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Pharmacologic management of diabetic peripheral neuropathic pain

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Introduction: Diabetic peripheral neuropathic pain (DPNP) is a debilitating and distressing complication that occurs in patients with diabetes mellitus. This article provides an overview of diabetic peripheral neuropathy focusing on DPNP.

Areas covered: This article reviews the diagnosis, pathogenesis, prevention and treatment of diabetic neuropathy and neuropathic pain. A comprehensive and systematic Medline search of the published literature for treatment of diabetic peripheral neuropathy was done from 1965 to December 2012. Studies not in English language were excluded.

Expert opinion: Neuropathic pain is difficult to treat, and patients rarely experience complete pain relief. Despite several pharmacological agents being used in the treatment of DPNP, only duloxetine and pregabalin have evidence-based support for controlling DPNP.

Keywords: diabetic neuropathy, duloxetine, neuropathic pain, peripheral neuropathy, pregabalin

1. Introduction

Diabetes mellitus (DM) is a chronic medical condition affecting over 300 million people world-wide [1]. Diabetic polyneuropathy (DPN), one of the microvascular complications of diabetes is a common, debilitating and distressing complication that develops in up to 30 – 50% of patients with DM [2]. This disorder is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after exclusion of all other causes of neuropathy. DPN, also referred to as distal symmetrical sensory polyneuropathy (DSP), has two main clinical consequences: diabetic peripheral neuropathic pain (DPNP) and the insensate foot which predisposes to neuropathic foot ulceration. Foot ulceration often leads to amputation which can have a significant impact on both quality of and life expectancy in the patient with diabetes [3].

With the growing epidemic of obesity, the prevalence of pre-diabetes (impaired glucose tolerance and impaired fasting glucose) and type 2 DM is expected to increase along with the burden of this complication [4]. Neuropathic pain has a negative impact on the quality of life of patients greatly affecting all areas of a patient's life, including activities of daily living, mood, sleep, self-worth, independence, ability to work and enjoyment of life. The neuropathic pain of diabetes is described by patients in numerous ways, for example 'deep-seated aching', 'burning', 'electric', 'sharp', 'achy', 'tingling', 'numbness' or 'stabbing'. The pain and parasthesias are typically noted to be worse at night and when patients are tired or stressed [5]. Pain associated with DPN typically starts in the feet and later moves proximally in the so called 'stocking and glove' distribution. Common locations of pain include the toes, the metatarsal areas of the feet, dorsum of feet, hands, calves and heels.

Article highlights.

- DPN is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after exclusion of all other causes of neuropathy.
- A thorough history and physical exam is the key to the diagnosis of DPN.
- Early intensive glucose control is effective in preventing DPN particularly in patients with type 1 DM.
- Hyperglycemia is one of the major contributors in the etiology of DPN and is highly correlated with the progression of neuropathy.
- Uncontrolled DM is associated with multiple complications of which diabetic painful neuropathic pain is a common, debilitating and distressing complication that affects up to 30 – 50%.
- Pain associated with DPN is localized predominantly in the feet and typically may worsen at night and lessen with ambulation.
- Several pharmacological agents are useful for treatment of DPNP as monotherapy or in drug combinations and include predominantly antidepressants (tricyclic's and selective serotonin or serotonin–NE inhibitors) and antiepileptics.
- TCAs have been used for the treatment of DPNP; however, due to high incidence of adverse events they are not tolerated well by patients limiting their long-term usefulness.
- Duloxetine and pregabalin are the only two pharmacological agents approved by US FDA to treat PDNP.
- Duloxetine is considered a first-line agent by most evidence-based guidelines and this is based on its proven efficacy for neuropathic pain being demonstrated in high-quality studies and also due to its cost-effectiveness.
- Other agents recommended include opioid analgesics, tramadol, NSAIDs or topical lidocaine alone or in combination.
- Despite multiple agents being available for treatment of DPNP, none have demonstrated to alter the course of the disease or provide 100% relief of pain.

This box summarizes key points contained in the article.

When advanced, DPN may involve the fingers and hands. Pain is the most common symptom that prompts the patient to seek medical attention. Symptoms can be accompanied by sensory loss and pain may persist over several years causing considerable disability in some patients [5] and partially remit in patients with shorter duration of pain or diabetes, preceding weight loss and less severe sensory loss [6]. Despite the availability of several agents to treat DPNP, pain relief is reportedly incomplete and thus poses a challenge to providers involved in the care of these patients. We review the diagnosis, pathogenesis and management options for the treatment of DPNP with a focus on the only two agents approved by the US Food and Drug Administration (FDA): duloxetine and pregabalin.

2. Diagnosis

A thorough history and physical exam with a careful evaluation of the neurological systems and foot exam is the key to the diagnosis of DPN. To diagnose DPN, other etiologies of painful or painless sensory neuropathy should be ruled out including chronic inflammatory demyelinating polyneuropathy, B_{12} deficiency-associated neuropathy, hypothyroidism and uremia. The presentation of typical pain symptoms, decreased sensation and absent reflexes is highly suggestive of PDNP.

Three distinct types of pain have been described in patients with DPNP: dysesthesic pain, paresthetic pain and muscular pain, each of them have a different pathogenesis and anatomical distribution. Dysesthesic pain is an unpleasant sensation and presents as a burning or itching sensation. Paresthetic pain presents as pins and needle sensation. Both dysesthetic and paresthetic pains are mediated through small fibers. In contradistinction, large fiber neuropathy more commonly presents as a deep, dull or aching muscular pain. In most patients there is a mixed neuropathy although occasionally they may have selective involvement. Table 1 shows the clinical features of small and large fiber DPNP.

Physical exam may reveal a decrease in vibratory sensation or altered superficial pain and temperature sensation. A 128-Hz tuning fork placed on the bony prominence at the dorsum of the great toe can be used to assess for vibratory sensation or a 10-g Semmes–Weinstein monofilament is used to gauge pressure sensation. Failure to sense the 5.07 monofilament or the tuning fork indicates an insensate foot. Conversely the ability to sense the 5.07 monofilament does not rule out milder forms of DPN. Superficial pain sensation is tested with a pinprick. The monofilament examination, vibration testing with a tuning fork, and superficial pain sensation all have similar efficacy in detecting neuropathy. In addition, assessing patients' mobility, gait and balance should be part of neurologic exam. Screening for neuropathy should be considered at least annually in all patients with DM. In patients with DPN, evaluation for other microvascular complications such as retinopathy and nephropathy should also be undertaken.

3. Pathogenesis

The precise mechanism involved in generation of neuropathic pain is unclear although a variety of potential mechanisms have been postulated. Hyperglycemia is highly correlated with the development and progression of neuropathy and there is a growing interest in the role of rapid and tight glycemic control. Approximately 50% of patients who have had diabetes for over 25 years will develop neuropathy and majority of those who are symptomatic will complain of pain [7,8]. Neuropathy is usually a late finding in type 1 diabetes; however, it can be an early finding in type 2 diabetes – sometimes present at the time of diagnosis.

Table 1. Clinical features of small and large fiber diabetic peripheral neuropathy.

Small fiber
Pain predominates, often burning and superficial
Allodynia (pain from normal stimuli such as bed sheets)
Defective warm thermal sensation
Defective sweating (dry feet)
Impaired vasodilatation (cold hands/feet)
Large fiber
May involve sensory and motor nerves
Most distal nerves affected in a stocking-glove distribution
More neurologic signs than symptoms
Impaired vibratory perception
Depressed or absent deep tendon reflexes
Pain is deep – described as gnawing

Experimental studies in animals and in non-diabetic individuals have demonstrated hyperglycemia to cause a decrease in pain threshold [9,10]. Metabolic factors that have been implicated include abnormalities of the polyol pathway leading to neuronal sorbitol accumulation, reduction in myo-inositol and protein kinase with subsequent nerve damage. Arterio-venous shunting leading to endoneural hypoxia has also been implicated [11]. Furthermore, when the disposal of intracellular glucose is impaired, alternate pathways are activated which results in oxidative stress and neuronal injury [12,13]. Advanced glycosylation end products (AGEs) formed by attachment of carbohydrate to proteins or lipids decreases their function and also initiates an inflammatory cascade contributing further to oxidative stress. Thus, in patients with diabetes, painful neuropathic symptoms may be relieved by an improvement in metabolic control [14]. Other mechanisms put forth include changes in sodium and calcium channel distribution and expression, peripheral sensitization, altered neuropeptide expression, changes in peripheral blood flow and damage to small fibers [15]. Neuro-transmitters such as serotonin (5-HT) and norepinephrine (NE) have also been demonstrated to play a significant role in the modulation of endogenous analgesic mechanisms through the pain pathways in the brain and spinal cord [16].

4. Prevention

Early intensive therapy is the key to preventing microvascular complications from DM. Data from DCCT and UKPDS have provided evidence supporting this in patients with type 1 and type 2 DM, respectively [17-19]. A 20-year follow-up of the two groups of patients from the DCCT (EDIC) showed that the intensive insulin-treated group continued to have a much lower incidence of neuropathy than the conventional group, although at the time of this follow-up both groups had comparable glycemic control [20]. More recently the effect of tight glucose control on neuropathic pain has been suggested to be more robust among patients with type 1 versus type 2 diabetes [21]. These studies highlight the

importance of early aggressive glycemic control with the aim of preventing long-term complications particularly in patients with type 1 DM. Besides optimizing glycemic control, other modifiable risk factors for DPNP include hypertension, hyperlipidemia, smoking, obesity, heavy alcohol use and vitamin B6 and B12 deficiency. Non-modifiable risks for neuropathy include older age, longer duration of diabetes, genetic profile, height and gender (males greater than females).

Metformin has greatly improved the management of type 2 DM by suppressing glucose production by the liver which significantly lowers the HbA1c level. However, metformin has been shown to be associated with vitamin B12 deficiency in up to 30% of patients and is known to be a contributing factor to the development of neuropathy [22,23]. Previous studies have shown that there is a dose-dependent decrease in vitamin B12 concentration with an increase in dose of metformin [23]. Proposed mechanism of metformin-induced vitamin B12 deficiency is likely secondary to disruption in its absorption within the ileum [24,25]. Thus, patients on metformin particularly those taking metformin for longer than 3 years or taking over 1000 mg per day should be monitored for signs and symptoms of neuropathy and have B12 levels checked. Neuropathy from B-12 deficiency is reversible and should be treated aggressively.

5. Pharmacologic treatment options

The first step in the management of DPNP is glycemic control and correction of any other metabolic derangements. Besides optimizing glycemic control, patients often require pharmacological intervention for management of their pain symptoms. Despite several effective agents being available, many patients are unable to achieve clinically significant pain relief. Providers should have a clear understanding of various therapeutic options and their potential benefits and adverse effects of each before considering initiating a medication. Various therapeutic schemes and treatment algorithms have been proposed. **Figure 1** shows a recently published algorithm for treatment of DPNP [21]. Effective treatment requires a balance between pain relief that is achieved and the adverse effects associated with the agent in question. Management of DPNP in any given patient must be individualized and associated co-morbidities must be taken into consideration. Different agents may be appropriate for different patients, and one may need to try multiple agents before finding one that works effectively for an individual patient. Combination therapies may provide increased pain relief but remain largely unstudied. It should be noted that none of the currently available drugs for DPNP has been shown to modify the underlying mechanisms or alter the clinical course of the disease.

Agents for DPNP currently available as monotherapy or in combination with drug combinations and the various therapeutic targets modulating the treatment of DPNP are shown in **Figure 2** [26]. These include predominantly antidepressants
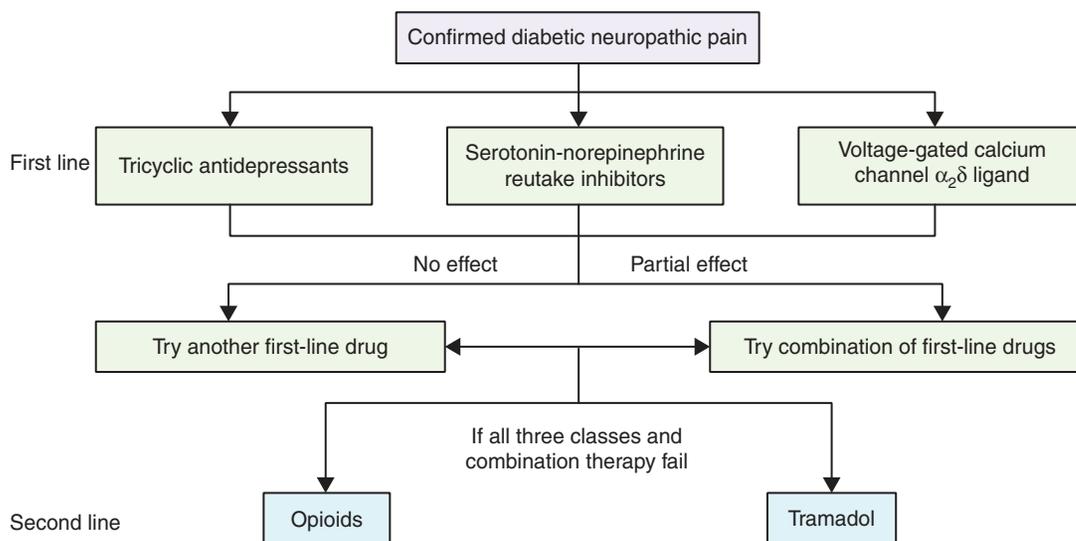
Figure 1. Treatment algorithm for diabetic painful neuropathic pain.
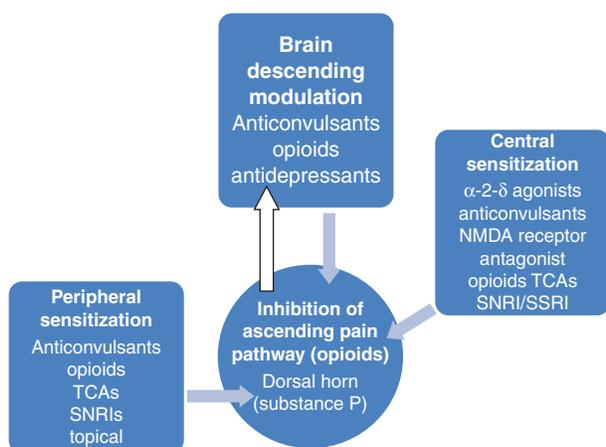Reproduced with permission from [21].

Figure 2. Therapeutic targets modulating diabetic peripheral neuropathic pain.
Reproduced with permission from [26].

(tricyclic's and selective serotonin or serotonin–NE inhibitors) and anti-epileptics which have been used with varying degrees of success in the treatment of DPNP. No studies have any of these agents provided 100% relief of neuropathic pain. Careful titration of these agents is needed to reduce adverse events and increase tolerability as a result delaying the process of pain relief. **Table 2** shows the most commonly used drugs for the treatment of DPNP.

5.1 Tricyclic anti-depressants
Tricyclic anti-depressants (TCAs) have been the most widely studied of all agents used for the treatment of DPNP. Amitriptyline and imipramine are serotonin and NE reuptake inhibitors that mediate their pharmacological effects centrally to reduce the perception of pain. However, due to their effects on α-adrenergic, H1-histamine, muscarinic cholinergic and N-methyl-D-aspartate receptors, there is a high incidence of adverse events and thus are not tolerated well by patients [27,28]. Furthermore, TCAs should be used with caution in patients who have a history of cardiovascular disease or those over 65 years of age. Some of the adverse effects reported with TCAs include orthostatic hypotension, cardiac arrhythmias, dizziness and sedation [28]. TCAs have also been associated with significant weight gain.

5.2 Other antidepressants
Venlafaxine is a member of the serotonin–NE reuptake inhibitor (SNRI) group of antidepressants. Venlafaxine and its active metabolite are potent inhibitors of neuronal serotonin and NE reuptake and weak inhibitors of dopamine reuptake [29]. Venlafaxine is also thought to work centrally by decreasing the perception of pain. In a randomized controlled trial for treatment of DPNP, extended-release (ER) venlafaxine demonstrated a significant degree of pain relief at the higher doses of 150 – 225 mg daily but not a dose of 75 mg daily [30]. The strength of the findings from this study is limited by the short duration of this trial. Nausea and somnolence were the most common side effects of venlafaxine, and blood pressure and cardiac rhythm changes occurred more often with venlafaxine treatment than with placebo. Duloxetine, another SNRI, is the first agent approved by the FDA for the treatment of DPNP and is discussed below.

5.3 Antiepileptics
Carbamazepine is a first generation anticonvulsant used in the treatment of DPNP and the evidence for its efficacy in the

Table 2. Pharmacologic options for treatment of DPNP.

First-tier agents (≥ 2 RCTs)
Duloxetine (SNRI)
Pregabalin (α2-δ calcium channel modulator)
TCAs (antidepressants)
Second-tier agents (1 RCT + evidence of other painful neuropathies)
Gabapentin (α2-δ calcium channel modulator)
Venlafaxine (SNRI)
Oxycodone, morphine (opioids), tramadol (weak opioid)
Carbamazepine may be considered
Topical therapies
Capsaicin
Lidocaine 5% patch
Clonidine

Modified from Ziegler [28].
DPNP: Diabetic peripheral neuropathic pain; RCT: Randomized controlled trial;
SNRI: Serotonin-norepinephrine reuptake inhibitor;
TCA: Tricyclic antidepressant.

treatment of DPNP is limited from small studies [31]. Carbamazepine blocks peripheral sodium channels on nerve fibers. Although carbamazepine has good efficacy in the treatment of DPNP, it has not been evaluated in randomized trials for the treatment of painful diabetic neuropathy. However, the associated hematologic effects limit its use and patients require careful monitoring [32,33]. Lamotrigine, also a peripheral sodium channel blocker, is less efficacious than carbamazepine has been rarely associated with aplastic anemia and toxic epidermal necrolysis [34]. Topiramate works peripherally as a sodium channel blocker and at the GABA receptor. This drug has been demonstrated to reduce pain intensity and sleep disruption in patients with DPNP [35]. However, the adverse effects, such as cognitive slowing, dizziness and a small risk of kidney stones and closed-angle glaucoma limit the use of this agent even though it has the positive side effect of inducing weight loss. Valproic acid another antiepileptic at a dose of 500 – 1200 mg daily has been shown to be effective for reducing DPNP in two small placebo-controlled trials. However, due to its teratogenic effects it is not recommended in women of childbearing age [36].

Gabapentin is commonly used in the treatment of neuropathic pain and it mediates its effects peripherally to decrease pain perception [37]. The efficacy of gabapentin in the treatment of neuropathy has been evaluated in several studies. However, the findings have not been consistent [38]. At least two of the studies have showed statistically significant efficacy of gabapentin over placebo while one other study did not [39]. Gabapentin is reported to have few side effects, the most common being sedation and dizziness. Furthermore, it is cleared renally and not hepatically metabolized, thereby decreasing its interaction with other medications. The drug also has poor bioavailability and must be given three times a day and often in doses as high as 3600 mg a day for control of DPNP. Pregabalin has structural similarity to gabapentin but no known activity

at GABA or benzodiazepine receptors [40] and is discussed in detail below.

5.4 Duloxetine versus pregabalin

Of all the pharmacological agents used clinically to treat PDNP only two have been approved for use by the FDA: pregabalin and duloxetine. Duloxetine hydrochloride is a dual reuptake inhibitor of both 5-HT and NE (SNRI) transporters making it efficacious in the treatment of persistent neuropathic pain in humans. The efficacy of duloxetine has been evaluated in several studies and reduced pain by 8 – 13% compared to placebo [41-43]. Kajdasz *et al.* [44] in a *post-hoc* analysis evaluated the efficacy of duloxetine in which data were pooled from three controlled studies [41,42,45]. The average 24-h pain intensity reduction was reported to be 47.2% at 60 mg/day and 48.2% at 120 mg/day compared with placebo (27.9%) corresponding to a number needed to treat (NNT) of 5.2 and 4.9 at the two doses, respectively. The study by Goldstein *et al.* [45] was a randomized, double-blind, 12-week study in which duloxetine at both 60 and 120 mg/day demonstrated significant improvement in the 24-h pain score compared to placebo. The number of patients achieving a 50% reduction in the 24-h Average Pain Score was significantly greater in the duloxetine-treated groups (49% and 52% in the 60 mg/day and 120 mg/day, respectively) compared with placebo (26%, $p < 0.05$). Similarly Raskin *et al.* [41] also demonstrated in a multicenter, double-blind, randomized, placebo-controlled trial with 348 patients, duloxetine-treated groups to significantly improve 24-h pain score compared to placebo. They reported a 50%, 75% and 100% reduction in the 24-h average pain response rate that was achieved by 30%, 11% and 4% of patients, respectively, in the placebo group, 50%, 20% and 5% of patients, respectively, in the duloxetine 60 mg/day group, and 39%, 22% and 8% of patients, respectively, in the duloxetine 120 mg/day group. Wernicke *et al.* [42] in a double-blind study, in which the primary outcome measure was weekly mean score of 24-h average pain severity, demonstrated a 50% reduction in the pain response achieved by 27% of patients in the placebo-treated group, versus 43% and 53% in the duloxetine-treated groups at 60 mg/day and 60 mg twice a day, respectively ($p < 0.001$ versus placebo). Patients treated with duloxetine were reported to require significantly less supplemental analgesics and affected pain directly rather than indirectly through mood improvement. In general, duloxetine has been demonstrated to be well tolerated and safe in all studies with somnolence, nausea, dizziness, decreased appetite and constipation being the most common adverse effects reported. Furthermore, duloxetine does not affect glycemic control, lipid profiles or cause QT prolongation. Thus, duloxetine-treated patients with DM do not require any additional cardiovascular assessments than they do for their underlying diabetes.

The effect of pregabalin for treatment of DPNP has also been evaluated in several studies. Pregabalin mediates its analgesic effects by binding to the α2-δ subunit of calcium

channels in hyperexcitable afferent neurons. It has a sixfold higher affinity to the α2-δ subunit of calcium channels compared to gabapentin and decreases release of NE, glutamate and substance P, thus reducing transmission of pain signals to the brain [46]. In a pooled analysis of seven randomized clinical trials, pregabalin treatment at total daily doses of 150, 300 and 600 mg compared with placebo, resulted in a statistically significant reduction in the mean pain score, which was the primary end point of all studies [47-53]. Lesser et al. [54] demonstrated pregabalin to relieve pain in responders by 48% at 600 mg/day versus 18% for placebo. Freeman et al. [47] studied the efficacy, safety, tolerability of pregabalin in over 1,500 patients with DPNP over a period of 5 – 13 weeks. The response rates defined as ≥ 50% pain reduction were 47% at 600 mg/day, 39% at 300 mg/day and 27% at 150 mg/day compared to placebo (22%) corresponding to a NNT of 4.0, 5.9 and 19.0, respectively. The median time to onset of a 1-point improvement (on a 11-point Likert-like numeric rating scale) was 4 days, 5 days, and 13 days with pregabalin at 600 mg/day, 300 mg/day, and 150 mg/day, respectively, versus 60 days in patients receiving placebo.

Pregabalin is generally well tolerated and causes less sedation than gabapentin. Rare but serious adverse events, including rhabodmyolysis, acute renal failure, hyperthermia and secondary acute-angle glaucoma have been reported thus requiring patients on pregabalin therapy to be closely monitored for myopathy and ocular complaints. In addition, pregabalin also causes peripheral edema and weight gain with this effect being intensified when given concurrently with thiazolidinediones [55]. Pregabalin is typically initiated at 75 mg twice a day (total 150 mg/day) and the dose is slowly increased to 150 mg two times a day over a week or more. Like gabapentin, the dosage of pregabalin must be titrated based on the glomerular filtration rate (GFR) in patients with chronic kidney disease. Pregabalin is classified as a Schedule V drug in the USA but there was no evidence of diversion, abuse or addiction in the pregabalin clinical program safety database.

In a more recent study in treatment-resistant patients, duloxetine was shown to provide better analgesic effect in comparison to pregabalin [56]. This was a double-blind randomized parallel-group study to evaluate duloxetine (60 mg/daily) and pregabalin (300 mg/daily) as combination therapy in non-responders to monotherapy after initial treatment phase at standard doses of each drug. Patients not responding entered the intensive phase where the dose of monotherapy was doubled or the other drug was added at its full dose for an additional period of 7 weeks, followed by a 2-week tapering phase. The purpose of the intensive phase was to investigate whether combination or high-dose therapy was a better option for patients with incomplete pain relief. In the initial period, 52% of the patients in the duloxetine group had a reduction in the pain intensity by 30% compared to 36.9%. In the same study there was a 50% reduction in

pain intensity in 40% of duloxetine-treated patients versus 27.8% in the pregabalin group. Among the nonresponders, after 8 weeks of treatment (in the intensive period), there was no difference if the 2 drugs were combined at the standard doses or given in high doses in both groups.

Tanenberg et al. [57] showed that in patients with suboptimal response to gabapentin, addition of duloxetine was effective in reducing pain symptoms similar to that achieved with duloxetine or pregabalin alone. In this 12-week, randomized, multicenter, open-label noninferiority study, patients with inadequate response to gabapentin after 5 weeks of treatment were randomized to receive either duloxetine monotherapy, a combination of duloxetine plus gabapentin or pregabalin monotherapy. Antidepressant use was permitted at the discretion of the investigator to mimic a real-world clinical practice. Among patients not concomitantly being treated with an anti-depressant, who switched from gabapentin to either duloxetine or pregabalin, treatment with duloxetine was associated with greater pain relief than pregabalin. Thus switching to duloxetine rather than pregabalin may provide greater pain reduction in antidepressant non-users, beginning as early as 4 weeks after switching from gabapentin monotherapy. Pregabalin and gabapentin, both anticonvulsants, have similar proposed mechanisms of action; however, duloxetine, an antidepressant, works through a different mechanism of action compared with either pregabalin or gabapentin. Among antidepressant non-users, switching from gabapentin to duloxetine provided better pain relief while adding duloxetine to patients already taking an antidepressant from a different class did not provide a substantially improved pain response compared to pregabalin. In a recent study, Yarnitsky et al. [58] described a paradigm of conditioned pain modulation (CPM) in which two identical noxious test stimuli are delivered before and then simultaneously with, a noxious conditioning stimulus. Using this paradigm they demonstrated that neuropathic pain was efficaciously treated by duloxetine in patients with less efficient CPM. Thus based on a patient's pain modulation pattern and a specific drug's efficacy treatment of neuropathic pain can be individualized to meet a given patients need. As a result of reduction in pain, both pregabalin and duloxetine improve physical and social functioning, limitations due to physical and emotional problems, mental health, vitality and decreased sleep interference, with an overall improvement in quality of life.

A recent review by Spallone (2012) provides a critical evaluation of guidelines on the management of DPNP [59]. These guidelines put forth by experts from a number of professional organizations make evidence-based recommendations and provide a comprehensive approach to the treatment of neuropathic pain that has been established in multiple randomized clinical trials. Collectively, the guidelines recommend considering TCAs, SNRIs and α2-δ ligands as various treatment options for DPNP. Duloxetine is considered a first-line medication by all the recent guidelines with the exception of

those of American Academy of Neurology (AAN) that give this drug a second-line label [43]. The European Federation of Neurological Societies (EFNS) Task Force also recommends TCAs (25 – 150 mg/day), gabapentin (1200 – 3600 mg/day), pregabalin (150 – 600 mg/day) and SNRI (duloxetine 60 – 120 mg/day) as first line treatment in DPNP [60]. The recommendation of duloxetine as a first-line agent is based on its proven efficacy in the treatment of neuropathic pain and also due to its cost-effectiveness. Cost-utility studies of pregabalin versus duloxetine for treatment of DPNP using a decision tree model demonstrate duloxetine to be more cost-effective than pregabalin with an incremental cost of $187 [61].

5.5 Other agents

Other agents recommended for the treatment of DPNP include topical lidocaine alone or in combination with opioid analgesics or tramadol for patients with localized peripheral pain. Wolff *et al.* [62] recently reported in their review the evidence supporting the use of 5% lidocaine medicated plaster (LMP) for the relief of DPNP. Pain reduction with LMP was found to be comparable to those of amitriptyline, capsaicin, gabapentin and pregabalin. Tramadol, a weak opioid, acts through both monoaminergic (like the TCAs) and opioid receptors centrally to block pain perception. In a double-blind randomized trial Harati *et al.* [63] demonstrated pain intensity score to be 1.4 ± 0.1 in tramadol-treated group versus 2.2 ± 0.1 in the placebo group by day 42 ($p < 0.001$) with a average tramadol dose of 210 ± 113 mg/day. Tramadol is recommended only when the first-line therapeutic agents (alone or in combination) have failed to adequately control pain. In addition, tramadol has lower abuse potential than other opioids. However, tramadol has side effects that are common to opioids, such as constipation, urinary retention, and central nervous system effects. It should be avoided in patients with a history of opioid abuse. Opioids such as morphine (from 15 to 300 mg/day) and oxycodone (40 – 60 mg/day) are often used for treatment of DPNP [64,65]. However, their side effects and abuse potential limit their long-term use. In a recent study, rodents with streptozotocin-induced diabetes, silencing endogenous Rab7 restored μ-opioid responsiveness with improved pain relief [66]. Short-acting opioids are often combined with pregabalin in the treatment of DPNP due to coexisting musculoskeletal and neuropathic pain conditions [67]. In a recent study Yao *et al.* [68] demonstrated that sustained-release oxycodone was efficacious and safe in the treatment of moderate to severe DPNP.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used in the treatment of DPNP [69]. Since NSAIDS work best on nociceptive pain it is not surprising that they have limited efficacy in DPNP. Furthermore, great caution must be exercised when using NSAIDs in this population because this class may worsen underlying renal dysfunction. Topical agents such as capsaicin have also been used effectively with some relief of neuropathic pain. Capsaicin is a topically applied alkaloid that acts peripherally by depleting the neurotransmitter substance P from sensory nerves. It is not absorbed significantly into the systemic circulation. Stinging and burning are the most common adverse effects reported during application. It must be applied four times a day to the painful area and the pain with application decreases after the first week of use. Capsaicin is a reasonable alternative in patients with contraindications or intolerance to oral agents. In the capsaicin study group, 69.5% reported clinical improvement in pain status in comparison to the controls (53.4%, $p = 0.012$) [70,71]. In patients with chronic painful diabetic neuropathy unresponsive or intolerant to conventional therapy, topical capsaicin 0.075% was shown to be beneficial than controls. There was a decrease in mean pain intensity by 16% in capsaicin-treated subjects versus 4.1% in the controls [72]. However, in a more recent study 0.025% capsaicin gel was found to be safe and well tolerated but did not provide significant pain relief in patients with DPNP. The primary efficacy end-point in this study was percent change in visual analog scale score of 28.8 mm and 34.6 mm for capsaicin-treated versus placebo, respectively [73]. Martini *et al.* [74] recently reported a mathematical pharmacodynamic model to assess the magnitude and onset/offset times of effect of a single capsaicin 8% patch application in the treatment of DPNP in 91 patients. They reported a reduction in pain in two-thirds of the patients following a single 8% capsaicin patch with long-lasting pain relief. Topical clonidine gel has also been shown to reduce the intensity of pain in patients with DPNP. The study found clonidine to be safe and side effects were minimal. Clonidine application was found to be superior with a mean decrease of foot pain of 2.6 compared to 1.4 with placebo, respectively [75]. **Table 3** lists the treatment grades for the various agents derived from evidence-based information in published clinical trials. Clinicians should use these guidelines based on their strengths and evidence-based information with personal clinical judgment to make appropriate decisions for every individual patient. It is important to note that although all the agents reviewed decrease pain perception, none of them modify the disease course.

6. Conclusions

DPNP remains a significant problem affecting patients with DM affecting quality of life and activities of daily living. Unfortunately neuropathy and DPNP are under diagnosed and undertreated. Good communication between patient and provider is critical for both the diagnosis and therapeutic decisions. Discussion about efficacy, side effects and cost is needed about which medication to start. The patient must be informed of the expectations of a medication's effectiveness, the need for monitoring for adverse events and adherence to the medication plan to prevent relapse of symptoms. Both patients and providers should have realistic goals and expectations before initiation of therapy.

Table 3. Treatment grades of pharmacological agents used for DPNP: summary of evidence.

Class/drugs	Treatment grade for DPNP
Antidepressants	
SNRI (duloxetine)	2A
Tricyclic's (amitriptylline)	2B
venlafaxine	2B
Antiepileptics	
Pregabalin	2A
Gabapentin	2B
Valproic acid	2B
Lamotrigine	2C
Opioids (oxycodone, tramadol)	2C
Other agents	
Topical capsaicin	2B
Lidocaine patch	2B

Grade: 1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients; 2. Weak recommendation: Benefits and risks closely balanced and/or uncertain; A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form; B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form; C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws.
Modified from Bril *et al.* [43].

7. Expert opinion

In 2011, the International Diabetes Federation (IDF) estimated the worldwide prevalence of DM at 366 million persons and projects the disease to affect 552 million persons by 2030 [76]. In the USA today there are about 24 million cases of diabetes and approximately 1 out of 4 persons over age 65 has the disease [77]. In a recent community-based study in England, the overall prevalence of clinical DPN was 49%, while the prevalence of painful neuropathic symptoms was 34% [78]. Extrapolating this data one can estimate there are over 8 million persons in the US and over 100 million persons worldwide with symptomatic DPN.

A recent US survey of 112 persons with DPNP, noted average and worst pain scores (BPI-DPN, 0 – 10 scales) were 5.0 ± 2.5 and 5.6 ± 2.8. In this group, 46.7% received NSAIDs and 43% required opioids while only 27% were prescribed anticonvulsants and 18% SNRIs. The authors concluded that there is a 'substantial patient-level burden among subjects with painful DPN' [79]. The results of this survey suggest that most patients in the USA with DPNP are not receiving the FDA approved medications for DPNP: pregabalin and duloxetine. This prescribing discrepancy may reflect the higher cost of the newer drugs and/or a lack of knowledge about the current treatment of DPNP by primary care physicians. Of particular concern are: i) the large number of patients on NSAIDs which are generally not effective in DNPN and ii) the apparent overprescribing of addictive opioids. The report also noted poor sleep, loss of productivity and high healthcare resource utilization rates in these under-treated patients. Clearly more education of physicians and other providers on the treatment of DPNP is needed.

In a recent review article on current treatments for DPNP, three published consensus treatment algorithms were compared. The authors noted that 'all three algorithms recommend gabapentin, pregabalin, TCAs, venlafaxine, and duloxetine as first-line treatments' and the 'choice of agent is largely dependent on the comorbidities of the patient and side-effect profiles of the drugs' [21]. The drugs listed in this algorithm are supported by level A or B evidence. The algorithm we prefer (**Figure 1**) is from this article and is almost identical to an algorithm published by Tesfaye *et al.*, behalf of the Toronto Expert Panel on Diabetic Neuropathy which included eight of the world's leading experts on DPN [16].

For those physicians who utilize all the drugs in our armamentarium, it is difficult to select the best drug since the FDA approved drugs are relatively equivalent in efficacy in terms of pain relief with a few caveats. Subgroup analysis of a recent study noted that duloxetine was superior to pregabalin for those patients not taking an antidepressant and the drugs were of equal efficacy in those on antidepressants [57,80]. It should be noted that in the USA, the pregabalin dose for DPNP is limited to 300 mg/day by the FDA, but most countries allow up to 600 mg/day for this drug [60]. The duloxetine recommended dose for DPNP is 60 mg/day and studies did not show greater benefit for large doses. Nevertheless, US physicians frequently prescribe maximum doses of both drugs (600 mg pregabalin and 120 mg duloxetine) on an *off-label* basis. Many patients do not have an adequate respond to either of these two drugs and they are often prescribed a second or third drug despite the fact that there is a paucity of published studies on drug combinations for this condition. Additional research is necessary to develop new compounds and study the efficacy of drug combinations for DPNP. As of 2013, the side effect profile may be the most important factor determining the best drug for each patient.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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