Diabetic Neuropathy: Part 2
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Introduction
Diabetic neuropathy (DN) is a major cause of disability and reduced quality of life. In the previous review we discussed the prevalence, classification, clinical features, pathophysiology and recent advances in the diagnosis of diabetic neuropathy. This section will focus on the traditional and the upcoming therapeutic modalities of this common and troublesome complication of diabetes.

Advances in Management
The existing treatment for Diabetic neuropathy can be subdivided into pathogenesis based and/or symptom based therapy. Currently, the only well-established effective therapeutic modality is intensified metabolic control.

Pathogenesis Based Treatment
Glycaemic Control
The first step in the management of any diabetic polyneuropathy is good glycaemic control. The effect of intensive glucose control on the incidence of polyneuropathy in T1DM was initially studied in DCCT trial. Intensive therapy led to an overall risk reduction of 60% in the development of clinical diabetic neuropathy at 5 years.1 The EDIC (Epidemiology of Diabetes Interventions and Complications) study has further substantiated this information by following the patients of DCCT trial for another 13-14 years.2 On the other hand data from studies of T2DM is less convincing. While the UKPDS study (United Kingdom Prospective Diabetes Study) found significantly reduced risk of neuropathy in the group receiving intensive glycaemic control,3 the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) found no reduction in the risk of new neuropathy in the intensive arm.4 This data suggests that other risk factors like obesity, dyslipidaemia may be important contributors to the risk of neuropathy in T2DM.

Treatment of other risk factors
Growing evidence indicates that factors other than hyperglycaemia play a role in neuropathy risk and pathogenesis. Among 1172 patients with type 1 diabetes without baseline neuropathy followed in the Eurodiab study, hypertension, smoking, obesity, and serum triglycerides were independent risk factors for neuropathy.5 The effective management of hypertension, hyperlipidaemia, obesity and smoking might modify the course of neuropathy in diabetes but this still needs to be proven in future clinical trials.

Reduction of oxidative stress
Oxidative stress is an important component in diabetic neuropathy pathogenesis. Alpha lipoic acid (ALA), Acetyl-L carnitine and Benfotiamine are potential drugs which reduce oxidative stress and have a direct effect on neuropathic injury.6

Alpha lipoic acid is a potent antioxidant and serves a critical role in mitochondrial energy metabolism.7 The efficacy of intravenous ALA (600 mg IV for 3 weeks) has been established by a meta-analysis of 4 prospective trials, wherein it was found to improve both positive neuropathic symptoms and neuropathic deficits.8 Evidence for oral treatment is still conflicting.9 Oral ALA may be started at a dose of 300 mg daily and titrated to 600 mg twice daily.

Acetyl-L carnitine, another antioxidant was found efficacious in alleviating pain and improving nerve fibre regeneration and vibration perception in patients with established diabetic neuropathy in two parallel randomized, blinded controlled trials on 1257 subjects after 52 weeks of treatment.10 Two doses were tested - 500 mg and 1000mg. The higher dose was found to be more effective.

Benfotiamine or S-benzoylthiamine O-monophosphate is a vitamin B1 derivative with antioxidant properties. In a randomized placebo controlled phase III study using 300 mg and 600 mg Benfotiamine (165 diabetic neuropathy subjects), significant improvement was seen in neuropathic Total Symptom Score and its pain subscore over 6 weeks with greater benefit in the 600 mg dose group.11

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**Aldose Reductase Inhibitors (ARIs)**

Aldose reductase is an enzyme in the polyol pathway, whose activation is believed to be an important contributor to the development of diabetic neuropathy. However, the efficacy of ARIs in reversing clinical diabetic neuropathy is still not clearly established.

Epalrestat is the only ARI currently available commercially and has been approved in Japan since 1992. In a 3-year open-label RCT in 594 DN subjects, epalrestat 150 mg/day prevented the deterioration of median motor NCV and minimum F wave latency. Patients’ symptoms (such as numbness, sensory abnormality, and cramping) improved significantly with epalrestat. Ranirestat and Fidarestat are other ARIs undergoing evaluation in phase 3 clinical trials. The effort now is to test these drugs in patients with milder disease, whose diabetes is under better control with a more realistic goal of slowing disease progression.

**Immunosuppressants**

Immunosuppressing therapies have been used in diabetic lumbosacral radiculoneuropathy, based on the evidence that it may have an autoimmune basis. Therapies tried include corticosteroids and immunoglobulins.

**Symptomatic treatment**

Pain management still remains the mainstay of treatment in patients with diabetic neuropathy as it significantly affects the quality of life. Research into this aspect has generated several guidelines, the most thorough and recent ones being, the 2006 and 2010 guidelines from the European Federation of Neurological Societies (EFNS) task force and the 2011 guidelines from the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. According to these guidelines, several classes of drugs are effective in treating diabetic neuropathic pain (summarized in Table).

Till now only duloxetine and pregabalin were formally approved by the FDA for the treatment of diabetic peripheral neuropathic pain. Recently Tapentadol ER (opioid agonist and norepinephrine reuptake inhibitor) has received FDA approval for the same.

Several treatment algorithms have been designed for the treatment of neuropathic pain, the important ones being those from Jensen et al, the EFNS, and Dworkin et al. All three algorithms recommend α-2-δ agonist (gabapentin, pregabalin), tricyclic antidepressants (TCAs), and Selective serotonin noradrenaline reuptake inhibitors (SNRIs — venlafaxine, and duloxetine) as first-line treatments and support opioid analgesics and tramadol as second-line treatments. The choice of the first line agent is made taking into account the co-morbidities and contraindications. For example, TCAs are relatively contraindicated in diabetic patients with a history of heart disease, elderly patients on other concomitant medications such as diuretics and antihypertensives and patients with co-morbid orthostatic hypotension. In those with liver disease duloxetine should not be prescribed and pregabalin or gabapentin should be avoided in those with oedema. Cost is another important issue that needs consideration especially in resource poor settings. TCAs are the most affordable of the first line agents. Gabapentin and venlafaxine are cheaper than pregabalin.

![Figure: Treatment algorithm for painful diabetic neuropathy.](image-url)
and duloxetine, respectively. If pain is inadequately controlled despite titration to maximum tolerated dose, one can switch to an alternative first line agent. Combination of 1st line therapies may be considered if there is pain, despite a change in first-line monotherapy. If pain still persists opioids such as tramadol and oxycodone may be added as second line agents. The algorithm is summarised in Figure. A brief description of the first and second line drugs is given below.

**First Line Agents**
- Tri cyclic antidepressant (amitriptyline, imipramine, nortriptyline and desipramine) — Several well designed studies have proven the efficency of tricyclic antidepressssants in the treatment of diabetic neuropathic pain. While the EFNS guidelines do not recommend a specific drug out of the class, AAN guidelines recommend the use of amitriptyline. Amitriptyline is started at a dose of 10 mg 2 hours before going to bed and increased in 10 mg increments every 5 days to the required dose (usual dose 25-100mg/day). After reaching 50mg, the dose can be stepped up in 25mg increments. A particular advantage of amitriptyline is that it helps in sleep initiation even at low dose. This is particularly beneficial as

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Special comments</th>
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<tbody>
<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>Block the reuptake pumps at the serotonergic and noradrenergic synapses</td>
<td>Amitryptyline 25-100 mg/day, Imiprmine 10-150 mg/day</td>
<td>Anticholinergic effects - dry mouth, postural dizziness, sedation, constipation, urinary hesitancy, heart block in elderly</td>
<td>Evidence from several RCTs, Avoid in diabetic patients with cardiovascular disease (risk of sudden cardiac death at dose &gt; 100 mg/day), Avoid in autonomic neuropathy (exacerbates postural hypotension)</td>
</tr>
<tr>
<td>Selective serotonin noradrenaline reuptake inhibitors (SNRIs)</td>
<td>Increase synaptic availability of 5-HT and noradrenaline in the descending pathways that are inhibitory to pain impulses</td>
<td>Duloxetine 60-120 mg/day, Venlafaxine 150-225 mg/day</td>
<td>Somnolence, nausea, hypertension, Venlafaxine causes clinically significant ECG changes</td>
<td>Avoid venlafaxine in coexistent cardiac disease, Avoid duloxetine in liver disease</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin and pregabalin bind to the α-2-δ subunit of the calcium channel reducing calcium flux, and thus resulting in reduced neurotransmitter release in the hyperexcited neurone.</td>
<td>Gabapentin 900-3600 mg/day, Pregabalin 300-600 mg/day</td>
<td>Dizziness, Somnolence</td>
<td>Avoid gabapentin and pregabalin in peripheral oedema</td>
</tr>
<tr>
<td>Opioid agonists</td>
<td>Analgesia mediated by µ receptor agonist effect (widely distributed on structures involved in nociceptive processing along entire neuraxis)</td>
<td>Tramadol 200-400 mg/day, (Also blocks reuptake of serotonin and norepinephrine) Oxycodone 20-80 mg/day, Morphine sulphate SR 20-80 mg/day</td>
<td>Constipation, drowsiness, nausea, vomiting, dizziness, physical and psychological dependence, analgesic tolerance, withdrawal with abrupt discontinuation, worsening of depression, sleep disturbances, amenorrhea, impotence</td>
<td>Contraindicated in respiratory depression, hypersensitivity, GI obstruction, Tapentadol and tramadol can precipitate serotonin syndrome when used with any serotoninergic drugs (SSRIs, SNRIs, TCAs, Triptans, MAOIs), Do not use in severe hepatic/renal dysfunction.</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>Depletes substance P from nerve terminals</td>
<td>Tapentadol 100-600 mg/day (4-6 divided doses) Extended release formulation 100-500 mg/day (twice daily). Also acts as norepinephrine reuptake inhibitor, Topical capsaicin (0.075%) is applied sparingly 3-4 times per day to affected area</td>
<td>Worsens neuropathic symptoms for first 2-4 weeks of application.</td>
<td></td>
</tr>
</tbody>
</table>

Other drugs: Dextromethorphan, Isosorbide dinitrate spray, nicotine derivative - ABT 594, Botulinum toxin, Levodopa and lidocaine patch.
neuropathic pain becomes worse at night making it difficult for the person to fall asleep. Common dose related side effects include dry mouth, constipation, urinary retention, orthostatic hypotension, somnolence and confusion. As elderly patients can develop heart block, an electrocardiogram (ECG) should be done before starting these drugs. It should also be avoided in diabetic patients with cardiovascular disease (risk of sudden cardiac death at dose >100mg/day) and autonomic neuropathy (exacerbates postural hypotension). Patients taking monoamine oxidase inhibitors should not take tricyclics.

- Serotonin Noradrenaline reuptake inhibitors - Both the EFNS and AAN guidelines support the use of duloxetine (dose 60-120 mg/day) and venlafaxine (dose 75-225mg/day). Common side effects include nausea, somnolence, dry mouth, and constipation. Appetite suppression is common, but is often regarded as a benefit of the drug. Venlafaxine should be avoided in coexistent cardiac disease (produces clinically significant ECG changes) and duloxetine should be avoided in liver disease.

- α-2-δ agonist — Pregabalin is classified as effective with level A evidence by both the EFNS and the AAN guidelines. The recommended dose for pregabalin is 300-600mg a day. Dose escalation of pregabalin can begin at 75mg twice daily, and increase by 75mg increments to 150mg twice daily. Gabapentin is also classified as effective and the recommended dose is 900-3600mg/day (level A evidence by the EFNS, level B drug by AAN). Dose escalation of gabapentin should begin at 300mg (taken 2 hours before bedtime), increasing in 300mg increments every 3 to 7 days to 600mg three times daily. Side effects include dizziness, somnolence and oedema.

Second line agents

- Opioid agonists — Opioid agonists have a defined role as adjunctive therapies in the treatment of diabetic neuropathic pain and have been recommended by both AAN and EFNS guidelines. The major concern of treating physicians with the use of opioids is dependence and addiction. Physical dependence does occur but it is rarely a problem. However one has to be cautious if there is history of alcohol and drug abuse. Constipation is the most common side effect of low-dose oral opiate (hydrocodone and oxycodone) use. Prophylactic institution of a bowel control regimen helps prevent constipation. Tramadol (opioid agonist and serotonin-norepinephrine reuptake blocker) alone or in combination with paracetamol is also effective and does not produce significant tolerance. Tapentadol is the novel opioid agonist that has recently been shown to be superior to placebo in reducing neuropathic pain in a randomized trial cohort of 395 subjects with diabetic neuropathy.

Non pharmacological therapy

Lack of response and unwanted side effects of conventional drug treatments forces many sufferers to try alternative therapies such as acupuncture, near-infrared phototherapy, low intensity light amplification by stimulated emission of radiation (LASER) therapy, magnetic field therapies, transcutaneous electrical stimulation (TENS), frequency modulated electromagnetic neural stimulation (FREMS) therapy, high frequency external muscle stimulation and as a last resort, implantation of electrical spinal cord stimulator.

A recent follow-up of patients fitted with electrical spinal cord stimulators found that stimulators continued to be effective 10 years after implantation. But it is reserved as a last option as the procedure is invasive and is available only at specialist centres.

New Therapies on Horizon

Various agents at different stages of development are currently in the pipeline as disease modifying or symptomatic agents. The future probably belongs to targeted therapies like gene therapy because of their theoretical ability to target a therapy specifically to the nerve or neuron without encountering off target side effects. For example, one study of IM injection of a plasmid containing the vascular endothelial growth factor A gene, VEGFA, demonstrated a small benefit by improving the nerve conduction velocity, IENFD and neurological impairment score. Other drugs under evaluation are PKC (Protein Kinase C) inhibitors like Ruboxistaurin mesylate, NMDA receptor antagonists like Indantadol, newer antiepileptics like lacosamide, acetyl L-carnitine, Olesoxime — a cholesterol like compound with neuroprotective, neuroregenerative and analgesic action, various antioxidants, lipid lowering therapy, nerve growth factors like Coleneuramide, Iroxanadine (p38 kinase activator), C-peptide and Islet neogenesis associated protein.

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Prevention of Complications

Patients with diabetic neuropathy are at increased risk of falls especially when walking on uneven surfaces. Hence they should be counselled regarding risk of falls and given physical therapy intervention after gait evaluation.

Foot ulceration and consequent digit, foot, or limb amputation is another common diabetic complication.
Daily self-examination, with a foot mirror if necessary; pediatric consultation and maintenance for toenails and bunions; orthotic foot support, and use of protective, wide based shoes with adequate toe box and ankle support are recommended for patients at risk for ulcers. If stasis ulcers develop, nonsurgical debridement, application of hydrogels, and empiric antibiotic coverage for wound flora are appropriate therapy.

**Summary**

To conclude, effective management of hyperglycaemia, symptom control, and prevention of foot ulcers and infection through screening and surveillance remain mainstays of diabetic neuropathy management. Traditional and rational diabetic neuropathy treatments will be supplemented by novel cell based therapy and targeted drug delivery systems in the future.

**References**