

Painful diabetic neuropathy: an update

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ABSTRACT

Diabetes, a silent killer, is a leading cause of neuropathy. Around 50% of diabetic patients develop peripheral neuropathy in 25 years. Painful diabetic neuropathy manifests as burning, excruciating, stabbing or intractable type of pain or presents with tingling or numbness. The pathophysiology of this condition is due to primarily metabolic and vascular factors. There is increase in sorbitol and fructose, glycated endproducts, reactive oxygen species and activation of protein kinase C in the diabetic state. All these factors lead to direct damage to the nerves. The first step in the management of painful diabetic neuropathy is a tight glycaemic control. Currently there is no drug which can halt or reverse the progression of the disease. Most of the therapies prevalent aim at providing symptomatic relief. Antidepressants like tricyclic antidepressants (TCAs) and selective norepinephrine reuptake inhibitors (SNRIs) have good efficacy in controlling the symptoms. Selective serotonin reuptake inhibitors have not shown the same consistent results. Anticonvulsants including pregabalin, gabapentin and lamotrigine have shown good results in the control of symptoms whereas same was not found with carbamazepine, oxcarbazepine and topiramate. Topical agents (capsaicin, topical nitrates and topical TCAs) and local anaesthetics have also been used with good results. Use of opioids and non steroidal anti-inflammatory drugs although common but is not preferable. The newer therapies under studies are NMDA antagonists, aldose reductase inhibitors, neurotropic factors, vascular endothelial growth factor, Gamma linolenic acid, protein kinase C beta inhibitors, immune therapy, hyperbaric oxygen and alpha lipoic acid.

KEYWORDS: Painful Diabetic Neuropathy, Pathophysiology, Drugs, Treatment

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doi : 10.5214/ans.0972.7531.1118409

Introduction

Diabetes mellitus is a leading cause of diabetic neuropathy, resulting in great morbidity, mortality and deteriorates ones quality of life, and poses a huge financial burden for patient and patient's caregivers.¹ Diabetic neuropathy is very broad and heterogeneous term which encompasses a number of mono and polyneuropathies as well as plexopathies and radiculopathies. It was first described by Marchel de Calvi in 1864, who stated neuropathy as a consequence rather than a cause of diabetes.² This article primarily discusses about painful diabetic neuropathy (PDN).

Definition

An international meeting on the diagnosis and management of diabetes produced a consensus statement defining diabetic peripheral neuropathy as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."³ Other causes of neuropathy such as hereditary, inflammatory, and other metabolic neuropathies should be actively excluded.

Clinical manifestations

Patients with painful diabetic neuropathy characteristically present with tingling sensation, numbness, burning, excruciating stabbing type of pain, sometimes intractable and may be associated with paraesthesia and hyperesthesia coupled with deep aching in feet or hands. This is typically a

distal symmetrical sensorimotor type of neuropathy. The other clinical characteristics are due to involvement of both small and large (mixed sensorimotor) fibres. Initially, the most distal parts of the extremities are affected, leading to typical gloves and stocking pattern of sensory loss, indicating the involvement of longest nerve fibres. This is followed by involvement of distal upper limbs, the anterior aspect of trunk and subsequently the vertex of the head. Overall there occurs a disturbance of light touch sensation, sensitivity to pressure and vibration, and joint position sense. It typically affects at night and over all it affects the individual's quality of life including mobility, work, sleep, mood, self worth, recreation and social activities.⁴

Epidemiology

Poor glycaemic control is a major risk factor for development of diabetic neuropathy. A direct relationship has been found between duration of poor glycaemic control and diabetic neuropathy. It has been observed that an estimated 50% of patients develop peripheral neuropathy 25 years after the initial diagnosis of diabetes mellitus. The prevalence of PDN ranges from 10% to 20% of patients with diabetes and in those with diabetic neuropathy it ranges from 40% to 50%.^{5,6,7} Hyperglycemia, as causative factor in neuropathy, was established from randomised prospective trial namely Diabetes Control and Complication Trial. This landmark trial demonstrated that a tight glycaemic control leads to significant re-

duction in development and progression of clinical neuropathy by 64%.^{8,9} Other comorbid factors associated with diabetic neuropathy are hyperlipidemia, hypertension, cigarette smoking, consumption of alcohol, and obesity.

Classification

There are many types of neuropathy with varying clinical presentations. Peripheral neuropathy can manifest either with painful or painless symptoms or both. The two most common types of diabetic neuropathies associated with pain are acute sensory neuropathy and chronic sensorimotor neuropathy. Acute sensory type neuropathy presents with either acute or subacute onset characterized by severe sensory symptoms, usually with a few, if any, clinical signs. It is usually associated with hyperglycemia or intensification of glycaemic control and may gradually lessen as euglycemia is obtained. Chronic sensory-motor neuropathy is the most common form of DPN, associated with symptomatic pain and clinical signs of neuropathy.

Pathophysiology

Pathophysiology of diabetic neuropathy involves both metabolic and vascular factors. Hyperglycemia is central to pathogenesis which results in the following (Fig. 1):

Increased sorbitol and fructose

Hyperglycemia leads to increased activity of the enzyme aldose reductase (rate

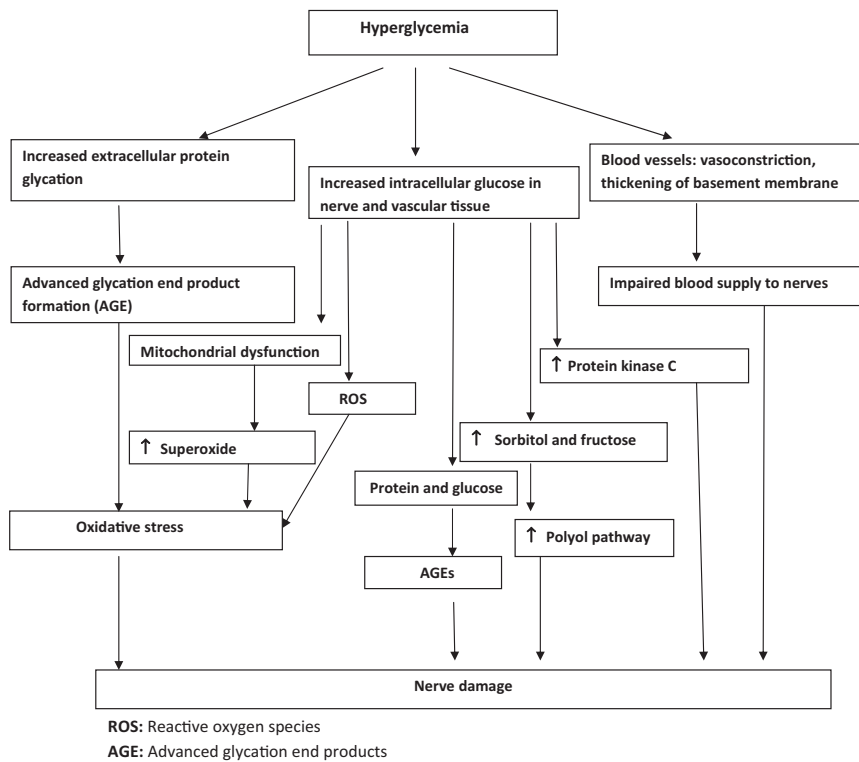


Fig. 1: Pathophysiology of diabetic neuropathy

limiting step in polyol pathway) which leads to the accumulation of the sorbitol and fructose and a decrease in free nerve myoinositol (competition for myoinositol uptake into tissue). It also causes imbalance in the nicotinamide adenine dinucleotide phosphate and its reduced form. Reduced NADPH is a cofactor for the enzyme nitric oxide synthase which reduces nitric oxide formation, which is a major vasodilator. All these factors leads to impairment of the blood supply to the nerves.¹⁰

Advanced glycation end products

Hyperglycemia leads to incorporation of glucose into the proteins nonenzymatically by an unregulated glycation reaction.¹¹ The different proteins that get glycosylated include haemoglobin, plasma albumin, lipoproteins, fibrin and collagen. All these glycosylated end products gradually form fluorescent cross linked protein products called advanced glycation end products. They are responsible for causing the tissue damage because of their reactivity and protein cross linking.

Reactive oxygen species

Auto-oxidation of the excess glucose leads to formation of reactive oxygen species. These oxygen free radicals cause

damage of the nerves by a direct toxic effect or by inhibiting the nitric oxide production by the endothelium thereby leading to ischemia of nerves. Hence oxidative stress is also predominantly implicated in neuropathy

Inappropriate activation of protein kinase C and others:

Other factors contributing to neuropathy are inappropriate activation of protein kinase C, decrease in the nerve growth factor (responsible for the regeneration of the nerves), biochemical abnormalities like decreased gamma-linolenic acid, which is precursor of a prostanoid including prostacyclin. Prostacyclin is a potent vasodilator, and if reduced blood flow it leads to reduced blood flow.

Assessment of neuropathy

A careful history regarding pain, discomfort, or numbness in the legs should be conducted. Epidemiological studies have confirmed that nerve conduction studies are the most valuable tool for evaluation of nerve conduction.¹² A careful clinical examination should be conducted along with specified tests. Use of monofilament to evaluate the touch sensitivity and tactile circumference discrimination are the two commonly used methods.^{13,14,15,16} Other in-

struments like neuropathy symptom score and neuropathy symptom profile are used to assess the symptom quantitation.^{17,18} Vibration test by tuning fork is done by placing it on the bony prominence at the dorsum of the great toe. Patient is then asked to state when they first feel the vibration and when it ceases. This test should be repeated twice on each foot. Apart from this, patients' mobility, gait, and balance should also be assessed.

Mechanism of pain generation in painful diabetic neuropathy

Sensitization

The underlying mechanism for generation of pain is hyperexcitability in primary afferent nociceptors (peripheral sensitization), which occurs due to damage to peripheral nerves. This in turn leads to hyperexcitability in central neurons (central sensitization) and generation of spontaneous impulses within the axon as well as the dorsal root ganglion of these peripheral nerves. Sensitization refers to a lowered activation threshold, increased response to a given stimulus, and abnormal spontaneous activity. It is a self resolving process except if in chronic disease such as diabetes with ongoing damage, spontaneous symptoms continues to be generated due to continued sensitization and altered processes in nociceptors.¹⁹

Sympathetic nervous system

The role of sympathetically mediated pain in PDN has been demonstrated in different studies. In one of the study, impaired sympathetically mediated vasoconstriction in patients with PDN was demonstrated suggestive of inappropriate local blood flow regulation in these patients.^{20,21}

Role of sodium channels

At the site of injury and along the length of axon, there occurs accumulation of sodium channels. This phenomenon leads to ectopic electric discharge and hyperexcitability leading to the increased bursts of electrical impulses to the dorsal horn, alteration in gating mechanism and substance P expression.²²

Long term potentiation

Peripheral excitation leads to central excitation, which further leads to activation of N-methyl D-aspartate (NMDA) receptors, which are located post synaptically in dorsal horn. Activation of NMDA receptors leads to glutamate release,

causing synaptic potentiation, which are much larger postsynaptic potentials known as long term potentiation. This phenomenon has been observed in various pain states.^{19,22}

Treatment of neuropathy

Control of hyperglycaemia

It has already been documented that the optimal control of hyperglycaemia by intensive therapy in type 1 diabetes reduces the appearance of neuropathy by 60% over a 5 year period.⁸ Adequate glycaemic control is achieved by either oral hypoglycaemic, euglycaemic agents or insulin therapy.

Specific therapy

An ideal agent should prevent or arrest the progressive loss of nerve function and improves symptoms with minimal side effects. A large number of agents have been tried and tested in number of randomized controlled trials which includes antidepressants, anticonvulsants, opioids, N-Methyl-D-Aspartate (NMDA) receptor antagonists, and antiarrhythmics. Topical agents and aldose reductase inhibitors (Alrestatin/Sorbinil/Tolrestat/Zepolrestat), Non steroidal antiinflammatory drugs (NSAIDs), protein kinase C inhibitors, gamma-linolenic acid, nerve growth factor (recombinant human nerve growth factor/ Insulin like growth factor-1), vascular endothelial growth factors, immune therapy, acupuncture, hyperbaric oxygen, and physical therapies also have been tested.

Antidepressants

Amitriptyline was introduced in 1977 while others include imipramine, nortriptyline and desipramine which are the me-

tabolites of amitriptyline and imipramine, respectively. Duloxetine is the only antidepressant approved by FDA for diabetic neuropathic pain. SSRIs that have been studied include venlafaxine, citalopram and paroxetine and fluoxetine for diabetic neuropathy. (Table 1)

Mechanism of action

Serotonin and norepinephrine, together with endogenous opioids and gamma amino butyric acid modulate actions of the nociceptive pathways. Presynaptic reuptake inhibition of serotonin and norepinephrine increases the levels of these amines in the synaptic clefts which causes increased pain suppression induced by the descending inhibitory pathways. Hence, the central mechanism by which antidepressants act is by diffuse noxious inhibitory control by inhibition of presynaptic reuptake of serotonin and norepinephrine. TCAs also block α -adrenergic, H1-histamine, muscarinic cholinergic, and N-methyl-D-aspartate receptors.²³ TCA also act on peripheral nociceptors, descending inhibitory pathways, central sensitization and brain areas involved in pain and emotional processing. SSRIs work by the inhibition of presynaptic reuptake of serotonin but not norepinephrine.

Clinical studies

Among the tricyclic antidepressants (TCA), amitriptyline is most commonly prescribed and has demonstrated significant benefits in burning, aching, sharp, throbbing or stinging type of pain.²⁴ Selective serotonin reuptake inhibitors has been studied and studies have not shown great

efficacy. There is some evidence from small controlled studies, to support the use of paroxetine and citalopram in dosages of up to 40 mg/day in diabetic neuropathic pain. Selective Norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine has been found to be equivalent in efficacy to TCAs.²⁵ Raskin *et al.* evaluated the effect of duloxetine in doses of 60 and 120 mg in 348 patients with diabetic neuropathy for 12 weeks and reported it to be effective and well tolerated.²⁶ In one of the cross over trial, while comparing duloxetine with amitriptyline, it was found that duloxetine was preferred by patients although efficacy of both the drugs was similar.²⁷ There is a limited data on efficacy of, selective serotonin reuptake inhibitors, hence they have not been approved for the treatment of neuropathic pain.

Anticonvulsants

Mechanism of action

Anticonvulsants (Table 2) act by different mechanism which includes sodium channel blockade, potentiation of G-amino butyric acid activity, calcium channel blockade, antagonism of glutamate at N-Methyl-D-Aspartate receptors. Pregabalin has been FDA approved for diabetic neuropathy. It has anti-epileptic, analgesic and anxiolytic activity. Although mechanism of action is unclear, it is postulated that it reduces excitatory neurotransmitter release by binding to the α -2- δ protein subunit of voltage-gated calcium channels. It is known to interact with L-amino acid transporters and also binds with high affinity to α -2- δ subunit of calcium channels. Valproate has been studied in different placebo

Table 1: Antidepressants in diabetic neuropathy

Medication	Effective dosage range	Time to effect (weeks)	Adverse drug reactions
Amitriptyline	100–150 mg/day	6 to 8	Dry mouth, sedation, dizziness, confusion, arrhythmias, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain
Nortriptyline	100-150 mg/day	6	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias
Imipramine	150 mg/day	4	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias
Desipramine	200–250 mg/day	6	Dry mouth, sedation, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias, dizziness
Venlafaxine	150–225 mg/day	4 to 6	Headache, nausea, sedation, constipation, dizziness, dry mouth, sexual dysfunction, hypertension, seizures, diarrhoea
Duloxetine	600-120 mg/day	4	Nausea, somnolence, dizziness, dry mouth, constipation, sweating, weakness, headache, diarrhoea

Table 2: Antidepressants in diabetic neuropathy

Medication	Effective dosage range	Time to effect (weeks)	Adverse drug reactions
Pregabalin	300–600 mg/day	4–6	Peripheral edema, dizziness, somnolence ataxia, tremor, blurred vision, diplopia weight gain
Gabapentin	2,400–3,600 mg/day	4	Somnolence, dizziness, ataxia, nausea dry mouth, constipation, nystagmus, leucopenia, weight gain.
Valproate	1,000–1,200 mg/day	4	Dizziness, somnolence, alopecia, insomnia nausea, diarrhea, vomiting thrombocytopenia, tremor, weakness.
Lamotrigine	200–400 mg/day	6–8	Dizziness, ataxia, sedation, headache blurred vision, diplopia, nausea, rash, confusion, nystagmus, rhinitis.
Topiramate	300–400 mg/day	12	Dizziness, ataxia, psychomotor slowing, memory problems, speech difficulties, nausea, migraine, weight loss, anorexia Significant: metabolic acidosis, nephrolithiasis, hyperthermia, central nervous system effects, secondary angle closure glaucoma.
Carbamazepine	600 mg/day	4	Agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus

controlled trials and has demonstrated efficacy in neuropathic pain.^{28,29} Lacosamide is a novel anticonvulsant that selectively enhances the slow inactivation of voltage-dependent sodium channels, and interacts with a neuronal cytosolic protein, the collapsin response mediator protein 2 (crmp-2), which plays an important role in nerve sprouting and excitotoxicity.

Clinical studies

Pregabalin is a second agent approved for diabetic neuropathic pain. In one of the trial comparing pregabalin (300 mg/day) with placebo in patients with peripheral diabetic neuropathy, pregabalin showed a significant improvement in the mean pain scores, mean sleep interference, mood disturbance, and tension-anxiety during week 1, which remained significant throughout the study, but were associated with dizziness and somnolence compared with placebo.³⁰ A multicentric double blind study has demonstrated the beneficial effect of gabapentin in both type 1 and type 2 diabetic patients.³¹ Recently lamotrigine, an antiepileptic displayed beneficial effects in neuropathic pain. A randomized double blind, cross over study in 59 patients supported the use of lamotrigine as compared to placebo at different doses (200, 300 and 400 mg/day).³² Similar results were depicted when lamotrigine was compared to amitriptyline.³³ However, it is advisable to monitor drug therapy with these agents as they are associated with various adverse drug reactions. There is limited data regarding the efficacy of carbamazepine, oxcarbazepine and topiramate. Lacosamide

has been tried in clinical trials of diabetic neuropathy but still more rigorous studies are needed to establish its efficacy.

Topical agents

Capsaicin

Topical preparation of capsaicin, an extract from chilli pepper, and leads to depletion of substance P, which is the most commonly, implicated neurotransmitter in the pain transmission pathway. If applied, 0.075% multiple times a day is effective, but is associated with burning sensation that may persist for several weeks.³⁴

Topical nitrate

It has been observed in experimental models that impaired nitric oxide generation induces hyperalgesia. A randomized trial reported local application of topical nitrate resulted in significant reduction in pain and burning sensation over 4 weeks in diabetic patient.³⁵

Topical TCAs

Among the various available preparations, studies regarding topical doxepin have demonstrated a noticeable decrease in the pain scores (6.22 to 5.04; $p < 0.010$) as compared to placebo which showed increase in the pain scores (6.49 to 6.91).³⁶

Local anaesthetics and antiarrhythmics

Mechanism of action

Lidocaine by virtue of its sodium channel blocking property, blocks both peripheral nociceptor sensitization and central

nervous system hyperexcitability. Local anaesthetics remain in the skin and have an excellent safety profile. Intravenous lidocaine has shown to ameliorate intractable painful diabetic neuropathy in those who have failed to respond to or are intolerant to available conventional therapies.³⁷ Mexilitine is a class 1B antiarrhythmic agent and a structural analog of lignocaine. Mexilitine has been found to be effective in reducing nocturnal pain and sleep disruption in neuropathic pain patients.³⁸ It is not used because of its side effects and the need for regular electrocardiogram monitoring.

Opioids Analgesics

The use of opioids for neuropathic pain remains controversial. Opioids such as morphine, methadone and time released formulations of oxycodone have been found to be effective in relieving neuropathic pain. Morphine in combination with gabapentin has led to a greater reduction in the total score on the Short-Form McGill Pain Questionnaire at lower doses of each drug than either drug used as a single agent, although constipation, sedation, and dry mouth were frequent adverse effects in patients with diabetic neuropathy.³⁹ Oxycodone has advantages over morphine which includes its higher bioavailability, more potency and lesser adverse drug reactions. Oxycodone has demonstrated beneficial effect on mean daily pain (both steady pain and brief pain) as well as on total pain and disability in one of the placebo controlled trial.⁴⁰ Tramadol, a opioid-like, centrally acting synthetic narcotic analgesic has been confirmed to be efficacious

in a neuropathic pain with added advantages of no abuse potential. A multicentric, double blind, randomized controlled trial demonstrated significant improvement in pain and physical and social functioning, but no benefit on sleep was observed. Significant side effects were somnolence, nausea, constipation, and headache.⁴¹ Caution should be advised in patients with substance abuse while prescribing opioids analgesics. Opioids analgesics and tramadol have demonstrated efficacy in treating patients having coexisting osteoarthritis responsible for non-neuropathic pain.

Nonsteroidal antiinflammatory drugs (NSAIDS)

NSAIDS act by decreasing pain and inflammation by inhibiting cyclooxygenase which decreases prostaglandin synthesis. A single blind 24 week placebo controlled study demonstrated statistically significant reduction in paraesthesia scores by both Ibuprofen (600 mg four times a day) and sulindac (200 mg twice a day) in 18 veterans with diabetic neuropathy.⁴² They have a beneficial effect in acute phase of neuropathic pain especially the gnawing type of pain. Caution is advised regarding their propensity to impair renal function and cause gastrointestinal bleeding.

Physical and surgical therapy

Acupuncture has found to be associated with reduction in the use of other analgesics and benefits lasts for 6 months.⁴³ However, controlled studies are needed to confirm these results. Transcutaneous electrical nerve stimulation has been tried with modest success. Other less rigorously tested methods include surgical sympathectomy, spinal cord stimulation, central neuraxial blockade, static magnetic field therapy, low-intensity laser therapy and monochromatic infrared light.

NMDA antagonists

Newer agents have been tried include ketamine, memantine (20-55 mg per day) and dextromethorphan (380 mg per day). A small study conducted on diabetic neuropathic patients dextromethorphan demonstrated a reduction in pain by 24% in comparison to placebo.⁴⁴ In one of the cross over trial comparing dextromethorphan plus memantine with placebo, no statistically significant response for pain reduction was found, although in 10 dextromethorphan responders, showed a significant dose-response effect on pain intensity.⁴⁵

Aldose reductase inhibitor

Aldose reductase inhibitors interfere with the polyol pathway, which in turn prevent the conversion of glucose to sorbitol. Drugs which have shown such effect in human and animal models are tolrestat, zopolrestat, eolrestat, alrestat. Human studies of these drugs have shown inconsistent result either due to small sample size or due to insufficient duration of trial. They also produced unacceptable toxicity.^{46,47}

Neurotropic factors

Animal studies have demonstrated the role of neurotropic factors in the regeneration of nerves. Examples of neurotropic factors are nerve growth factors, brain derived neurotropic factors, neurotrophins, insulin like growth factors and glial cell derive neurotropic factor. TX14 a prosaposin derived neurotrophic peptide has shown efficacy in two different rat models.⁴⁸ On the other hand these benefits are not seen in clinical trials in humans. A large phase 3 study of recombinant human nerve growth factor in patients with diabetic polyneuropathy did not reveal any significant benefit.⁴⁹

Vascular endothelial factors (VEGF)

The role of VEGF has generated a lot of interest in the therapy of neuropathy. Its potential role in the diabetic neuropathy has been documented in rat and rabbit models of diabetes. VEGF gene administration has shown to restore nerve conduction velocity, nerve blood flow and nerve vessel number to normal in diabetic neuropathy.^{50,51}

Gamma linolenic acid

Gamma linolenic acid is an important constituent of the neuronal membrane and has shown to preserve nerve blood flow. One of the trial demonstrated improvement in clinical assessment of the condition and electrophysiological tests.⁵²

Protein kinase C beta inhibitors

One of the postulated factors in the development of diabetic neuropathy is neural vascular insufficiency. Protein Kinase C (PKC) activation is a critical step in the pathway to diabetic microvascular complications. Ruboxistaurin mesylate (LY333531) is a protein kinase C β inhibitor. A multinational, randomized, phase-2, double-blind, placebo controlled trial to test the efficacy and tolerability of ruboxistaurin in patients with diabetic neuropathy showed a statistically significant improvement in symptoms in ruboxistaurin-treated neuropathy groups.⁵³

Immune therapy

Various forms like chronic inflammatory demyelinating polyneuropathy, multiple motor polyneuropathy, vasculitis and monoclonal gammopathy of unknown significance (MGUS) in diabetes has been shown to improve with immune therapy.^{54, 55}

Hyperbaric Oxygen

Its use is still debatable as the pathogenesis in diabetic foot is impaired oxygen delivery to the tissue, so this therapy might be effective in neuropathy by promoting oxygen delivery from plasma to the affected tissues.⁵⁶

Alpha Lipoic acid

Alpha lipoic acid is a antioxidant, with free radical scavenging property. It has shown efficacy in modifying natural history of peripheral diabetic neuropathy and improving symptoms in diabetic neuropathy.^{57,58}

Miscellaneous agents

Pentoxifylline, clonidine, reiki therapy and vitamins have been tried with inconsistent results. Angiotensin converting enzyme inhibitors (ACE inhibitors) have shown effectiveness in neuropathy due to unclear mechanism.⁵⁹

Table 3 describes the drug of choice for different types of pain

Table 3: Drug of choice for different types of diabetic neuropathy pain

S.No.	Symptomology	Drug of choice
1	Lancinating pain	Carbamazepine Amitriptyline
2	Pain with depression	Duloxetine Fluoxetine
3	Casualgia	Carbamazepine Pregabalin
4	Gnawing pain	Non steroidal anti-inflammatory drugs Opioids
5	Burning pain localized to particular area	Capsaicin Amitriptyline cream Duloxetine patch

Table 4: The American Academy of Neurology has released new guidelines on the treatment of painful diabetic neuropathy (2011).⁶⁰

	Level of evidence	
Level 1	Strong evidence	
	Recommended drug and dose	
	Pregabalin, 300–600 mg/d	
Level 2	Moderate evidence	
	Recommended drug and dose	Not recommended
	Gabapentin, 900–3,600 mg/d	Oxcarbazepine
	Sodium valproate, 500–1,200 mg/d	Lamotrigine
	Venlafaxine, 75–225 mg/d	Lacosamide
	Duloxetine, 60–120 mg/d	Clonidine
	Amitriptyline, 25–100 mg/d	Pentoxifylline
	Dextromethorphan, 400 mg/d	Mexiletine
	Morphine sulphate, titrated to 120 mg/d	Magnetic field treatment
	Tramadol, 210 mg/d	Low-intensity laser therapy
	Oxycodone, mean 37 mg/d, max 120 mg/d	Reiki therapy
	Capsaicin, 0.075% QID	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation 3–4 weeks	
Level 3	Weak evidence	
	Venlafaxine	
	Gabapentin	
	Lidoderm patch	
Level 4	Insufficient evidence	
	Topiramate	Fluoxetine
	Desipramine	Combination of nortriptyline and fluphenazine
	Imipramine	Vitamins
	α -lipoic acid	Combination of amitriptyline with electrotherapy

Recently new guidelines have been recommended regarding painful diabetic neuropathy (2011) (Table 4).

Conclusion

Diabetic neuropathy is associated with long term diabetes. Tight glycaemic control along with preventive management helps to prevent neuropathic complications. Newer advances still in developmental stage includes glutamate antagonists, cytokine inhibitors, vanilloid- receptor agonists, catecholamine modulators, ion-channel blockers, anticonvulsants, opioids, cannabinoids, COX inhibitors,

acetylcholine modulators, adenosine receptor agonists. Pharmacotherapeutic strategies are the cornerstone of neuropathy treatment but still results are inconclusive, hence vigorous research should be directed towards these aspects to find a better counterparts.

The article complies with International Committee of Medical Journal Editor's uniform requirements for the manuscripts.

Competing interests – None, Source of Funding – None

Received Date : 19 August 2011

Revised Date: 30 August 2011

Accepted Date : 5 September 2011

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