

# Recent advances in the management of diabetic distal symmetrical polyneuropathy

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## ABSTRACT

There is now little doubt that poor blood glucose control is an important risk factor for the development of diabetic peripheral neuropathy (DPN). Furthermore, traditional cardiovascular risk factors for macrovascular disease appear to be associated with an increased risk of DPN. The recently established International Expert Group on Diabetic Neuropathy has recommended new criteria for the diagnosis of DPN in the context of clinical and research settings. Studies in experimental diabetes examining the pathogenesis of DPN have identified a number of metabolic abnormalities including polyol pathway hyperactivity, increased advanced glycation end-point formation, alterations in the protein kinase C beta pathway through diacylglycerol and oxidative stress. There is now strong evidence implicating nerve ischemia as the cause of DPN. Studies in human and animal models have shown reduced nerve perfusion and endoneurial hypoxia. These endoneurial microvascular changes strongly correlate with clinical severity and the degree of nerve-fiber pathology. Unfortunately, many compounds that have been effective in animal models of neuropathy have not been successful in human diabetic neuropathy. The only compounds found to be efficacious in human diabetic neuropathy, and are in clinical use, are the anti-oxidant,  $\alpha$ -lipoic acid and the aldose reductase inhibitor, epalrestat. Overall, the evidence emphasizes the importance of vascular dysfunction, driven by metabolic change, in the etiology of DPN, and highlights potential therapeutic approaches. Epidemiological data on diabetic painful neuropathic pain (DPNP) are limited. In one population-based study, the prevalence of DPNP, as assessed by a structured questionnaire and examination, was estimated at 16%. It was notable that, of these patients, 12.5% had never reported symptoms to their doctor and 39% had never received treatment for their pain. Thus, despite being common, DPNP continues to be underdiagnosed and undertreated. Pharmacological treatment of DPNP include tricyclic compounds, serotonin noradrenalin reuptake inhibitors, the anti-oxidant  $\alpha$ -lipoic acid, anticonvulsants, opiates, membrane stabilizers, topical capsaicin and so on. Management of the patient with DPNP must be tailored to individual requirements and will depend on the presence of other comorbidities. (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2010.00083.x)

**KEY WORDS:** Diabetic peripheral neuropathy, Diabetic neuropathy, Painful diabetic neuropathy

## INTRODUCTION

Diabetic polyneuropathy is very common, affecting approximately 50% of both type 1 and type 2 diabetic patients<sup>1</sup>. It has major detrimental effects on sufferers, as it confers much morbidity and is associated with increased mortality<sup>2</sup>. Diabetic polyneuropathy is not a single entity, but encompasses several neuropathic syndromes (Figure 1). Autonomic neuropathy can affect virtually every system of the body, and once it is well established it is very difficult to treat.

Symmetrical polyneuropathies can manifest as typical and atypical diabetic peripheral neuropathies (DPN). The Toronto Diabetic Neuropathy Expert Group recently provided a case definition for DPN<sup>3</sup>: "Typical DPN, also known as chronic distal symmetrical polyneuropathy (DSPN) is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to

metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. An abnormality of nerve conduction (NC) tests, which is frequently subclinical, appears to be the first objective quantitative indication of the condition. The occurrence of diabetic retinopathy and nephropathy in a given patient strengthen the case that the polyneuropathy is attributable to diabetes."

DSPN, which is the focus of the present article, is by far the commonest neuropathic syndrome associated with diabetes, and results in both insensitivity of the feet and/or diabetic peripheral neuropathic pain (DPNP), which can be disabling. DSPN is often found in association with autonomic neuropathy. The other manifestations of diabetic polyneuropathy are relatively rare (Figure 1).

## DIAGNOSIS AND CLINICAL IMPACT OF DSPN

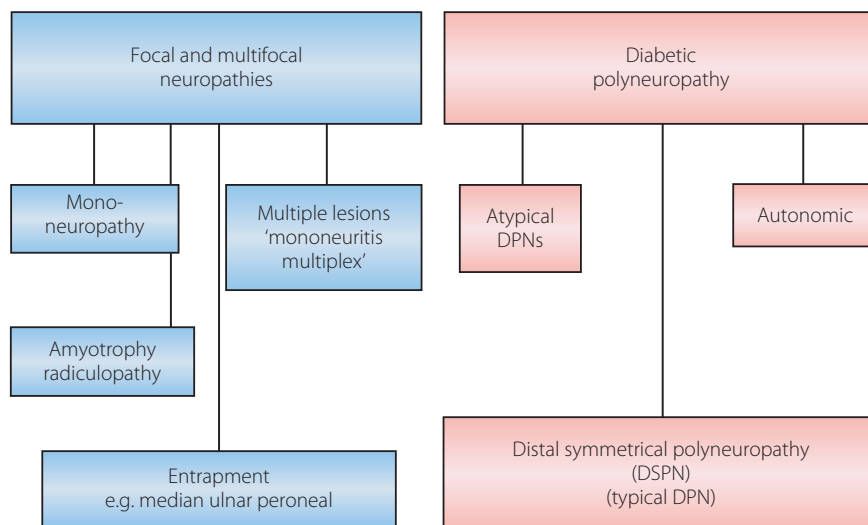
The onset of DSPN is heralded by sensory symptoms that start in the toes and then progress proximally to involve the feet and legs in a stocking distribution. When the disease is well

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**Figure 1** | Classification of diabetic polyneuropathy. Adapted from Reference 3.

established in the lower limbs in more severe cases, there is upper limb involvement, with a similar progression proximally starting in the fingers. As the disease advances, clear motor manifestations, such as wasting of the small muscles of the hands and limb weakness, become apparent. Crucially, sometimes there is sensory loss, which the patient might not be aware of and the first presentation might be a foot ulcer. Approximately one-third of neuropathic subjects experience a progressive build-up of unpleasant sensory symptoms in the lower limbs including tingling (paresthesia), pain (burning, shooting, lancinating or aching in character), allodynia (contact pain) or unusual sensations (such as a feeling of swelling of the feet or coldness of the legs when clearly the lower limbs look and feel fine, odd sensations on walking likened to “walking on pebbles” or “walking on hot sand” etc.). DPNP is characteristically more severe at night and often disturbs sleep<sup>4</sup>. It also has a major impact on functionality (e.g. ability to maintain work), mood and quality of life<sup>4</sup>. Depressive symptoms as a result of the unremitting pain are common<sup>5</sup>.

The natural history of DPN remains poorly understood, because of lack of well-designed prospective studies. One study reported that neuropathic symptoms remain or get worse over a 5-year period in patients with DSPN<sup>6</sup>. A major drawback of that study was that it involved highly selected patients from a hospital base. Another study reported improvements in painful symptoms with worsening of quantitative measures of nerve function over 3.5 years<sup>7</sup>. At follow up, 3.5 years later, one-third of the 50 patients had died or were lost to follow up. Clearly, this is also a major drawback. There was symptomatic improvement in DPNP in the majority of the remaining patients<sup>7</sup>. It should be noted that many of the subjects were being treated with pain relieving drugs that might also have influenced the findings. Despite symptomatic improvement, small-fiber function deteriorated significantly<sup>7</sup>. There is thus a need for

large, population-based, prospective studies of patients with DPNP aimed at examining the natural history and potentially modifiable risk factors.

### ESTIMATING SEVERITY OF DSPN

For a given patient, it is not enough to make the diagnosis of the presence of neuropathy. Similar to other complications of diabetes, such as retinopathy and nephropathy, it is desirable to assess severity of DSPN. The Toronto Expert Group suggested a reliable objective and quantitative measure; that is, NC abnormality as the minimal criteria for the diagnosis of DSPN<sup>3</sup>. When NC values have not been assessed, the Expert Group recommended that it is not possible to provide a “confirmed” diagnosis of DSPN – only a “possible” or “probable” diagnosis<sup>3</sup>. There are several instruments that evaluate combinations of neuropathy symptoms, signs and neurophysiological test abnormalities giving scores for severity of DSPN<sup>8–11</sup>. For clinical trials where accurate assessment of DSPN is necessary, the following approach to estimating severity suggested by Dyck *et al.* can be used (Table 1)<sup>3,12</sup>. It is important to exclude other causes of sensorimotor polyneuropathy. For epidemiological surveys or controlled clinical trials of DSPN, the Toronto Expert Group advocated the use of a NC test as an early and reliable indicator of the occurrence of this neuropathy<sup>3</sup>. The group also emphasized that to be reliable, the test must be carried out rigorously using appropriate reference values corrected for applicable variables<sup>3</sup>. Recent studies emphasize the importance of the proficiency of the clinical neurological assessment<sup>3,11,13</sup>.

### MANAGEMENT APPROACHES FOR DSPN

Current strategies for the treatment of DSPN are based on: (i) improving glycolic control and reducing other risk factors for the development of polyneuropathy; (ii) symptomatic treatment of DPNP; (iii) treatment based on pathogenetic mechanisms;

**Table 1** | Staged severity of distal symmetrical polyneuropathy

Grade 0	No abnormality of NC; e.g., $\Sigma$ 5 NC nds < 95th percentile or another suitable NC criterion
Grade 1a	Abnormality of NC; e.g., $\Sigma$ 5 NC nds $\geq$ 95th percentile, without symptoms or signs
Grade 1b	NC abnormality of stage 1a plus neurological signs typical of DSPN but without neuropathy symptoms
Grade 2a	NC abnormality of stage 1a with or without signs (but if present <2b) and with typical neuropathic symptoms
Grade 2b	NC abnormality of stage 1a, a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without neuropathy symptoms

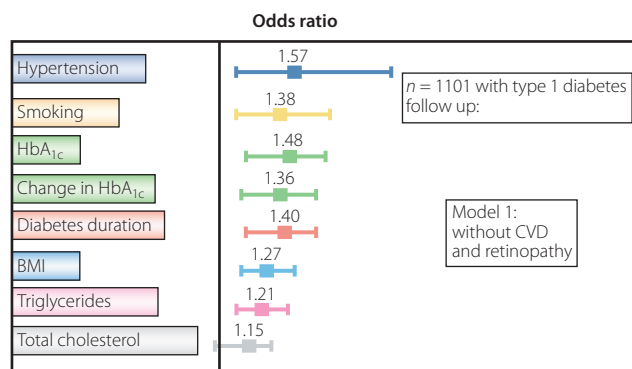
Adapted from Reference 3. DSPN, distal symmetrical polyneuropathy; NC, nerve conduction; nds, normal deviates.

and (iv) treatment of foot, autonomic and other complications. This article will review recent advances in the management of DSPN, focusing on the first three strategies.

#### Improving Glycemic Control and Reducing Other Risk Factors for DSPN

In the Rochester Diabetic Neuropathy Study cohort, where clinical parameters and NC tests were used, the prevalence of DSPN was 54% in patients with type 1 diabetes mellitus and 45% in patients with type 2 diabetes mellitus<sup>1</sup>. Where NC tests were not used, clinic- and population-based studies showed surprisingly similar prevalence rates for DSPN, affecting approximately 30% of all diabetic people<sup>14</sup>. The EURODIAB Prospective Complications Study, which involved the examination of 3250 type 1 patients from 16 European countries, found a prevalence rate of 28% for DSPN at baseline<sup>15</sup>, very strongly related to poor glycemic control. The follow-up study also showed that over a 7-year period, approximately one-quarter of type 1 diabetic patients developed DSPN; with age, duration of diabetes and poor glycemic control being major factors<sup>16</sup>. The development of neuropathy was also associated with potentially modifiable cardiovascular risk factors, such as hypertension, hyperlipidemia, obesity and cigarette smoking (Figure 2)<sup>16</sup>. Recently, other studies have also implicated cardiovascular risk factors, such as obesity<sup>17</sup> and triglycerides<sup>18</sup> in the pathogenesis of DSPN. In a cohort of participants with mild to moderate diabetic neuropathy, Wiggins *et al.*<sup>19</sup> also found that elevated triglycerides correlated with myelinated fiber loss independent of disease duration, age, diabetes control or other variables. These data support the evolving concept that hyperlipidemia might be instrumental in the progression of diabetic neuropathy.

Based on recent epidemiological studies, correlates of DSPN include increasing age, increasing duration of diabetes, poor glycemic control, retinopathy, albuminuria and vascular risk factors<sup>16</sup>. In type 2 diabetes, waist circumference, peripheral arterial disease and increasing age were found to be significant



**Figure 2** | Risk factors for incident neuropathy. The EURODIAB Prospective Complications Study showing odds ratios for the various risk factors for distal symmetrical polyneuropathy in a cohort of 1101 type 1 diabetes mellitus patients followed for  $7.3 \pm 0.6$  years. Adapted from Reference 16. BMI, body mass index; CVD, cardiovascular disease.

risk factors for the development of DSPN<sup>17</sup>. DSPN is also a major risk factor (predictor) for mortality, even more so than microalbuminuria and HbA<sub>1c</sub><sup>2</sup>. Elevated vibration threshold has also been found to be a risk factor for mortality in diabetic patients<sup>20</sup>.

There is now little doubt that good blood sugar control prevents/delays the onset of diabetic neuropathy in type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) conclusively showed that intensive diabetes control could both prevent and retard the development of DSPN and autonomic neuropathy<sup>21</sup>. More recently, the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that the benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years beyond the end of the DCCT, despite similar HbA<sub>1c</sub> levels<sup>22</sup>. However, in type 2 diabetes patients, the results are not clear-cut, with only modest slowing down of the progression of DSPN<sup>23</sup>. In the Steno 2 study, intensive multifactorial intervention significantly reduced the progression of autonomic neuropathy, but not DSPN, although the method used to define DSPN (vibration perception threshold) was inappropriate<sup>24</sup>. Despite these inconsistencies, current good clinical practice remains to intensively manage hyperglycemia and other cardiovascular risk factors as part of the overall management of patients with DSPN.

#### Advances in the Symptomatic Treatment of DPNP

Epidemiological data on DPNP are limited. In one population-based study the prevalence of DPNP, as assessed by a structured questionnaire and examination, was estimated at 16%<sup>25</sup>. It was notable that, of these patients, 12.5% had never reported symptoms to their doctor and 39% had never received treatment for their pain. In a more recent population-based study, the overall prevalence of DPNP was staggeringly high, affecting approximately one in four diabetic subjects (26%)<sup>26</sup>. Thus, despite being common, DPNP continues to be underdiagnosed and undertreated.

**Table 2** | Pharmacological treatment of diabetic peripheral neuropathic pain showing some of the commonly prescribed treatments

Tight glucose control (HbA <sub>1c</sub> 6–7%)
Lifestyle modification (diet, exercise)
Management of cardiovascular risk factors
Tricyclic antidepressants
Amitriptyline 10–75 mg/day
Imipramine 10–75 mg/day
Serotonin noradrenalin reuptake inhibitors
Duloxetine 60–120 mg/day (indicated for DPNP by FDA)
Venlafaxine 150–225 mg/day
Anticonvulsants
Gabapentin 300–3600 mg/day
Pregabalin 300–600 mg/day (indicated for DPNP by FDA)
Carbamazepine 200–800 mg/day
Opiates
Tramadol 200–400 mg/day
Oxycodone 20–80 mg/day
Morphine sulphate SR 20–80 mg/day
Capsaicin cream
(0.075%) Applied sparingly 3–4 times per day
Combination treatment
Morphine sulphate SR and gabapentin
Oxycodone SR and gabapentin

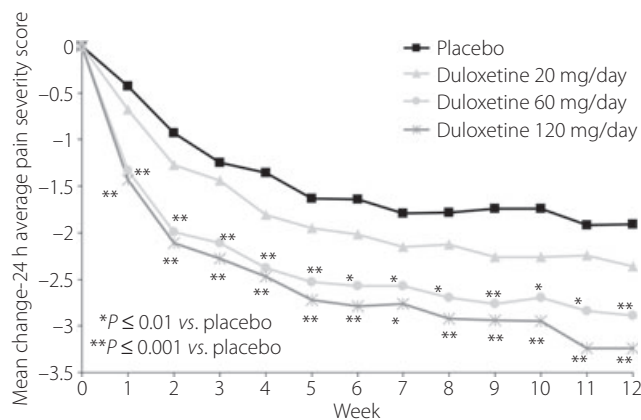
DPNP, diabetic peripheral neuropathic pain; FDA, US Food and Drug Administration; SR, sustained release.

A range of simple numeric rating scales can be used to assess the frequency and severity of DPNP<sup>27</sup>. Other, non-diabetic causes of neuropathic pain must be excluded. Severity of pain can be assessed by the visual analogue scale (VAS) or the numerical rating scale (NRS), such as the 11-point Likert scale (0 no pain, 10 worst possible pain), which has been most widely used in recent DPNP clinical trials. Several validated scales and questionnaires including the Brief Pain Inventory<sup>28</sup>, the Neuropathic Pain Symptoms Inventory<sup>29</sup>, the Neuropathic Pain Questionnaire<sup>30</sup>, the McGill Pain Questionnaire<sup>27</sup> and so on can also be used. Quality of life (QOL) improvement should also be assessed, preferably using a validated neuropathy-specific scale, such as NeuroQol<sup>31</sup> or the Norfolk Quality of Life Scale<sup>32</sup>. Outcomes must be measured using a patient-reported improvement in scales of pain and QOL, as measured on validated instruments.

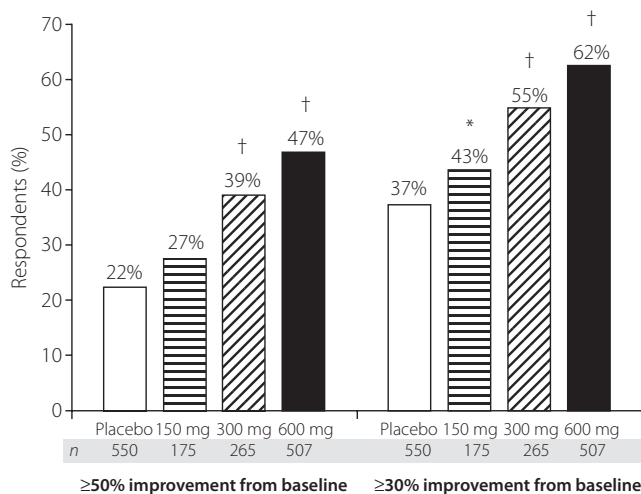
Managing DPNP in clinical practice can be a clinically challenging problem. However, over the past decade, new and effective compounds have undergone clinical trials and are already being used in clinical practice<sup>33</sup>. Table 2 shows the main pharmacological agents used to treat DPNP.

### Tricyclic Antidepressants

Several randomized controlled trials have shown the efficacy of tricyclic antidepressants (TCA) in DPNP<sup>34–36</sup>. However, TCA also have many side-effects including anticholinergic effects, such as dry mouth, sweating, sedation and dizziness. Treatment is ideally started with a small dose (10 mg) of either amitripty-



**Figure 3** | The efficacy of duloxetine in improving 24-h average pain scores. Reproduced from Reference 38 with permission of the International Association for the Study of Pain (IASP).

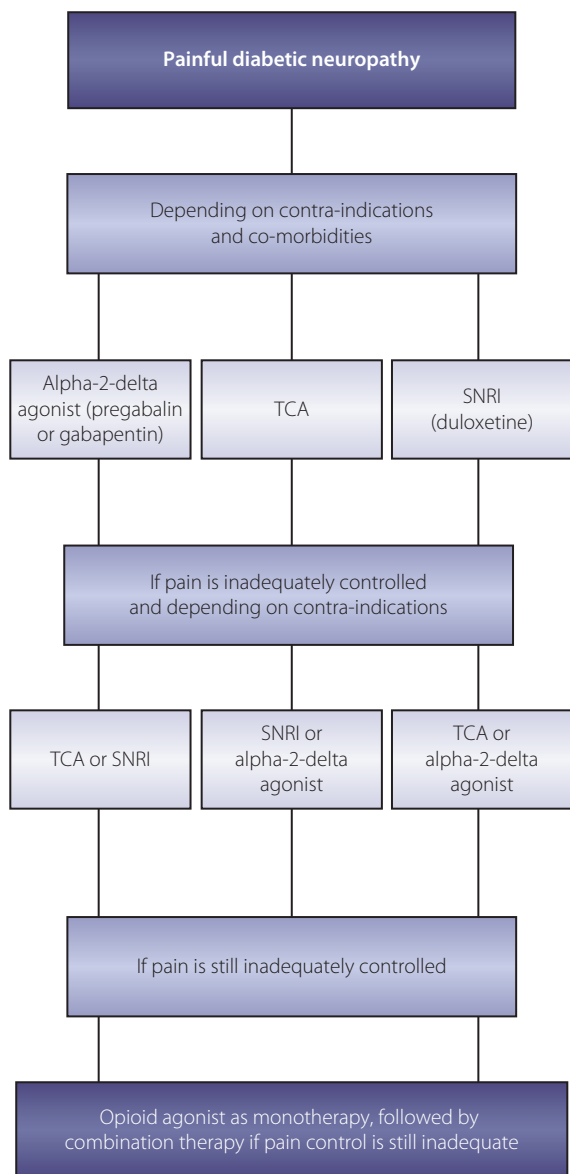


**Figure 4** | Proportion of patients meeting  $\geq 50\%$  and  $\geq 30\%$  improvement using pregabalin in seven clinical trials. Copyright 2008 American Diabetes Association from *Diabetes Care* 2008; 31: 1448–1454 (Reference 44). Reprinted with permission from the American Diabetes Association.

line or imipramine at night, as there is nocturnal exacerbation of painful symptoms and these antidepressants will assist with sleep. The dose can then be gradually titrated depending on adverse events and efficacy. Care should be taken not to exacerbate symptoms of postural hypotension, such as dizziness, in those with autonomic neuropathy. In addition, recent data from a retrospective study including 58,956 person years follow up on TCA therapy show an increased risk of sudden cardiac death associated with TCA doses in excess of 100 mg/day<sup>37</sup>. This is a major argument against the use of TCA in diabetic patients with cardiovascular disease.

### Serotonin Noradrenalin Re-uptake Inhibitors

Serotonin noradrenalin re-uptake inhibitors (SNRI), such as duloxetine, relieve pain by increasing synaptic availability of



**Figure 5** | Treatment algorithm for diabetic peripheral neuropathic pain. Reprinted from Reference 33. SNRI, serotonin noradrenalin re-uptake inhibitor; TCA, tricyclic antidepressant.

5-hydroxytryptamine (5-HT) and noradrenalin in the descending pathways that are inhibitory to pain impulses. The efficacy of duloxetine in DPNP has been investigated in three identical trials and pooled data from these shows that the 60 mg/day and 120 mg/day doses are effective in relieving painful symptoms, starting within a week<sup>38–40</sup>. Efficacy was maintained throughout the treatment period of 12 weeks, and 45–55% of patients achieved  $\geq 50\%$  pain reduction (Figure 3)<sup>41</sup>.

The number needed to treat (NNT) to achieve at least 50% pain reduction, which is generally accepted as being clinically meaningful, was 4.9 for 120 mg/day and 5.2 for 60 mg/day<sup>41</sup>. A particular advantage of duloxetine was that there was no weight

gain during prolonged treatment of up to a year. The most frequent adverse effects of duloxetine include nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite. These adverse events are usually mild to moderate and transient. To reduce the chance of adverse events, our clinical experience suggests a starting dose of 30 mg/day for approximately a week. It might be helpful to advise the patient to take the medication with or after food.

Venlafaxine at a dose of 150–225 mg/day is also effective in relieving DPNP, although clinically significant electrocardiogram changes have been reported as adverse events<sup>42</sup>. This is a major concern, as many diabetic patients have coexistent cardiac disease.

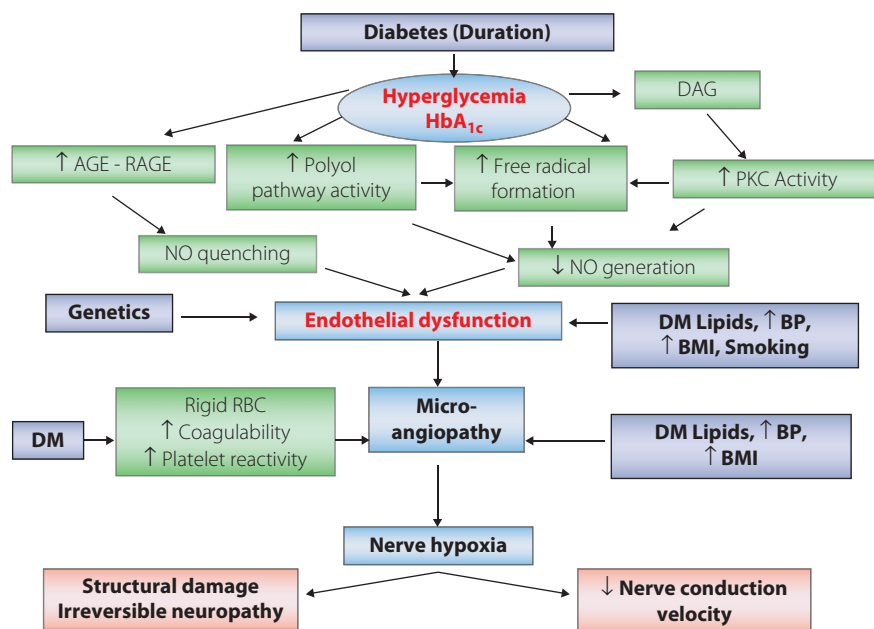
#### Anticonvulsants

Gabapentin and pregabalin bind to the  $\alpha$ -2- $\delta$  subunit of the calcium channel, reducing calcium flux and thus resulting in reduced neurotransmitter release in the hyperexcited neurone. Gabapentin is well established as a treatment for DPNP, although the doses in clinical practice are much lower than the dose used in the main clinical trial of up to 3600 mg per day<sup>43</sup>.

Evidence for the efficacy of pregabalin in DPNP is even better, as there have been several clinical trials in DPNP that showed its efficacy compared with a placebo<sup>44</sup>. One study examined a combined analysis of six controlled trials of 5–12 weeks duration, and found 39% and 46% of patients with DPNP treated with pregabalin 300 and 600 mg/day, respectively, achieved at least 50% pain relief<sup>45</sup>. Data from seven clinical trials involving pregabalin showed a NNT of 4.04 for the 600 mg/day and 5.99 for the 300 mg/day (Figure 4)<sup>44</sup>. Only the 600 mg/day dosage showed efficacy when given b.i.d.<sup>44</sup>. The median time to onset of a sustained ( $\geq 30\%$  at end-point) 1-point improvement was 4 days in patients treated with pregabalin at 600 mg/day and 5 days in patients treated with pregabalin at 300 mg/day<sup>44</sup>. Pregabalin is licensed for the management of DPNP. The most frequent side-effects are dizziness, somnolence, peripheral oedema, headache and weight gain.

#### Opioid Agonists

The weak opiate derivative, tramadol, has been found to be effective in relieving neuropathic pain<sup>46</sup>. Another opioid, oxycodone slow release, has also been shown to be effective in the management of neuropathic pain<sup>47</sup>. Traditionally, clinicians have been rather conservative in the use of opioid agonists, prescribing them as an add-on to other therapy, although clinical evidence to support this approach is somewhat limited. In one cross-over study, low dose combination therapy with gabapentin and morphine was significantly more effective than either monotherapy at a higher dose<sup>48</sup>. However, combination treatment was associated with a higher frequency of adverse effects than monotherapy<sup>48</sup>. Prolonged-release oxycodone was also found to enhance the effects of existing gabapentin therapy in patients with DPNP<sup>49</sup>. More recently, the combination of



**Figure 6** | Current thinking with regard to the pathogenesis of diabetic peripheral neuropathies. Deficits in neurotrophic factors and autoimmunity might also play a part. AGE, advanced glycation end-point; AGE-RAGE, advanced glycation end-point receptor for AGE; BMI, body mass index; BP, blood pressure; DAG, diacylglycerol; DM, diabetes mellitus; NO, nitric oxide; PKC, protein kinase C; RBC, red blood cell.

nortriptyline and gabapentin was found to be superior to either treatment on its own<sup>50</sup>.

### Topical Capsaicin

Topical capsaicin works by depleting substance “P” from nerve terminals, and there might be worsening of neuropathic symptoms for the first 2–4 weeks of application. Topical capsaicin (0.075%) applied sparingly 3–4 times per day to the affected area has also been found to relieve neuropathic pain<sup>51</sup>.

### Lacosamide

Lacosamide is a sodium channel modulator and a promising treatment for DPNP. In a phase II study, lacosamide was found to be beneficial in relieving DPNP<sup>52</sup>. Phase III, placebo controlled trials are now required to evaluate its efficacy, both on its own or as a combination treatment with another effective agent.

### $\alpha$ -Lipoic Acid

Infusion of the anti-oxidant  $\alpha$ -lipoic acid at a dose of 600 mg i.v. per day over a 3-week period has been found to be useful in reducing neuropathic pain<sup>53</sup>. A meta-analysis including 1258 patients from four prospective trials showed that treatment with  $\alpha$ -lipoic acid (600 mg/day) for 3 weeks was associated with a significant and clinically meaningful improvement in positive neuropathic symptoms (pain, burning, paresthesia and numbness), as well as neuropathic deficits<sup>53</sup>. Oral treatment with  $\alpha$ -lipoic acid for 5 weeks improved neuropathic symptoms and deficits in patients with DPN<sup>54</sup>. An oral dose

of 600 mg once daily appears to provide the optimum risk-to-benefit ratio<sup>54</sup>, but a confirmatory larger trial might be required.

### Treatment Algorithm

A recent consensus meeting evaluated the trial evidence for the various pharmacological treatments for DPNP and suggested a treatment algorithm (Figure 5)<sup>33</sup>. The panel compared the relative efficacy and safety of treatments for DPNP and recommended that a TCA, SNRI or an  $\alpha$ -2- $\delta$  agonist should be considered for first-line treatments (Figure 5). On the basis of trial data, duloxetine would be the preferred SNRI and pregabalin would be the preferred  $\alpha$ -2- $\delta$  agonist. Initial selection of treatment will be influenced by the assessment of contraindications, consideration of comorbidities and cost; for example, in diabetic patients with a history of heart disease, elderly patients on other concomitant medications such as diuretics and antihypertensives, patients with comorbid orthostatic hypotension and so on, TCA have relative contraindications. In patients with liver disease, duloxetine should not be prescribed, and in those with edema, pregabalin or gabapentin should be avoided. If pain is inadequately controlled, depending on contraindications, a different first-line agent might be considered as shown in Figure 5.

A combination of first-line therapies might be considered if there is pain, despite a change in first-line monotherapy (Figure 5). If pain is inadequately controlled, opioids such as tramadol and oxycodone might be added in a combination treatment.

Abnormality	Compound	Aim of treatment	Status of randomized clinical trials
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbitinil		Withdrawn (adverse events)
	Tolrestat		Withdrawn (adverse events)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (adverse events)
	Lidorestat		Withdrawn (adverse events)
	Fidarestat		Effective in phase II trials
	Ranirestat		Effective in phase II trial
	Epalrestat		Marketed in Japan
<i>myo</i> -Inositol ↑	<i>myo</i> -Inositol	Nerve <i>myo</i> -inositol ↑	Equivocal
γ-Linolenic acid synthesis ↓	γ-Linolenic acid	Essential fatty acids metabolism ↑	Withdrawn (effective: deficits)
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in randomized clinical trials (studies ongoing)
	Vitamin E	Oxygen free radicals ↓	Effective in one randomized clinical trial
Nerve hypoxia ↑	Vasodilators	Nerve blood flow ↑	
	ACE inhibitors		Effective in phase II trial
	Prostaglandin analogs		Effective in phase II trial
	PhVEGF <sub>165</sub> gene transfer	Angiogenesis ↑	Phase III trial ongoing
Protein kinase C ↑	Protein kinase C β inhibitor (ruboxistaurin)	Nerve blood flow ↑	Phase III trial ongoing
C-peptide ↓	C-peptide	Nerve blood flow ↑	Effective in phase II trials
Neurotrophism ↓	Nerve growth factor	Nerve regeneration, growth ↑	Ineffective
	BDNF	Nerve regeneration, growth ↑	Ineffective
Long-chain fatty acid metabolism ↓	Acetyl-L-carnitine	Long-chain fatty acid accumulation ↓	Ineffective
Nonenzymatic glycation ↑	Aminoguanidine	Advanced glycation end product accumulation ↓	Withdrawn

**Figure 7** | Compounds that have undergone trials for the treatment of diabetic peripheral neuropathies (adapted from Reference 64). Copyright 2008 American Diabetes Association from *Diabetes Care* 2008; 31: S255–S261. Reprinted with permission from the American Diabetes Association. ACE, angiotensin-converting enzyme; BDNF, brain-derived neurotrophic factor.

### Non-pharmacological Treatments

Lack of response and unwanted side-effects of conventional drug treatments force many sufferers to try alternative therapies, such as acupuncture<sup>55</sup>, near-infrared phototherapy<sup>56</sup>, low intensity laser therapy<sup>57</sup> and transcutaneous electrical stimulation<sup>58</sup>, frequency modulated electromagnetic neural stimulation (FREMS) therapy<sup>59</sup>, high frequency external muscle stimulation<sup>60</sup> and, as a last resort, implantation of an electrical spinal cord stimulator<sup>61</sup>. Unfortunately, most of the studies involving non-pharmacological agents are uncontrolled

and there is a need for randomized controlled trials in this respect.

### TREATMENT BASED ON PATHOGENETIC MECHANISMS

Studies in experimental diabetes examining the pathogenesis of DPN have identified a number of abnormalities, including increased advanced glycation end-point formation, polyol pathway hyperactivity, oxidative stress, alteration in the protein kinase C (PKC)-β pathway through diacylglycerol (Figure 6)<sup>62,63</sup>.

There is now a consensus that the etiology of DPN is probably multifactorial. Several compounds including several aldose reductase inhibitors (ARI), the anti-oxidant  $\alpha$ -lipoic acid, the PKC- $\beta$  inhibitor ruboxistaurine and two ACE inhibitors targeting these abnormal pathways have undergone clinical trials. The full list of clinical trials is very long indeed (Figure 7)<sup>64</sup>. Unfortunately, most of these trials have failed to show unequivocal slowing of the progressive nerve damage in DPN. Only the ARI, epalrestat<sup>65,66</sup> and the anti-oxidant  $\alpha$ -lipoic acid<sup>153,54</sup> are in clinical use.

## CONCLUSIONS

Despite several well-designed recent trials looking at slowing the inexorable, progressive decline in nerve function associated with DPN, no novel treatment has emerged. This might be a result of the fact that DPN has a multifactorial etiology and treatment that blocks a single pathway is unlikely to succeed.

Current recommendation for first-line therapies for DPNP is a TCA, duloxetine or anticonvulsants (such as pregabalin or gabapentin), taking into account patient comorbidities and cost. Optimization of glycemic control and aggressive management of cardiovascular risk factors are also clearly important. Combination therapy might be useful, but further research is required. Studies are required on direct head-to-head comparative trials and long-term efficacy of drugs, as most trials have lasted <4 months. Key target areas generating or modulating pain in DPNP including peripheral small fibers with modulation at the level of the spinal cord<sup>67</sup>, the thalamus<sup>68,69</sup> and the other pain matrix areas in the brain require further studies in order to develop more effective treatments. The association of DPNP with autonomic neuropathy also merits further investigation<sup>70</sup>. There is also a need for further controlled trials to investigate non-pharmacological treatments. Despite many trials looking for effective pathogenetic treatments for DSPN, only two compounds,  $\alpha$ -lipoic acid and epalrestat, are in clinic use. Thus, further research is required to find more effective, novel compounds that are able to slow and perhaps reverse this progressive disease.

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