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What is New in the Management of Diabetic Peripheral Neuropathy?

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) has been recognized as a major complication of diabetes since the mid-1800s. Dycket al.[1] described the disorder as a symmetrical sensorimotor polyneuropathy attributable to chronic hyperglycemia, associated metabolic derangements, cardiovascular risk covariates, and microvessel alterations. DPN is the most common long-term complication. Affecting 50% of the diabetic population. Prevalence increases with duration of diabetes and poor glycemic control.

Painful diabetic peripheral neuropathy occurs in approximately 25% of patients with diabetes mellitus who are treated in the office setting and significantly affects quality of life. It typically causes burning pain, paresthesias, and numbness in a stocking-glove pattern that progresses proximally from the feet and hands. Clinicians should carefully consider the patient's goals and functional status and potential adverse effects of medication when choosing a treatment for painful diabetic peripheral neuropathy. Pharmacologic and non-pharmacological interventions are available for the treatment of painful DPN. However, there are few high-quality, head-to-head clinical trials comparing these therapeutic approaches, and because the available studies use varying methodologies, it is difficult to know which treatment strategy may be most effective.

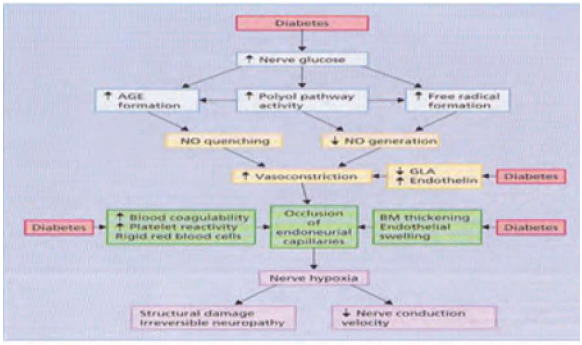

Figure 1 Pathophysiology: biochemical and vascular factors

RISK FACTORS

The major risk factor for diabetic neuropathy is hyperglycemia. In addition to poor glycemic control, moresevere symptoms of diabetic neuropathy are associated with advanced age, hypertension, the duration of diabetes, dyslipidemia, smoking, and heavy alcohol intake.[2] In the Rochester Diabetic Neuropathy Study, the severity of diabetic retinopathy, the duration of diabetes, and the presence of elevated glycosylated hemoglobin (HbA1c) were the main risk factors for diabetic polyneuropathy.[3] The Seattle Diabetic Foot Study found that both sensory and autonomic neuropathy independently influenced the risk of foot ulcers in diabetic veterans.[4]

CLINICAL FEATURES

Symptoms

- Numbness, loss of feeling, prickling, tingling
- Aching pain

- Burning pain
- Lancinating pain
- Unusual sensitivity or tenderness when feet are touched (allodynia)

Signs

- Diminished vibratory perception
- Decreased knee and ankle reflexes
- Reduced protective sensation, such as pressure, hot and cold, pain
- Diminished ability to sense position of toes and feet

Motor symptoms of DPN may be proximal or distal, and focal or diffuse. In the hands, motor symptoms can involve impaired coordination, as demonstrated by difficulty using a key or opening a jar. Because of this loss of dexterity, patients may be unable to check their blood pressure, draw up the proper insulin dose, and maintain their prescribed exercise regimen. Patients with motor symptoms may also show limb weakness, with frequent tripping or toe scraping; difficulty getting up from a prone position; or weakness in the knees when walking up stairs.[5]

The potentially severe pain associated with DPN may lead to insomnia, depression, anxiety, work and activity impairments, and a reduced quality of life (QOL).[6] DPN can also negatively affect patients' gait and posture, which increases their risk of accidental injury compared with healthy individuals.[7] If undiagnosed, DPN can lead to foot ulcers and amputation, especially when the disorder is concurrent with peripheral artery disease.[8]

MANAGEMENT OVERVIEW

Treatment goals in DPN patients include pain modulation, enhanced glucose control, restoration of function, and patient education.[9]

With regard to pain modulation, a 30% reduction in pain, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with DPN.[10] Clinicians should use a pain scale that allows both nocturnal and diurnal mapping, so that they may target the patient's treatment to problematic time periods.

Prevention and Treatment Strategies

A healthy diet and structured exercise that includes balance and resistance training have been shown to increase cutaneous re-innervation, reduce pain, and reduce the risk of falls in patients with DPN.[11] Lowering HbA1c levels can improve peripheral small nerve-fiber function, nerve conduction, and vibration threshold abnormalities.[12] The HbA1c goal is generally less than 7% for most DPN patients, and clinicians should take into account the risks of hypoglycemia and a reduced life expectancy with more stringent targets.[13] There is even evidence suggesting that patients with a history of intensive glycemic control have a "metabolic memory," which can play an important role in preventing the development of DPN.[14] In patients with type 2 diabetes, intensive treatment can achieve significant improvements in the sensation of touch in the upper extremities.[15] In the BARI 2D trial, the use of sensitizing oral medications, such as metformin and thiazolidinediones, significantly reduced the incidence of DPN.[16]

PHARMACOTHERAPY

Although several medications have been implicated for the treatment of DPN, there is limited clinical evidence to determine which agent is most effective, and there is no specific treatment to target the underlying nerve damage. USFDA has approved only three medications (i.e., pregabalin, duloxetine, and tapentadol extended release [ER]) for the treatment of DPN.[17] The choice between first- and second-line agents differs between guidelines because of the differences in the methodology and criteria used in the clinical investigation of these drugs. Generally, tricyclic antidepressants (TCAs), serotonin/norepinephrine reuptake inhibitors (SNRIs), or gamma-aminobutyric acid (GABA) analogs are first-line agents followed by opioids and topical treatments as second-line options.

TCAs

TCAs are generally first-line options for DPN, with multi modal actions. Primarily, they inhibit there uptake of serotonin and noradrenaline but may

have additional effects because of antagonism of N-methyl-D-aspartate, serotoninergic, histaminergic, muscarinic,and alpha adrenergic receptors.[18] Amitriptyline has been a first-line option for the treatment of DPN for several years. Mechanistically, it has an added effect of sodium channel blockade[18] and, compared with other TCAs, has a higher likelihood of causing anticholinergic effects. The recommended starting dose of amitriptyline is 25 mg daily titrated by 25 mg every 3 to 7 days as tolerated to a target dose of 150 mg/d.[19] Although there are no specific dosage recommendations for patients with renal or hepatic impairment, caution should be exercised in these patient populations because amitriptyline is hepatically metabolized but renally eliminated.[19]

ANTICONVULSANTS

Several anticonvulsants have also been studied to assess their efficacy in the treatment of DPN. Although not approved in the United Sates for the treatment of neuropathic pain, gabapentin has been widely used off-label inseveral countries to treat DPN. Gabapentin essentially mimics the actions of the neurotransmitter GABA, butits pain-relieving effects are likely caused by additional inhibition of the a2d unit of the calcium channel.[18] Furthermore, gabapentin has been shown to be the most favorable agent based on safety and efficacy in are cent meta-analysis.[20] The most significant dose limiting side effect with gabapentin is sedation and dizziness; however, other side effects such as weight gain, blurred vision, and edema may also occur.[21] Starting doses of gabapentin are 100 to 300 mg/d,with target doses of 900 to 3600 mg/d in divided dosing.[19]

Pregabalin, a more potent GABA analog, was the second agent to be FDA approved in June 2012 for the treatment of DPN. The starting dose is usually 50 mg 3 times daily, which can be titrated within 1 week to a target dose of 100 mg 3 times daily.[19] Although doses as high as 900 mg/d have been studied,treatment with doses greater than 300 mg/d is not recommended because of dose-dependent adverse effects.[19] Associated side effects with the use of pregabalin are somnolence, dizziness, confusion,ataxia, peripheral edema, and weight gain.

SNRI

Both serotonergic and noradrenergic pathways are hypothesized to be involved in pain, making SNRIs another class of potential treatment options. The first drug to be approved for DPN by the US FDA in 2004, duloxetine, is classified as an SNRI. Data from randomized controlled trials and a recent Cochrane review showed significant improvement in pain scores with the use of duloxetine 60 mg and 120 mg.[22] However, additional studies have shown no significant differences in efficacy between 60 mg once daily and 120 mg (60 mg twice daily), with higher doses being less tolerable.[23] Thus, duloxetine doses should not exceed 60 mg/d, and patients should be started at a lower dose of 20 to 30 mg/d to assess safety and tolerability.[19] Duloxetine should be avoided in patients with hepatic impairment and requires renal dose adjustments.

Opioids

The use of opioids for the treatment of DPN remains controversial. Most studies have not established substantial risk-benefit ratios, and long-term adverse effects can be concerning in this patient population.[18]

Tramadol, an opioid receptor agonist, has been shown to be effective for the treatment of symptomatic neuropathic pain. In August 2012, tapentadol ER became only the third agent to be FDA approved in the United Sates for the treatment of diabetic neuropathic pain. The mechanism of effect is likely caused by a combination of m-opioid receptor agonism and norepinephrine reuptake inhibition.[24] The recommended dose is 10 to 250 mg twice daily with a maximum dose of 500mg/d, but opioid-naive patients should be started at alower dose of 50 mg twice daily.[25]

Topical Agents

Capsaicin, a topical alkaloid derivative from red chili peppers, has also been effective for the treatment of DPN. Patient counselling points with capsaicin focus on the burning sensations associated with its

use. Although these sensations usually dissipate over time with continued use, they may occur with warm/hot water contact or in hot weather.[26] Additionally, it is important to counsel patients on the avoidance of eye contact with the use of capsaicin. Other topical options include lidocaine 5% patches, which have also been used for localized neuropathic pain, although further studies are needed to confirm their efficacy.

TREATMENT OPTIONS FOR DPN

Glucose Control

The reports from DCCT emphasized a role for intensive glucose control through insulin, in both primary and secondary prevention of DPN in patients of type 1 diabetes mellitus (T1DM). The prevalence of DSPN remained lower in the intensive insulin therapy group of the DCCT many years after the initial intervention, which has been termed a memory effect.[27]

In patients of T2DM, the role of intensive glycemic control in preventing and managing DPN is less clear as studies are contradictory. A recent meta-analysis of randomized controlled trials found no significant benefit.[28]

Isletcell transplantation is considered as a less invasive option in patients with type 1 diabetic kidney transplant patients with marked improvement in neurophysiology in these patients, although skin biopsy results showed no improvement.[29]

Table 1 |

Class	Medications	Mechanism of Action
Tricyclic Anti-depressants	Amitriptyline, Desipramine, Imipramine, Nortriptyline	Inhibition of reuptake of serotonin and/or norepinephrine, block of sodium channels, anticholinergic
GABA Analogues	Gabapentin, Pregabalin	Decreases release of glutamate, norepinephrine, and substance P with ligands on voltage-gated calcium channels
Serotonin Norepinephrine reuptake inhibitors	Duloxetine, Paroxetine, Venlafaxine	Inhibition of both serotonin and norepinephrine reuptake
Anticonvulsants	Carbamazepine, Lamotrigine, Oxcarbazepine, Sodium valproate, Topiramate	Inhibition of voltage-gated sodium channels, resulting in reduced peripheral nerve excitability
Topical analgesics	Capsaicin 0.0075%, Lidocaine 5% patch	Desensitization of epidermal nociceptors and blocking nerve conduction
Analgesic opiates	Morphine, Oxycodone, Tramadol	μ-Receptor agonism, inhibition of norepinephrine and serotonin reuptake
Aldose reductase inhibitor	Epalrestat	Inhibition of enzyme associated with hyperglycemia linked ischemic nerve injury
Miscellaneous	α-Lipoic acid	Anti-oxidant

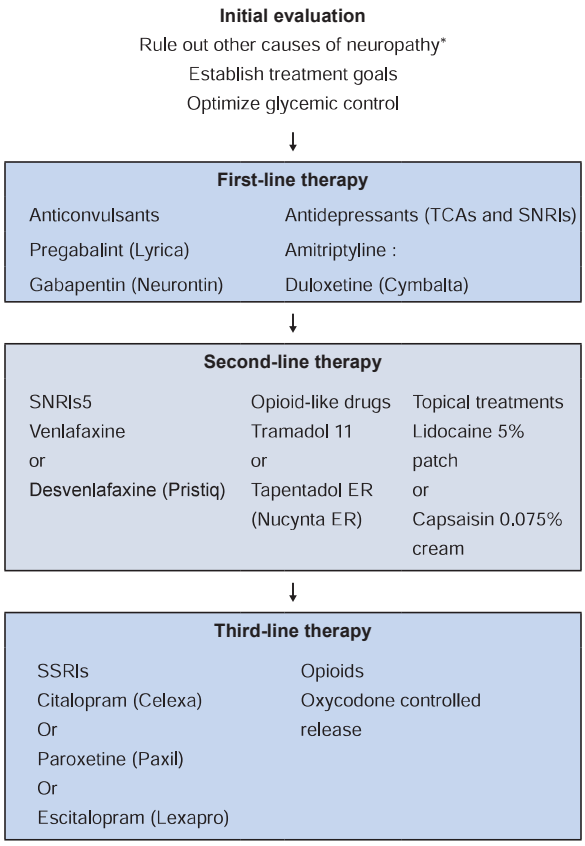

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Figure 2 Management algorithm

NEWER MODALITIES OF THERAPY

Potential Future Agents for Treatment of DPN[30]

1. The oral anti-epileptic drug, ***lacosamide*** selectively enhances slow inactivation of voltage-gated sodium channels without affecting

fast inactivation and may modulate collapsing-response mediator protein 2 (CRMP-2), a protein that is involved in neuroplastic processes such as neuronal outgrowth and the modulation of NMDA receptor subunit NR2B.

2. ***Tebanicline*** (ABT-594) is a neuronal nicotinic acetyl cholin receptor agonist that exhibits potent analgesic activity in preclinical models of acute, chronic, and neuropathic pain.
3. ***NGX-4010*** is a rapid delivery dermal patch containing high (8%) concentration of transcapciasin. It can be applied to the painful skin area for the treatment of peripheral neuropathic pain.
4. ***Chembridge-5861528*** attenuates development of mechanical hypersensitivity.
5. Purinergicreceptor modulators. ***Puerarin*** can improve the total effective rate, correct NCV that was decreased.
6. Adenosine receptor modulator
7. Endocannabinoid modulators ***UCM707*** and ***AM404***
8. Natural Vitamin E, ***tocotrienols***, possessing powerful neuro-protective, anti-oxidant, anti-cancer, and cholesterol lowering properties.
9. Vascular endothelial growth factor
10. ***Botulinum toxin type A***, showing analgesic effects independent of its action on muscle tone, possibly by acting on neurogenic inflammation or inhibiting the release of neurotransmitters.

NON-PHARMACOLOGICAL TREATMENT

- ***Intraneural Facilitation***. This approach aims to bias blood flow into the neural fascicle, improve endoneurial capillary circulation, and reverse intrafascicular ischemia. This passive technique includes stretching muscles, mobilizing joints, tractioning skin, distending visceral structures, and distorting blood vessels to reroute blood to the ischemic nerves.[31]
- ***Pulsed Electromagnetic Field Therapy.*** Pulsed electromagnetic field combined with traditional physical therapy program has a positive effect on diabetic neuropathy symptoms.
- Different alternative therapies are acupuncture,[32] near-infrared phototherapy,[33] low-intensity laser therapy,[34] transcutaneous electrical stimulation,[35] high-frequency external muscle stimulation,[36] and as a last resort, implantation of an electrical spinal cord stimulator.[37]

Brief on Interventional Therapy

Interventional treatments, such as nerve blocks or surgical procedures that deliver drugs to targeted areas, or modulation of specific neural structures, provide alternative treatment strategies in selected patients with refractory neuropathic pain. Although generally safe (Fig. 2), spinal cord stimulation and peripheral nerve stimulation have been associated with hardware-related, biological complications, such as infections and programming-related or treatment-related adverse effects (including painful paresthesias).[38,39]

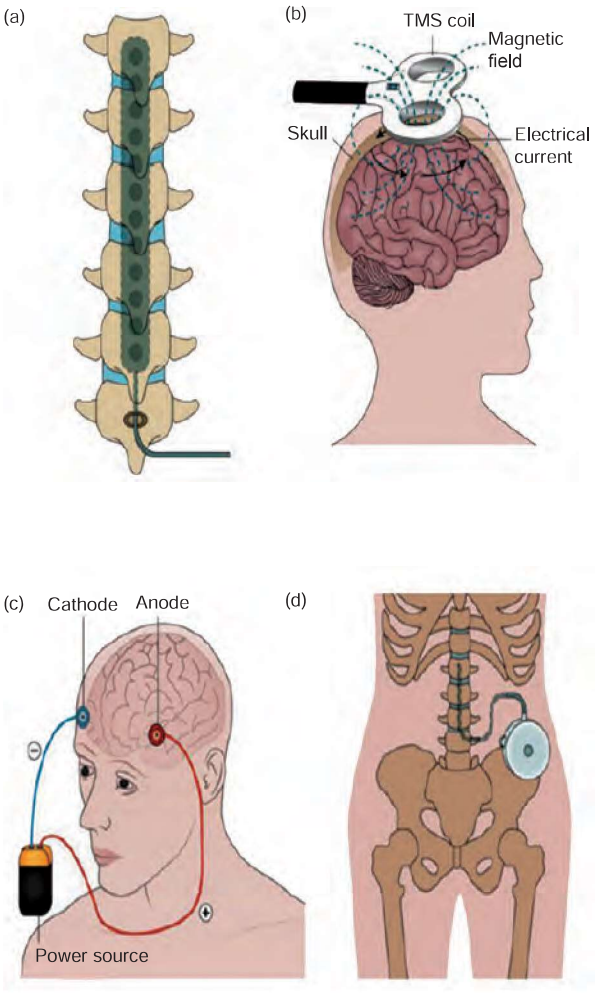

Figure 2 (a) Spinal cord stimulation traditionally applies a monophasic square-wave pulse (at a frequency in the 30–100 Hz range) that results in paraesthesia in the painful region. **(b)** Cortical stimulation involves the stimulation of the pre-central motor cortex below the motor threshold using either invasive epidural or transcranial non-invasive techniques (such as repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation). **(c)** Deep brain stimulation uses high-frequency chronic intracranial stimulation of the internal capsule, various nuclei in the sensory thalamus, periaqueductal and periventricular grey, motor cortex, septum, nucleus accumbens, posterior hypothalamus, and anterior cingulate cortex as potential brain targets for pain control. **(d)** Intrathecal treatments provide a targeted drug delivery option in patients with severe and otherwise refractory chronic pain. The pumps can be refilled through an opening at the skin surface.

GENE THERAPY

In a randomised, blinded trial of intramuscular gene transfer using plasmid vascular endothelial growth factor to treat DPN; efficacy against both sensory loss and diabetic neuropathic pain was seen.[40]

CONCLUSION

This is the era of excellent scientific innovations in the field of biotechnology and medical engineering. We are always in search of modalities that can overcome the barriers. Gene therapy for human neuropathy is moving towards clinical application. Satisfactory treatment of neuropathy remained a headache for the medical fraternity over the decades. We hope for the best in near future.

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