The Review of DIABETIC STUDIES

REVIEW

Treating Diabetic Neuropathy: Present Strategies and Emerging Solutions

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■ Abstract

Diabetic peripheral neuropathies (DPN) are a heterogeneous group of disorders caused by neuronal dysfunction in patients with diabetes. They have differing clinical courses, distributions, fiber involvement (large or small), and pathophysiology. These complications are associated with increased morbidity, distress, and healthcare costs. Approximately 50% of patients with diabetes develop peripheral neuropathy, and the projected rise in the global burden of diabetes is spurring an increase in neuropathy. Distal symmetrical polyneuropathy (DSPN) with painful diabetic neuropathy, occurring in around 20% of diabetes patients, and diabetic autonomic neuropathy (DAN) are the most common manifestations of DPN. Optimal glucose control represents the only broadly accepted therapeutic option though evidence of its benefit in type 2 diabetes is unclear. A number of symptomatic treatments are recommended in clinical guidelines for the management of painful DPN, including antidepressants such as amitriptyline and duloxetine, the γ-aminobutyric acid analogues gabapentin and pregabalin, opioids, and topical agents such as capsaicin. However, monotherapy is frequently not effective in achieving complete resolution of pain in DPN. There is a growing need for head-to-head studies of different single-drug and combination pharmacotherapies. Due to the ubiquity of autonomic innervation in the body, DAN causes a plethora of symptoms and signs affecting cardiovascular, urogenital, gastrointestinal, pupillomotor, thermoregulatory, and sudomotor systems. The current treatment of DAN is largely symptomatic, and does not correct the underlying autonomic nerve deficit. A number of novel potential candidates, including erythropoietin analogues, angiotensin II receptor type 2 antagonists, and sodium channel blockers are currently being evaluated in phase II clinical trials.

Keywords: diabetic peripheral neuropathy · small fiber · polyneuropathy · alpha-lipoic acid · nerve fiber density

1. Introduction

Diabetes is associated with target-organ damage, including the microvascular triopathy of nephropathy, neuropathy, and retinopathy. These complications are associated with significant healthcare costs; the United States alone spends $245 billion in their management [1]. Recent estimates from the IDF show that the current worldwide prevalence of diabetes is 8.3%, with projections suggesting that by 2030 the number of adults with diabetes will increase by 69% [2]. This rising global burden of diabetes will clearly impact the prevalence and social burden of its complications. Diabetic neuropathy is one of the most common complications of diabetes, affecting at least 50% of patients with diabetes during their lifetime [3]. It has significant adverse consequences for patients, as it interferes with their everyday physical acting, leads to psychiatric comorbidities, and causes disability in patients with diabetes [4]. The human and economic burden of diabetic neuropathy is considerable for both patients and healthcare systems [5, 6].

Abbreviations:
ACE – angiotensin-converting enzyme
ADA – American Diabetes Association
ALA – alpha-lipoic acid
ARI – aldose reductase inhibitor
CAN – cardiovascular autonomic neuropathy
CCM – corneal confocal microscopy
CVD - cardiovascular disease
DAN – diabetic autonomic neuropathy
DCCT – Diabetes Control and Complications Trial
DPN – diabetic peripheral neuropathy
DSPN – distal symmetrical polyneuropathy
EDIC – Epidemiology of Diabetes Interventions and Complications
EFNS – European Federation of Neurological Society
EPO – erythropoietin
IASP – International Association for the Study of Pain
IENFD – intraepidermal nerve fiber density
NCV – nerve conduction velocity
NICE – National Institute for Health and Care Excellence UK
pDPN – painful diabetic peripheral neuropathy
QST - quantitative sensory testing
SNRI – serotonin norepinephrine reuptake inhibitor
T1D – type 1 diabetes mellitus
T2D – type 2 diabetes mellitus
TCA – tricyclic antidepressant
UKPDS – United Kingdom Prospective Diabetes Study
VAS – visual analogue scale
VPT – vibration perception threshold

Though diabetic neuropathy essentially involves damage or dysfunction affecting nerve fibers, its presentations are manifold. In about one fifth of patients, painful diabetic peripheral neuropathy (pDPN) predominates, and has a significant negative impact on health-related quality of life and general function [7]. Other manifestations include small-fiber neuropathy, autonomic neuropathy, diabetic amyotrophy, radiculopathy, mononeuritis multiplex, mononeuropathy, and treatment-induced neuropathy [8]. Diabetic autonomic neuropathy (DAN) can cause orthostatic hypotension, cardiac autonomic instability, and a range of debilitating manifestations, including gastroparesis, postural hypotension, urinary retention, and erectile dysfunction [9]. Furthermore, in the ACCORD trial, the risk of death in diabetic patients with DAN was 1.44-2.15 fold greater than in those without DAN [10].

Despite the significant individual and social burden associated with diabetic neuropathy, its treatment remains unsatisfactory. This is in part due to the innately unpredictable and complex nature of the disease, combined with limited systematic diagnostic testing, which differs from diabetic retinopathy and nephropathy, where the disease is more predictable and the diagnostic testing is widespread and systematically applied. Although the ADA recommends neuropathy testing annually after 5 years of type 1 diabetes and from the diagnosis of type 2 diabetes onwards, the testing advocated (monofilament/clinical examination) detects only advanced disease, and is rarely implemented [11]. Many therapies have been the subject of clinical trials for diabetic neuropathy and painful diabetic neuropathy. However, there are currently no FDA-approved therapies for diabetic neuropathy, and only three approved therapies for pDPN. Polypharmacy is associated with its own risks, especially since medications used for neuropathic pain are not specifically targeted on peripheral nociceptive pathways, and therefore demonstrate undesirable adverse effect profiles [12-14]. To address this unmet need, an unwieldy guideline jungle has emerged to build consensus on therapeutic approaches for diabetic neuropathy [15]. In the present review, we aim to provide a pragmatic guide on a range of treatments that have been evaluated in diabetic neuropathy.

2. Diagnosis and assessment

In 2010, the Toronto consensus panel on diabetic neuropathy subdivided the disease into typical and atypical diabetic neuropathy [8]. Typical DPN is “a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates.” Atypical variants of diabetic neuropathy differ in onset, course, manifestations, associations, and putative mechanisms, and are likely to be associated with pain and/or dysautonomia.

The presentation of diabetic neuropathy is variable, although the clinical picture is most frequently dominated by pain. Of note, pain is reported by approximately one third of patients with diabetes, regardless of associated neurological deficits [7]. The classical description is that of an unremitting burning pain that is characteristically worse at night, with a gradual distal-to-proximal progression of symptoms in a glove-and-stocking distribution [16]. A number of other features have been associated with the pain of diabetic neuropathy (**Table 1**). Motor symptoms occur less frequently, and typically appear as the disease progresses. Deficits in deep-tendon reflexes are similarly associated with advanced disease. It has been suggested that damage to small nerve fibers (carriers of nociceptive and thermal signals) may precede damage to large nerve fibers (that convey

proprioception, innervate skeletal muscles, and mediate tendon reflex) [17]. Additionally, autonomic neuropathy can occur concurrently or independently of the somatic and motor dysfunction. The ubiquity of autonomic innervation in the body translates into a diverse clinical profile of DAN, which may occur in patients within two years of the diagnosis of diabetes, yet it remains an underdiagnosed entity in clinical practice [18].

In the clinic, painful diabetic neuropathy should be evaluated against a combination of typical symptoms of painful neuropathy, associated with neurological deficits [16]. A number of tools have evolved to aid the clinician in the diagnosis of diabetic neuropathy. The Toronto group highlighted the role of a multi-pronged approach that should consider signs or symptoms supported by neurophysiological studies and quantitative sensory testing [8]. Although nerve conduction studies are commonly advocated to confirm the diagnosis of DPN, and to assess its progression or regression in a clinical research setting, they may not detect the earliest nerve fiber damage, and only test a minority of nerve fibers, namely the large myelinated fibers [19, 20]. However, pain, temperature, autonomic function, and wound pathophysiology are largely dependent on small nerve fibers [21]. Newer techniques assess these small nerve fibers, and thus represent an intuitively attractive paradigm. Two such techniques include the visual quantification of intra-epidermal nerve fibers through skin biopsy and corneal confocal microscopy, which allows non-invasive in-vivo imaging of corneal nerves [19, 22].

Various tools have been validated to assess the neurological impairment in diabetic neuropathy. These include the Michigan Neuropathy Screening Instrument (MNSI) and Neuropathy Disability Score (NDS) [23, 24]. Pain-specific questionnaires have also been utilized to quantify painful symptoms. The available instruments include the Brief Pain Inventory [25], Neuropathic Pain Questionnaire (NPQ) [26], McGill Pain Questionnaire, and visual analogue scales (VAS) [27, 28]. Additionally, neuropathy-specific quality of life measures, such as the Europol [29] and the Norfolk Quality of Life Scale [30] may play a role in identifying patient-important factors in neuropathy.

DAN is typically diagnosed through the assessment of the signs and symptoms attributable to the dysfunction of a particular organ system [8]. Cardiovascular autonomic neuropathy is perhaps the most prominent representative of the dysautonomic syndromes encountered in diabetes. Relatively simple tests, such as heart-rate variability, deep breathing, Valsalva maneuver, and blood pressure changes in response to posture can be used to assess CAN [31] (**Table 2**).

Table 1. Symptoms associated with painful diabetic neuropathy

Symptoms associated with painful diabetic neuropathy
Pain
Paresthesia
Allodynia
Impairment of vibration sense
Reduced thermal sensation
Loss of pinprick sensation
Bed sheet or sock intolerance
Restless legs syndrome

In the Rochester Diabetic Neuropathy Study, Dyck *et al*. found that in 10% of diabetic patients with neuropathy, the cause of neuropathic impairment was not attributable to diabetes [32]. This shows that it is always important to consider the differential diagnosis, which may help to identify potentially more serious or treatable causes (**Table 3**) in patients before reaching a firm diagnosis of diabetic neuropathy. We highlight a practical approach to the patient with diabetic neuropathy (**Figure 1**). Patients with diabetic neuropathy should be routinely counseled about their disease, in particular focusing on patient concerns and expectations, and the opportunity should be used to emphasize the role of satisfactory glycemic control. The lifetime risk of a patient with diabetes developing a foot lesion, including ulcers, Charcot

Table 2. Commonly used tests for autonomic function

Tests for autonomic function
Resting heart rate
Cardiac responses to deep breathing
Cardiac responses to Valsalva maneuvers
Cardiac responses to standing
Tilt-table tests
Quantitative Sudomotor Axon Reflex Testing (QSART)
Sympathetic skin responses
Thermoregulatory sweat test
Specialized tests for genitourinary and gastrointestinal autonomic dysfunction

foot abnormalities, injuries, infections, and lower-extremity amputation, has been estimated at 15-25% [33]. As neuropathy progresses, unsteadiness and gait abnormalities may be encountered, while motor dysfunction may predispose to inadvertent minor foot injuries. Thus, patients should be advised on the need for meticulous foot hygiene, appropriate footwear, and mobility support as needed.

Table 3. Important alternative causes of neuropathy to consider in the diabetic patient

Alternative causes of neuropathy
Malignancy
Toxins (e.g. alcohol, medication)
Infections (e.g. HIV)
Metabolic dysfunction (e.g. vitamin B deficiency)
Autoimmune diseases
Hereditary
Hematological
Trauma

3. Pathogenetic treatments

A number of different therapeutic approaches that target the various pathogenetic mechanisms of diabetic neuropathy have been the subject of clinical trials (**Figure 2**). These treatments aim to impact favorably the underlying pathophysiological aberrations encountered in DPN by targeting different elements in the pathways leading to neurovascular dysfunction. Whilst numerous pathogenetic treatments have shown promise in experimental and early phase II studies, a recurring theme has been the lack of 'translation' into phase III clinical trials. Thus, at present there are no licensed medications in the US or UK for the treatment of diabetic neuropathy [34].

The obvious question is why no pathogenetic treatment for DPN has proved sufficiently efficacious to achieve regulatory approval. Ziegler and Luft suggested that, until the mid-1990s, trials were hampered by a generally poor design, short follow-up, and by being limited to patients with advanced DPN [35]. They suggested that trials, involving patients with early DPN, conducted over 3-5 years to establish a delay or arrest in the progression of neuropathy, rather than reversal, were more likely to be successful.

In 2007, Tesfaye *et al*. reported on the placebo-treated arms of two randomized controlled trials of ruboxistaurin in DPN, and found significant improvements in signs, symptoms, and quantitative vibration testing [36]. They concluded that studies of >12 months are needed to demonstrate deterioration in any placebo-treated DPN group. In the same year, Dyck *et al*. examined the challenges of selecting appropriate end-points for clinical trials by examining data from the placebo-treated groups of two large intervention trials and the Rochester Diabetic Neuropathy Study [37]. They concluded that there were three main reasons for the inability of these studies to demonstrate the continuous worsening of neuropathic end-points:

- A strong placebo effect for symptoms and signs
- Measurement noise
- The fact that DPN may progress more gradually than previously thought

Commenting on the work by Dyck *et al.*, Boulton further suggested a role for concomitant treatments (such as ACE inhibitors and lipid-lowering regimens) for cardiovascular comorbidities in people with diabetes [38]. These therapies might also positively impact peripheral nerve function, and therefore act as confounding factors in studies. Boulton reinforces the need for selecting robust end-points for future studies, which should not be prone to the variability that afflicts quantitative sensory testing and patient-reported outcome measures. This means that skin biopsy and corneal confocal microscopy may be suitable objective end-points in clinical intervention trials.

3.1 Glycemic control

Although no trial has suggested that strict glycemic control relieves pain in patients with painful DPN, erratic glucose control is associated with painful symptoms in diabetic neuropathy. Studies in type 1 diabetes (T1D) have suggested a role for optimal glycemic control in the management of diabetes. The Eurodiab Insulin-Dependent Diabetes Mellitus (IDDM) study found that suboptimal glycemic control was associated with the development of DPN in a large cohort of ~3,000 people with T1D. 1,172 patients with T1D were assessed for neuropathy at baseline (1989 to 1991) and at follow-up (1997 to 1999), with a mean follow-up period of 7.3 ± 0.6 years. A standardized protocol for the evaluation of DPN included clinical evaluation, quantitative sensory testing, and autonomic-

function tests. A number of factors were independently associated with the incidence of neuropathy, including duration of diabetes, HbA1c status, and change in HbA1c value during follow-up [39]. Other than glycemic control, the incidence of neuropathy was associated with potentially modifiable cardiovascular risk factors, including body-mass index, smoking, hypertension, and raised triglyceride level [39]. Other observational studies since then have emphasized the link between poor glycemic control and DPN [40, 41].

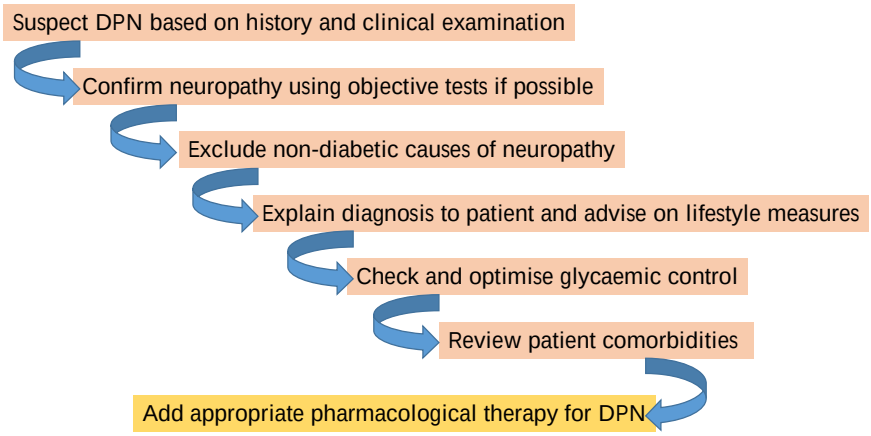

Figure 1. Stepwise approach to diagnosis and management of diabetic peripheral neuropathy (DPN)

Further evidence supporting the role of glycemic control in both primary and secondary prevention of DPN in patients with T1D comes from the Diabetic Control and Complications Trial (DCCT). This 10-year, 1,400-patient, multi-center study found that T1D patients, randomized to the intensive glucose control arm, had a 60% reduction in incidence of DPN and a 45% reduction in CAN with intensive treatment during the course of the trial. The Epidemiology of Diabetes Interventions and Complications (EDIC) was an observational study that followed up 90% of the DCCT cohort to determine the long-term impact of prior improvement in glycemic control on micro- and macrovascular outcomes [42, 43]. At the first EDIC study examination, HbA1c separation between the DCCT intensive and conventional groups narrowed substantially to 7.9% versus 8.3%. By the 5th year of the EDIC study, the difference in HbA1c between groups was no longer statistically significant (8.1% versus 8.2%; p = 0.099). Remarkably, despite no difference in glycemic control, the prevalence and incidence of DPN and CAN was significantly reduced in patients who received prior intensive insulin treatment compared with patients who received standard insulin therapy during the DCCT. This protective effect of prior intensive glycemic control (termed metabolic memory) persisted until 13 to 14 years after the end of the DCCT. For CAN, differences in glycated hemoglobin levels during the DCCT explained almost all of the protective effects of intensive versus standard therapy on the risk of incident CAN, supporting early commencement of intensive treatment in T1D. This highlights the importance of early diagnosis and timely intervention to reduce risk factors in the treatment of diabetic neuropathy.

In T2D, there is less evidence of benefits from intensive glycemic control. The United Kingdom Prospective Diabetes Study (UKPDS) emphasized the impact of glycemic control on microvascular complications in T2D, and reported a significant risk reduction for cardiovascular disease (CVD) and amputation for every 1% reduction in mean HbA1c [44]. A lower rate of impaired vibration perception threshold (VPT) with intensive therapy versus standard therapy was found, though this became significant after 15 years only (relative risk 0.60, 95% confidence interval 0.39-0.94), with no significant advantage observed at 3, 6, 9, and 12 years. The reduction in microvascular complications with intensive glycemic control in T2D was also suggested by a 6-year randomized, prospective study [45]. In 2011, Boussageon *et al*. conducted a meta-analysis of 7 trials involving over 34,000 patients, but they did not find a reduction in the incidence of DPN in patients managed through intensive glycemic control [46]. Furthermore, a Cochrane review of 17 randomized trials concluded that tight glycemic control prevented neuropathy in T1D, but a trend towards reduced incidence in T2D was not significant [47]. However, it should be noted that these meta-analyses have significant limitations as the targeted glucose levels, therapeutic strategies, outcome measures, trial design, and duration of follow-up differ between the separate studies. In particular, the majority of these

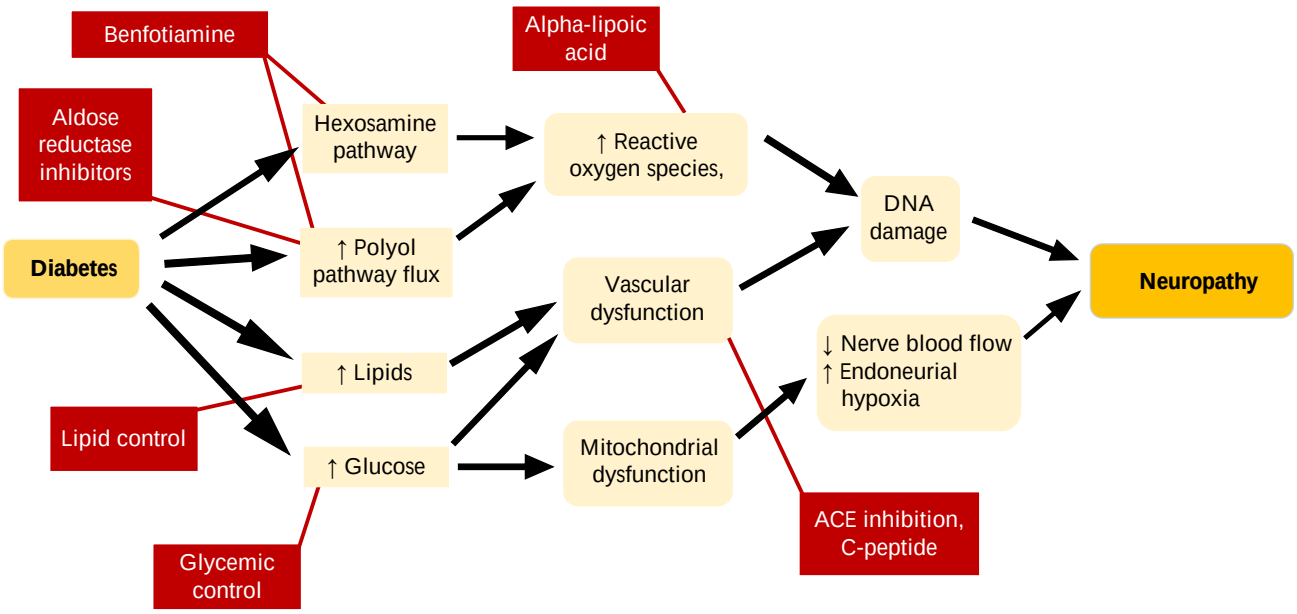

Figure 2. Integrating pathophysiology of diabetic neuropathy and the sites of action of pathogenetic drugs. *Abbreviations*: ARI – aldose-reductase inhibitor, ACE – angiotensin-converting enzyme, AGE – advanced glycation end-product.

studies utilized crude neuropathy end-points, including monofilament, foot exam, and vibration perception; these end-points cannot be expected to detect an improvement in underlying neuropathy.

The Veterans Affairs Cooperative Study reported no difference in the prevalence of autonomic neuropathy in T2D between the intensive and standard therapy arms at 2 years [48]. In contrast, the Steno-2 Trial reported that an intervention that integrated glucose control and multiple cardiovascular risk factor management reduced the prevalence of CAN, but not somatic neuropathy assessed using VPT, among patients with T2D and microalbuminuria [49].

Despite the conflicting evidence, optimization of glycemic control remains a broadly accepted first step and major aspect in the management of diabetic neuropathy, possibly with escalation to more intensive control in higher risk individuals. It should be noted that in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, an intensive glucose-lowering regimen was associated with increased mortality (hazard ratio 1.22, 95% confidence interval 1.01 to 1.46, p = 0.04), suggesting that the harm associated with hypoglycemia and weight gain may offset the potential benefit of tight control [10]. Furthermore, three factors predicted the increased mortality in this study, namely poor glycemic control, aspirin use, and surprisingly, a history of diabetic neuropathy [50]. Therefore, the therapeutic escalation to more intensive glycemic control therapy should be considered with caution, especially in patients with diabetic neuropathy.

3.2 Pancreas transplantation

The only known therapy to restore insulin secretion in response to feedback mechanisms in patients with diabetes is pancreas transplantation [51, 52]. Differing lengths of time for improvement in DPN have been reported in patients treated with pancreas transplantation. Fioretto *et al.* found that the reversal of DPN is evident 10 years after transplantation [53]. Other observational studies have suggested that markers of DPN start recovering far earlier. Agudo *et al.* have reported an increase in action potential amplitude and conduction velocity at 3 months and 1 year after transplantation in a small study involving 26 patients [54]. In the controlled study by Kennedy *et al.*, an improvement in sensory and motor function 12 months and 24 months after pancreas transplantation was reported in a cohort of 61 patients with T1D, although neurophysiological and autonomic function tests did not demonstrate re-

covery [55]. Navarro *et al*. reported similar findings in 115 T1D patients who underwent pancreas transplantation. These patients showed an improvement in composite scores assessing motor and sensory neuropathy, but only slight improvement in autonomic function after a longer 10-year follow-up [56].

Boucek *et al*. assessed intraepidermal nerve fiber density (IENFD), an objective test proposed as a gold standard for assessing the benefits of therapeutic intervention, in 18 subjects following pancreas and kidney transplantation [57]. They found that only 3 patients showed an improvement in IENFD, suggesting that some patients' DPN may have reached a non-reversible stage. However, it should be noted that all these studies used different outcome measures to assess DPN with variable follow-up periods. Hence, it is likely that the improvement in DPN reported in the literature depends entirely on the end-point used to assess DPN. Indeed, in a contemporary cohort of 15 patients, we found no significant changes in electrophysiology, quantitative sensory testing, and IENFD 6 months after transplantation, but corneal confocal microscopy, an objective test for assessing small nerve fiber damage, demonstrated significant improvement [58].

While pancreas transplantation therapy may represent the most effective method for restoring normoglycemia, its application is limited to patients with end-stage kidney disease or, less frequently, to patients with T1D and unpredictable hypoglycemia. This limitation is due to the restricted and unpredictable availability of suitable organs, complications of surgery, and the risks of long term immunosuppression. Recently, islet-cell transplantation has been considered as a less invasive alternative for suitable patients with diabetes. Del Carro and colleagues reported marked improvement in neurophysiology in a cohort of T1D patients, with no change in skin biopsy findings [59].

3.3 α-lipoic acid

Oxidative stress arises in the hyperglycemic state from an increased production of reactive oxygen species, which is due to the auto-oxidation of the excess glucose and a failure in antioxidant mechanisms [60]. These oxygen-free radicals mediate endothelial dysfunction by inhibiting nitric oxide, leading to ischemic nerve damage. Alpha-lipoic acid (ALA) is a free radical scavenger that alleviates this oxidative stress. It is used for the treatment of DPN in a number of countries, but currently does not have regulatory approval in the UK and US. ALA was found to be well-tolerated and efficacious in the management of painful DPN when administered parenterally. Indeed, Ziegler *et al*. reported a clinically significant improvement in the symptoms of DPN after administration of a 600 mg daily dose of ALA over 3 weeks in their meta-analysis of four placebo-controlled trials [61]. However, in the more recently published Neurological Assessment of Thioctic Acid in Diabetic Neuropathy (NATHAN) 1 study, a 4-year, multicenter, randomized controlled trial comparing ALA with placebo, Dyck *et al*. found no improvement in neurophysiology, quantitative sensory testing (QST), and composite neuropathy scores [37]. Importantly, the primary end-point did not deteriorate significantly in placebo-treated subjects, emphasizing the recurrent issue of a lack of placebo decline in trials of human DSPN [37].

3.4 Aldose reductase inhibitors

Aldose reductase is the rate-limiting enzyme in the polyol pathway for glucose metabolism [62]. Hyperglycemia increases the activity of aldose reductase, leading to reduced production of the vasodilator nitric oxide and eventually perpetuating ischemic nerve injury. Aldose reductase inhibitors (ARIs) have shown improvements in nerve conduction velocity, myelinated nerve fiber density, and regenerative clusters in sural nerve biopsies [63], but have consistently failed in phase III clinical trials [64]. There are also concerns about toxicity; given the limited efficacy, this has precluded their use in patients [65]. Epalrestat is the only ARI which is licensed in Japan and India based on randomized controlled trials [66]. However, a Cochrane collaboration review of 32 trials comprising 4,970 participants found no overall benefit of ARIs in DPN [67].

3.5 Benfotiamine

Benfotiamine is a fat-soluble derivative of thiamine, and has been shown in animal models to inhibit three major pathways implicated in oxidative stress and vascular dysfunction in diabetes: the advanced glycation end-product pathway, the hexosamine pathway, and the protein kinase-C-diacylglycerol pathway [68]. Although benfotiamine appears to be an appealing treatment option given its multimodal actions, clinical trials are inconclusive about its efficacy. One placebo-controlled phase III trial reported an improvement in patient-reported symptoms in the per-protocol

arm of the study, although no improvement was noted in the intent-to-treat group compared with placebo [69]. Furthermore, the authors reported no difference in peripheral nerve function between the placebo and treatment arms of the study [69].

3.6 Angiotensin-converting enzyme (ACE) inhibitors

The development and progression of nephropathy, retinopathy, and neuropathy are closely related. Angiotensin-converting enzyme (ACE) inhibitors delay progression of both nephropathy and retinopathy. Therefore, we have previously investigated the effect of ACE inhibition on diabetic neuropathy. We found an improvement in neurophysiology after 12 months of treatment with the ACE inhibitor trandolapril in 41 normotensive patients with DPN, although there was no difference in measures of autonomic function compared with placebo [70]. In a larger study, Ruggenenti *et al*. reported a reduction in the progression of neuropathy with the ACE inhibitor delapril [71].

3.7 Protein kinase C activation

Free radicals generated by the hyperglycemia-induced activation of protein kinase C (PKC) are thought to play a role in the pathogenesis of DPN by altering vascular permeability and causing vasoconstriction. The PKC inhibitor ruboxistaurin has been evaluated in clinical trials [72, 73]. A recent systematic review of six randomized controlled trials concluded that it offered no benefit in the treatment of DPN [74].

3.8 C-peptide

C-peptide deficiency is an important contributing factor to the characteristic functional and structural abnormalities of the peripheral nerves [75]. C-peptide binds to cell membranes, resulting in stimulation of endothelial nitric oxide synthase (eNOS) and Na^+, K^+-ATPase [76]. In the Joslin 50-Year Medallist Study, protection from diabetic complications (i.e. retinopathy, nephropathy, and neuropathy) was thought to be due to the presence of enriched protective factors against microvascular complications [77]. In two double-blind, placebo-controlled studies in T1D patients, C-peptide replacement or placebo was given with the patients' regular insulin therapy [78, 79]. Sensory nerve conduction velocity (NCV) assessed in the sural nerve showed a significant improvement. Whilst further detailed large randomized controlled trials of sufficient quality and length are required to assess the effectiveness of C-peptide as a therapeutic intervention, a large phase III trial reported no significant improvement in neurophysiology in 2015.

3.9 Actovegin

Actovegin is a deproteinized hemoderivative extracted from calf blood through ultrafiltration. It exerts an insulin-like effect by stimulating glucose transport, pyruvate dehydrogenase, and glucose oxidation [80]. In a multicenter, randomized, placebo-controlled, double-blind trial, actovegin was found to improve VPT and quality of life [80]. Despite the improvements seen in this trial, further, more comprehensive clinical trials are needed to confirm its benefits in the treatment of DPN [65].

3.10 Other pathogenetic treatments

Inconsistent blood glucose control has been particularly associated with DPN, and it has been hypothesized that stable glycemic control may play a role in the treatment and prevention of neuropathy. Near-normal glycemia can be achieved in people with diabetes treated with continuous subcutaneous insulin infusion (CSII). These patients show improvements in neurophysiology and painful symptoms [47]. Azmi *et al*. recently reported corneal nerve regeneration in a cohort of subjects managed by CSII compared with subjects managed by a multiple daily injection insulin regimen, despite no difference in HbA1c over 2 years of follow-up [81]. Interestingly, in this study, QST and neurophysiology showed no improvement.

A sural nerve biopsy study has reported an association between dyslipidemia and DPN; higher triglyceride levels were correlated with a reduction in myelinated fiber density [82]. Fried *et al*. suggested that lowering blood lipid levels may prevent or alleviate the symptoms of DPN [83]. Indeed, Smith *et al*. reported that a decrease in triglyceride levels in a cohort of patients with impaired glucose tolerance managed by lifestyle interventions was associated with an increase in IENFD [84]. Furthermore, a recent double-blind, placebo-controlled study of rosuvastatin showed an improvement in neurological deficits, symptoms, and nerve conduction parameters of DPN after 12 weeks [85]. The FIELD study reported a significant reduction in minor amputations in T2D patients receiving fenofibrate [86]. This result points to an important role for triglycerides or alternative mechanisms of benefit for PPARα agonists.

4. Symptomatic treatment

Symptomatic treatment of pain is a mainstay in the treatment of diabetic neuropathy. A number of agents have been evaluated in clinical trials [15]. These treatments aim to alleviate painful symptoms, but are not targeted at the underlying pathophysiology, nor do they redress impairments such as sensory deficits from neuropathy. Navigating through the pain management in DPN can be daunting given the limited efficacy and side-effect profiles of the various medications for pDPN. Various guidelines and a number of different algorithms have been proposed to simplify the approach to treatment (**Table 4**) [15]. Typically, neuropathic pain medications provide limited pain relief. It is therefore important for clinicians to discuss management options and expectations with patients, with the aim of providing clinically meaningful pain relief to patients, and improving their quality of life. Indeed, 30% pain relief or a 2-point reduction in pain on the 10-point Likert scale has been reported to be clinically meaningful to patients [87]. Additionally, careful consideration of patient factors is important before starting therapy as medical and psychiatric comorbidities may influence the choice of medication.

Safety and effectiveness of analgesic medications for pDPN are usually compared on the basis of numbers needed to treat (NNT) or numbers needed to harm (NNH) to achieve 30% or 50% pain relief. Head-to-head trials are being conducted to compare efficacy and safety of different agents or combined regimens to improve the design of multidrug therapy for DPN.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended in DPN because of their possible adverse properties to cause gastrointestinal hemorrhage and exacerbate preexisting renal failure in diabetes. Despite these properties, they continue to be frequently prescribed. A study examined the general practice records of 16,690 patients with DPN and postherpetic neuralgia, and found that 43% of patients were managed with NSAIDs [88]. In contrast, most published guidelines (**Table 4**) recommend tricyclic agents (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or γ-aminobutyric acid (GABA) analogues (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments [15].

4.1 Tricyclic agents

Primarily based on cost considerations, TCAs have been the first-line treatment of choice for neuropathic pain for many years. In contemporary clinical care, they are less used because of the frequency and severity of their adverse effects [15]. Developed initially as antidepressants, TCAs exert a range of effects, including inhibition of serotonin and noradrenaline reuptake from synaptic clefts and acting as antagonists on N-methyl-D-aspartate (NMDA), 5-HT, histamine, muscarinic, and alpha-adrenergic receptors [89]. Some agents, such as amitriptyline, may have a role in sodium channel blockade. The exact mechanism by which they alleviate neuropathic pain remains unknown. Trials of TCAs in DPN are limited because of small sample sizes and inconsistent and inaccurate approaches to phenotyping neuropathy and assessing pain relief. Furthermore, the high doses used in clinical trials are rarely replicated in clinical practice because of the predictable anticholinergic side-effects of TCAs. Rudroju *et al.* reported that amitriptyline was the least safe and effective agent in a meta-analysis of six antidepressants and GABA analogues in the treatment of DPN [90]. However, two small crossover trials found evidence of benefits for active treatment with amitriptyline and desipramine over placebo in treating painful DPN [91, 92]. Additionally, evidence from randomized controlled trials indicates that imipramine is superior to placebo in managing diabetic neuropathic pain [93, 94].

Table 4. Comparison of selected guideline recommendations for drugs used for pain in diabetic neuropathy

Drug	AAN (2011)	NICE (2013)	EFNS (2010)	NeuPSIG IASP (2015)
TCAs			1st line	
Amitriptyline	2nd line	1st line		
Desipramine				1st line
Imipramine				
SNRIs	2nd line		1st line	1st line
Duloxetine		1st line		
Venlafaxine				
GABA analogues			1st line	1st line
Gabapentin		1st line		
Pregabalin	1st line	1st line		
Opioids	2nd line		2nd line	2nd line
Tramadol		2nd line		
Topical				
Capsaicin (0.075% cream)				

Legend: AAN – American Academy of Neurology, EFNS – European Federation of Neurological Societies, GABA – gamma aminobutyric acid, NeuPSIG IASP – Neuropathic Pain Special Interest Group of the International Association for the Study of Pain, NICE – National Institute for Health and Clinical Excellence, SNRI – serotonin norepinephrine reuptake inhibitor, TCA – tricyclic antidepressant.

4.2 Serotonin norepinephrine reuptake inhibitors (SNRIs)

SNRIs are selective inhibitors of serotonin and norepinephrine that exert their effects by disrupting the balance of neurotransmitters and stimulating descending inhibitory pathways to alleviate pain [95]. The SNRI duloxetine was the first drug to be approved by the FDA for the treatment of DPN [96]. In one of the early randomized, double-blind, placebo-controlled trials, Goldstein *et al*. compared doses of 20 mg, 60 mg, and 120 mg duloxetine with placebo in 457 patients [97]. 60 mg and 120 mg duloxetine were associated with a significant improvement in 24-hour average pain scores. Lunn *et al*. found that 60 mg and 120 mg daily doses were efficacious for the treatment of painful DPN in their analysis of data from eight studies (n = 2,728) [98]. Although the overall safety profile of duloxetine is superior to amitriptyline, with less prevalent anticholinergic side-effects [90], Goldstein *et al*. found that 20% and 14% of patients in their cohort treated with a daily dose of 60 mg duloxetine reported somnolence and constipation, respectively [97]. Furthermore, metabolic side-effects, including raised fasting glucose levels and weight gain, have also been described.

Venlafaxine is another SNRI that has been investigated in the context of DPN, and found to be efficacious, though it is not approved by the FDA, for this indication. Venlafaxine has been reported to be superior to placebo in alleviating the symptoms of pDPN at doses above 150 mg per day, though clinically significant electrocardiogram changes were reported in seven patients [99]. Two recent meta-analyses have suggested that venlafaxine is superior to duloxetine for treating pDPN and only sodium valproate was more efficacious when a numeric rating scale was used to assess pain relief [100, 101]. However, most trials evaluating venlafaxine in DPN are constrained by their small sample sizes and limited data about long-term safety. Thus, this option cannot be recommended ahead of duloxetine.

4.3 Anti-convulsants

Carbamazepine was among the first traditional anticonvulsants to be used for the management of painful neuropathy. Carbamazepine acts by inhibiting voltage-gated sodium channels, resulting in reduced peripheral nerve excitability. Early placebo-controlled trials suggested that carbamazepine may be useful in controlling neuropathic pain [102, 103]. Although a Cochrane review found limited evidence for its efficacy [100], In their meta-analysis, Griebeler *et al*. compared the effectiveness of agents used for managing painful DPN, and suggested that carbamazepine was effective in the treatment of DPN [100]. Carbamazepine is associated with myelosuppression and osteoporosis; its use has been largely superseded in clinical practice by other agents.

Oxcarbazepine, a keto-analogue of carbamazepine, caused a >50% improvement in the primary end-point of patient-reported pain scores in a multicenter trial [104]. However, two later studies found no improvement in the VAS score from baseline after treatment with oxcarbazepine [105, 106].

Gabapentin is a structural analogue of the neurotransmitter GABA that exerts its analgesic effect through inhibition of the $\alpha_2\delta$ unit of the presynaptic calcium channel [107]. In the first double-blind placebo-controlled trial, investigating gabapentin for treating painful DPN, Backonja *et al*. randomized 165 patients to either gabapentin or placebo [108]. They reported a significant improvement in pain scores and quality of life after 8 weeks of treatment. More recently, Mellegers *et al*. carried out a systematic review of 35 studies [109]. They reported that gabapentin was an effective agent for treating neuropathic pain. A Cochrane review supported the use of gabapentin for DPN with an NNT of 5.8 [110]. In a recent analysis, comparing six agents for treating painful DPN, Rudroju *et al*. reported that gabapentin offered the most favorable balance between safety and efficacy [90]. Therefore, gabapentin is frequently advised as a first-line treatment option in guidelines for the treatment of neuropathic pain [15].

Pregabalin is a GABA derivative with greater potency than gabapentin. It exerts its analgesic effect in a manner similar to gabapentin. Four double-blind placebo-controlled trials reported a significant improvement in pain scores following treatment with pregabalin [111-114]. This effect was found to be dose-dependent. The most beneficial effect in terms of pain relief, mood improvement, and sleep interference was reported with a dose of 600 mg. Snedecor and colleagues recently found in their meta-analysis of pharmacological agents for painful DPN that pregabalin resulted in the greatest pain relief when a VAS was used as outcome measure [101]. Based on the efficacy of pregabalin use in clinical trials, it remains one of the few agents licensed for treatment of neuropathic pain of DPN in both the USA and UK. Pre-

gabalin use is associated with a number of adverse effects, including mood disturbance, peripheral edema, and sedation, even if there are minimal interactions with other medications. Abrupt discontinuation of pregabalin has been linked to cerebral edema and encephalopathy. Therefore, patients should be warned against abruptly stopping the therapy. Sicras *et al*. carried out a cost-comparative analysis of patients treated with either pregabalin or gabapentin [115]. They reported that pregabalin therapy resulted in reduced overall healthcare cost compared with gabapentin.

Raskin *et al*. found that topiramate alleviated neuropathic symptoms in a large placebo-controlled trial [116]. Similar results were reported in the subsequent open-label extension of this study [117]. However, three subsequent studies have reported no significant change in pain scores with topiramate therapy [118].

Lamotrigine, an antiepileptic agent with antinociceptive properties has also been evaluated. In two large placebo-controlled studies [119, 120], inconsistent pain relief was reported in diabetic patients randomized to the higher-dose lamotrigine group, while no significant effect was found in the low-dose lamotrigine group. Indeed, Wiffen *et al*. found no evidence for a benefit with lamotrigine in their Cochrane review [121].

4.4 Opioid analgesia

At analgesic doses, opioids modulate pain signals by activating spinal and supraspinal mechanisms via μ, δ, and κ type opioid receptors [89]. Tramadol is primarily a μ receptor agonist that also inhibits serotonin and norepinephrine reuptake. Harati *et al*. randomized 131 patients to either treatment with tramadol or placebo in a multicenter, outpatient, double-blind, parallel-group study [122]. They found that an average dose of 210 mg/day tramadol resulted in significant pain relief, as assessed through a Likert scale, and also improved social and physical functioning of subjects. These benefits persisted in the open-label extension of this 6-week trial. However, higher doses of tramadol were associated with frequent adverse effects, including nausea (23%), constipation (21%), and headache (17%).

In 2012, the extended-release (ER) formulation of tapentadol, a partial μ agonist with a norepinephrine reuptake inhibitory effect, received approval from the FDA for the relief of neuropathic pain. Schwartz and colleagues administered tapentadol ER in a 3-week open-label study with 588 patients [123]. 395 patients reported at least a one-point reduction in pain intensity on a numeric rating scale. These patients were subsequently randomized 1:1 to receive either placebo or a fixed optimal dose of tapentadol ER for a 12-week double-blind phase. Patients in the tapentadol arm of this trial reported a significant reduction in pain intensity compared with placebo. It has been proposed that tapentadol suppresses neuropathic pain through opioid spinal-supraspinal synergy in addition to the μ-opioid agonist and norepinephrine inhibitory effect [124].

Oxycodone, an opioid with greater bioavailability and potency than morphine, but with a diminished side-effect profile, has also been studied in pDPN. Gimbel *et al*. found that a 20 mg controlled-release dose reduced pain intensity in 159 patients [125]. In a smaller placebo-controlled crossover study of 36 patients, active treatment with oxycodone was associated with a significant improvement in average daily pain scores [126]. A recent meta-analysis by Snedecor and colleagues found that oxycodone was superior to tapentadol for pain relief in pDPN, although the data are limited by the small sample size and duration of clinical trials [101].

The use of long-term opioid therapy in DPN remains controversial because of the paucity of data on the risk-benefit ratio, considering that opioids are associated with significant long-term adverse effects, including nausea, constipation, itching, dizziness, suppression of the pituitary axis, immunological changes, and the potential for dependence and abuse. Opioids stimulate the mesolimbic reward center in the brain [127], leading to feelings of pleasure which can encourage craving and compulsive use. Indeed, opioids are among the most frequently misused prescription medication in the US [128], causing major concerns about their long-term use. This limits the wide use of opioids, and it is recommended that clinicians assess the risk of opioid misuse prior to prescribing opioids using a validated screening tool such as the Opioid Risk Tool (ORT) or the Diagnosis, Intractability, Risk, Efficacy (DIRE) score [128].

4.5 Topical therapies

Zhang *et al*. reported in a meta-analysis that topical application of capsaicin, an alkaloid derived from red chilli peppers, is effective in treating painful DPN [129]. The Capsaicin Study Group reported a significant reduction in pain intensity in a double-blind placebo-controlled trial involving 277 patients [130]. However, capsaicin therapy is asso-

ciated with complete or nearly complete epidermal denervation in patients with subsequent impaired nerve regeneration [131]. Therefore, it cannot be recommended for DPN as it may result in an increased risk of foot ulceration due to denervation.

Campbell and colleagues assessed the role of topical 0.1% clonidine, an alpha-2 adrenergic receptor agonist with an established role in managing acute pain, in the treatment of DPN [132]. The integrity of nociceptive function was evaluated at baseline in 179 subjects by assessing the intensity of pain reported following the application of topical capsaicin. The patients were subsequently randomized either to the clonidine or the placebo arm of the trial. The authors reported a non-significant trend towards reduction in pain scores in patients receiving active treatment. Interestingly, when only patients with functional (and possibly sensitized) nociceptors in the affected skin, i.e. those with a positive capsaicin response, were considered, topical clonidine gel caused a significant reduction in pain intensity.

Topical nitrate has also been shown to benefit pDPN. Yuen and colleagues found that treatment with isosorbide dinatrate spray caused a significant reduction in pain intensity and burning discomfort in a double-blind crossover study of 22 patients [133].

Furthermore, 5% lidocaine plasters applied for 18 hours per day were shown to improve pain scores and quality of life ratings significantly in a small open-label 3-week study of 56 patients with pDPN [134]. In a recent comparative meta-analysis, Snedecor *et al*. reported that lidocaine plasters may be as efficacious as pregabalin [101].

Intradermal botulinum toxin type A (BTX-A) has been demonstrated to reduce pain and improve sleep quality in 18 patients with DPN in a double-blind crossover study [135]. Indeed, a recent meta-analysis of two studies in pDPN showed an improvement of 1.96 VAS points. The authors concluded that the tests for significance, low overall risk of bias, and minimal statistical heterogeneity suggested an impact of BTX-A on pain scores in pDPN with a need for further large-scale controlled trials [136].

5. Non-pharmacological approaches

As conventional medical therapies may be unsuitable or inadequate in some patients with painful neuropathy, a number of other non-conventional therapies have been proposed. Various forms of electrical stimulation have been used to manage pain in DPN, including transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation, and frequency-modulated electromagnetic neural stimulation. In a review of eight studies, evaluating the role of electrical stimulation in DPN, Thakral and colleagues found that in six of these studies electrical stimulation was associated with an improvement in pain compared to sham treatment or placebo [137].

The role of acupuncture in managing chronic pain has been extensively investigated. Studies have recently examined its role in relieving the pain associated with DPN. In a recent single-blind trial in 45 subjects with painful DPN, Garrow *et al*. reported an improvement in pain in the acupuncture-treated group when compared with sham treatment [138]. However, Chen *et al*. suggest that it is difficult to draw conclusions from clinical trials evaluating acupuncture because these trials generally employ unconventional outcome measures of pain and have weak study designs [139].

Recently, Singleton and colleagues considered the impact of an exercise intervention on epidermal innervation, which is significantly reduced in DPN [140]. 100 patients with diabetes, but without peripheral neuropathy, were allocated to either a lifestyle counseling group or a weekly exercise intervention group. Interestingly, at the end of the one-year follow-up period, intraepidermal nerve fiber density was significantly higher in the exercise group, but unchanged in the lifestyle-counseling cohort. Similar results were reported in a cohort of patients with the metabolic syndrome [141]. While these studies suggest that regular exercise prevents DPN in diabetic patients, the significance of these findings needs to be validated in future trials to define better the type and duration of exercise and lifestyle modification required for potential benefits in patients with DPN.

6. Combination therapy for DPN

While guideline-creating organizations recommend a broad range of medications for DPN, there is increasing recognition among clinicians that monotherapy rarely provides adequate analgesia. Frequently, DPN management requires a combination of drugs to achieve adequate pain control. However, most studies only compare pharmacological therapies against placebo or sham treatment. Given the refractory nature of painful neuropathy to monotherapy, there is a growing need for comparative studies between different pharmacological agents.

Although data comparing drug combinations are sparse, some trials have compared monotherapy and combined therapy regimens. Gilron *et al.* conducted a small study in 56 patients with DPN or post-herpetic neuralgia who were randomized in a 1:1:1 ratio to receive one of three sequences of daily oral gabapentin, nortriptyline, or their combination [142]. Combination therapy was found to be superior in providing pain relief compared to gabapentin and nortriptyline alone, suggesting that dual therapy with these agents should be considered in patients who show only a partial response to one of these agents. Similarly, another study reported that combination therapy with morphine and gabapentin had superior efficacy with a similar adverse-effect profile compared with monotherapy with either agent at maximal tolerated doses [143].

Recent studies have also focused on head-to-head comparisons between individual pharmacological agents. Bansal *et al.* reported in a head-to-head comparison that pregabalin was more effective in providing pain relief in DPN than amitriptyline [144]. In a large multicenter, double-blind, parallel-group study in over 800 patients, Tesfaye and colleagues found that 60 mg/day duloxetine was more effective than 300 mg/day pregabalin ($p < 0.001$) in the initial 8-week phase [145]. Subsequently, a 50% response rate for pain relief was observed in 52.1% for combination and 39.3% for high-dose monotherapy ($p = 0.068$).

More recently, large meta-analyses have aimed to compare different therapies for painful neuropathy [100, 101]. Snedecor and colleagues evaluated data from 58 randomized controlled trials (n = 11,883), and evaluated the relative equivalence among the interventions studied [101]. Pregabalin (≥300 mg/day) was found to be the most effective agent when assessed by a 100-point VAS; topiramate was the least effective. A similar analysis was conducted by Griebeler *et al.* who considered 65 randomized controlled trials (n = 12,632) [100]. Comparing 27 different pharmacologic agents, Griebeler *et al.* reported that SNRIs showed greater pain reduction than anticonvulsants and TCAs. Although these studies may provide a convenient template for drawing relative comparisons between different drugs, the results of these studies should be interpreted with caution. It is difficult to assess and compensate for bias because of the well-documented dissonance in outcome measures, sample sizes, trial designs, and follow-up periods used in the clinical trials. This makes it challenging to draw meaningful conclusions when comparing effectiveness of different agents. Furthermore, in clinical practice, the choice of a pharmaceutical agent is also likely to be influenced by patient-specific factors, such as comorbid conditions and the potential for drug interaction and adverse effects.

7. Upcoming strategies for the treatment of painful neuropathy

Vincent and colleagues have proposed a number of cellular mechanisms as target sites for developing novel treatments of DPN [146]. The temperature-sensitive transient receptor potential channel (TRP) represents an attractive target in the pain pathway in DPN, especially as depression of TRPV1 response by capsaicin has been shown to be an effective treatment strategy [147].

Verheyen *et al.* have suggested that targeting the pathogenetic pathways implicated in DPN by utilizing vascular endothelial growth factor (VEGF) and VEGF-derived peptides may be an option for future therapies [148]. However, a recent clinical trial of VEGF in DPN was stopped due to lack of efficacy [149].

The angiotensin II type 2 receptor (AT_2R) axis has been found to play a substantial role in promoting nociceptive signaling by stimulating hyperexcitability and persistent ectopic firing of first-order sensory neurons. Rice *et al.* have demonstrated that EMA401, a novel small molecule AT_2R antagonist, provides significant pain relief in post-herpetic neuralgia in a novel, phase II randomized, placebo-controlled trial of 183 patients [150]. This drug remains in development as a therapeutic agent for neuropathic pain of different etiologies.

Intrathecal drug delivery systems have been used for intractable pain; they allow concentrated delivery of medication into the cerebrospinal fluid, and limit the risk of systemic adverse effects [151]. Morphine and ziconotide (a selective N-type voltage-gated calcium channel blocker) have been approved for intrathecal delivery, although their use has not been evaluated in DPN. However, implantation of intrathecal delivery systems must be undertaken with caution in patients with diabetes, given the risk of impaired wound healing and relative immunosuppression.

Erythropoietin (EPO), produced *in situ* by cells under stress, has been found to antagonize the production of pro-inflammatory molecules, and to promote tissue healing. While EPO has been found to ameliorate experimental DPN, its use is limited by serious adverse effects, in particular increased thrombotic risk [152]. ARA 290, a non-hematopoietic peptide designed from the structure

Table 5. Manifestations of diabetic autonomic neuropathy (DAN)

System	Symptoms	Treatment
Cardiovascular	Resting tachycardia, reduced exercise tolerance, orthostatic hypotension, asymptomatic myocardial ischemia	Symptomatic treatment including ACE-inhibitors, beta-blockers, clonidine, graded exercise programs, lifestyle advice, managing cardiovascular comorbidity
Gastrointestinal	Esophageal dysmotility, gastroparesis, diarrhea, bacterial overgrowth	Prokinetic agents, anti-diarrheals (e.g. loperamide), laxatives (e.g. lactulose), antiemetics
Genitourinary	Erectile dysfunction, cystopathy, Female sexual dysfunction	PDE5 inhibitors (e.g. sildenafil), psychological counseling, prostacyclin, lubricants, intermittent catheterization
Metabolic	Hypoglycemic awareness, autonomic failure	Optimal glycemic control
Sudomotor	Anhidrosis, heat intolerance, gustatory sweating, dry skin	Emollients, vasodilators, glycopyrrolate, botulinum toxin

Legend: ACE – angiotensin-converting enzyme, PDE5 – phosphodiesterase 5.

of erythropoietin, selectively interacts with the EPO receptors that mediate tissue protection. In a recent phase-2 trial to evaluate the activity of ARA 290 in type 2 diabetes and pDPN, ARA 290 (4 mg) or placebo were self-administered subcutaneously daily for 28 days, and the subjects were followed up for an additional month without further treatment. Neuropathic symptoms were found to improve significantly in the ARA 290 group. Also, a significant improvement in corneal nerve morphology was found using corneal confocal microscopy, an objective test for DPN, in patients randomized to the ARA 290 arm of the trial relative to placebo. ARA 290 remains in development for DPN and type 2 diabetes [152].

8. Diabetic autonomic neuropathy (DAN)

The underlying pathological mechanisms of DAN can include metabolic damage to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. The manifestations of DAN are manifold (**Table 5**), and a number of autonomic function tests have been used for its assessment. These are outside the remit of this review and are discussed elsewhere [9]. Recently, corneal confocal microscopy has been shown to have an extremely high sensitivity and specificity for diagnosing DAN [153]. In general, the treatment of DAN seeks to alleviate the specific constellation of signs and symptoms affecting the cardiovascular, urogenital, gastrointestinal, pupillomotor, thermoregulatory, and sudomotor systems. Currently, no treatment results in complete resolution of the underlying pathophysiological abnormalities and treatment of DAN is an unmet need in clinical practice.

8.1 Cardiac autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) is characterized by aberrant autonomic function of the cardiovascular system. It is the most prevalent and commonly studied form of DAN [18]. The prevalence of CAN ranges from 2.5% to 50% in different cohorts. CAN has been shown to negatively impact mortality due to its relationship with serious comorbidities (including silent myocardial ischemia, coronary artery disease, stroke, diabetic nephropathy, and increased perioperative morbidity). Thus, the management of CAN has important implications for prognosis in diabetes.

Data from the DCCT has demonstrated that intensive glycemic control can delay or prevent the onset of DAN in patients with type 1 diabetes, with a reduction in the prevalence of CAN by 53% in the intensive glycemic therapy group [154]. The benefits of early intensive glucose control persisted during EDIC, with a slower decline in cardiac autonomic function in patients in the intensive therapy group of the DCCT [42].

However, the situation in patients with type 2 diabetes is less clear. The VA Cooperative Study showed that strict glucose control and intensive insulin therapy did not affect the prevalence of CAN [48]. In contrast, the Steno-2 trial reported that a multifactorial cardiovascular risk intervention appeared to lower autonomic dysfunction by 63% [155]. However, glucose-lowering therapy appeared to have the least impact in preventing DAN compared with antihypertensive drugs, lipid-lowering agents, antiplatelet therapy, and vitamin-mineral supplementation.

Another drug class that has been studied in the context of DAN is ARI. In a recent meta-analysis, Hu *et al*. evaluated the efficacy and safety of ARIs for the treatment of CAN in diabetes, based on cardiac autonomic function tests [156]. From their

analysis of ten studies, the authors concluded that ARIs improved cardiac autonomic function, with an acceptable safety profile for all agents except tolrestat. Other treatment strategies that have been suggested for CAN are shown in **Table 5**.

8.2 Gastrointestinal autonomic neuropathy

Gastrointestinal secretions and motility are controlled by interactions between the autonomic and enteric nervous systems [157]. Therefore, DAN can affect the gastrointestinal system at any level, and patients report a wide range of symptoms. Also, the diagnosis is frequently based on exclusion. Although esophageal dysmotility has been reported in patients with diabetes, it remains an uncommon manifestation of DAN [18]. In some cases, especially if accompanied by gastroparesis or delayed gastric emptying, esophageal dysmotility in diabetes can predispose to or worsen gastroesophageal reflux disease. It has been suggested that this should be managed conservatively using protein pump inhibitors [158].

Gastroparesis appears to occur frequently in patients with diabetes, but is asymptomatic in most cases. One study reported that impaired gastric emptying was present in as many as 50% of patients with type 2 diabetes. In symptomatic cases, high-fiber diets are advocated, although these are often empirical recommendations and require further investigation. Prokinetic agents, including erythromycin, metoclopramide, and domperidone, remain the treatments of choice [159]. In severe cases, a jejunostomy may be indicated.

The management of other gastrointestinal complications of DAN, such as diarrhea or constipation that affect 20% and 25% of patients respectively, is largely symptomatic [18]. The management of diarrhea should rely on correcting deficiencies in fluid and electrolyte balance [160]. Antidiarrheal medications such as loperamide may help to control the number of stools. Clonidine has also been shown to play a role in improving diabetic diarrhea. Constipation is usually managed conservatively with lifestyle advice focused on diet and exercise, but some patients may require the use of laxatives which should be prescribed in line with local guidelines for constipation [18].

8.3 Genitourinary autonomic neuropathy

MuCulloch and colleagues have reported the prevalence of erectile dysfunction (ED) in males with diabetes to be around 35-75% [161]. It is closely related to endothelial dysfunction; thus it is important to screen the patient for cardiovascular disease [162]. ED is managed through a multifactorial strategy. Patients should be advised to abstain from smoking or alcohol and, where possible, medications known to cause ED should be discontinued to eliminate other risk factors. Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil and tadalafil form the mainstay of the treatment [162, 163]. These agents exert their effects by stimulating the accumulation of cGMP and increasing blood flow through the corpus cavernosum. They have been shown to have little effectiveness in diabetic subjects compared with subjects without diabetes. Therefore, diabetic patients often require higher doses of these oral agents. PDE5 inhibitors may be contraindicated in cardiovascular disease or for patients on nitrate-containing drugs. In these men, prostacyclin injected directly into the corpus callosum may be considered [164].

Bladder dysfunction has been commonly reported in patients with type 1 and type 2 diabetes, although its prevalence and manifestations vary greatly between cohorts [165]. A comprehensive history and autonomic function testing may aid the clinician in diagnosing bladder dysfunction due to diabetes, which may be clinically silent, initially. The treatment aims to prevent urinary retention and infection. In a meta-analysis of 56 randomized controlled trials, Chapple *et al.* showed that antimuscarinic agents are generally safe and effective in patients with diabetes and overactive bladder [166]. Behavioral modalities such as pelvic-floor exercises have also been found to be effective in patients with stress, urge, and mixed incontinence [165]. Treatment of detrusor areflexia varies according to severity, and can involve exercises to encourage micturition, alpha-blocking agents such as doxazosin to encourage external sphincter relaxation, intermittent catheterization, or surgical interventions such as sacral neuromodulation or vesical neck resection.

9. Conclusions

Diabetic neuropathy is a highly prevalent and disabling condition associated with significant healthcare costs. Although diabetic neuropathies differ in clinical course, distribution, fiber involvement, and pathophysiology, two major categories include painful neuropathy and autonomic neuropathy. At present, there are no pathogenetic treatments for DPN apart from improved glycemic control.

Painful DPN is common, difficult to manage, and therefore distressing. A plethora of agents has been the subject of formal clinical trials, but achieving adequate pain relief is difficult. At present, there are only two FDA-approved medications for painful diabetic neuropathy, but a number of other agents have shown some efficacy in clinical trials. Therefore, selection of the appropriate therapy depends on the medical and psychiatric co-morbidities, potential adverse effects, and drug interactions in an individual patient.

Autonomic neuropathy has diverse clinical manifestations depending on the autonomic pathways affected by diabetes. These autonomic manifestations are responsible for the most troublesome features of DPN, and result in significant mortality and morbidity. The treatment of autonomic neuropathy depends largely on the clinical features of the disease, and is affected by the inability to resolve successfully the underlying pathophysiological deficit. Given the limitations of current therapies for DPN, further studies are necessary for identifying the best combinations of treatments for diabetic neuropathy.

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