ABSTRACT
Diabetic neuropathy is a common complication of diabetes and is associated with peripheral nerve dysfunctioning and is the greatest source of morbidity and mortality in diabetic individuals, and India being the diabetic capital of the world with around 41 million diabetics in India alone the number is constantly rising. There are certain complications associated with diabetes and diabetic neuropathy is one of them, and it seems to be highly prevalent amongst the diabetic individuals. This review focuses on the risk factors, pathophysiology & various types of diabetic neuropathies. It also gives an insight detail of the current treatment options including pharmacological and non-pharmacological treatment and newer drug approaches for the disease.

KEYWORDS: diabetes, diabetic neuropathy, oxidative stress, nerve stimulation.

INTRODUCTION
One of the most common complications of diabetes is the involvement of the peripheral and autonomic nervous systems. An important risk factor for the development of diabetic neuropathy in patients with type 1 or type 2 diabetes is duration and severity of hyperglycemia.\textsuperscript{[1]} A simple definition of diabetic neuropathy is “the presence of symptoms and/or signs of peripheral nerve dysfunction in person with diabetes after the exclusion of other causes.”\textsuperscript{[1, 2]} In the Western world, Diabetes is the leading cause of neuropathy and happens to be most common complication and greatest source of morbidity and mortality in diabetes patients.\textsuperscript{[4]}
All peripheral nerves including pain-fibres, motor neurons and the autonomic nervous system are affected by Diabetic neuropathy. The pathogenesis of diabetic neuropathy is yet to be understood completely. It is suggested that hyperglycemia leads to changes in the nerve tissue.\[32\] In some patients, the manifestations of diabetic neuropathy may precede glucose intolerance and the diabetic neuropathy may be thought to be of a different origin then diabetes.\[64\] Patients with diabetic neuropathy commonly complain of symptoms of neuropathic pain.\[9\] Focal mononeuropathies can result in third and sixth cranial nerve palsies, painful intercostal neuropathy, and isolated muscle weakness involving the hip girdle.\[11\] Patients with diabetic peripheral neuropathy manifest painful symptoms, which are commonly characterized as burning, aching, tingling, cold, lancinating, allodynia, and/or numbness.\[12,13\]

The majority of patients with painless DPN are unaware of their condition, which can be particularly dangerous because patients may not be able to feel any injury to the foot. If not recognized and treated aggressively and quickly, these injuries may result in foot ulcers, infections, and even an amputation. For this reason, DPN is often referred to as the “forgotten complication” of diabetes.\[63\]

The pharmacologic agents used in the treatment of neuropathy include anticonvulsants, antidepressants, opioids, anti-arrhythmics, cannabinoids, aldose reductase inhibitors, protein kinase C inhibitors, antioxidants (-lipoic acid), transketolase activators (thiamines and allithiamines), topical medications (analgesic patches, anesthetic patches, capsaicin cream, clonidine), and others. The nonpharmacologic modalities include infrared therapy, shoe magnets, exercise, acupuncture, external stimulation.\[65\]

**Epidemiology**

From a comprehensive data of epidemiological studies it has been estimated that the prevalence of neuropathy in diabetes patients is approximately 30% in hospital patients and 20% in community patients. The overall annual incidence of neuropathy was ~2% and 3% in United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) respectively.\[4\] type 2 diabetes is three to four times more common in South Asians than in Europeans as per studies conducted in UK. Asian-Indians are amongst the high prevalence group of type 2 diabetes and a high familial aggregation of type 2 diabetes. The prevalence of type 2 diabetes was about 50% among the offspring of conjugal type 2 diabetic parents in India, which is the highest prevalence rate reported until
now. In a population-based survey in an urban population in South India, it was found that there was a 40% increase in the prevalence of diabetes over a period of 6 years, from 8.2% in 1988–1989 to 11.6% in 1994–1995.\textsuperscript{[5, 6]} According to the comprehensive evaluation methods, neuropathy was present in 66% of diabetic patients and in one series 8% have neuropathy at the time of diagnosis of DM and 50% of patients have diabetic neuropathy after 25 years of age.\textsuperscript{[6]} Even with the intensive insulin therapy, as reported in the Diabetes Control and Complications Trial, the incidence of clinically detected neuropathy per patient per year was as high as 7.0% and without the conventional therapy, the incidence of neuropathy increased to as much as 16.1%.\textsuperscript{[7]} diabetes is more pronounced in India than rest of the world as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.\textsuperscript{[62]}

**RISK FACTORS**

Certain complications such as Age, dyslipidemia, hypertension, peripheral vascular disease, weight changes and other end-organ complications can raise the likelihood of neuropathy.\textsuperscript{[6]} The primary risk factor for diabetic neuropathy is hyperglycemia, but certain other factors such as cigarette smoking, alcohol consumption, height, and hypercholesterolemia are all considered independent risk factors for diabetic neuropathy.\textsuperscript{[4, 6, 8]}

**Classification of diabetic neuropathy\textsuperscript{[11]}**

**A. DIFFUSE**

1. Distal symmetric sensori-motor polyneuropathy
2. Autonomic neuropathy
   a. Cardiovascular
   b. Gastrointestinal
   c. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

**B. FOCAL**

1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy (amyotrophy)
DISTAL SENSORY AND SENSORIMOTOR POLYNEUROPATHY

The term peripheral neuropathy describes symmetric and universal damage to adjacent nerves. The damage and clinical manifestations are usually located distally with a proximal progression.\cite{66} Sensorimotor polyneuropathy (DSP) represents a diffuse symmetrical and length-dependent injury to peripheral nerves that has major implications on quality of life.\cite{67}

**Autonomic neuropathy**

Autonomic dysfunction is one of the characteristic manifestations of diabetic neuropathy, and this type of neuropathy can be life-threatening. Many systems such as cardiac, respiratory, urinogenital, are effected by autonomic neuropathy.\cite{15}

**Cardiovascular autonomic neuropathy**

Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system.\cite{16} It has been shown to be the most important risk factor for silent ischemia in patients with diabetes.\cite{70} It has been shown that chronic hyperglycemia causes progressive of autonomic neural dysfunction that develops parallel to peripheral neuropathy, e.g., beginning distally and progressing proximally.\cite{69} It is significantly associated with overall mortality and in some cases to the studies associated with morbidity such as silent myocardial ischemia, coronary artery disease, stroke, diabetic nephropathy progression, and perioperative morbidity.\cite{16}

**Gastrointestinal autonomic neuropathy**

Peripheral autonomic neuropathy may affect motility at any level of the gastrointestinal tract.\cite{17} It may be caused by autonomic neuropathy with decreased activity of lower oesophageal sphincter (LES), reduction in LES pressure, impaired clearance function of the tubular oesophagus and delayed gastric emptying.\cite{18} The prevalence of symptoms caused by gastrointestinal dysfunction may reach 76% in a non-selected population of diabetic patients.\cite{19}

**Genitourinary autonomic neuropathy**

In the urinogenital system impotence due to autonomic neuropathy in a diabetic is characterized by a gradual onset of erectile failure with normal libido progressing to a total loss of erection.\cite{68} The neurogenic bladder, also called cystopathy, may be due to DAN. An examination of the neuroanatomy of the genitourinary system provides an insight into the extent to which autonomic fibers are involved with its proper control.\cite{20}
FOCAL AND MULTIFOCAL DIABETIC NEUROPATHIES
Diabetic patients may develop focal and multifocal neuropathy that includes cranial nerve involvement, limb and truncal neuropathies. Patients experience trophic changes in the feet, pains and autonomic disturbances. This neuropathic pattern tends to occur after 50 years of age, mostly in patients with chronic diabetes mellitus. Conversely, the focal diabetic neuropathies, which are often associated with inflammatory vasculopathy on nerve biopsies, remain self-limited.\[21\]

Cranial Neuropathies
Diabetic cranial neuropathies is one of the greatest neurological complications among diabetic patients. It usually involves cranial nerves III, IV, and VI, causing acute onset of ophthalmoplegia. There is Paralysis of the third, fourth, or sixth cranial nerve as a complication of diabetes mellitus (DM).\[22\]

Diabetic Thoracoabdominal/Truncal Neuropathy/ Radiculopathy
This type of neuropathy is basically characterized by pain in chest or abdominal pain. Neuropathic pain is typically unilateral and there is as ‘burning’ sensation or a ‘deep ache’ in the chest and abdominal region. The Examination reveals sensory loss to light, touch or pin prick, altered sensation and a zone of hyperalgesia, which has dermatomal distribution and does not cross the midline.\[23\] There is a reduction in epidermal and dermal nerve fibers compared to biopsies from asymptomatic areas as seen in Skin biopsies of the affected areas of the chest or trunk.\[24\] The physical sign of bulging of the abdominal wall may be seen frequently. This condition is self-limiting with complete resolution within one to three years.\[25\]

Diabetic Lumbosacral radiculoplexus neuropathy(Bruns-Garland syndrome)
Lumbosacral radiculoplexus neuropathy (LRPN) in diabetic patients is a distinct clinical condition characterized by debilitating pain, weakness and atrophy and it most commonly affects the proximal thigh muscles asymmetrically.\[26\] The weakness starts on one side spreading to the other side in an asymmetrical manner. Patients also complain of sensory symptoms in the thigh such as severe pain, dysesthesiae and paraesthesiae.\[27\] The cause of Diabetic Lumbosacral radiculoplexus neuropathy is a multifocal, perivascular, polymorphonuclear/mononuclear vasculitis with endoneurial or subperineural IgM and endothelial activated complement (C5b–9) deposits, that produces ischemia and there is
myelinated/unmyelinated fiber loss involving lumbosacral roots plexus, and peripheral nerves.[6]

**Limb Neuropathies**

Limb neuropathies in diabetics include two major mechanisms: nerve infarction and entrapment. Nerve infarctions present with pain having abrupt onset, which is followed by variable weakness and atrophy. Limb Neuropathy are marked by slow recovery over the period of month, owing to axonal degeneration being the primary pathology. The nerves most affected are Median, ulnar, and peroneal.[52]

**Multifocal diabetic neuropathy**

Multifocal neuropathies having a prominent vascular component or a compressive aetiology as opposed to the predominant metabolic component in DSDP.[29] It is characterized by a relatively rapid onset, and complete recovery. Proximal motor neuropathy affects patients over the age of 50 and is usually characterized by pain and weakness in the quadriceps. It has a relatively good prognosis with pain resolving within 1 year though residual discomfort may persist for a couple of years also there is third cranial nerve palsy that has a sudden onset but complete recovery is unusual.[30]

**PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY**

The understanding of the pathogenesis of diabetic neuropathy in recent years has increased to a great extent, and new drugs that target the pathophysiological mechanisms are currently being studied.[31] The pathological mechanisms implicated in diabetic neuropathy, include microvascular damage, metabolic disorders, and changes in the interactions between neuronal and immunological systems in parallel with glial cells activation.[32]

Various factors such as Metabolic and vascular/hypoxic appear to be involved in diabetic polyneuropathy. Advanced glycosylation end products may damage capillaries, inhibit axonal transport, Na+ /K+-ATPase activity and cause axonal degeneration. Hyperglycemia and increased intracellular Glucose may saturate normal glycolysis. Extra glucose may enter the polyol pathway and activates aldose, which converts it to fructose and sorbitol. Their Accumulation results in reduced nerve myoinositol and membrane Na+ /K+-ATPase activity, impaired axonal transport leading to structural damage. Nerve ischemia may result from increased endoneurial vascular resistance to hyperglycemic blood. In experimental animals, the metabolism of nerve growth factor (NGF) is impaired, which is the basis for
clinical studies.\textsuperscript{[33]} Recent evidences have suggested that hyperglycemia contributes to a state of heightened oxidative stress and the generation of reactive oxygen species that are important in the development of neuropathy and other microvascular diabetes complications. Various metabolic pathways such as polyol pathway probably contribute to hyperglycemia-induced oxidative stress, including the protein kinase C (PKC) activation, and accumulation of the end products of autoglycation (ie, advanced glycation endproducts).\textsuperscript{[34]}

**Polyol pathway**
The polyol pathway consists of two enzymes. The first enzyme, Aldose Reductase (AR), which reduces glucose to sorbitol with the aid of its co-factor NADPH, and the second enzyme, sorbitol dehydrogenase (SDH), with its co-factor NAD+, converts sorbitol to fructose, a process that increases the ratio of NADH/NAD and may result in both oxidative stress and activation of protein kinase C.\textsuperscript{[35]} AR has a low affinity for glucose when euglycemia is present, thus when blood glucose is in the reference range, it accounts for only a small percentage of glucose being metabolized. Evidence have suggested that polyol pathway is active in the kidney when hyperglycemia is present. AR and SDH have been identified in glomerular cells, including mesangial cells, and increased sorbitol levels are observed in mesangial cells exposed to high concentrations of glucose.\textsuperscript{[36]}

**Hexosamine pathway**
Similar to polyol pathway, this pathway also gets activated when there is excess glucose present in the cell. But here, the intermediate product of glycolysis, fructose-6-phosphate shifts to enter hexosamine pathway and gets converted to glucosamine-6-phosphate by the enzyme glutamine fructose-6-phosphate aminotransferase (GFAT).\textsuperscript{[37]} Then, the UDPGlcNAc attaches to the serine and threonine residues of transcription factors. The Hyperglycemic conditions create additional flux through hexosamine pathway ultimately resulting in an increased activation of Sp1, a transcription factor implicated in diabetic complications. Activation of Sp1 leads to overexpression of transforming growth factor-β1 (TGF-β1) and plasminogen activator inhibitor-1 (PAI-1). The PAI-1 is upregulated by both hexosamine and PKC pathways. Therefore Collectively, activation of hexosamine pathway is implicated in multiple metabolic derangements in diabetes.\textsuperscript{[38]}

**Oxidative stress pathway**
Diabetes results in increased oxidative stress, and elevated oxidative stress plays an important role in the pathogenesis of diabetic complications. Increased oxidative stress in diabetes
promotes the development of neuropathy, myocardial injury, and retinopathy.[39] The potential role in diabetic neuropathy of mitochondria of sensory neurons located in dorsal root ganglia has been suggested by several studies. These mitochondria are especially vulnerable, because the hyperglycemic neuron are the origin of production of reactive oxygen species, which can damage their DNA and membranes. Deregulation of fission and fusion proteins that control mitochondrial shape and number can impair cell functions and might lead to degeneration of these neurons.[14]

**AGE pathway**

Although the precise mechanisms underlying diabetic neuropathy remain unclear, there is evidence that hyperglycemia-induced formation of advanced glycation end products (AGEs) is related to diabetic neuropathy; AGE-modified peripheral nerve myelin is susceptible to phagocytosis by macrophages and contributes to segmental demyelination; modification of major axonal cytoskeletal proteins such as tubulin, neurofilament, and actin by AGEs results in axonal atrophy/degeneration and impaired axonal transport; and glycation of extracellular matrix protein laminin leads to impairment in regenerative activity in diabetic neuropathy. Recently, the receptor for AGEs (RAGE) has been found to colocalize with AGEs in diabetic peripheral nerves. This suggests that, in diabetic neuropathy, AGEs and AGE/RAGE interactions induce oxidative stress, resulting in upregulation of nuclear factor (NF)-kappaB and various NF-kappaB-mediated proinflammatory genes, and exaggerate neurological dysfunction, including altered pain sensation. Additionally, AGE/RAGE-induced oxidative stress further accelerates formation of glycoxidation products such as Nepsilon-(carboxymethyl)lysine and pentosidine.[14, 40]

**Protein kinase C activity in diabetic neuropathy**

The protein kinase C (PKC) pathway is an important mechanism of tissue damage by which hyperglycaemia. High glucose levels lead to increase in the diacylglycerol (DAG) concentration, which in turn activates the PKC pathway. Furthermore overproduction of the PKC -β-isoform is thought to increase the expression of the angiogenic protein, vascular endothelial growth factor (VEGF), and various inflammatory mediators that contribute in development of microvascular diabetic complications such as diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease.[80] The activation of PKC pathway leads to altered vasoconstriction and the capillary permeability; it may also result in hypoxia,
angiogenesis, basement membrane thickening, and may also cause endothelial proliferation.[81]

**Diagnosis of neuropathic pain**

**Electrodiagnostic testing**

Neuropathy can be diagnosed with nerve conduction studies and electromyography (EMG). EMG and NCV (nerve conduction velocity) best detect involvement of large peripheral nerve fibres that convey joint position sense and vibration. In patients with painful polyneuropathy involving small nerve fibres the EMG and NCV may be normal, and therefore, the diagnosis of a polyneuropathy should not be ruled out in such cases.[51]

**Quantitative sensory testing (QST)**

The assessment and quantification of sensory function in patients with neurologic symptoms is performed with quantitative sensory testing (QST) systems. QST measures the detection threshold of accurately calibrated sensory stimuli. The stimuli often used include vibratory stimulus, thermal stimulus, or painful stimulus, since they relate to distinct neuroanatomic pathways with discrete fiber populations.[71]

**PHARMACOLOGICAL TREATMENTS**

There is no specific treatment available for DPN but this decease could be managed using different therapeutic strategies. Drugs used to treat DPN include antidepressants (primarily tricyclic antidepressants [TCAs], antiepileptics, NSAIDS, Opioids, Inhibitors of Protein Kinase C pathway and others. Carbamazepine was the first medication studied for use in the treatment of DPN. Amitriptyline was first studied in an open-label study in 1977.[42] The other agents used for treatment of DPN include opiates, capsaicin, lidocain, l-carnitine & alpha-lipoic acid.[41]

**Antidepressants in neuropathic pain**

Evidence suggest that the TCAs provide relief and control in peripheral neuropathic pain.[43] TCAs are used as a first line therapy for diabetic peripheral neuropathic pain but their mechanism of action is not yet clearly understood. Amitriptyline & nortriptyline have been used in the treatment of DPN without FDA approval.[41] Based upon clinical experience it may be suggested that antidepressants are often very helpful in the treatment of neuropathic pain. The maximum effective dose of amitriptyline is about 75 mg at night.[44]
Antiepileptics in neuropathic pain
Antiepileptic drugs provide with a very useful option for treating neuropathic pain, although their effectiveness in treating painful diabetic neuropathy is remains controversial. The dose of carbamazepine for neuropathic pain is 100 mg/kg/day and of phenytoin is 150 mg/kg/day. Other antiepileptic used in DPN include gabapentin, topiramate and valporic acid.

Opioids
Many physicians prescribe opioids to treat neuropathic pain. There are evidences which suggest that some opioids show a good therapeutic effect in this disease. The best studied opioid is the orally administered drug tramadol. Opioid agonists such as codeine, morphine, oxycodone, and fentanyl mimic the activity of enkephalins and endorphins at the central descending pathways of the pain-processing loop. Adverse effects of opioids, that include constipation, nausea, sedation, and the potential for addiction, limit their use among phycians. Tramadol, 200-400 mg/day, is significantly effective in diabetic neuropathic pain and painful polyneuropathy.

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs such as aspirin and ibuprofen find limited use in treatment of neuropathic pain. The NSAIDs exert the adverse effect on renal function, and therefore their use for DPN should be discouraged. The COX-2 inhibitors are main monitored for adverse cardiovascular events and cannot be recommended for the long-term administration needed to treat patients with neuropathic pain syndromes.

Inhibitors of Protein Kinase C pathway
Activation of PKC pathway leads to free radical production, leading to diabetic microvascular complications. Activation of PKCβ by hyperglycaemia is considered to have potential role in microvascular complications of DN. Hyperglycemic activation of PKCβ causes abnormal signalling and other complications like cytokine activation and inhibition, vascular alterations, cell cycle and transcriptional factor deregulation, and abnormal angiogenesis. Ruboxistaurin inhibits PKC-β activation and has been particularly successful in supressing the progress of DN, but is yet to be approval.
**Alpha-lipoic acid**

It should be noted that none of the drugs described above affect the underlying neuropathic process but rather only provide symptomatic relief, which stops as soon as they are discontinued. Studies have found that alpha-lipoic acid, available in the United States as an over-the-counter supplement, may actually control the underlying disease process as well as improve pain. A study showed that alpha lipoic acid, 600 mg, given 3 times daily for 5 weeks improved pain, paresthesias, and numbness.\[63 . 75]\n
**Topical Agents**

**Lidocaine**

Topical 5% lidocaine patches (Lidoderm, Endo) have been approved by the FDA for the treatment of postherpetic neuralgia. This way of treatment results in minimum adverse event and interaction. Although lidocaine has not been indicated for DPN, studies suggested its role as adjunctive therapy.\[49]\n
Generally 4 patches are used every 24 hours. Generally there are no adverse effects shown by lidocaine, but rash and pruritus have been reported in a few patients.\[50]\n
**Capsaicin**

Capsaicin is a neurotoxin with analgesic properties. It is an alkaloid derived from chillies, which depletes the neurotransmitter substance from sensory nerves and causes degeneration of epidermal nerve fibres. Controlled trials with 0.075% capsaicin in painful diabetic neuropathy have shown mixed results. Benefit was reported in 3 out of 5 studies in diabetic neuropathy.\[51]\n
**Herbal Drug Treatment**

**Phenolic Compounds**

Phenolic acids are contained in a large amount of vegetables and fruits, and possess many physiological and pharmacological properties which are attributed to their ability to inhibit oxidative stress induced by free radicals and protect photooxidation.\[76]\n
Experiments demonstrate the powerful effects of phenolic acids on biological responses free radical scavenging agents. Additionally, phenolic acid have also been shown to exhibit anti-inflammatory, antiallergic, antimutation effects, and inhibit cardiovascular diseases.\[77, 78]\n
**Evening Primrose Oil**

Evening primrose oil is a rich source of Ω-6 essential fatty acids (primarily GLA and LA). It extracted from the seeds of Oenothera biennis. Commercial preparations of evening primrose
typically contain to 8% GLA and 72% LA. A recent study reveals that a mixture of α-lipoic acid and evening primrose oil was effective in causing improvement in neuropathic pain, through increasing PGE1 synthesis.\textsuperscript{[79]}

**Pharmacological treatment approaches for painful diabetic peripheral neuropathy**\textsuperscript{[61]}

<table>
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<tr>
<th>S.NO</th>
<th>CLASS</th>
<th>DRUG</th>
<th>DOSE</th>
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<tbody>
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<td>1.</td>
<td>TCAs</td>
<td>Amitriptyline Imipramine</td>
<td>25-75 mg/day 25-75 mg/day</td>
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<td>2.</td>
<td>SSRIs/SNRIs</td>
<td>Duloxetine Venlafaxine</td>
<td>60-120 mg/day 150-225 mg/day</td>
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<td>3.</td>
<td>Anti-convulsants</td>
<td>Gabapentin Pregabalin Carbamazepine Topiramate</td>
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<tr>
<td>4.</td>
<td>Opiates</td>
<td>Tramadol Oxycodone Morphine sulphate (sustained release)</td>
<td>200-400 mg/day 20-80 mg/day 20-80 mg/day</td>
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<tr>
<td>5.</td>
<td>Natural products</td>
<td>Capsaicin cream</td>
<td>0.075% used in 4 times a day</td>
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**New drug approaches**

*Lacosamide*

Lacosamide is sodium channel blocker, that selectively enhances the slow inactivation of voltage-dependent sodium channels.\textsuperscript{[53]} Although it failed to get approval for painful diabetic peripheral neuropathy from either the FDA or the EMA.\textsuperscript{[54]}

*Tapentadol,*

Tapentadol is a μ-opioid agonist and norepinephrine reuptake inhibitor that has been found to be an effective medication for a wide variety of chronic pain conditions. It has also exhibits fewer gastrointestinal side effects than most traditional opioid-based therapies. Tapentadol extended release has been recently demonstrated to be effective in the management of painful diabetic neuropathy.\textsuperscript{[55]}

*KU32*

KU-32 is a novel novobiocin-based Hsp90 inhibitor that can protect against neuronal cell death in vitro with minimal cytotoxicity to neurons. KU-32 protected against sensory neuron death and demyelination, and reversed the sensory deficits associated with diabetic peripheral neuropathy.\textsuperscript{[57]}
NON PHARMACOLOGICAL APPROACHES

Percutaneous electrical nerve stimulation

PENS is a useful nonpharmacological therapeutic modality for treating diabetic neuropathic pain. In addition to decreasing extremity pain, PENS therapy improved physical activity, sense of well-being, and quality of sleep while reducing the need for oral nonopioid analgesic medication. The use of electrical stimulation in patients with diabetic neuropathy has been proposed as an alternative non-pharmacological treatment. The effects of TENS may be explained by the production of endogenous opioids and gate control mechanisms. Several studies have demonstrated that low-frequency TENS increases the release of endogenous opioids, which have modulatory effects on the nucleus of the solitary tract (NTS) and, consequently, on the central nervous pathway of cardiovascular control.

Benefits of exercise intervention in reducing neuropathic pain

Lifestyle interventions, including exercise, are the first line in diabetes treatment. Acutely, exercise reduces blood glucose levels via uptake of glucose into active muscles. Exercise also stimulates glucose transporter type 4 (GLUT4) translocation, enhancing glucose uptake into muscle cells and compensating for impaired insulin sensitivity associated with diabetes. Although both aerobic and resistance exercise offer benefits to the patient with diabetes, a combination of the two may be more effective in controlling blood glucose. Exercise also enhances insulin action for 2 to 72 hours.

CONCLUSION

DSPN, the most common presentation in diabetes, leads to significant pain, morbidity, and reduced quality of life. The costs associated with DN are high. The root cause of DN is hyperglycemia and associated metabolic imbalance. Although numerous biochemical mechanisms have been identified for DN, but oxidative stress is thought to be a common etiologic factor. The treatment of DN is initiated with optimizing glycemic control followed by control of pain. If oxidative stress is assumed to be only an additional factor in DN, then antioxidants should be supplemented with conventional treatments. However, the discovery of new drugs to treat DN continues to remain a challenge requiring intensive long-term investigation.

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