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Review

Treatment of diabetic peripheral neuropathy: a review

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Keywords
neuropathic pain; noradrenaline reuptake inhibitors; opioids; pregabalin; tricyclic antidepressants

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Abstract

Objectives This review surveys current pharmacotherapies available for the treatment of diabetic peripheral neuropathy (DPN), emphasising their mechanisms of action.

Methods A comprehensive literature review focusing on the 'pharmacotherapy and treatment of diabetic peripheral neuropathy' was conducted. The Database of International Pharmaceutical Abstracts, EMBASE, PubMed, OVID, Scopus, Google and Google Scholar were searched, and reference lists of relevant articles were also included.

Key findings Diabetic peripheral neuropathy is often inadequately treated, and the role of improving glycaemic control specifically in type-2 diabetes remains unclear. It is crucial to explore the mechanisms of action and effectiveness of available therapies. Major international clinical guidelines for the management of DPN recommend several symptomatic treatments. First-line therapies include tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors, and anticonvulsants that act on calcium channels. Other therapies include opioids and topical agents such as capsaicin and lidocaine. The objectives of this paper are to review current guidelines for the pharmacological management of DPN and to discuss research relevant to the further development of pharmacological recommendations for the treatment of diabetic neuropathy.

Summary Diabetic neuropathy is a highly prevalent, disabling condition, the management of which is associated with significant costs. Evidence supports the use of specific anticonvulsants and antidepressants for pain management in patients with diabetic peripheral neuropathy. All current guidelines advise a personalised approach with a low-dose start that is tailored to the maximum response having the least side effects or adverse events.

Introduction

Diabetes has become an epidemic problem in the 21st century. According to the International Diabetes Federation, the global population of diabetes patients is predicted to reach a pandemic level of 366 million by 2030, double the number from 2000.[1] Diabetic peripheral neuropathy (DPN) is the most common diabetic complication, the most common form of neuropathy, and the leading cause of disability, foot ulceration and ultimately amputation. Furthermore, twenty to thirty per cent of DPN patients suffer neuropathic pain,[2–4] which is often chronic, severe and difficult to treat and manage. This pain negatively affects quality of life and poses a significant burden, increasing associated health costs. It has been estimated that the total yearly per-patient cost of diabetes is $6632[5]; the cost is twofold greater for those with peripheral neuropathy, and fourfold for those with moderate to severe pain.[5] Patients with DPN also score higher for the experience of anxiety, depression and sleep disturbances.[6,7]

The major sign and symptom of DPN is symmetrical sensory pain affecting the lower limbs.[8] Other presentations include atypical pain, numbness, pins and needles, and hot or burning sensations.[9] It can also feature other presentations of nerve motor dysfunction, such as muscle weakness, poor balance and propensity to fall.

Treatment of DPN is challenging, and effective therapies are not available for many patients; therefore, developing improved pharmacotherapy and guidelines are essential. In the last twenty years, a number of professional associations

have published many different international clinical practices; these help physicians choose appropriate pharmacotherapy plans for the management of DPN.[10] There is a limited literature with regard to pharmacological and combination treatment to prevent or reverse DPN changes or to provide total pain relief. There are a number of unmet needs in the therapeutic management of painful DPN. These include the need for randomised controlled trials with active comparators and data on the long-term efficacy of agents used. Finally, there is a need for appropriately designed studies to investigate non-pharmacological approaches.

This paper will discuss pharmacotherapy approaches based on a literature review of existing studies, guidelines and clinical practices for the treatment of diabetic neuropathy.

Methods

A comprehensive literature review focusing on the 'pharmacotherapy and treatment of diabetic peripheral neuropathy' was conducted. The Database of International Pharmaceutical Abstracts, EMBASE, PubMed, OVID, Scopus, Google and Google Scholar were searched, and reference lists of relevant articles were included.

Search strategy and inclusion criteria

The key words used were 'diabetic neuropathy', 'DPN', 'Diabetes Guideline', 'diabetic complications', 'Drugs', 'pharmacotherapy', 'pharmaceuticals', combined with 'drugs' and 'medicines.' The term 'DPN' was also searched in combination with 'Opioids, Pregabalin, Serotonin–noradrenaline reuptake inhibitors, Tricyclic antidepressants' and 'gabapentin, duloxetine, tramadol, opioids, lidocaine patch, and capsaicin patch'. Additional journal articles not found through searching the above databases were individually retrieved. The websites of relevant organisations, such as the WHO, were also consulted for research articles. The search was limited to the period from January 1990 to December 2019. Articles that the author considered not relevant were excluded from the review.

Out of the initial return of 613 articles, 56 were chosen for further screening and analysis. The final analysis consisted of 93 articles (Figure 1).

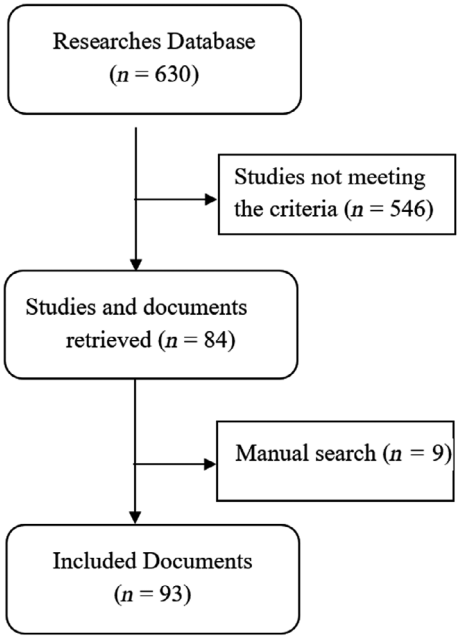

Figure 1 Schematic diagram elaborating the selection of studies/documents.

Results and discussion

Pathophysiology of DPN

The pathogenesis of DNP is not fully understood. Several theories have been proposed to explain the pain related to the diabetic neuropathy. Diabetic peripheral neuropathy is characterised by diffuse damage to the peripheral nerve fibres. About 30–90% of patients with diabetes have peripheral neuropathy. Diabetic sensorimotor polyneuropathy (DSPN), the most common type of diabetic neuropathy, is associated with pain, an impaired quality of life, significant morbidity and increased healthcare costs.[11] An increased free-radical production along with defective antioxidant mechanisms can generate oxidative stress that has been linked to the development of DSPN. Other theories suggested changes in the blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channel expression and more recently, central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways.[11,12] Additionally, several risk factors are associated with DNP including worsening glucose tolerance, older age, longer diabetes duration, drinking alcohol and cigarette smoking.

Approach considerations

Almost 90% of diabetic foot ulcers can be attributed in a whole or in part to diabetic neuropathy. Any patient with clinical evidence of DPN should be considered at risk for foot ulceration and educated regarding foot care.[13] Ulcer occurrence can be decreased by 50%, and the need for major amputation in non-ischaemic limbs eliminated, by patient education, simple hygienic practices, provision of

appropriate footwear, regular foot examination and the prompt treatment of minor injuries.[14,15]

Glycaemic control

The Diabetes Controls and Complications Trial (DCCT) demonstrated that tight control of blood glucose in patients with type-1 diabetes reduces the risk of DPN by 60%.[16] The same is not the case for type-2 diabetes; several studies have demonstrated that aggressive glycaemic control has no meaningful impact on patient risk for polyneuropathy.[17,18] A systemic review by Callaghan et al. did indicate that glycaemic control prevents the development of polyneuropathy in patients with either type of diabetes. However, tight control also increased the risk of adverse events, namely hypoglycaemic episodes.[19] Another meta-analysis of randomised control studies by Boussageon et al. indicated no significant benefit from intensive glycaemic control in terms of reducing DPN in patients with type-2 diabetes.[20]

Relieving pain

Peripheral neuropathy is the most common type of diabetic neuropathic pain, and its most common sign and symptom is moderate to severe pain.[11,21] International guidelines issued by the American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG IASP) and the National Institute for Health and Care Excellence (NICE) all agree that the first-line medications for treatment are calcium channel α_2-δ ligands (gabapentin and pregabalin) and antidepressants that inhibit reuptake of both serotonin and noradrenaline.[12] Some patients may benefit from opioids or topical therapy with capsaicin or transdermal lidocaine (Table 1).

First-line therapy

Tricyclic antidepressants and selective serotonin and noradrenaline reuptake inhibitors. Tricyclic antidepressants (TCAs) include imipramine and amitriptyline (tertiary amines) along with desipramine and nortriptyline (secondary amines). These block the reuptake of noradrenaline and serotonin by the presynaptic neuron. Another proposed mechanism of action that may contribute to their analgesic effect is blocking the uptake of both 5HT and noradrenaline; meanwhile, their adverse effects likely result from actions on histaminic and muscarinic receptors. Control studies have consistently supported the efficacy of TCAs in treating painful DPN.[22,23] Tricyclic antidepressants are well-absorbed via oral administration, and their lipophilic nature allows them to be widely distributed and to readily penetrate into the central nervous system (CNS). However, they have inconsistent, low bioavailability due to variable first-pass metabolism in the liver, and require uptitration to effective doses, often over a period of 6–8 weeks.[24–27] Side effects include dry mouth, orthostatic hypotension, constipation and urinary retention. Moreover, TCAs are contraindicated in patients with glaucoma, prostate hypertrophy or certain cardiac conduction disturbances.[28,29] Secondary amines are better tolerated than tertiary amines.[30–32]

Serotonin and noradrenaline reuptake inhibitors. Simultaneous inhibition of noradrenaline and serotonin reuptake can relieve pain associated with DPN, postherpetic neuralgia, fibromyalgia and lower back pain.[33] We identified 13 studies that demonstrated the effects of serotonin and noradrenaline reuptake inhibitors (SNRIs) in treating DPN. Duloxetine was the most studied SNRI, with eight randomised controlled trials (RCTs) showing a positive effect for duloxetine compared with placebo.[34–42] A meta-analysis review revealed that duloxetine (60 mg) was significantly more effective than placebo, with a pain reduction of 50% and a NNT of 5 (Table 2).[39] In an open-label, randomised, non-inferiority comparison, duloxetine showed the same efficacy as pregabalin in treating patients with painful DPN.[40] Relative to TCAs, duloxetine has fewer and more favourable side effects due to having less effect on cholinergic and histaminic receptors; constipation was reported in one study.[41] Due to its efficacy, safety profile and cost-effectiveness,[42] duloxetine was endorsed in the 2013 NICE guidelines (Table 1).

Venlafaxine is a potent inhibitor of serotonin reuptake; it also inhibits noradrenaline reuptake at medium to high doses. Review studies revealed that venlafaxine at 150–225 mg/day is significantly more effective than placebo, with a 50% reduction in pain (NNT = 3.6).[43,44] Venlafaxine takes 2–4 weeks for effective treatment (Table 2), and when coming off treatment, patients should taper the dose gradually to prevent the risk of adverse events.[45] Nausea, headache and insomnia are its most common side effects, although increased blood pressure and heart rate have been reported at high doses.[46] It is worth noting that venlafaxine does not have FDA approval for treating DPN. A positive effect of venlafaxine's major metabolite, desvenlafaxine, on DPN has been reported by one RCT at doses of 200–400 mg/day, with good tolerability in both short and long terms.[47]

Calcium channel α_2-δ ligands. Gabapentin and pregabalin both act on the α2-δ l subunit of the presynaptic Ca^{++} channel through the same mechanism[48]; the result is to decrease the release of neurotransmitters, mainly glutamate

Table 1 Selected guideline recommendations for drugs used for pain in diabetic neuropathy

Drug	NNT	AAN	NICE	EFNS	NeuPSIG IASP	Mechanism of action
GABA analogues				Fist line	Fist line	
Pregabalin	5.0	First line	First line			Bind to voltage-gated calcium channels and reduces the synaptic release of several neurotransmitters
Gabapentin	6.0		First line			
TCAs				First line		
Amitriptyline	1.3	Second line	First line			Inhibit reuptake of noradrenaline and serotonin
Imipramine	2.2	Second line			First line	
Desipramine	2.6				First line	
SNRIs		Second line		First line	First line	
Duloxetine	5.0		First line			Inhibit reuptake of noradrenaline and serotonin augmenting descending inhibitory pathways
Venlafaxine	3.1					
Opioids		Second line		Second line	Second line	
Strong opioids	4.1			Second line		
Tramadol	4.4		Second line	Second line		Partial μ-receptor Agonists weak opioid and inhibits noradrenaline and serotonin reuptake
Topical						
Capsaicin (0.075% cream)	6.6			Second line		By depleting substance P at vanilloid nerve
Lidocaine 5% patch	4.0		Second line	Second line		Local anaesthetic

AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; IENFD, intraepidermal nerve fibre density; NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; NICE, National Institute for Health and Care Excellence; NNT, Number Needed to Treat for at least 50% pain relief. Adapted Ref. [11].

Table 2 Recommended doses of drugs or drug classes with strong or weak recommendations[a]

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line, adequate trial 3–8 weeks
Gabapentin extended release	1200–3600 mg, in two divided doses	First line, adequate trial 3–8 weeks
Pregabalin	300–600 mg, in two divided doses	First line, adequate trial 6–8 weeks
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine[b]	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line, adequate trial 4–6 weeks
Tricyclic antidepressants[a]	25–150 mg, once a day or in two divided doses	First line, adequate trial 6–8 weeks
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30–60 min every 3 months	Second line (peripheral neuropathic pain)
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain), adequate trial 3 weeks
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line, adequate trial 4–6 weeks

[a]Consider lower starting dosages and slower titration in geriatric patients. [b]Duloxetine is the most studied, and therefore recommended, of the serotonin–noradrenaline reuptake inhibitors.

and noradrenaline and to some extent substance P.[49] Several studies have shown a significant effect for gapabentin in reducing DPN, and some that it moreover improved sleep, mood and quality of life.[50–56] Doses used ranged from 900 to 3600 mg/day; the efficacy may decrease with decreasing dose, and the NNT to achieve 50% pain

reduction was calculated to be 6 (Table 2). Due to the non-linear kinetics of gabapentin, the dose should be gradually increased until reaching 1800–3600 mg/day in divided doses and should be reduced in renal disease. Gabapentin is well-tolerated by the elderly because of its relatively mild adverse effects and possibly also due to having few drug interactions.[24]

Pregabalin is a more potent calcium channel α2-δ ligand approved by the FDA for treating DPN. Its efficacy has been demonstrated in several randomised studies,[57–61] and one meta-analysis comparing number of drugs found pregabalin to be the most efficacious agent.[62] Pregabalin produces a dose-dependent response in terms of reduced anxiety, reduced sleep disorders and improved quality of life, and the speed of onset of pain relief make it more favourable in patients with chronic pain.[63–66] An initial dose of 150 mg/day is recommended, particularly for older patients; however, it may be gradually increased to achieve maximum benefit at 300–600 mg/day. The NNT to achieve 50% pain reduction was calculated to be 5 (Table 2).[11]

Second-line therapy

Opioid analgesics. Opioid analgesics can be used as first-line therapy in selected clinical situations.[8] However, due to their safety profile and potential for abuse, many guidelines consider opioids as second- or more recently as third-line therapies (Table 1).[26] Several studies have demonstrated positive effects of strong opioids in the management of peripheral neuropathy.[67–73] Oxycodone, morphine and methadone are the strongest opioids used in treating neuropathic pain.[74] A Cochrane review by McNicol *et al.*[75] additionally evaluated strong opioids in treating neuropathic pain and revealed significant pain reduction compared with placebo; however, the studies used were of short duration (<2 weeks), and the risk of opioid misuse or abuse has not been evaluated for patients with chronic neuropathy. Oxycodone dosages range from 10 to 120 mg/day, and morphine from 90 to 240 mg/day with maximum benefit at 180 mg/day; the NNT was 4.1.[26] Further studies are needed to evaluate the long-term risk of chronic opioid use in the management of neuropathic pain.

Tramadol. Tramadol is a partial μ-receptor agonist and a weak opioid that inhibits noradrenaline and serotonin reuptake. Most international guidelines consider tramadol to be a second-line therapy, reserved for those who did not respond to or experienced withdrawal symptoms from first-line therapy.[76–80] Harati *et al.*[78] used a double-blind randomised trial to evaluate the efficacy and safety of tramadol as a treatment for DPN pain. They found that a dose of 210 mg/day was more significant and effective than placebo in relieving DPN pain ($P < 0.001$). A Cochrane review that assessed the efficacy of tramadol considered results from six RCTs and found tramadol to be effective at doses of 200–400 mg/day with a calculated NNT of 4.4 (95% CI: 2.9–8.8). However, not all studies reported all outcomes; therefore, data regarding the efficacy of tramadol in neuropathic pain is limited.[81] Its most common adverse effects are constipation, nausea, somnolence, dizziness and orthostatic hypotension. Doses should be reduced in elderly patients and in patients with hepatic or renal impairment.

Third-line therapy

Topical medications. Chilli pepper (*Capsicum*) extracts have long been used as rubefacients in the treatment of painful disorders. Capsaicin is an alkaloid derived from red chilli peppers. Pharmacologically, it works by depleting substance P at vanilloid nerve receptors, which causes a reduction in the conveyance of painful stimuli to the CNS.[82] The Capsaicin Study Group undertook a RCT to assess the efficacy of topical capsaicin cream (0.075%) in relieving DPN-associated pain.[83] They observed significant enhancement in pain relief compared with placebo (58.4% vs 45.3%). The most common side effects were transient burning, sneezing and coughing.

Lidocaine. Lidocaine patches 5% work as peripheral analgesics; lidocaine has low systemic absorption and is used in combination with other analgesic drugs.[84] Very few studies comparing topical lidocaine with other agents exist (Table 3). One study showed pain relief comparable to pregabalin (55% vs 66%); however, more enhancement in quality of life was observed in the lidocaine group.[85]

Other treatments

Alpha lipoic acid. Alpha lipoic acid (ALA) is an antioxidant agent that has been studied for the treatment of DPN. It directly relieves pain by reducing oxidative stress, which is an important mechanism in the pathogenesis of DPN pain.[85] In one RCT assessing the effect of ALA on DPN pain, patients reported greater improvement than with placebo.[85] Additionally, a meta-analysis that used 448 patients and a daily intravenous dose of 600 mg for 3 weeks identified greater pain relief through one year of follow-up.[86] Relative to other DPN treatments, ALA has fewer adverse effects (mainly nausea and vomiting).

Acupuncture. One single RCT to evaluate the effect of acupuncture in DPN pain reported an enhancement in

Table 3 Characteristics of key studies included in this review

Study/year	Study design	No. patients/ studies	Investigational drugs	Daily dose (mg)	Maximum Daily dose	Side effects	Key findings
Rowbotham *et al.* 2005 [30]	Double-blind RCT	47 patients postherpetic neuralgia	Desipramine Amitriptyline Fluoxetine	25 25 20	150 150 60	Dry mouth and constipation/insomnia	Desipramine produced the greatest reduction in pain intensity (47%), followed by amitriptyline (38%) and fluoxetine (35%)
Watson *et al.* 1998 [31]	A randomized, double-blind, crossover trial	31 patients postherpetic neuralgia	Amitriptyline nortriptyline	10–20	20 and 10 for aged >65 years	Epigastric pain, bad dreams, and perspiration slurred speech and urinary retention	No difference with regard to relief of steady pain by visual analogue scales for pain and pain relief
Bansal 2011 [25]	A network meta-analysis	21 trials with diabetic neuropathy	Duloxetine Venlafaxine Amitriptyline Pregabalin Valproate Gabapentin	30–120 37.5–225 10–150 150–600 500–1200 100–3600	120 225 150 600 1200 3600	Sedation, anticholinergic effects/somnolence at 600 mg pregabalin	Gabapentin was found to be most efficacious and amitriptyline to be least safe among the treatments included in the study
Max *et al.* 1992 [27]	RTC cross over study	108 patients with diabetic neuropathy	Desipramine Amitriptyline Fluoxetine	12.5–150 12.5–150 20–40	150 150 40	Confusion, hypotension/ rash, hypotension	Desipramine has the same effect of Amitriptyline in decreasing DPN. Fluoxetine same as placebo
Iqbal *et al.* 2018 [33]	Review	188 paper with diabetic neuropathy	Pregabalin Gabapentin Duloxetine Venlafaxine Amitriptyline	25–75 TID 100–300 TID 20–30 37.5 10–25 mg	300–600 900–3600 60–120 75–225 25–100 m	Somnolence Dizziness Somnolence Nausea Abdominal pain	Duloxetine and pregabalin remain first-line therapy for neuropathic pain in DPN in all 5 of the major published guidelines
Wernicke *et al.* 2006 [35]	Double-blind RCT	329 patients with diabetic neuropathy	Duloxetine	106, placebo 111, 60 mg/day 112, 120 mg/day	120	Nausea, dizziness, somnolence, and fatigue	Duloxetine at 60 mg QD and 60 mg BID is effective and safe in the management of diabetic peripheral neuropathic pain
Allen *et al.* 2014 [47]	Double-blind RCT	412 patients with diabetic neuropathy	Desvenlafaxine	50, 100, 200, or 400 mg/day	400	Nausea and dizziness were the most common adverse events leading to discontinuation	13 weeks study Desvenlafaxine was effective in relieving pain associated with DPN at doses of 200 and 400 mg/day
Gorson *et al.* 1999 [51]	Double-blind RC	40 patients With diabetic neuropathy	Gabapentin	Placebo 300 900	900	Drowsiness (six patients), fatigue (four), and imbalance (three)	The mean reduction in the MPQ score was 8.9 points with gabapentin compared with 2.2 points with placebo ($P = 0.03$, two sample t test)

Table 3 (*Continued*)

Study/year	Study design	No. patients/ studies	Investigational drugs	Daily dose (mg)	Maximum Daily dose	Side effects	Key findings
Tölle *et al.* 2008 [65]	Randomized, double-blind study	395 patients With diabetic neuropathy	Pregabalin	Placebo 150 300 600	600	Pregabalin was well-tolerated at all dosages; adverse events were generally mild to moderate	Statistically significant reduction in pain was observed in patients on pregabalin 600 mg/day, and 46% of patients treated with 600 mg/day pregabalin reported >50% improvement in mean pain scores from baseline
Watson *et al.* 2003 [73]	RCT	36 patients with diabetic neuropathy	Oxycodone	10–40/q12h vs Placebo Recue with paracetamol	40	Somnolence, nausea, constipation	On VAS score: 40 mg oxycodone resulted in significantly lower ($P < 00.001$) mean daily pain
Harati *et al.* 1998 [78]	Randomized, double-blind, placebo-controlled study	131 patients with diabetic neuropathy	Tramadol	50–200/day not exceeds 400/day vs placebo	200	Nausea, constipation, headache and somnolence	Tramadol, at an average dosage of 210 mg/l per day, was significantly ($P < 0.001$) more effective than placebo for treating the pain of diabetic neuropathy
Capsaicin Study Group 1991 [83]	RCT	252 patients with diabetic neuropathy	Capsaicin	Capsaicin 0.075% vs Vehicle cream	0.075%	Transient burning, sneezing, and coughing	Statistical significance favouring capsaicin compared with vehicle for improvement in pain relief
Baron *et al.* 2009 [84]	RCT	96 patients with postherpetic neuralgia (PHN) and 204 painful diabetic polyneuropathy (DPN)	Lidocaine	5% lidocaine medicated plaster with pregabalin	5%		In PHN, more patients responded to 5% lidocaine medicated plaster treatment than to pregabalin (62.2% vs 46.5%), while response was comparable for patients with painful DPN (66.7% vs 69.1%)
Garrow *et al.* 2013 [87]	Pilot. RCT	45 patients	Acupuncture	Five standardised acupuncture points on the lower limb of each leg		Chest pains, exacerbated leg pain and localised leg swelling	Over the 10-week treatment period, small improvements were seen in VAS −15 (−26 to −3.5), MYMOP −0.89 (−1.4 to −0.3), SPS −2.5 (−4.2 to −0.82) and resting diastolic BP −5.2 (−10.4 to −0.14) in the true acupuncture group

MPQ, McGill pain questionnaire; MYMOP, medical outcome profile; QD, once daily; RCT, randomized control trial; SPS, sleep problem scale; VAS, visual analogue scale.

pain relief in 45 subjects, compared with placebo.[87] However, a systematic review by Chen *et al*. found that clinical trials studying the effects of acupuncture lack robust outcome measures (Table 3). Given this deficit of high-quality RCTs, acupuncture has not been approved for treatment of DPN.[88]

Role of the pharmacist

Recently, the role of pharmacists has expanded from product-oriented to patient-oriented.[89] The inclusion of pharmacists on an interdisciplinary primary care team is a promising strategy for improving pain management.[90] Pharmacists are the first healthcare provider patients encounter when inquiring about treatment options regarding DPN pain. Additionally, pharmacists are the providers with primary responsibility for safely and accurately distributing a medication product to a patient with DPN.[91] It is important for pharmacists to provide counselling about dosage information, side effects, and the importance of regular foot examinations. Furthermore, the importance of regular exercise should be stressed; in addition to helping improve glucose control, exercise may prevent not only the progression but possibly even the onset of DPN.

Conclusion

Pharmacological treatment remains the mainstay for treating DPN, with pregabalin, gabapentin and SNRIs being considered first-line therapies. Many pharmacological options are palliative and do not target the underlying mechanisms that cause pain. Throughout the large number of RCTs included in this review, with pharmacological treatment only moderate pain relief was achieved.

Declarations

Conflict of interest

The author(s) declare(s) that they have no conflicts of interest to disclose.

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