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Review Article

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Current pharmacotherapeutic approaches to treat diabetic neuropathy

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ABSTRACT

Nerve damage that occurs in people with diabetes is called diabetic neuropathy. This condition is a complication of diabetes and results from chronically high blood glucose. It is one of the most frustrating and debilitating complications of diabetes because of the pain, discomfort and disability. Usually more than 50% of patients with duration of diabetes of 25 years or more are affected, making it as one of the most common disease of the nervous system. One of the largest published series reported a prevalence of 7.5% even at the time of diagnosis of diabetes. Some patients find some relief from neuropathy by keeping blood sugars as closely controlled as possible, getting regular exercise and keeping their weight under control. Surprisingly, clinicians have also found that certain antidepressants may be helpful and can take the edge off the pain of neuropathy. To diagnose diabetic neuropathy, the foot and ankle surgeon will obtain the patient's history of symptoms and will perform simple tests on the feet and legs which include assessment of the patient's reflexes, ability to feel light touch, and ability to feel vibration. The mechanisms involved in the development of diabetic neuropathy include changes in the blood vessels that supply the peripheral nerves; metabolic disorders, such as the enhanced activation of the polyol pathway; myo-inositol depletion; and increased non-enzymatic glycation. Treatment includes the most effective antidepressants as tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin nor-epinephrine reuptake inhibitors. Clinical studies of diabetic neuropathy indicate that the first line treatment should be tricyclic antidepressants, which are followed by anticonvulsants and then opioids. In this review, we will discuss on diabetic neuropathy and its current treatment strategies.

Keywords: Diabetic neuropathy, Diagnostic method, Management, Neurotrophic factors.

INTRODUCTION

Diabetic neuropathy (DN) is a progressive and diverse situation affecting sensory, motor, and autonomic neurons [1]. It is a frequent obstacle of type1 and type2 diabetes [2].The most significant cause of morbidity is refractory pain in the absence of painful stimuli and/or in response to a normally innocuous stimulus. The causes of neuropathic pain are anonymous but mostly due to neural hyper excitability. It is often refractory to cure. The drugs used to treat DN are non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, opiates, tricyclic antidepressants and anticonvulsants. Combinations of drugs with the risk of drug interactions are often employed to improve outcomes [3]. Drug therapy is often ineffective and complicated by surplus adverse effects. Thus, there is need for management along with treatment. An internationally agreed simple definition of diabetic neuropathy for clinical practice is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" [1]its due to hereditary, wicked, noxious and infectious food, immune mediated, neoplastic, and secondary to other illnesses. The exposition of DN masquerade as demyelination, intoxicating

neuropathy and neuropathies of endocrine system thus proceeding to diagnose DN it is essential to prohibit the supplementary causes of nerve dysfunction [4].

EPIDEMIOLOGY: DN affects 1.9% inhabitants globally in 2010. Diabetes is the primary cause of death between all and neuropathy is the frequent impediment and greatest source of morbidity and transience in patients suffering from diabetes. Approximately 20% patients suffering from diabetics have occurrence of neuropathy [5] Foot ulcers occur within 15% patients of diabetes which leads to non-agonizing extremity amputation [6,7]**.**

CLINICAL MANIFESTATIONS: DN is chronic and progressive disease associated with tenderness, lack of sensation, increase in pain, and subterranean aching which increased during night and developed specially in feet and lower legs(Table 1). It affects patient's life including its sleep, confidence, annoyance, self-determination, working power, and interpersonal relationships. Diverse symptoms of autonomic neuropathy markedly reduce the Quality of Life (QOL) of patients [8].

Table 1: Clinical Manifestation

1	Sensory disturbance is dominant
2	A disorder of an inferior limb is dominant, and a disorder of a superior limb is mild
3	Vibratory sensation is disordered since early stage
4	A tendon reflex of an inferior limb decreases since early stage
5	Ophthalmoplegia often accompanies
6	Autonomic neuropathy often accompanies

PATHOGENESIS AND MECHANISM OF DIABETIC NEUROPATHY:

Pathological mechanism

The pathological mechanism of diabetic neuropathy cannot be explained with a single cause, and various hypotheses have been proposed. These are roughly divided into metabolic, vascular, and neuroregeneration disorder hypotheses. (Table 2)

Table 2: Pathogenesis and Mechanism of Diabetes Neuropathy

1	Activation of polyol pathway
2	Down-regulation of intracellular myoinositol
3	Dysfunction of protein kinase C
4	Down-regulation of intracellular cyclic AMP
5	Inhibition of Na^+/K^+/ATPase
6	Degradation of nitric oxide
7	Advance of protein glycation
8	Increase of free radical
9	Disorder of polyunsaturated fatty acid synthesis
10	Disorder of prostaglandin synthesis
11	Action attenuation of a nerve growth factor
12	Nerve blood flow degradation, nerve vascular resistance enhancement

Potential pathogenesis of diabetic neuropathy

Impairment of polyol pathway

Altered peripheral nerve polyol metabolism has been implicated as a central factor in the pathogenesis of diabetic neuropathy. Aldose reductase converts glucose to sorbitol (such aspolyol) using nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme. Sorbitol is further converted to fructose by sorbitol dehydrogenase using nicotinamideadenine dinucleotide (NAD+) as a coenzyme, constituting the bypass polyol pathway of glucose metabolism. In hyperglycaemia accompanying diabetes, the cellular glucose level rises independently from insulin, resulting in enhancement of aldose reductase activity, which elevates the intracellular sorbitol level and, subsequently, the intracellular osmotic pressure. This condition inducesfunctional and structural abnormalities in tissue and cells.

Table 3: Diagnostic Technique

1	Visual examination	Change in skin, ulcer
2	Neuropathic pain assessment	Michigan Neuropathy Screening Instrument (MNSI)
3		Neuropathy Disability Score (NDS)
4		Brief Pain Inventory (BPI)
5		Neuropathic Pain Questionnaire (NPQ)
6		Neuropathic Pain Symptom Inventory (NPSI)
7	Peripheral motor neuropathy	degeneration of muscle, Muscle strength
8		Deep tendon reflex at Achilles tendon
9	Sensory function	Pinprick test, Temperature perception, Vibration perception
		Neurothesiometer, Touch sensation 10 g monofilament (SW monofilament)
		Nerve conduction study
11	Skin biopsy	Quantification of intra-epidermal nerve fiber
12	Skin blood flow measurement	Measurement microvascular perfusion
13	QOL questionnaire	
	Norfolk QOL questionnaire	Specific symptoms and impact of large, small and autonomic nerve-fiber functions
	Neuro QOL	Patients' perceptions of the impact of neuropathy and foot ulcers
	PN-QOL-97	Health-related quality of life measure for Peripheral neuropathy
14	New tests	
	Large fiber function test	Steel ball-bearing
		Tactile circumferential discriminator
		Autonomic nerve conduction study
	Small fiber function test	NeuroQuick
		Neuropad

An aldose reductase reduces glucose in sorbitol. This reaction oxidizes nicotinamide adeninedinucleotide phosphate (NADPH) to $NADP^+$ (the oxidized form of NADPH). Subsequently, sorbitol dehydrogenase enzymatically oxidizes sorbitol to fructose, which also produces nicotinamide adenine dinucleotide (NADH) from nicotinamide adenine dinucleotide (NAD^+). The inhibition of the aldose reductase is one of key element in the prevention of diabetic complications.

In addition to osmotic pressure elevation, sorbitol accumulation decreases the intra cellular myoinositol content, which inhibits phosphoinositol metabolism and reduces protein kinase-C and Na^+/K^+/ATPase activities in peripheral nerves, being involved in the manifestation of diabetic neuropathy [9].

Activation of protein kinase C

Hyperglycaemia promotes the synthesis of an endogenous protein kinase C activator, diacyl-Glycerol. Actually, excess activation of β2-type protein kinase C in cardiovascular tissue in an animal diabetes model has been reported. Enhanced vascular protein kinase C is involved in permeability, the contractile force, and the differentiation and proliferation of cells.

Excess protein kinase C activation induces ischemia in peripheral nerves through increased vascular permeability and thickening of the basement membrane and causes neuropathy.

Increase in oxidative stress

Hyperglycaemia enhances NADPH oxidase expression and the endothelial nitric oxidesynthase (eNOS) uncoupling reaction in vascular endothelial cells, through which superoxideis excessively produced [4]. Nitric oxide (NO) is essential for endothelial cell function. Excess superoxide decreases NO by binding to it, and this binding reaction promotes the secondary synthesis of reactive oxygen species (ROS), such as peroxynitrite and hydroxylradicals. ROS have strong cytotoxicity, and an increase in ROS induces neurosis.

Increase in oxidative stress

Free radicals are reactive chemical entities that are short lived species containing one or more unpaired electrons. They can also be considered as necessary evil for signaling involved in normal process of differentiation and migration. The free radicals induce damage to cells by passing the unpaired electron resulting in oxidation of cell components and molecules. They are generally very unstable and very much reactive. These free radicals are somewhere responsible in causing Diabetic neuropathy.

Table 4: Usual Effective Dosages and Titration Schemes for the Treatment of Diabetic Neuropathy

S No.	Medication	Usual effective dosage range	Titration scheme	NNT (95% CI) to achieve 50% pain reduction	Time to effect
1	**Tricyclic Antidepressants**				
	Amitriptyline	100–150 mg/day (150 mg at bedtime or	Day1: 12.5 mg/day	2.1 (1.8–2.6)	6–8 weeks
		75 mg twice daily)	Days 2–7: 25 mg/day Week 2: 50 mg/day		
			Week 3: 75 mg/day		
			Week 4: 100 mg/day		
			Weeks 5–8: 150 mg/day		
	Nortriptyline	100–150 mg/day	Day 1: 12.5 mg/day Days 2–7: 25 mg/day	Cannot calculate NNT similar to desipramine	6 weeks
		(50 mg three times daily)	Week 2: 50 mg/day		
			Week 3: 75 mg/day		
			Week 4: 100 mg/day		
			Weeks 5–8: 150 mg/day		
	Imipramine	150 mg/day	Week 1: 25 mg twice daily	2.1 (1.8–2.6)	4 weeks
		(75 mg twice daily)	Week 2: 50 mg twice daily		
			Week 3: 75 mg twice daily		
	Desipramine	200–250 mg/day (250 mg daily or125 mg twice daily)	Week 1: 50 mg/day Week 2: 100 mg/day	2.5 (1.9–3.6)	6 weeks
			Week 3: 200 mg/day		
			Week 4: 250 mg/day		
2	**Other Antidepressants**				
	Venlafaxine	150–225 mg/day (75 mg three times daily)	Week 1: 37.5 mg/day Week 2: 75 mg/day	5.5 (3.4–14)	4–6 weeks
			Week 3: 150 mg/day		
			Week 4: 225 mg/day		
	Duloxetine	60–120 mg/day (60 every day or twice a day)	Week 1: 10 mg/day Week 2: 20 mg/day Week 3: 60 mg/day	4 (3–9)	4 weeks
			Week 4: 120 mg/day		
3	**Antiepileptics**				
	Carbamazepine	600 mg/day (200 mg three times daily)	Weeks 1–2: 100 mg three times daily	2.3 (1.6-3.9)	4 weeks
			Week 3: 200 mg three times daily		
	Lamotrigine	200–400 mg/day (200 mg twice daily)	Week 1: 25 mg/day Week 2: 50 mg/day	4.0 (2.1–42)	6–8 weeks
			Week 3: 100 mg/day		
			Week 4: 200 mg/day		
			Week 5: 400 mg/day		
	Valproate	1,000–1,200 mg/day	Week 1: 600 mg/day	2.5 (1.8–4.1)	4 weeks
		(500 mg twice daily or 400 mg three times daily)	Week 2: 1,200 mg/day		
	Topiramate	300–400 mg/day	Week 1: 25 mg/day Week 2: 50 mg/day	7.4 (4.3–28)	12 weeks
		(200 mg twice daily)	Week 3: 75 mg/day		
			Week 4: 100 mg/day		
			Week 5: 150 mg/day		
			Week 6: 200 mg/day		
			Week 7: 300 mg/day		
			Week 8: 400 mg/day		4 weeks
	Gabapentin	2,400–3,600 mg/day	Week 1: 300 mg at bedtime	3.9 (3.2–5.1) for doses ≥ 2,400 mg/day	
		(1,200 mg three times daily or 900 mg four times daily)	Week 2: 300 mg twice daily		
			Week 3: 300 mg three times daily		
			Week 4: 600 mg three times daily		
			Week 5 : 900 mg three times		4–6

			daily		weeks
	Pregabalin	300–600 mg/day	Week 1: 150 mg/day	4.2 (3.4–5.4)	
		(300 mg twice daily or	Week 2: 300 mg/day		
		200 mg three times daily)	Week 3: 600 mg/day		
			(Dosed twice or three times daily)		
4	**Others**				
	Capsaicin cream	0.075% four times daily	No titration needed	6.7 (4.6–12)	8 weeks
	Tramadol	200–400 mg/day	Week 1: 50 mg/day	3.5 (2.4–6.4)	6 weeks
		(100 mg four times daily)	Week 2: 100 mg/day		
			Week 3: 150 mg/day		
			Week 4: 200 mg/day		
			Week 5: 300 mg/day		
			Week 6: 400 mg/day		
	Mexilitine	450–675 mg/day	Week 1: 225 mg/day	2.2 (1.3–8.7)	1–4 days
		(225 mg three times daily)	Week 2: 450 mg/day		
			Week 3: 675 mg/day		

Other factors

Bone marrow-derived proinsulin and tumor necrosis factor-α (TNFα)-producing cells appear in a diabetic state. These cells enter the dorsal root ganglions and peripheral nerves (axon and Schwann cells) and induce cell fusion. Fused cells impair Ca^{2+}homeostasis and induce apoptosis. The appearance of these abnormal cells is resolved by insulin treatment. It has also been clarified that the abnormality of intracellular signal transmission systems innerve tissues including that of insulin signals is closely involved in abnormal peripheral nerve function. The peripheral neuropathy developmental mechanism may be a new target of neuropathy treatment, other than blood glucose control [10].

Increase in blood sugar activates sorbitol accretion which leads to enhance cellular osmolarity and shunts the phosphor gluconate pathway while increasing in oxidative stress and construction of advanced glycation end products. Hyper excitability of principal afferent nociceptors results from the damage of peripheral nerves leads to hyper excitability in central neurons and production of impulses within ganglions and axons [11].

Factors linked to type 1 and type 2 diabetes cause damage in DNA, endoplasmic reticulum trauma, mitochondrial multifarious dysfunction, cell death and loss of Neurotrophic signaling which escort neuropathy. The consequences of pathways in this network will fluctuate among cell nature, disease contour, and instance.

CLASSIFICATION OF DIABETIC NEUROPATHY:

In diabetic neuropathy, sensory neuropathy is dominant, but subjective sensory symptoms generally do not extend to the proximity from the ankle joint in many cases, and its onset is associated with numbness and pain of the toes and sole. The fingers are asymptomatic in this stage, showing “tabi (socks with the big toe separated)-type” sensory symptoms, and this pattern is frequently noted in routine medical practice. The diabetic neuropathy is classified in Figure 1.

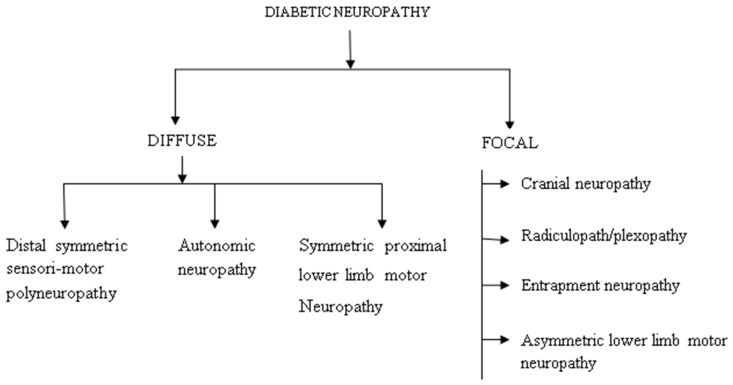

Figure 1: Classification of Diabetic Neuropathy

In the late stage, “glove-socks-type” sensory abnormality manifests. Diabetic neuropathy cases with the expansion of sensory symptoms to the precordium and parietal region have been reported. This neurologic manifestation

pattern is derived from the advancement pattern of axon degeneration, and it occurs because the nerves in the lower limbs are longer than those in the upper limbs.

Since diabetic neuropathy progresses slowly, the divergence between the upper and lower limb symptoms may continue for a relatively long time. Regarding sensory disturbance, in diabetic neuropathy in which positive symptoms of the feet, such as numbness and pain, develop in the early to middle stage and negative symptoms, such as hypoesthesia, develop in the terminal stage, generally, an abnormal autonomic nerve function appears from the early stage and then autonomic nerve symptoms may manifest, but the manifestation of motor neuropathy is late [8].

DIAGNOSTIC TECHNIQUES: Various diagnostic techniques are used now a day for the diagnosis of Diabetes neuropathy, primarily visual examination is done for diagnosis later on we go for other methods including biopsy. Various methods are mentioned in Table 3.

MANAGEMENT: Neuropathic pain is tricky to treat is often chronic and can be unbearable.

Prevention is the most excellent stratagem because there are no treatments which relive the pain completely. For the prevention, controlling lipid and hypertension is the best along with that taking aspirin daily, ceasing smoking prevents diabetic neuropathy.

The ABCs of diabetic neuropathy management [13]
A: Antidepressants, anticonvulsants, topical anesthetics are the first-line treatments
B: Blood sugar management
C: Cardiovascular risk factor reduction
D: Diet and exercise for weight management
E: Emerging therapies for diabetes and neuralgia
F: Foot care to reduce infections and amputations

TREATMENT OF DIABETIC NEUROPATHY: Mainly by two ways:
1. Symptomatic treatment.
2. Treatment for nerve regeneration.

Symptomatic treatment: Major classes of drugs are used to treat DN. Their classification dose and other information's are mentioned in Table 4.

Tri-cyclic antidepressants (TCAs): Desipramine, amitriptyline, imipramine, and clomipramine have demonstrated the best efficacy. One head-to-head comparison of desipramine with amitriptyline showed no difference in efficacy but suggested that desipramine was better tolerated. In second study comparing desipramine with placebo demonstrated improvement in a majority of patients who had previously failed to receive pain relief from amitriptyline or had discontinued taking it due to bothersome side effects. Clomipramine exhibited efficacy analogous to that of desipramine.

The severity of adverse effects associated with TCAs is attributed to their relative affinities for muscarinic, histaminic (H1), and α1-adrenergic receptors. Xerostomia, blurred vision and urinary retention are the adverse effect associated with TCAs.

Drug like amitriptyline, clomipramine, and doxepin shows more affinity towards histamine and α1-adrenergic receptors causes sedation and orthostatic hypotension. TCA can be chooses on the basis of individual acceptability and its adverse effects. Thus desipramine is used as drug of choice for DN because of its relative tolerability compared with other TCAs.

Selective serotonin-reuptake inhibitors (SSRIs): Clinically used SSRIs for the treatment of diabetic neuropathy is sertraline paroxetine, citalopram, and fluoxetine. Normally, SSRIs are improved tolerated and not as much of valuableas TCAs, and it ought not to be considered for DN.

Other antidepressants: Extended release bupropion shows additional value for neuropathic pain of diverse cause with a little bit of side effects such as dry mouth, wakefulness, and pain.

- Extended-release venlafaxine is also effective in DN. Patients being paid with venlafaxine reported significantly lower pain and better pain relief
- Gabapentin an anticonvulsant that is promising as a first-line agent for the treatment of neuropathy. People experience vertigo and perplexity long with somnolence.
- Carbamazepine shows neuron stabilization by inhibition of ionic conductance through its anticonvulsant and analgesic mechanisms of action. The adverse effects are somnolence, dizziness, and ataxia tends to limit its use in clinical practice.
- Oxcarbazepine is chemically related and has a mechanism of action similar to that of carbamazepine, and it is reported that it have much better adverse effect and drug interaction profile.
- Other drugs: zonisamide, lamotrigine and Phenytoin
- Opioid analgesics, tramadol, and non-steroidal antiinflammatory drugs (NSAIDs): The chemical nature and chronicity of neuropathic pain prohibit the use of opioid analgesics for DN. These drugs provide just marginal assistance along with risk of sedation, dependence, constipation, and nausea. Tramadol has opioid analgesic and serotonergic properties are beneficial for neuropathic pain and also show some side effects such as tiredness, vertigo, and dry mouth.

Thus on the basis of above explanation we can say that tramadol is a harmless and efficient medication for diabetic sensorimotor neuropathy, and the dosage required for therapeutic effect is relatively high.

The use of NSAIDs in diabetes patients must be prefaced with the caution that they can impair renal function in vulnerable individuals by inhibiting prostaglandin which can cause GI bleeding. Both ibuprofen (600 mg four times daily) and sulindac (200 mg twice daily) demonstrated statistically significant reductions in paresthesia scores compared with placebo. The paresthesia scale is no longer frequently used, and merely those patients with "moderate pain" veteran relief.

Mexiletine and lidocaine: Mexiletine (type-Ib antiarrhythmic drug) is used for DN and it is considered that it shows its analgesic and antiarrhythmic effects by membrane-stabilizing Na+ -channel antagonism. Several studies show relatively improvement in tenderness and paresthesia.

Levodopa: A double-blind, placebo-controlled study with sensorimotor neuropathy demonstrated a significant decline in pain. The study was too small to make any conclusions about clinical significance.

Dextromethorphan: It is a partial antagonist of the N-methyl-D-aspartate receptor, which is concerned for the intervention of neuropathic pain. A study shows decline in pain compared with placebo with an average dosage of 381 mg/day. While receiving dextromethorphan several patients experienced side effect viz. sedation and unsteadiness.

Topicals: Capsaicin cream and isosorbide-dinitrate spray: Capsaicin is extracted from capsicum peppers and produces a dose-dependent desensitization of type C nociceptive fibers by depleting the substance P. The prevalent available study of an analgesic treatment for diabetic sensorimotor neuropathy was conducted by the Capsaicin Study Group which shows that capsaicin provide much relief in pain and its intensity and improved global assessment scores along with side effects such as burning, rashes, irritation and cough.

A study of isosorbide-dinitrate spray for diabetic neuropathy demonstrated safety and efficacy in 22 patients with refractory pain and burning with a statistically and clinically significant reduction in pain and burning.

Complementary and alternative therapies: Electro stimulation has been shown to provide temporary relief of pain associated with DN, but the probability and efficiency of continuation rehabilitation stay notorious. In a transcutaneous electrotherapy study of 31 patients with diabetic neuropathy to take a portable electrotherapy machine home for one week of self-administration. Patients were assigned to therapy with either active or inactive electrodes. The analysis for groups consisted of placing electrodes as instructed and administering electrical shock for 30 minutes per-day. Consequence showed that active therapies have better neuropathic symptoms with no side effects as compared to sham group.

In a related study, percutaneous electrical nerve stimulation (PENS) was examined for value in the treatment of DN. The therapy consists of puncturing spongy tissue and muscle of limbs at a vigor of 1- 3 cm and applying blinking frequencies of electrical stun using acupuncture needles.

Patients experienced reduction of pain in lower-extremity when compared to control.

In theory, electro stimulation could produce analgesia by inducing the release of endogenous opioid-like chemicals which sustain a responsibility for electrotherapy.

Thioctic acid, or α-lipoic acid is used as substitute treatment for the treatment of DN. A study with diabetic neuropathy patients, intravenous infusions of α-lipoic acid proved secure and successful relief in short-term throbbing and blazing. In general the 600-mg dose created the optimal statistically and clinically significant pain relief compared with other doses and placebo, and 93% of patients receiving the 600-mg infusions rated their tolerance as good. The limitation of this treatment is clinically a patient requisite i.v. infusion daily for half an hour. The t½ of α-lipoic acid construe for regulation of neuropathy [14].

TREATMENT FOR NERVE REGENERATION: The agents used for nerve regeneration are known as neurotrophic factors. The neurotrophic factor is defined as a naturally occurring protein that is released by target tissues of amenable neurons, binds with its receptors and is retro-gradelyelated through the measures of second messenger systems. A large number of neurotrophic factors have been discovered that make use effects on specific neurons. A number of these factors might offer evidence in the treatment of diabetic neuropathy. All of them are beneath assessment and no one of them is vacant for clinical use. Among all neurotrophin gene family nerve growth factor (NGF), brain derived neurotrophic factors, neurotrophin, insulin like growth factor, and glial cell derived neurotrophic factor are in use [4].

Neurotrophic factors:

- Neurotrophins (NT): Nerve growth factor, Brain- derived neurotrophic factor, NT – 3, NT-4/5, NT - 6
- Haematopoietic cytokines: Ciliary neurotrophic factor, LIF, Oncogene M, Interleukin (IL- 1, IL – 3, IL – 6, IL – 7, IL – 9, IL – 11), Granulocyte colony- stimulating factor
- Insulin - like growth factors (IGF): Insulin, IGF – I, IGF - II
- Heparin - binding family: Acidic fibroblast growth factor (FGF), Basic FGF, int - 2 onc, hst/k-fgfonc, FGF – 4, FGF – 5, FGF – 6, Keratinocyte growth factor
- Epidermal growth factor (EGF) family: EGF, Transforming growth factor (TGF) - α

TGF - β family (TGF - β1, TGF - β2, TGF - β3)
Glial - derived neurotrophic factor
Neurturin, Persephin, Activin A, Bone morphogenetic protein.

Tyrosine kinase - associated cytokines: Platelet - derived growth factor, Colony - stimulating factor – 1, Stem cell factor.

DRUGS APPROVED BY FDA: The only two drugs approved by FDA for diabetic neuropathy which have sufficient efficacy are the antidepressant duloxetine and the anticonvulsant pregabalin. Pregabalin is a highly potent and higher effective analogue of gabapentin. Evidence of its efficacy is derived from three pivotal clinical trials in diabetic painful neuropathy. Various drugs used to treat diabetic neuropathy are there which are currently in preclinical trials (Table 5).

Table 5: Recent Drugs in Preclinical Studies

DRUG	PHASE	COMPANY
Tapentadol Extended Release (ER)	PHASE III	Cetero Research
Duloxetine	PHASE III	Eli Lilly and Company
Pregabalin	PHASE III	Eli Lilly and Company
MK-6096	PHASE II	Merck
Esli carbazepine acetate (BIA 2-093)	PHASE III	Bial - Portela C S.A.
AVP-923	PHASE III	Avanir Pharmaceuticals
Nucynta ER (extended release)	PHASE III	Janssen Pharmaceuticals
Zenvia	PHASE III	Avanir Pharmaceuticals
Ranirestat	PHASE III	Weill Cornell Medical Center
Topical Clonidine Gel	PHASE III	BioDelivery Sciences
Ruboxistaurin Mesylate (LY333531)	PHASE III	BioDelivery Sciences
Zenarestat	PHASE III	BioDelivery Sciences
Minalrestat	PHASE III	BioDelivery Sciences
Zopolrestat	PHASE III	BioDelivery Sciences
SB-509	PHASE II	BioDelivery Sciences
Quigley QR333	PHASE II	QuigleyCorporation

Various antioxidants used to treat diabetic neuropathy are there which are currently in preclinical trials (Table 6).

Table 6: Recent patent agents used in Diabetics Neuropathy

Patent Number	Filing Date	Inventor	Route of Administration
US 0131536	NOV, 2007	Ahmed Massoud	Oral
US 0047370	APR, 2008	Sam Schwartz	Topical
CA 2690086	JUL, 2008	Tsuno	Oral
US 0186908	AUG, 2008	Norman Cameron	Oral or Parenteral

Some Patents are also filed which are also used in treating diabetic neuropathy (Table 7).

Table 7: List of Antioxidants which are in clinical trial for the treatment of Diabetic Neuropathy

DRUGS	SPONSOR	PHASE
Ascorbic Acid (Vitamin C)	Washington State University	PHASE I
N- Acetyl cysteine	University of Turin, Italy	PHASE III
Allopurinol, α-lipoic acid, nicotinamide	University of Michigan	PHASE III
Metanx (a medicinal food)	Pamlab, L.L.C., USA	PHASE IV
Hemoderivative of calf blood (Actovegin)	Nycomed, Denmark	PHASE III
Controlled nitric oxide releasing patch	Fundacion Cardiovascular de Colombia	PHASE III
BK-C0701	Bukwang Pharmaceuticals	PHASE III

Non-pharmacological Approaches: Patient education is considered essential to promote glycaemic control and help avoid the late complications of diabetic neuropathy. Some patients with PDN may not achieve adequate relief with conventional therapy or may suffer from adverse effects of the prescribed treatments. Non-pharmacological approaches have been proposed for these patients. Various nutritional approaches are there to treat diabetic neuropathy (Table 8).

Table 8: Nutritional Treatment for Diabetic Neuropathy

Treatment	Mechanism of Action	Conclusion
Gamma linolenic acid (GLA)	Produce deformable RBCs, Regenerate veins/capillaries, over long period stimulate nerve growth	Stimulate COX 1 expression and production of PGI_2
Vitamin E	Synergistic to GLA	Protects PGI_2 improve capillary permeability
Niacin	Improved blood circulation, expand capillaries	Participates in glucose metabolism and in nervous system
Taurine	TNF- α over expression	Increase insulin sensitivity

Various forms of electrical stimulation have been used to manage pain in diabetic neuropathy, including transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation and frequency-modulated electromagnetic neural stimulation. A recent review analysed eight studies that evaluated the use of electrical stimulation in PDN. Six of these studies found significant pain relief in patients treated with electrical stimulation compared with placebo or sham treatment, suggesting a likely role for treating diabetic neuropathic pain.

A single-blind placebo-controlled randomized trial to evaluate the use of acupuncture in PDN in 45 subjects recently reported an improvement in the outcome measures used to assess pain in the acupuncture arm relative to sham treatment. However, Chen and colleagues suggest that it is difficult to draw meaningful conclusions from acupuncture trials in diabetic neuropathy as trials often have flawed study design and avoid the use of the robust outcome measure of pain in diabetic neuropathy [15].

CONCLUSION

In Diabetes mellitus, either insulin depletion or resistance to insulin occur, resulting in hyperglycaemia and abnormalities in carbohydrates, protein and fat metabolism. This persistence hyperglycaemia often leads to micro-vascular and macro-vascular complications such as neuropathy, nephropathy and retinopathy. In diabetic neuropathy, there occurs altered neuronal structure and function due to oxidative stress through activation of several biochemical pathways.

Treatment should emphasize on optimizing glycaemic control and patient education. Till date ,suitable treatment for controlling diabetic neuropathy still await except two drugs approved by FDA .Several drugs have been declined in clinical trials due to in tolerable side effects and some are yet to be in some phase of clinical trials which will have great impact in diabetic neuropathy .A combination of treatment also serves as an effective means of therapy in many studies and provides hope in order to stop the progression of disease .Even though research is going on and fruitful results from preclinical studies have been reported ,but whether these will be beneficial in therapeutics is still a matter of debate.

PDN is common and is associated with significant impairment in the quality of life of patients with diabetes. Despite its high burden, it remains underdiagnosed and undertreated. Treatment which repairs nerves has yet to be found and translated into clinical trials and eventually approved therapy in clinical practice. Whilst a number of treatment options exist and various guidelines and algorithms have been formulated, none are satisfactory. Various symptomatic treatments have been proposed to manage neuropathic pain but few have been found to be effective, with only three medications currently FDA approved for PDN. Future research must establish the most efficacious drug combinations and in addition exploit new mechanisms and investigate new drugs for the treatment of pain in diabetic neuropathy.

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