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DIAGNOSIS AND TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY- A REVIEW

VARSHA VINCENT[1*], ADHITHYA A[1], ADITHYA SATHEESH KUMAR[1], SREE LAKSHMI D R, SOUMYA R V[2],ANJANA U J[3], PRASOBH G R[4], DNITHIN MANOHAR R[5]

1. 5th Year Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala
2. Associate Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala
3. Assistant Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala
4. Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala
5. HOD, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala

ABSTRACT:

Painful diabetic peripheral neuropathy (PDPN) affects nearly a quarter of people with diabetes, impacting over 100 million individuals worldwide. Despite its high prevalence, PDPN is often underdiagnosed and undertreated, leading to impaired daily functioning, depression, sleep disturbances, financial instability, and a decreased quality of life. The pain associated with PDPN is complex, intertwined with poor sleep and low mood, necessitating a holistic patient-centered approach alongside pharmacological therapy.

Managing patient expectations is a significant challenge, as successful treatment outcomes typically involve a 30–50% reduction in pain, and complete pain-free outcomes are rare. While the past two decades have seen a lack of new analgesic agents for neuropathic pain, the future holds promise with over 50 new molecular entities reaching clinical development and showing benefits in early-stage trials.

This review comprehensively examines the current approaches to diagnosing PDPN, available tools and questionnaires for clinicians, international guidelines on PDPN management, and existing pharmacological and non-pharmacological treatment options. The synthesis of evidence and guidance from reputable organizations provides a practical guide to treating PDPN. Emphasis is placed on the necessity for future research into mechanistic-based treatments to prioritize the development of personalized medicine in addressing this challenging condition.

Keywords: diabetic peripheral neuropathy, painful diabetic peripheral neuropathy, diabetes complications, pharmacotherapy

INTRODUCTION

In 2021, the global frequency of diabetes mellitus was estimated at 537 million and is anticipated to rise to 783 million by2045.[1] Diabetic neuropathy affects up to 50 of cases with diabetes [2,3] and refers to a heterogenous group of conditions which affect the nervous system leading to a range of clinical donations. [4]The most current form is diabetic supplemental neuropathy (DPN), a symmetrical, length-dependent sensorimotor polyneuropathy.[5] DPN generally presents in a " sock and glove " distribution, beginning distally and moving proximally with complaint progression, with lower- branch long axons being most vulnerable to damage.[4] DPN may lead to neuropathic pain[6] and is the largest initiating trouble factor for nethermost ulceration and amputation.[7] Painful DPN (PDPN) affects 20 – 24 of cases with diabetes and leads to crippled quotidian functioning, depression, sleep disturbance, financial instability, [8] and dropped

quality of life(QoL).[9] PDPN is characterised as burning, jingling, and electric shock- suchlike sensation which may be accompanied by negative symptoms (numbness) or positive symptoms (paraesthesia, allodynia (pain sensitisation following typically non-painful stimulation) and hyperalgesia (abnormally increased perceptivity to pain).[4] PDPN is underdiagnosed and undertreated by healthcare professionals.[10] Several challenges live in the operation of PDPN including lack of timely opinion, PDPN refractory to anti- neuropathic remedy, an absence of mechanistic-based treatmentin routine clinical practice, and inconsistencies between international guidelines. In this narrative review, we bat practical guidance and challenges for the clinical operation of PDPN.

SCREENING

The screening process for diabetic peripheral neuropathy (DPN) involves a combination of history and clinical neurological examination, with guidelines recommending screening for individuals with type 2 diabetes at the time of diagnosis and those with type 1 diabetes five years post-diagnosis.[11] The screening includes assessing small-fibre and large-fibre function through various examinations, such as temperature/pinprick sensation and vibration sensation usinga 128-Hz tuning fork. An annual 10-g monofilament test is recommended for assessing the risk of foot ulceration. Despitethe lack of a dedicated screening program, opportunistic detection through clinical signs and symptoms or diabetic foot screening is common.[12]

DIAGNOSIS DIAGNOSING DPN:

Attesting the opinion of DPN requires objective measures in addition to clinical features. The Toronto Census criteria set out delineations for the minimum criteria demanded for DPN judgments including “possible DPN” symptoms or signs of DPN; “probable DPN” symptoms and signs of DPN, “vindicated DPN” symptoms or signs of DPN and vagrancy- whams conduction abnormality or abnormality of another validated measure of small- fibre neuropathy; and “subclinical DPN” vagrancy- whams conduction abnormality or abnormality of another validated measure of small- fibre neuropathy without symptoms or signs. Vagrancy- whams conduction studies measure the function of large (β) fibres which are only affected in the ultimate stages of DPN. For case, individualities may present with severe pain but normal vagrancy- whams conduction studies. Skin dissection has been considered the reference standard system to quantify small vagrancy- whams fibres by an assessment of intra- epidermal vagrancy- whams fibres.[13]In vivo corneal confocal microscopy(CCM) is a non- invasive imaging fashion which evaluates small vagrancy- whams fibres through quantification of the corneal sub basal vagrancy- whams plexus.[13]The effectiveness of CCM in DPN has been fully excavated and has demonstrated good-to- excellent individual ability particularly in combination with artificial intelligence deep knowledge ways.[14]Other sensitive tests for DPN include the Sudo scan test to determine electrochemical skin conductance, and the LDI- Flare technique which assesses the neurogenic flare response to nociceptive instigations. still, in clinical practice, utmost judgments are predicated on only history and clinical neurological examination, with objective measures primarily used in cases with atypical donations, specialist centres or in clinical disquisition.[15]

DIAGNOSING PDPN:

The IASP defines habitual supplemental neuropathic pain as “habitual pain caused by a lesion or complaint of the supplemental somatosensory nervous system”.[16] The opinion of PDPN is made clinically with symptoms and/ or signs of neuropathic pain in a typical distribution. Tools and questionnaires are a precious resource and grease accurate opinionof pain, determine the case’s neuropathic pain phenotype, and assess the goods of pain on a case’s quotidian functioning, mood, and QoL.

TOOLS AND QUESTIONNAIRES:

The “Douleur Neuropathique 4 Questions” (DN4- Interview) is a validated network tool which can be used in the individual work- up of PDPN, 27 conforming of 10 particulars divided into four questions. Questions 1 and 2 are interview questions, and questions 3 and 4 relate to physical examination. Each positive item scores a point, with the maximum score being 10. A score of 3 has a perceptivity and particularity of 84, positive predictive value of 71, and negative predictive value of 92 for diagnosing PDPN. The PAIN DETECT questionnaire (PD- Q) can be used to determine the presence of neuropathic pain and has demonstrated a perceptivity of 85, particularity of 80 and positive predictive value of83.[17] The McGill Pain Questionnaire allows quantification of a case’s private pain experience through a pain standing index assigned to word descriptors, the number of word descriptors chosen, and an intensity scale of the case’s current pain. On diagnosing PDPN clinicians should also elicit the effect of the neuropathic pain on a case’s quotidian functioning, QoL and sleep. The detail Pain Inventory for cases with PDPN (BPI- DPN) can be used to assess pain interference on quotidian functioning, QoL and mood. The validated instrument includes a four- item pain harshness scale and a seven-item pain interference scale. The Norfolk Quality of Life Questionnaire- Diabetic Neuropathy(QOL- DN) is another tool which can be utilised to determine the goods of pain on a cases ’ QoL questionnaires include the Chronic Pain Sleep Inventory(CPSI) which can be utilised to assess the effect of habitual pain on a case’s quality of sleep; the force for

measuring depression created by Beck et al to enable quantitative assessment of the intensity of a case's depression; and the EQ- 5D questionnaire which can be employed to estimate a case's position of mobility, tone- care, capability to engagein usual exertion, as well as their experience of discomfort, pain, anxiety, and depression.[18]

AUTONOMIC NEUROPATHY:

The relationship between PDPN and autonomic dysfunction has been excavated in several studies, with inconsistent findings reported. While some studies have demonstrated lower autonomic dysfunction in people with PDPN compared to those with royal DPN, other studies have set up no clear association between PDPN and autonomic neuropathy.[19] Further disquisition is necessary to fully understand the relationship between symptoms in DPN and autonomic neuropathy, with an association furnishing another implicit practical tool for croakers to use in opinion.

DIFFERENTIAL DIAGNOSIS:

Differential diagnoses for PDPN involve excluding other causes of small fiber neuropathy through clinical history, examination, and biochemical tests. This includes considerations such as vitamin B12 deficiency, alcohol-related neuropathy, genetic neuropathies, hypothyroidism, neoplasia, and neurotoxic drugs. Screening for vitamin B12, liver function, thyroid function, vitamin D, estimated glomerular filtration rate (eGFR), and magnesium levels is recommended. Deficiencies in B1, B6, and B12 should be addressed with replacement therapy.[20]

Other differentials for PDPN encompass conditions like Morton's neuroma, radiculopathy, entrapment neuropathy (e.g., carpal tunnel syndrome), and chronic inflammatory demyelinating polyneuropathy (CIDP). Nerve conduction studies play a crucial role in assessing CIDP, and prompt diagnosis may lead to potential treatments with high-dose steroids, immunosuppressive, or immunoglobulin therapy. Carpal tunnel syndrome and lumbar radiculopathy should be considered based on symptomatology, with MR spinal imaging aiding in the diagnostic process.[21]

RISK FACTOR REDUCTION FOR DPN

Acceptable glycaemic control detainments the progression of DPN and onset of neuropathy in cases with type 1 diabetes .Still, there is shy validation to demonstrate bettered glycaemic control alone detainments the progression of DPNin type 2 diabetes, but remains a pivotal hand of multifactorial trouble factor modification as recommended by the ADA .Type 2 diabetes is a complex complaint, and several factors may contribute to the lack of validation on the impact of glycaemic control alone on the progression of DPN in this condition. Foremost, type 2 diabetes is a heterogenous conditionin which glycaemia is a single hand of the pathogenesis of DPN type 2 diabetes. The ADA recommends optimising glycaemic control in cases with type 1 and type 2 diabetes to delay progression of DPN. Still, there are no robust validation for improvement in glycaemic control modifying pain intensity in PDPN. Lipid control and lipid lowering antidotes have been shown to have associations with the trouble of developing DPN and a reduction in the progression of DPN singly. still, further prospective randomised trials are demanded to give farther robust data on the goods of lipid control and lipid lowering antidotes on vagrancy- whams fibre regeneration and improvement in neuropathy symptoms. Again, there is negligible validation for lipid control or lipid lowering antidotes to be used therapeutically in PDPN.[22]

LIFE STYLE MODIFICATIONS

Regular aerobic and strengthening exercise have demonstrated reductions in neuropathic pain, advancements in small vagrancy- whams fibres, and reductions in pain interference. Singleton et al employed a similar protocol to the Diabetes Prevention Programme (DPP) (5 – 7 weight loss with diet and exercise) in cases with impaired glucose forbearance, demonstrating advancements in neuropathic pain and small vagrancy- whams fibre density on skin dissection.[23]

NON-PHARMACOLOGICAL TREATMENTS

Several non- pharmacological treatments can be used in the operation of PDPN including cerebral remedy, acupuncture, salutary supplements, transcutaneous electrical vagrancy- whams stimulation (knockouts), frequency rhythmic electrical modulated system (FREMS), and spinal cord stimulation (SCS). But most non- pharmacological treatments have poor strength of validation, piecemeal from SCS, still may be considered in select cases.[24]

TENS and FREMS:

TENS is a non- invasive treatment which applies an electrical current to vagrancy- whams fibres through electrodes on the skin. It's theorised that a reduction in pain may be due to endogenous opioid release, gate control proposition, and dilation of blood vessels.TENS has shown pledge as a treatment in the operation of PDPN; still, further large- scale prospective trials are demanded.[25] FREMS is another non- invasive treatment which applies series of electrical beats through electrodes attached to a case's lower branches. Two RCTs have demonstrated advancements in pain with FREMS, with a recent birdman RCT study (The FREMSTOP Study) chancing that FREMS could be integrated into the treatment

algorithm for cases who have shy response to two classes of neuropathic pain specifics, demonstrating reductions in pain and increased perceived impact of treatment by the cases.[26]

SPINAL CORD STIMULATION:

SCS involves implantation of a pulsation creator into the lower reverse which is connected to percutaneous leads which are placed in the epidural space. SCS can be conducted using low frequency (LF- SCS, 10 – 100 Hz) or high frequency (HF-SCS 1 – 10 kHz). Two RCTs have demonstrated that LF- SCS can significantly reduce pain in cases with PDPN and meliorate QoL. LF- SCS can beget paraesthesia which can be uncomfortable for cases. HF- SCS does not beget significant paraesthesia and a recent RCT from the US demonstrated significant reductions in pain (≥ 50 pain relief on VAS) and improvement in health- related QoL in cases with PDPN using 10 kHzSCS. of the actors endured study- related adverse events including infection, crack dehiscence, and crippled mending with 2 taking explanation. Another recent regular review and network meta- analysis of SCS in PDPN concluded that SCS provides pain relief and health- related QoL advancements, with the relative benefits of LF- SCS vs HF- SCS remaining uncertain due to the current lack of head-to-head RCTs in the area.[27]

MONOCHROMATIC INFRARED ENERGY:

Monochromatic infrared energy (MIRE) has been studied as an implicit treatment for PDPN. MIRE employs light witha wavelength of 890 nm, which is believed to pierce the skin and promote kerchief regeneration. various studies have estimated the effectiveness of MIRE for PDPN with mixed findings. Two RCTs reported significant improvement in supplemental sensation with MIRE. still, a double- visionless, randomized, sham- controlled trial reported no significant differences in quality of life (QoL), Michigan Neuropathy Screening Instrument (MNSI), vibration perception threshold (VPT), Semmes- Weinstein mono- filaments (SWM), or vagrancy- whams conduction velocity between MIRE and sham remedy for sensitive neuropathy in DPN. Another randomized, sham- controlled study, specifically examining cases with PDPN, reported that while there was no change in intraepidermal vagrancy- whams- fibre density with short- term MIRE use, there was a characteristic benefit and an improvement in QoL.[28]

PSYCHOLOGICAL THERAPY:

In cases with comorbid cerebral torture, cerebral remedy can be utilised.80 samples of cerebral remedy include cognitive behavioural remedy (CBT), behavioural remedy, and acceptance and commitment remedy (ACT). An RCT birdman study assessing the use of CBT in cases with PDPN demonstrated significant diminishments in pain strictness and intensity in actors who entered CBT versus treatment as usual. A Cochrane review demonstrated that CBT has a smallor truly small salutary effect in the reduction of pain (moderate quality validation), torture (moderate quality validation), and disability (low- quality validation) in cases with habitual pain. The validation for behavioural remedy and ACT was truly low-moderate quality, preventing conclusions being drawn on the benefits warrant of benefits.[28]

PHARMACOLOGICAL TREATMENTGABAPENTINOIDS:

Pregabalin and gabapentin, classified as α2δ ligands, bind strongly to the α2δ protein subunit of voltage-gated calcium channels. These channels, primarily present in the central nervous system, regulate excitatory neurotransmitter release by influencing synaptic vesicle exocytosis and inhibiting their diffusion into the synaptic cleft. Pregabalin, with FDA approval, is a frontline treatment for PDPN, starting at 25–75 mg twice or three times per day, titrated up to 300 mg twice per day. Common adverse effects include weight gain, peripheral edema, dizziness, somnolence, and headaches. Gabapentin, another first-line option, initiates at 100–300 mg three times per day, reaching a maximum of 1200 mg three times per day. Adverse events encompass dizziness, fatigue, somnolence, ataxia, viral infections, and fever. Caution is advised in patients with specific conditions, and gabapentinoids are contraindicated in pregnancy.[29]

TRICYCLIC ANTIDEPRESSANTS:

Tricyclic Antidepressants (TCAs) hinder noradrenaline and serotonin reuptake in the central descending pain modulatory systems and exhibit antagonistic effects on opioid and N-methyl-D-aspartate receptors. Amitriptyline, the widely used TCA for PDPN, starts at 10–25 mg once daily, titrated to a maximum of 75 mg once daily. Nortriptyline, though potentially more effective, has conflicting evidence. Adverse events involve dizziness, drowsiness, somnolence, headaches, dry mouth, nausea, constipation, orthostatic hypotension, and arrhythmias. TCAs should be used cautiously in specific populations and are contraindicated in severe hepatic impairment, cardiovascular diseases, urinary retention, constipation, orthostatic hypotension, and with monoamine oxidase inhibitors.[30]

SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS:

Duloxetine and venlafaxine, as SNRIs, inhibit serotonin and noradrenaline uptake, enhancing descending inhibitionof centrally sensitized pain. Duloxetine, FDA-approved, begins at 30–60 mg daily, titrated up to 120 mg daily. Adverse events encompass nausea, somnolence, headaches, and dry mouth. SNRIs are cautioned in specific medical conditions and are absolutely contraindicated in severe hepatic impairment, renal impairment with a CrCl <30 mL/min, pregnancy, breastfeeding, uncontrolled hypertension, and with monoamine oxidase inhibitors.[31]

SNRI/OPIOID DUAL MECHANISM AGENTS AND OPIOIDS:

Tramadol and tapentadol, SNRI/opioid dual-mechanism agents, block μ opioid receptors and inhibit serotonin and noradrenaline reuptake. Tramadol is recommended as a second-line analgesic treatment, with common adverse events such as nausea, vertigo, and constipation. Tapentadol can be considered if tramadol is ineffective or unavailable, with initial doses and adverse effects outlined. These agents should be used cautiously in specific conditions and are contraindicated in severe hepatic impairment, pregnancy, and breastfeeding.[32] Oxycodone, a strong opioid, blocks μ opioid receptors and may be used as a third-line treatment if combination therapy proves insufficient. Opioid use is recommended only after exhausting first- and second-line options. Adverse effects include drowsiness, nausea, constipation, and pruritus. The IDF emphasizes assessing tolerance, risk of abuse, and regular re-evaluation for treatments lasting over 3 months.[33]

TOPICAL TREATMENTS:

The capsaicin 8% patch, approved by the FDA and European Medicines Agency, functions by binding to the transient receptor potential vanilloid 1 (TRPV1) receptor, desensitizing it, and depleting substance P. Recommended as a third-line treatment by the IDF, its application to the feet offers weeks-to-months of pain relief. Adverse events include application site pain, erythema, burning sensation, and extremity pain. Recent studies highlight its efficacy in pain relief and nerve regeneration in both DPN and PDPN. The lidocaine 5% patch reduces pain impulses through voltage-gated sodium channel antagonism and membrane stabilization of small nerve fibers. Despite Cochrane review concerns about limited RCTs, it has shown efficacy in open-label studies for PDPN, neuropathic pain, and post-herpetic neuralgia, improving pain and quality of life. Nitric oxide donors like isosorbide mononitrate spray or glyceryl trinitrate patches demonstrate efficacy in small trials and may be used in combination with the lidocaine 5% patch, offering an alternative in cases with limited oral pharmacotherapy options.[34]

REFRACTORY PDPN:

For refractory PDPN cases unresponsive to initial treatments, referral to pain specialists, pain management services, endocrinologists, or neurologists with pain expertise is recommended. Further investigation may be necessary if doubts persist about the diagnosis. Specialized pain services may explore additional options, such as lidocaine infusions, botulinum toxin, and spinal cord stimulation (SCS). Lidocaine infusions, administered intravenously over an hour, may provide effective short-term pain relief in refractory neuropathic pain, particularly in a specialist setting.[35]

MAXIMUM-DOSE MONOTHERAPY VERSUS MAXIMUM-DOSE COMBINATION THERAPY:

The OPTION-DM study explored the benefits of combination therapy, comparing it with mono-pharmacotherapies (amitriptyline, pregabalin, duloxetine).[36] Involving 130 patients, the trial assigned participants to three treatment pathways and demonstrated three main findings: (1) First-line mono-pharmacotherapies were similarly efficacious. (2) Combination therapy provided additional pain relief for patients with suboptimal pain relief on mono-pharmacotherapy.
(3) Various combination therapies (e.g., amitriptyline and pregabalin) were similarly efficacious. The study validated the use of combination therapy in patients with suboptimal pain relief on mono-pharmacotherapy. An NIHR HTA assessment suggested comparable patient outcomes at similar costs, indicating that the optimal treatment may depend on patient preferences regarding side effects.[37]

MAXIMUM-DOSE MONOTHERAPY VERSUS STANDARD DOSE COMBINATION THERAPY:

In the COMBO-DM study, comparing maximum-dose monotherapy with standard dose combination therapy (using pregabalin and duloxetine), 804 patients were randomly assigned to either 60 mg/day of duloxetine or 300 mg/dayof pregabalin. After an initial 8-week period, non-responders received either maximum-dose monotherapy (duloxetine 120mg/day or pregabalin 600mg/day) or standard dose combination therapy (duloxetine 60 mg/day and pregabalin 300 mg/day). After a subsequent 8 weeks, both groups showed clinically relevant pain reduction, with no significant differences in neuropathic pain between maximum-dose monotherapy and standard dose combination therapy. This study highlighted the feasibility of combination pharmacotherapy for PDPN.[38]

NOVEL PHARMACOTHERAPIES:

While current therapies for Painful Diabetic Peripheral Neuropathy (PDPN) have limitations, several novel pharmacotherapies are under investigation. Dextromethorphan, an NMDA receptor antagonist, co-administered with a P4502D6 inhibitor, demonstrated efficacy in Phase III trials. Desvenlafaxine, a metabolite of venlafaxine, exhibited improved efficacy in a multi center trial.[39] EMA401, an angiotensin II type 2 receptor (AR2) antagonist, showed promisein a placebo-controlled trial for post-herpetic neuralgia. ARA290, a non-hematopoietic peptide, acted as an erythropoietin receptor agonist and TRPV1 receptor antagonist, with reported analgesic effects in PDPN and sarcoid neuropathy. ISC 17536, a novel TRPA1 pain receptor inhibitor, demonstrated potential benefits in a subpopulation with preserved small nerve fiber function. Tanezumab, a fully humanized monoclonal antibody targeting nerve growth factor (NGF), reduced DPN-associated pain in a reported study.[40] ATP-gated receptor channels P2X3 and P2X2/3 antagonists (A-317491 and sinomenine) show promise in animal models and may warrant investigation in human trials. Topical agents like clonidine, amitriptyline, ketamine, and gabapentin gel are also being explored for refractory neuropathic pain. Vitamin D supplementation has shown potential in managing PDPN, with studies indicating its association with diabetes complications. A single intramuscular dose of vitamin D3 demonstrated substantial pain relief and improved quality of life in a Pakistani study. However, robust randomized controlled trials are needed to establish its effectiveness. The development of these novel pharmacotherapies holds promise for transforming the landscape of neuropathic pain management.[41]

MECHANISM BASED THERAPY:

Understanding the neurobiological processes of Painful Diabetic Peripheral Neuropathy (PDPN) is crucial for future mechanism-based therapies. Differentiating patients based on the irritable vs non-irritable nociceptor phenotype, a concept proposed by Fields et al in post-herpetic neuralgia, is integral to identifying effective treatments. Studies on oxcarbazepine and lidocaine patches (Na channel antagonists) show greater efficacy in patients with the irritable nociceptor phenotype, indicating a potential role for these drugs in managing symptoms associated with aberrant Na channel activity. Similarly,a negative study of topical clonidine in PDPN demonstrated benefits in individuals with functional nociceptors, suggesting that assessing cutaneous nociceptor function could guide the selection of patients for topical therapy. In a randomized crossover trial of pregabalin, non-responders had lower intraepidermal nerve fiber density, emphasizing the potential importance of small nerve fibers in drug therapeutic effects.[42]

Recent shifts in understanding DPN and PDPN pathomechanisms highlight the association with central nervous system pathology. Efficiency in conditioned pain modulation (CPM) and Hoffman's reflex dependent depression (HRDD) are emerging as measures predicting responses to tapentadol, duloxetine, and gabapentin therapy. Patient stratification based on sensory phenotype offers a promising avenue for personalized treatment in neuropathic pain. Prospective studies should consider detailed sensory phenotyping at baseline to identify subgroups that may benefit from specific therapeutic interventions.

CONCLUSION:

The management of Painful Diabetic Peripheral Neuropathy (PDPN) presents numerous challenges, including underdiagnosis and undertreatment. Attaining complete pain resolution is rare, and a 30–50% reduction is considered a favourable outcome. Medications used often carry a significant side effect burden, necessitating careful consideration of comorbidities and contraindications. The trial-and-error approach to anti-neuropathic pain therapy selection is common, highlighting the need for more effective treatments.[43]

Further research is imperative to develop mechanistic-based treatments, paving the way for individualized pain management. Future clinical trials should incorporate detailed pain phenotyping to enhance our understanding and improve the outcomes for individuals with PDPN.

REFERANCE:

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
2. Callaghan BC, Price RS, Chen KS, Feldman EL. The importance of rare subtypes in diagnosis and treatment of peripheral neuropathy: a review.
   3. JAMA Neurol. 2015;72(12):1510–1518. doi:10.1001/jamaneurol.2015.2347
4. Iqbal Z, Azmi S, Yadav R, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin The. 2018;40(6):828–849. doi:10.1016/j.clinthera.2018.04.001
5. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136–154. doi:10.2337/dc16-2042

6. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments.
7. Diabetes Care. 2010;33(10):2285–2293. doi:10.2337/dc10-1303
8. Tesfaye S, Vileikyte L, Rayman G, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev. 2011;27(7):629–638. doi:10.1002/dmrr.1225
9. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. Endocrinol Metab Clin North Am. 2013;42(4):747–787. doi:10.1016/j. ecl.2013.06.001
10. Stewart WF, Ricci JA, Chee E, Hirsch AG, Brandenburg NA. Lost productive time and costs due to diabetes and diabetic neuropathic pain in the US workforce. J Occup Environ Med. 2007;49(6):672–679. doi:10.1097/JOM.0b013e318065b83a
11. Alleman CJ, Westerhout KY, Hensen M, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. Diabetes Res Clin Pract. 2015;109(2):215–225. doi:10.1016/j.diabres.2015.04.031
12. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med. 2004;21(9):976–982. doi:10.1111/j.1464-5491.2004.01271.x
13. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022;28(10):923–1049. Doi:10.1016/j.eprac.2022.08.002
14. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. Diabetes Care. 2006;29 (4):883–887. Doi:10.2337/diacare.29.04.06.dc05-2180
15. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53–59. Doi:10.1097/j.pain.0000000000001365
16. Spallone V, Morganti R, D'Amato C, Greco C, Cacciotti L, Marfia GA. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. Diabet Med. 2012;29(5):578–585. Doi:10.1111/j.1464-5491.2011.03500.x
17. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22(10):1911–1920. Doi:10.1185/030079906x132488
18. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1(3):277–299. Doi:10.1016/0304-3959(75)90044-5
19. Price R, Smith D, Franklin G, et al. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. Neurology. 2022;98(1):31–43. Doi:10.1212/wnl.0000000000013038
20. D'Amato C, Morganti R, Di Gennaro F, Greco C, Marfia GA, Spallone V. A novel association between nondipping and painful diabetic polyneuropathy. Diabetes Care. 2014;37(9):2640–2642. Doi:10.2337/dc14-0528
21. Ziegler D, Tesfaye S, Spallone V, et al. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: international expert consensus recommendations. Diabetes Res Clin Pract. 2022;186:109063. Doi: 10.1016/j.diabres.2021.109063
22. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. Endocrine Connections. 2019;8(10):1324–1329. Doi:10.1530/ec-19-0382
23. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376(9739):419–430. Doi:10.1016/s0140-6736(10)60576-4
24. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103–117. Doi:10.1016/0168-8227(95)01064-k
25. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006;29(6):1294–1299. Doi:10.2337/ dc06-0224
26. Amato Nesbit S, Sharma R, Waldfogel JM, et al. Non-pharmacologic treatments for symptoms of diabetic peripheral neuropathy: a systematic review. Curr Med Res Opin. 2019;35(1):15–25. doi:10.1080/03007995.2018.1497958
27. Bosi E, Bax G, Scionti L, et al. Frequency-modulated electromagnetic neural stimulation (FREMS) as a treatment for symptomatic diabetic neuropathy: results from a double-blind, randomised, multicentre, long-term, placebo-controlled clinical trial. Diabetologia. 2013;56 (3):467–475. Doi:10.1007/s00125-012-2795-7
28. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. JAMA Neurol. 2021;78(6):687–698. Doi:10.1001/jamaneurol.2021.0538

29. Rastogi A, Uppula P, Saikia U, Bhansali A. Effect of monochromatic infrared energy on quality of life and intraepidermal nerve fiber density in painful diabetic neuropathy: a randomized, sham control study. Neurol India. 2021;69(5):1331–1337. Doi:10.4103/0028-3886.329614
30. Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020;8(8):Cd007407. Doi: 10.1002/14651858.CD007407.pub4
31. Sloan G, Alam U, Selvarajah D, Tesfaye S. The treatment of painful diabetic neuropathy. Curr Diabetes Rev. 2022;18(5): e070721194556. Doi:10.2174/1573399817666210707112413
32. Alam U, Sloan G, Tesfaye S. Treating pain in diabetic neuropathy: current and developmental drugs. Drugs. 2020;80(4):363–384. Doi:10.1007/ s40265-020-01259-2
33. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med. 2014;161(9):639–649. Doi:10.7326/m14-0511
34. Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled study. J Pain. 2017;18(1):42–53. Doi:10.1016/j.jpain.2016.09.008
35. Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2016;9(9): Cd012329. Doi:10.1002/14651858.Cd012329
36. Iacob E, Hagn EE, Sindt J, et al. Tertiary Care Clinical Experience with Intravenous Lidocaine Infusions for the Treatment of Chronic Pain.Pain Med. 2018;19(6):1245–1253. Doi:10.1093/pm/pnx167
37. Tesfaye S, Sloan G, Petrie J, et al. Optimal pharmacotherapy pathway in adults with diabetic peripheral neuropathic pain: the OPTION-DM RCT. Health Technol Assess. 2022;26(39):1–100. Doi:10.3310/rxuo6757
38. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"–a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013;154 (12):2616–2625. Doi: 10.1016/j.pain.2013.05.043
39. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth. 2014;113(1):148–156. Doi:10.1093/bja/aeu056
40. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain. 2012;153(6):1193–1198. Doi: 10.1016/j.pain.2012.02.021
41. Jarvis MF, Burgard EC, McGaraughty S, et al. A-317491, a novel potent and selective non-nucleotide antagonist of P2X3 and P2X2/3 receptors, reduces chronic inflammatory and neuropathic pain in the rat. Proc Natl Acad Sci U S A. 2002;99(26):17179–17184. Doi:10.1073/ pnas.252537299
42. Rao S, Liu S, Zou L, et al. The effect of sinomenine in diabetic neuropathic pain mediated by the P2X (3) receptor in dorsal root ganglia. Purinergic Signal. 2017;13(2):227–235. Doi:10.1007/s11302-016-9554-z
43. Alam U, Fawwad A, Shaheen F, Tahir B, Basit A, Malik RA. Improvement in neuropathy specific quality of life in patients with diabetes after vitamin D supplementation. J Diabetes Res.2017;2017:7928083. Doi:10.1155/2017/7928083