An introduction to Diabetic Neuropathy: A Review

Dr. Zaffar Hussain
Associate Professor, Department of Medicine, Institute of Asian Medical Sciences, Srinagar, India

ABSTRACT
Diabetic neuropathy is the most frequent and devastating complication of diabetes mellitus leading to great morbidity and mortality, resulting in a massive financial burden for diabetes care. The prevalence of diabetic neuropathy ranges from 10% within one year of diagnosis of diabetes mellitus to 50% of patients with diabetes for greater than 25 years. Symptoms associated with large fibre damage include weakness, numbness, burning or tingling, and loss of balance, while those related with small fibre damage include pain, anaesthesia to pin and temperature sensation, and autonomic dysfunction. Chronic persistent hyperglycaemia is the key component and should not be overlooked because the progression of the disease may lead to diabetic foot. The objective of the article is to provide a detailed summary of definition, pathogenesis, classification, diagnosis and management of the patients with diabetic neuropathies. Good clinical history and complete physical examination including foot inspection to support the need for regular self-care are the basis of assessment followed by therapeutic and laboratory studies. Strict control of blood sugar is the single utmost preventive measure for diabetic neuropathy. Timely diagnosis and management of dyslipidaemia and hypertension, may aid to prevent, delay, or slow the development of diabetic neuropathy. Management of painful diabetic neuropathy includes tricyclic compounds, serotonin–norepinephrine reuptake inhibitors (e.g. duloxetine), antiepileptics (e.g. pregabalin), opiates, and physical therapies, the antioxidant alpha lipoic acid and topical medications.

Keywords: Diabetic neuropathy; hyperglycaemia; hypertension; dyslipidaemia.

INTRODUCTION
Diabetes mellitus is an emerging global health problem that involves the general population in an overwhelming manner, and is a physical, psychological, and economic cataclysm to a number of those patients who are afflicted by it. Diabetic neuropathy is the most frequent and worrying complication of diabetes mellitus, leading to vast morbidity and mortality and resulting in a massive financial burden for diabetes care.[1] The prevalence of diabetic neuropathy ranges from 10% within one year of diagnosis of diabetes mellitus to 50% of patients with diabetes for greater than 25 years.[2] Duration of diabetes, age, long-term poor blood sugar control (raised HbA\textsubscript{1c}), high blood pressure, high triglyceride levels are the various risk factors studied and proved that raises the likelihood of neuropathy.[3] The exact pathogenesis of diabetic neuropathy in spite of current advances remains enigmatic ; however, unanimity is in the fact that neuropathy in diabetes mellitus is a multifaceted disease. Chronic persistent hyperglycaemia is a key component in the development of diabetic peripheral neuropathy, the diabetic condition produces impaired neurotropism, axonal transport and gene expression through four main pathways viz. Polyol pathway (Sorbitol pathway), Advanced glycation end products (AGE’S), Protein Kinase C Pathway (PKC pathway) and Hexosamine pathway.[4,5,6,7,8 ] The most common presentation of diabetic peripheral neuropathy is diabetic peripheral neuropathic pain (DPNP), which characteristically manifests as burning, shooting pain in the feet or lower limbs. Symptoms related with large fibre damage include weakness, numbness, burning or tingling, and loss of balance, while those related with small fibre damage include pain, anaesthesia to pin and temperature sensation, and autonomic dysfunction.[9,10,11] Clinical diagnosis of diabetic neuropathy is established on the basis of good clinical history, complete physical and neurological examination, and includes certain diagnostic tests like vibration perception threshold, monofilament test, electromyography (EMG) and nerve conduction studies, (NCS), [12,13,14] Foot wounds are the

*Corresponding Author Address: Zaffar Hussain, Associate Professor, Department of Medicine, Institute of Asian Medical Sciences, Srinagar, India; E-mail ID: hussainzaffar6@gmail.com
most common diabetes related cause of hospitalisation and are a common forerunner to amputation.[15,16] Tight glycaemic control is the single greatest preventive measure of diabetic neuropathy.[17]

MATERIALS AND METHODS
Exploration of published articles associated to Diabetic neuropathy was conducted and abstracts and full articles were incorporated for the groundwork of this review from online basis. I have measured for the review in the progression obtained from scientific publications with validation based methods and information Scrutiny. The databases utilized for obtaining information are scientific research publications from indexed journals available through Pub Med, Scopus, Google Scholar and Science Direct. The inclusion criteria were primarily literature of well-designed and controlled studies with obvious results precise for diabetic neuropathy.

RESULTS

Definition: Diabetes is one of the principal causes of peripheral neuropathy, a heterogeneous set of disorders that can affect neuronal function throughout the body.[12,18] In 1998, an International consensus group approved the following definition for use in clinical practice:

“Diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in persons with diabetes after the ruling out of other causes which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infections, immune-mediated, neoplastic, and secondary to other systemic illness.[12,19,20] The WHO definition for diagnosis of diabetic neuropathy is a functional one. It is characterised by a decline and damage of nerve function leading to a loss of sensation, ulceration, and following amputation.[21] The most recent discussion on definition of diabetic neuropathy is to be found in the report of the 2009 Toronto neuropathy expert group meeting, defined diabetic peripheral neuropathy as a “symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro-vessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates.[22] Diabetic peripheral neuropathy is a typical form of axonal neuropathy associated with diabetes and is defined clinically by progressive disease that initially includes distal and symmetrical peripheral neuropathy of sensory nerve fibres, with eventual autonomic and motor system involvement.[1]”

Classification: Three classification systems have been used in the 2005 American Diabetes Association statement.[12,18]

Three classification systems for diabetic neuropathies:-
A. Clinical classification of diabetic neuropathies

Polyneuropathy

- Sensory
- Acute sensory
- Chronic sensorimotor

Autonomic

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Other

Proximal motor (amyotrophy)

Truncal

B. Patterns of neuropathy in diabetes

Length-dependent diabetic polyneuropathy

- Distal symmetrical sensory polyneuropathy
- Large fibre neuropathy
Painful symmetrical polyneuropathy
Autonomic neuropathies
Focal and multifocal neuropathies
- Cranial neuropathies
- Limb neuropathies
- Proximal diabetic neuropathy of the lower limbs
- Truncal neuropathies
Non-diabetic neuropathies more common in diabetes.
- Pressure palsies
- Acquired inflammatory demyelinating polyneuropathy

C. Classification of diabetic neuropathy
Rapidly reversible
- Hyperglycaemic neuropathy
Generalised symmetrical polyneuropathies
- Sensorimotor (chronic)
- Acute sensory
- Autonomic
Focal and multifocal neuropathies
- Cranial
- Thoracolumbar radiculoneuropathy
- Focal limb
- Proximal motor (amyotrophy)
Superimposed chronic inflammatory demyelinating neuropathy

Epidemiology: The epidemiology of diabetic neuropathies is poorly understood. This contemplates variations in diagnostic criteria, prejudiced patient enrolment, and the asymptomatic character of many neuropathies and the huge number of patients with undiagnosed diabetes mellitus. In spite of the limitations, it is known that diabetes mellitus is the principal cause of neuropathy in the western world, and that neuropathies are the most common long term micro-vascular complication of diabetes.[23,24] The prevalence of diabetic neuropathy vary broadly from 5% to 60% and sometimes 100% if patients with asymptomatic nerve conduction dysfunction are incorporated.[25] A case control study conducted by Booya et al has found neuropathy in 10% of diabetic patients at the instance of diagnosis and in general in 50% of patients with a 25-year history of the disease.[26] On the other hand, one more population-based cohort study have shown that 66% of type I and 59% of type 2 diabetes had objective evidence of diabetic peripheral neuropathy.[11] In the united states, the prevalence of painful diabetic neuropathy has been approximate among 20–24% of diabetic patients with peripheral neuropathy.[27]In a current Monica/Kora study from Augsburg, Germany, the prevalence of painful neuropathy was found to be 13.3% in diabetic subjects, 8.7% in people with impaired glucose tolerance, 4.2% in people with impaired fasting glucose, and 1.2% in people with normal glucose tolerance.[28] While, studies conducted in the Middle East Region, reports higher rates of painful diabetic peripheral neuropathy, ranging from 35% to 65%.[29,30] The incidence of diabetic neuropathy in India is not well documented but in a research survey from South India 19.1% type 2 diabetic patients had peripheral neuropathy. According to estimation, two-thirds of the diabetic patients have clinical or subclinical neuropathy.[4] However it is estimated from a comprehensive collection of epidemiological studies that the overall prevalence of neuropathy in diabetic patients is about 20-30%.[1]

Risk factors: Clinical trials in patients with type 1 or type 2 diabetes have revealed that poor control of blood sugar is a greater risk factor for diabetic peripheral neuropathy, but other risk factors are implicated as well. The EURODIAB IDDM Complications Study, which enrolled 3250 patients with type 1 diabetes from 31 centres in 16 European countries, revealed that diabetic peripheral neuropathy was associated to both blood sugar control and duration of diabetes mellitus. In spite of good blood sugar control (HbA1c<5.4%) patients still developed microvascular disease, suggestive of that factors other than blood sugar control and duration of diabetes are involved.[31] Statistics from the EURODIAB cohort study of patients with type 1 diabetes mellitus shown that over a 7-year period, about one-fourth of type 1 diabetic patients developed diabetic peripheral neuropathy; with age, duration of diabetes mellitus and poor blood sugar control being major risk factors for diabetic peripheral neuropathy.
Pathogenesis: The exact pathophysiological mechanisms of diabetic peripheral neuropathy remains enigmatic; and multiple hypotheses have been postulated however, consensus is that neuropathy in diabetes mellitus is a multifactorial disease. Chronic persistent hyperglycaemia is a key component in the development of diabetic peripheral neuropathy.[4] The diabetic condition produces impaired neurotropism, axonal transport and gene expression through four major pathways:

Polyol pathway (Sorbitol pathway): Chronic persistent hyperglycaemia causes increased levels of intracellular glucose in nerves, results in the saturation of the normal glycolytic pathway. The glucose uptake into peripheral nerve is not insulin dependent; thus it is proportionate to ambient blood glucose levels. Extra glucose is transported into the polyol pathway and transformed into sorbitol and fructose with the help of enzymes aldose reductase and Sorbitol dehydrogenase.[37] Accumulation of Sorbitol and fructose results in reduced nerve myoinositol, decreased membrane Na⁺/K⁺ ATPase action, impaired axonal transport, and structural dysfunction of nerves, causing abnormal action potential transmission.[5]

Advanced glycation end products (AGE’S): The non-enzymatic reaction of extra glucose along with proteins, nucleotides, and lipids results in advanced glycation end products (AGE’S) that might play a function in unsettling neuronal integrity and repair mechanisms through meddling with nerve cell metabolism and axonal transport.[6]

Protein Kinase C Pathway (PKC pathway): PKC becomes stimulated either directly by glycolytic intermediates or indirectly as a next messenger for stress hormones, leading to increased vascular disease process, inflammation and oxidative stress.[7]

Hexosamine pathway: Incomplete glycolysis causes accumulation of glycolytic intermediates and leads to escape of fructose-6-phosphate along the hexosamine pathway that increases vascular disease process and more reactive oxygen species (ROS) generation.[7] Other metabolic factors includes distorted fatty acid metabolism with reduction of prostaglandin precursors particularly linolenic acid and PGE, which has a key role in regulating tissue Na⁺/K⁺ ATPase action, and reduced concentration of nerve growth factors. Therefore, metabolic derangements, microvascular insufficiency, autoimmune mechanisms and deficiencies of neurotropism results in the multifaceted mechanisms results in nerve injury, dysfunction and ultimately diabetic neuropathy [8] as shown in flow chart below.

Clinical features: The most common presentation of diabetic peripheral neuropathy is diabetic peripheral neuropathic pain (DPNP), which characteristically manifests as burning, shooting, or stabbing pain in the feet or lower limbs.[9,10] Neuropathic pain is defined by the International association for the study of pain as “Pain initiated or caused by a primary lesion or dysfunction of the nervous system.[38] Peripheral nerves are composed of large and small diameter nerve fibres. Symptoms related with large fibre dysfunction include weakness, numbness, tingling, and loss of balance, while those related with small fibre damage include pain, anaesthesia to pin and temperature sensation, and autonomic dysfunction. Among the forms of peripheral nervous system dysfunction associated with diabetes mellitus and, by far the most common is distal symmetrical polyneuropathy (DSPN).[11] In distal symmetrical polyneuropathy, the manifestation and development of symptoms depend on the length of the nerves so that it primarily affects the longest nerves in the feet. DSPN involves all fibre types, but small fibre dysfunction may dominate, particularly in the early stages of neuropathy.[14] Early symptoms, which are exacerbated at night, includes bilateral symmetrical foot paraesthesia and pain, frequently presented as tingling, burning, prickling, shooting-pain, deep aching, pins and needles, tightness, or cold sensations. If not already present, confirmation of large fibre dysfunction, such as sensory loss, numbness, tingling, and loss of coordination may appear as the neuropathy progresses. Motor symptoms and signs are usually minor and occur late. All symptoms shift centrally over time to involve the proximal lower and upper limbs. This typical pattern of sensory symptoms in DSPN is termed as “stocking-glove” distribution.[39]
Flow chart in pathogenesis of diabetic neuropathy

Diabetes Mellitus

Hyperglycaemia

PKC

Impaired n-6 fatty acid metabolism

Polylol pathway

Sugar Autoxidation

Advanced glycation

Oxidative Stress

Triglycerides LDL

Endothelial dysfunction

Capillary blood flow

Endoneurial hypoxia

Nerve dysfunction
Differential Diagnosis: Patients suspected of having neuropathy should go through a complete clinical history, physical and neurological examination because the causes of neuropathy in patients with diabetes can range from simple benign processes to malignancy.[40,41,42] The preliminary step in the assessment of diabetic peripheral neuropathy is to establish the presence of neuropathy. Once a diagnosis of neuropathy has been established, laboratory studies to rule out other contributing or etiologic factors is appropriate.[43,44,45]

The Differential Diagnosis of Diabetic peripheral neuropathy [40,41,42,43]

Autoimmune disorders: SLE, Behçet’s syndrome, Sjogren’s syndrome, Antiphospholipid a ntibody syndrome, multifocal motor neuropathy.

Amyloid neuropathy, paraproteinemia

Demyelinating polyneuropathies

Guillain-Barré syndrome

Endocrine/Metabolic abnormalities

Hypothyroidism, Acromegaly, Uremia.

Hereditary neuropathies

Hereditary, Sensory and Autonomic neuropathy, C harcot-Marie-Tooth disease, Friedreich’s ataxia.

Traumatic

Entrapment syndromes

HIV medications: nucleoside analogue

Zalcitabine, Stavudine, Didanosine

Infections

Hepatitis B and C, AIDS, leprosy, Lyme disease

Inflammatory nerve disorders

Vasculitis, chronic inflammatory demyelinating polyradiculopathy(CIDP), sarcoidosis, primary biliary cirrhosis

Malignancies

Neoplasms, lymphoma, Hodgkin’s lymphoma, Multiple myeloma, Paraneoplastic syndromes

Medications

Amiodarone, colchicine, isoniazid, metronidazole, nitrofurantoin, phenytoin, lipid-lowering agents (statins, fibrates). Nutritional deficiency (vitamins B₁ and B₁₂, folate or copper). Chemotherapy including platinum-based therapy.

Nutraceuticals

Prolonged pyridoxine use,

Prolonged exposure to cold or hypoxia

Toxic

Alcohol, toxic exposure to heavy metals (arsenic, lead, mercury).

Diagnosis: Thorough clinical history and complete physical and neurological examination including foot inspection to support the need for regular self-care are the basis of assessment followed by therapeutic and laboratory studies.

A comprehensive history includes documentation of symptoms of diabetic neuropathy like tingling, burning, or prickling sensations, sharp pains, touch hypersensitivity, numbness and insensitivity, and reassessment of diabetes history like age, duration, disease management, blood sugar records, and prior HbA₁c levels. A careful history also includes differential diagnosis because diabetes is not the only cause of peripheral neuropathy.[46,47] A detailed examination with shoes and stockings removed should be performed to screen and assess vibration perception threshold (using a 128-Hz tuning fork), light touch (cotton wisp), pressure (10-g monofilament), superficial pain (sterile safety pin), temperature sensation, ankle and knee jerk reflexes and joint proprioception test.[12,13]

Vibration perception threshold (VPT) measurements are usually done by using Biothesiometry. Though detections of impairment of vibration sense using tuning fork (128HZ) is sufficient when a biothesiometer is not available. The biothesiometer is basically a glorified tuning fork and can be used for the assessment of vibration in a graded mode using a dial up to a limit of 50mv. If the patient is having neuropathy the recording is usually more than 15mv (mild), more than 25mv (moderate), and more than 40mv is measured as severe form of neuropathy.[21] Untimely loss of protective sensation can be detected in the foot of the diabetic patients by using the 10 g monofilament. Ten sites are selected and the monofilament is applied with adequate pressure to bend the filament for the period of not less than 2 seconds. It is tested for three times at each site and it is sufficient if patient answers correctly in 2 out of 3 applications. Failure to feel the monofilament in more than 4 sites denotes loss of protective sensation and higher risk of ulcer formation. This test is 95% sensitive and 80% specific.[48] Electrophysiological tests have emerged as vital specialist tools in the assessment of diabetic neuropathies. Electrophysiology tests, consisting of electromyography (EMG) and nerve conduction studies, (NCS) are the standard diagnostic tests for distal symmetrical polyneuropathy[14]. Though, these studies only detect injury to large diameter nerves (characterized by slowing and reduced amplitude of sensory nerve action potentials) and do not detect isolated small fibre damage that often occurs early in the neuropathic progression. Of the methods that have been developed to assess anatomical loss of small diameter nerves, neurodiagnostic skin biopsy is preferable to sural nerve biopsy because it is an easier, safer, and more sensitive diagnostic option. Some authorities advocate the further use of a clinical scoring system that grades the degree of

neuropathy on the basis of symptoms, deep tendon reflexes and sensory scores such as the Toronto clinical neuropathy scoring system, which is weighted to highlight sensory symptoms. This scoring system has been validated, and correlates well with electrophysiological findings and blood sugar control.[49] Recommended screening laboratory panel includes Antinuclear antibodies, Rheumatoid factor, Complete blood cell count, complete metabolic panel, Lipid profile, C-reactive protein or Erythrocyte sedimentation rate, HIV,hepatitis B and C, Serum and urine protein electrophoresis, HbA1C levels, Kidney function, Thyroid function, Urinalysis, Vitamin B12 , Homocysteine, Folate, Vitamin B1, and Vitamin B6 levels.[43,44,45]

Complications: Diabetic foot is one of the devastating chronic complications of diabetes mellitus. An orthodox triad of neuropathy, ischemia, and infection characterises the diabetic foot. Approximately 25% of those with diabetes mellitus will develop a foot ulcer. More than half of all foot ulcers (wounds) will turn out to be infected; requiring hospitalisation and 1 in 5 will require amputation. Diabetic peripheral neuropathy should not be underestimated, because it may lead to life threatening complications. The insensitivity or loss of pain in diabetic neuropathy can lead to foot ulceration and a host of accidental, but severe injuries. Patients, who have lost sensation in their hands, cannot sense hotness and frequently burn themselves while cooking or ironing. Those patients who have lost sensation in their feet frequently sustain puncture wounds, friction wounds and burns that can turn out to be infected and/or ulcerated and eventually lead to amputation. In fact, it has been reported that specifically, after an early amputation, 7 out of 10 patients require contra lateral amputation within 5 years and 50% will die within 3 years. This is equivalent in terms of morbidity and mortality to a high grade malignancy.[50,51,52,53,54]

Management
Prevention: An abundance of data supports the significance of tight blood sugar control in the prevention of diabetic neuropathy, so optimal blood sugar control should always be the target when managing the patient with diabetic neuropathy. The American Association of Clinical Endocrinologists recommends an HbA1C value of less than 6.5% in diabetic patients to prevent diabetic neuropathy. [17,55] Timely diagnosis and management of dyslipidemia and hypertension, may aid to prevent, delay, or slow the development of diabetic neuropathy.[56]

Foot care: Physicians must examine the diabetic patient’s feet at each visit to detect any evidence of neuropathy or early lesions. Patients should be instructed to inspect their feet regularly for any signs of dry or cracking skin, fissures, plantar callus formation, and infection.[57] Patients should also be instructed to trim their toenails with great caution and to be wary about foot hygiene, and must wear proper footwear and avoid sources of possible trauma to the insensate feet, such as walking barefoot, and exposing their feet to hot substance or chemicals.[58]

Treatment: The recent approach to management of painful DPN centres around achieving and maintaining strict blood sugar control as a primary step. The evaluation and pharmacological treatment of painful DPN has been reviewed by the Toronto Consensus Panel and recommended the various pharmacological agents for painful DPN.[59]

SYMPTOMATIC PHARMACOLOGICAL TREATMENT OF PAINFUL NEUROPATHY
Tricyclic antidepressants (TCAs): Numerous randomized clinical trials have supported the use of these drugs in the management of neuropathic pain. The mechanisms by which these drugs relieve pain include inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems and more recently, the antagonism of N-methyl-D aspartate receptors, which mediate hyperalgesia and allodynia. Best results have been achieved with amitriptyline and imipramine. The dosage of both of these agents required for symptomatic relief is similar (25–150 mg daily), though in elderly patients it can be useful to start at 10 mg daily. [60] Physicians must be careful when prescribing these drugs for patients with narrow-angle glaucoma, epilepsy, benign prostatic hyperplasia, orthostatic hypotension, urinary retention, impaired liver function, or thyroid dysfunction due to anticholinergic effects of Tricyclic antidepressants. QTC interval must be primarily assessed in those with additional risk factors of syncope, cardiovascular disease, electrolyte imbalance, and older age (>60yrs). [61,62]

Selective serotonin reuptake inhibitors (SSRIs) and Serotonin-norepinephrine reuptake inhibitors (SNRIs): These agents are thought to inhibit pain by interfering with descending pain inhibition pathways of the brainstem and spinal cord.[63] SSRIs (Citalopram and Paroxetine) are considered less efficacious than SNRIs.[64] SNRIs (Venlafaxine and Duloxetine) are a promising class of atypical antidepressants for the management of
Diabetic Peripheral Neuropathic pain. They are better tolerated and have less drug interactions than TCAs. A 2007 Cochrane review examined three studies of Venlafaxine for neuropathic pain, revealing a NNT of 3.1.[65]

**Antiepileptic:** Gabapentin and Pregabalin are recently confirmed in RCT as first line treatment for Diabetic Peripheral Neuropathic pain.[66] The pharmacologic effects of gabapentin and pregabalin are thought to be mediated through activity at the α2δ subunit of presynaptic calcium channels in the central nervous system.[67,68] Currently, duloxetine and pregabalin are the only agents that have been permitted by the FDA for the treatment of DPNP.[69,70]

**Opioids:** The opioid-like centrally acting agent tramadol has been revealed to be helpful in the management of patients with painful neuropathy in a randomized controlled trial.[71] A follow-up study to the original trial suggested that symptomatic relief could be maintained for at least 6 months usage [72] Two randomized controlled trials have established the effectiveness of controlled-relief oxycodone for neuropathic pain in diabetes.[73,74]

**Other Pharmacological Treatments**
Mexiletine is a Class 1B antiarrhythmic agent and is a structural analog of lignocaine. Its effectiveness in neuropathic pain has been confirmed in Randomised controlled trials.[75] Regular ECG monitoring is necessary and its short-term use should be reserved for patients who have failed to respond to other agents. Preliminary studies using two inhibitors of N-methyl-D-Aspartate (NMDA) receptors give preliminary confirmation for efficacy of these agents. A small study of the NMDA receptor antagonist dextromethorphan [76] and a larger study of memantine suggest that this class of drugs might prove to be useful in treating neuropathic pain in the future.[77]

**TOPICAL AND NONPHARMACOLOGICAL TREATMENTS OF PAINFUL NEUROPATHY**

**Topical Agents**
Capsaicin: Capsaicin, which is the "hot" ingredient of red chilli pepper, depletes tissue of substance P and reduces chemically-induced pain. There have been a number of controlled studies of topically-applied capsaicin cream (0.075%) in the treatment of painful diabetic neuropathy. Although a meta-analysis suggests overall efficacy from a number of trials.[78]

Topical Nitrate: A Randomised controlled study recommended that the local application to the feet of isosorbide dinitrate spray was useful in relieving pain and a burning sensation of painful neuropathy.[79]

Lidocaine: A pilot study of topically-applied 5% lidocaine by a patch demonstrated improvements in pain and QoL outcomes during a 3-week treatment period.[80]

**OTHER PHYSICAL THERAPIES**
Various physical therapies have been proposed and do have support from small-controlled trials: these include low-intensity laser therapy[81], monochromatic Infrared light treatment [82], percutaneous electrical nerve stimulation [83], and static magnetic field therapy.[84]

**DISEASE-MODIFYING TREATMENTS**
A number of agents intended at correcting the underlying pathogenesis of diabetic neuropathy are currently under research, but none is licensed for use in the United States by the Food and Drug Administration (FDA).

**Aldose Reductase Inhibitors:** The aldose reductase inhibitors block the rate-limiting enzyme, aldose reductase, in the sorbitol pathway. Several aldose reductase inhibitors have been studied for the last 20 years in the management of diabetic neuropathy. Of the many published studies, symptomatic relief was reported in a large multicenter study by using the drug tolrestat [85], and pain relief was also reported with epalrestat in a 12-week controlled study.[86]

**Alpha Lipoic Acid:** There is ample evidence to support the role of oxidative stress in the pathogenesis of neuropathy. Studies with the antioxidant alpha lipoic acid have provided support of potential efficacy for this agent which might well be useful both for neuropathic symptom relief, and for modifying the progression of neuropathy.[87,88]

**PKC-β Inhibition:** Preliminary data suggest that treatment with the PKC-β inhibitor, Ruboxistaurin, might improve the symptoms of diabetic neuropathy.[89]

**CONCLUSION**
Diabetic neuropathy is a worrying complication of diabetes mellitus because of the enfeebling symptoms it causes or associated higher risk of other complications, in particular those involving the lower limbs. The significance of a detailed history and clinical examination including foot inspection together with an understanding approach, and a serious effort to stabilize glycaemic control cannot be overemphasized, it
should be remembered that all patients with diabetic peripheral neuropathy are at higher risk of foot ulceration and should be given preventative foot care education. The management of diabetic neuropathy remains an intimidating challenge to the physicians. Main problems in this area remain the dearth of large multicenter trials, the frequency of adverse effects and lack of randomised controlled trials using comparator therapies rather than a placebo.

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