Painful Diabetic Neuropathy (PDN) is one of the most common forms of neuropathic pain and a frequent reason for presentation to the physician. It is often associated with mood and sleep disturbances. Patients may also complain of decreased physical activity and mobility, increased fatigue, and negative effects on their social lives.

Pain syndromes that last less than 6 months are classified as acute. These include the insulin neuritis syndrome, which occurs often at the beginning of therapy for diabetes and is self-limiting. Pain syndromes lasting longer than 6 months are classified as chronic.

**EPIDEMIOLOGY**
Approximately 50% of patients who have had diabetes for > 25 years develop neuropathy, of whom 50% will have pain as a symptom. Neuropathy is a late finding in type 1 diabetes; however, it can be an early finding in type 2 diabetes.

**PATHOPHYSIOLOGY**
PDN may result from several varieties of diabetic neuropathy, the most common of which is distal sensory neuropathy. However, chronic sensori motor neuropathy is more debilitating.

PDN is commonly caused by involvement of either the C fibres or the Aδ fibres. PDN caused by the involvement of small nerve fibers (C fibres), may present without objective clinical findings, such as decreased peripheral reflexes or abnormalities, on routine electrophysiological studies. Small fiber neuropathies may manifest as a number of different clinical symptoms, including allodynia, burning pain, defective warm thermal sensation, and defective autonomic function, e.g. decreased sweating, dry skin, and impaired vasomotor control. Large fibre (Aδ) pain is deep-seated gnawing, dull or cramping with impaired vibration perception and position sense, depressed tendon reflexes, and sensory ataxia with marked electrophysiological abnormalities.

Allodynia, hyperalgesia, and spontaneous pain may be related to ectopic nerve impulses or abnormal expression of neurotransmitters and their receptors and ion channels.

Multiple mechanisms related to hyperglycemia may contribute to the pathogenesis of diabetic neuropathy. All these mechanisms represent potential therapeutic targets for patients with PDN. In addition, insulin resistance is an atherogenic state, contributing to the development of neuropathy through microvascular insufficiency. During the early course of introduction, insulin itself can produce a self-limiting insulin neuritis that is painful, but intensive treatment of critically ill patients with insulin reduces the development of neuropathy.

Glucose or serum insulin level plays an important mediating factor in the painful symptoms and there may be a direct hyperalgesic effect of hyperglycemia on the dorsal root ganglia. Recovery from painful diabetic neuropathy is more likely to occur if patients are maintained in good diabetic control, which is particularly true if the onset of painful symptoms is acute or sub - acute but is less evident when the onset is insidious and is followed by sensory loss. However other reports seem to indicate that hyperglycemia may not
be an important mediating factor in painful neuropathy.  

**TYPES**

**Acute Painful Neuropathy**

A predominantly small-fiber neuropathy, which is manifested by pain and paresthesias early in the course of diabetes is characteristic. It may occasionally be associated with the onset of insulin therapy and then, it is termed insulin neuritis. All acute neuropathies are of less than 6 months duration. Symptoms often are severe at night. Pain often occurs at the onset of the disease and is often worsened by initiation of therapy with insulin or sulfonylureas.

Acute neuropathy may be associated with profound weight loss and severe depression that has been termed diabetic neuropathic cachexia. It is more common in males. It is self-limiting and responds to symptomatic treatment. Conditions like amyloidosis, arsenic poisoning, Fabry’s disease, HIV infection, and alcoholism should be ruled out.

**Chronic Painful Neuropathy**

Onset is later, often many years after detection of diabetes, and the pain persists for longer than 6 months and becomes debilitating. This condition can result in tolerance to narcotics and analgesics, finally resulting in addiction. It is extremely resistant to all forms of intervention. Pathophysiologic changes in the nervous system can produce both positive symptoms like spontaneous pain and negative symptoms such as loss of sensory quality. Symptoms are prominent in small-fiber neuropathies.

**CLINICAL MANIFESTATIONS**

A simple definition of diabetic neuropathy is “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.” The importance of excluding nondiabetic causes was emphasized in the Rochester Diabetic Neuropathy Study, in which up to 10% of peripheral neuropathy in diabetic patients was deemed to be of nondiabetic etiology.

The pain associated with PDN is often described as tingling, numbness, burning, electrical, or stabbing with parasthesia, hyperesthesia, and deep aching. The pain is typically greater at night. PDN typically develops in the feet and lower legs; however, it may also involve the hands. Neuropathy is chronic and progressive.

**DIAGNOSIS**

The diagnosis of PDN is a diagnosis of exclusion. Patients with PDN should be evaluated for chronic inflammatory demyelinating polyneuropathy, B12 deficiency, hypothyroidism, and uremia by evaluating serum B12, thyroid function tests, blood urea nitrogen, and serum creatinine. Patient should also be evaluated with a 10-g monofilament, 128 Hz tuning fork for vibration and superficial pain sensation testing.

The physical exam should also evaluate for signs of decreased arterial flow, altered reflexes, deformities, ulcers, or slow healing wounds, claw toes and Charcot’s arthropathy.

**Treatment**

Treatment of DPN is challenging and drugs used are broadly categorized into anti depressants and anti epileptics.

1. **Antidepressants**: TCAs are the most studied agents in the treatment of PDN. Amitriptyline was the first TCA to be studied, followed by imipramine. Both drugs are balanced serotonin and noradrenaline reuptake inhibitors which also block a-adrenegic, muscarinic cholinergic, H1-histamine and N-methyl-D-aspartate receptors. TCAs act centrally to reduce the perception of pain. Amitriptyline and imipramine have an NNT of 2.1 (95% confidence interval [CI] 1.8-2.6) to obtain one patient with a 50% pain reduction. They have been studied in multiple placebo - controlled trials. Nortriptyline and desipramine are the metabolites of amitriptyline and imipramine, respectively, and are primarily noradrenaline reuptake inhibitors which also block a-adrenergic, H1-histamine, muscarinic cholinergic, and NMDA receptors. Desipramine has been more extensively studied among the two.

Doxepin is another drug in this group with similar properties, which is also being used topically. Simply put, TCAs are the drugs which are the most cost effective medication. On the flip side, TCAs are relatively contraindicated in patients with a history of ischemic cardiovascular disease, are associated with orthostatic hypotension, dizziness and sedation and cause significant weight gain, especially amitryptiline. Age > 65 yrs is also a relative contraindication. Sedation however, subsides after 3-4 weeks of continued use. Doxepin is the least cardiotoxic TCA.

2. **Other antidepressants**

(a) Duloxetine was the first agent approved by the FDA for the treatment of PDN. It inhibits both serotonin and norepinephrine transporters. Effective doses vary from 60 and 120 mg/day. It is contraindicated in hepatic insufficiency and alcoholism. Blood pressure, heart rate,
and liver enzymes need monitoring.  

(b) Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake. It decreases central pain perception. However it is less efficacious than TCA. Side effects include somnolence, nausea, sweating, tachycardia and hypertension.

(c) SSRIs have been found to be of not much benefit.

ANTI EPILEPTICS

Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, and zonisamide), potentiation of Gamma-aminobutyric acid activity (tiagabine and topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate, and zonisamide), antagonism of glutamate at N-methyl-d-aspartate receptors (felbamate), or 3-hydroxy-5-methyl-4-isoxazole propionic acid(felbamate, topiramate)\(^{10}\). The evidence supporting the use of AEDs for the treatment of PDN is still in evolution. Patients who fail to respond to one AED may respond to another or to two or more drugs in combination.

(a). Carbamazepine: The first ever drug studied for PDN. Carbamazepine acts peripherally by blocking the sodium channels on the A\(_\delta\) nerve fibers. Although carbamazepine is good in the treatment of PDN, it also is associated with aplastic anemia and cognitive defects. Patients must be carefully monitored for the same. In a double-blind, placebo-controlled, crossover trial, 40 patients (30 women and 10 men; mean age, 56.4 yr) received either carbamazepine (200 mg/d) or placebo for 1 wk and reported their pain using a 10-cm analog scale\(^{11}\). Carbamazepine provided significant relief of diabetic peripheral neuropathy pain compared with placebo on d 10 and 14 (P < 0.05).

(b). Lamotrigine: It also acts peripherally to block the sodium channel. It is less effective than Carbamazepine. It can cause aplastic anemia and toxic epidermal necrolysis. Moreover, titration needs to be very slow to prevent Stevens-Johnson syndrome and bradycardia.

(c). Valproate: Valproate also acts peripherally. It is also not very effective. It can lead to thrombocytopenia, aplastic anemia, toxic epidermal necrolysis, and pancreatitis. Liver function tests and complete blood count with platelets must be done periodically.

(d). Topiramate: It is a a fructose analogue. It acts peripherally as a sodium channel blocker and at the GABA receptor. It is one of the very few agents causing weight loss. It is not very effective, as demonstrated by three simultaneous, placebo controlled studies of topiramate for PDN which did not show significance\(^{12}\). Side effects of topiramate included diarrhea, loss of appetite, kidney stones, closed-angle glaucoma and somnolence. Starting dose is 25 mg at night, hiked to 50 mg/d after 4 wk; to a maximum dose of 100 mg for pain relief. A study by Vinik et al\(^{13}\) reported that topiramate relieves symptoms of PDN and improves conduction amplitudes as well as causes an increase in intraepidermal nerve fibers hypothesizing that topiramate may exhibit potential for altering the basic biological nerve dysfunction in diabetic neuropathy.

(e). Phenytoin: Phenytoin has traditionally been used in the treatment of painful neuropathies. However, multiple studies have shown only questionable benefit\(^{14,15}\). It can cause hyperglycemia and precipitate hyperosmolar diabetic coma. There is also a risk of peripheral neuropathy with phenytoin related to duration of use and increased serum levels.

(f). Gabapentin: It acts peripherally to decrease pain perception. Starting dose is 300 mg at bedtime, increased over 5 - 6 weeks to 3600 mg / day\(^{6}\). Higher doses cause significant side effects including dry mouth, constipation, nystagmus, leucopenia, weight gain, somnolence, dizziness, ataxia and nausea. Gabapentin has the additional benefit of improving sleep, which is often compromised in patients with chronic pain. Further, gabapentin is not heptatically metabolized, significantly decreasing its interaction with other medications.

(g). Pregabalin: Pregabalin is only the second agent approved by the FDA for PDN after Duloxetine. It blocks pain perception by acting peripherally at the GABA receptor. Pregabalin is well tolerated and causes less sedation than Gabapentin. However, it has the potential to cause acute renal failure, hyperthermia, secondary acute-angle glaucoma, prolong PR interval, peripheral edema, dizziness, somnolence, ataxia, tremor, blurred vision, diplopia and weight gain, albeit rarely. Starting dose is 75 mg at bedtime, increased over 4 - 5 weeks to 600 mg / day\(^{6}\).

TOPICAL ANALGESICS

1. Capsaicin: Capsaicin is an alkaloid derived from chillies. It has been used for local pain since mid 19th century\(^{16}\).
Capsaicin causes pain-relief by reversibly depleting sensory nerve endings of substance P and by reversibly reducing the density of epidermal nerve fibers. Major obstacle to compliance is the intense burning sensation but it decreases with chronic use. Co-administration of GTN can reduce the discomfort associated with application and also enhance the analgesic effect. The same effect can also be produced by pre-application of 5% lignocaine cream. Sneezing can also occur due to application of capsaicin over dry skin and subsequent inhalation of the capsaicin dust. It must be applied 4 times a day to the entire painful area using gloves. Up to four weeks time must elapse before the effects of capsaicin become apparent.

2. Tricyclic antidepressants: When TCAs are applied topically, side effects are uncommon, yet pain relief occurs. This is possibly mediated by their peripheral actions via peripheral adenosine receptors, sodium channels.

A small randomized, placebo-controlled trial of 40 subjects who had neuropathic pain of mixed etiology produced a reduction of 1.18 on a 0-to-10 linear visual analog score relative to placebo use with the application of a doxepin 5% cream. Side effects were not significant. Amitryptiline and Doxepin are the major TCAs studied and Doxepin has been introduced for wide spread use.

3. Glutamate receptor antagonist: Glutamate receptors are expressed on peripheral nerve terminals and may contribute to peripheral nociceptive signalling. Ketamine is the prototype. However, focus of experimentation has been pain of malignant origin and PDN is still an unexplored field for this group of drugs.

4. Other drugs like clonidine, opioids and cannabinoids are mainly used in malignant pain; however, potential for their use in PDN warrants further investigation.

OTHER THERAPIES
1. Tramadol and Dextromethorphan: Tramadol acts through both monoaminergic and opioid mechanisms. It blocks pain perception centrally. Tramadol has lower abuse potential than other opioids. Dextromethorphan is an opioid. Side effects constipation, urinary retention, and central nervous system effects.

2. Mexilitine: It is an oral analog of lidocaine. It acts peripherally as an ion channel blocker to prevent pain perception. It is a class IB antiarrhythmic agent. It is the fastest acting agent with pain relief, usually within 1-4 days. Mexilitine has the potential to cause arrhythmias, hepatotoxicity, agranulocytosis and toxic epidermal necrosis. It is absolutely contraindicated in patients with second- and third-degree atrioventricular block.

3. Insulin: Continuous intravenous insulin infusion has been efficacious in a few patients. Onset of pain relief is usually within 48 hours.

4. Lignocaine: It can relieve refractory pain if given as an I.V infusion for 10-20 days. If pain relief occurs, this can be followed up by oral mexiletine.

Adjunctive care and supportive therapy:
It is essential to devise an individualized physical fitness programme to improve strength and balance in patients with large-fiber neuropathy. Less labour intensive activities like Yoga and breathing exercises can be helpful. Psychological counseling, bio feed back techniques and judicious use of trans cutaneous nerve stimulation coupled with timely referral to a pain management clinic form the cornerstone of DPN management.

PREVENTION
Strict glycemic control is the best preventive measure for Neuropathy. In addition, controlling hypertension and hyperlipidemia, daily aspirin use, smoking cessation and moderating alcohol consumption are also helpful.

In conclusion, DPN is a difficult condition to treat and is associated with significant morbidity and poor quality of life. Our present understanding of this condition, its pathophysiology and the mechanism of action of various drugs is sketchy at best. More work needs to be done to unravel the knotty issues involved in its management and in the meanwhile prevention by adhering to good glycemic control and moderation in personal habits seem to be the safest bets to keep this problem at bay.

REFERENCES

2. Holder MD, Bolger GT. Chronic sweet intake lowers pain thresholds without changing brain mu- or delta-opiate receptors. Behav Neural


