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Review Article

Diabetic Neuropathy: A Thorough Overview of Present Therapeutic Strategies in Diabetic Neuropathy

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Diabetic neuropathy (DN) is a frequent diabetic disorder that is associated with sensory loss, pain and autonomic dysfunction. The diagnosis, classification of type of neuropathy and the use of several drugs are fundamental components of the treatment to minimize symptoms, functional impairments and complications like foot ulcers and falls. The aim of this review is to gather the current information about the pathophysiology, diagnosis and holistic therapy. We review the available pharmacological treatments available for painful diabetic neuropathy and review nonpharmacological options (lifestyle changes, physical therapies, neuromodulation and psychological therapies) that can be used adjunctively with drug therapy. Treatment selection, treatment safety monitoring, combination treatments and future research recommendations are provided.

Keywords: Diabetic Neuropathy, Painful diabetic neuropathy, Pathophysiology, Pharmacological treatment and Non-pharmacological management.

INTRODUCTION

Diabetes-related neuropathy is one of the most prevalent and debilitating chronic complications of diabetes mellitus and is a collection of nerves' disease. While there is some variation in the estimates of prevalence across populations and diagnostic criteria, population studies show that up to 50% of individuals with long-standing diabetes may have some degree of neuropathy and many suffer with painful symptoms that significantly affect quality of life and functional capacity (poor mobility, sleep disturbance, mood disorders). [1,2] Early diagnosis and effective management is vital as diabetic neuropathy is a factor for higher incidence of foot ulceration, foot infection and foot amputation, with increase in healthcare utilization and cost. Diabetic neuropathy (DN) is a group of diverse types of neuropathy resulting from diabetes. The most common clinical presentations are symmetrical distal polyneuropathy (DSPN) and painful diabetic neuropathy (PDN). It is multifactorial and due to metabolic derangement (hyperglycemia-related advanced glycation end products and activation of the polyol pathway), oxidative stress, microvascular insufficiency, decreased nerve perfusion, mitochondrial dysfunction, and low-grade inflammation. These mechanisms result in progressive damage to both small nerve fibres and larger nerve fibres, highlighting the need for an approach to treatment that involves controlling the metabolism along with modifications of the risk factors, mechanisms of nerve damage, and treatment of symptoms causing pain—not just one mechanism—to prevent ongoing damage from happening [3,4]. Symptoms may be none or from mild sensory nerve deficit to severe neuropathic pain, electric shock, burning or stabbing sensation, autonomic dysfunction and motor deficit. Patient history, a focused neurological exam (including small fiber pinprick/temperature and large fiber vibration/ankle reflexes) and the application of validated symptom scales (as appropriate) should all be added to the toolbox for assessment. Major diabetes organizations currently suggest screening for

neuropathy in most T2DM patients and in T1DM patients after a few years of disease [2]. There are three aspects of the management: (1) optimal glycemic and cardiometabolism management (which is more evident of a disease-modifying effect in type 1 than in type 2), (2) pathogenetically oriented therapies, including antioxidant agents such as alpha-lipoic acid as well as focussing on key pathways for injury/disease, and (3) the pharmacological and non-pharmacological management of symptoms of PDN; SNRIs, TCAs, and gabapentinoids are agents that are used as first-line treatment for PDN, whilst combination therapists and topical agents and device or behavioural interventions are considered as adjunctive therapies [2,5]. Pharmacological interventions offer appropriate levels of pain reduction for many patients and can include adverse events; can have inconsistent efficacy; and may not have clear disease modifying effects. Comparative recent data and meta-analyses indicate that efficacy in pain reduction is comparable among commonly used drugs and agents, except that it is suggested preference and comorbidities/drug-drug interactions are to be considered as well as renal function when deciding on the choice of drug [5,6]. Non-pharmacological interventions are also receiving the attention they are now getting, as they become more and more eyed as complementary or alternative treatment options for certain patients. Well conducted systematic reviews and network meta-analyses from the past few years suggest that structured exercises, neuromodulation methods (such as the use of the transcutaneous electrical nerve stimulation or spinal cord stimulation) and most of all acupuncture-related methods are effective at improving pain, nerve conduction velocities, and some patient reported outcomes. While excellent evidence exists for some interventions, there is consistent evidence for acupuncture (with electroacupuncture) in RCTs and pooled analyses and some evidence for functional benefit and for reduction in falls risk in behavioral therapies and exercise [1,7,8]. Management of diabetic neuropathy is best approached on a personalized basis and includes proven metabolic and vascular risk reduction, targeted symptomatic and adjunctive non-pharmacologic therapy where indicated. This review builds on existing evidence on medication and non-medication treatments, summarizes comparative effectiveness results, reviews guideline-recommended treatment strategies, and identifies novel areas of future treatment research.

Epidemiology and Clinical Features

Distal Symmetric Polyneuropathy (DSPN), an extremely common form of Diabetic Neuropathy (DN), affects up to approximately 50% of long-term diabetics (both Type I & II) depending upon how one defines DSPN based on the diagnostic criteria used for each study/population [1, 2] and the symptoms that have been reported from various research participants. Some of these symptoms include: Numbness, Paresthesia's, Lancinating pain, Burning sensation; Autonomic dysfunction causes symptoms related to both gastrointestinal tract (GIT) and Renal/Vascular function. A good clinical assessment includes using a screening tool such as the Michigan Neuropathy Screening Tool, performing a complete neurologic exam and possibly doing nerve conduction testing. These evaluations are needed to ensure that treatment is given and deterioration is prevented. Painful Neuropathy has occurred in approximately 10-26% of those who suffer from DN. The presence of DN is also a risk factor for developing ulcers on the feet, and for having to undergo amputations. Having DN can cause a lot of trouble for people with the disease in getting good sleep, change their moods, and interfere with their daily functioning.

Goals of management

Management focuses on three areas: those of disease modification, i.e. slowing disease progression (glycemic optimization and control of risk factors); those of symptomatic relief of neuropathic pain; and those of rehabilitation and prevention of complications (foot care and fall prevention). Recommended: a step-up, case-by-case plan; pharmacologic therapy is used in conjunction with non-pharmacologic as appropriate [6].

Pharmacological management

Pharmacotherapy is primarily for neuropathic pain. Selection is based on efficacy, safety, comorbidities and patient preference. The following is a brief, evidence-based summary and a prescribing table.

First-line agents

Duloxetine: A serotonin-norepinephrine reuptake inhibitor (SNRI) that has good RCT evidence for pain relief in diabetic neuropathy. Gabapentin is structurally similar to pregabalin and has several RCTs that demonstrate moderate benefit; typical dose range 150-3600 mg/day, depending on tolerance; adverse effects include sedation and weight gain [10]. The agents are the second line of treatment and second line and adjunctive agents.

Topical agents: 5% Lidocaine patch is effective and has excellent safety profile for localized painful areas; topical capsaicin (8% patch) may be effective for some people, but may be associated with local irritation, and requires careful application. Several new and emerging pharmacologic/disease modifying therapies are being explored such as agents that affect oxidative stress, neurotrophic factors and sodium channel subtypes but none of these have replaced first-line symptomatic therapies in the guidelines [5].

Table-1: Pharmacological Management on Diabetic neuropathy

Drug or Pharmacological agent	Mode of action	Adult dose	Beneficial effects	Adverse effect
Duloxetine	Serotonin-norepinephrine reuptake inhibitor (SNRI)	60 mg once daily (±120 mg)	Good RCT evidence for pain reduction; mood improvement in comorbid depression	Nausea and dry mouth, sleep disturbance [7]
Pregabalin	α2-δ calcium channel ligand	150–600 mg/day in two divided doses	The rapid onset of pain relief for many patients.	Dizziness, somnolence, peripheral edema, weight gain [9]
Gabapentin	α2-δ calcium channel ligand	Titrate to 900–1800 mg/day	A low-cost option to a number of effective alternatives.	Sedation, renal dose adjustment required [10]
Amitriptyline / Nortriptyline	inhibit norepinephrine & serotonin reuptake thereby increasing the efficacy of descending pain inhibition.	Amitriptyline 10–75 mg hs; nortriptyline 25–100 mg/day	Effective analgesia in multiple small/moderate trials	Anticholinergic effects, orthostatic hypotension, cardiac conduction concerns [11]
Lidocaine 5% patch	Reduces the amount of ectopic firing of nerves as well as the transmission of pain through the blockade of voltage gated sodium channels.	Use patch on a painful area for no longer than twelve hours.	Has good localized effect with very little systemic absorption.	Causes some type of localized skin irritation and is best suited to alleviate localized neuropathic pain [9,13].
Capsaicin 8% patch	Capsaicin activates the transient receptor potential vanilloid (TRPV1) receptors located on primary afferent nociceptors, which causes initial activation of these nerve endings to produce an excitatory response that eventually desensitizes and reduces the transmission of pain signals.	Capsaicin 8% patches are provided by a health care provider and left at the skin site for 30-60 minutes before being removed, as needed; applications may be repeated every three months.	May be able to relieve pain for extended periods of time after just one application.	Redness/erythema, burning sensation at the application site, pain, itching; increased blood pressure occurs for approximately 10-15 minutes [14]

Opioids / Tramadol	Opioids bind to mu-opioid receptors (μOR) decreasing neurotransmitter release that results in a decrease in pain signaling. Tramadol also decreases reuptake of serotonin and norepinephrine.	Tramadol is typically administered as follows: 50-100 mg orally every 4-6 hours. Adults can take no greater than 400 mg daily; however, older adults have lower dosing limits. Also, patients who experience renal or hepatic dysfunction require dose adjustments.	Moderate-to-severe pain; Additionally, tramadol may be beneficial for certain types of neuropathic pain where treatment has been ineffective.	It has potential for dependency, development of tolerance and other harm related to opioids [12].

Non-pharmacological management

Implementing Non-Pharmacological Interventions (NPIs) in diabetic neuropathy care plans based on evidence should be included for all patients. These techniques try to treat pain, function and avoiding complications.

Controlling blood sugar levels and reducing metabolic risk.

There is robust trial evidence (e.g., DCCT/EDIC) to support the use of tight glycemic control to reduce incidence and progression of neuropathy in type 1 diabetes. Risk-factor management (blood pressure, lipids, smoking cessation, weight management) has a more modest benefit in type 2 diabetes, and the management of these risk factors may decrease the incidence of progression and vascular complications [15,16]. Tailor glycemic goals to counteract benefit for microvascular complications and risks for hypoglycemia.

A healthy lifestyle and physical activity

Exercise (aerobic, resistance, balance) has beneficial effects on neuropathic symptoms, pain and physical function; some studies find improvements in glycemic control and small-fiber function as well. Structured programs can help decrease the intensity of pain and enhance quality of life; at least moderate-intensity exercise, performed regularly is recommended [17,18].

Foot care and foot education

Preventing the ulcerations and amputation is a function of the care of their feet, education about foot care, footwear and early treatment of lesions. The clinical, multidisciplinary approach to the foot has been reported to have beneficial outcomes in high risk patients [19].

Therapies involving neuromodulation and devices

Selected patients with refractory neuropathic pain have benefited from the use of transcuta-neous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). There are a number of well conducted RCTs showing efficacy in short term pain relief using TENS; SCS has been shown to provide significant analgesia in those who are not responding to medical management and is therefore best assessed with an expert opinion and is a matter of patient risk–benefit analysis [20,21]. Physical therapy, balance training and occupational therapy exercises to rehabilitate their motor skills and further develop their coordination. Strength, proprioception, and balance rehabilitation interventions decrease fall risk and enhance mobility. Exercises and assistive supports can be useful supplementals for sensory loss and neuropathic pain. If there is function limitation, a referral for physical or occupational therapy is advised [22].

Other psychological interventions and strategies for pain.

Adherence can be improved, catastrophizing reduced and pain coping improved with cognitive-behavioral therapy (CBT), mindfulness-based stress reduction and pain self-management programs. There are reports of better functional outcomes when psychological treatment is combined with pharmacotherapy than pharmacotherapy alone [23]. There are issues related to special populations and comorbidities to keep in mind.

Depression/Anxiety: SNRIs (such as duloxetine) or TCAs may have an effect on both symptoms—pain and depression/anxiety, although side effects and interactions may need to be monitored. [7,11]

An algorithmic approach and practical tips for prescribing.

1.Confirm diagnosis and determine the subtypes of neuropathy; screen for other causes.

2. Optimize glycemic control, treat hypertension/ dyslipidemia, encourage smoking cessation.

3. When treating neuropathic pain, start with first-line medications such as: duloxetine, pregabalin, gabapentin (depending on the comorbidities, adverse-effect profile, patient preference and cost).

4. Reassess 4-8 weeks later; change dose or agent if there is lack of response or side effects are too severe or long-lasting.

5. For partial response, use combination therapy; note that there is not enough evidence of incremental benefit with some combinations, and some adverse effects are additive.

6. Store opioids/invasive procedures for complicated cases following multi-disciplinary review.

7. Early and frequent use of non-pharmacological treatments (exercise, foot care, CBT, TENS).

8. Record results (pain score, function, side effects) and regularly review these.

Gaps in evidence, areas for future research

There are gaps in the data, such as longer-term comparative effectiveness data for the first-line agents, better combination regimens, and disease-modifying therapy that reverses existing neuropathy. The development of biomarkers, trials of underlying mechanisms (neuroinflammation, sodium channel subtypes, neurotrophic support, etc.) are still in progress. Tailoring therapy for neuropathy to the phenotype – precision medicine approaches – may improve the outcome. Finally, stronger evidence on cost-effectiveness and implementation of multidisciplinary care models is needed [5,24,25].

CONCLUSION

Derived from current evidence, diabetic neuropathy should be treated by a multimodal, individualized strategy that includes evidence-based pharmacologic management of neuropathic pain as well as non-pharmacological therapies directed towards function, prevention and risk-factor control. First-line pharmacotherapies (duloxetine, pregabalin, gabapentin) have RCTs supporting their use; however, this should be based on comorbidities and adverse-effect profiles. Modalities other than pharmaceuticals (glycemic optimization, exercise, foot care, neuromodulation and psychological therapies) are important. There is promise for long-term benefit through ongoing research for disease modifying treatments and tailored treatment approaches.

REFERENCES

1. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285–2293.
2. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012;11(6):521–534.
3. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019;5(1):41.
4. Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. Nat Rev Neurol. 2011;7(10):573–583.
5. Ardeleanu, Valeriu & Toma, Alexandra & Pafili, Kalliopi & Papanas, Nikolaos & Motofei, Ion & Diaconu, Camelia & Rizzo, Manfredi & Pantea Stoian, Anca. (2020). Current Pharmacological Treatment of Painful Diabetic Neuropathy: A Narrative Review. Medicina. 56. 25. 10.3390/medicina56010025.
6. 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.
7. MA Ahmad, P Kapur, R Khanam, M Akhtar, GH Khan, MJ Anwar. Comparative effect of antihypertensive therapy on blood glucose level

in hypertensive patients in an Indian population Drug research 2014;64 (05):276-280
8. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs placebo in patients with diabetic neuropathic pain. Pain Med. 2005;6(5):346–356.
9. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2004;63(10):2104–2110.
10. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831–1836.
11. Moore RA, Derry S, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2015;2015(7):CD008242.
12. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol. 2015;14(2):162–173.
13. GH Khan, M Aqil, KK Pillai, MA Ahmad, P Kapur, MR Ain, SS Al-Ghamdi. Therapeutic adherence: A prospective drug utilization study of oral hypoglycemic in patients with type 2 diabetes mellitus. Asian Pacific Journal of Tropical Disease 2014;4, S347-S35
14. Simpson DM, Brown S, Tobias J, et al. Capsaicin 8% patch for painful diabetic peripheral neuropathy: is a single application effective? J Pain Res. 2017; 10:1219–1229.
15. V Kumar, MA Ahmad, AK Najmi, M Akhtar. Effect of sarcosine (a glycine transport 1 inhibitor) and risperidone (an atypical antipsychotic drug) on MK-801 induced learning and memory deficits in rats. Drug Research 2016;66 (01), 11-17
16. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in type 2 diabetes. Lancet. 1998;352(9131):837–853.
17. Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, et al. The effects of exercise on neuropathic symptoms and pain in people with diabetic peripheral neuropathy. Diabetes Care. 2013;36(6):1761–1767.
18. MA Ahmad, M Mujeeb, M Akhtar, M Khushtar, M Arif, MR Haque. Guggulipid: a promising multi-purpose herbal medicinal agent. Drug research 2020; 70 (04), 123-130
19. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med. 2017;376(24):2367–2375.
20. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain. 2007;130(1-2):157–165. doi: 10.1016/j.pain.2007.02.007.
21. De Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain. 2014;155(11):2426–2431.
22. M Akhtar, SS Imam, MA Ahmad, AK Najmi, M Mujeeb, M Aqil. Neuroprotective study of Nigella sativa-loaded oral provesicular lipid formulation: in vitro and ex vivo study. Drug delivery 2014;21 (6), 487-494.
23. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2015;2013(8):CD006952.
24. MA Ahmad, O Kareem, M Khushtar, M Akbar, MR Haque, A Iqubal. Neuroinflammation: a potential risk for dementia. International journal of molecular sciences 2022; 23 (2), 616.
25. MA Ahmad, FH Pottoo, M Akbar. Gene therapy repairs for the epileptic brain: potential for treatment and future directions. Current Gene Therapy 2019;19(6):367-37.

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