Diabetic Peripheral Neuropathy: Current Concepts and Future Perspectives

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Abstract

Background: Peripheral Diabetic Neuropathy (PDN) is the clinical condition and one of the most common complications of diabetes affecting approximately 50% of people. Out of it, 16% to 33% of the patients manifest Neuropathic Pain (NP) associated with PDN. Neuropathic Pain in PDN arises due to nerve fiber injury both at the central and peripheral level and the pain is so severe that these patients have higher health care costs due to hospitalizations that are more frequent and thus, it affects their quality of life. Management of PDN includes both preventions of hyperglycemia and cardiovascular risk factors known to exacerbate neuropathy and the treatment of neuropathic pain. This review article focuses on current aspect and future perspective of epidemiology, basic understanding and recent advances of the mechanisms and therapeutics of PDN.

Methods: All relevant data, RCTs, meta-analysis, review article and case reports (1976-2014) with relevance to PDN were accessed and incorporated in this review article.

Results: In the results we describe here the treatment protocol of neuropathic pain including PDN according to (NeuPSIG) The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain guidelines, Canadian pain society (CNS), European Federation of Neurological Societies guidelines (EFNS), American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine guidelines (AANEM). NeuPSIG guidelines recommend the use of TCAs, duloxetine, Venlafaxine, gabapentin, pregabalin and topical lidocaine as first line therapy. Tramadol and opioids as a second line and certain antidepressant medications (eg., bupropion, citalopram and paroxetine), certain antiepileptic medications (eg., carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid), topical low-concentration capsaicin, dextromethorphan, memantine, and mexiletine as third line therapy. According to Canadian Pain Society, the analgesic agents for Neuropathic Pain including PDN are certain antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin) as a first line. Second-line treatments recommended are serotonin-noradrenaline reuptake inhibitors and topical lidocaine. Tramadol and controlled-release opioid analgesics are recommended as third-line treatments for moderate to severe pain. Fourth-line treatments include cannabinoids, methadone, and anticonvulsants (lamotrigine, topiramate and valproic acid), but this line of medications has lesser evidence of efficacy. EFNS

Guidelines recommended TCA, gabapentin, pregabalin and SNRI [selective serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine)] as first-line treatment in Painful Peripheral Neuropathy (PPN) particularly in PDN. Tramadol is recommended as second line except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or those with predominant coexisting non-neuropathic pain. Third-line therapy includes strong opioids. According to AAN, AANEM, and AAPM&R evidence-based guidelines for the treatment of painful diabetic neuropathy, they classified the therapy into recommended and non-recommended drugs where recommended drugs include pregabalin, gabapentin, valproate, Venlafaxine, duloxetine, amitriptyline, Dextromethorphan, morphine sulfate, tramadol, oxycodone, capsaicin, isosorbide dinitrate spray and electrical stimulation.

Conclusion: In conclusion, PDN, being the most important underlying causes for neuropathic pain, remains a challenging condition to manage. It requires increased level of awareness and special communication between patients and pain specialist to the extent that all decisions about which therapy to start with and when to switch over to the next option with an alternative mechanism of action are especially needed.

Introduction

Neuropathic pain is defined by International Association for Study of Pain (IASP) as pain arising as a direct consequence of lesion or disease of the system either somatosensory system either at peripheral or central level [1]. Diabetic neuropathy and Postherpetic neuralgia are major causes of neuropathic pain. It has been seen that neuropathy is a common complication of diabetes, affecting up to 50% of patients [2-6]. A consensus statement produced by an international meeting on the diagnosis and management of diabetic neuropathy defined it as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[7]. Although, there are many types of neuropathy with a variety of clinical presentations. This article focuses on one type of neuropathy, Peripheral Diabetic Neuropathy (PDN). In this review, we will focus on current aspect, future perspective, epidemiology, basic understanding and recent advances in mechanisms and management of diabetic neuropathy.

Epidemiology

Peripheral Diabetic Neuropathy (PDN), the most common complication of diabetes, is defined as a symmetrical, length-dependent distal sensorimotor polyneuropathy, a consequence of metabolic and microvascular alterations. PDN is the clinical condition [8] and approximately 50% patients will have pain as a symptom of neuropathy [9]. This pain is very severe and usually exacerbated by activity and relieved with rest and very different from musculoskeletal pain or vascular insufficiency. Because of the severity of pain, the quality of life of patients affected and increases health care cost [10,11].

The prevalence of DPN in the United States is approximately 50% of patients with type 1 and type 2 diabetes [2] and 16% to 33% of people with diabetes of >25years develop PDN [4], thus it is a common clinical problem. One study conducted in Finland found a prevalence of neuropathy up to 8.3% in newly diagnosed type 2 diabetes [12]. Discussing the pathophysiology, hyperglycemia is highly correlated with the development and progression of all neuropathies, including PDN [13,14]. The Diabetes Control and Complications Trial (DCCT) showed that tight glycemic control will reduce the incidence of neuropathy by 60 % [15] However, even in patients with long-term excellent glycemic control (A1C < 8%), the lifetime incidence of PDN remains 20% [16].

Other risk factors thought to be associated with diabetic neuropathy are hyperlipidemia, hypertension, cigarette smoking, consumption of alcohol, and weight. However, there has been no absolute evidence regarding the association of attributing these risk factors in reducing diabetic neuropathy or any other long-term complications. Although prevention of these risk factors may reduce an incidence of coronary artery disease, peripheral vascular disease, and stroke.

Pathophysiology

Neuropathic Pain is a complex, chronic pain state that usually is accompanied by tissue injury. It is common in clinical practice and presents a challenge to patients and clinicians alike. With neuropathic pain, the nerve fibers are damaged, may become dysfunctional or injured. Neuropathic Pain is the result of disease or injury to the peripheral or central nervous system (spinal or supraspinal nervous system) and the lesion may occur at any point. These damaged nerve fibers include a change in nerve function- both at the site of the injury and areas around the injury [17] and they send incorrect signals to other pain centers. The impact of a nerve fiber injury includes a change in nerve function—both at the site of the injury and areas around the injury [17]. Clinical manifestations of Neuropathic Pain typically include positive sensory phenomena such as spontaneous pain, paraesthesias, allodynia, and hyperalgesia [18]. Features that differentiate Neuropathic Pain from other types of pain include pain and sensory symptoms lasting beyond the healing period.

The theories regarding the pathophysiology of Neuropathic Pain are multiple. Before going into details, a short review regarding pain circuit is needed. There are two types of pain circuits: facilitatory and inhibitory circuits' facilitatory circuit responsible for pain sensation, and is particularly mediated by glutamate (excitatory neurotransmitter) mediated receptors. The inhibitory circuits cause pain suppression mainly mediated by GABA (gamma amino butyric acid), which is an inhibitory neurotransmitter. The mechanism underlying neuropathic pain, however, is not as clear. Several animal studies have shown that many mechanisms may be involved. First order neurons may increase their firing if they are partially damaged due to increase in the number of sodium channels and thus enhanced depolarization leads to spontaneous pain and movement-related pain. Impairment of Inhibitory circuits at the level of the dorsal horn or brain stem allows uninhibited transmission of pain impulses. In addition, there are several changes in the central processing of pain where there is increased the sensitivity of spinal neurons and decrease in activation thresholds resulting in central sensitization phenomenon operating in patients of diabetic neuropathy. Raja, et al. [19] in an interesting study described that blockade of α -adrenergic receptor function with intravenous infusion of the antagonist phentolamine also leads to pain relief. Thus, there also can be the affiliation of the sympathetic nervous system towards neuropathic pain.

The exact mechanism of nerve damage in diabetic neuropathy is still unclear, metabolic and vascular/hypoxic factors appear to be involved [20]. Advance Glycosylation End Products (AGEP) may damage capillaries; inhibit axonal transport leading to axonal degeneration. Increase production of sorbitol due to activation of polyol pathway causes structural nerve damage. Also, increased endoneurial vascular resistance to hyperglycemic blood can lead to nerve ischemia.

Classification

In the present review article, our emphasis is primarily on painful diabetic neuropathy, which is a polyneuropathy, and here we will classify based on the above only. There are two types of PDN (a) acute sensory neuropathy and (b) chronic sensorimotor neuropathy. Acute sensory neuropathy is usually associated with hyperglycemia and resolves with normal glucose levels. It is without associated signs. Chronic sensorimotor neuropathy causes long-term pain. In next Para, we have described the chronic distal sensory and sensorimotor polyneuropathy.

Symptoms and Signs of Distal Sensory and Sensorimotor polyneuropathy

Thomas, et al has described the commonest variety of neuropathy in diabetic patients, distal sensory neuropathy where insidious onset is common [22]. Initially small and large fibers may be affected in varying degrees, but later typically, both are affected. This is a length-dependent process, and a distal part of the longest nerves affected earliest. Thus, the earliest symptoms typically involve the toes and then ascend. The arms are involved later, less often and less severely, also in a distal-to-proximal pattern. Early arm involvement warrants consideration of entrapment neuropathies. If severe, the midline abdomen and the head may be involved. The most common symptoms are numbness, tingling, and pain. Commonly patients present

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Table 1: Classification of Diabetic Neuropathy.
Symmetric polyneuropathies
Chronic sensory or sensorimotor
Acute or chronic selective small-fiber painful
Autonomic
Symmetric, lower limb, motor
Focal and multifocal neuropathies
Cranial nerves
Asymm trunk/ limb, single/multiple nerves
CIDP
Mixed forms
Florian P Thomas, the spectrum of neuropathy, Associate Professor of Neurology, Molecular Virology, and Molecular Microbiology and Immunology Saint Louis VA Medical Center, Saint Louis University School of Medicine Saint Louis, MO 63110 ThomasFP@slu.edu) [24].

Table 2: AAN, AANEM, and AAPM&R evidence-based guidelines for the treatment of painful diabetic neuropathy (Bril, et al. [99]).		
Level	**Recommended**	**Not Recommended**
A	Pregabalin 300–600 mg/ day	Oxcarbazepine
B	Gabapentin (900–3600 mg/ day)	Lamotrigine
	Valproate 500–1200 mg/ day	Lacosamide
	Venlafaxine 75–225 mg/ day	Clonidine
	Duloxetine 60–120 mg/ day	Pentoxifylline
	Amitriptyline 25–100 mg/ day	Mexiletine
	Dextromethorphan 400 mg/ day	Magnetic field Stimulation
	Morphine sulphate titrated to 120 mg/ da	Low-intensity laser treatment
	Tramadol 210 mg/ day	Reiki therapy
	Oxycodone, mean 37 mg/ day, maximum 120 mg/ day	-
	Capsaicin, 0.075% QID	-
	Isosorbide dinitrate spray	-
	Electrical stimulation percutaneous nerve stimulation × 3–4 weeks	-
AAN: American Academy of Neurology; AANEM: American Association of Neuromuscular and Electrodiagnostic Medicine; AAPMR: American Academy of Physical Medicine and Rehabilitation		

Table 3: Rehabilitation techniques used in Neuropathic Pain and their indications [125].	
Cognitive behavioral therapy	Elderly patients with neuropathic pain
Relaxation Techniques	Chronic Pain
Acupuncture	Spinal Cord Injury
Mirror Therapy	Phantom Pain Complex Regional Pain Syndrome (CRPS) Stroke
Graded Motor Imagery	Stroke
Visual Illusion	Spinal Cord Injury

with foot pain, which can be deep, aching, stabbing tingling, burning, "like water running over the skin, or electric shock-like, or increase the sensitivity of pain even on light touching (allodynia-like). The pain get worse at night and disturb sleep and sometimes it is associated with numbness, and patients may describe this sensation like "wearing gloves or socks". Gait ataxia may be reported with increased number of falls. Distal weakness is less common and occurs in later stages. Examination generally demonstrates distal generalized sensory loss, with reduced or absent ankle jerks with the loss of pinprick sensation [23].

Diagnosis

The diagnosis of PDN is based on symptoms and physical examination, including blood pressure recording, heart rate, muscle strength, reflexes and sensitivity to position changes, vibration, temperature, or light touch, and foot examination. If

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the patient seems to be positive for peripheral neuropathy, then there is the need for more frequent foot examination where nylon monofilament similar to a hairbrush or von frey hairs is used to assess protective sensation (mechanical nociceptive threshold test). Temperature perception and sense of vibration also need to be assessed. Other tests that can be used to assess the extent of nerve damage include nerve conduction studies or electromyography and sural nerve biopsy.

Nerve conduction velocity/ Electromyography

Since diabetic neuropathy is usually both axonal and demyelinating [25], it leads to chronic neuropathy, and here lower limbs are affected foremost. Thus, Nerve Conduction Velocity (NCV) is highly sensitive to detect a sensory abnormality, which demonstrates conduction slowing and decrease in amplitude. However, sensory responses disappear in more severe cases. Motor NCS may demonstrate slowing and decrease in amplitude in advance cases, even in the absence of neuropathic signs and symptoms.

EMG may be normal in mild or asymptomatic subjects, but demonstrates denervation in more severe cases and worse distally [22,26].

A sural nerve biopsy finding shows loss of myelinated and unmyelinated axons. Demyelination is also seen by fiber teasing and reduplication of the basal lamina [20] leading to the thickness of walls of small neural blood vessels, particularly endoneurial capillaries.

However, other etiologies of painful peripheral neuropathy should also be ruled out. Patients with diabetic neuropathy are also at risk of other types of neuropathy including B12 deficiency, chronic inflammatory demyelinating neuropathy, hypothyroidism, RLS ("Restless leg syndrome"), PLMS ("Periodic limb movement in sleep") and uremia and thus need to be evaluated for the above, including thyroid function tests, ANA (antinuclear antibody), rheumatoid factor, ESR, immunofixation electrophoresis, CBC and iron studies. However, recent reports suggest some of these patients have impaired glucose tolerance [27]. In addition, HIV, HCV also to be ruled out if suspected.

Management

Prevention: It includes strict optimization of blood sugar levels, cessation of smoking, reduction in alcohol intake, control of hyperlipidemia and hypertension. It has been seen that daily intake of aspirin, graded motor imagery [28-30], antioxidant and herbal therapy also have a role in the prevention of PDN.

Treatment: Diverse pharmacological treatments of NP have become available, and interpreting the data on their efficacy and safety involves substantial complexities and ambiguities. Here we will describe the NEUPSIG (The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain) pharmacological guidelines [31], for the management of Neuropathic Pain including painful diabetic neuropathy. According to Dworkin RH, et al. [31] Tricyclic antidepressants, dual reuptake inhibitors of serotonin and norepinephrine, calcium channel α2- δ2 ligands (i.e., gabapentin and pregabalin),

and topical lidocaine were recommended as first-line treatment options on the basis of the results of randomized clinical trials. On the other hand, Opioids and tramadol were recommended as second-line treatments and in exceptional cases, it can be considered for first-line use. Third line medications include certain antidepressant medications (e.g., bupropion, citalopram, and paroxetine), certain antiepileptic medications (eg., carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid).

Several recent clinical trials have examined the role of botulinum toxin, [30,31] 8% concentration capsaicin patch [32,33], lacosamide [34-38], selective serotonin reuptake inhibitors [39-42], and combination therapies [43-46] in various Neuropathic Pain conditions.

These consensus guidelines are not applicable on pediatric patients, patients with trigeminal neuralgia (for which separate treatment recommendations are available, [47-50] or conditions that are not clearly NP (e.g., fibromyalgia and irritable bowel syndrome). The guidelines Emphasize on combination therapy because single drug therapy may not provide adequate pain relief to the patients of neuropathic pain.

First Line Therapy

Antidepressants with both norepinephrine and serotonin Reuptake Inhibitors

A large number of placebo-controlled RCTs have found tricyclic antidepressants (TCAs) to be efficacious for several different types of NP [51]. TCAs were introduced in the late 1950s and it is the most studied class of a drugs in the treatment of PDN. This group of drug also treats depression, common comorbidity in patients with chronic pain, but their analgesic efficacy has also been studied. Amitriptyline was the first TCA to be studied in 1977 [52]. It was a serotonin and noradrenaline reuptake inhibitors, it also blocks alpha

Adrenergic, H1- histamine, muscarinic cholinergic, and N-methyl-D-aspartate receptors [53]. Amitriptyline has been a first-line treatment for Neuropathic Pain for many years. Other TCAs include Imipramine which is also a serotonin and noradrenaline reuptake inhibitor and it block a- adrenergic, H1-histamine, muscarinic cholinergic, and N-Methyl-D-aspartate receptors [52]. Imipramine has been studied in six placebo-controlled trials [54–57] and efficacy has not been proven.

TCAs act centrally to reduce the perception of pain. TCAs generally have the lowest NNT (number 1needed to treat) of the medications used to treat PDN. On the basis of trials conducted to evaluate the efficacy of TCAs in patients of PDN, ~30% of patients obtain 50% pain relief. They are also inexpensive and convenient to give due to single daily dosing. However, anticholinergic adverse effects are common and include dry mouth, orthostatic hypotension, constipation, and urinary retention. Low doses initially, titrated dosing or using a secondary amine TCA (Nortriptyline and desipramine are a metabolite of amitriptyline.) reduces these adverse effects. Cardiac toxicity is a concern with TCAs thus according to NeuPSIG guidelines it is

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recommended to prescribe TCAs with caution in patients with an ischemic cardiac disease or ventricular conduction abnormalities, limiting the dosages to less than 100 mg/d and when possible, electrocardiogram to be done for patients older than 40 years. It takes about 6 to 8 weeks of the timeperiod for an adequate pain relief with TCA.

Duloxetine and venlafaxine

These are selective serotonin-norepinephrine reuptake inhibitors (SSNRIs that have been studied in peripheral NP (a third SSNRI, milnacipran, has been studied only in fibromyalgia). Duloxetine has shown consistent efficacy in painful DPN [58] with 1-year effectiveness in an open-label trial [59]. In a recent Post Hoc Analysis by Tanenberg, et al. [60] it was concluded that in patients with DPN inadequately treated with gabapentin without the concomitant use of antidepressants, switching to duloxetine instead of pregabalin might provide better pain reduction. Teninberg, et al. [60] also emphasize that in nonrespondents to gabapentin who were concomitantly using Antidepressants, switching to duloxetine and Pregabalin may provide similar pain reduction. Duloxetine has not been studied in other types of neuropathies, thus, its efficacy is not known. Duloxetine has been effective in treating depression, and anxiety disorder with 60mg of daily dosing. The most common adverse effect of duloxetine is nausea, which seems to be reduced by administering 30 mg once daily for 1 week before increasing it to 60 mg once daily. Duloxetine has no effect on ECG and blood pressure [61] and a recent review concluded that aminotransferase monitoring is unnecessary [62]. Duloxetine along with pregabalin are approved by USFDA for the treatment of PDN [60].

Venlafaxine has shown efficacy in painful DPN and painful polyneuropathies of all origins [58]. It requires 2 to 4 weeks to titrate effective dosage (i.e., 150-225 mg/d). It is available in short- and long-acting preparations. Cardiac conduction abnormalities have been reported with this drug in a small number of patients [63] and it can increase blood pressure, therefore, venlafaxine should be prescribed with caution in patients with cardiac disease. In addition, Venlafaxine should not be abruptly stopped but need to be tapered because of the risk of withdrawal syndrome [64].

Calcium channel α2 - δ2 ligands (Gabapentin and Pregabalin)

Gabapentin and pregabalin each bind to voltage-gated calcium channels at the δ2-δ2 subunit and inhibit neurotransmitter release. Several clinical trials have proven its efficacy in NP as compared to placebo [58,50]. However there is no specific clinical trial has been done in patients of PDN. Gabapentin and pregabalin have few drug interactions, but both can produce dose-dependent dizziness and sedation, which can be reduced by starting with lower dosages and titrating cautiously. Dosage reduction is required in patients with renal insufficiency and dosage calculation is done using creatinine clearance for both medications. Gabapentin pharmacokinetics is nonlinear (due to saturable absorption), and thus dosing requires careful titration. Treatment should be initiated at low dosages with gradual

increases until pain relief, or 3600 mg/d in 3 divided doses is reached. An adequate trial of treatment with gabapentin can require 2 months or more for effective trial. Gabapentin has similar efficacy to Pregabalin. However, pregabalin has linear pharmacokinetics, and dosing is simpler. The drug is given at 150 mg/d in 2 or3 divided doses, which is then titrated up to 300 mg/d after 1 or 2 weeks.

For patients who tolerate 300 mg/d, but pain relief is not adequate, the dosage can be further titrated to 600 mg/d. These higher dosages are not effective and are associated with greater adverse effects. Pregabalin may provide analgesia more quickly than gabapentin because the initial dosage of 150 mg/d has been found to be efficacious in some trials and the total time required to titrate to a full dosage is less [65]. This drug has fewer adverse effects including rhabdomyolysis, acute renal failure, central nervous system effects, hyperthermia, and secondary angle glaucoma and it should not be ignored. Thus, patients on pregabalin need to be carefully monitored for myopathy. It is advised to avoid this drug in patients with hypertension and congestive heart failure. In the United States, pregabalin is a Schedule V drug.

Topical Lidocaine

The 5% lidocaine patch has been proven to be very effective and have excellent tolerability in RCTs involving patients with different types of peripheral NP [58,50]. However, individual role in DPN has not yet been studied. As a topical treatment without any significant systemic absorption, the local reactions are more common as compared to systemic side effects and decreased drug interactions attribute to safer choice in older patients or patients with complex NP (Table 2). Lidocaine gel (5%), which is less expensive than the lidocaine patch, has also shown efficacy in allodynia [58,50]. Topical lidocaine is most appropriate in well-localized NP, and it is unlikely to be effective in patients with central NP, thus attempts to predict the category of patients likely to be benefited from lidocaine are still unsuccessful [66,67].

Second Line Therapy

In Certain circumstances tramadol and opioid analgesics have shown efficacy in several high-quality RCTs involving patients with different types of NP, but there is no RCTs has been done in patients of PDN. With this class of drugs, long-term safety and efficacy are the matter of concern in relation to the first-line medications. The NeuPSIG guidelines recommend that tramadol and opioids should typically be reserved for patients who have not responded to first-line medications. However, in acute NP, NP due to cancer, episodic exacerbations of severe NP these medications are recommended as first-line treatments, as well as when titrating one of the first line medications to provide prompt pain relief.

Tramadol

Tramadol, which has shown efficacy in several NP conditions, but no RCTs, has studied its efficacy in patients of DPN. It is a weak opioid μ-receptor agonist that also inhibits reuptake of serotonin and norepinephrine. Like strong opioid analgesics, it provides

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relatively rapid pain relief, although it may be somewhat less efficacious than strong μ-agonists (e.g., morphine and oxycodone) [50]. The risk of abuse with tramadol seems considerably less than that with opioid analgesics [58] but the adverse effect of tramadol is similar to that of opioids. However, tramadol also lowers the seizure threshold and has some interactions with certain medications e.g., SSNRIs and Selective Serotonin Reuptake Inhibitors (SSRIs) leading to serotonin syndrome, a potentially fatal reaction. Although the risk of serotonin syndrome is quite rare but should be the matter of concern. Dosing of tramadol is typically started with 50 mg once or twice daily and then increased gradually as needed to a maximum of 400 mg/ d; older patients and those with renal or hepatic dysfunction should be maintained with lower dosages as they are more prone to drug accumulation.

Opioids

Several RCTs [58,68] has shown that opioid analgesics provide greater pain relief than placebo in different types of NP as found with TCA and gabapentin [69]. However, one study [70] studied the efficacy of morphine and had shown a small effect in reduction of neuropathic pain. RCTs to see the role of opioids in patients of DPN has not been done. Concerns including risks of hypogonadism, immunologic changes, and opioid misuse or abuse, and long-term safety, opioids are not recommended for routine first-line use and should generally be reserved for patients who do not respond to the first-line medications. Constipation, nausea, and sedation are the most common side effects of opioids. Thus initiating treatment with low dosages and titrating gradually can reduce nausea and sedation. Long term opioids therapy causes physical dependence thus its dosages need to be tapered in patients on long-term therapy of opioids and also instruct patients not to stop it abruptly. The opioid-prescribing guidelines recommend the use of lowest effective dosage and monitoring for signs of inappropriate use [71-73]. Use of extended-release formulations is recommended for opioids and has been shown to be efficacious in NP trials.

Third-line Medications

Several additional medications have shown efficacy for the treatment of NP in either a single RCT or inconsistently across multiple RCTs. The NeuPSIG guidelines recommend that these medications should generally be reserved for patients who cannot tolerate or who do not respond adequately to first- and second-line medications. These medications include certain antidepressant medications (eg., bupropion, citalopram, and paroxetine), certain antiepileptic medications (eg., carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid), topical low-concentration capsaicin, dextromethorphan, memantine, and mexiletine [58].

Lamotrigine

Its efficacy in PDN has been studied in two trials, one open-label [74] and one parallel placebo controlled [75] and it is less effective and has side effects.

Sodium valproate

Two studies evaluated its efficacy [76,77] and the drug was found to be efficacious in PDN and associated with lesser side effects.

Topiramate

One class II study [78] evaluated its efficacy in patients of PDN and reported small effect compared to placebo and an NNT of 6.6% for >30% pain reduction. It acts peripherally as a sodium channel blocker and at the GABA receptor and has several side effects such as cognitive slowing, dizziness, and risk of kidney stones. In one study group of patients' topiramate was discontinued due to side effects.

Mexiletine

It is an oral analog of lidocaine and is a class IB antiarrhythmic agent and it acts peripherally as an ion channel blocker to suppress pain. It has been evaluated in five studies [79-83] in patients of PDN and found to be effective in relieving pain. It has a faster onset of action but associated with side effects such as toxic epidermal agranulocytosis and hepatotoxicity. It is contraindicated in patients with second and third degree AV block. Patients on mexiletine therapy should be monitored for CBC, platelet count, ECG and liver enzymes tests.

Carbamazepine

Carbamazepine drug typically reserved and indicated in the management of trigeminal neuralgia. It acts by blocking the sodium channels on the A-delta nerve fibers and has a good efficacy but associated with several side effects including aplastic anemia. In one study Chakrabarti AK, et al [84] studied its efficacy in patients of PDN and was not found to be effective in relieving pain. Gomez-Perez FJ, et al. [85] evaluated the efficacy of carbamazepine in PDN and results were found to be negative. Recently Grosskopf, et al, done a placebo-controlled trial and evaluated efficacy of oxcarbazepine [86] (having a benign side effect profile), in patients of PDN and it was not found to be efficacious. In another trial, Dogra et al also showed similar results in patients of PDN [87]. However, Beydoun et al showed 50% pain reduction in patients of PDN compared with placebo [88].

Central NP

Relatively few RCTs have been conducted in patients with NP caused by lesions in the central nervous system. No study has been conducted as regards to the efficacy of cannabinoids in PDN. In some trials, cannabinoids appear to be efficacious in multiple sclerosis associated NP, but the use of cannabinoids is limited due to poor availability and risks of abuse leading to psychosis, especially in high-risk individuals [58,89,90]. Patients with central NP who do not respond adequately to these medications can be treated with the first and second-line medications that have established efficacy in peripheral NP.

Miscellaneous Drugs

In this section, we briefly discuss several recent RCTs for a

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certain miscellaneous group of drugs that should be considered in future efforts for the treatment guidelines. These studies have been selected because they involve novel treatments.

Botulinum toxin: Efficacy of botulinum toxin in the treatment of cervical dystonia and various types of spasticity is well established, but its role in PDN has been suggested by Finnerup NB, et al. [51] On the basis of this research and observations, a double-blind trial was conducted in which 29 patients with PHN or posttraumatic or postoperative NP and mechanical allodynia. They were randomized to intradermal injection of botulinum toxin type A or matching placebo within the area of allodynia [91]. Pain intensity decreased during 24 weeks' time period and brush-evoked allodynia were significantly reduced at 4 and 12 weeks after treatment in patients who received botulinum toxin vs. placebo.

8% Concentration capsaicin patch: It is an alkaloid derived from chilies. It has the peripheral action by decreasing the neurotransmitter substance P from sensory nerves. It is applied topically and is not absorbed in the systemic circulation. Topical low-concentration capsaicin is currently considered as a third-line treatment of NP. But the role of capsaicin patch has not been established in patients of PDN. A high-concentration capsaicin patch has been studied in multiple RCTs in patients with PHN and painful HIV neuropathy [92] and results of 2 phase 3 trials in PHN showed that a single application of the high-concentration patch vs a low-concentration control patch was efficacious in reducing pain from the second week after the capsaicin application throughout a subsequent 8-week period [32,33].

The high-concentration capsaicin patch help in reducing the dosage of existing pharmacological agents, if applied to the patients of neuropathic pain. Its single application provides pain relief for 2-3 months .and thus reducing the dose requirement of other pharmacological agents. However, the long-term benefits and safety of repeated applications of this treatment are unknown, because skin biopsy studies have shown transient epidermal denervation by Capsaicin [93] and failure of heat sensation [94].

Lacosamide: Lacosamide is a new antiepileptic medication that has activity at voltage-gated sodium channels. In addition to epilepsy, lacosamide has been studied extensively in painful DPN. Rauck RL, et al. [34] in single phase 2 trial evaluated the efficacy of lacosamide in PDN and it has been proven to be effective. Shaibani A, et al. [35] in a parallel group phase 3 trial, found evidence of lacosamide in relieving pain in patients of PDN. Wymer, et al [36] also found similar results in PDN. Also, in an RCT evidence of efficacy of lacosamide in PDN was seen [37]. Later on in a trial by Hidvegi T, et al. [38] concluded the statistical significance of the result in patients of PDN was marginal *(P =.0507),* Despite its approval for adjunctive treatment of partial onset seizures, lacosamide was not approved for the treatment of painful DPN by either the food and drug administration or the european medicines agency. It will be difficult to define recommendations for lacosamide for the treatment of NP. In the United States, lacosamide is a Schedule V drug.

Selective serotonin re-uptake inhibitors

As previously mentioned, SSRIs have been considered third-line medications for patients with NP including PDN. This is because the evidence of the analgesic efficacy of this class of antidepressants in patients of PDN has been inconsistent. In one older study by Sindrup SH, et al. [39] showed evidence of moderate effect of paroxetine in PDN**.** In another trial, Paroxetine was not found to be effective in patients of PDN [40] In a trial by Sindrup SH, et al. [40] evaluated the efficacy of citalopram [95] in PDN and showed a moderate effect. No efficacy for fluoxetine [41] compared with placebo in several clinical trials was seen in this group of patients.

A recent crossover RCT showed escitalopram benefited patients with PDN, compared with placebo, a benefit that appeared to be independent of antidepressant effects. However, the authors concluded that escitalopram "appears to have a clinically relevant effect in only a few patients and … can probably not be recommended as first or second line treatment in neuropathic pain" p281 [42]. In recent years after their introduction, SSRIs began to replace TCAs in psychiatry as first-line medications for the treatment of depression, due to safety against overdose, with lesser side effects and lack of need of titration. Hence, careful re-evaluation is needed for the role and efficacy of SSRIs in the patients of NP.

Doxepin: Doxepin, which is similar in function to amitriptyline and imipramine, has not been evaluated in the treatment of PDN.

Clonidine: Its efficacy has been evaluated in some studies and has shown no benefit in relieving pain in PDN.

NSAIDs: NSAIDs have also been used in PDN; however, it has been associated with renal dysfunction and hence should be used with caution.

Carisbamate: Recently Smith T, et al. [96] evaluated the efficacy of this newly developed therapeutic agent in patients of PDN and post-herpetic neuralgia. 3 RCTs were done, I and 2 RCTs were placebo controlled and evaluated efficacy over 4 weeks' period. Third RCTs evaluated the efficacy in these patients over a period of 15 weeks. Carisbamate was given in a dosage of 400mg/ day in 1 and 2 trials and 800mg/ day, 1200 mg/day given in 3 RCT. This drug however, is well tolerated but did not demonstrate efficacy in Neuropathic Pain across these studies.

Combination Therapies

Most of the studies have demonstrated the effects of individual medications in specific conditions. However, as indicated earlier, no medication is universally effective. Hence, in clinical practice 2 or more medications are often used in combination to possibly achieve either an additive beneficial effect or a reduction in the adverse effects associated with the use of single medications particularly if they act at different sites in pain signaling pathways or modulate different neurotransmitter systems. In one of the first RCTs of combination therapy for NP, the combination of gabapentin and extended-release morphine combination required lower dosages of both medications and

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resulted in better pain relief as compared to single medication when administered to the patients [97]. In another RCT by Hanna M, et al. [43] concluded consistent results when given the combination of extended release oxycodone or matching placebo in the combination with existing gabapentin treatment in patients of PDN.

Recent RCTs have examined the combination of nortriptyline and gabapentin [44] and was found to be superior to either of these 2 medications administered alone in patients of DPN. Baron R, et al. [45] studied the combinations of pregabalin and topical 5% lidocaine and results showed efficacy in patients of PDN. Sodium valproate and glyceryl trinitrate spray combination has been studied in one study [46] and have shown that combination therapies may have a role in the treatment of NP but the relevant data in support of it in patients of PDN has not been studied till now.

Keeping in view of all above RCTs on combination therapy, additional studies are needed to develop guidelines on it and benefit of polypharmacy.

Adding to the management guidelines of neuropathic pain, according to Canadian pain society guidelines [47] on pharmacological management of chronic Neuropathic Pain including PDN, Moulin DE et al recommended analgesic agents for first-line treatments are certain antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin). Second-line treatments, recommended are serotonin noradrenaline reuptake inhibitors and topical lidocaine. Tramadol and controlled-release opioid analgesics are recommended as third-line treatments for moderate to severe pain. Fourth-line treatments include cannabinoids, methadone and anticonvulsants (lamotrigine, topiramate and valproic acid), but this line of medications has lesser evidence of efficacy. Treatment must be individualized for each patient based on efficacy, side-effects and drug availability and cost. Further studies are suggested to compare the efficacy of individual medications, combinations of medications and long-term outcomes.

According to EFNS guidelines on the pharmacological treatment of Neuropathic Pain including Painful Diabetic Neuropathy: 2010 revision [98]. Attal, et al. [98] recommended TCA, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) as first-line treatment in NP particularly in PDN. Tramadol is recommended as the second line except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or those with predominant coexisting non-neuropathic pain. Third-line therapy includes strong opioids however its long-term safety and efficacy is a topic of concern.

According to AAN, AANEM guidelines, the management of Neuropathic Pain including PDN is tabulated below [99].

American Academy of Neurology (AAN); American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM); American Academy of Physical Medicine and Rehabilitation (AAPMR).

Non-Pharmacological Management

Laser therapy

The laser is another physical therapy agent that can be used in the treatment of neuropathic pain. However, its efficacy is still not being studied in patients of PDN. Very low level of laser has been shown effective in patients with neuropathic pain [100]. It decreases pain and inflammation, in addition to improving functional ability. In rats, it has been studied that it decreases the level of (HIF 1-a) hypoxia-induced factor, which is a modulator in inflammation and released after chronic constrictive nerve injury [101]. However, other studies of the effectiveness of laser therapy in neuropathic pain are also done in rats [102,103]. But, there is not enough evidence to suggest that it is effective in neuropathic pain in diabetic patients.

Interventional pain management

Sympathetic blocks (lumbar sympathetic blocks and thoracic paravertebral blocks)

The sympathetic nervous system has been implicated in pain associated with painful diabetic neuropathy. But, therapeutic intervention targeted at the sympathetic nervous system has not been established. In a case report Jianguo, et al. [104] tested the hypothesis that sympathetic nerve blocks significantly reduce pain in a patient with painful diabetic neuropathy who has failed multiple pharmacological treatments. The diagnosis of small fiber sensory neuropathy was based on clinical presentations and confirmed by skin biopsies. A series of 9 lumbar sympathetic blocks over a 26-month period provided sustained pain relief in his legs. Additional thoracic paravertebral blocks were given to control pain in the trunk which is occasionally be seen in severe diabetic neuropathy cases due to extensive involvement of the intercostal nerves. These blocks provided sustained and significant pain relief and improvement in the quality of life. They thus provided the first clinical evidence of the significant role of sympathetic nervous system in painful diabetic neuropathy and sympathetic blocks can be an effective management modality of painful diabetic neuropathy.

Spinal Cord Stimulation (SCS)

It is an invasive treatment for chronic pain based on electrical stimulation of the dorsal columns of the spinal cord. Mechanisms being not known, believed to involve spinal and supraspinal effects. It is a proven effective therapy for various types of mixed neuropathic conditions but the effectiveness of SCS treatment for PDN is not well established. However, recently Slangen, et al. [105] suggested that Spinal Cord Stimulation (SCS) may have positive effects in resolving neuropathic pain in DPN. There was also one randomized control trial by De Vos, et al. [106], which investigated the effectiveness of SCS in patients with PDN. Sixty patients with PDN in the lower extremities refractory to conventional medical therapy were taken and followed for 6 months. They were randomized 2:1 to best conventional medical practice with (SCS group) or without (control group), and both groups were assessed at regular intervals. At each follow-up visit, the EuroQoL 5D, the Short Form Mcgill Pain Questionnaire

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(SF-MPQ) and a Visual Analogue Scale (VAS, ranging 0–100) were used to measure pain intensity. The results have showed the patients in the SCS group unlike those in the control group, experienced reduced pain and improved health and quality of life after 6 months of treatment. In patients with refractory painful diabetic neuropathy spinal cord stimulation therapy is quite effective and significantly reduced pain and improved quality of life.

Electrical stimulation

Pulsed-dose electrical stimulation is evaluated as an analgesic modality in patients with painful diabetic neuropathy. Using a knitted silver-plated nylon/Dacron stocking electrode, patients were given electrical stimulation over the period of 1 month and using a 10 cm visual analog scale, the pain was measured. Pain measurements were found to be significantly reduced at the end of the 4-week therapy and at 1 month after complete discontinuation of therapy than at the initiation of therapy. The results of this study show that nocturnal doses of pulsed-electrical stimulation may be effective in reducing subjective, burning, diabetic Neuropathic Pain in a group of patients with grossly intact protective sensation and relatively good distal vascular perfusion. To the authors' knowledge, this is the first analytic report of pulsed-dose electrical nerve stimulation delivered through a stocking electrode for treatment of symptomatic diabetic neuropathy in the medical literature [107].

Neurostimulation techniques (never been explored in cases of PDN)

Transcranial Magnetic Stimulation (TMS) and Cortical Electrical Stimulation (CES), Spinal Cord Stimulation (SCS) and Deep Brain Stimulation (DBS) have also been found to be effective in the treatment of neuropathic pain, but the role in PDN is still not been established. Lefaucheur, et al. [107,108] investigated 60 patients with chronic unilateral Neuropathic Pain caused by one of the following lesions: thalamic stroke, brainstem stroke, spinal cord lesion, brachial plexus lesion, or trigeminal nerve lesion. Transcranial magnetic stimulation was applied 3 weeks apart in two sessions, with a frequency of 10 Hz. The pain level of patients was assessed with Visual Analog Scale (VAS). Thirty-nine patients reported a decrease in pain depending on the localization and cause of pain.

Capel, et al. [109] have done a randomized, placebo-controlled study and evaluated the effects of CES in 27 patients with spinal cord injury. The pain was assessed with VAS and McGill Pain Questionnaire, but other functional related factors like depression, anxiety, analgesic usage were also monitored. In this study, patients receiving CES reported the decrease in pain intensity.

Another randomized placebo-controlled study was done by Tan, et al. [110] using CES in 38 spinal cord injury patients who suffered from chronic neuropathic and musculoskeletal pain for at least 3 months. The patients in CES group have reported a decrease in pain intensity immediately, and this decrease did not change over time. However, the result was not statistically significant. Despite several studies being done on neurostimulation, definitive result in patients of Neuropathic Pain is very small.

TENS

It is one of the best modalities in neuropathic pain. In a study, Jin DM, et al. [111]. evaluated the role of TENS and has shown evidence of efficacy in the treatment of Neuropathic Pain due to PDN The mechanism being TENS acts centrally, it activates μ-opioid receptors in spinal cord and brainstem when applied in low frequency while high-frequency TENS produces its effect via δ-opioid receptors. European Federation of Neurological Societies (EFNS) has published a guideline about the use of therapeutic electrical neurostimulation techniques in chronic Neuropathic Pain [112]. The guideline suggests that the effectiveness of TENS depends on the intensity, frequency, duration and the number of sessions. In this guidelines, they also suggested that acupuncture-type TENS (0-4 Hz) has been found more acceptable when compared to high-frequency TENS due to increased sensation of numbness but sufficient evidence is not there. Also, Several clinical trials evaluate the role of TENS in Neuropathic Pain and was found to be effective [113-115]. As a result, TENS can be effective in the treatment of painful peripheral neuropathy. However, we cannot comment on TENS efficacy appropriately due to inadequate study designs and short follow-up durations. There is need for more randomized, double blind studies done with larger patient groups, particularly in patients of PDN.

Other physical therapy modalities

Include pain modulators like hot and cold packs, ultrasound, short wave diathermy, low-frequency currents (diadynamic currents, interferential currents) and techniques like high voltage galvanic stimulation (Table 3).

Hot and cold applications: Hot and cold applications can be used together as in contrast baths. Sometimes fluidotherapy or whirlpool can also be chosen for this purpose. In all these superficial heat agents should not be applied because of the risk of an increase in pain. The modalities have been found to be effective in chronic pain, but there is a definite need of studies which support their effectiveness [116].

Ultrasound and short wave diathermy: Ultrasound and short wave diathermy which are deep heating agents like are not recommended in the treatment of neuropathic pain. They are helpful especially in joint contractures, and adhesions. It increases the flexibility of collagen fibers and circulation of connective tissues which help functional restoration. It may provide to decrease neuropathic pain.

Massage: Massage is also not recommended. In AIDS patients with neuropathic pain, massage therapy has been applied but there have been no significant changes on pain intensity [117]. There is another study that has investigated the role of massage in spinal cord injury patients. While the study claims that massage appears as one of the effective ways of therapy, it does not specify the type of pain [118].

Rehabilitation: It is s also an essential part of treatment in Neuropathic Pain (Table 3). The main aims of rehabilitation are

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to decrease pain and improve dysfunction, increase quality of life, and to decrease intake of medications. One of the major parts of rehabilitation methods are therapeutic exercise, however, there is no sufficient evidence supporting it. There are several therapeutic exercises have already been used in the rehabilitation program such as conditioning, strengthening and stretching exercises. Kuphal, et al. [119] developed a Neuropathic Pain model in rats by making injury to their sciatic nerve and showed that 25 days of exercises in water and swimming decreased pain, reduced edema, and inflammation. The purposes of behavioral therapy are to treat emotional and mental dysfunction, relieving the patient from anxiety or depression, psychosocial treatment approaches, cognitive behavioral methods have showed that psychosocial support increases the efficacy of treatment. We should include psychosocial management programs to our standard therapy regimens in neuropathic pain. The use of CBT is gradually increasing in neuropathic pain. Especially in elderly patients, relaxation techniques, the accurate planning of activity-rest cycles, cognitive reconstruction, and meditation can be used [120]. Cha, et al. [121] investigated the healing effect of acupuncture in neuropathic pain induced in rats and found out that acupuncture is effective in the treatment of neuropathic pain.

Rapson, et al. [122] applied electro acupuncture in 36 Spinal Cord Injury (SCI) patients with neuropathic pain 5 times a week for 30 minutes and suggested that pain intensity decreased after therapy and there were not any side effects.

Mirror therapy and graded motor imagery: Mirror therapy and graded motor imagery are rehabilitation procedures developed with the hope of correcting phantom limb and chronic low back pain, which is due to primary somato sensory cortical changes.

Mirror therapy is one of the rehabilitation methods that are widely used in patients suffering from neuropathic pain. In mirror therapy, the patient puts his affected limb into mirror box and keeps the unaffected side in front of the mirror. Unaffected limb in front of the mirror makes simple movements, patient imagines doing same movements with the affected limb. Although it may increase the pain but the patient tries to tolerate it. This method has been used in this method has been used in patients with stroke, phantom limb pain and Complex Regional Pain Syndrome (CRPS) [123]. In a randomized controlled study with 22 patients with amputated limbs, 4 weeks of mirror therapy were compared with covered mirror therapy (sham mirror therapy) and mental imagery [124]. There was a significant decrease in VAS in mirror therapy group compared with the others.

Graded Motor Imagery (GMI) is a comprehensive program, which activates cortical motor networks and improves cortical organization in three steps: laterality training, imagined hand movements, and mirror visual feedback [28]. Moseley, et al. [29] has done one study in CRPS type 1 patients which received GMI for 6 weeks, 2 weeks in each step, and compared with conventional physical therapy and medication. The study was done in 51 patients and showed the significant decrease in pain in GMI group compared with other groups. However, Johnson, et al. [30] failed to show the effectiveness of GMI in CRPS patients.

There is definitely a need for more evidence regarding the role of both mirror therapy and GMI in neuropathic pain.

New recent potential therapies

Now in clinical trials: Two treatments that might be useful in opposing some of the pathogenic factors that are thought to lead to neuropathy are now in clinical trials.

α-lipoic-acid: This free radical scavenger antioxidant has been shown to be efficacious in the management of painful neuropathies when administered parenterally [126] Infusion of the anti-oxidant a-lipoic acid at a dose of 600 mg i.v. per day over a 3-week period has been found to be useful in reducing neuropathic pain 53. A meta-analysis including 1258 patients from four prospective trials showed that treatment with a-lipoic acid (600 mg/day) for 3 weeks was associated with a significant improvement in neuropathic pain, as well as neuropathic deficits [127]. Oral treatment with a-lipoic acid for 5 weeks improved neuropathic symptoms and deficits in patients with DPN [128].

Protein kinase C inhibition: Elevated protein kinase C activities thought to play a significant role in the etiology of diabetic microvascular complications. Studies have been conducted using a protein kinase C- β inhibitor (LY333531) [129]. A preliminary study suggested the possibility of this agent improving positive symptoms of allodynia and prickling pain. Large, phase III, multicenter clinical trials are in progress [130].

Below is the table 4 describing the latest compounds acting on pathogenic factors of diabetic neuropathies that have undergone trials for eliciting the treatments of the same.

Discussion

Despite being common, DPN continues to be under diagnosed and undertreated and thus management of the patients with DPN must depend on individual requirements and on the presence of other comorbidities. Pharmacological treatment of DPN includes tricyclic compounds, serotonin-noradrenalin reuptake inhibitors, the anti-oxidant-lipoic acid, anticonvulsants, opiates, membrane stabilizers, topical capsaicin and so on.

Although poor blood glucose control in diabetic patients is an important risk factor for the Development of Peripheral Neuropathy (DPN). Furthermore, traditional cardiovascular risk factors for macrovascular disease also leads to an increased risk of DPN. Recently several studies in experimental diabetes examining the pathogenesis of DPN have identified a number of metabolic abnormalities (as described in figure 1) including polyol pathway hyperactivity, increased advanced glycation end-point formation, alterations in the protein kinase C beta pathway through diacylglycerol and oxidative stress. There is now strong evidence suggesting nerve ischemia as the cause of DPN. Various Studies in human and animal models have shown reduced nerve perfusion and endoneurial hypoxia as the leading cause neuropathic pain. These endoneurial microvascular changes strongly correlate with clinical severity and the degree of nerve-fiber ischemia. Thus, with regard to this several clinical trials have been done to evaluate the efficacy of compounds in the treatment of diabetic peripheral neuropathy in animals and

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Table 4: Compounds that have undergone trials for the treatment of diabetic peripheral neuropathies (adapted from Reference [131]). ACE: Angiotensin-Converting Enzyme; BDNF: Brain-Derived Neurotrophic Factor.

Abnormality	Compound	Aim of Treatment	Status of randomized clinical trials
Polyol pathway↑	Aldose reductase inhibitors Sorbinil Tolrestat Ponalrestat Zopolrestat Zenarestat Lidorestat Fidarestat Ranirestat Epalrestat	Nerve sorbitol↓	Withdrawn (adverse events) Withdrawn (adverse events) Inefective Withdrawn (marginal efects) Withdrawn (adverse events) Withdrawn (adverse events) Efective in phase II trials Efective in phase II trial Marketed in Japan
myo-Inositol↑	myo-Inositol	Nerve myo-inositol↑	Equivocal
γ-Linolenic acid synthesis↓	γ-Linolenic acid	Essential fatty acids metabolism↑	Withdrawn (effective: deficits)
Oxidative stress↑	α-Lipoic acid	Oxygen free radicals↓	Effective in randomized clinical trials (studies ongoing)
	Vitamin E	Oxygen free radicals↓	Effective in one randomized clinical trial
Nerve hypoxia↑	Vasodilators	Nerve blood flow↑	
	ACE inhibitors Prostaglandin analogs PhVEGF165 gene transfer	Angiogenesis↑	Effective in phase II trial Effective in phase II trial Phase III trial ongoing
Protein kinase C↑	Protein kinase Cβ inhibitor (ruboxistaurin)	Nerve blood flow↑	Phase III trial ongoing
C-peptide↓	C-peptide	Nerve blood flow↑	Effective in phase II trials
Neurotrophism↓	Nerve growth factor	Nerve regeneration, growth↑	Ineffective
	BDNF	Nerve regeneration, growth↑	Ineffective
Long-chain fatty acid metabolism	Acetyl-L-carnitine	Long-chain fatty acid accumulation↓	Ineffective

Table 5: Usual Effective dosages & Titration Schemes for the treatment of PDN [134].

Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
Tricyclic antidepressants				
Amitriptyline	100–150 mg/ day (150 mg at bedtime or 75 mg twice daily)	Day 1: 12.5 mg/ day	2.1 (1.8–2.6) [50]	6–8 weeks
		Days 2–7: 25 mg/ day		
		Week 2: 50 mg/ day		
		Week 3: 75 mg/ day		
		Week 4: 100 mg/ day		134)
		Weeks 5–8: 150 mg/ day		
Nortriptyline	100-150 mg/ day (50 mg three times daily)	Day 1: 12.5 mg/ day	Cannot calculate NNT; similar to desipramine	6 weeks
		Days 2–7: 25 mg/ day		
		Week 2: 50 mg/ day		
		Week 3: 75 mg/ day		
		Week 4: 100 mg/ day		
		Weeks 5–8:150 mg/ day		
Imipramine	150 mg/ day (75 mg twice daily)	Week 1:25 mg twice daily	2.1 (1.8–2.6) [50]	4 weeks
		Week 2:50 mg twice daily		
		Week 3:75 mg twice daily		
Desipramine	200–250 mg/ day (250 mg daily or 125 mg twice daily)	Week 1:50 mg/ day	2.5 (1.9–3.6) [50]	6 weeks
		Week 2:100 mg/ day		
		Week 3:200 mg/ day		
		Week 4:250 mg/ day		

Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
Other antidepressants				
Venlafaxine	150–225 mg/ day (75 mg three times daily or extended release formulation daily)	Week 1: 37.5 mg/ day	5.5 (3.4–14) [50]	4–6 weeks
		Week 2: 75 mg/ day		
		Week 3: 150 mg/ day		
		Week 4: 225 mg/ day		
Duloxetine	60–120 mg/ day (60 every day or twice a day)	Week 1: 10 mg/ day	4 (3–9) [135]	4 weeks
		Week 2: 20 mg/ day		
		Week 3: 60 mg/ day		
		Week 4: 120 mg/ day		
Antiepileptics				
Carbamazepine	600 mg/ day (200 mg three times daily)	Weeks 1–2: 100 mg three times daily	2.3 (1.6-3.9) [50]	4 weeks
		Week 3: 200 mg three times daily		
Lamotrigine	200–400 mg/ day (200 mg twice daily)	Week 1: 25 mg/ day	4.0(2.1–42) [50]	6–8 weeks
		Week 2: 50 mg/ day		
		Week 3: 100 mg/ day		
		Week 4: 200 mg/ day		
		Week 5: 400 mg/ day		
Valproate	1,000–1,200 mg/ day (500 mg twice daily or 400 mg three times daily)	Week 1: 600 mg/ day	2.5(1.8–4.1) [50]	4 weeks
		Week 2: 1,200 mg/ day		
Topiramate	300–400 mg/ day (200 mg twice daily)	Week 1: 25 mg/ day	7.4 (4.3–28) [50]	12 weeks
		Week 2: 50 mg/ day		
		Week 3: 75 mg/ day		
		Week 4: 100 mg/ day		
		Week 5: 150 mg/ day		
		Week 6: 200 mg/ day		
		Week 7: 300 mg/ day		
		Week 8: 400 mg/ day		

Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
Gabapentin	2,400–3,600 mg/ day (1,200 mg three times daily or 900 mg four times daily)	Week 1: 300 mg at bedtime	3.9 (3.2-5.1) for doses ≥ 2,400 mg/ day [50]	4 weeks
		Week 2: 300 mg twice daily		
		Week 3: 300 mg three times daily		
		Week 4: 600 mg three times daily		
		Week 5 : 900 mg three times daily		
Antiepileptic				
Pregabalin	300–600 mg/ day (300 mg twice daily or 200 mg three times daily)	Week 1: 150 mg/ day	4.2 (3.4–5.4) [50]	4–6 weeks

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		Week 2: 300 mg/ day		
		Week 3: 600 mg/ day		
		(Dosed twice or three times daily)		
Others				
Capsaicin cream	0.075% four times daily	No titration needed	6.7 (4.6–12)	8 weeks
Tramadol	200–400 mg/ day (100 mg four times daily)	Week 1: 50 mg/ day	3.5 (2.4–6.4) [50]	6 weeks
		Week 2: 100 mg/ day		
		Week 3: 150 mg/ day		
		Week 4: 200 mg/ day		
		Week 5: 300 mg/ day		
		Week 6: 400 mg/ day		
Mexiletine	450–675 mg/ day (225 mg three times daily)	Week 1: 225 mg/ day	2.2 (1.3–8.7) [50]	1–4 days
		Week 2: 450 mg/ day		
		Week 3: 675 mg/ day		
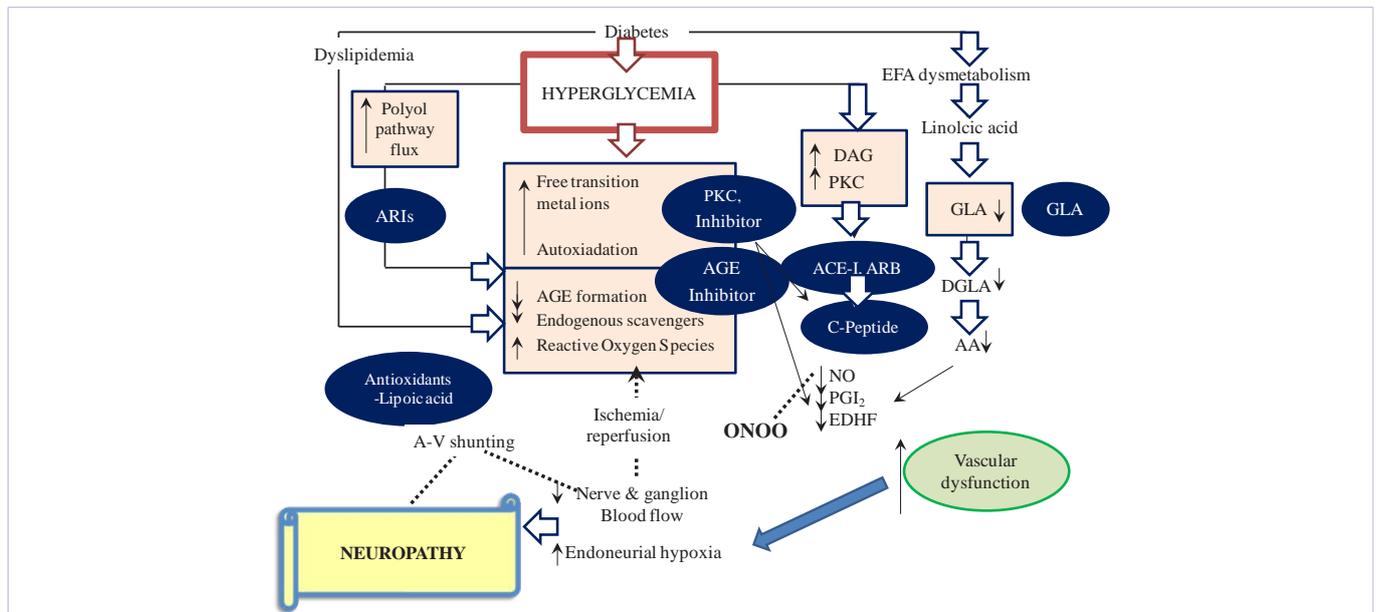
Figure 1: Explaining pathophysiology of Painful Diabetic Sensorimotor neuropathy [21]. ARI-Aldose Reductase Inhibitors; ACE-angiotensin converting enzymes; ARB-Angiotensin Receptor Blocker; GLA-Gamma-linoleic acid; DGLA-dihomo gamma linoleic acid; EDHF-Endothelium Derived Hyperpolarizing Factor; OONO-Peroxynitrite

humans. However, unfortunately, they were effective in animal models of neuropathy but have not been successful in human diabetic neuropathy. The only compounds found to be efficacious in human diabetic neuropathy, and are in clinical use, are the anti-oxidant, a-lipoic acid and the aldose reductase inhibitor, epalrestat.

Suggestions

Genetics and DPN

Gottfried Rudofsky, et al. [132] did one study and found that genotypes of TLR4 gene particularly Asp299Gly and Thr399Ile

have less prevalence of Diabetic Neuropathy in Patients with Type 2 Diabetes. But, very few researches have been done in this regard. However, genomic study can help in preventing the neuropathic complications in such patients particularly in those cases who has positive family history, as this will help them in creating awareness and thus regular checkups and follow-ups in turn shall reduce incidence, health care costs and improve their quality of life. Hence, further studies are suggested for genomic association between type 1 and 2 diabetes with painful PDN.

Conclusion

DPN, being the most important underlying causes for

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neuropathic pain, remain a challenging condition to manage and despite several well-designed recent trials looking at slowing the progressive decline in nerve function associated with DPN, no novel treatment has emerged. This might be due to multi factorial etiology and treatment targeting single pathway. As of today TCAs, Gabapentin/ pregabalin remain the first line therapy drugs, keeping in mind the role of duloxetine/ lacosamide for better pain management. Duloxetine and pregabalin are the only two drugs approved so far by US FDA for the management of DPN [62]. In addition, Optimization of glycemic control and aggressive management of cardiovascular risk factors are also clearly important. Combination therapy might be useful, but further research is required. Studies are required on comparative trials and long-term efficacy of drugs, as most trials are short termed. The areas generating or modulating pain in DPN including peripheral small fibers, at the level of a spinal cord, the thalamus and the other pain matrix areas in the brain require further studies in order to develop more effective treatments. The association of DPN with autonomic neuropathy also requires further investigation [133]. In spite of many trials eliciting the role of pathogenic factors in the remedy of DPN, only two compounds, a-lipoic acid, and epalrestat, are in clinic use. Thus, further research is required to find more effective, novel compounds that are able to slow the disease progression. There is also a need for further controlled trials to investigate non-pharmacological treatments.

Lastly, regarding the line of management, we emphasize that it requires increased level of awareness and special communication between patients and pain specialist to the extent that all decisions about which therapy to start with and when to switch over to the next option with an alternative mechanism of action are also needed.

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