4 weeks improved

reactive oxygen metabolites (ROMs) and high density lipoprotein-cholesterol (HDL-C) [Gianturco *et al.* 2009]. In a small study of nine type 1 diabetic patients, ALA (600 mg/day twice) in combination with benfotiamine (300 mg/day twice) down regulated markers of ROM, reduced hexosamine activity by 40%, prostacyclin synthase activity by 70% and normalized AGE formation [Du *et al.* 2008]. However, in a double-blind, randomized, placebo-controlled study of an oral controlled-release formulation of ALA in 40 type 1 diabetic adolescents, no significant effects were observed on markers of oxidative damage [Huang and Gitelman, 2008]. Tankova and coworkers investigated the effect of 600 mg/day intravenous ALA for 10 days followed by 60 days of oral ALA in 23 patients and showed improvements in clinical signs of oculomotor, trochlear and abducent nerve mononeuropathies (double vision, ptosis) with an improvement in the Total Symptom Score (TSS) and an effect on peripheral and autonomic neuropathy [Tankova *et al.* 2005]. The SYDNEY 2 trial assessed the effects of 600, 1200 and 1800 mg oral ALA versus placebo in 181 diabetic patients over 5 weeks and showed an improvement in the TSS, neuropathy symptoms and change score (NSC), neuropathy impairment score (NIS) and patients' global assessment of efficacy [Ziegler *et al.* 2006].

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is regarded as a potent stimulator of angiogenesis and vasculogenesis in health and disease [Carmeliet, 2003] and acts through binding to the tyrosine kinase receptors VEGFR-1 and VEGFR-2 [Storkebaum *et al.* 2004]. Numerous studies have demonstrated the central role of

VEGF in the pathogenesis of diabetic retinopathy (DR) and diabetic macular oedema (DMO). Increased VEGF levels and VEGFR-2 expression have been found in models of experimental diabetes [Gilbert *et al.* 1998]. Tissue hypoxia is known to trigger an increase in VEGF content [Shweiki *et al.* 1992] and increased VEGF activity causes angiogenesis in DR [Aiello *et al.* 1994].

To date, there are two US Food and Drug Administration (FDA)-approved anti-VEGF agents, pegaptanib (Macugen, OSI/Eyetechnology, Melville, NY, USA) and ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA), for use in DR but also DMO. Pegaptanib targets the VEGF165 isoform and has been found to inhibit VEGF's actions on endothelial mitogen activity and vascular permeability [Ishida *et al.* 2003]. Ranibizumab is a recombinant, humanized, antibody fragment that binds all VEGF isoforms [Nicholson and Schachat, 2010]. Bevacizumab (Avastin, Genentech, Inc.) is currently being evaluated in clinical trials to prove its safety and efficacy for intraocular use [Nicholson and Schachat, 2010]. In 40 type 2 diabetic patients with proliferative retinopathy, a single intravitreal injection of Bevacizumab in addition to standard laser treatment resulted in complete regression of proliferative change in 87.5% compared with only 25% in the sham group at week 6, however, by week 16 recurrence of Proliferative Diabetic Retinopathy (PDR) meant that the complete regression rate was identical in the two groups [Mirshahi *et al.* 2008]. Similarly in DMO, the benefits of triamcinolone and bevacizumab versus bevacizumab compared with standard macular laser photocoagulation have been shown to be short lived with no correlation between reduction in macular thickness and visual acuity [Faghihi *et al.* 2008].

In the nervous system, VEGF also appears to have a beneficial effect as it has been shown to be neuroprotective promoting elongation of neurites and proliferation of nonneural cells [Storkebaum *et al.* 2004]. Experimental studies report upregulation of VEGF in response to ischaemia [Samii *et al.* 1999] and a key role of VEGF in maintaining neuronal integrity and preventing hypoxic death of Schwann cells [Schratzberger *et al.* 2000]. Intramuscular administration of an engineered zinc finger protein activator of VEGF-A has been shown to prevent sensory and motor nerve conduction velocity deficits [Price *et al.* 2006]. More recently it has been shown to correct endogenous VEGF-A protein levels in L4/5 dorsal root ganglia and protect against mechanical allodynia

[Pawson *et al.* 2009]. Topical application of VEGF has also been previously shown to accelerate diabetic wound healing in experimental models of diabetes [Galiano *et al.* 2004].

The role of VEGF in human diabetic neuropathy has not been explored fully and data remains somewhat confusing. Thus, Quattrini and colleagues demonstrated a significant reduction in VEGF expression in skin biopsies from the dorsum of the foot which was related to the severity of neuropathy in diabetic patients [Quattrini *et al.* 2008]. However, serum VEGF level have been found to be increased in diabetic patients with symptomatic neuropathy [Deguchi *et al.* 2009]. Bevilacqua and coworkers assessed 10 diabetic and 10 nondiabetic subjects and showed an increase in plasma VEGF during frequency modulated electromagnetic simulation (FREMS), providing a mechanistic basis for the beneficial effect of FREMS on NCV [Bevilacqua *et al.* 2007], but also highlighting the potential for variability when assessing serum VEGF levels. In a randomized, double-blinded study intramuscular gene transfer at eight standardized sites adjacent to the sciatic, peroneal, and tibial nerves was undertaken in 39 diabetic patients who received plasmid VEGF (VEGF-1/VEGF-A or VEGF-2/VEGF-C) whilst 11 received placebo over 6 months. An improvement in neuropathic symptoms was observed but without an effect on nerve conduction or quantitative sensory examination [Ropper *et al.* 2009]. Although an increased incidence of side effects was observed this was not characterized by increased oedema or haemorrhage, as might have been predicted recently with the demonstration of increased capillary leakage following VEGF treatment [de Leeuw *et al.* 2008]. Thus, the demonstration of a clinical benefit for diabetic neuropathy after VEGF treatment is at best, limited.

Painful diabetic neuropathy

Assessment of severity of neuropathic pain

The accurate assessment for the presence and severity of painful symptoms in patients with diabetic neuropathy is very important, not just to ensure a correct diagnosis but also to assess the benefits of treatment, especially with the potential for a large placebo effect as discussed elsewhere in this review. Many different questionnaires and scores have been developed or adopted to quantify neuropathic pain. The McGill Pain Questionnaire is the most frequently used questionnaire, but it

was not developed originally for diabetic neuropathic pain. Recently, more specific scores have been developed for diabetic painful neuropathy and include the Brief Pain Inventory short form for peripheral diabetic neuropathy (BPI-PDN) [Sorensen *et al.* 2006b]. The BPI is a patient-completed numeric rating scale that assesses the severity of pain and its impact on daily functioning on a 7-item pain interference scale. The Neuropathic Pain Questionnaire (NPQ) was developed to provide a general assessment of neuropathic pain and discriminate between neuropathic and nonneuropathic pain [Gore *et al.* 2007]. An additional diagnostic tool, the pain diagnostic questionnaire (DN4), has been shown to distinguish neuropathic from nociceptive pain [Calcutt and Backonja, 2007]. Follow-up assessment of pain in PDN can be undertaken using either the NPQ or the other recently developed tool, the Neuropathic Pain Symptom Inventory (NPSI), which is a self-questionnaire designed to evaluate different symptoms of neuropathic pain [Kelly *et al.* 2005]. The NPSI includes 10 descriptors that allow for the discrimination and quantification of clinically relevant aspects of neuropathic pain. It has been suggested that this pain questionnaire may be able to characterize subgroups of patients with neuropathic pain, and verify differential responses to pharmacologic or other treatment interventions. Finally, the Neuropathic Pain Scale has been designed specifically to monitor effects of therapy on neuropathic pain [Malik *et al.* 2005].

Treatment of painful diabetic neuropathy

Small fibre damage is an essential prerequisite for the development of PDN. However, additional alterations which include both peripheral and central sensitization make the treatment of this condition difficult. Hence, whilst many approaches have been advocated for the treatment of PDN, achieving >50% relief is rare and side effects limit dose titration. Thus, an improvement in the understanding of the pathogenesis of pain in diabetic neuropathy may lead to new more targeted treatments, with better efficacy and less side effects. Whilst the traditional approach has been to change or substitute treatments, owing to a lack of efficacy or side effects, a growing body of recent data suggests that combining lower doses of agents which act on different pain pathways may achieve better efficacy with fewer side effects [Baron *et al.* 2009; Zin *et al.* 2009; Hanna *et al.* 2008]. This establishes a new paradigm for future clinical trials in PDN

[Backonja *et al.* 2006]. The goal of this review is not to exhaustively detail all of the studies in PDN as several recent excellent reviews and analyses provide this [Noble *et al.* 2010; Wiffen *et al.* 2010; Moore *et al.* 2009; Ziegler, 2008a, 2008b]. Tables 2, 3 and 4 provide a summary of available treatments.

Placebo effect in double-blind trials of painful diabetic neuropathy

A recognized but unaddressed issue in trials of PDN is the 'placebo effect' and merits consideration [Wymer *et al.* 2009; Katz *et al.* 2008; Quessy and Rowbotham, 2008; Turner *et al.* 1994]. Quessy and Rowbotham have suggested that the true mean pain score reduction in trials of PDN is around 26–27% [Quessy and Rowbotham, 2008]. Several recent studies in PDN have shown a placebo effect which has approached and even surpassed that of the active therapy, obscuring the precise treatment effect of the active treatment (Table 5).

Pregabalin has been studied extensively in parallel cohort designed studies. In a meta-analysis of pregabalin in acute and chronic pain [Moore *et al.* 2009], a subgroup analysis in PDN trials showed that those achieving at least 50% pain reduction in the placebo arm (PA) was 23%, 26% and 25% and discontinuation due to a lack of efficacy was 7%, 8% and 14% in combined studies of 150 mg ($n = 2$ studies), 300 mg ($n = 4$ studies) and 600 mg ($n = 6$ studies), respectively. Although discontinuation was greater than in the treatment arm (TA) it still suggests that subjects gain a sufficient benefit to continue with the sham treatment. In a study of patients with postherpetic neuralgia and PDN comparing oxycodone against placebo with a dose titration of Pregabalin, a greater response rate (~50% pain reduction) was observed in the PA in three of the four groups with pregabalin dose titration [Zin *et al.* 2009]. Furthermore, prior to the initiation of Pregabalin, 34.5% of patients in the PA compared with 23.2% in the Oxycodone arm obtained at least 50% pain reduction.

Duloxetine, a dual reuptake inhibitor of serotonin and noradrenaline [Schuessler, 2006], has been placed as a first-line therapy for PDN in the 2010 National Institute for Health and Clinical Excellence (NICE) guidance on pharmacological management of painful neuropathy. However, three key studies have demonstrated the efficacy of Duloxetine in PDN with a mean percentage change from baseline in the PA of 33%, 29% and 24%, respectively [Raskin *et al.* 2006; Wernicke *et al.*

Table 2. Pathogenetic treatment options for diabetic neuropathy.

Mechanism of effect	Class of drug	Drug	Dose per day (mg)	Side effects	Comment
Glycaemic control	Insulin	–	–	Hypoglycaemia	Proven in type 1 but not type 2 diabetes mellitus
Glycaemic control	Pancreas transplantation [Mehra <i>et al.</i> 2007]	–	–	Immunosuppression	Data limited
Oxidative stress	Alpha-lipoic acid [Ziegler <i>et al.</i> 2004]	Alpha-lipoic acid	600 mg IV 1200–1800 mg orally		No long-term data
Aldose reductase (AR) inhibition	Aldose reductase inhibitors [Oates, 2008]	Epalrestat			Only licensed in Japan
Improved blood flow	Angiotensin-converting enzyme inhibitors [Malik <i>et al.</i> 1998; Reja <i>et al.</i> 1995]	Trandolopril Lisinopril			More studies needed

Table 3. Symptomatic treatment options for diabetic neuropathy.

Mechanism of effect	Class of drug	Drug	Dose per day (mg)	Side effects	Comment
Pharmacotherapy	Tricyclic antidepressants (TCAs)	Amitriptyline [Max <i>et al.</i> 1992]	20–150	+++	Sedation and anticholinergic side effects
		Imipramine	25–150	+++	Sedation and anticholinergic side effects
	Selective serotonin reuptake inhibitors (SSRIs)	Duloxetine [Raskin <i>et al.</i> 2006]	60–120		Approved by FDA Metabolic side effects
	Anticonvulsants	Gabapentin [Wiffen <i>et al.</i> 2010]	900–3600	+	Somnolence
		Lamotrigine [Wiffen <i>et al.</i> 2010]	200–400	+	Nausea, headache
		Carbamazepine [Wiffen <i>et al.</i> 2010]	200–600	++	Agranulocytosis
		Pregabalin [Freeman <i>et al.</i> 2008]	300–600		FDA approved, pedal oedema
	Antiarrhythmics	Mexilitene [Carroll <i>et al.</i> 2008]	Up to 900	+++	Nausea, Tremor, increased arrhythmia risk
	Opioids	Tramadol [Freeman <i>et al.</i> 2007]	50–400	++	Sedation, constipation
		Oxycodone [Zin <i>et al.</i> 2009]	40–60	+++	Sedation, constipation
Topical agents	Capsaicin [Tandan <i>et al.</i> 1992]		Topical		Intraepidermal nerve fibre loss
	Glyceryl trinitrate (GTN) [Agrawal <i>et al.</i> 2009]		Topical spray		Headache, tolerance

2006; Goldstein *et al.* 2005]. The Duloxetine studies have also shown variability in the PA with the percentage demonstrating 50% pain response ranging from 26% to 30%. Lacosamide, a new investigational drug in epilepsy and neuropathic pain, slowly inactivates voltage-gated sodium channels and interacts with a collapsin response mediator

protein-2 [Errington *et al.* 2008; Sheets *et al.* 2008; Bretin *et al.* 2006]. In a phase 2 double-blind randomized controlled trial the Lacosamide arm achieved an average Likert pain scale score (last observation carried forward [LOCF]) of 3.7 ± 2.6 compared with a baseline of 6.6 ± 1.6 [Rauck *et al.* 2007]. However, the PA achieved a Likert pain scale

Table 4. Placebo response of trials of duloxetine, venlafaxine, glyceryl trinitrate/sodium valproate and cannabinoids.

Trial	Drug	Number in placebo group	Length of trial(weeks)	Percentage change from baseline of pain scores	Percentage of placebo responders
Goldstein <i>et al.</i> [2005]	Duloxetine	115	12	33%	26% (50% pain improvement)
Raskin <i>et al.</i> [2006]	Duloxetine	116	12	29%	30% (50% pain improvement)
Wernicke <i>et al.</i> [2006]	Duloxetine	108	12	24%	27% (50% pain improvement)
Rowbotham <i>et al.</i> [2004]	Venlafaxine	81	6	27%	34% (50% pain improvement)
Selvarajah <i>et al.</i> [2009]	Sativex	14	12	37%	64% (30% pain improvement)
Agrawal <i>et al.</i> [2009]	Sodium valproate + GTN	GTN + placebo = 20 Placebo + Sodium valproate = 20 Placebo + placebo = 21	12	36% 23% 6%	n/a

Table 5. Nonpharmacological symptomatic treatment options for diabetic neuropathy.

Mechanism of effect	Type of treatment	Comment
Physical therapy	Electrical spinal cord stimulation	Highly invasive Limited data
	Transcutaneous electrical nerve stimulation (TENS)	Limited data
	Percutaneous electrical nerve stimulation (PENS)	Limited data
	Magnetic field therapy	Limited data
	Low-intensity laser therapy (LILT)	Limited data
	Monochromatic near-infrared treatment (MIRE)	Limited data
	Dressings	Limited data
	Acupuncture	Limited data
Others	Yoga	Limited data
	Psychological support	Limited data

score (LOCF) of 4.5 ± 2.6 compared with a baseline of 6.5 ± 1.7 . Despite this marked placebo effect Lacosamide was superior to the placebo, but it raised questions regarding the repeatability of such an intervention, given the extensive placebo effect. Thus, in a recent study of three fixed-dose regimens, 68% of participants in the PA reported 'feeling better' on the patient global impression change (PGIC) evaluation compared with 69%, 81% and 83% on Lacosamide 200, 400 and 600 mg, respectively [Wymer *et al.* 2009]. Similarly, on the Likert pain scale the PA demonstrated a least-squares mean change of -1.6 from baseline and the only group which was significantly different from placebo was Lacosamide 400 mg.

In the only published trial of a medicinal cannabis-based product in the treatment of PDN, thirty subjects were randomised to either Sativex (tetrahydrocannabinol and cannabidiol) or placebo [Selvarajah *et al.* 2009]. The placebo effect was actually greater than with Sativex, with a reduction in all modalities of the pain diary score; indeed the mean reduction in the total pain score in the PA was 37% compared with 20% with active treatment.

Such a significant placebo effect is worthy of further investigation, particularly when planning future trials of agents for PDN. The possible predictors of the placebo response have been assessed in three trials of Lamotrigine using pooled data of 252 placebo subjects (222 had PDN) [Irizarry *et al.* 2009]. A higher baseline pain score and a faster rate of recruitment were both identified as independent predictors of the placebo response. In an analysis of the Sativex trial, Selvarajah and colleagues suggested that depression may potentially be an important confounding factor as subjects with depression have a higher baseline pain score and consequently by entering a trial respond better to both the placebo and active drug [Selvarajah *et al.* 2009]. With depression being so common in PDN this confounding factor should clearly be accounted for, however, exclusion by assessing depression scores may not suffice [Vileikyte *et al.* 2009]. Indeed the placebo response is a well-known entity in trials of depression [Dworkin *et al.* 2005]. Also centres that recruit at a faster rate may introduce bias as they may represent those centres where more of the subjects have intractable PDN and are therefore more eager to participate in novel treatments [Irizarry *et al.* 2009].

The placebo response is also thought to vary along the time course of a trial [Quessy and Rowbotham, 2008], hence the FDA and other regulatory agencies require studies of at least 12 weeks for chronic pain [Rappaport, 2007]. The premise being that a placebo effect is thought to stabilize after an initial period of several weeks [Katz *et al.* 2008; Dworkin *et al.* 2005] with longer-term trials producing a plateau. However, an analysis of the placebo response variability in trials of PDN did not show such a plateau and variability may exist beyond 19 weeks [Quessy and Rowbotham, 2008].

A number of approaches have been suggested to separate the drug from the placebo response [Dworkin *et al.* 2005] and include use of a placebo run-in period (in order to cull placebo responders), flexible dosing and the exclusion of subjects with mild pain [Katz *et al.* 2008; Quessy and Rowbotham, 2008]. However, the incorporation of these designs into clinical trials of pain has shown little benefit. Indeed McQuay conducted a review of the placebo response and concluded that the greatest determinants of the placebo response are in fact random factors [McQuay, 2008]. Thus, the placebo effect is certainly one that should be considered prior to the initiation of any new study in PDN. Perhaps the current double-blind parallel randomised controlled designs in trials of PDN require modification, to minimise the placebo effect and limit obscuration of the true treatment effect.

Novel approaches for the treatment of painful diabetic neuropathy

Given the limitations of current treatments of PDN in relation to limited therapeutic effect, significant side effects and the placebo effect, we briefly review novel mechanisms and agents currently in development which may have therapeutic potential in PDN.

Transient receptor potential vanilloid receptor 1 (TRPV1). TRPV1 is a nonselective cation channel abundantly expressed in C-fibres [Wong and Gavva, 2009] and several observations suggest a potentially important role in the modulation of TRPV1 as a therapeutic for pain. Capsaicin can cause desensitization of TRPV1 channels and relieves pain in humans [Knotkova *et al.* 2008] and pain behaviour in animals [Szallasi and Blumberg, 1999, 1993]. Similarly, antagonists at the TRPV1 receptor relieve pain behaviour in rodent models of inflammation [Joshi *et al.* 2009], osteoarthritis and cancer.

Furthermore, TRPV1 knockout mice display reduced sensitivity to noxious stimuli [Christoph *et al.* 2008]. Of the TRPV1 agonists, capsaicin is the most widely studied in PDN. Its use has been limited to topical administration, due to its very narrow therapeutic index and undesirable side effects following systemic administration. Topical administration however is not without its drawbacks; unlike its more potent analogue Resiniferatoxin (RTX), Capsaicin evokes an excitatory response prior to desensitization and this has been postulated as one of the reasons for noncompliance during clinical trials. Twenty two patients with chronic severe PDN were randomized to 0.075% topical Capsaicin or vehicle for 8 weeks and reported a significant improvement in pain intensity (16% versus 4.1%) and pain relief (44.6% versus 23.2%) in the Capsaicin group [Tandan *et al.* 1992]. A follow-up open-label study by the same group noted improvement or complete cure of pain in 50% of patients. A similar study reported a 90% improvement in symptoms in those treated with Capsaicin [Scheffler *et al.* 1991]. A larger study found topical Capsaicin to be equivalent in efficacy to Amitriptyline, but with a better safety profile [Biesbroeck *et al.* 1995]. The Capsaicin Study Group carried out a multicentre, double-blind, vehicle-controlled trial of topical capsaicin in 252 patients with painful DPN and reported a significant reduction in pain scores versus vehicle [The Capsaicin Study Group, 1991]. In each of these trials, capsaicin was well tolerated, the most common side effect being that of localized burning which improved over the duration of the trial. A systematic review of Capsaicin trials of six randomised controlled trials in neuropathic pain and the relative benefit of topical Capsaicin compared to placebo produced a number needed to treat (NNT) of 5.7 [Mason *et al.* 2004]. A higher concentration dermal patch has been tried recently in patients with human immunodeficiency virus (HIV)-related painful neuropathy and showed efficacy, tolerability and safety for at least 12 weeks [Simpson *et al.* 2008a, 2008b]. However, topical Capsaicin produces a uniform epidermal nerve fibre injury with a marked reduction in IENFD which takes ~50 days to recover [Polydefkis *et al.* 2004]. Thus, it is not surprising that it works for 12 weeks. However, given that IENFD loss is already considerable in diabetic patients, may be related to the genesis of pain [Sorensen *et al.* 2006a] and demonstrates slower rates of regeneration [Polydefkis *et al.* 2004], the authors would not recommend this treatment for patients with PDN.

This is particularly relevant in diabetes as small fibres regulate skin vasomotor responses and sweating, disturbance of which may predispose to ulceration [Demiot *et al.* 2006; Fromy *et al.* 2002]. There are several ongoing phase 2 and 3 trials investigating the use of injectable preparations of capsaicin in a variety of pain syndromes and an excellent review of trials using Capsaicin in other pain syndromes can be found elsewhere [Knotkova *et al.* 2008]. The results of clinical trials with topical RTX in patients with PDN have never been published. Although several different molecules selectively antagonize the TRPV1 receptor and many have been tested *in vitro* and in rodents, there are very limited data in humans [Chizh *et al.* 2007]. Some clinical trials were terminated early due to hyperthermia whilst [Gavva *et al.* 2008] the results of other phase 1 trials are yet to be published [Madej *et al.* 2009]. Thus, the clinical potential for TRPV1-related treatment remains to be explored in DPN.

Tumour necrosis factor α . Tumour necrosis factor (TNF)- α is one of a group of pro-inflammatory cytokines which mediate hyperalgesia in a diverse range of inflammatory and neuropathic conditions [Uceyler and Sommer, 2008]. TNF- α production is upregulated following nerve injury and linked to hyperalgesia, whilst cytokine inhibitors and anti-inflammatory cytokines have an analgesic effect. TNF- α and Interleukin-2 (IL2) levels are increased in painful neuropathies compared with nonpainful neuropathies [Uceyler *et al.* 2007]. TNF- α may also be involved in the pathogenesis of experimental diabetic neuropathy [Satoh *et al.* 2003]. Although the precise mechanism is not clear, TNF- α level is higher in the serum of diabetic patients compared with normal individuals and it has been implicated in the development of diabetic microangiopathy and macroangiopathy [Katsuki *et al.* 1998]. In a recent study of gluteal fat biopsies from obese patients, adiponectin was shown to be a modulator of local vascular tone by increasing nitric oxide bioavailability, but this capacity was lost in obesity by the development of adipocyte hypertrophy, leading to hypoxia, inflammation (increased TNF receptor 1) and oxidative stress [Greenstein *et al.* 2009]. Hypertriglyceridaemia has recently been associated with the development of diabetic [Vincent *et al.* 2009; Wiggin *et al.* 2009] and idiopathic small fibre [Tavakoli *et al.* 2010; Smith and Singleton, 2008] neuropathy and can of course induce TNF- α production [Liu *et al.* 2008]. In experimental diabetes a reduction in

NCV occurs following the administration of TNF- α [Satoh *et al.* 2003] which improves following the administration of the antioxidant N-acetylcysteine [Sagara *et al.* 1996]. The administration of insulin and antioxidant therapy results in a reduction of TNF- α and an improvement in neuropathy [Sharma *et al.* 2007]. Furthermore, experiments using antibodies to TNF- α and other cytokines have shown a marked reduction in hyperalgesia and mechanical allodynia [Schafers *et al.* 2001]. TNF- α also induces the upregulation of cyclooxygenase-2 (COX-2) and associated immuno-inflammatory substances including prostaglandin E2 (PGE2), IL6 and calcitonin gene related peptide (CGRP) [Ma and Quirion, 2006] and appears to be involved in the regulation of nerve growth factor (NGF) [Takei and Laskey, 2008].

Several commonly prescribed drugs in diabetes such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers have been shown to have anti-TNF properties *in vivo* and *in vitro* [Madej *et al.* 2009]. And indeed both Lisinopril [Reja *et al.* 1995] and Trandalopril [Malik *et al.* 1998], have been shown to ameliorate diabetic peripheral neuropathy. In animal studies, Gliclazide [Qiang *et al.* 1998a], and Troglitazone [Qiang *et al.* 1998b] have been shown to inhibit TNF- α and ameliorate neuropathy. A large questionnaire-based retrospective study of 33,000 Japanese patients with diabetes found a reduction in reported symptoms of neuropathy in those treated with Troglitazone [Satoh *et al.* 2003]. Although Troglitazone has been withdrawn both Pioglitazone and Rosiglitazone are currently prescribed for improving glycaemic control. Anticytokine treatment such as Infliximab, thalidomide and lenalidomide have been successfully used in the treatment of complex regional pain syndromes [Bernateck *et al.* 2007; Schwartzman *et al.* 2003]. However, there are case reports of infliximab-induced acute sensory motor neuropathy, which merits caution [Faivre *et al.* 2010]. Hence, the potential for these therapies in the treatment of PDN, especially if they only need to be administered intermittently, is worthy of exploration.

Protein kinase-C inhibitors. The link between protein kinase C (PKC)- β activation, endoneurial ischaemia and neuropathy is well established and prompted the now-aborted Ruboxistaurin (PKC- β inhibitor) clinical trial programme in diabetic neuropathy. A randomized control trial

of Ruboxistaurin versus placebo showed no overall differences between the groups in terms of the primary endpoint (vibration detection threshold) but there was a significant reduction in symptom scores in the Ruboxistaurin treated group [Vinik *et al.* 2005]. In a more recent but relatively small study Ruboxistaurin improved skin blood flow and improved the neuropathy symptom score [Casellini *et al.* 2007]. However, PKC comprises a group of key regulatory enzymes which modulate neuronal function, the synthesis and release of neurotransmitters and the regulation of receptors. Experimental studies have implicated the role of PKC activation in the development of neuropathic pain and PDN [Kamei *et al.* 2001]. In postchemotherapy painful neuropathy, increased phosphorylation of other PKC isoforms (γ/ϵ) has been demonstrated in the thalamus and periaqueductal gray which can be inhibited and is associated with pain relief after supraspinal administration of the PKC specific inhibitor calphostin C [Norcini *et al.* 2009]. In diabetic mice activation of Ca^{2+} -dependent PKC in the spinal cord has been shown to contribute to the development of mechanical allodynia [Honda *et al.* 2007]. Furthermore, a recent study has shown the fascinating interaction between several different pain pathways with PKC as a central mediator, as enkephalin-mediated activation of the presynaptic delta-opioid receptor prevents increased neuronal Na (v) 1.7 in dorsal root ganglion (DRG) via inhibition of PKC [Chattopadhyay *et al.* 2008]. Hence, the future role of PKC in PDN needs to be explored.

Sodium channel antagonists. The important role of voltage-gated sodium channels has been established primarily in experimental studies which have causally linked changes in sodium channel expression and modulation to channel gating properties or current density in nociceptor neurones and different pain states [Dib-Hajj *et al.* 2009a, 2009b]. The sodium channel isoforms Na (v) 1.3, Na (v) 1.7, Na (v) 1.8, and Na (v) 1.9 are particularly important in the pathophysiology of pain. Thus, gain-of-function mutations in SCN9A, the gene encoding Na (v) 1.7, has been linked to a twofold increase in firing frequency following depolarization of DRG neurones [Estacion *et al.* 2009] providing a basis for the association with inherited erythromelalgia [Fischer *et al.* 2009; Han *et al.* 2009] and paroxysmal extreme pain disorder, while

loss-of-function mutations in SCN9A has been linked to complete insensitivity to pain.

Nonspecific sodium channel blockers such as Mexilitene, a class Ib sodium channel antagonist, are used for the treatment of neuropathic pain and cardiac arrhythmias. As a general rule, most treatment guidelines recommend Mexilitene as a third-line agent [Dworkin *et al.* 2007] owing to its limited efficacy and side effects. A meta-analysis of 19 trials using either lidocaine or Mexilitene found that both of these drugs were superior to placebo and equal to morphine, gabapentin, Amitriptyline, and amantadine for neuropathic pain [Tremont-Lukats *et al.* 2005]. No major adverse events were reported in the clinical trials and the most common side effects were drowsiness, fatigue, nausea and dizziness. A Cochrane database review also reached the same conclusions [Challapalli *et al.* 2005]. European guidelines however do not recommend the use of Mexilitene for DPN [Attal *et al.* 2006]. In order to overcome the problems associated with the use of Mexilitene, a group in Stanford has identified factors which may help to identify those patients who may tolerate chronic Mexilitene therapy [Carroll *et al.* 2008]. A fascinating study in a girl with inherited erythromelalgia suggests that some patients with this condition may show a favourable response to Mexilitene due to a use-dependent effect on mutant Na (v) 1.7 channels [Choi *et al.* 2009].

These data suggest that future strategies which may prove to be more efficacious must involve isoform-specific blockers of these channels, facilitated by studies of ion-channel pathophysiology to define specific abnormalities in ionic conductance and allow tailored pharmacologic blockade or modulation [Kuwabara and Misawa, 2008].

Nonpharmacological treatment of diabetic neuropathy

Whilst pharmacotherapy is the mainstay of therapy for the relief of PDN [Max *et al.* 1992]. Alternative nonpharmacological treatments such as acupuncture [Abuaisha *et al.* 1998], transcutaneous electrical nerve stimulation (TENS) [Kumar and Marshall, 1997], spinal cord stimulation [Tesfaye *et al.* 1996], percutaneous electrical nerve stimulation (PENS) [Hamza *et al.* 2000], low-intensity laser therapy (LILT) [Zinman *et al.* 2004] and monochromatic infrared light [Leonard *et al.* 2004] are used in patients who are unresponsive or cannot tolerate

pharmacotherapy, however the evidence for these approaches is limited and needs to be carefully reviewed.

Acupuncture. Acupuncture, developed in Chinese medicine in the fifth century BC was first brought into Europe in the 17th century [Hsu, 1996]. Its major attraction is that it is relatively inexpensive, painless and free from side effects. Its efficacy in diabetic painful neuropathy is supported by a small number of clinical trials which has facilitated its acceptance in pain clinics in most countries [Andersson and Lundberg, 1995]. The mechanism of action of acupuncture remains unclear [Eshkevari and Heath, 2005; Eshkevari, 2003], however it has been proposed that acupuncture stimulates A- δ and c afferent fibres in muscles which activates the spinal cord, midbrain and hypothalamus leading to the release of endorphins in the peripheral circulation and CSF and inducing analgesia via enkephalins which block neuropathic pain [Eshkevari, 2003; Abuaisha *et al.* 1998]. A small study in diabetic patients with painful neuropathy demonstrated a significant improvement in pain relief and the ability to sleep at night [Abuaisha *et al.* 1998]. Another study claimed multiple benefits using wrist ankle acupuncture, but also claimed to improve blood sugars and lipids, lower blood viscosity and restore the 'function of peripheral nerve cells' [Jiang *et al.* 2006]. Electroacupuncture (EA) has been shown to be efficacious via the release of a number of neuropeptides depending on the frequency of stimulation, with 2 Hz releasing enkephalin, b-endorphin and endomorphin, whilst 100 Hz releases dynorphin [Han, 2004]. EA has also been shown to decrease substance P and increase beta endorphin levels [Lee *et al.* 2009]. Beyond simple symptom relief the potential for this therapy has also been explored in a small study of diabetic patients with diabetic gastroparesis and demonstrated an improvement in gastric emptying time as well as the Gastroparesis Cardinal Symptom Index (GCSI) [Wang *et al.* 2008].

Electrical spinal cord stimulation. Spinal cord stimulation has been used over the last 40 years [Shrivastav and Musley, 2009] and the original idea was pioneered in the late 1960s by Dr Norman Dhealy, a neurosurgeon, who implanted the first dorsal column stimulator in a patient suffering from terminal metastatic cancer. Currently, it is widely used for the management of different types of chronic neuropathic or intractable pain [Shrivastav and Musley, 2009].

A simplistic explanation for the mode of action of electrical spinal cord stimulation (ESCS) is that of the production of an electrical field on the dorsal horns of the spinal cord. However, recent data generated in an experimental mononeuropathy model using tactile thresholds has demonstrated that ESCS may activate the descending serotonergic pathways, thus inhibiting spinal nociceptive processing [Song *et al.* 2009]. Two small studies have shown ESCS to be effective in 6/10 patients with chronic intractable PDN, to achieve relief within 3 months of implantation followed by continued relief for a mean of 3.3 years in the six patients who achieved an initial response. The expense and invasive nature precludes recommendation as a routine option for treatment [Chong and Hester, 2007; Daousi *et al.* 2005], however a cost-effectiveness analysis of ESCS has shown that whilst the cost was greater than for conventional pain therapy in the first 2.5 years, it became less after this period especially as 15% of patients were able to return to work [Kumar *et al.* 2002].

Transcutaneous electrical nerve stimulation. In a study of diabetic patients with mild to moderate neuropathic pain, TENS showed an improvement in pain, numbness and allodynia [Forst *et al.* 2004]. Another study showed cyclic doses of electrical stimulation through a contact stocking electrode may be effective in alleviating neuropathic pain. However, pain relief was maintained after discontinuation of therapy [Armstrong *et al.* 1997; Kumar and Marshall, 1997], questioning the direct efficacy of this treatment and invoking the 'placebo effect'. In a recent analysis from the American Academy of Neurology the effectiveness of TENS was assessed from two Class II studies and given a Level B recommendation for the treatment of PDN [Dubinsky and Miyasaki, 2010].

Percutaneous electrical nerve stimulation. Three weeks of treatment with PENS showed a significant improvement in neuropathic pain for more than 6 months, questioning the direct benefit of this treatment and again raising the intriguing role of the 'placebo effect'. In addition to decreasing extremity pain, PENS therapy improved physical activity, sense of well-being and quality of sleep while reducing the requirement of oral nonopioid analgesic medication [Hamza *et al.* 2000].

Magnetic field therapy. Magnetic field therapy has been employed in a range of medical problems including arthritis, chronic pain, wound healing, insomnia and headaches [Colbert *et al.* 2009]. A placebo-controlled trial has shown that transcranial magnetic stimulation is effective for the treatment of postherpetic neuralgia and central poststroke pain [Khedr *et al.* 2005]. Static magnetic field therapy delivered by wearing a constant multipolar sole in the shoe significantly reduced neuropathic pain in a multicentre parallel group study [Weintraub *et al.* 2003]. Repetitive transcranial magnetic stimulation at the prefrontal [Borckardt *et al.* 2007], motor [Andre-Obadia *et al.* 2008] and somatosensory cortex [Topper *et al.* 2003] has been shown to provide relief for disabling and refractory neuropathic pain. However, pulsed low-frequency electromagnetic fields delivered in a repetitive and cumulative manner failed to show a benefit in neuropathic pain [Weintraub *et al.* 2009]. Frequency-modulated electromagnetic neural stimulation (FREMS), however, has been shown to increase microvascular blood flow and provide pain relief, but needs to be confirmed in larger study [Conti *et al.* 2009].

Low-intensity laser therapy. LILT has been shown to be beneficial in several pain models including patients with neuropathic pain [Chow *et al.* 2009]. The exact mechanism of pain relief is not established but increased release of serotonin and endorphin as well as anti-inflammatory effects have been suggested. There is only one clinical trial in which the administration of biweekly therapy over 4 weeks in 50 diabetic patients showed a reduction in weekly mean pain scores [Zinman *et al.* 2004].

Monochromatic near-infrared treatment. Several studies have shown that temporary application of monochromatic near infrared photo energy (MIRE; Anodyne Therapy System) increases foot sensitivity and reduces neuropathic pain [Harkless *et al.* 2006; DeLellis *et al.* 2005; Leonard *et al.* 2004; Prendergast *et al.* 2004] and this has been attributed to the release of nitric oxide [Goldberg, 2005].

Nerve decompression. Decompression of nerves in the lower extremity has been claimed to improve sensation and provide pain relief and has therefore been proposed for use in patients with neuropathy who have failed conventional medical treatment [Valdivia *et al.* 2005].

However, a systematic review showed that only class IV studies supported the utility of this therapy, hence the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has concluded that this treatment is unproven (Level U) until prospective randomized controlled trials with standard definitions and outcome measures of neuropathy are undertaken [Chaudhry *et al.* 2006].

Dressings. Whilst a number of dressings including OpSite, Fixomull and Lycra[®] have been used to treat patients with PDN [Troy, 2002], the evidence for their efficacy is limited. In a small study of 33 patients with PDN OpSite was applied to one and then the other painful leg for 4 weeks each. Pain as assessed by visual analogue scale was significantly reduced in the OpSite-treated limbs which was associated and a significant improvement in contact discomfort, sleep, mood, appetite and mobility with a reduction in paracetamol intake [Foster *et al.* 1994]. Given the limited evidence base and the fact that OpSite film can result in an increased risk of fungal and bacterial infection [Strickland, 1997], this treatment is not recommended.

Exercise. Specific exercise such as tai chi chuan has been shown to improve fasting blood glucose and peripheral NVCs in patients with type 2 diabetes [Hung *et al.* 2009; Orr *et al.* 2006]. Patients with mild to moderate neuropathic pain have demonstrated an improvement in symptoms after 30–40 minutes of yoga for 40 days [Malhotra *et al.* 2002]. In a study of 149 patients with type 2 diabetes, 40 days of yoga therapy improved blood glucose in 104 patients, particularly those with a short duration of diabetes and good glycaemic control [Nayak and Shankar, 2004; Jain *et al.* 1993].

Psychological therapy. Depression among diabetic patients is reported to be almost double compared with nondiabetic patients [Yoshida *et al.* 2009; Egede *et al.* 2002; Anderson *et al.* 2001]. In a recent longitudinal study, neuropathy itself has been shown to be a risk factor for depressive symptoms by generating pain and unsteadiness, with the latter being particularly related to a perception of diminished self-worth due to an inability to perform normal social roles [Vileikyte *et al.* 2009]. Thus, psychological treatment may be another nonpharmacological treatment for this group of patients and has been shown to have a positive effect on the quality of

life and emotional well-being in diabetic patients [Yalcin *et al.* 2008].

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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