Characteristics and Treatment of Painful Diabetic Neuropathy

Sandra Sif Gylfadottir and Nanna Brix Finnerup

1 Definition, Epidemiology, Diagnosis, and Characteristics

Painful diabetic neuropathies include painful diabetic radiculoplexopathy, mononeuropathies, treatment-induced neuropathies induced by fast improvement of glycemic control after hyperglycemia, entrapment neuropathies, and distal symmetrical sensorimotor polyneuropathies [1]. The focus of this chapter will be on painful diabetic polyneuropathy (P-DPN) as this group represents the majority of the patients in clinical setting [2] and the diagnostic and treatment approaches to the different types of painful diabetic neuropathies are similar, except for treatment-induced neuropathy (discussed in chapter "Asymmetric Diabetic Neuropathy: Radiculoplexus Neuropathies, Mononeuropathies, and Cranial Neuropathies").

Pain is defined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [3]. P-DPN is a subgroup of neuropathic pain, which is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [4]. Of patients with DPN, 25–50% experience pain due to their DPN [5–11]. Many factors influence the prevalence estimates of P-DPN, including different definitions and assessment methods of P-DPN as well as differences in duration and type of diabetes [8, 12–19].

Patients with P-DPN often complain of both painful and non-painful sensations. Non-painful sensations include paresthesia, which are not unpleasant, e.g. tingling, and dysesthesia, which are unpleasant sensations, e.g. pricking. The pain can be spontaneous or evoked and examples of neuropathic pain symptom descriptions can be burning, squeezing, shooting, or pricking pain, although the pain can be described in a similar way as in other pain conditions [20]. Therefore the pain description itself is normally not sufficient to diagnose P-DPN and it has to be confirmed by a clinical examination and supportive diagnostic tests. Evoked pain to, e.g. touch or cold is uncommon in P-DPN compared to some other neuropathic pain conditions. Pain and other abnormal sensory symptoms usually start in the feet and may spread to the legs and hands in the most severe cases.

The clinical examination consists of a standard neurological examination with a focus on sensory examination of feet and hands, or any other affected area. In Fig. 1 there are examples of tools that can be used in the bedside examina-

S. S. Gylfadottir (✉) · N. B. Finnerup
Department of Clinical Medicine, Danish Pain Research Center, Aarhus University, Aarhus, Denmark

Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
e-mail: sifgyl@clin.au.dk; finnerup@clin.au.dk

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tion of a patient presenting with P-DPN. In 2016 the International Association for the Study of pain special interest group on neuropathic pain (NeuPSIG) proposed an upgraded grading system for neuropathic pain, both for research and clinical practice [21, 22]. Applying this for P-DPN (Fig. 2), possible P-DPN requires a history of P-DPN, pain in the feet, and a diagnosis of diabetes. Probable P-DPN additionally requires sensory signs in the same area, and definite P-DPN requires abnormal tests that confirm a structural or functional damage to the sensory nerves (examples: skin biopsy and nerve conduction studies). At all stages it is important to consider other causes of polyneuropathy with similar or the same symptom presentation (i.e. alcohol or chemotherapy induced, infective or inflammatory polyneuropathy) or conditions presenting with painful feet or legs (i.e. arthritis, spinal stenosis, herniated disc, peripheral arterial diseases) [10].

Fig. 1 Example of tools that can be used in the bedside examination of the patient presenting with P-DPN. Left to right: tuning fork for vibration sense, brush for light brush stroking, Neuropen® for light touch and pinprick sensation, reflex hammer, temperature rolls, cotton wool swab, and ear pin

It is difficult to replace bedside clinical examination with standardized assessment tools, although they can be useful in screening, epidemiological research, and to aid in the diagnosis of neuropathic pain [23]. An example of screening and diagnostic tool is the douleur neuropathique en 4 questions (DN4). The DN4 consists of seven questions and a clinical examination part and was designed to discriminate neuropathic pain from other types of pain [24]. The questions are focused on pain and paresthesia (pins and needles, numb-

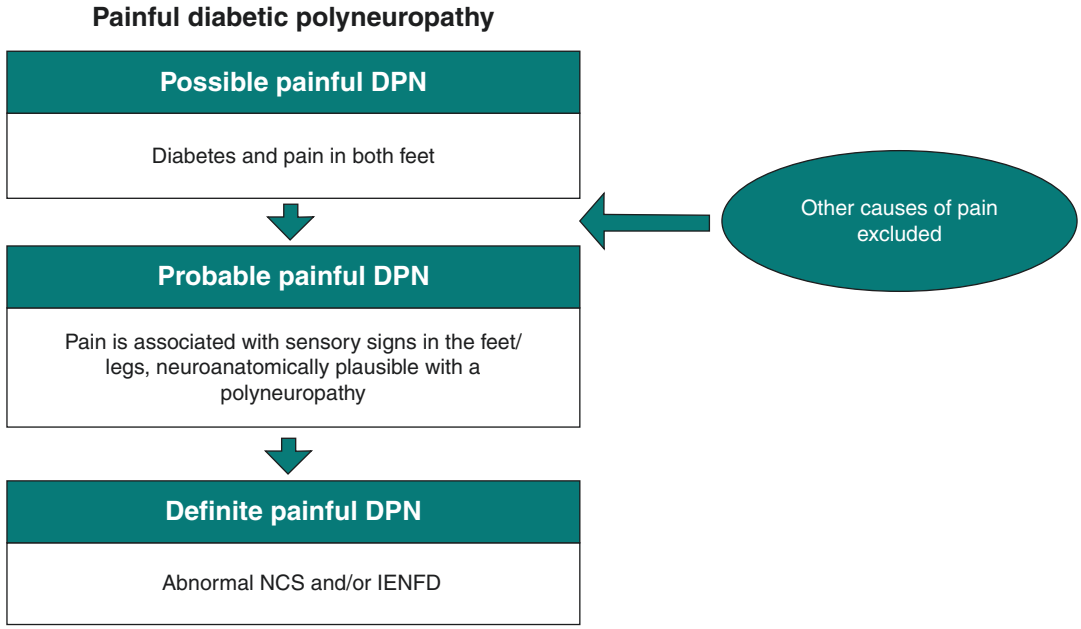

Fig. 2 The diagnosis of P-DPN [21]. At all steps, other causes of pain and neuropathy should be considered

ness, itching, burning, painful cold, and electric shock sensation) and the examination of brush and pinprick hypoesthesia and dynamic mechanical allodynia (DMA) in the feet/legs. The DN4 questionnaire part has been validated and used for P-DPN [19, 24, 25]. In a recent validation study in type 2 diabetes patients, the sensitivity and specificity of the DN4 questionnaire for definitely diagnosed P-DPN were 80.0 (44.4; 97.5) and 89.9 (83.6; 94.3), respectively, for a cut of point ≥3/7 [10]. An example of a questionnaire that can be used to quantify and characterize the symptoms of neuropathic pain is the neuropathic pain symptom inventory (NPSI) with 12 questions about the presence, character, and intensity of pain and the answers can be converted into sum scores [26]. Other neuropathic pain tools are available, such as the PainDETECT, the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire, and the Neuropathic Pain Questionnaire [23]. The numerical rating scale (NRS) from 0 to 10 or a Visual Analog Scale (VAS) is used to measure the intensity of the pain with 0 being no pain and ten the worst pain imaginable and is simple to administer [27]. In the assessment of pain it is also important to assess the impact of pain on daily activities, sleep, mood, function, and quality of life.

It is a puzzle why some patients with DPN develop painful symptoms, while others do not [28, 29]. Most studies are cross-sectional, and there is generally a lack of longitudinal studies to elucidate the natural course of the disease and the risk factors for developing neuropathic pain in diabetes. Type 2 diabetes compared to type 1 diabetes and higher measures of HbA1c have been associated with P-DPN. Recent studies have also found correlation of P-DPN with increased severity of neuropathy [7, 8, 30–32]. Other risk factors that have been linked to P-DPN are smoking, female sex, increasing age, obesity, and the co-occurrence of other diabetic complications [16, 33, 34]. The genetic component in the risk profile of P-DPN is described in chapter "The Genomics of Diabetic Neuropathy".

Psychosocial factors such as reduced quality of life, depression, sleep deprivation, and anxiety have consistently been shown to be associated with P-DPN and pain intensity [7, 12, 17, 31, 32, 35–40]. Most studies are cross-sectional and have therefore not examined the causal relationship between having a chronic neuropathic pain and mental health. A large questionnaire study of Danish patients with type 2 diabetes and neuropathy found that both patients with DPN with and without pain reported worse mental health and quality of life, although patients with pain were more severely affected [38].

2 Treatment of P-DPN

Information about pain and pain mechanisms and discussion of aggravating and alleviating factors and pain coping strategies are often the first step in pain treatment. While the evidence for psychological and self-care interventions are limited for chronic pain, most guidelines recommend this in the treatment of chronic pain [41]. For any treatment, realistic expectations for the outcome should be discussed with the patient, as often only partial pain relief can be expected. A multidisciplinary approach with physicians, pain nurses, psychologists, social workers, and physiotherapists may be needed in severe pain that is not easily treated [42–44]. Furthermore, a close collaboration between diabetes treatment units and primary care physicians, which patients attend regularly, and pain clinics may be helpful and convenient for the patients.

3 Pharmacological Treatment

Currently there is no generally established disease modifying therapy for P-DPN and the aim of the treatment is therefore mainly improvement of modifiable risk factors, quality of life, and symptomatic pain relief.

3.1 Pathogenesis Orientated Treatment

Optimal glycemic control and the assessment of vascular and lifestyle risk factors are important.

It is well known that hyperglycemia plays a role in the pathogeneses of neuropathy [45], and it may contribute to the pathogeneses of neuropathic pain, although the evidence for improved glycemic control as a pain relief is limited as there is a lack of randomized controlled studies [43, 46, 47]. In a meta-analysis, enhanced glycemic control was significantly effective in the prevention of neuropathy in type 1 diabetes patients, but not in type 2 diabetes [48]. A clinical study in type 2 diabetes however showed improvement in neurophysiological parameters with strict blood sugar control without hypoglycemia for a longer period of time in patients with poor glycemic control [49].

Alpha-lipoic acid (ALA) is suggested to be a causative treatment of DPN by having beneficial effects on vascular dysfunction, tissue hypoxia, and glucose utilization. It is also suggested to prevent painful symptoms by possibly suppressing the activation of TRPV1 channel via activation of the NF-κB, a cellular nuclear transcription factor protein complex, but with limited effect from clinical trials [50–53]. Another potential neuroprotective agent in DPN is Actovegin that consists of filtered extract from calf serum and is thought to have antihypoxic effect on tissue. In a multicenter, double blinded, randomized trial, treatment with Actovegin improved symptoms of neuropathy including pain, paresthesia, and numbness and the improvement was considered to be clinically relevant [54, 55].

Vitamin D has been thought to play a role in peripheral neuropathy by stimulating keratinocytes in the skin to produce nerve growth factor, with D vitamin as a potential therapeutic agent [56]. No randomized, double-blinded studies have assessed the efficacy of vitamin D in P-DPN [57, 58].

3.2 Symptomatic Treatment

The challenges in the medical treatment of neuropathic pain lie in the relatively high numbers needed to treat (NNT) which is the number of patients needed to treat for one to have 50% pain reduction and often intolerable side effects of the medication [59]. Additionally patients with P-DPN can be elderly and suffer from other chronic diseases or other macro- or microvascular diabetes complications, for example, heart and kidney diseases, potentially reinforcing the side effects or rendering the recommended treatment contraindicated.

In 2016 the neuropathic pain special interest group of the International Association for the Study of Pain (NeuPSIG) presented treatment guidelines for neuropathic pain based on systematic review and meta-analysis [59]. These recommendations are based on a large number of studies and apply to patients with neuropathic pain of many etiologies, based on the conclusion made by the authors that the effect of the treatment does not depend on the etiology [59]. These recommendations are in line with other recommendations for painful DPN, from the European Federation of Neurological Societies (EFNS) [60], the American Academy of Neurology [61], the Agency for Health Research and Quality (AHRQ) [62], the Toronto Expert Panel on Diabetic Neuropathy [46], and a recent meta-analysis on P-DPN [63].

3.3 Guideline Recommendations

Pregabalin and gabapentin, tricyclic antidepressants (TCA), and serotonin noradrenaline reuptake inhibitors (SNRIs) are recommended as a first-line therapy with a strong recommendation and moderate to high quality of evidence [60, 61, 63]. In terms of safety, there is no evidence to suggest one of these drugs is above others [59, 64]. Duloxetine has been recommended for painful DPN. Capsaicin 8% and lidocaine 5% patches are recommended as a second-line therapy with moderate to high quality of evidence and a week's recommendation for use. Finally, botulin toxin A subcutaneous injection is recommended as third-line treatment option (Table 1 and Fig. 3) [59].

The results for combination therapy were inconclusive in both meta-analyses [59, 63], although the search for sufficient pain relief in the clinical setting often results in a combination

Table 1 Guidelines recommendation

	Daily doses	Common side effects	Precautions
First-line recommendations			
Tricyclic antidepressants (TCAs)	25-(100) 150 mg, starting with doses of 10–25 mg	Sedation, dry mouth, constipation, blurred vision, weight gain, orthostatic hypotension with risk of falls in elderly patients.	People with seizures, glaucoma, cardiac diseases, and dysuria and the elderly >65 years.
			ECG before starting treatment for QT interval.
Serotonin-norepinephrine inhibitors (SNRIs)	60–120 mg for duloxetine and 150–225 mg for venlafaxine in one dose	Nausea, somnolence, dizziness, constipation, dry mouth, hypertension. Often mild and transient side effects	In people with seizures, glaucoma, uncontrolled hypertension, and in the elderly.
Pregabalin	300–600 mg in two doses/day	Dizziness, somnolence, headache, peripheral edema, and weight gain. Risk of suicidal thoughts	Reduced doses in people with impaired kidney function
Gabapentin	900–3600 mg in three doses/day	Same as for pregabalin	Same as for pregabalin
Second-line recommendations			
Lidocaine 5% patches	One to three patches in the painful area up to 12 h	Mild redness, swelling, irritation, change in skin color, and numbness	Avoid contact with eyes, nose, and mouth
Capsaicin 8% patches	One to four patches in the painful area for 30–60 min every 3 months	Local discomfort and skin reaction/burning	Should not be used in the face and on or near mucous membranes

Examples of SNRIs: Venlafaxine, Duloxetine, TCAs: Amitriptyline, Nortriptyline, Imipramine. For detailed information on doses, side effects, and precautions, please refer to individual product information

of more than one of the recommended drugs, preferable using drugs with different modes of action. The question whether it is better to increase the drug dose of a monotherapy with one of the recommended drugs or if it is better to combine two drugs in patients that do not respond to a standard dose was addressed in the COMBO-DN study of patients with P-DPN [65]. The comparison between high recommended dose of pregabalin or duloxetine in patients that did not respond to standard dose was compared to the effect of a combination therapy of the two drugs at moderate dosages, with no differences between the groups, although the combination therapy was considered well tolerated and safe [65]. It is worth noting that patients with diabetes often receive multiple medication for glycemic control, hypertension, and dyslipidemia and in some cases medication for sleep disturbances, depression, or anxiety. Polypharmacy may therefore raise concerns about compliance, adherence, and drug–drug interactions [66].

3.4 Modes of Action, Recommended Dose, and Side Effects

Tricyclic antidepressants (TCAs) act on the noradrenergic system by inhibiting presynaptic reuptake of monoamines (noradrenalin and serotonin) and the place of action for the TCAs is thought to be both central and peripheral [20, 67]. Other mechanisms may also be involved, including blockade of voltage-gated sodium channels and NMDA (*N*-methyl-D-aspartate) receptors [68, 69]. Experimental data have suggested that TCAs work through an effect on β2 adrenergic receptors. However, a recent randomized controlled trial found that the tricyclic antidepressant imipramine but not the β-agonist terbutaline had effect on painful polyneuropathy suggesting that β2 agonisms are not a clinical important mechanism of action of TCAs in painful polyneuropathy [70]. Examples of TCAs are amitriptyline, nortriptyline, and imipramine and the overall

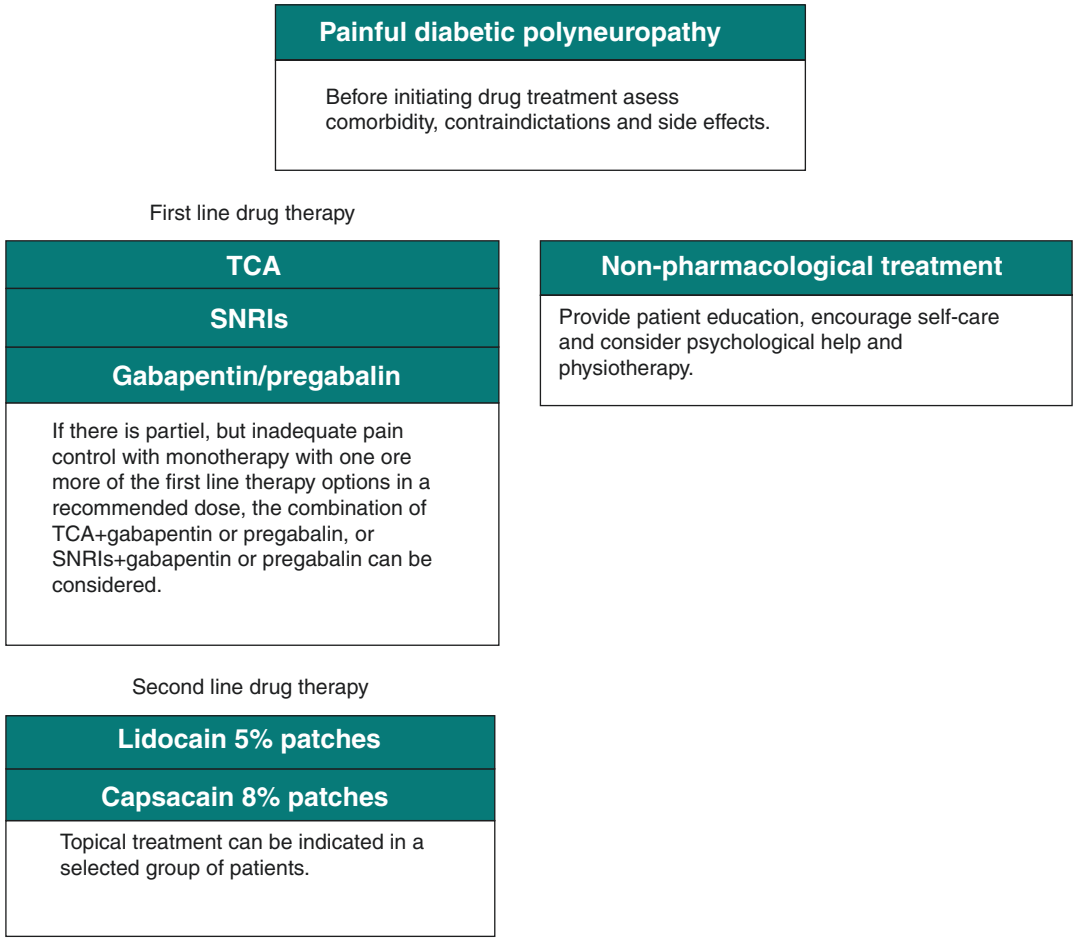

Fig. 3 Treatment algorithm for P-DPN

number of patients needed to treat (NNT) to achieve at least 50% reduction in pain intensity for one patient for TCAs in neuropathic pain was 3.6 (95%CI 3.0–4.4) where most trials included amitriptyline [59]. A starting dose of 10–25 mg increasing with 10 mg every fifth day until desired pain relief is obtained where maximum dose of 100–150 mg is recommended. The most common side effects are dry mouth, constipation, sedation, blurred vision, weight gain, and orthostatic hypotension with the risk of falls in elderly patients. An ECG before treatment is recommended to exclude prolongation of PR and QT intervals. Secondary amines (nortriptyline and desipramine) have lower affinity for muscarinic acetylcholine receptors and imipramine has lower affinity to block histaminergic H1 receptors than amitriptyline and may therefore cause less sedative side effects [69, 71]. Caution should be shown in the treatment of elderly people >65 years where lower doses are required because of risk of sedation, falls, and sudden cardiac death [72, 73].

SNRIs also target the serotonin noradrenergic system by inhibiting presynaptic reuptake of serotonin and noradrenalin, augmenting descending inhibitory pathways. Examples are duloxetine and venlafaxine. Most common adverse effects are nausea, somnolence, dizziness, constipation, and dry mouth; these side effects are often mild and transient. Recommended daily doses are 60–120 mg/day for duloxetine and 150–225 mg/day for venlafaxine. The NNT for 50% pain reduction for SNRIs is 6.4 (95% CI 5.2–8.4) [20, 59].

The group of antidepressants should be tried for some time for pain relief before switching to another drug because lack of effect [69]. In patients with concomitant depression TCAs and SNRIs may have some effect on depressive symptoms [41].

Gabapentin and pregabalin have similar modes of action and bind to the α2δ subunit of the presynaptic voltage-gated calcium channels and thereby reduce Ca^{2+} influx resulting in decreased neurotransmitter release [20, 67]. The site of action can be peripheral, spinal, and supraspinal. The NNT for pregabalin is 7.7 (6.5; 9.4) and for gabapentin 7.2 (5.9; 9.1) [59]. Common side effects are dizziness, somnolence, peripheral edema, headache, and weight gain. Daily doses for gabapentin are 900–3600 mg daily in three doses starting with 300 mg/day and for pregabalin 300–600 mg in two doses starting with 75 mg/day. There are increasing concerns and evidence for misuse of gabapentin and pregabalin [74].

Topical treatment with capsaicin 8% and lidocaine 5% patches can be beneficial in a selected group of patients. Capsaicin binds to the transient receptor potential vanilloid 1 (TRPV1) on nociceptors desensitizing them for 12 weeks. Normally one to four patches are applied in the painful area for 30–60 min every 3 months. Lidocaine inhibits ectopic nerve activity by blocking voltage-gated sodium channels [20]. One to three lidocaine 5% patches are applied in the painful area for up to 12 h.

3.5 Other Pharmacological Treatment Options

Tramadol and strong opioids have also shown some effect in randomized controlled trials of short duration, but are generally not recommended for the treatment of chronic non-malignant pain because of long-term consequences, risk of abuse and dependence, and lack of effect on functional status [75–78]. If opioids are indicated for medium-term use, a low dose in a monitored setting following local opioid prescribing guidelines is recommended [76, 78]. Tramadol, which is a centrally acting synthetic opioid working on both opioid and monoaminergic pathways, may be considered for flares of pain. A range of drugs have inconclusive evidence based on conflicting results from randomized trials, including lamotrigine, oxcarbazepine, topiramate, and selective serotonin-reuptake inhibitors, and thus there is no evidence to support their use for P-DPN, and further studies are needed to support their use, e.g. in specific subtypes of patients [59]. One study found oxcarbamazepine to be effective in a subgroup of patients with painful polyneuropathy and a sensory phenotype with preserved small-fiber sensation (cold and warm sensation and sensory hypersensitivity compared to those without), but these results have not been confirmed [79]. Recent systematic reviews find no evidence for the use of cannabinoids, cannabis, and cannabis-based medicines in chronic pain [80, 81]. The NeuPSIG guidelines have a weak recommendation against the use of cannabis-based medicines in neuropathic pain because of lack of effect in clinical trials, potential misuse, diversion, and long-term mental health risks [59].

3.6 Emerging Treatment Possibilities

Several drug classes are currently in clinical development for neuropathic pain, although to date, we have seen a failure in developing new drug classes for neuropathic pain [82, 83]. A peripherally acting drug EMA401, which is a competitive antagonist to angiotensin II type 2 receptor, showed promising effects in peripheral neuropathic pain [84], but recently phase 2 trials have been terminated due to safety reasons. Antibodies targeting the activity of human nerve growth factors are also in development for pain. Recombinant human nerve growth factor had no effect on diabetic polyneuropathy in a large trial but showed some effect on pain in the legs, which was one of many secondary outcomes [85]. Tanezumab, a humanized monoclonal antibody against nerve growth factor was found to reduce

P-DPN despite early study termination due to a partial clinical hold by the US Food and Drug Administration (FDA) due to joint-related safety [86], but currently the drug is only being developed for osteoarthritis and other pain types. Subtype-selective sodium channel inhibitors, in particular $Na_v1.7$ blockers, are also being investigated for neuropathic pain.

4 Nonpharmacological Treatment

The first treatment of neuropathic pain offered to patients is most often pharmacological, but it is also important to consider nonpharmacological treatment options, either as the only treatment or as an addition to medical treatment.

With a general agreement of having P-DPN being associated with worse mental health, there are paradoxically few studies that have examined the effect of psychological treatment in P-DPN [39, 87]. Psychological therapy for chronic pain may consist of cognitive behavioral therapy (CBT), a traditional therapy form that helps patients to identify, change, and provide coping strategies for negative thoughts or behavior associated with pain. Another therapy form derived from CBT also used in the treatment of pain is acceptance and commitment therapy (ACT) which integrates acceptance, cognitive defusion, and mindfulness to produce more psychological flexibility [88]. In a recently published single arm primarily feasibility trial with online ACT treatment in patients with P-DPN the clinical outcomes showed beneficial effect on psychological functions and pain intensity, although the study has limitations due to design [89]. In a newly updated systematic review of the effect of psychological therapies on the broad spectrum of chronic pain, compared to standard treatment or waiting list, there was only very small to small beneficial effect of CBT in pain reduction, disability, and stress [90]. In separate studies of neuropathic pain and P-DPN the evidence was too sparse and insufficient to make any conclusions on the effect of psychological treatment in pain relief [39, 87]. Therefore psychological treatment may have a place in the treatment of painful DPN although the evidence is sparse.

Physiotherapy treatment options can be aimed at pain reduction, preserve function level, and prevent immobilization or it can consist of therapeutic exercise [91]. In a qualitative study, patients with P-DPN described walking difficulties and other impacts of pain on physical functions [92]. A review of physical therapy in chemotherapy induced neuropathy showed that there was possible a symptom effect, although with limited evidence [93].

In general, physical activity in adjutancy to other treatments or alone could have positive effects on P-DPN, although the evidence is limited with a high risk of bias [94, 95].

Yoga, mindfulness, and meditation are gaining increased popularity as a treatment option in various conditions, often for the improvement of mental health and quality of life, but data on the efficacy for pain relief are few or missing in the treatment of neuropathic pain, the same is for acupuncture [95–97].

Neurostimulation has been used as a treatment option in P-DPN. Examples are spinal cord stimulation (SCS) and transcutaneous electrical stimulation (TENS). According to the newly published guidelines from the European Academy of Neurology (EAN), there is weak evidence for adding spinal cord stimulation (SCS) to the pharmacological treatment in P-DPN compared with pharmacological treatment alone [98] and a recent meta-analysis including randomized controlled trials concluded that SCS was effective for pain relief compared to standard care [99]. A Cochrane review of TENS treatment for neuropathic pain could not conclude whether the treatment was effective compared to sham therapy or not, because of the size and quality of the included studies, neither were side effects nor adverse events adequately addressed in the studies [100].

5 Conclusion

Painful neuropathy is a common and often disabling consequence of diabetes. It is a neuropathic pain and is caused by the lesion of the

peripheral nerves. The pharmacological treatment is challenging and often provides only partial pain relief at best. Therefore both nonpharmacological and pharmacological treatments are recommended.

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