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REVIEW

State-of-the-art pharmacotherapy for diabetic neuropathy

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ABSTRACT

Introduction: The global epidemic of diabetes has led to an epidemic of diabetes complications. Diabetic neuropathy is the most common microvascular complication, of which diabetic peripheral neuropathy (DPN) and autonomic neuropathy (AN) are the most prevalent, affecting ~50% of patients. DPN results in pain with a poor quality of life and a loss of sensation with an increased risk of foot ulceration. Autonomic neuropathy can cause significant morbidity in a minority and is associated with increased mortality. The cornerstone of treatment to prevent or limit the progression of DPN/AN is multifactorial risk factor modification including treatment of glycemia, lipids and blood pressure. Whilst, there are no FDA-approved disease-modifying therapies, there are a number of therapies to relieve symptoms in DPN and AN.

Areas covered: The authors discuss current approved therapies for painful diabetic neuropathy and autonomic neuropathy. They also address the potential role of improving risk factors to limit the development and progression of diabetic neuropathy and new pathogenetic and pain-relieving treatments.

Expert opinion: The FDA-approved Pregabalin and Duloxetine over 25 years ago and Tapentadol, 6 years ago for painful diabetic neuropathy. There are currently no FDA-approved disease-modifying treatments for diabetic neuropathy which has been attributed to inappropriate models of the disease with limited translational capacity and major limitations of trial designs and endpoints in clinical trials.

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1. Introduction

In 2017, the International Diabetes Federation estimated the prevalence of diabetes at 425 million people worldwide rising to 628 million by 2045 [1]. Diabetes has reached epidemic proportions worldwide and so has the burden from its complications. Indeed, ~12% of global health expenditure is directed towards diabetes and its complications [1].

Diabetic neuropathy is a neurodegenerative disorder of peripheral nerves that preferentially targets sensory and autonomic axons and later motor axons [2]. The most prevalent form is diabetic peripheral neuropathy (DPN), a distal, symmetrical, length-dependent sensorimotor polyneuropathy. It is the primary cause of diabetic foot ulceration and non-traumatic amputations [3]. DPN manifests in a 'stocking and glove' distribution affecting the hands and lower limbs. The prevalence of DPN can be as high as 50% depending on age and type and duration of diabetes [4]. In Pirart's now famous study initiated in the 1940s, the prevalence of DPN was assessed longitudinally over 25 years in 4400 patients [4]. Fifty percent of adults had DPN at 25 years which correlated with the duration of disease. However, recent studies show that DPN develops in adolescents. In the SEARCH for Diabetes in Youth Study [5], the prevalence of DPN was 7% in patients with type 1 diabetes and 22% in type 2 diabetes (age ≤20 years with a duration of diabetes >5 years) [6]. Symptomatic painful DPN (pDPN) can affect up to one-third of people with diabetes [7] and is generally underreported by healthcare professionals [8,9]. It results in somnipathy, depression, poor quality of life and unemployment [10–13] and reduces a person's ability to socially function.

Autonomic neuropathy is a diffuse neuropathy, which affects the cardiac, gastrointestinal, and genitourinary autonomic plexus leading to cardiac autonomic neuropathy (CAN), gastrointestinal dysmotility, diabetic cystopathy, and erectile dysfunction, respectively. CAN is a silent but major contributor to mortality in patients with diabetes [14–17]. Based on the Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) study, the prevalence of CAN in type 1 diabetes after 15 years was close to 60% [18].

This review focuses on current treatment options for DPN, pDPN, and autonomic neuropathy.

1.1. Mechanism of peripheral nerve injury

The pathology of DPN is of a distal sensory predominant demyelination, axonal degeneration, and endoneurial

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Article highlights

- There is a major unmet clinical need for the treatment of diabetic polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN). The mainstay of therapy to prevent or halt the progression of DPN and AN is multifactorial risk factor modification.
- There are no disease-modifying therapies and beyond multifactorial risk factor modification, symptomatic treatment remains the mainstay of the management of painful DPN (pDPN) and AN.
- FDA-approved therapies for the relief of neuropathic pain were empirically identified from centrally-acting drugs for depression (Duloxetine) and epilepsy (Gabapentin and Pregabalin). These drugs were not developed based on a neurobiological understanding of pDPN.
- Novel pharmacotherapies have putative superior efficacy and adverse events profile e.g., Mirogabalin has better relief of neuropathic pain and reduced somnolence. P2X3 antagonists targeted the cough hypersensitivity pathway may relieve neuropathic pain and clinical trials are eagerly awaited.
- A major unmet need in the development of disease modifying therapies is an easily accessible biomarker for diagnosing and monitoring DPN. Corneal confocal microscopy is a rapid non-invasive method to visualise small nerve fibres to identify early neuropathy and assess treatment response.

Biomarkers to enrich clinical trials of patients with pDPN to increase the responder rate are required.

microangiopathy [19–21]. Hyperglycaemia activates several downstream metabolic cascades such as increased flux of the polyol pathway, enhanced advanced glycation end-product formation, activation of protein kinase C, exaggerated oxidative stress and inflammation [19].

1.2. Pathogenetic therapies

Diabetic neuropathy is the strongest predictor of mortality in type 2 diabetes [22], and yet it remains the only microvascular complication of diabetes without a pathogenetic treatment [2]. Unfortunately, numerous pathogenetic treatments targeting the underlying molecular mechanisms have failed in phase 2/3 clinical trials [23], including aldose reductase inhibitors, benfotiamine, protein kinase C inhibitors and C-peptide [24]. At present, there are no US Food and Drug Administration (FDA) approved disease-modifying treatments for DPN.

1.3. Endpoints for DPN

Endpoints recommended by health regulatory authorities such as the FDA and EMA including nerve conduction studies and quantitative sensory testing, targeting predominantly large nerve fibers have failed. Despite this, professional organizations such as the ADA and Neurodiab continue to endorse consensus guidance focused on symptoms, signs and nerve conduction and the monofilament [25]. Small nerve fibers are the earliest to degenerate and also have a large capacity for repair [26–29]. Robust quantification techniques like skin biopsy with assessment of intraepidermal nerve fiber density (IENFD) or corneal confocal microscopy with quantification of several corneal nerve parameters have now become available [30–32]. They represent a minimally invasive and completely non-invasive technique to monitor progression and repair in future clinical trials of DPN.

1.4. Glycemic control

Glycemic control is the only approach convincingly shown to prevent or delay the progression of neuropathy in patients with type 1 diabetes [33]. Callaghan et al [34] undertook a Cochrane Review of 17 randomized studies (type 1 diabetes: 7 studies, type 2 diabetes: 8 studies, mixed etiology: 2 studies) and concluded that enhanced glucose control significantly prevented the development of clinical neuropathy and reduced nerve conduction and vibration threshold abnormalities in type 1 diabetes. This conclusion was driven primarily by data from the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study which demonstrated benefit of early good glycemic control on DPN and CAN in type 1 diabetes [14]. In the DCCT, the risk reduction for incident DPN with intensive glucose control was 64% after 6.5 years [14]. In the EDIC study, HbA1c in the standard and intensive treatment groups was similar by the fifth year (8.1% vs 8.2%); but the prevalence of DPN and CAN remained significantly lower in patients who had earlier intensive treatment during DCCT [35], demonstrating the concept of 'metabolic memory' [36]. Indeed, even in severe DPN in type 1 diabetes, complete normalization of glycemic control through pancreatic and kidney transplantation results in regeneration of small nerve fibers within 6 months followed by an improvement in symptoms and nerve conduction at 24 and 36 months, respectively [37].

In type 2 diabetes, the evidence for improved glycemic control slowing down progression of neuropathy is less strong [38,39]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) showed no improvement in DPN after a follow-up of 5-year [39] and indeed there was an excess of mortality and hypoglycemia in those who were intensively treated [40]. Indeed, in the Cochrane analysis by Callaghan et al [34], enhanced glycemic control had a non-significant effect on sensory loss and no benefit on nerve conduction and vibration threshold abnormalities [34]. Thus, given the marginal benefits, individualized glycemia targets will be appropriate for older patients to avoid increased risk of hypoglycemia and mortality [41].

1.5. Lipids

There is a robust body of data showing an association between plasma lipoproteins and triglycerides and the risk of DPN [42,43]. In an analysis of participants with mild to moderate diabetic neuropathy, elevated triglycerides correlated with myelinated fiber density loss independent of disease duration, age and glycaemic control [43]. The Pittsburgh Epidemiology of Diabetes Complications Study also showed that high-density lipoprotein cholesterol was associated with DPN [44,45]. Cholesterol-lowering therapy in the form of statins and ezetimibe [46,47] and triglyceride lowering therapy in the form of fibrates [46] may reduce progression and severity of DPN. Well planned randomized trials are needed to

evaluate the impact of lipid-lowering therapy on DPN. Statins may rarely induce an acute painful neuropathy in some individuals [48]. Alpha-lipoic acid, a potent antioxidant has shown favorable results with a reduction in neuropathic symptoms, but a limited impact on neurological deficits [49–51].

1.6. Renin-Angiotensin-Aldosterone System

A small open label study of lisinopril in hypertensive subjects (n=13) showed improvements in nerve conduction over 12 weeks [52]. Subsequently, an RCT of trandolapril showed an improvement in nerve conduction, amplitude, and latency in normotensive patients with mild diabetic neuropathy over 1 year [53]. Also, quinapril increased parasympathetic activity in patients with AN and had a sustained effect at 6 months [54] and 2 years [55]. It has been postulated that addressing the parasympathetic/sympathetic imbalance may contribute to the reduction in the risk of malignant ventricular arrhythmias in AN [54].

1.7. Multifactorial Intervention

The STENO-2 study [56] in patients with type 2 diabetes and microalbuminuria showed that 4 years of intensive multifactorial treatment (weight, hyperglycemia, hypertension, dyslipidemia) slowed the progression of autonomic neuropathy in the 21-year follow-up analysis [57], but had no impact on DPN. However, the primary end point for DPN was the assessment of vibration perception, an imprecise and highly variable endpoint.

1.8. Diet, lifestyle and weight loss

Weight loss may not only modulate insulin resistance leading to a remission of diabetes [58], but may also reverse DPN [30]. Intervention with diet and exercise in people with IGT using the Diabetes Prevention Programme (DPP) protocol (aim 5-7% weight loss) resulted in an increase in IENFD, improved neuropathic pain and sural nerve amplitude [30]. Bariatric surgery results in reduced macrovascular disease and mortality [59] and an improvement in symptoms, signs, and small nerve fibers [60,61]. A meta-analysis of 4 studies of bariatric surgery showed an improvement in symptoms and signs with reductions in the neuropathy symptoms score (NSS) (ES = - 3.39, 95%CI: - 4.51 to - 2.28, P< 0.0001) and neuropathy disability score (NDS) (ES = - 0.63, 95%CI: - 1.12 to - 0.13, P<0.013) [62]. Importantly, acute neuropathies can occur after bariatric surgery due to micronutrient deficiencies [63,64] and need to be considered if there is an acute worsening of neuropathic symptoms.

1.9. Treatment of Painful DPN

In clinical practice the approach to alleviate the symptoms of pDPN is to try different therapies until one is successful or try a combination of therapies. A successful outcome is considered with moderate improvement (~30-50%) in pain and a >50% pain reduction is considered a good outcome [65]. FDA approved drugs for neuropathic pain with number needed to treat for benefit (NNTB) and number needed to treat for harm (NNTH) (Table 1) and NICE recommended treatment (Table 2) with adverse events for each therapy are provided. It must be noted that trials of drugs for neuropathic pain, including FDA-approved serotonin norepinephrine reuptake inhibitors (SNRIs) and alpha 2 delta ligands lack long-term clinical trial efficacy and safety data [66] although this should not negatively impact their use as pDPN is a highly debilitating condition. Randomized clinical trials rarely extend beyond 20 weeks in pDPN [66].

The prescription of medications for pDPN is agnostic in nature and lacks a mechanism-based approach. However, improved clinical phenotyping and targeting of therapies based on co-morbid conditions such as anxiety and depression may result in improved outcomes [67]. Superficial clinical phenotyping in relation to symptomatology has not been shown to improve the response to therapy [68]. However, more detailed phenotyping using quantitative sensory testing (QST) has shown promise with patients with an irritable nociceptor (IN) (n=31) compared to a non-irritable nociceptor (n=52) phenotype showing a significantly greater response to oxcarbazepine by reducing the overall NNTB from 6.9 to 3.9 [69]. The relative efficacy of 5% lignocaine was assessed in 15 patients with IN and 25 patients with non-IN and showed a greater effect in those with IN, on pain paroxysms and deep aching pain [70]. There is preclinical evidence on rate-dependent depression (RDD) of the spinal H-reflex acting as a marker for spinal disinhibition in a subset of pDPN [71]. RDD may be a treatment response biomarker of spinally mediated pain to allow a personalized medicine approach in pDPN, specifically utilizing therapies such as SNRI's that target descending spinal inhibitory pathways [72].

The potential benefit and overall efficacy of pregabalin and duloxetine was studied in the COMBO-DN Study. This was a multi-national randomized double blind, parallel group trial to compare the efficacy and tolerability of high dose monotherapy (duloxetine 120mg/day or pregabalin 600mg/day) to standard dose combination therapy (duloxetine 60mg/day plus pregabalin 300mg/day) in patients with pDPN, resistant to standard dose monotherapy [73]. There were no significant difference in Brief Pain Inventory (BPI) in standard dose combination therapy compared to high dose monotherapy therapy in those not achieving adequate pain relief on standard dose duloxetine (60mg/day) or pregabalin (300mg/day) monotherapy [73]. However, in a secondary analysis of the initial monotherapy run-in phase, duloxetine (60mg/day) was superior to pregabalin (300mg/day) at 8-weeks. Further, exploratory post hoc analyses of COMBO-DN showed that high-dose monotherapy was more favorable in patients with severe pain, whereas combination therapy was more beneficial in patients with moderate and mild pain [74].

1.10. Antidepressants

1.10.1. Tricyclic Antidepressants (TCAs)

TCAs are thought to indirectly modulate the opioid system in the brain via serotonergic and norepinephrine neuromodulation, amongst other properties [75–77]. Careful dose titration is required over a period of 6-8 weeks before reasonable effects are noted, hence compliance may sometimes be compromised [78]. TCAs are first- or second-line recommendations

Table 1. FDA approved drugs for neuropathic pain in adults with their respective Dose Range, NNTB and NNTH.

Medication	Dose Range in Adults	NNTB (95% C.I)				Reference
Pain Reduction of at least:		**30%**	**50%**	NNTH (95% C.I)		
Anti-Convulsants						
Gabapentin	300-3600 mg/day	NS	6.6 (5.0-9.7)**	At least one AE** 7.5 (6.1-9.6) AE Withdrawal 30 (20-66)		[192,193]
Pregabalin	100-600 mg/day	6.2 (4.3-11)*	6.1 (4.7-8.8)*	300 mg/day: Somnolence 9.5 (7.0-15), Dizziness 4.8 (3.9-6.2), AE leading to withdrawal 11 (7.8-19)	600 mg/day:Somnolence 5.2 (4.1-7.0), Dizziness 3.8 (3.2-4.9), AE Withdrawal 7.1 (5.3-11)	[194,195]
Lamotrigine	25-500 mg/day	NS	NS	At least one AE 10 (6.5-27) Participants with a rash 27 (16-89)***		[196,197]
Carbamazepine†	100-1200 mg/day	NS	1.9 (1.6-2.5)††	Any Adverse Event 2.6 (2.1-3.5)		[198–200]
Opioids						
Morphine	Titration dependent on pain severity	NNTB for Moderate improvement 3.7 (2.6-6.5)		NS		[201,202]
Tramadol hydrochloride	50-400 mg/day	NS	4.4 (2.9-8.8)	At least one AE 4.2 (2.8-8.3) AE Withdrawal 8.2 (5.8-14)		[104,203]
Tapentadol ER	50-500 mg/day	NS		NS		[204,205]
Tricyclic Antidepressants						
Nortriptyline hydrochloride	10-150 mg/day	NS		NS		[206,207]
Desipramine hydrochloride	10-150 mg/day	NS		NS		[208,209]
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)						
Duloxetine	30-120 mg/day	5 (3-7)‡	5 (4-7)‡	AE leading to Withdrawal 18 (13-30)		[83,210]
Selective Serotonin Reuptake Inhibitors (SSRI)						
Fluoxetine	30-120 mg/day	NS		NS		[82,211]
Topical Treatments						
5% Lidocaine patch	1-3 patches applied daily for a maximum of 12 hours	NS		NS		[212,213]
8% Capsaicin Patch	1-4 patches for 30 minutes depending on the size of the treatment area on the feet	NS		Achieved ≤90% of patch exposure time 77 (45-260)§ Dermal Irritation Score ≥ 2 at 2 hours 9.6 (7.7-13) Dermal Irritation Score ≥ 0 at 2 hours 4.5 (3.3-6.7)		[214,215]

* Gabapentin ≥1800 mg/day or Encarbil 1200 mg/day compared with placebo for pDPN ** Pregabalin 600mg/day compared with placebo for pDPN *** Includes participants with chronic neuropathic pain conditions other than pDPN and fibromyalgia † Carbamazepine is indicated as a first-line treatment for trigeminal neuralgia †† Adults with neuropathic pain treated with carbamazepine 100-2400 mg/day ‡ Adults with painful neuropathy or pDPN treated with 60 mg/day duloxetine § The number of participants with this outcome is small compared to the included total participants. AE = Adverse Event ER = Extended Release NNTB = Number Needed to Treat for Benefit NNTH = Number Needed to Treat for Harm NS = Not calculated or measurement combined with another variable

in all five international guidelines on pain management in pDPN, with most citing amitriptyline as the drug of choice amongst the TCAs. The recent 2017 diabetic neuropathy position statement of the American Diabetes Association stated that TCAs should be used with caution given their higher risk profile, particularly in elderly populations or those with underlying cardiovascular disease [79]. The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation published a joint statement concluding that amitriptyline has the greatest efficacy amongst TCAs [80]. Studies have shown superior efficacy of imipramine, but there is insufficient evidence to advocate routine use [81].

Fluoxetine is FDA-approved treatment for pDPN. In one study, a trial of fluoxetine in patients who received relief from TCAs but resulted in withdrawal due to adverse effects suggested benefit from a trial of fluoxetine therapy [82]. However, a Cochrane Systematic Review of antidepressants for the treatment of neuropathic pain found a lack of data to support the use of Fluoxetine in pDPN [82].

1.11. Serotonin- Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine has FDA approval for the treatment of pDPN. A Cochrane review of duloxetine which included 8 trials (n=2,728) showed that duloxetine 60mg/day was superior to placebo with a 50% pain reduction by 12 weeks (NNTB=5, 95% CI 4-9) [83]. Duloxetine has lower rates of anti-cholinergic side effects compared to amitriptyline resulting in a superior adverse events profile, but side effects include somnolence and constipation [84]. A post hoc analysis of three pooled double blind, placebo-controlled trials evaluating the use of duloxetine in older patients (aged >65 years) advocates the safety and efficacy of this drug in an older adult population [85].

Venlafaxine has shown efficacy in treating pDPN in a double blind placebo-controlled trial in which visual analogue pain intensity scales were used as the primary outcome measure [86], but is not approved by the FDA for neuropathic pain. A Cochrane collaboration systematic review [82] of venlafaxine for the treatment of neuropathic pain reported an NNTB of 3.1 (95% CI 2.2-5.1), which is comparable to amitriptyline [87]. Venlafaxine has also shown superiority to duloxetine

Table 2. **NICE Recommended Drugs for Neuropathic Pain in Adults with Adverse Event Data** [215,216].

Treatment	NICE Recommendation	Common Adverse Events	Serious Adverse Events	Reference
Gabapentin	1-2	Dizziness, Fatigue, Somnolence, Dry mouth. Weight gain, Peripheral oedema, Headache	Angioedema, Hepatotoxicity, Rhabdomyolysis, Suicidal thoughts and behaviour, Ataxia, Seizures (after rapid discontinuation), Thrombocytopenia	[193]
Pregabalin	1-2	Somnolence, Dizziness, Ataxia, Fatigue	Stevens-Johnson syndrome Suicidal thoughts and behaviour Seizures (after rapid discontinuation)	[195]
Duloxetine	1-2	Nausea, Somnolence, Dizziness, Constipation, Dyspepsia, Diarrhoea Dry mouth, Anorexia, Headache, Diaphoresis, Insomnia, Fatigue, Decreased libido	Severe hyponatremia, Stevens-Johnson syndrome, Seizures, Fragility bone fractures, Shift to mania (bipolar disorder), Hepatotoxicity, Suicidal thoughts and behaviour, Serotonin syndrome, Glaucoma, Hypertensive crisis, Cardiac arrhythmias, Neuroleptic malignant syndrome, Gastrointestinal Haemorrhage, Delirium, Myocardial infarction,	[83]
Amitriptyline*	1-2	Dry mouth, Fatigue, Headache, Dizziness, Insomnia, Orthostatic hypotension, Anorexia, Nausea, Urinary retention, Constipation, Blurred vision, Disturbance, Mydriasis, Weight gain, Somnolence	Bone marrow suppression, Delirium, Heart failure exacerbation, Strokes, Seizures, Hepatotoxicity, Suicidal thoughts and behaviour, Mania (bipolar disorder), Neuroleptic malignant syndrome, Serotonin syndrome, Severe hyponatremia, Cardiac arrhythmias, Conduction abnormalities, Myocardial infarction, Fragility bone fractures	[217]
Tramadol	3	Somnolence, Constipation, Nausea, Vomiting, Light-headedness, Dizziness	Respiratory depression, Serotonin syndrome, Seizures, Hypertension, Neonatal opioid withdrawal syndrome	[104]
Capsaicin 0.075% cream**	3	Burning, Stinging, Erythema Coughing, Sneezing***	No Data	[219]

Recommendations are indicated as 1 = First Choice, 2 = Second Choice 3 = Third Choice. * The NNTB for amitriptyline is 5.1 (95% C.I 3.5-9.3), however this Includes participants with chronic neuropathic pain conditions other than pDPN at multiple dosages ** The NNT for 0.075% both 0.025% Capsaicin cream combined is reported as 8.1 (95% C.I 5.7-14) in participants with post-herpetic neuralgia and painful diabetic peripheral neuropathy *** Reporting of adverse events was inconsistent and incomplete in the included studies NICE = National Institute of Clinical Excellence

in some studies, however there is a lack of larger comprehensive trials [87]. Venlafaxine must also be slowly weaned to reduce the potential for adverse events [88]. Desvenlafaxine, has been evaluated in a single randomized controlled trial and has shown some efficacy [89]

1.12. Anticonvulsants

Anticonvulsant medications have been used in the treatment of pDPN [90]. Cochrane reviews have shown limited efficacy with carbamazepine and oxcarbazepine in the treatment of pDPN, hence they are not recommended [91,92].

1.13. Alpha 2 Delta Ligands

Both gabapentin and pregabalin are commonly prescribed as first line agents for pDPN. Gabapentin is a lipophilic analogue of gamma-aminobutyric acid (GABA) that binds to the alpha 2/Delta 1 subunit of the voltage-gated calcium channel on the presynaptic membranes and reduces excitability of chiefly glutaminergic neurons [93]. In a systematic review of 35 studies, gabapentin was found to be effective in reducing neuropathic pain (n=727), however, its effectiveness may be reduced if administered at low doses [94]. A meta-analysis of 21 trials compared the efficacy and safety of 6 agents for neuropathic pain and concluded that gabapentin provided a good balance between safety and efficacy for the treatment of pDPN [95].

Pregabalin is FDA approved for pDPN based on several robust-randomized control trials, which have all shown efficacy compared to placebo [96–98]. Furthermore, a comparative meta-analysis with other drugs found pregabalin to be the most efficacious in reducing VAS pain scores [99]. Pregabalin promotes sleep whereas duloxetine showed increased sleep fragmentation in a placebo controlled trial evaluating the efficacy of pregabalin, amitriptyline and duloxetine [100]. Indeed somnolence is a common side effect of pregabalin and other studies have demonstrated an improvement in sleep and quality of life in patients with pDPN [101,102]. Other side effects include edema and mood disturbance and pregabalin needs to be weaned as abrupt discontinuation has been linked to seizures, cerebral edema and encephalopathy [103].

1.14. Opioid Analgesia

1.14.1. Partial Mu Receptor Agonists

A Cochrane review found that the efficacy of tramadol in neuropathic pain was determined in small studies with a potential risk of bias and concluded that there was insufficient data of adequate quality to provide convincing evidence that tramadol is effective in relieving neuropathic pain [104]. However, tramadol is recommended as 2nd or third line in pDPN, especially to treat break-through pain in combination with other neuropathic pain agents. However, one must be cautious when using tramadol in combination with TCAs and SNRIs due to the increased risk of serotonin syndrome with confusion, seizures, labile blood pressure and in extreme cases, coma, and death.

Modified release Tapentadol has been approved by the FDA for the treatment of neuropathic pain. A 12-week open label study in 396 patients with pDPN demonstrated a 30% pain reduction in 65% of patients and a 50% pain reduction in 34.9% of patients [105] and another 12 week study confirmed this data [106].

1.14.2. Opioid Agonists

A Cochrane Collaboration review of 31 studies evaluated the use of opioids in neuropathic pain. Shorter duration studies were found to provide only equivocal efficacy of opioids in reducing the intensity of neuropathic pain. The intermediate-term studies demonstrated significant efficacy of opioids over placebo however the results are likely to be subject to significant bias due to drop out and small size of the studies [107].

1.14.3. Topical Medications

Topical treatments may be indicated where patients cannot tolerate conventional systemic therapies due to adverse events [108]. Furthermore, the risk of drug–drug interactions are also significantly reduced making topical therapies more attractive for a growing number of patients with multiple co-morbidities and polypharmacy.

Capsaicin is a transient receptor potential vanilloid 1 receptor (TRPV1) agonist and is a naturally occurring alkaloid found in red chili peppers. A double blind placebo controlled trial (n=277) from the capsaicin study group found a significant reduction in pain using 0.0075% topical capsaicin as measured by physicians global evaluation and visual analog scales [109]. It is currently recommended as third line therapy in the UK's NICE guidelines and second line by the American Academy of Neurology for the treatment of neuropathic pain. Patients frequently experience burning pain when it is applied, and compliance may be an issue as it needs to be applied four times daily.

The capsaicin 8% patch has an FDA label for neuropathic pain and can be applied every three months or as warranted by the return of pain [110,111]. In a large study, the 8% capsaicin patch reduced average daily pain scores and improved sleep interference scores after one application for 30 minutes (n=186) compared to placebo (n=183), which were maintained for up to 12 weeks as measured by the Brief Pain Inventory (BPI) [112]. The capsaicin 8% group had a mean decrease in average daily pain score of 28% (SD 27.3%) compared to the placebo group 21% (SD 29.4%) from baseline to weeks 2-12; p = 0.018 [112]. The capsaicin 8% patch is well tolerated with no deterioration over the course of a 52-week safety study as measured by the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN), Utah Early Neuropathy Scale (UENS), standardized sensory testing and reflex function [113]. One of the main concerns is that the application of even low dose capsaicin results in impaired thermal nociception and loss of intraepidermal nerves [114] which could increase the risk of diabetic foot ulceration.

In a systematic review of 38 studies, 5% Lidocaine patch was found to produce a significant pain reduction comparable to amitriptyline, capsaicin, gabapentin and pregabalin [108] and it has fewer and less clinically significant side effects compared to systemic agents [108].

Topical isosorbide dinitrate has shown a reduction in pain intensity in a double blind trial (n=22) [115]. Furthermore, a case series of 18 patients treated with glyceryl-trinitrate (GTN) patches showed a reduction in pain scores [116]. Topical lidocaine and GTN patches may be used in combination to provide 24-hour pain cover with alternating 12-hour application of each therapy.

1.14.4. Vitamin D

A number of studies have assessed the analgesic effect of vitamin D in pDPN in recent years [117–122]. Lower vitamin D correlates with increasing severity of neuropathic pain and increases thermal thresholds [123]. The NHANES study showed a clear association between vitamin D insufficiency (classified as a 25(OH)D <75 nmol/l) and pDPN [124]. In a study from Pakistan 141 patients with pDPN received a single high dose of intramuscular vitD3 (cholecalciferol 600,000IU) which resulted in ~70% reduction in pain scores [117] with additional improvements in quality of life (QoL), wellbeing and reduced emotional distress [125]. A recent meta-analysis showed an improvement in pain scores in favour of vitamin D supplementation (1.14 (95% CI = 1.22 to 1.67, p<0.0001) [126]. A large-scale RCT is required to determine the place of vitamin D in the treatment of pDPN.

1.15. Developmental treatments

We now consider a number of development therapies which are mainly in phase 2/3 clinical trials for the treatment of pDPN.

1.16. Nav Channel Antagonist

Voltage-gated sodium channels (NaV) present a potential therapeutic target in the treatment of pDPN [127]. Both experimental and clinical studies have suggested that polymorphisms and mutations in a number of pain-related genes are involved in the facilitation or inhibition of nociception [127,128]. The current concept is that modulation of the ion channels expressed by certain genes may modify the neuropathic pain experience and the response to analgesics [127]. Voltage-gated sodium channel (Nav) genes hold most promise due to their key role in nociception and the pathogenesis of small fiber neuropathies. Peripheral nociceptive neurons express a variety of sodium channel isoforms including Nav1.3, Nav1.5, Nav1.7, Nav1.8, and Nav1.9, and each isoform plays a key role in the physiology of nociception [129].

The PROPANE study group suggested that underlying hyperexcitability induced by the β2-subunit mutation (gain of function) of the Nav 1.7 channel may contribute to pDPN [128]. There are currently a number of potential molecules, which modulate this channel, but none have received marketing authorization. Of these Vixotrigine, a selective antagonist of NaV 1.7 is in phase 2 trials for small fiber neuropathy and pDPN [128]. Unfortunately, trials in lumbosacral plexopathy and trigeminal neuralgia have failed to meet their primary outcome measure. There are also some positive data in phase 2 trials for VX-150 an inhibitor of NaV 1.8 channels in small fiber neuropathy (NCT03304522).

1.16.1. Cibinetide

Cibinetide (ARA290) is a novel 11 amino acid non-hematopoietic peptide that interacts with high affinity and selectively with the innate repair receptor [130]. The innate repair receptor mediates tissue protection through activation of anti-inflammatory pathways [131]. Cibinetide has shown small improvement in glycemia and lipids and neuropathic symptoms as well as small fiber neuropathy detected with corneal confocal microscopy in a phase 2 study in diabetic neuropathy [132]. A further phase 2 study of Cibinetide in sarcoidosis confirmed regeneration of small nerve fibers with an improvement in neuropathic pain [133].

1.17. Trazadone plus Gabapentanoids

The separate but synergistic modulatory effects of polypharmacy may provide analgesic effect in combination therapy at much lower doses than each drug individually [134]. Trazodone is a second-generation antidepressant with strong sedative activity exerting its effects via 5-HT_2, α_1, and H_1 blocking properties and inhibiting presynaptic uptake of serotonin [135]. It has been widely used as a hypnotic drug for decades in subtherapeutic antidepressant doses of 100 mg or less [135] and its sedative effect is beneficial in disorders where somnipathy is a key feature [136,137]. In an uncontrolled open label 24 week study in fibromyalgia, trazodone (50-300 mg/day) significantly improved pain severity and depression [135]. Combination with pregabalin (75-450 mg/day) further potentiated this improvement [135]. Forty-six percent of patients had a moderate-substantial decrease in pain scores [135]. There is currently a phase 2 trial for pDPN comparing the efficacy of trazadone/gabapentin combination in three doses (trazadone/gabapentin: 2.5/25 mg, 5/50 mg, 10/100 mg) to gabapentin monotherapy and placebo (NCT03749642) [138].

1.17.1. Olodanrigan

Angiotensin 2 is an endogenous effector of the renin-angiotensin system and induces neuronal excitability at the dorsal root ganglion (DRG) [139]. Angiotensin 2 type 2 receptor (AT_2R) has been localized in cultured neurons of human and rat DRG [140]. Olodanrigan (EMA 401 or PD-126055) is an AT_2R antagonist, which is being developed for the treatment of variety of pain conditions including neuropathic pain and pDPN [141]. Treatment with Olodanrigan has resulted in dose-related functional inhibition of capsaicin responses in a cell culture study [140]. In a phase 3 RCT of Olodanrigan in post-herpetic neuralgia, 100 mg twice daily, a mean reduction in pain scores of −2.29 ± 1.75 was superior to placebo (−1·60 ± 1·66, p=0.0066) at 28 days [142]. Olodanrigan was well tolerated and the adverse event rate was similar to placebo [142].

1.17.2. PL37

Opioids often constitute the mainstay of treatment for nociceptive pain due to trauma, cancer, and inflammation, but limited efficacy for neuropathic pain in addition to dependence makes them less attractive in the management of pDPN. Dual inhibitors of enkephalinases (DENKI) are a novel class of analgesics for chronic pain, which inhibit the activity of enkephalin-degrading enzymes peripherally, increasing the half-life and local concentration of enkephalins, potent endogenous analgesics [143,144]. Importantly, PL37 enhances the opioidergic pathway without resulting in dependence, therefore the abuse/misuse potential is low [143]. DENKI's have been previously shown to produce antinociception in a rat sciatic nerve constriction model [145] and in experimental diabetic neuropathy [146]. Administration of PL37 in an experimental model of chemotherapy-induced neuropathy resulted in a reduction in neuropathic pain [144]. A phase 2 placebo-controlled clinical trial of PL37 in addition to gabapentin or pregabalin was completed in 2016 (EudraCT Number, 2013-004876-37), but the trial status is listed as 'prematurely ended' and the results are yet to be published.

1.17.3. P2X3

P2X3 is a protein, which is encoded by the P2RX3 gene [147] and is a key sensory purinergic receptor in the peripheral nervous system responsible for irritation and pain. The P2X3 receptor functions as a ligand-gated ion channel and transduces ATP-evoked nociceptor activation. ATP signalling results in neuronal sensitization and neuropathic pain [148]. Gefapixant (MK-7264 or AF-219) and BLU-5937 are potent, selective P2X3 receptor antagonist and have been initially trialled (in phase 2/3 studies) as an antitussive therapy in refractory chronic cough [149]. P2X3 may have an effect on neuropathic pain and future trials in pDPN are expected [150].

1.18. Dextromethorphan/Quinidine combination (DMQ)

Dextromethorphan has multiple mechanisms of action including as a non-selective serotonin reuptake inhibitor and a sigma-1 receptor agonist [151,152], the latter of which modulates calcium signaling in the central nervous system [153]. Quinidine is a class 1 anti-arrhythmic agent and acts as a Nav 1.5 channel inhibitor [154]. The combination of DMQ has been evaluated in two studies. In an early open label multi-center dose escalation study, where an incremental increase of 30/30mg to a maximal dose of 120/120mg showed an improvement in the pain intensity rating scale and pain relief rating scale [155]. In a further phase 3 RCT of pDPN (90 days), 379 patients with diabetes received either placebo (n=131), DMQ 30/30mg (n=125) or DMQ 45/30mg (n=123) and both dose combinations of DMQ were superior to placebo with significant improvements in the pain rating scale, pain intensity rating scale, sleep rating scale and activity rating scale [156].

1.19. Autonomic Neuropathy

The foundations of treatment for autonomic neuropathy are good glycemic control and cardiovascular risk management [157]. The DCCT showed that intensive glycemic control in patients with type 1 diabetes reduced the development of CAN by 45% [158]. Hypertension, obesity, hyperlipidemia, and smoking have been implicated in the development of CAN [39,159–163] and the STENO-2 trial showed that intensified multifactorial treatment in patients with type 2 diabetes

reduced the risk of CAN progression by 68% [164,165]. There are no FDA-approved disease-modifying treatments to reverse CAN. Initially there were favorable results for alpha-lipoic acid (ALA) on CAN [50]. However, more recently a study to evaluate triple anti-oxidant therapy (allopurinol (300mg qd), ALA (600mg bd) and nicotinamide (750mg bd)) in patients with type 1 diabetes and mild-moderate CAN found no benefit [166]. Lifestyle interventions, increased physical activity, β-adrenergic blockers, aldose reductase inhibitors, ACE inhibitors, ARBs, and antioxidants have all shown benefit [167] but primarily in modulating sympathovagal imbalance in early disease rather than providing a mortality benefit in severe, symptomatic CAN. Patients with resting tachycardia or orthostatic hypotension have substantial denervation and represent the severest end of the spectrum.

1.20. Orthostatic Hypotension (OH)

OH, can initially be managed with non-pharmacological treatment which includes encouraging physical activity and exercise to avoid deconditioning and fluid and salt repletion with a careful review of any medication which may exacerbate this condition. Fludrocortisone is effective however there are concerns over supine hypertension, hypokalemia, congestive cardiac failure and peripheral edema [168]. Midodrine is an FDA approved treatment for the management of orthostatic hypotension. Droxidopa is an orally active synthetic precursor of norepinephrine and has recently been approved by the FDA for the treatment of symptomatic neurogenic orthostatic hypotension [169].

1.20.1. Gastroparesis

Gastroparesis is defined as the delayed removal of stomach contents in the absence of a physical obstruction [170]. The mainstay of treatment is dietary modifications, hydration, and improving glycemic control. Pharmacologic treatment with prokinetics can be used to increase gastric motility, However, their use is limited by side effects. Metoclopramide is the only drug approved by the FDA and EMA for short-term treatment of gastroparesis [171]. New therapies currently under investigation include motilin receptor agonists, ghrelin receptor agonists, and neurokinin receptor antagonists [172]. Mechanical options for intervention include transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy [172]. In severe intractable cases of gastroparesis laparoscopic pyloroplasty or gastrectomy may be options.

1.20.2. Diabetic Diarrhea

Diabetic diarrhea is a troublesome complication where the underlying mechanism is not fully understood [1]. The diagnosis depends on ruling out other causes of diarrhea. There are a number of options including anti-diarrheal agents, antibiotics to eradicate bacterial overgrowth, somatostatin analogues, oral and topical clonidine, and selective serotonin 5-hydroxy tryptamine type 3 (HT3) receptor antagonists [173,174].

1.20.3. Erectile Dysfunction (ED)

The incidence of ED is approximately three-fold higher in men with diabetes compared with the general population [175] and the prevalence varies from 35-75% [176]. In a comprehensive systematic review and meta-analysis of 145 studies the prevalence of ED in diabetes was 52.5% (95% CI:48.8 – 56.2) [177]. The pathophysiology of ED in diabetes is multifactorial, consisting of both vascular, hormonal, and neurologic insults [175]. There are a number of therapeutic options for management of ED including phosphodiesterase type 5 (PDE5) inhibitors which remain the mainstay of initial therapy [178]. Avanafil, sildenafil, tadalafil, and vardenafil are all proven to be safe and effective for managing ED [179–185]. Additional treatments include testosterone replacement therapy, intracavernosal injection therapy, vacuum constriction devices (VCDs), intraurethral prostaglandin suppositories and surgical placement of a penile prosthesis [178]. Multifactorial therapy is warranted in more complex cases which may include psychological intervention [178].

2. Expert Opinion

The pandemic of diabetes complications, particularly diabetic neuropathy demands early and effective therapy to prevent and treat this debilitating condition. Small fiber neuropathy occurs at the earliest stage of DPN and indeed it occurs in recently diagnosed T2DM and subjects with prediabetes. Small nerve fibers constitute the majority of axons in the peripheral nerve and are the earliest to be damaged and show repair even in advanced disease. The primary endpoint(s) for future clinical trials of drugs that target pathogenetic mechanisms should include a quantitative measure of small nerve fibers. Both skin biopsy, quantifying intra-epidermal nerve fibers, and corneal confocal microscopy (CCM), quantifying corneal nerve fibers represent ideal surrogate biomarkers and endpoints of DPN. CCM is non-invasive, reiterative, and readily lends itself to rapid quantification which increases its clinical utility significantly [29,186]. The lack of treatments targeted at the pathogenesis of diabetic neuropathy is a major failure of the scientific community and in particular regulatory bodies such as the FDA and EMA, who continue to advocate the use of inappropriate large fiber endpoints for clinical trials. In particular, the FDA need to rapidly review the current status quo of so-called tried and tested endpoints such as symptoms, signs, and neurophysiology, which to date have failed to show benefit in multiple clinical trials of DPN [25].

The need for sensitive and reiterative biomarkers for the early detection of neuropathy is paramount to developing valid screening programmes. As scientists working in the field of DPN, we look enviously to colleagues who research and manage people with retinopathy and nephropathy. They have simple but effective screening methods that detect subclinical pathology [187]. This allows clinicians to instigate early intervention(s) based on individualized risk-based screening. By contrast, patients examined with the 10-g monofilament or 128Hz tuning fork will be missed even though they have mild DPN. There is an urgent need for individualized, risk-based screening for DPN. Additionally, there is no screening for CAN, despite it being

strongly associated with major cardiovascular events and mortality [159]. Intensive control of cardiovascular risk factors can reduce the progression of CAN as shown by the Steno-2 studies and early recognition is imperative [188].

Symptomatic treatment of pDPN remains the mainstay for treating diabetic neuropathy. However, pDPN has a complex aetiology with both peripheral and central mechanisms. No single therapeutic agent is available which will target these multiple pathological processes, especially without unwanted central side effects. Pregabalin, gabapentin, TCAs and SNRIs are first-line therapies for treating pDPN, yet only 1 in 4 patients will achieve a 50% improvement in pain. An increase in response rate will entail optimization of the pharmacokinetic and pharmacodynamic properties of neuropathic pain medication. This has been achieved recently with Mirogabalin, although at present it is only licenced in Japan [189,190]. Future RCTs should be directed to determine efficacy of combination therapy versus well-established monotherapy. Other avenues to improve response rates include the development of pain biomarkers to determine therapeutic response which would ideally predict optimal and individualize pharmacological treatments. Two putative biomarkers of therapeutic response to neuropathic pain show promise. Functional Magnetic Resonance Imaging (fMRI) may provide brain-based biomarkers of pain [138]. A previous fMRI study showed that gabapentin suppressed the secondary mechanical hyperalgesia-evoked neural response in the descending pain modulatory system and suppressed resting state functional connectivity during central sensitization, whereas, Ibuprofen showed no change when compared with placebo [191218]. Another, potential therapeutic response biomarker for pDPN and neuropathic pain is the rate-dependent depression (RDD) of the spinal H-reflex [72]. Loss of RDD indicates reduced descending inhibitory pathway function which is augmented by SNRI's such as Duloxetine. Thus, the detection of RDD may allow a personalized medicine approach to select either SNRI or non-SNRI-based neuropathic pain treatments.

Diabetic neuropathy screening demands tools, which are fit for purpose i.e. detect early disease. There is also an urgent need to utilise biomarkers with a greater ability to determine a therapeutic response for both disease-modifying and pain-relieving treatments.

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