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REVIEW ARTICLE

Treating Pain in Diabetic Neuropathy: Current and Developmental Drugs

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Abstract
There is a high prevalence of painful diabetic polyneuropathy (pDPN) with around one-third of all patients with diabetes suffering from pDPN. pDPN has debilitating consequences, with a major impact on morbidity and quality of life. Unfortunately, there is no globally licenced pharmacotherapy that modulates the underlying disease mechanisms to prevent or halt the progression of diabetic neuropathy. The cornerstone of treatment therefore remains optimising glycaemic control and cardiovascular risk factors, and symptom control. Evidence from placebo-controlled studies has shown that antidepressants and anticonvulsants are effective for alleviating pDPN. Current clinical guidelines recommend the treatment of pDPN through the use of amitriptyline (tricyclic antidepressant), duloxetine (serotonin norepinephrine reuptake inhibitor), gabapentin and pregabalin (α2-δ ligands), tramadol and tapentadol (μ receptor agonists and norepinephrine reuptake inhibitors) and topical agents such as capsaicin (transient receptor potential V1 receptor desensitizer), although the latter is known to cause degeneration of small nerve fibers. pDPN can be difficult to treat, which frustrates healthcare providers, patients and caregivers. There is an additional need for clinical trials of novel therapeutic agents and optimal combinations for the management of pDPN. This article reviews the pharmacological management of pDPN, emerging therapies, the difficulties of placebo response in clinical trials and novel proposed biomarkers of treatment response.

1 Introduction

Diabetes has reached epidemic proportions worldwide, with the International Diabetes Federation estimating a prevalence of 425 million people worldwide in 2017, which will rise to 628 million by 2045 [1]. In the UK, the prevalence of diabetes currently stands at around 3.8 million people and is projected to rise to 5 million by 2025 [2]. The earliest presenting and most prevalent complication of diabetes is diabetic peripheral neuropathy (DPN) and it is the primary cause of diabetic foot disease, including ulceration and non-traumatic amputations [3]. DPN is enormously expensive to healthcare systems, with around one-quarter of the diabetes healthcare expenditure in the USA spent on DPN and its sequelae [4]. Up to one-third of patients with DPN suffer with neuropathic pain (painful diabetic polyneuropathy, pDPN) [5–7]. This condition causes a series of unpleasant symptoms, which often results in sleep disturbance, poor quality of life, depression, and unemployment [8–11]. The treatment of pDPN continues to pose a major challenge. In this narrative review, we evaluate the evidence on currently utilized pharmacotherapy with an additional focus on emerging therapies.

2 Methods

A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE/MEDLINE, PubMed, OVID) using keywords, for example: ‘painful diabetic neuropathy’, ‘antidepressants’,

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Key Points

Painful diabetic neuropathy predominantly affects the feet and legs, and arises as a direct consequence of abnormalities of the somatosensory system. A large proportion of patients never receive treatment.

Specific risk factors for painful diabetic neuropathy are not entirely clear. However, underlying cardiovascular risk co-variates including glycaemic control, hypertension, hyperlipidaemia, and smoking, should be modified to prevent the progression of diabetic neuropathy.

Pharmacological treatments for painful diabetic neuropathy include antidepressants (serotonin norepinephrine reuptake inhibitors and tricyclics) and anticonvulsants, which are considered to be first-line agents but only provide partial pain relief. Novel agents are in the pipeline that are currently in or have completed phase II and III trials.

'anticonvulsants', and reference lists of relevant articles with the authors' expertise in pDPN. Articles published from inception of databases to November 2019 were identified. Authors excluded studies that were not considered relevant to the aims of this article. Further appraisal of selected articles was undertaken and relevant explanatory data from the selected articles were included in the review as descriptive prose. Reported trials have focused on typical symmetrical pDPN and not other forms of peripheral nerve lesions/disease in diabetes, i.e. mononeuritis multiplex, diabetic amyotrophy, etc. Included studies used standard definitions and diagnostic criteria for pDPN.

3 Epidemiology

The reported prevalence of DPN is widely variable within the literature. Epidemiological studies have examined heterogenous patient populations and used different case-definitions for neuropathy [12]. A seminal study assessed the prevalence of DPN longitudinally over 25 years in a large number of patients ($N=4400$), using reduced sensation or decreased or absent ankle reflexes to define DPN [13]. At 25 years 50% of patients had DPN, and the diagnosis positively correlated with the duration of diabetes. Another large multicentre study ($N=6500$) of patients with predominantly type 2 diabetes (T2D) found 28.5% of the population had DPN, with increasing prevalence related to older age and duration of diabetes [14]. The PROMISE study followed patients at risk of developing diabetes longitudinally [15]. Interestingly, the prevalence of neuropathy was 50% in patients who developed diabetes, 49% in those with pre-diabetes and 29% in controls [16]. The progression of glucose intolerance over 3 years predicted a higher risk of peripheral neuropathy ($P=0.007$) and nerve dysfunction ($P=0.002$) [16].

In the Diabetes Control and Complications Trial (DCCT), the prevalence of DPN in the conventional treatment arm was ~ 20%, whilst in the intensive treatment arm it was 10% after 5 years, in those with type 1 diabetes (T1D) who were non-neuropathic at baseline [17]. The Epidemiology of Diabetes Interventions and Complications (EDIC) was the observational follow-up of DCCT. The study showed that after approximately 26 years of diabetes, DPN was present in 25% and 35% of patients in the intensive and conventional treatment arms, respectively [18]. The EURODIAB IDDM study showed similar prevalence rates (28% DPN at baseline) with risk factors including age, duration of diabetes, HbA1c and elevated triglycerides [19]. Even in adolescents with diabetes there is an excessive burden of DPN. In the SEARCH for Diabetes in Youth Study [20], in those of an age of 20 years or less with a duration of diabetes of greater than 5 years, the prevalence was 7% in patients with T1D and 22% in T2D [21].

In general, there is a paucity of data on the prevalence of pDPN. The reported prevalence has varied from 8 to 26%, depending on the diagnostic criteria and population studied [5, 22]. However, in the largest community-based study in the UK of ~ 15,000 patients with diabetes, one-third had pDPN symptoms, regardless of their neuropathic deficit [7]. There was an increased risk of painful symptoms in patients with T2D, women and people of South Asian origin [7]. The prevalence of pDPN in the USA is estimated at 20–24% among patients with peripheral neuropathy [23]. Unfortunately, there are data to suggest that mortality is higher in patients with severe chronic pain [24]. Importantly, neuropathic pain in diabetes is under-reported. In a population-based study ($N=350$), the prevalence of painful DPN, as assessed by structured questionnaire and examination, was estimated at 16%; however, of these, 12.5% had never reported symptoms to their doctor and 39% had never received treatment for their pain [25]. Sadosky et al. [26] also reported significant clinical misperceptions by healthcare professionals in the perceived prevalence of pDPN compared to actual estimates reported by patients.

4 Symptoms and Signs of Diabetic Polyneuropathy (DPN)

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" [27]. The neuropathic pain features of DPN were notably

documented by Pavy in the latter part of the 19th century, and in an address to the British Medical Association, he observed that pDPN was "of a burning and unremitting quality, often with a nocturnal exacerbation" [28].

DPN encompasses an array of both 'positive' and 'negative' sensory symptoms. The symptom of pain is a subjective experience that is the result of a complex interaction of sensory input, mood and behaviour incorporating cultural and societal influences. pDPN is often described as burning, prickling or pins and needles, shooting or electric shock-like, cramping, aching and hypersensitive to touch in the lower limbs [12]. Nocturnal exacerbation is a typical characteristic of pDPN often leading to sleep interference. Deep burning pain is considered a good discriminator of painful neuropathy as suggested by the EURODIAB study [19]. Of non-painful symptoms, numbness (dead feeling) and tingling are the most frequently experienced by patients with DPN [19].

5 Pharmacotherapy in Painful DPN

5.1 Current US Food and Drug Administration Treatments

There is a paucity of disease-modifying therapies targeting the natural history of DPN; therefore, symptomatic treatment is the mainstay of management for pDPN. There are currently four US Food and Drug Administration (FDA)-approved treatments available to ameliorate pain of pDPN: pregabalin (Lyrica), duloxetine (Cymbalta), fluoxetine (Prozac) and tapentadol (Nucynta). Drugs approved for other indications such as post-herpetic neuralgia include gabapentin (Neurontin) and lidocaine (Lidoderm patch). Tricyclic antidepressants (TCA) such as amitriptyline are commonly used 'off label' to treat pDPN.

Although fluoxetine has a label for the treatment of pDPN, there is a lack of data to support its use, with only one small study (N = 12 participants) in pDPN included in a Cochrane review [29]. Fluoxetine will not be considered further due to a lack of evidence [29] and efficacy and lack of any recommendation for use in international guidelines [30–34]. Currently utilized pharmacotherapies are detailed in Table 1.

5.2 Aldose Reductase Inhibitors and Alpha-Lipoic Acid: Do They Provide Symptom Relief?

Aldose reductase inhibitors have been successful in reversing experimental diabetic neuropathy [35], although this has not been translated to human clinical trials [36]. A number of aldose reductase inhibitors have been withdrawn due to toxicity or lack of efficacy [36]. In addition, there is limited evidence on their effects on symptom relief [36]. Epalrestat is the only aldose reductase inhibitor licensed for the treatment of DPN. It was initially licenced/marketed in Japan and now is available in other counties such as India and China. Of other disease-modifying agents, alpha-lipoic acid has shown some benefit in treating neuropathic symptoms. The SYDNEY 2 trial [37] and a meta-analysis of clinical trials of alpha-lipoic acid suggested some improvement in nerve function and symptoms [38]. However, it was acknowledged that included studies had methodological flaws [38] and currently there is no recommendation for its use by the FDA or the European Medicines Agency (EMA). In view of the limited good quality methodological data on use in neuropathic pain, the disease-modifying agents aldose reductase inhibitors and alpha-lipoic acid, will not be further discussed in this manuscript. Again, there is a lack of any recommendation for their use in symptom control for pDPN in any international guidelines [30–34].

5.3 International Consensus

There are five major international guidelines that give recommendations for the pharmacological treatment of pDPN [30–34]. A summary of their recommendations is given in Table 2. The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE) and American Academy of Neurology (AAN) give recommendations specifically for pDPN. However, the National Institute for Health and Care Excellence (NICE) guidelines offer recommendations for neuropathic pain of all aetiologies and the European Federation of Neurological Societies (EFNS) for painful polyneuropathy, including pDPN.

Pregabalin, gabapentin, duloxetine/serotonin noradrenaline re-uptake inhibitors (SNRIs) and amitriptyline/TCAs are recommended as the first or second-line agents for the treatment of pDPN in all five guidelines [30–34]. There is consensus among all the guidelines in giving pregabalin first-line status. Moreover, duloxetine/SNRIs are given first-line status in all guidelines, with the exception of the AAN as only one duloxetine trial was graded as class 1 evidence, due to completion rates being < 80% in other duloxetine trials [31]. Additionally, gabapentin is given first- or second-line status by all guidelines [33]. The guidelines then differ on the selection and hierarchy of the other therapeutic agents. The ADA guidelines do not recommend any other agents than pregabalin, gabapentin, amitriptyline and duloxetine [31]. Agents other than gabapentanoids, TCAs and SNRIs are all classed as less than first line [30, 32–34].

5.4 Gabapentanoids (Calcium Channel α_2-δ Ligands)

The α_2-δ ligands were initially developed as anticonvulsant agents prior to being marketed for neuropathic pain [39,

Table 1 Drug therapy for painful diabetic neuropathy

Treatment (references)	Initial dosage	Maintenance dosage	Common adverse reactions and approximate prevalence	Serious adverse reactions
Amitriptyline [73, 105, 107]	10–25 mg once per day	25–100 mg once daily	Dry mouth (9–34%) Sedation (34–46%) Dizziness (5–21%) Headache Insomnia Orthostatic hypotension Nausea Blurred vision Urinary retention	Cardiac arrhythmias Seizures Hepatotoxicity Suicidal thoughts Serotonin syndrome Hyponatraemia Interstitial lung disease
Duloxetine [134–136]	60 mg once per day	60–120 mg per day	Nausea (23–37%) Dry mouth (12–32%) Headache (12%) Dizziness (9–20%) Somnolence (9–20%) Diarrhoea (8–14%) Sweating (6–9%) Tremor (3–10%) Insomnia (10%) Constipation (10%)	Serotonin syndrome Stevens-Johnson syndrome Urinary retention Hepatic failure Hypertensive crisis Interstitial lung disease Hyponatraemia Serizures
Gabapentin [54]	100–300 mg, 1–3 times per day	1,200 mg–3,600 g per day in 3–4 divided dosages	Dizziness (19%) Somnolence (14%) Gait disturbance (14%) Peripheral oedema (7%) Dry mouth Weight gain Headache	Stevens-Johnson syndrome Suicidal thoughts and behaviour Seizures (after rapid discontinuation) Confusion Hepatitis Withdrawal reactions
Pregabalin [77, 80]	25–75 mg 2–3 times per day (usual starting dose is 75mg per day/twice daily with subsequent up-titration depending on age and renal function)	150–600 mg in 2–3 divided dosages	Dizziness (7–28%) Peripheral oedema (6–16%) Somnolence (6–25%) Weight gain (5–9%) Weakness (2–9%) Headache (7%) Dry mouth (2–6%)	Angioedema Stevens-Johnson syndrome Hepatotoxicity Rhabdomyolysis Suicidal thoughts Seizures (after rapid discontinuation) Thrombocytopenia Cardiac arrhythmia Pulmonary oedema
Venlafaxine [140]	37.5 mg once per day	75–225 mg per day	Nausea (10–22%) Somnolence (15%) Sweating (5–10%) Vomiting (6%) Insomnia (5–10%) Diarrhoea Dry mouth Headache Anorexia	Same as duloxetine
Tramadol [150]	50 mg 1–4 times per day	100 mg four times per day	Constipation (29%) Somnolence (33%) Nausea (26%) Headache Dizziness (36%) Sweating	Seizures Serotonin syndrome (particularly if prescribed with selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics) Hallucinations Opioid abuse/misuse
Tapetandol Extended Release (ER) [153–155, 255]	50 mg twice daily	250 mg twice daily	Constipation (~23%) Somnolence (15%) Nausea (30%) Headache Dizziness (24%) Sweating	Same as tramadol and angioedema

Table 2 Current guidelines for the treatment of painful diabetic neuropathy

Treatment	NICE	AACE	EFNS	AAN	ADA
Amitriptyline	1–2	1	1	2	2
Duloxetine	1–2	1	1	2	1
Pregabalin	1–2	1	1	1	1
Gabapentin	1–2	1	1	2	2
Lidocaine 5%	NM	2	NM	3	NM
Valproate	NM	NM	NR	2	NM
Venlafaxine ER	NR	NM	1	2	NM
Capsaicin 0.075% cream	3	NM	NR	2	NM
Tramadol	3 (short term)	2	2–3	2	3
Tapentadol ER	Research recommendation only	NM	NM	NM	3
Dextromethorphan	NM	NM	NR	2	NM

Recommendations are indicated as 1 = first choice, 2 = second choice 3 = third choice

ER extended release, *NM* not mentioned, *NR* not recommended, *NICE* National Institute of Clinical Excellence[30], *AACE* American Association of Clinical Endocrinologists [32], *EFNS* European Federation of Neurological Societies Task Force [34], *AAN* American Academy of Neurology [33], *ADA* American Diabetes Association [31]

40]. Pregabalin and gabapentin are widely used pharmacotherapeutic agents for pDPN, whereas mirogabalin is an emerging therapy in this drug class [39, 40]. Gabapentin and pregabalin are γ-aminobutyric acid (GABA) mimetics; however, they do not bind to the GABA receptor, but exert their analgesic effect through high affinity binding and modulation of the calcium channel α_2-δ proteins in the dorsal root ganglion (DRG) [40]. Modulation of these channels decreases the number of synaptic vesicles fusing with the presynaptic membrane, reducing the release of a number of neurotransmitters (e.g. GABA, glutamate, noradrenaline, substance P and calcitonin gene-related peptide) into the synapse [40, 41]. Compared with other anticonvulsant drugs the α_2-δ ligands do not have significant drug interactions, predominantly as a result of their lack of hepatic metabolism or their modulation of cytochrome P450 activity [42].

5.5 Gabapentin

Gabapentin was the first α_2-δ ligand to receive approval for the treatment of neuropathic pain. It reaches a maximum plasma concentration approximately 3 h after oral ingestion [42–44]. Its half-life is 6–8 h, consequently the drug is typically administered three times daily [44]. A dosing regimen with titration up to 1800 mg and maximum upper dose of 3600 mg is recommended in pDPN [45]. Dose adjustment in individuals with a creatinine clearance of less than 79 ml/min is also advised [46].

Backonja et al. performed an 8-week double-blind, randomized, controlled trial (RCT) of gabapentin monotherapy for the treatment of pDPN ($N = 165$) [47]. The treatments were titrated to a maximum tolerated dose over 4 weeks, followed by a further 4-week fixed treatment period. The highest dose of gabapentin, 3600 mg, was achieved by 67% of patients. Compared with placebo, gabapentin-treated patients had lower pain scores ($p < 0.001$) with improvements in quality of life, mood and sleep. The most common adverse events associated with gabapentin were dizziness (24%), somnolence (23%) and confusion (8%). Further smaller studies have found gabapentin to be more effective than placebo at maximum doses of 1200 mg [48] and 3600 mg [49], but not 900 mg/day [50]. Comparator studies have shown gabapentin to have equal [51] or superior efficacy to amitriptyline [52]. In order to overcome the pharmacokinetic limitations of gabapentin, alternative preparations have been trialed. A large RCT ($N = 421$) of a gabapentin pro-drug, gabapentin enacarbil, however did not lead to significant reductions in the mean 24-h pain intensity score compared with placebo [53].

Meta-analyses and systematic reviews have found gabapentin to be superior to placebo in the treatment of pDPN and other aetiologies of neuropathic pain [54–56]. A Cochrane review of nine RCTs, including three unpublished studies [54], calculated a number-needed-to-treat for benefit (NNTB) of 5.9 (95% confidence interval (CI) 4.6–8.3) to reduce pain intensity by at least 50%. None of the included studies met first-tier evidence criteria, nor were there any unequivocally unbiased studies; however, the pain intensity reduction was consistent across studies at gabapentin doses of 1200 mg or more. Moreover, a recent meta-analysis by the Neuropathic Pain Specialist Interest Group of the International Association for the Study of Pain (NeuPSIG) found gabapentin to have a NNTB of 6.3 (95% CI 5.0–8.3) [55]. Rudroju et al. [56] concluded from a network meta-analysis comparing the efficacy and safety of six antidepressants and anticonvulsants, that gabapentin was the most efficacious treatment. Gabapentin also showed the most favorable benefit-risk balance and the fewest study withdrawals due to adverse effects compared to the other five agents [56].

5.6 Pregabalin

Pregabalin is one of the most commonly recommended treatments of neuropathic pain [31]. It is the second α_2-δ ligand to be developed and was granted approvals approximately 10 years after gabapentin. The pharmacological profile and structure of pregabalin is similar to its predecessor [57]. However, it is more potent and displays a superior preferable pharmacokinetic properties [43, 58]. It is absorbed

more quickly from the gastrointestinal tract and achieves peak blood concentrations 1 h after oral administration [43]. Unlike gabapentin, it has linear pharmacokinetics over its recommended dose ranges. The average half-life is 6 h and it is therefore normally administered in two or three divided doses [43, 57]. Pregabalin may be initiated at 75 mg twice per day and the maximal approved dose for the treatment of pDPN is 300 mg in the USA and 600 mg in Europe [59]. Similar to gabapentin, a dose reduction is required if creatinine clearance is less than 60 ml/min.

Rosenstock et al. performed a double-blind RCT of pregabalin 300 mg/day and placebo over a period of 8 weeks ($N = 146$) [60]. In comparison to placebo, the pregabalin-treated group had a statistically significant reduction in mean pain scores by the end of week 1, which persisted throughout the study. Moreover, pregabalin treatment significantly improved sleep interference, mood disturbance and tension anxiety scores. Adverse events were more common in the pregabalin-treated group (62% pregabalin vs. 29% placebo), but these were mostly mild or moderate. Dizziness, somnolence, infection and peripheral edema were the most commonly reported adverse events. Subsequent studies have found pregabalin at doses greater than 300 mg to be superior to placebo, but associated with more adverse events than lower doses [61–66]. When prescribed at sub-maximal doses (i.e. 150–300 mg), some studies have shown pregabalin to be superior to placebo, but a number of recent, and in some cases very large, trials did not meet their primary endpoint [53, 67–72]. A number of head-to-head studies have also demonstrated a similar efficacy of pregabalin to a number of other pharmacotherapeutic agents [53, 71–76]. Many of these studies are quite small and are likely to be underpowered [72–75]. However, a large RCT designed to assess the efficacy of high-dose monotherapy or combination therapy of pregabalin and duloxetine, found pregabalin 300 mg per day was less efficacious than duloxetine 60 mg per day during the 8-week monotherapy phase ($N = 804$) [76]. When responders to monotherapy were removed from the study, there was a trend towards superiority of pregabalin 600 mg per day versus duloxetine 120 mg per day ($p = 0.068$), although the study was not designed to assess this comparison.

Pooled analyses and systematic reviews consistently find pregabalin to be more efficacious than placebo for treating neuropathic pain at doses of 300 mg and 600 mg per day [55, 77–84]. Higher doses are associated with more adverse events but doses of ≤ 150 mg are unlikely to be effective [77, 81]. A Cochrane Database review found the NNTB for 50% pain reduction in pDPN to be 7.8 (95% CI 5.4–14) with pregabalin 600 mg per day [77, 85]. In fact, a large percentage of improvement in pDPN is thought to be associated with improvements via an indirect effect of improving sleep [86].

The most common adverse events related to pregabalin are similar to those of gabapentin, including: dizziness, somnolence, euphoria, peripheral edema and weight gain [77, 87, 88]. These adverse events are typically mild or moderate. Despite pregabalin being associated with weight gain, Parsons et al. performed a pooled-analysis on data from 11 double-blind RCTs and found no clinically meaningful effect of pregabalin on metabolic parameters such as HbA1c [89].

There have been recent concerns regarding the misuse and safety of pregabalin and gabapentin, which has led to its reclassification to a controlled drug in the UK [90, 91]. These changes have led to an increased regulation of the prescription, storage, dispensing and disposal of both agents. The change has been implemented due to increasing reports of deaths, primarily with recreational misuse [92]. At therapeutic doses, pregabalin and gabapentin have a low risk of addiction [93]. However, prescription of these agents should be avoided, or administered with caution, in patients with substance misuse disorders [90, 94].

5.7 Mirogabalin

Mirogabalin is an emerging α_2-δ subunit ligand for the treatment of neuropathic pain that has recently gained its first approval in Japan [39, 95]. Whereas pregabalin and gabapentin are non-selective ligands for the α_2-δ-1 and α_2-δ-2 subunit of the voltage-gated calcium channel, mirogabalin has a longer dissociation half-life against the α_2-δ-1 compared with the α_2-δ-2 subunit [39, 96]. These unique binding characteristics may result in a putative improved safety profile with superior analgesic effects. A recent large phase 3 RCT ($N = 834$) found mirogabalin 30 mg per day to be superior to placebo [97]. The most common adverse events were similar to those seen using other α_2-δ ligands, including: somnolence, dizziness, peripheral edema and weight gain; however, these were generally mild or moderately severe. A phase 2 RCT of mirogabalin at doses of 15 mg, 20 mg and 30 mg per day found it to be superior to placebo in reducing mean daily pain scores [98]. Javed et al. compared the efficacy of mirogabalin in these studies against other neuropathic pain agent NNTs and suggested that mirogabalin may have a similar efficacy but potentially lower rate of adverse events [39]. Therefore, mirogabalin may be an efficacious and tolerable treatment option for pDPN in the near future.

5.8 Tricyclic Antidepressants

TCAs were first developed in the 1950s, and remain popular treatments for depression. Additionally, they are commonly prescribed and recommended agents for the treatment of neuropathic pain and pDPN [77]. Their analgesic action is not completely understood but involves a multimodal mechanism, including inhibition of noradrenaline and serotonin

reuptake from the synaptic cleft, variable degrees of anticholinergic inhibition, indirect dopaminergic action and possibly sodium channel blockade [99–101]. Amitriptyline is the most commonly prescribed TCA for neuropathic pain. It is rapidly absorbed, but has a low bioavailability because of a large first-pass effect [102]. The terminal elimination half-life ranges from 12.9–36.1 h. Dosing for neuropathic pain starts at 10–25 mg in the evening with up-titration over a number of weeks to a maximum dose of 75 mg per day, or occasionally higher.

Small placebo-controlled RCTs have found amitriptyline to be superior to placebo; however, in two of these studies the dose used was over the recommended prescribing doses in current clinical practice (> 100 mg/day) [74, 103–105]. Small comparator studies have shown amitriptyline to be equally efficacious to α_2-δ ligands [51, 73, 74, 106], other TCAs [103, 105], topical capsaicin [107], lamotrigine [108] and duloxetine [74, 109]. Meta-analyses have found amitriptyline to be more effective than placebo in the treatment of pDPN [110]. Finnerup et al. calculated the combined NNTB for TCAs to be 3.6 (3.0–4.4), whereas the Cochrane Database Library review calculated an NNTB of 5.1 (3.5–9.3) for amitriptyline in the treatment of neuropathic pain [55, 111]. However, the Cochrane Collaboration review concluded that there was a lack of supportive unbiased evidence for a beneficial effect [111]. A network meta-analysis for commonly used pDPN agents by Rudroju et al. found amitriptyline to have the second lowest efficacy, only above placebo, with the lowest safety profile and lowest benefit-risk balance [56]. Other small studies have shown efficacy of other TCA agents (e.g. imipramine, nortriptyline and desipramine), although the evidence for their use is limited [103, 105, 112–118]. Amitriptyline does not require dose adjustment in renal dysfunction but should be used with caution in patients with a history of epilepsy, cardiovascular disease and in the elderly [100–102]. Common adverse events include: drowsiness, dry mouth, constipation, difficulty urinating, tachycardia, dizziness/postural hypotension, sexual dysfunction and headache [111, 119]. Amitriptyline has been utilized as a first-line agent for neuropathic pain for decades. Unfortunately, it has limited robust supporting evidence and dose escalation may often be restricted due to common adverse effects and comorbidities [56, 111].

5.9 Serotonin Norepinephrine Reuptake Inhibitors

Duloxetine is approved for the treatment neuropathic pain and is one of the most widely studied, prescribed and recommended agents for pDPN. Duloxetine relieves neuropathic pain through inhibition of serotonin and norepinephrine reuptake, which enhances descending inhibition of pain [120–122]. Duloxetine is rapidly absorbed, reaching maximal plasma concentrations approximately 6 h after administration, reaching a steady state in the bloodstream within 3 days [121]. Patients with hepatic impairment have a reduced ability to metabolize and eliminate duloxetine; therefore, it is not recommended in patients with hepatic insufficiency [121, 123]. Dose adjustment is not required in mild to moderate renal impairment, but prescription is not recommended for patients with a creatinine clearance < 30 ml/min [123]. Co-prescription with serotonergic drugs (e.g. selective serotonin reuptake inhibitors (SSRIs) and TCAs) increases the risk of serotonin syndrome and should be avoided, particularly monoamine oxidase inhibitors or tramadol [123].

Goldstein et al. [124] performed an large placebo-controlled RCT to determine the efficacy of duloxetine in the treatment of pDPN ($N = 457$). Participants were randomly allocated to placebo or duloxetine at 20 mg, 60 mg or 120 mg, with a 1:1:1:1 allocation ratio. Duloxetine 60 mg and 120 mg met the primary efficacy outcome, reducing 24-h average pain scores compared with placebo. Two further RCTs similarly found duloxetine 60 mg and 120 mg to be superior to placebo for pDPN [125, 126]. Adverse events and study discontinuations were more common in the duloxetine-treated groups, including nausea, somnolence, dizziness, reduced appetite, dry mouth, anorexia, sweating and weakness [124–126]. All three of the aforementioned studies found duloxetine to be safe and well tolerated in three open-label 52-week continuation studies [127–129].

Duloxetine has been compared with a number of other pharmacotherapeutic agents in head-to-head trials. Duloxetine 60 mg has been shown to be superior to pregabalin 300 mg in two RCTs [76, 130] and pooled analysis [110]. However, other studies have found duloxetine to have similar or inferior efficacy to pregabalin and/or gabapentin [56, 74, 131, 132]. Small studies demonstrated no difference in the efficacy of duloxetine and amitriptyline [74, 109, 133]. Overall, duloxetine dosed at 60 mg or greater is effective in treating pDPN, but not at 40 mg or lower doses [134]. The NNTB of duloxetine 60 mg daily for 50% reduction in pain is 5.0 (95% CI 4.0–7.0). The rates of adverse events in placebo-controlled RCTs are greater for duloxetine (72.4%) than placebo (57.2%) [135]. The most common is nausea, with dry mouth, dizziness, somnolence, fatigue, insomnia, constipation, reduced appetite and sweating occurring less frequently [124–126, 134, 135]. Most adverse events occur early after the onset of treatment, are mild to moderate, and do not worsen with time [136]. In order to reduce nausea patients can be advised to take duloxetine with or after food.

Venlafaxine, an alternative SNRI, has also been studied in the treatment of neuropathic pain. A double-blind RCT compared venlafaxine extended-release at 75 mg or 150/225 mg versus placebo for the treatment of pDPN [137]. Venlafaxine was superior to placebo at doses of 150/225 mg. However, notably there were cases of atrial fibrillation in those

treated with venlafaxine and hence the reluctance of some consensus panels to include venlafaxine as first-line agent for pDPN [138]. Other studies have also found venlafaxine to be efficacious in the treatment of neuropathic pain [49, 83, 110]. However, there are only a limited number of relatively small studies [139–141]. The NeuPSIG meta-analysis of 14 studies including SNRIs (duloxetine 20–120 mg; venlafaxine 150–225 mg) had a combined NNTB of 6.4 (95% CI 5.2–8.4) [55].

5.10 Combination Therapy

There is often limited benefit of any one agent as monotherapy, which reflects the complex aetiology of neuropathic pain and challenge of treating it. Combination therapy is frequently used to good effect in clinical practice; however, there are only a small number of studies testing combination therapies. The largest trial in pDPN is COMBO-DN (Combination vs. Monotherapy of pregabalin and duloxetine in DPN) ($N = 804$), which studied duloxetine and pregabalin monotherapy at high doses versus a combination of these two agents at standard dosing [76]. The aim of the study was to determine whether the combination of duloxetine and pregabalin at standard doses (60 mg and 300 mg per day, respectively) was superior to the maximum recommended dose of either agent (120 mg and 600 mg per day, respectively) in non-responders to standard doses of pregabalin and duloxetine. There were no significant differences in the primary outcome between high-dose monotherapy or standard-dose combination therapy. The 50% response rates were 52.1% for combination and 39.3% for high-dose monotherapy ($p = 0.068$). However, the trend of the primary outcome and secondary outcomes consistently favoured combination therapy over monotherapy. Further combination studies have been trialled in patients with neuropathic pain of varying aetiologies. Gilron et al. [142] performed a double-blind, randomized, active placebo-controlled, four-period crossover trial to determine the efficacy of gabapentin, morphine or their combination against placebo for the treatment of neuropathic pain ($N = 57$; 35 pDPN and 22 post-herpetic neuralgia). Combination therapy with gabapentin and morphine at lower doses was more effective than monotherapy of either agent at higher doses. Further comparator studies have reported the efficacy of a number of different treatment combinations for neuropathic pain, including nortriptyline and gabapentin [143], prolonged-release oxycodone and gabapentin [144], imipramine and pregabalin [118], and nortriptyline and morphine [145]. However, not all combination therapy studies have been positive [146–148].

Based on the COMBO-DN study, the combination of duloxetine and pregabalin appears to be safe and efficacious. A meta-analysis of two studies combining gabapentin plus opioid therapy demonstrated superiority compared with gabapentin alone, but with greater adverse events [149]. Two of the international guidelines give recommendations for combining neuropathic pain therapies, but the NeuPSIG recommendations concluded that there is inconclusive evidence [55]. The EFNS guideline suggests TCAs may be combined with gabapentin or opioids [34]. The ADA position statement recommends a trial of combining two of the following three agents: gabapentanoids, SNRIs or TCAs if monotherapy fails, and considering the addition of tramadol/tapentadol if the two-agent combination is inadequate [31].

5.11 Opioid Analgesia

5.11.1 Partial μ Receptor Agonists

Tramadol is a centrally acting synthetic opioid with weak affinity at the μ opioid receptor; however, it has an additional effect in inhibiting norepinephrine and serotonin re-uptake [150]. In an early study of tramadol in pDPN ($N = 131$), an average dosage of 210 mg per day was more effective than placebo ($p < 0.001$) and resulted in better in physical ($p = 0.02$) and social functioning ($p = 0.04$) ratings. However, a Cochrane Collaboration review found the evidence of quality to be low for the efficacy of tramadol in neuropathic pain [151]. The included studies were generally small and short, with a potential for bias. However, three studies reported improvements in pain of 50% or more. A meta-analysis of these three trials showed a risk ratio in favour of tramadol of 2.16 (1.02–4.58) and a NNTB for 50% pain reduction of 4.4 (95% CI 2.9–8.9) [151]. The risk ratio for adverse events compared with placebo was 4.1 (95% CI 2.0–8.4) and the number-needed-to-treat for an additional harmful outcome (NNTH) was 8.2 (95% CI 5.8–14). There is insufficient data of adequate quality to provide convincing evidence that tramadol is effective in relieving neuropathic pain [151]. Despite these shortgivings, tramadol is still recognised as a second- or third-line therapy in all five of the major international guidelines [30–34]. It may be used to treat breakthrough pain in combination with first-line therapy; however, its use in combination with TCAs and SNRIs is cautioned due the potential for adverse reactions including serotonin syndrome, confusion and seizures. The most frequently associated adverse events are fatigue, dizziness and constipation.

Tapentadol has a similar mode of action to tramadol; however, it has stronger affinity at the μ receptor (than tramadol) with inhibition of norepinephrine and serotonin re-uptake. The μ opioid agonism interrupts synaptic transmissions of ascending pain signals at the level of the spinal cord and activates descending inhibition supraspinally, while norepinephrine and serotonin re-uptake increases descending inhibitory tone [152]. To date, there are three published RCTs of tapentadol in pDPN [153–155]. In one of the largest studies by Vinik et al. ($N = 318$), pain score improvements

achieved during the open-label titration period with tapentadol extended release (ER) were maintained during the double-blind phase in patients randomized to tapentadol ER, but diminished in patients randomized to placebo. Treatment-emergent adverse events (≥ 10%) in the tapentadol ER group during the double-blind maintenance phase were nausea (21.1%) and vomiting (12.7%). A pooled analysis of 396 patients with pDPN demonstrated a 30% pain reduction in 65% of patients and a 50% pain reduction in ~ 35% of patients [156]. Incidences of treatment-emergent adverse events were 56% with placebo and 75% with tapentadol ER during maintenance [156]. In 2012, the FDA approved the use of tapentadol ER for the treatment of neuropathic pain [153].

5.11.2 Traditional Opioid Agonists

The use of opioids should be limited wherever possible in view of increasing concerns of dependency, especially with long-term use, and a lack of efficacy in treating pDPN [157]. Suppression of the hypothalamic-pituitary axis with long-term opioid use is an underappreciated problem. This condition can be life threatening, with opioid-induced adrenal insufficiency occurring in up to 29% of people on long-term opioids [158]. The analgesic efficacy of opioids in chronic neuropathic pain is subject to substantial uncertainty and should only be considered when first- to third-line therapies fail. The extent of physician-initiated opioid use in patients with pDPN is in contrast with current clinical guidelines and evidence-based medicine [159]. Traditional opioids (not tramadol or tapentadol) should therefore be actively discouraged as a first-line treatment for pDPN [159] and are generally considered a last oral pharmacological option (or third line) by clinical guidelines due to lack of efficacy, side-effect profile and risk of abuse. However, there is growing evidence that opioid use (again excluding tramadol and tapentadol) in a pDPN population is markedly high. A retrospective analysis of records from 8000 patients with pDPN found that 56% received an opioid before prescription of a first-line drug [160]. Another retrospective study suggested that over half of patients with diabetes were receiving no physician-prescribed treatment in the year following diagnosis of DPN, 54% of those who subsequently received treatment were prescribed opioids and 33% were given the opioid as first-line treatment [161]. Moreover, the availability of alternative non-opioid first-line drugs neither prevented nor replaced opioid use or prescribing in pDPN in the USA [160].

Two short-term RCTs of oxycodone have shown efficacy in pDPN (4 weeks/6 weeks) [162, 163]; however, one of these studies had a small sample size ($N = 36$) and was thus liable to bias. It is known that stronger effect estimates are seen in small to moderately sized trials than in the largest trials [164], therefore caution should be exercised when considering these results. A Cochrane Collaboration review [165] evaluated the use of ten different opioids in 31 trials in the treatment of neuropathic pain. Six studies ($N = 170$) found that mean pain scores with opioids were ~ 1.5 points (out of 10) lower than placebo. It was concluded that the evidence was derived from studies with features likely to overestimate treatment effects [165]. The subsequent meta-analysis demonstrated at least 33% pain relief in 57% of participants receiving an opioid versus 34% of those receiving placebo with a NNTB of 4.0 (95% CI 2.7–7.7) [165]. Assessing the number of participants achieving at least 50% pain relief, the NNTB was 5.9 (3.0–50.0) [165]. The most common adverse event was constipation (34% opioids vs. 9% placebo: NNTH 4.0; 95% CI 3.0–5.6) [165]. It was concluded that further RCTs are required to determine unbiased estimates of long-term efficacy, safety (including addiction potential) and effects on quality of life [165]. Cochrane reviews for oxycodone, hydromorphone, levorphanol, fentanyl, methadone and morphine in neuropathic pain have all shown low-quality evidence for efficacy [166–169]. Traditional opioids may be considered on a case-by-case basis, particularly in those refractory to traditional anti-neuropathic agents.

5.12 Other Treatments for pDPN

A number of additional therapies including sodium valproate, carbamazepine, oxcarbazepine, topiramate, lacosamide, phenytoin, levetiracetam and zonisamide have been trialled in neuropathic pain; however, the level of evidence to support their use is limited [170]. In the Cochrane overview of "antiepileptic drugs for neuropathic pain and fibromyalgia", the author's conclusions provided an overall summary of the data: "other antiepileptic drugs (other than pregabalin and gabapentin), there was no evidence, insufficient evidence, or evidence of a lack of effect" [170]. However, there is evidence from clinical practice and experience that some patients can achieve good results with anticonvulsants other than gabapentin or pregabalin. Two studies in pDPN of sodium valproate showed some benefit in pain relief [171, 172]. Valproic acid inhibits GABA transaminase, and thus increases levels of GABA in the central nervous system. It is also thought to block sodium and calcium channels at the DRG, and thus modulate pain processing at the spinal cord. A gain of function in the 'gatekeeper' sodium$_v$ channels has been reported in a significant proportion of pDPN patients [173]. It may be that targeting this population with therapies that may modulate sodium channels may provide more targeted pain relief; however, this requires further scientific investigation [174].

5.13 Topical Pharmacological Therapies

The management of DPN can be challenging and often requires a multifaceted approach in reducing pain and improving functioning. Numerous topical therapies have been evaluated in pDPN. These treatments may be particularly useful in patients who are unable to tolerate conventional first- or second-line oral therapies [175].

5.13.1 Topical Lidocaine

Lidocaine antagonises voltage-gated sodium channels (including Nav 1.7 and 1.8) and stabilises the neuronal membrane potential on hyperexcitable small nerve fibers, with a subsequent reduction of ectopic neuronal discharges [75, 176]. Barbano et al. [177], in an open-label, flexible-dosing, 3-week study with a 5-week extension, showed a 42% improvement in the Brief Pain Inventory by week 3 in those treated with a lidocaine 5% patch. In a network systematic review and meta-analysis conducted by Wolff et al. [178] of 23 studies, significant pain reduction was shown with the 5% lidocaine patch, which was comparable to that with topical capsaicin, amitriptyline, gabapentin and pregabalin [178]. The lidocaine patch had fewer adverse events and less significant adverse effects compared to systemic therapies [178]. Another systematic review and meta-analysis has also reported similar efficacy with pregabalin to the 5% lidocaine patch [83]. Typically, a 5% lidocaine plasters (up to four) may be applied for up to 18 h and is effective in providing analgesia in pDPN [177].

5.13.2 Topical Nitrates

Topical nitrates are commonly used off-label treatments of pDPN, but only on the basis of a handful of small clinical trials [159]. Impaired nitric oxide (NO) synthesis has been found to play a role in DPN pathogenesis [12]. The use of topical nitrate underpins the theory that impaired nitric oxide synthesis (endothelial and neuronal) is an important causative factor in the pathogenesis of DPN [179]. Several studies suggest that NO production is reduced in diabetes and that the decrease of NO may be related to the pathogenesis of diabetic endothelial damage. The vasodilatory response of vessels to nitrates suggests a potential role in pDPN [164]. There are alterations of neuronal NO synthase in DRG cells and spinal cord that contribute to spinal sensory processing and neuronal plasticity in the dorsal horn (spinal cord) that have been detailed in animal models of DPN [180].

Yuen et al. in a double-blind crossover trial recruiting 22 patients showed a reduction in pain and pain intensity utilising a locally/topically administered isosorbide dinitrate spray [181]. Subsequently, Rayman et al. determined a reduction in local pain scores in a case series of patients ($N=18$) treated with 5 mg glyceryl-trinitrate (GTN) patches applied to the shins [182]. Topical lidocaine and GTN patches may be used in combination to provide 24-h pain cover with alternating 12-h application of each therapy [12, 159].

5.13.3 Topical Capsaicin

The use of capsaicin is limited by the required frequency of application (four times daily) and burning pain induced on topical administration. It is an alkaloid found in chilli peppers that selectively binds to the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, which is present on A-delta and C-fibers. This causes an influx of sodium and calcium that results in the release of substance P. The depletion of substance P and desensitisation of TRPV1 causes a reduction of painful stimuli [183, 184]. The capsaicin study group conducted a double-blind RCT ($N=252$) to determine the efficacy and safety of 0.075% topical capsaicin and found improvements in pain and pain intensity [185]. However, two studies of capsaicin cream have shown only minimal benefits in pain relief [186, 187]. Capsaicin is currently recommended as third-line therapy for local neuropathic symptoms in the NICE guidelines [CG173] and second-line therapy (class B evidence) in the AAN for the treatment of neuropathic pain (2011) [33, 138], although AAN guidelines are due to be updated shortly. A major concern is that capsaicin leads to small nerve fiber denervation with subsequent aberration in nociception [188]. At present, we do not recommended capsaicin in the treatment of pDPN for this reason [188].

The 8% capsaicin patch is not currently included in any published international guidance for pDPN. A 12-week double-blind trial in patients with pDPN provided modest improvement in both pain and sleep quality compared to placebo [189]. There are again limited data on the 8% capsaicin patch, with only one further 52-week study published to date reporting no negative functional or neurological effects compared to standard of care [190]. However, skin biopsies were not conducted to determine alterations in small nerve fibers [190].

5.13.4 Other Topical Therapies

Other topical treatments include amitriptyline and clonidine, and both have been trialled in pDPN. However, current data relating to these treatments are severely limited and no recommendation can be made for their use, although one RCT of topical clonidine did show improvements in pain in the foot in people with functional (irritable) nociceptors

(ascertained through a burning response to topical capsaicin) [191, 192].

5.14 Intravenous Lidocaine

Intravenous (IV) lidocaine has been used in the treatment of intractable pDPN for a number of years. The first published therapeutic success, in 1943, was with IV novocaine successfully used in a series of burns patients [193]. Subsequently, a double-blind RCT in patients with intractable pDPN ($N = 15$) refractory to traditional neuropathic pain medication [194] showed a significant analgesic effect with an IV lidocaine infusion at doses of 5 mg/kg and 7.5 mg/kg (a change of 1 point on the pain-intensity scale), which continued for up to 28 days [194]. There was only one adverse event (light-headedness), although this cohort was notably small. It is postulated that lidocaine modifies sodium channel expression at the DRG reducing peripheral nociceptive sensitisation [195] and may also have anti-inflammatory mechanisms modulating inflammatory cytokines [196], which are thought to have a role in hyperalgesia and central sensitisation [197]. However, the most recent study of IV lidocaine in an RCT assessing its efficacy in painful neuropathy showed no additional analgesic benefit when compared to the control infusion [198].

5.15 pDPN in Older Adults and the Elderly

The worldwide population, including those with diabetes, is ageing, and it is well recognised that pain and disability increases with age. In the USA the incidence of diabetes increases with age until about 65 years, after which both incidence and prevalence seem to plateau [199]. As a result, older adults with diabetes may have long-standing diabetes with onset in middle age or earlier. In older adults with diabetes, DPN is especially troublesome due to its detrimental effects on stability, sensorimotor function, gait and activities of daily living [200]. In addition, drug therapy may also need to be tailored in the older and elderly population. TCAs have a high incidence of anticholinergic effects, and warnings for their use include the presence of glaucoma, urinary retention, arrhythmias and myocardial infarction. There are data to suggest that TCAs were associated with increased relative risk and higher doses (amitriptyline 100 mg equivalent) should be used cautiously, particularly in patients with an elevated baseline risk of sudden death [201]. Caution is therefore urged in the use of TCAs (particularly in higher doses) in an elderly age group. Alternative anti-neuropathic agents with theoretical superior cardiovascular safety profile should instead be considered, for example duloxetine and pregabalin [202, 203].

6 Therapies in Development for pDPN

Current therapies in development are detailed below. Most novel and those in phase 2 or 3 trials are discussed. Details of developmental therapies including parent pharmaceutical companies are shown in Table 3.

6.1 Nav Channel Antagonist

A substantial number of patients with DPN develop chronic painful neuropathy; however, the genetic factors that predispose to neuropathic pain in DPN remain to be fully elucidated [204]. Voltage-gated sodium channel genes are among the most relevant due to their key role in the pathogenesis of painful small fiber neuropathies. Sodium channel therapeutic targets provide a novel approach to the treatment of pDPN [205]. In a recent study by the PROPANE study group, underlying hyperexcitability induced by the β2-subunit mutation (gain of function) of the Nav 1.7 channel has been shown [204]. Vixotrigine is a selective Nav 1.7 channel antagonist currently undergoing phase 3 trials for pDPN and small fiber neuropathy [204]. However, most recent RCTs in lumbosacral plexopathy and trigeminal neuralgia have unfortunately failed to show any benefit.

6.2 Trazadone Plus Gabapentanoids

The combination of trazadone (50–300 mg/day) plus pregabalin (75–450 mg/day) has previously been trialled in a two-phase, open-label uncontrolled study for 24 weeks in fibromyalgia [206]. With the addition of pregabalin (to trazadone), 46% of patients had a moderate-substantial decrease in pain scores [206]. Trazodone is a well-established second-generation antidepressant that has a potent secondary sedative activity. It is frequently used as a sedative primarily in subtherapeutic antidepressant doses (≤ 100 mg) in particular in disorders where disturbed sleep is a cardinal feature, such as fibromyalgia [207, 208]. Trazodone exerts its effect by antagonism of 5-HT_2, α_1 and H_1 and inhibition of serotonin reuptake presynaptically. The separate modulatory action of the gabapentanoids and trazadone may provide an analgesic effect in combination therapy at much lower doses than each drug individually. Currently, a phase 2 trial is underway of trazadone/gabapentin combination for pDPN comparing the efficacy of placebo, gabapentin monotherapy and trazadone/gabapentin combination in three doses (trazadone/gabapentin: 2.5/25 mg, 5/50 mg, 10/100 mg) (NCT03749642).

6.3 Olodanrigan

Olodanrigan, which is also known as EMA 401 or PD-126055, is an angiotensin 2 type 2 receptor (AT_2R)

Table 3 Emergent therapies for painful diabetic polyneuropathy (pDPN)

Therapy	Company name	Mechanism of action
Mirogabalin (Tarlige)	Daiichi Sankyo Co., Ltd., Tokyo, Japan	Binds to the $\alpha2\delta_1$ subunit of $VGCC_1$ and $VGCC_2$ with higher specificity than $\alpha2\delta_2$ resulting in analgesia with fewer central nervous system adverse effects than pregabalin. Is currently only licenced in Japan for use
Dextromethorphan/ quinidine combination (Nuedexta)	Avanir Pharmaceuticals, Inc., Aliso Viejo, USA	Dextromethorphan is a σ1 receptor agonist and an uncompetitive NMDA receptor antagonist. Quinidine inhibits cytochrome P450 2D6 increasing plasma concentration of dextromethorphan. The therapeutic mechanism is unknown
Cibinetide (ARA290)	Araim Pharmaceuticals, Inc., New York, USA	Preclinical models suggest cibinetide has a high affinity and selectivity for innate repair receptor (IRR) triggering and promoting tissue protection and repair. There is suggestion that cibinetide antagonizes $TRPV_1$ channels upregulated in neuropathic pain conditions
PL37[4]	eNovation Chemicals LLC., New Jersey, USA	The proposed mechanism of action from preclinical data indicates that PL-37 inhibits enkephalinases increasing the concentrations of enkephalins at the site of peripheral nociceptor. Enkephalins have a high affinity for μ-opioid receptors and δ-opioid receptors eliciting lasting analgesic effects similar to those of morphine but with fewer adverse events
Low-dose gabapentin/ trazodone combination	Angelini Pharma, Inc., Rome, Italy	Trazodone is multi-functional, and inhibits serotonin reuptake and competitively blocks histamine and α1-adrenergic receptors. Gabapentin interacts with the α2δ subunits of VGCC1 and VGCC2. Low-dose trazodone and gabapentin taken in combination may lessen the frequency of excitatory post-synaptic currents or irritable nociceptors
Olodanrigan (EMA401)2	MedChemExpress LLC., New Jersey, USA	Upregulation of angiotensin II receptors (AT2R) and transient vanilloid receptor 1 (TRPV1) contributes to neuropathic pain signals through sensitisation and decreased activation thresholds of irritable nociceptors. Olodanrigan antagonises AT2R and inhibits the direct phosphorylation of TRPV1
Vitamin D3	–	Studies have demonstrated a link between vitamin D deficiency and the prevalence of DPN. Intramuscular injections of vitamin D were associated with significant reductions in symptoms of pDPN

antagonist that is being developed for the treatment of neuropathic pain, pDPN, postherpetic neuralgia and inflammatory pain indications [209]. Anand et al. [210] found that AT_2R expression was localised in small/medium-sized cultured neurons of human and rat DRG. Subsequently, treatment with EMA401 resulted in functional inhibition of capsaicin responses in a dose-response relationship. AT_2R activation is thought to increase kinase levels in DRG neurons such as levels of protein kinase A (PKA), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) [211], and olodanrigan antagonises this effect. In the first phase 2, double-blind RCT, using a novel study design, EMA401 100 mg twice daily provided superior relief of postherpetic neuralgia compared with placebo [212]. Mean pain scores were lower with olodanrigan compared with placebo from baseline to the final week of treatment [− 2.29 (SD: 1.75) vs. − 1.60 (SD: 1.66)].

6.4 PL37

PL37 is the first orally administered dual inhibitor of enkephalinases (DENKI) [213]. Enkephalinases inhibit the activity of enkephalin-degrading enzymes hence increasing the half-life and local concentration of enkephalins, which are potent natural analgesics, and enhancing the body's natural pain control mechanism. An experimental rodent model showed the increase in endogenous enkephalin levels induced by PL37 reduced neuropathic pain [214]. A phase 2 clinical trial of PL37 with gabapentin or pregabalin or placebo plus gabapentin or pregabalin has been undertaken; however, the results are yet to be published (EudraCT Number, 2013-004876-37). This molecule effectively enhances the opioidergic system to relieve pain without the potential for abuse/misuse.

6.5 Cibinetide

Cibinetide, also known as ARA290, is a non-hematopoietic peptide that is closely related to erythropoietin. It interacts selectively with the innate repair receptor that mediates tissue protection [12]. In a double-blind, placebo-controlled trial, ARA290 demonstrated improvements in HbA1c, lipid profiles and neuropathic symptoms. Additionally, participants with small nerve fiber deficits showed improvements in corneal nerve fiber density, with no change in the placebo group [215]. Cibinetide therefore improves both metabolic control and neuropathic deficits in T2D [215]. A further

study of cibinetide also confirmed improvements of small nerve fibers with improvements in pain in sarcoidosis [216].

6.6 Dextromethorphan/Quinidine Combination

Dextromethorphan/quinidine (DMQ) has been evaluated in two studies. In an early open-label multicentre dose-escalation study (max DMQ 120/120 mg in increments of 30/30 mg), improvements were seen in pain intensity-rating and pain relief-rating scales [217]. Subsequently, a 13-week, phase 3 RCT ($N=379$) included subjects with pDPN who received placebo, DMQ 45/30 mg or DMQ 30/30 mg [218]. DMQ resulted in significant improvements in the 11-point numerical Pain Rating Scale ($p<0.0001$) with improvements in pain intensity, and pain interference with sleep and activities (all $p<0.0001$) [218].

6.7 Vitamin D

The analgesic effect of vitamin D (vitD) in DPNP has gained considerable attention in the medical and scientific community in recent years [219–224]. Lower vitD levels are known to correlate with greater severity of neuropathic pain, and measures of nerve dysfunction [225]. The NHANES study (weighted sample $N=8.82$ million) showed a clear association between vitD insufficiency (< 75 nmol/l) and pDPN [226].

A recent study in type 2 diabetes with group stratification based on neuropathy and pain phenotype showed, after adjusting for confounders, vitD levels were significantly lower in pDPN [225]. A study in a South Asian population ($N=141$) with DPNP showed that a single high dose (600,000 IU) of intramuscular cholecalciferol resulted in 70% pain relief [227]. VitD is effective in improving the quality of life (QoL) in patients with pDPN, with reduced emotional distress and overall improvements in wellbeing [228]. A short-term (8 weeks) non-randomized but placebo-controlled trial ($N=112$) of oral vitD3 resulted in a reduction in the neuropathic symptom score (NSS), but with no changes were observed in clinical signs or neurophysiological assessments [221]. To date, this is the only published placebo-controlled trial. Future large-scale RCTs are required to determine the place of vitD in the treatment algorithm of pDPN, particularly in view that vitD is a relatively safe therapy with a limited side-effect profile.

7 Placebo Response, Failed Therapies and Trial Design

A number of RCTs in neuropathic pain have failed to demonstrate differences between the active therapy and placebo, in part due to a high placebo effect [229–234]. A high placebo effect has been previously shown in trials of analgesics [235] and thus may mask the positive treatment effect in neuropathic pain trials [236]. Freeman et al. [237] evaluated patient-level data from 16 double-blind RCTs of pregabalin in pDPN ($N=3053$) and postherpetic neuralgia ($N=1460$). Data were pooled to examine the placebo response and its predictors [237]. The authors concluded that younger age, higher mean baseline pain score, longer study duration, higher ratio of patients on active treatment to placebo, and study conducted post-marketing approval were all significantly associated with a higher placebo response ($p<0.05$). Interestingly, there was a trend towards an increased placebo response in all studies over time without any corresponding change in the response to pregabalin [237]. As discussed earlier, lamotrigine does not have a significant place in neuropathic pain therapy [238] due to limited evidence regarding efficacy. However, placebo response was evaluated in three trials of lamotrigine ($N=252$ placebo; $N=222$ pDPN) [239]. Again, a higher baseline pain score was identified as an independent predictor of the placebo response in addition to a faster rate of recruitment. The large placebo response noted may have obscured the true treatment effect. Selvarajah et al. [240] concluded that depression is an important confounder with depressed participants having a higher baseline pain score. As a consequence, depressed participants show better response to both placebo and active therapy [240]. In the single published study of Sativex (medicinal cannabis), the placebo effect was superior to Sativex, with the mean total pain score reduced by 37% compared with 20% for active therapy [240]. Despite the FDA requiring trials of at least 20 weeks to determine analgesic efficacy, there is little indication that the placebo response reaches a plateau even by 19 weeks [241, 242].

Clinical trial design for neuropathic pain agents has received some consideration in view of the issues pertaining to the placebo response [243]. A placebo run-in period, discontinuation of prior analgesic treatments, flexible dosing rather than fixed-dose assignments, exclusion of subjects with mild pain at baseline and specificity of the pain score instrument have all been considered as putative approaches in minimising the placebo effect to tease out the true treatment benefits [235, 241]. However, in a review of placebo effect in pain, it was suggested that the greatest determinants of the placebo response are random factors [244]. Incorporating factors that influence placebo response into clinical trial design may result in the ability to more accurately and sensitively measure a treatment effect; however, there needs to be international consensus on the appropriate methodology to enrich neuropathic pain trials.

8 Neuropathic Pain Biomarkers for Treatment Response

Pain is a complex and subjective physiological and psychological experience and is therefore inherently difficult to study and treat [245]. The individual variability in pain perception poses additional challenges to assessing and treating pain [246, 247]. Currently, at best, 50% pain relief in 50% of patients treated with monotherapy is considered a favourable outcome [179]. Furthermore, whether a drug will offer analgesic efficacy at an individual level is unpredictable. Current neuropathic pain therapies have accompanying side effects (nausea, sedation, dizziness, dry mouth, weight gain, falls) that occur in 40% of people and are dose dependent [248]. A major unmet need of patients with pDPN is the ability to predict whether a particular drug is likely to be efficacious at an individual level and obviate ineffective therapy that may consequently result in adverse events. To date, there are no validate pain biomarkers of therapeutic response; however, we present current innovative methods that may be utilized in the future.

Functional magnetic resonance imaging (fMRI) may provide brain-based biomarkers of pain [245]. The identification of fMRI-based biomarkers for pain would be extremely useful in clinical practice in determining prognosis and importantly in identifying likely patient responders to a particular therapy. The largest study of brain structural alterations in DPN and pDPN showed cortical atrophy localised within the somato-motor cortex and insula [249]. There are additionally abnormal cortical interactions within the somato-motor network that correlate with pain and behaviour in pDPN [250]. Recently, a well-phenotyped fMRI study found that ventrolateral periaqueductal grey functional connectivity is altered in patients suffering from pDPN, which correlates with spontaneous and allodynic pain [251]. Such biomarkers may facilitate decisions in analgesic selection. For instance, Wanigasekera et al. [252] determined the utility of fMRI with a capsaicin-induced central sensitisation to differentiate anti-neuropathic therapy (gabapentin) from ineffective (ibuprofen) treatment and both from placebo. Gabapentin suppressed the secondary mechanical hyperalgesia-evoked neural response in a region of the brainstem's descending pain modulatory system and suppressed resting state functional connectivity during central sensitisation [252]. Ibuprofen showed no difference when compared with placebo [252].

Neuropathic pain phenotyping has been suggested as a method for determining therapeutic response. In a secondary analysis of the COMBO-DN study, treatment effect showed a trend for high-dose monotherapy in severe pain, whereas combination therapy favoured moderate-mild pain [253]. In a systematic review by Rolim et al. [254], four RCTs were identified and investigated with three main results in relation pain phenotypes. Paroxysmal pain was found to have a better response to pregabalin [118], the preservation of thermal sensation or nociception anticipated a positive response to the topical treatment of pain [191, 254]. In addition, after failure on duloxetine (60 mg per day), patients with evoked pain or severe deep pain had a better response to a combination of duloxetine/pregabalin, while those with paraesthesia/dysesthesia benefited from high-dose duloxetine monotherapy (120 mg per day) [253, 254].

Future clinical trials incorporating concomitant pain phenotyping with fMRI are warranted to delineate treatment response biomarkers of anti-neuropathic agents in pDPN.

9 Conclusion

pDPN is a highly prevalent, misdiagnosed, expensive and inadequately treated condition. In view of a lack of understanding of the pathogenesis of the condition, symptomatic treatment to reduce the morbidity and improve physical functioning and quality of life remains the cornerstone of management. Currently recommended therapies with the most substantial clinical evidence include agents from the TCA, SNRI and gabapentanoid drug classes. However, even these treatments only have partial efficacy, which is often offset by intolerable side effects. Moreover, the evidence for combining medications is limited, although this is very common in clinical practice. Further well-conducted, large head-to-head comparator trials and combination trials of existing agents are urgently required. A number of agents with novel therapeutic targets are currently in process. However, future clinical trials should include strategies for placebo response to ensure the true treatment effect is observed. Finally, sensory phenotyping and fMRI may represent novel methods of determining treatment response.

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Compliance with Ethical Standards

Conflict of interest UA. has received honoraria for educational meetings from Sanofi, Napp, Boerhringer Ingelheim, Pfizer and Eli Lilly, and is currently a local investigator for BIIB074 (Vixotrigine) (Biogen: NCT03339336). G.S. has none to declare. S.T. reports grants from Impeto Medical; personal fees from Neurometrix, Pfizer, Miro, Worwag Pharma, Mundipharma, Merck and Mitsubishi Pharma; and personal fees and other from Novo Nordisk.

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References

1. IDF. IDF diabetes atlas. 8th Edition ed: Web; 2017.
2. Diabetes UK. Diabetes: facts and stats. In: Diabetes UK, editor. Web; 2017.
3. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. Endocrinol Metab Clin N Am. 2013;42(4):747–87.
4. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care. 2003;26(6):1790–5.
5. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care. 2006;29(7):1518–22.
6. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. Pain Med (Malden, Mass). 2008;9(6):660–74.
7. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011;34(10):2220–4.
8. Zelman DC, Brandenburg NA, Gore M. Sleep impairment in patients with painful diabetic peripheral neuropathy. Clin J Pain. 2006;22(8):681–5.
9. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manag. 2005;30(4):374–85.
10. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. J Diabetes Complic. 2006;20(1):26–33.
11. Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. J Pain. 2006;7(12):892–900.
12. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin Therap. 2018.
13. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl). Diabete Metab. 1977;3(4):245–56.
14. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36(2):150–4.
15. Kayaniyil S, Retnakaran R, Harris SB, Vieth R, Knight JA, Gerstein HC, et al. Prospective associations of vitamin D with beta-cell function and glycemia: the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. Diabetes. 2011;60(11):2947–53.
16. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Retnakaran R, Gerstein HC, et al. Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. Diabetes Care. 2015;38(5):793–800.
17. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
18. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, et al. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care. 2010;33(5):1090–6.
19. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352(4):341–50.
20. Hamman RFBR, Dabelea D, D'Agostino RB Jr, Dolan L, Imperatore G, Lawrence JM, Linder B, Marcovina SM, Mayer-Davis EJ, Pihoker C, Rodriguez BL, Saydah S. The SEARCH for diabetes in youth study: rationale, findings, and future directions. Diabetes Care. 2014;37:3336–44.
21. Jaiswal M, Divers J, Dabelea D, Isom S, Bell RA, Martin CL, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for diabetes in youth study. Diabetes Care. 2017;40(9):1226–32.
22. Ziegler D. Painful diabetic neuropathy: treatment and future aspects. Diabetes/Metab Res Rev. 2008;24(Suppl 1):S52–7.
23. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain. 2002;18(6):350–4.
24. Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. Eur J Pain (London, England). 2010;14(4):380–6.
25. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabetic Med. 2004;21(9):976–82.
26. Sadosky A, Hopper J, Parsons B. Painful diabetic peripheral neuropathy: results of a survey characterizing the perspectives and misperceptions of patients and healthcare practitioners. Patient. 2014;7(1):107–14.
27. Kennedy R, Abd-Elsayed A. The International Association for the Study of Pain (IASP) classification of chronic pain syndromes. In: Abd-Elsayed A, editor. Pain: a review guide. Cham: Springer; 2019. p. 1101–3.
28. Pavy FW. Introductory address to the discussion on the clinical aspect of glycosuria. Lancet. 1885;126(3250):1085–7.
29. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Syst Rev. 2007(4).
30. (NICE) NICE. Neuropathic pain in adults: pharmacological management in non-specialist settings. NICE 2018.
31. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136–54.
32. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. Endocr Pract. 2015;21(Suppl 1):1–87.
33. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011;76(20):1758–65.
34. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113–1188.
35. Oates PJ. Aldose reductase, still a compelling target for diabetic neuropathy. Curr Drug Targets. 2008;9(1):14–36.

36. Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev. 2007(4):CD004572.
37. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care. 2006;29(11):2365–70.
38. Han T, Bai J, Liu W, Hu Y. A systematic review and meta-analysis of alpha-lipoic acid in the treatment of diabetic peripheral neuropathy. Eur J Endocrinol. 2012;167(4):465–71.
39. Javed S, Alam U, Malik RA. Mirogabalin and emerging therapies for diabetic neuropathy. J Pain Res. 2018;11:1559–66.
40. Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin–calcium channel alpha2-delta [Cavalpha2-delta] ligands. Pain. 2009;142(1–2):13–6.
41. Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca^{2+} channel alpha2delta ligands: novel modulators of neurotransmission. Trends Pharmacol Sci. 2007;28(2):75–82.
42. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia. 2002;57(5):451–62.
43. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49(10):661–9.
44. Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. Palliat Med. 2004;18(1):5–11.
45. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003;25(1):81–104.
46. Inc. P-DDoP. [
47. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831–6.
48. Pérez HE, Sánchez GF. Gabapentin therapy for diabetic neuropathic pain. Am J Med. 2000;108(8):689.
49. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromuscul Dis. 2001;3(2):53–62.
50. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry. 1999;66(2):251–2.
51. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med. 1999;159(16):1931–7.
52. Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. J Pain Symptom Manag. 2000;20(4):280–5.
53. Rauck R, Makumi CW, Schwartz S, Graff O, Meno-Tetang G, Bell CF, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract. 2013;13(6):485–96.
54. Wiffen PJ, Derry S, Bell RF, Rice AS, Tölle TR, Phillips T, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6:CD007938.
55. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73.
56. Rudroju N, Bansal D, Talakokkula ST, Gudala K, Hota D, Bhansali A, et al. Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. Pain Phys. 2013;16(6):E705–14.
57. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. Drugs. 2004;64(24):2813-20; discussion 21.
58. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs. 2003;12(4):663–72.
59. Juhn MS, Parsons B, Varvara R, Sadosky A. Pregabalin for painful diabetic peripheral neuropathy: strategies for dosing, monotherapy vs. combination therapy, treatment-refractory patients, and adverse events. Curr Med Res Opin. 2015;31(5):1017–26.
60. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110(3):628–38.
61. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004;63(11):2104–10.
62. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain. 2005;115(3):254–63.
63. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain. 2005;6(4):253–60.
64. Tölle T, Freynhagen R, Versavel M, Trostmann U, Young JP. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain. 2008;12(2):203–13.
65. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol. 2008;8:33.
66. Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabet Med. 2011;28(1):109–16.
67. Raskin P, Huffman C, Toth C, Asmus MJ, Messig M, Sanchez RJ, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clin J Pain. 2014;30(5):379–90.
68. Raskin P, Huffman C, Yurkewicz L, Pauer L, Scavone JM, Yang R, et al. Pregabalin in patients with painful diabetic peripheral neuropathy using an NSAID for other pain conditions: a double-blind crossover study. Clin J Pain. 2016;32(3):203–10.
69. Huffman C, Stacey BR, Tuchman M, Burbridge C, Li C, Parsons B, et al. Efficacy and safety of pregabalin in the treatment of patients with painful diabetic peripheral neuropathy and pain on walking. Clin J Pain. 2015;31(11):946–58.
70. Mu Y, Liu X, Li Q, Chen K, Liu Y, Lv X, et al. Efficacy and safety of pregabalin for painful diabetic peripheral neuropathy in a population of Chinese patients: a randomized placebo-controlled trial. J Diabetes. 2018;10(3):256–65.
71. Smith T, DiBernardo A, Shi Y, Todd MJ, Brashear HR, Ford LM. Efficacy and safety of carisbamate in patients with diabetic neuropathy or postherpetic neuralgia: results from 3 randomized, double-blind placebo-controlled trials. Pain Pract. 2014;14(4):332–42.
72. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain. 2015;156(10):2013–20.
73. Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. Diabet Med. 2009;26(10):1019–26.

74. Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 2012;35(12):2451–8.
75. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin. 2009;25(7):1663–76.
76. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013;154(12):2616–25.
77. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev. 2019;1:CD007076.
78. Zhang SS, Wu Z, Zhang LC, Zhang Z, Chen RP, Huang YH, et al. Efficacy and safety of pregabalin for treating painful diabetic peripheral neuropathy: a meta-analysis. Acta Anaesthesiol Scand. 2015;59(2):147–59.
79. Parsons B, Li C. The efficacy of pregabalin in patients with moderate and severe pain due to diabetic peripheral neuropathy. Curr Med Res Opin. 2016;32(5):929–37.
80. Hurley RW, Lesley MR, Adams MC, Brummett CM, Wu CL. Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. Reg Anesth Pain Med. 2008;33(5):389–94.
81. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care. 2008;31(7):1448–54.
82. Serpell M, Latymer M, Almas M, Ortiz M, Parsons B, Prieto R. Neuropathic pain responds better to increased doses of pregabalin: an in-depth analysis of flexible-dose clinical trials. J Pain Res. 2017;10:1769–76.
83. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract. 2014;14(2):167–84.
84. Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. Curr Med Res Opin. 2010;26(10):2411–9.
85. Lampl C, Schweiger C, Haider B, Lechner A. Pregabalin as mono- or add-on therapy for patients with refractory chronic neuropathic pain: a post-marketing prescription-event monitoring study. J Neurol. 2010;257(8):1265–73.
86. Vinik A, Emir B, Parsons B, Cheung R. Prediction of pregabalin-mediated pain response by severity of sleep disturbance in patients with painful diabetic neuropathy and post-herpetic neuralgia. Pain Med. 2014;15(4):661–70.
87. Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia. 2011;52(4):826–36.
88. Freynhagen R, Serpell M, Emir B, Whalen E, Parsons B, Clair A, et al. A comprehensive drug safety evaluation of pregabalin in peripheral neuropathic pain. Pain Pract. 2015;15(1):47–57.
89. Parsons B, Emir B. Glycemic and serum lipid control in patients with painful diabetic peripheral neuropathy treated with pregabalin. J Diabetes Complic. 2017;31(2):489–93.
90. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs. 2017;77(4):403–26.
91. England N. Rescheduling of gabapentin and pregabalin as schedule 3 controlled drugs. https://www.england.nhs.uk/wp-content/uploads/2019/03/pregabalin-and-gabapentin-guidance-v1.pdf2019
92. K D. Handling of gabapentin and pregabalin as schedule 3 controlled drugs in health and justice commissioned services. https://www.england.nhs.uk/publication/handling-of-gabapentin-and-pregabalin-as-schedule-3-controlled-drugs-in-health-and-justice-commissioned-services/. NHS, England; 2019
93. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28(6):491–6.
94. Bonnet U, Richter EL, Isbruch K, Scherbaum N. On the addictive power of gabapentinoids: a mini-review. Psychiatr Danub. 2018;30(2):142–9.
95. Deeks ED. Mirogabalin: first global approval. Drugs. 2019;79(4):463–8.
96. Field MJ, Li Z, Schwarz JB. Ca^{2+} channel alpha2-delta ligands for the treatment of neuropathic pain. J Med Chem. 2007;50(11):2569–75.
97. Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Mirogabalin for the treatment of diabetic peripheral neuropathic pain: a randomized, double-blind, placebo-controlled phase III study in Asian patients. J Diabetes Investig. 2019.
98. Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D, et al. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: a randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes Care. 2014;37(12):3253–61.
99. Lawson K. A brief review of the pharmacology of amitriptyline and clinical outcomes in treating fibromyalgia. Biomedicines. 2017;5(2).
100. Chong MS, Hester J. Diabetic painful neuropathy: current and future treatment options. Drugs. 2007;67(4):569–85.
101. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005;96(6):399–409.
102. Bryson HM, Wilde MI. Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states. Drugs Aging. 1996;8(6):459–76.
103. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992;326(19):1250–6.
104. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology. 1987;37(4):589–96.
105. Vrethem M, Boivie J, Arnqvist H, Holmgren H, Lindström T, Thorell LH. A comparison a amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain. 1997;13(4):313–23.
106. Chou R, Carson S, Chan BK. Gabapentin versus tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. J Gen Intern Med. 2009;24(2):178–88.
107. Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, Singh SP, et al. A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. Adv Ther. 1995;12(2):111–20.
108. Jose VM, Bhansali A, Hota D, Pandhi P. Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabetes Med. 2007;24(4):377–83.
109. Kaur H, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in

painful diabetic neuropathy: a randomized, double-blind, crossover clinical trial. Diabetes Care. 2011;34(4):818–22.
110. Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Carranza Leon BG, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med. 2014;161(9):639–49.
111. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015(7):CD008242.
112. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain. 1991;45(1):3–9 **(discussion 1–2)**.
113. Sindrup SH, Gram LF, Skjold T, Grodum E, Brøsen K, Beck-Nielsen H. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol. 1990;30(5):683–91.
114. Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. JAMA. 1984;251(13):1727–30.
115. Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;1:CD011209.
116. Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014(9):CD011003.
117. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014(5):CD010769.
118. Holbech JV, Bach FW, Finnerup NB, Brøsen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain. 2015;156(5):958–66.
119. Leucht C, Huhn M, Leucht S. Amitriptyline versus placebo for major depressive disorder. Cochrane Database Syst Rev. 2012;12:CD009138.
120. Sansone RA, Sansone LA. Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. Innov Clin Neurosci. 2014;11(3–4):37–42.
121. Hunziker ME, Suehs BT, Bettinger TL, Crismon ML. Duloxetine hydrochloride: a new dual-acting medication for the treatment of major depressive disorder. Clin Ther. 2005;27(8):1126–43.
122. Marks DM, Shah MJ, Patkar AA, Masand PS, Park GY, Pae CU. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. Curr Neuropharmacol. 2009;7(4):331–6.
123. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. Clin Pharmacokinet. 2011;50(5):281–94.
124. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005;116(1–2):109–18.
125. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005;6(5):346–56.
126. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006;67(8):1411–20.
127. Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. J Palliat Med. 2006;9(1):29–40.
128. Wernicke JF, Raskin J, Rosen A, Pritchett YL, D'Souza DN, Iyengar S, et al. Duloxetine in the long-term management of diabetic peripheral neuropathic pain: an open-label, 52-week extension of a randomized controlled clinical trial. Curr Ther Res Clin Exp. 2006;67(5):283–304.
129. Wernicke JF, Wang F, Pritchett YL, Smith TR, Raskin J, D'Souza DN, et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. Pain Med. 2007;8(6):503–13.
130. Tanenberg RJ, Clemow DB, Giaconia JM, Risser RC. Duloxetine compared with pregabalin for diabetic peripheral neuropathic pain management in patients with suboptimal pain response to gabapentin and treated with or without antidepressants: a post hoc analysis. Pain Pract. 2014;14(7):640–8.
131. Enomoto H, Yasuda H, Nishiyori A, Fujikoshi S, Furukawa M, Ishida M, et al. Duloxetine in patients with diabetic peripheral neuropathic pain in Japan: a randomized, doubleblind, noninferiority comparative study with pregabalin. J Pain Res. 2018;11:1857–68.
132. Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol. 2009;9:6.
133. Gao Y, Ning G, Jia WP, Zhou ZG, Xu ZR, Liu ZM, et al. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. Chin Med J (Engl). 2010;123(22):3184–92.
134. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014(1):CD007115.
135. Brunton S, Wang F, Edwards SB, Crucitti AS, Ossanna MJ, Walker DJ, et al. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. Drug Saf. 2010;33(5):393–407.
136. Gahimer J, Wernicke J, Yalcin I, Ossanna MJ, Wulster-Radcliffe M, Viktrup L. A retrospective pooled analysis of duloxetine safety in 23,983 subjects. Curr Med Res Opin. 2007;23(1):175–84.
137. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain. 2004;110(3):697–706.
138. NICE. Neuropathic pain in adults: pharmacological management in non-specialist settings [CG173]. 2013. https://www.nice.org.uk/guidance/cg173.
139. Aiyer R, Barkin RL, Bhatia A. Treatment of neuropathic pain with venlafaxine: a systematic review. Pain Med. 2017;18(10):1999–2012.
140. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015(8):CD011091.
141. Trouvin AP, Perrot S, Lloret-Linares C. Efficacy of venlafaxine in neuropathic pain: a narrative review of optimized treatment. Clin Ther. 2017;39(6):1104–22.
142. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352(13):1324–34.
143. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009;374(9697):1252–61.
144. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain. 2008;12(6):804–13.
145. Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. Pain. 2015;156(8):1440–8.
146. Tanenberg RJ, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management

in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clin Proc. 2011;86(7):615–26.
147. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. J Pain. 2010;11(5):462–71.
148. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology. 2005;103(1):140–6.
149. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev. 2012(7):CD008943.
150. Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6.
151. Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev. 2017(6).
152. Kurien T, Arendt-Nielsen L, Petersen KK, Graven-Nielsen T, Scammell BE. Preoperative neuropathic pain-like symptoms and central pain mechanisms in knee osteoarthritis predicts poor outcome 6 months after total knee replacement surgery. J Pain. 2018;19(11):1329–41.
153. Vinik AI, Shapiro DY, Rauschkolb C, Lange B, Karcher K, Pennett D, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. Diabetes Care. 2014;37(8):2302–9.
154. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth. 2014;113(1):148–56.
155. Vadivelu N, Kai A, Maslin B, Kodumudi G, Legler A, Berger JM. Tapentadol extended release in the management of peripheral diabetic neuropathic pain. Ther Clin Risk Manag. 2015;11:95–105.
156. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011;27(1):151–62.
157. Chou R, Fanciullo, G.J., Fine, P.G., et al. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain; 2009:113–30.
158. Nenke MA, Haylock CL, Rankin W, Inder WJ, Gagliardi L, Eldridge C, et al. Low-dose hydrocortisone replacement improves wellbeing and pain tolerance in chronic pain patients with opioid-induced hypocortisolemic responses. A pilot randomized, placebo-controlled trial. Psychoneuroendocrinology. 2015;56:157–67.
159. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin Ther. 2018;40(6):828–49.
160. Kozma CM, Benson C, Slaton TL, Kim MS, Vorsanger GJ. Opioids before and after initiation of pregabalin in patients with diabetic peripheral neuropathy. Curr Med Res Opin. 2012;28(9):1485–96.
161. Patil PR, Wolfe J, Said Q, Thomas J, Martin BC. Opioid use in the management of diabetic peripheral neuropathy (DPN) in a large commercially insured population. Clin J Pain. 2015;31(5):414–24.
162. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology. 2003;60(6):927–34.
163. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003;105(1–2):71–8.
164. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ (Clinical Research Ed). 2013;346:f2304-f.
165. McNicol ED, Midbari, A., Eisenberg, E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013;8.
166. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013(8).
167. Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database Syst Rev. 2016(7).
168. Derry S, Stannard C, Cole P, Wiffen PJ, Knaggs R, Aldington D, et al. Fentanyl for neuropathic pain in adults. Cochrane Database Syst Rev. 2016(10).
169. Stannard C, Gaskell H, Derry S, Aldington D, Cole P, Cooper TE, et al. Hydromorphone for neuropathic pain in adults. Cochrane Database Syst Rev. 2016(5).
170. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia—an overview of Cochrane reviews. Cochrane Database Syst Rev. 2013(11).
171. Agrawal RP, Goswami J, Jain S, Kochar DK. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. Diabetes Res Clin Pract. 2009;83(3):371–8.
172. Kochar DK, Rawat N, Agrawal RP, Vyas A, Beniwal R, Kochar SK, et al. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. QJM. 2004;97(1):33–8.
173. Wadhawan S, Pant S, Golhar R, Kirov S, Thompson J, Jacobsen L, et al. Na_V channel variants in patients with painful and non-painful peripheral neuropathy. Neurol Genet. 2017;3(6):e207.
174. Hoeijmakers JG, Faber CG, Merkies IS, Waxman SG. Channelopathies, painful neuropathy, and diabetes: which way does the causal arrow point? Trends Mol Med. 2014;20(10):544–50.
175. Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. Swiss Med Wkly. 2010;140:297–306.
176. Krumova EK, Zeller M, Westermann A, Maier C. Lidocaine patch (5%) produces a selective, but incomplete block of Adelta and C fibers. Pain. 2012;153(2):273–80.
177. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol. 2004;61(6):914–8.
178. Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. Swiss Med Wkly. 2010;140(21–22):297–306.
179. Peltier A, Goutman SA, Callaghan BC. Painful diabetic neuropathy. BMJ. 2014;348:g1799.
180. Cizkova D, Lukacova N, Marsala M, Marsala J. Neuropathic pain is associated with alterations of nitric oxide synthase immunoreactivity and catalytic activity in dorsal root ganglia and spinal dorsal horn. Brain Res Bull. 2002;58(2):161–71.
181. Yuen KC, Baker, N.R., Rayman, G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. . Diabetes Care. 2002;25:1699–703.

182. Rayman G, Baker NR, Krishnan ST. Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. Diabetes Care. 2003;26:2697–8.
183. Markovits E, Gilhar A. Capsaicin—an effective topical treatment in pain. Int J Dermatol. 1997;36:401–4.
184. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1. An update. Eur J Biochem. 2004;271:1814–9.
185. The Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical Capsaicin A multicenter, double-blind, vehicle-controlled study. Arch Intern Med. 1991;151(11):2225–9.
186. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group. Arch Intern Med. 1991;151(11):2225–9.
187. Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. Pain Pract. 2013;13(6):497–503.
188. Polydefkis M, Hauer P, Sheth S, Sirdofsky M, Griffin JW, McArthur JC. The time course of epidermal nerve fiber regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. Brain. 2004;127(Pt 7):1606–15.
189. Burness CB, McCormack PL. Capsaicin 8% patch: a review in peripheral neuropathic pain. Drugs. 2016;76(1):123–34.
190. Vinik AI, Perrot S, Vinik EJ, Pazdera L, Jacobs H, Stoker M, et al. Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: a randomised, 52-week, open-label, safety study. BMC Neurol. 2016;16(1):251.
191. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012;153(9):1815–23.
192. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clin J Pain. 2008;24(1):51–5.
193. Gordon RA. Intravenous novocaine for analgesia in burns: (a preliminary report). Can Med Assoc J. 1943;49(6):478–81.
194. Viola V, Newnham HH, Simpson RW. Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. J Diabetes Complic. 2006;20(1):34–9.
195. Rogers M, Tang L, Madge DJ, Stevens EB. The role of sodium channels in neuropathic pain. Semin Cell Dev Biol. 2006;17:571–81.
196. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology. 2000;93:858–75.
197. Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. Neuroscience. 2002;112:23–38.
198. Moulin DE, Morley-Forster PK, Pirani Z, Rohfritsch C, Stitt L. Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized-controlled trial. Can J Anaesth. 2019;66(7):820–7.
199. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults: a consensus report. J Am Geriatr Soc. 2012;60(12):2342–56.
200. Vinik AI, Strotmeyer ES, Nakave AA, Patel CV. Diabetic neuropathy in older adults. Clin Geriatr Med. 2008;24(3):407–35 **(v)**.
201. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther. 2004;75(3):234–41.
202. Yekehtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. J Tehran Heart Cent. 2013;8(4):169–76.
203. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. Ther Adv Drug Saf. 2014;5(1):38–56.
204. Alsaloum M, Estacion M, Almomani R, Gerrits MM, Bonhof GJ, Ziegler D, et al. A gain-of-function sodium channel beta2-subunit mutation in painful diabetic neuropathy. Mol Pain. 2019;15:1744806919849802.
205. Lauria G, Ziegler D, Malik R, Merkies IS, Waxman SG, Faber CG. The role of sodium channels in painful diabetic and idiopathic neuropathy. Curr Diab Rep. 2014;14(10):538.
206. Calandre EP, Morillas-Arques P, Molina-Barea R, Rodriguez-Lopez CM, Rico-Villademoros F. Trazodone plus pregabalin combination in the treatment of fibromyalgia: a two-phase, 24-week, open-label uncontrolled study. BMC Musculoskelet Disord. 2011;12(1):95.
207. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord. 2007;8:27.
208. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005;66(4):469–76.
209. Keppel Hesselink JM, Schatman ME. EMA401: an old antagonist of the AT2R for a new indication in neuropathic pain. J Pain Res. 2017;10:439–43.
210. Anand U, Facer P, Yiangou Y, Sinisi M, Fox M, McCarthy T, et al. Angiotensin II type 2 receptor (AT2 R) localization and antagonist-mediated inhibition of capsaicin responses and neurite outgrowth in human and rat sensory neurons. Eur J Pain (London, England). 2013;17(7):1012–26.
211. Chio CC, Chang YH, Hsu YW, Chi KH, Lin WW. PKA-dependent activation of PKC, p38 MAPK and IKK in macrophage: implication in the induction of inducible nitric oxide synthase and interleukin-6 by dibutyryl cAMP. Cell Signal. 2004;16(5):565–75.
212. Rice ASC, Dworkin RH, McCarthy TD, Anand P, Bountra C, McCloud PI, et al. EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: a randomised, double-blind, placebo-controlled phase 2 clinical trial. Lancet (London, England). 2014;383(9929):1637–47.
213. Tesfaye S. PL37: a new hope in the treatment of painful diabetic neuropathy? Pain Manag. 2016;6(2):129–32.
214. Thibault K, Elisabeth B, Sophie D, Claude FZ, Bernard R, Bernard C. Antinociceptive and anti-allodynic effects of oral PL37, a complete inhibitor of enkephalin-catabolizing enzymes, in a rat model of peripheral neuropathic pain induced by vincristine. Eur J Pharmacol. 2008;600(1–3):71–7.
215. Brines M, Dunne AN, van Velzen M, Proto PL, Ostenson CG, Kirk RI, et al. ARA 290, a nonerythropoietic peptide engineered from erythropoietin, improves metabolic control and neuropathic symptoms in patients with type 2 diabetes. Mol Med. 2015;20:658–66.
216. Culver DA, Dahan A, Bajorunas D, Jeziorska M, van Velzen M, Aarts L, et al. Cibinetide improves corneal nerve fiber abundance in patients with sarcoidosis-associated small nerve fiber loss and neuropathic pain. Invest Ophthalmol Vis Sci. 2017;58(6):Bio52–Bio60.
217. Thisted RA, Klaff L, Schwartz SL, Wymer JP, Culligan NW, Gerard G, et al. Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. Clin Ther. 2006;28(10):1607–18.

218. Shaibani AI, Pope LE, Thisted R, Hepner A. Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. Pain Med. 2012;13(2):243–54.
219. Basit A, Basit KA, Fawwad A, Shaheen F, Fatima N, Petropoulos IN, et al. Vitamin D for the treatment of painful diabetic neuropathy. BMJ Open Diabetes Res Care. 2016;4(1).
220. Bell DS. Reversal of the symptoms of diabetic neuropathy through correction of vitamin D deficiency in a type 1 diabetic patient. Case Rep Endocrinol. 2012;2012:165056.
221. Shehab D, Al-Jarallah K, Abdella N, Mojiminiyi OA, Al Mohamedy H. Prospective evaluation of the effect of short-term oral vitamin d supplementation on peripheral neuropathy in type 2 diabetes mellitus. Med Princ Pract. 2015;24(3):250–6.
222. Ghadiri-Anari A, Mozafari Z, Gholami S, Khodaei SA, Aboutorabi-Zarchi M, Sepehri F, et al. Dose vitamin D supplementations improve peripheral diabetic neuropathy? A before-after clinical trial. Diabetes Metab Syndrome. 2019;13(1):890–3.
223. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med. 2008;168(7):771–2.
224. Valensi P, Le Devehat C, Richard JL, Farez C, Khodabandehlou T, Rosenbloom RA, et al. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy. A preliminary report. J Diabetes Complic. 2005;19(5):247–53.
225. Shillo P, Selvarajah D, Greig M, Gandhi R, Rao G, Wilkinson ID, et al. Reduced vitamin D levels in painful diabetic peripheral neuropathy. Diabetic Med. 2019;36(1):44–51.
226. Soderstrom LH, Johnson SP, Diaz VA, Mainous AG 3rd. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001-2004 NHANES. Diabetic Med. 2012;29(1):50–5.
227. Basit A, Basit KA, Fawwad A, Shaheen F, Fatima N, Petropoulos IN, et al. Vitamin D for the treatment of painful diabetic neuropathy. BMJ Open Diabetes Res Care. 2016;4(1):e000148.
228. Alam U, Fawwad A, Shaheen F, Tahir B, Basit A, Malik RA. Improvement in neuropathy specific quality of life in patients with diabetes after vitamin D supplementation. J Diabetes Res. 2017;2017:7928083.
229. Dworkin RH, Turk DC, Peirce-Sandner S, McDermott MP, Farrar JT, Hertz S, et al. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. Pain. 2010;150(1):12–6.
230. Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand. 2004;110(4):221–31.
231. Silver M, Blum D, Grainger J, Hammer AE, Quessy S. Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain. J Pain Symptom Manag. 2007;34(4):446–54.
232. Vinik AI, Tuchman M, Safirstein B, Corder C, Kirby L, Wilks K, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. Pain. 2007;128(1–2):169–79.
233. Hauser W, Bartram-Wunn E, Bartram C, Reinecke H, Tolle T. Systematic review: Placebo response in drug trials of fibromyalgia syndrome and painful peripheral diabetic neuropathy-magnitude and patient-related predictors. Pain. 2011;152(8):1709–17.
234. Irving G. The placebo response: relationship to outcomes in trials of postherpetic neuralgia. Clin Drug Investig. 2010;30(11):739–48.
235. Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: relationship to study characteristics. Neurology. 2008;70(4):263–72.
236. Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain. 2012;153(6):1148–58.
237. Freeman R, Emir B, Parsons B. Predictors of placebo response in peripheral neuropathic pain: insights from pregabalin clinical trials. J Pain Res. 2015;8:257–68.
238. Wiffen PJ, Derry S, Moore RA. Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2013(12).
239. Irizarry MC, Webb DJ, Ali Z, Chizh BA, Gold M, Kinrade FJ, et al. Predictors of placebo response in pooled lamotrigine neuropathic pain clinical trials. Clin J Pain. 2009;25(6):469–76.
240. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128–30.
241. Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain. 2008;138(3):479–83.
242. Tavakoli M, Asghar O, Alam U, Petropoulos IN, Fadavi H, Malik RA. Novel insights on diagnosis, cause and treatment of diabetic neuropathy: focus on painful diabetic neuropathy. Ther Adv Endocrinol Metab. 2010;1(2):69–88.
243. Dworkin RH, Katz J, Gitlin MJ. Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. Neurology. 2005;65(12 Suppl 4):S7–19.
244. H.J. M. Placebo and control event rate. In: McQuay H.J., editor. Systematic reviews in pain research: methodology redefined. IASP Press, Seattle; 2008. pp. 51–6.
245. Mackey S, Greely HT, Martucci KT. Neuroimaging-based pain biomarkers: definitions, clinical and research applications, and evaluation frameworks to achieve personalized pain medicine. Pain Rep. 2019;4(4):e762.
246. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45–56.
247. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain. 2017;158(Suppl 1):S11–S18.
248. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia—an overview of Cochrane reviews. Cochrane Database Syst Rev. 2013(11):CD010567.
249. Selvarajah D, Heiberg-Gibbons F, Wilkinson ID, Gandhi R, Tesfaye S. A magnetic resonance imaging volumetry study of regional brain atrophy in diabetic peripheral neuropathy. Diabetes. 2018;67(Supplement 1):550-P.
250. Selvarajah D, Awadh M, Gandhi R, Wilkinson ID, Tesfaye S. Alterations in somatomotor network functional connectivity in painful diabetic neuropathy—a resting state functional magnetic resonance imaging study. Diabetes. 2018;67(Supplement 1):61-OR.
251. Segerdahl AR, Themistocleous AC, Fido D, Bennett DL, Tracey I. A brain-based pain facilitation mechanism contributes to painful diabetic polyneuropathy. Brain. 2018;141(2):357–64.
252. Wanigasekera V, Mezue M, Andersson J, Kong Y, Tracey I. Disambiguating pharmacodynamic efficacy from behavior with neuroimaging: implications for analgesic drug development. Anesthesiology. 2016;124(1):159–68.

253. Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, et al. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind. COMBO-DN study. Pain. 2014;155(10):2171–9.
254. Rolim LC, Koga da Silva EM, De Sá JR, Dib SA. A systematic review of treatment of painful diabetic neuropathy by pain phenotype versus treatment based on medical comorbidities. Front Neurol. 2017;8(285).
255. Vadivelu N, et al. Patient considerations in the use of tapentadol for moderate to severe pain. Drug Healthc Patient Saf. 2013;5:151–9.