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REVIEW ARTICLE

Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management

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Summary

Painful diabetic peripheral neuropathy (DPN) is common, is associated with significant reduction in quality of life and poses major treatment challenges to the practising physician. Although poor glucose control and cardiovascular risk factors have been proven to contribute to the aetiology of DPN, risk factors specific for painful DPN remain unknown. A number of instruments have been tested to assess the character, intensity and impact of painful DPN on quality of life, activities of daily living and mood. Management of the patient with DPN must be tailored to individual requirements, taking into consideration the co-morbidities and other factors. Pharmacological agents with proven efficacy for painful DPN include tricyclic anti-depressants, the selective serotonin and noradrenaline re-uptake inhibitors, anti-convulsants, opiates, membrane stabilizers, the anti-oxidant alpha-lipoic acid and topical agents including capsaicin. Current first-line therapies for painful DPN include tricyclic anti-depressants, the serotonin and noradrenaline re-uptake inhibitor duloxetine and the anti-convulsants pregabalin and gabapentin. When prescribing any of these agents, other co-morbidities and costs must be taken into account. Second-line approaches include the use of opiates such as synthetic opioid tramadol, morphine and oxycodone-controlled release. There is a limited literature with regard to combination treatment. In extreme cases of painful DPN unresponsive to pharmacotherapy, occasional use of electrical spinal cord stimulation might be indicated. There are a number of unmet needs in the therapeutic management of painful DPN. These include the need for randomized controlled trials with active comparators and data on the long-term efficacy of agents used, as most trials have lasted for less than 6 months. Finally, there is a need for appropriately designed studies to investigate non-pharmacological approaches. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords diabetic neuropathy; painful diabetic peripheral neuropathy; treatment

Abbreviations DPN – diabetic peripheral neuropathy; HADS – Hospital Anxiety and Depression Scale; QoL – quality of life; SNRIs – serotonin and noradrenaline re-uptake inhibitors; TCA – tricyclic anti-depressant

Introduction

This review by a group of Toronto Expert Panel on Diabetic Neuropathy examined the recent literature on painful diabetic peripheral neuropathy (DPN) and made consensus recommendations based on these. Although a summarized version of this review has recently been published [1], this

review examines the diagnosis and pharmacological management of painful DPN in more detail.

DPN is present in up to 50% of all diabetic patients with long duration of disease and is a major cause of morbidity that is also associated with increased mortality [2–4]. Of all the neuropathies in diabetes, chronic DPN is the commonest [2,5]. Up to 50% of all patients with DPN may experience painful symptoms, although many of these will not have pain of sufficient severity to warrant treatment. Of all the distressing symptoms of DPN, pain is the most prominent and most frequent reason for seeking medical attention. A definition of neuropathic pain in diabetes adapted from the original International Association for the Study of Pain's definition [6] is 'pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes'. Patients experiencing neuropathic pain in diabetes often find their symptoms difficult to describe as they are unfamiliar, but common descriptors include burning pain, 'electrical shock' type shooting pain down the legs, lancinating (often likened as 'stabbing' or 'knife-like' pains), uncomfortable tingling (paresthesia or novocaine-like) and many experience contact pain brought on by touching daytime socks or stockings or bedclothes at night (allodynia). Discomfort on walking may also be described as 'walking barefoot on marbles' or 'walking barefoot on hot sand'. Subjective sensations of altered temperature perceptions, such as the feet are very warm or very cold, are also common and non-specific aching feelings in the feet and cramp-like sensations in the legs are other frequently described symptoms [2,5]. Occasionally, these symptoms may progress from the feet up the limbs and involve the whole of the lower limbs and later there may be involvement of the upper limb, particularly the hand. It is important for the reader to appreciate that a host of other conditions can masquerade as neuropathy, including entrapments, fasciitis and claudication.

Neuropathic pain in diabetes is characteristically more severe at night often resulting in sleep disturbance [7], with severely affected patients complaining of being constantly tired because of severe sleep deprivation [8]. Together with painful symptoms during the day, this often leads to a reduction in individuals being able to perform daily activities. Relief of pain improves sleep and the degree of sleep loss predicts the response to analgesics. Pathway analysis has shown that there are both direct and indirect actions of agents that relieve pain on sleep disturbances [9]. The burden of painful DPN was reported to be considerable in one study which resulted in a persistent discomfort despite polypharmacy and high resource use and led to limitations in daily activities and poor satisfaction with treatments that were often deemed to be inappropriate. Chronic persistently painful DPN can be extremely distressing and might be associated with profound depression [10,11] together with anxiety [12] and sleep loss. While painful DPN contributed to depression, unsteadiness and its psychosocial consequences dominated this relationship over time [11]. Furthermore, a decline in neuropathy-related physical and psychosocial functioning over time contributed to further increments in depressive symptoms [11]. In one study conducted in a tertiary referral multi-disciplinary clinic for painful DPN comprising of patients with moderate or severe symptoms, over two thirds were found to have anxiety and/or depression [13] and >95% had sleep disturbances [12]. With respect to the natural history of painful DPN, there are very few appropriate studies, but it is generally believed that painful symptoms may wax and wane over the years and eventually become less prominent as the sensory loss worsens; however, others have suggested no appreciable occurrence of significant remissions [2].

Acute painful DPN

The above discussion has referred mainly to patients with the commonest variety of painful DPN, which is chronic distal symmetrical symptomatic polyneuropathy. The much less common though well-recognized acute painful DPN is a rare yet distinct variety of symmetrical polyneuropathies. It is characterized by severe sensory symptoms similar to those described above, but with few neurological signs on examination. The overriding symptom reported by all patients is severe pain and there may be associated weight loss, depression and, in men, erectile dysfunction [2,14]. This acute neuropathy typically follows some rapid change in glycaemic control, which might be either following sudden improvement of control such as 'insulin neuritis' [2,14] or following an episode of very poor glycaemic control typically in young type 1 patients such as following diabetic ketoacidosis, with the symptoms coming on after successful treatment of the acute exacerbation [2,5,14,15]. Although unfortunate, the term 'insulin neuritis' is here to stay despite the fact that it might be precipitated by sudden improvement of glycaemic control, consequent on other treatments such as oral hypoglycaemic agents. The prognosis of acute painful DPN is good with complete resolution of all symptoms usually occurring within a year of onset [2,5,15].

Epidemiology

Although the epidemiology and risk factors of DPN have been extensively studied [2,5], there are very few studies that look specifically at the prevalence of pain: the prevalence varies from 10 to 26% in a number of studies [5,16]. In one population-based study in urban Liverpool, UK, the prevalence of painful DPN as assessed by a structured questionnaire and examination was estimated at 16% [16]. Sadly, in these patients it was found that 12.5% had never reported their symptoms to their doctor and notably 39% had never received treatment for their pain [16]. Similarly, it is difficult because of the lack of studies to confirm specific risk factors for painful diabetic neuropathy other than the

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well-described relationship between sudden change of glycaemic control and acute sensory neuropathy as noted above.

Mechanisms of neuropathic pain in diabetes

The exact pathophysiological mechanisms of neuropathic pain in diabetes remain enigmatic although several mechanisms including neuro-structural correlates for painful neuropathy have been postulated (Table 1) [17]. Other potential mechanisms include the association of increased blood glucose instability in the genesis of neuropathic pain [18], an increase in peripheral nerve epineurial blood flow [19], altered foot skin microcirculation [20], reduced intra-epidermal nerve fibre density in the context of early neuropathy [21], increased thalamic vascularity [22] and autonomic dysfunction [23].

Assessment and diagnosis of painful DPN

As recommended by the American Diabetes Association Consensus Statement [24], the diagnosis of painful DPN in practice is a clinical one, relying on the patient's description of pain: symptoms distal, symmetrical and associated with noctural exacerbation and commonly used descriptors as noted above [24]. The clinical diagnosis may be supported by nerve conduction studies and quantitative sensory testing. Nerve conduction studies are particularly important to exclude other cases of pain, e.g. entrapment syndromes. The diagnostic criteria for DPN (possible, probable and confirmed) are discussed in Ref. [1]. On examination, there is usually blunting of sensation on clinical examination of the feet although occasionally as noted above in acute painful DPN, symptoms may be present in the absence of signs [2,5,14].

Table 1. Mechanisms of neuropathic pain

Peripheral mechanisms	Central mechanisms
Changes in sodium channel distribution and expression	Central sensitization
Changes in calcium channel distribution and expression	Aβ fibre sprouting into lamina II of the dorsal horn
Altered neuro-peptide expression	Reduced inhibition via descending pathways
Sympathetic sprouting	
Peripheral sensitization	
Altered peripheral blood flow	
Axonal atrophy, degeneration or regeneration	
Damage to small fibres	
Glycaemic flux	

Adapted from Ref. [17].

As diabetic neuropathy is a diagnosis of exclusion, a careful clinical history and a peripheral neurological and vascular examination of the lower extremities are essential to exclude other causes of neuropathic pain and leg/foot pain such as peripheral vascular disease, arthritis, malignancy, alcohol abuse and spinal canal stenosis [2,5,24]. As painful DPN is invariably symmetrical, patients with asymetrical symptoms and/or signs should be carefully assessed for other aetiologies of their symptomatology.

A number of simple numeric rating scales can be used to assess the frequency and severity of painful symptoms [25]. It is important to emphasize the difficulties in the description and assessment of painful symptoms that patients experience: pain is a very individual sensation and patients with similar pathological lesions may describe their symptoms in markedly different ways. It must also be remembered that as pain is a personal psychological experience, the external observer can play no part in its assessment or interpretation. Hence, the use of simple scales is recommended, such as simple visual analogue style, which is of course the oldest and best validated measure or the numerical rating scale, such as an 11-point Likert scale (0 = no pain to 10 = worst possible pain). Other validated scales and questionnaires including the neuropathic pain symptom inventory [26], the modified brief pain inventory [27], the neuropathic pain questionnaire [28], the LANNS pain scale [29] and the McGill Pain Questionnaire are often used in its shortened format [30]. Quality of life (QoL) might be assessed using generic instruments; however, an inherent limitation of these is that their content did not emerge from patients affected by neuropathic pain, unlike neuropathy-specific instruments that are based on the patient's experience of neuropathic pain. Thus, it may be preferable to use validated, neuropathy-specific QoL such as NeuroQol [31], Norfolk Quality of Life Scale [32] and Neuropathic Pain Impact on Quality-of-Life questionnaire (NePIQoL) [33]. The impact of painful symptomatology on mood can be evaluated using scales such as the Hospital Anxiety and Depression Scale (HADS) [34]. Similarly, there are a number of scales that might assess pain behaviour and sleep interference and the prediction of response to therapy [9,15].

For clinical trials of putative new therapies for painful DPN, rigorous patient selection with the use of neuropathic pain scales and outcome measures are indicated. Inclusion criteria for such trials would normally include neuropathic pain associated with diabetes for greater than 6 months but less than 5 years of duration, and mean weekly pain score of between 4 and 10 on an 11-point graphic rating scale, with exclusion of pain not associated with DPN, those with mono or proximal neuropathies, other non-neuropathic chronic pain and those with central causes of pain.

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Management of painful DPN

The assessment and treatment of painful DPN continues to pose a considerable challenge to clinicians and an empathic and multi-disciplinary approach is crucial as the impact of painful DPN is varied and multi-dimensional [5]. Ideally, a multi-disciplinary team might include input from diabetologists/endocrinologists, neurologists, the pain clinic team, specialist nurses, podiatrists, psychologists, physiotherapists and others. However, in most clinical settings this is not possible and the management falls mainly to the diabetes physician, the primary care physician or neurologist. Although strong evidence implicates poor glycaemic control as a pathogenetic mechanism in the aetiology of DPN, there is no proof from randomized controlled trials that this is the case for pain symptomatology. However, a number of observational studies suggest that poor or erratic glycaemic control contributes to the genesis of neuropathic pain [2] and there is also some evidence that increased blood glucose flux might contribute to neuropathic pain [18]. A randomized controlled trial in this area is unlikely and there is therefore general consensus that good blood glucose control should be the first step in the management of any form of diabetic neuropathy (with the caveats above on acute painful neuropathy). As other risk factors of large vessel disease are also common in DPN (e.g. hypertension, hyperlipidaemia), it is important to address these abnormalities in addition (with the caveat that the use of lipid-lowering drugs can case a painful neuropathic syndrome rarely).

Pharmacological management of painful DPN

A large number of pharmacological treatments with known efficacy in diabetic neuropathy are listed in Table 2, although only two (duloxetine and pregabalin) are approved for the treatment of neuropathic pain in diabetes by both the Food and Drugs Administration of the United States and the European Medicines Agency. It should be noted that, with the exception of tight glycaemic control, none of the treatments listed in Table 2 will have any effect on the natural history of DPN which is a progressive loss of nerve fibres: all are therefore symptomatic treatments only.

Tricyclic anti-depressants

Several randomized controlled trials and meta-analyses have confirmed the efficacy of tricyclic anti-depressants (TCAs) in painful DPN [35]. These agents have been shown to promote successful analgesia to thermal, mechanic and electrical stimuli in diabetic patients: putative mechanisms underlying these effects include the inhibition of noradrenaline and/or serotonin re-uptake synapses of central descending pain-controlled systems and more recently the antagonism of *n*-methyl-D-aspartate receptors, which mediate hyperalgesia and allodynia [36]. Amitriptyline and imipramine have balanced inhibition of noradrenaline and serotonin, which may be an advantage with respect to efficacy over noradrenergic compounds such as nortriptyline and desipramine, that on the other hand are better tolerated. In addition, drugs such as nortriptyline have less anti-cholinergic properties and cause less of the symptoms due to cholinergic blockade. If carefully titrated the number needed to treat (NNT) is 1.5–3.5 [15]. However, some of the trials were small and crossover that may have influenced the NNTs to be lower. As the TCAs have predictable and frequent side effects including drowsiness and anti-cholinergic effects, it is recommended to start at a small dose especially in older patients of 10 mg/day, increasing as needed to 75 mg/day. As data from a large retrospective study of patients on TCA therapy showed an increased risk of sudden cardiac death associated with doses of >100 mg/day [37], then caution should be taken in any patient with a history of cardiovascular disease in addition to older patients. Some authorities recommend that an electrocardiogram should be carried out and if there is prolongation of the PR or QTc interval these drugs should not be used.

Table 2. Lifestyle, metabolic control and pharmacological treatment approaches for painful diabetic peripheral neuropathy showing some of the commonly prescribed treatments

- Physiological glucose control (HbA_{1c} 6–7%)
- Lifestyle modification (diet, exercise)
- Management of cardiovascular risk factors
- Tricyclic anti-depressants
  - Amitriptyline 25–75 mg/day
  - Imipramine 25–75 mg/day
- Serotonin noradrenalin re-uptake inhibitors
  - Duloxetine 60–120 mg/day (indicated for painful diabetic peripheral neuropathy by US Food and Drug Administration and European Medicines Agency)
  - Venlafaxine 150–225 mg/day
- Anti-convulsants
  - Gabapentin 900–3600 mg/day
  - Pregabalin 300–600 mg/day (indicated for painful diabetic peripheral neuropathy by US Food and Drug Administration and European Medicines Agency)
  - Carbamazepine 200–800 mg/day
  - Topiramate 25–100 mg/day
- Opiates
  - Tramadol 200–400 mg/day
  - Oxycodone 20–80 mg/day
  - Morphine sulfate sustained-release 20–80 mg/day
- Capsaicin cream
  - (0.075%) Applied sparingly three to four times per day

Serotonin and noradrenalin re-uptake inhibitors

Serotonin and noradrenalin re-uptake inhibitors (SNRIs) such as duloxetine relieve pain by increasing the synaptic availability of 5-hydroxytryptamine and noradrenaline

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in the descending pathways that are inhibitory to pain impulses. A further advantage of duloxetine is that it has anti-depressant effects in addition to the analgesic effects in diabetic neuropathy. The efficacy of this agent has been confirmed in painful DPN in several similar clinical trials at doses of 60 or 120 mg/day [35,38]. The pooled data from three trials confirmed that efficacy was maintained throughout the treatment period of 12 weeks and that approximately 50% of patients had achieved at least 50% pain reduction [38].

The NNT to achieve at least 50% pain reduction (generally accepted to be clinically meaningful) was 4.9 for 120 mg/day and 5.2 for 60 mg/day [38]. An advantage of this agent is that it is not associated with weight gain and the most frequent adverse effects include nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite, although these tend to be mild to moderate and are transient.

Another SNRI, venlafaxine (dosages 150–225 mg/day), is also effective in relieving painful symptomatology [35], although cardiovascular adverse events limit its use in diabetes.

Anti-convulsants

Gabapentin and pregabalin, which bind to the α-2-δ subunit of the calcium channel, reducing calcium influx and thus resulting in reduced synaptic neurotransmitter release into the hyperexcited neurone are the two anti-convulsants most frequently used to treat neuropathic pain [35].

The evidence for the efficacy of the first generation agent (e.g. carbamazepine, phenytoin) is limited and mainly comes from small single-centre studies. Furthermore, these agents are associated with a relatively high frequency of adverse events, particularly central effects such as somnolence and dizziness [2,35]. Gabapentin is well established as a treatment of painful DPN, although doses typically prescribed in clinical practice are much lower than the doses used in the main clinical trial of up to 3.6 g/day [39].

The second commonly used agent in this group, pregabalin, has been shown to be highly effective in the treatment of painful DPN in several randomized controlled trials [35,40]. Based upon these and other evidence supporting its efficacy and tolerability, doses of 150–600 mg/day (in divided doses) for the treatment of diabetic neuropathic pain are recommended. The pooled analysis of seven randomized controlled trials in painful DPN has confirmed the efficacy and safety of pregabalin [40]. Data from this pooled analysis showed an NNT of 4.04 for 600 mg/day and 5.99 for 300 mg/day. The most frequent side effects for pregabalin are dizziness, somnolence, peripheral oedema, headache and weight gain.

Trials on anti-convulsants lamotrigine and lacosamide indicate some efficacy of these compounds, but the results are equivocal [35]. An open-label extension study of topiramate (up to 600 mg/day) in subjects with moderately to severely painful DPN suggested that pain relief was effective and the drug caused weight loss and improvement in lipid and blood pressure parameters but 39.5% of subjects discontinued, most often due to adverse events [41].

Local anaesthetic or anti-arrhythmic agents

The benefit of intravenous lidocaine (5 mg/kg over 30 min) in painful DPN was confirmed in a randomized double-blind placebo controlled trial [42]. However, oral dosing is unavailable and electrocardiogram monitoring is necessary during administration: its use is therefore limited to refractory cases of painful DPN.

Mexiletine is a class 1B anti-arrhythmic agent that is an orally available structural analogue of lidocaine. Its efficacy in reducing neuropathic pain has been confirmed in clinical trials, although a review of seven control trials suggested that mexiletine only provided a modest analgesic effect [43]: as regular electrocardiogram monitoring is necessary, the long-term use of mexiletine cannot be recommended.

A multicentre randomized, open-label, parallel-group study of lidocaine patch *versus* pregabalin with a drug washout phase of up to 2 weeks and a comparative phase of 4-week treatment period showed that lidocaine was as effective as pregabalin in reducing pain and was free of side effects [35].

Opioids

Many physicians are reluctant to prescribe opioids for neuropathic pain probably because of fear of addiction. However, there is randomized controlled trial evidence for some opiods and therefore there is a good rationale for their use in appropriate patient after trail in first-line therapy. Of the orally administered opioids, tramadol is the best studied. It is a centrally acting synthetic opioid with an unusual mode of action, working on both opioid and mono-aminergic pathways. It has a lower abuse potential than conventionally stronger opioids and development of tolerance is uncommon. In a randomized controlled trial, tramadol up to 200 mg/day was effective in the management of painful DPN with a follow-up showing that symptomatic relief could be maintained for at least 6 months [44]. Finally, two randomized trials have confirmed the efficacy of controlled release of oxycodone for neuropathic pain in diabetes [35,45]. All studies of opioids have only assessed relatively short-term use, so the risks of tolerance and dependence in longer term usage are yet to be quantified. In recognition of these potential problems, physicians should be alert to signs of abuse and should only use the opioids if other therapies have failed to providing sufficient pain relief.

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Comparative or combination trials

A major problem in the area of treatment of neuropathic pain in diabetes is the relative lack of comparative or combination studies: most cited studies in this review have been of active agents against placebo, whereas there is a need for more studies that compare a new drug with an active comparator or indeed two existing drugs with known efficacy. A recent example of such a trial is that of Bansal *et al*. [46] who compared amitriptyline with pregabalin in painful diabetic neuropathy in a randomized double-blind trial. This study confirmed that although there was little difference in efficacy, pregabalin was the preferred drug because of a superior adverse event profile. Similarly, Gilron *et al*. studied nortriptyline and gabapentin either in combination or alone in a randomized trial and confirmed that when given together, they were more efficacious than either drug given alone [47]. In a crossover study, low-dose combination therapy with gabapentin and morphine was significantly more effective than either monotherapy at higher doses [48].

Topical treatments

Topical treatments offer several theoretical advantages including minimal side effects, lack of drug interactions and no need for dose titration. However, few have been evaluated in well-designed randomized control trials. Topical capsaicin works by releasing substance 'P' from nerve terminals which become depleted and there might be worsening of neuropathic symptoms for the first few weeks of application. Topical capsaicin (0.075%) applied sparingly three to four times per day to the affected area has been found to relieve neuropathic pain [49] (see above on use of lidocaine in painful DPN).

Pathogenetic treatments

Although several disease-modifying agents are under investigation, only the anti-oxidant, α-lipoic acid, is supported by a meta-analysis and is available in certain countries [50]. Evidence supports the use of 600 mg i.v. per day over a 3-week period of this agent in reducing neuropathic pain [50]. The meta-analysis confirmed that the treatment was associated with a significant and clinically meaningful improvement in positive neuropathic symptoms as well as deficits. The results of long-term trials of oral α-lipoic acid for neuropathic symptoms and deficits are eagerly awaited.

Previous guidelines on treatment of diabetic neuropathic pain

In a recent review on the management of neuropathic pain, Freynhagen and Bennett [51] provided treatment recommendations based on recently published guidelines. They proposed a TCA (e.g. amitriptyline) or gabapentin or pregabalin as first-line approaches. They also recommended that the SNRI, duloxetine, could be the first- or second-line treatment. Previously, guidelines from the Canadian Pain Society [52] had made similar proposals with TCAs and anti-convulsants being the first-line treatments and the SNRI the second line. Finally, the European Federation of Neurological Society's Guidelines proposed that first-line treatments might comprise of TCAs, SNRIs, gabapentin or pregabalin [53]. Most recently, the UK National Institute for Health and Clinical Excellence published guidelines on the management of neuropathic pain in non-specialist settings, in which the management of painful DPN featured prominently [54]. While National Institute for Health and Clinical Excellence ranked the level of evidence of pain outcomes with duloxetine, pregabalin and gabapentin as similar, they propose that oral duloxetine should be the first-line treatment with amitriptyline as an alternative and pregabalin as a second-line treatment [54]. The proposal that oral duloxetine should be the first-line therapy does not appear to be based on efficacy but rather cost-effectiveness.

Recommendations for treatment algorithm

On the basis of the clinical trial evidence of the various pharmacological agents for painful DPN, the following treatment algorithm is recommended (Figure 1). The panel compared the relative efficacy and safety of treatments for painful DPN and recommended that a TCA, SNRI or an α-2-δ agonist should be considered for first-line treatments, provided there are no contraindications. On the basis of trial data, duloxetine would be the preferred SNRI and pregabalin would be the preferred α-2-δ agonist. If pain is inadequately controlled, depending upon contraindications, a different follow-up agent might be considered as shown in Figure 1.

Initial selection of treatment will be influenced by the assessment of contraindications, consideration of co-morbidities and cost; for example, in diabetic patients with a history of heart disease, elderly patients on other concomitant medications such diuretics and anti-hypertensives, patients with co-morbid orthostatic hypotension and so on, TCA have relative contraindications. In patients with liver disease, duloxetine should not be prescribed, and in those with oedema, pregabalin or gabapentin should be avoided (Table 3).

A combination of first-line therapies might be considered if there is pain, despite a change in first-line monotherapy (Figure 1). If pain is inadequately controlled, opioids such as tramadol and oxycodone might be added in a combination treatment.

Non-pharmacological treatments

A full review of studies on non-pharmacological treatments for painful DPN is beyond the remit of this review

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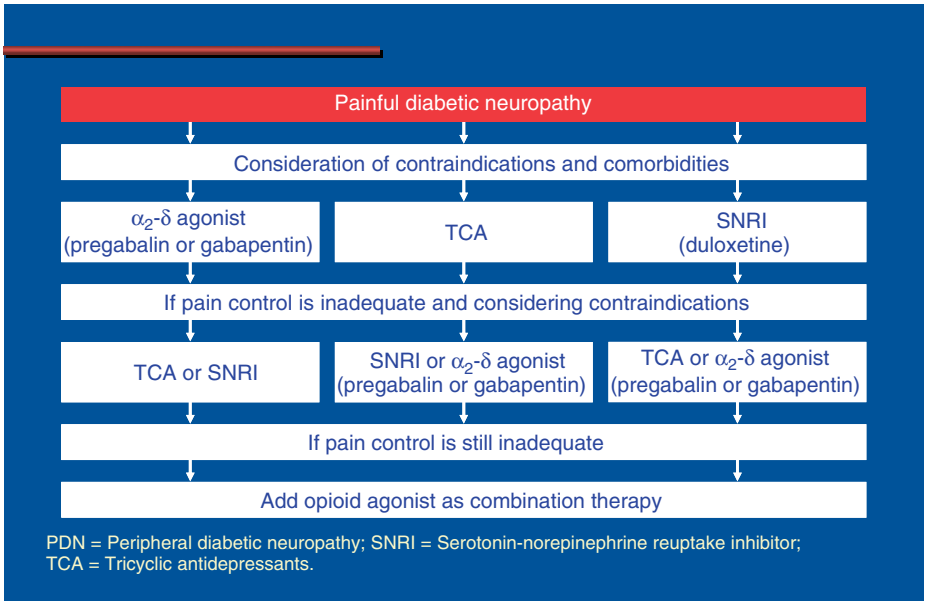

Figure 1. Treatment algorithm for painful diabetic peripheral neuropathy

Table 3. Tailoring treatment to the patient

Factor	Contraindication
Co-morbidities	
Glaucoma	TCAs
Orthostatic hypotension	TCAs
Cardiovascular disease	TCAs
Hepatic disease	Duloxetine
Oedema	Pregabalin, gabapentin
Unsteadiness and falls	TCAs
Other factors	
Cost	Duloxetine, pregabalin
Weight gain	TCAs, pregabalin, gabapentin

TCAs, tricyclic anti-depressants.

but suffice it to say that there are few well-designed trials in this area. However, lack of efficacy and unwanted side effects from conventional drug treatments might force many sufferers to try alternative therapies such as acupuncture [55], near-infrared phototherapy [56], low-intensity laser therapy [57], transcutaneous electrical stimulation [58], frequency-modulated electro-magnetic neural stimulation therapy [59], high-frequency external muscle stimulation [60] and as a last resort, the implantation of an electrical spinal cord stimulator [61].

Conclusions

Painful DPN is a significant clinical problem affecting up to a quarter of all diabetic patients and results in loss of quality of life. Despite this, it continues to be underdiagnosed and under-treated and this unsatisfactory scenario must change. The minimum requirements for diagnosis of painful DPN are assessment of symptoms and neurological examination, with shoes and socks removed. Bilateral sensory impairment is usually present. Other cause of pain should be excluded and contraindications for the use of individual drugs should be sought and catered for. Based on trial evidence, this panel recommends that first-line therapies for painful DPN should be one of the following:

1. a TCA
2. the SNRI duloxetine
3. the anti-convulsants pregabalin or gabapentin.

The decision should take into account patient co-morbidities and costs. Optimization of glycaemic control and aggressive management of cardiovascular risk factors are also clearly important. Combination therapy might be useful for those with more severe pain, but there is paucity of studies and further research is required. Studies are also required on direct head-to-head comparative trials and long-term efficacy of drugs, as most trials have lasted for less than 6 months. Key target areas generating or modulating pain in painful DPN including peripheral small fibres with modulation at the level of the spinal cord, the thalamus [22] and the other pain matrix areas in the brain require further studies in order to develop more effective treatments. The association of painful DPN with autonomic neuropathy also merits further investigation. Despite many trials looking for effective pathogenetic treatments for painful DPN, only the anti-oxidant intravenous α-lipoic acid has evidence from a meta-analysis and is in wide clinical use in certain countries. Thus, further research is required to find novel and more effective pathogenetic treatments for painful DPN.

Conflict of interest

None declared.

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Appendix

The Toronto Consensus Panel on Diabetic Neuropathy

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