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A REVIEW ON DIABETIC PERIPHERAL NEUROPATHY: PATHOPHYSIOLOGY, DIAGNOSIS AND PHARMACOTHERAPY

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ABSTRACT: Diabetic Peripheral Neuropathy (DPN) is a prevalent and debilitating complication of diabetes mellitus, impacting the global well-being of millions. This review provides a concise overview of the key aspects related to DPN, including its pathophysiology, diagnostic approaches, and current pharmacotherapeutic interventions. The pathophysiology involves intricate mechanisms driven by hyperglycemia-induced oxidative stress, inflammation, and metabolic dysfunction, resulting in peripheral nerve damage. Diagnosis relies on a combination of clinical and electrophysiological assessments. Pharmacotherapy, a pivotal component in DPN management, encompasses analgesics, anticonvulsants, and neurotrophic agents, aiming to alleviate symptoms and impede disease progression. The abstract underscores the need for a multidisciplinary approach and ongoing research to enhance the understanding and treatment of DPN, ultimately improving the quality of life for individuals affected by this complication.

INTRODUCTION: Diabetic peripheral neuropathy (DPN) is a well-recognized and common chronic complication that arises in individuals with diabetes mellitus, which significantly impacts the well-being of people world-wide [1]. According to the International Diabetes Federation (IDF) the global prevalence of diabetes was estimated to be 9.3% among adults aged 20 to 70years in 2019, affecting approximately 463 million individuals and is predicted to reach 366 million by 2030, which in turn is projected to rise to 700 million by 2045 [2, 3]. The prevalence of DPN varies depending on factors like the type and duration of diabetes, age, glycemic control and comorbidities.

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Diabetes is a common cause, and when DSPN (Distal symmetric polyneuropathy) is related to diabetes, it is often referred to as diabetic neuropathy [4, 5]. The prevalence of diabetes has been increasing globally, with both type 1 and type 2 diabetes contributing to the overall burden[6]. Moreover DPN- related sensory deficits can lead to an increased risk of foot ulcers, infections and lower extremity amputations. About 15-30% of all patients with diabetes are affected by painful DPN and several alternatives are required for management of pain [7, 8, 9, 10].

Diabetic peripheral neuropathy (DPN) can have a negative impact on the quality of life of patients as well [1]. DPN can contribute to sleep disturbances, may experience stress, anxiety, and depression [11, 12]. The symptoms of DPN include pain, numbness, tingling and loss of sensation in the feet and hands, which is presented with nerve motor dysfunctions, mobility and functional dependence. The pain is often described as burning, stabbing, throbbing or

electric shock-like which can be constant or intermittent [13, 14]. The therapy for DPN is challenging and involves a multifaceted approach that addresses both the underlying cause (diabetes) and the symptoms of neuropathy and hence no single or effective therapy is not available for every patient with DPN. Here the review will discuss on the pathophysiology diagnosis and pharmacotherapy of DPN.

METHODS: The search strategy involved the retrieval of relevant literature from health sciences databases (PubMed and Google scholar) in English language articles. The following keywords, “diabetes”, ”diabetes mellitus”, ”diabetic peripheral neuropathy”, “pharmacotherapy”, “patho-physiology”, “diagnosis” using combination of key words and Boolean operators (“diabetic peripheral neuropathy” AND “treatment”, “non-painful diabetic neuropathy” OR “painless diabetic neuropathy”, “diabetic peripheral neuropathy” AND “pathophysiology”, “diabetic peripheral neuropathy” AND “treatment”, “diabetic peripheral neuropathy” AND “opioids”, diabetic peripheral neuropathy AND serotonin reuptake inhibitors, diabetic peripheral neuropathy AND tricyclic antidepressants ,diabetic peripheral neuropathy AND capsaicin patch, diabetic peripheral neuropathy AND non -pharmacological treatment were included in the search. This review was mainly emphasized on human studies. The articles which were mainly on diabetic peripheral neuropathy were included in the study and summarized the diagnosis, pathophysiology and treatment. The articles that are found to be irrelevant and not in English were excluded from the study.

RESULTS AND DISCUSSION

Pathophysiology of DPN: Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus and is characterized by damage to the peripheral nerves. The pathophysiology of DPN is complex and not fully understood, but it is thought to involve a combination of metabolic, vascular, and neurodegenerative factors. DPN can be painful or non-painful, according to the neurological deficits and can be classified as: diffuse neuropathy, radiculopathy, mononeuropathy and others [15, 16]. DPN is characterized by diffuse neuropathy and about 75-90 % cases present with distal symmetric polyneuropathy (DSPN), which is associated with pain an impaired quality of life [17, 18]. Diabetes predominantly impacts the peripheral nervous system (PNS) [19]. Unlike motor neurons within the blood-brain barrier, PNS sensory neurons and their receptors lie outside this barrier, rendering them more prone to diabetes-related injury [20]. Among these sensory neurons are C-fibers, also known as "small fibers," responsible for conveying nociceptive information, particularly related to heat and pain [21]. These small fibers lack myelin, resulting in slow, continuous conduction due to a uniform distribution of ion channels along the axon. Additionally, there are small, thinly myelinated Aδ fibers and fully myelinated fibers (Aβ and Aα), collectively termed large fibers. Schwann cells provide myelin, forming nodes of Ranvier and paranodes critical for rapid nerve conduction and protecting large fibers from toxic substances [22].

Initial degeneration and loss of C fibers manifest in patients experiencing dysesthesias, such as new-onset pain, burning, or prickling in their feet. This is followed by the initial demyelination/ remyelination of large fibers [23, 24]. As the disease progresses, large fiber axonal loss occurs, leading to numbness and loss of proprioception in the feet, gradually spreading upward. This distal-to-proximal axonal loss and its accompanying symptoms characterize diabetic neuropathy [25].

Glucose dysregulation is one of the focused topics in diabetic neuropathy [26]. Hyperglycemia leads to the activation of polyol pathway, advanced glycation end products (AGEs) formation, and activation of protein kinase C (PKC). These processes contribute to cellular damage and oxidative stress in peripheral nerves. Excess glucose also enters the hexosamine pathway, generating inflammatory by-products and activating protein kinase C (PKC) due to diacylglycerol accumulation. PKC activation enhances insulin resistance, disrupts growth factor biology, and causes vasoconstriction of nerve blood vessels. Advanced glycation end products (AGEs), binding to receptors for AGEs (RAGEs), are additional by-products of excess glucose. Activation of AGEs and RAGEs results in downstream inflammation, ROS accumulation, and

reduced blood flow to peripheral nerves. While preclinical trials targeting RAGE activation showed promise, available compounds were too toxic for human trials and remain in therapeutic development [27].

Under normal conditions, glucose and lipids undergo distinct, highly regulated chemical reactions, leading to the transfer of electron donors to the mitochondrial electron transport chain. In the diabetic environment, excess glucose and lipids disrupt normal pathways and produce surplus electron donors that mitochondria cannot process. The consequence is bioenergetic failure [28], resulting in the loss of normal mitochondrial membrane function (mitochondrial depolarization), decreased ATP production, impaired mitochondrial trafficking, and the accumulation of ROS. This cascade leads to inflammation, endoplasmic reticulum stress, apoptosis of neurons, and axonal failure [29]. With diminished functional mitochondria in both the cell body and along the axons, both small and large nerve fibers, deprived of energy, lose their capacity to operate and undergo degeneration. The axons situated farthest from the cell body, such as those in the feet, are especially susceptible to this degeneration. Small fibers, responsible for conveying sensations of pain and dysesthesias, are particularly prone to the effects of this energy deprivation. While Schwann cells can offer some usable fuel, in the form of mitochondria, and protection from toxic substances to energy-depleted large, myelinated axons [30], small fibers lack this energy source and protective mechanism. This discrepancy elucidates why small fibers are the earliest to succumb to injury in response to diabetes and why symptoms such as pain and dysesthesias often manifest as the initial signs of Diabetic Peripheral Neuropathy (DPN).

Diagnosis: DPN is described as the occurrence of symptoms and/or signs indicative of peripheral nerve dysfunction in individuals with diabetes, following the exclusion of alternative causes. Neuropathy encompasses the manifestations of both the somatic and autonomic components of the peripheral nervous system. It is advisable to identify at least two abnormalities from symptoms, signs, abnormal nerve conduction, quantitative sensory tests, or quantitative autonomic nerve tests [31].

Peripheral neuropathy encompasses all conditions leading to damage to the peripheral nervous system, classified based on the site of nerve injury. Distal symmetrical polyneuropathy (DSP), mononeuropathy, and lumbar/cervical radiculopathy are the most prevalent forms of peripheral neuropathies. Uncommon sites of peripheral neuropathy include diffuse, length-independent neuropathy, multiple mononeuropathy, multiple radiculopathy, plexopathy, and nerve root exocrine neuropathy. Presently, the diagnosis of DPN relies mainly on characteristic symptoms and signs. Nerve conduction studies (NCS) are a gold standard technique for DPN diagnosis [32]. NCS assesses the occurrence and progression of DPN by detecting the peripheral nerve's ability to transmit electrical signals in patients with diabetic neuropathy. Despite being quantifiable, objective, and sensitive, NCS has drawbacks such as being time-consuming, expensive, requiring professional expertise, and proving challenging for large-scale screening [33]. Furthermore, NCS is limited to evaluating large nerve fibers, whereas small nerve fibers are the initial targets in DPN patients, escaping assessment through standard electrophysiological tests [34].

The application of electrophysiology should be advocated only when clinical presentations are atypical or the diagnosis remains unclear. Hence, it is crucial to implement simple and effective methods for DPN screening to enable early intervention and control [35].

Pharmacological Treatments:

Conventional Approaches to Treatment: Diabetic Peripheral Neuropathy (DPN) often experience pain [36], a concern that may not always be openly addressed [37]. DPN affects approximately 5% of the population, with diabetes. Managing pain is one of the critical components of DPN treatment, leading to the widespread use of various medication classes, including antidepressants, anticonvulsants, analgesics, and topical medications, to alleviate neuropathic pain associated with DPN. Numerous guidelines advocate for the use of pharmacological treatments, both approved and off-label, to reduce pain and enhance the quality of life (QOL) in DPN patients [38, 39, 40].

International guidelines, such as those provided by the American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), and the National Institute for Health and Care Excellence, recommend specific medication classes with the highest efficacy for DPN.

Tricyclic Antidepressants and Selective Serotonin and Noradrenaline Reuptake Inhibitors: Tricyclic antidepressants (TCAs), exemplified by amitriptyline, nortriptyline, desipramine, and nortriptyline, are recommended as the first-line treatment for Diabetic Peripheral Neuropathy (DPN) due to their analgesic properties, blocking the uptake of both 5HT and noradrenaline [41]. Another mechanism involves inhibiting the reuptake of norepinephrine and serotonin, modulating perception [42, 43]. Owing to their lipophilic nature, TCAs are widely distributed, easily penetrates the central nervous system (CNS), and are well-absorbed orally. However, their inconsistent and low bioavailability, influenced by variable first-pass effects, necessitates up titration to effective doses over 6-8 weeks [44, 45, 46, 47]. Due to the frequency and severity of adverse effects, including sedation, cardiac arrhythmias and postural hypotension, the use of TCAs is restricted. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are better tolerated than TCAs [48].

Serotonin and Noradrenaline Reuptake Inhibitors: Medications like duloxetine and venlafaxine, classified as SNRIs, increase the availability of norepinephrine and serotonin, thereby reducing pain signals. Duloxetine, the first drug approved for treating DPN patients, simultaneously inhibits the reuptake of noradrenaline and serotonin, relieving pain associated with DPN, postherpetic neuralgia, fibromyalgia, and lower back pain [49]. Duloxetine's exact mechanism of action remains unknown, but it is believed to potentiate serotonergic and noradrenergic activity in the CNS, particularly blocking norepinephrine reuptake, which has a beneficial effect on neuropathic pain [50, 51]. Compared to TCAs, duloxetine has fewer and more favorable side effects due to its lesser impact on cholinergic and histaminic receptors [52]. Venlafaxine, another SNRI, is not indicated for use in DPN patients but is approved for treating major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder [53]. Its common side effects include nausea, headache, and insomnia, while high doses may lead to increased blood pressure and heart rate [54]. Venlafaxine may pose a risk of clinically significant ECG changes, especially in patients at risk of cardiac arrhythmias, necessitating careful monitoring of blood pressure in individuals with a history of hypertension [55].

Anticonvulsants: Newer agents, such as pregabalin and gabapentin, along with traditional agents like carbamazepine and sodium valproate, have been utilized to treat Diabetic Peripheral Neuropathy (DPN) since the 1960s [56]. These compounds effectively manage neuropathic pain by modulating calcium channels, reducing the release of excitatory neurotransmitters, and normalizing abnormal pain signaling. Pregabalin and gabapentin act on the α2-δ1 subunit of the presynaptic Ca++ channel, employing the same mechanism to decrease the release of neurotransmitters, primarily glutamate and noradrenaline, and to some extent, substance P [57].

The American Academy of Neurology (AAN) guidelines recommend pregabalin and gabapentin for DPN treatment [58]. In the United Kingdom, guidelines from the National Institute for Health and Care Excellence (NICE) state that pregabalin reduces peripheral neuropathic pain compared with placebo, although the clinical trial evidence is considered of "very low quality" [59]. Conversely, Chong et al. preferentially cites gabapentin as the anticonvulsant of choice for DPN treatment due to the availability of less-expensive generic formulations compared with pregabalin and extensive clinical experience with its use [60].

According to AAN guidelines, valproate sodium is deemed "probably effective" in treating DPN, with recommended off-label dosages ranging from 500 to 1,200 mg per day [58]. However, due to its potential teratogenic effects, it should be avoided in individuals of childbearing age [38, 61]. As this drug has side effects such as weight gain and a possible worsening of glycemic control, it is not commonly chosen as an initial treatment for DPN [61]. Routine laboratory check-ups, including monitoring blood urea nitrogen, creatinine, transaminase, iron levels, complete blood count (including platelets), reticulocyte count, liver function tests, and

urinalysis, are essential when administering carbamazepine [62, 63].

Topical Medications: Topical medications, such as lidocaine patches or capsaicin cream, offer localized pain relief. Lidocaine acts as a local anesthetic, whereas capsaicin works by desensitizing the nerves. Derived from red chili peppers, capsaicin is an alkaloid that desensitizes afferent sensory nerves, leading to pain relief [64]. It achieves this by splitting substance P at vanilloid receptors, thereby reducing the conveyance of painful stimuli to the central nervous system [65]. Common side effects of capsaicin cream include transient burning, sneezing, and coughing [66]. Lidocaine, classified as an amide-type local anesthetic, blocks neuronal sodium channels, blunting the sensitization of peripheral nociceptors and, consequently, CNS hyperexcitability [67]. Lidocaine patches, at a 5% concentration, function as peripheral analgesics, with low systemic absorption, often used in combination with other analgesic drugs. While conventional treatment approaches play a crucial role in managing Diabetic Peripheral Neuropathy (DPN) by providing symptomatic relief and slowing disease progression, there remains a significant unmet need for more effective and targeted therapies.

The evolving understanding of DPN pathophysiology and ongoing advancements in medical research provide hope for the development of innovative treatments capable of modifying the course of DPN and enhancing the quality of life for individuals grappling with this debilitating condition.

TABLE 1: AN OVERVIEW OF DRUGS USED IN DIABETIC PERIPHERAL NEUROPATHY

Drug	Examples	Mechanism of action	Side effects
Antidepressants	Amitriptyline, Duloxetine	Modulate neurotransmitters, especially serotonin and norepinephrine	Sedation, dry mouth, constipation, dizziness
Anticonvulsants	Gabapentin, Pregabalin	Stabilize nerve cells and reduce abnormal electrical activity	Drowsiness, dizziness, weight gain
Analgesics	Tramadol, Tapentadol	Opioid receptor agonists and norepinephrine reuptake inhibitors	Nausea, constipation, dizziness, sedation
Topical Medications	Capsaicin cream, Lidocaine patches	Modulate pain signals locally	Skin irritation, burning sensation
Alpha-lipoic acid		Antioxidant, may improve nerve function	Nausea, skin rash, hypoglycemia (rare)
Tricyclic Antidepressants	Nortriptyline, Imipramine	Modulate neurotransmitters, especially serotonin and norepinephrine	Sedation, dry mouth, constipation, blurred vision
Antioxidants	Vitamin B complex, Vitamin E	Reduce oxidative stress and support nerve health	Generally well-tolerated

Role of Pharmacist: At present the role of pharmacist in the management of DPN is crucial and extends beyond simply dispensing medications. They provide information on DPN, its underlying causes, progression, and self-care strategies. Pharmacists can educate patients on lifestyle modifications, such as blood glucose control, smoking cessation and regular exercise, which are essential for managing DPN and preventing further complications. Pharmacists have a multifaceted role in the management, patient education, monitoring and follow up, collaborative care, adverse event monitoring and health promotion. By utilizing their expertise and close patient interaction, pharmacist can optimize medication therapy, enhance patient understanding and adherence, and improve outcomes for individuals with DPN.

CONCLUSION: Diabetic Peripheral Neuropathy (DPN) is a prevalent and impactful complication of diabetes mellitus, affecting millions of individuals worldwide. The rising global prevalence of diabetes underscores the increasing significance of DPN as a major health concern. This review has highlighted the multifaceted nature of DPN, encompassing its pathophysiology, diagnosis, and pharmacotherapy. The pathophysiology of DPN is complex and involves a combination of metabolic, vascular, and neurodegenerative factors. The impact on peripheral nerves, especially small fibers, leads to a range of symptoms, including pain, numbness, and sensory deficits. The progression of DPN is closely linked to factors such as hyperglycemia, activation of various pathways, and mitochondrial dysfunction.

Diagnosing DPN involves a comprehensive assessment of symptoms, signs, and objective measures, with nerve conduction studies being a gold standard technique. Early and accurate diagnosis is crucial for effective management and prevention of complications.

Pharmacotherapy for DPN is challenging, and no single, universally effective therapy exists. Conventional approaches include the use of tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, anti-convulsants, and topical medications. Each class of drugs has its mechanism of action and associated side effects, requiring careful consideration in individualized treatment plans.

Despite the current pharmacological options, there is a significant unmet need for more effective and targeted therapies. Ongoing research into the pathophysiology of DPN provides hope for the development of innovative treatments capable of modifying the course of the condition and improving the quality of life for affected individuals.

In the management of DPN, pharmacists play a crucial role beyond medication dispensing. They contribute to patient education, lifestyle modification guidance, adherence monitoring, and collaborative care. The evolving understanding of DPN and the active involvement of healthcare professionals, including pharmacists, offer optimism for better outcomes and improved quality of life for individuals grappling with this debilitating condition. Continued research, interdisciplinary collaboration, and patient-centered care are essential components in addressing the challenges posed by Diabetic Peripheral Neuropathy.

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