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DIABETIC NEUROPATHY: CURRENT THERAPIES AND NEW THERAPEUTIC APPROACHES

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ABSTRACT

Diabetic Neuropathy is a chronic complication of diabetes, which affects neuronal function of whole body. It affects both somatic and peripheral nerves and encompasses a variety of forms. Hyperglycemia induces oxidative stress and leads to activation of multiple biochemical pathways which are a major source of nerve damage. Various therapies are available as a symptomatic treatment but therapies to eradicate the root cause of disease are less available. This empathize the need for causally targeted therapies. This review covers the current symptomatic and causal therapies, also the new therapeutic approaches for identifying the therapeutic targets.

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INTRODUCTION:

Diabetes mellitus is a complex of metabolic disorders associated with insufficiency of insulin secretion, insulin action or both, and is manifested by hyperglycemia[1]. It is one of the most prevalent chronic diseases of modern societies and a major health problem in nearly all countries. Its prevalence has risen sharply worldwide during the past few decades[2]. This increase in prevalence is largely due to the epidemic of obesity and consequent type 2 diabetes but type 1 diabetes incidence is also rising in all developing countries[3]. Both type 1 Diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are characterized by the slow progression towards the generation of some specific lesions of the blood vessels affecting both small and larger vessels. The classical microvascular complications of diabetes are represented by diabetic retinopathy, diabetic renal disease, representing currently the main cause of renal substitution therapy in developed countries and diabetic neuropathy[4]. Neuropathy is a common complication of diabetes, affecting up to 50% of patients[5,6]. Diabetic neuropathies are a heterogenous group of conditions that involve different parts of the somatic and autonomic nervous system. They can be focal or diffuse, proximal or distal. The pathogenesis is also heterogenous, with different causative factors, including persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, and autoimmune mediated nerve destruction[7-9]. Symptomatic therapy has become available, and better and newer treatment based on etiologic factors are being explored with significant impact on morbidity and mortality [10]. New bioinformatics approaches can augment current studies and lead to new discoveries to illustrate the pathogenesis of diabetic neuropathy and to identify more effective molecular targets.

Diabetic Neuropathy

Definition, clinical signs, morphological changes:

Diabetic neuropathy (DN) is a chronic diabetes complication present in both two major phenotypes: T1DM and T2DM. It is a chronic microvascular complication affecting both somatic and autonomic peripheral nerves. It may be defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after the exclusion of other causes of neuropathy[11]. Many neuropathic patients have signs of neurological dysfunction upon clinical examination (decreased sensation for pain, temperature, vibration etc.) but have no symptoms (negative symptoms neuropathy). On the contrary, some patients have positive symptoms (burning, itching, freezing, pain, often with nocturnal exacerbations), usually with distal onset and proximal progression. Frequently, patients have signs of autonomic neuropathy such as resting tachycardia, postural hypotension, vomiting, diarrhea and poor glycemic control following gastrointestinal neuropathy, bladder dysfunction, erectile dysfunction, etc. Most often, DN represents an insidious and

progressive disorder which begins with a long asymptomatic stage. Regarding the morphological changes, characteristic are aspects of primary segmental demyelination of long axons, axonal degeneration, decrease density of small unmyelinated fibers, paranodal anarchic regeneration processes, and Waller's degeneration[12]

Pathogenesis of Diabetic Neuropathy

Hyperglycemia plays an important key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. Over the past 25 years animal experiments and in vitro studies have identified biochemical pathways likely to be important in the development of diabetic complications and all of these pathways are related to the metabolic and/or redox state of the cell. Pathways which are mainly driven by metabolism are: glucose flux through the polyol pathway; the hexosamine pathway; excess/inappropriate activation of protein kinase C (PKC) isoforms; accumulation of advanced glycation endproducts. While each pathway is devastating alone, but collectively all these pathways cause an imbalance in the mitochondrial redox state of the cell and lead to excess formation of reactive oxygen species (ROS)[13]**.** Increased oxidative stress within the cell leads to activation of the Poly(ADP-ribose) polymerase (PARP) pathway which regulates the expression of genes involved in promoting inflammatory reactions and neuronal pathway and also leading to the cascade process that finally activates four major pathways of diabetic complications i.e protein kinase pathway, polyol pathway, age pathway and hexosamine pathway[14]**.**

Polyol Pathway:

Hyperglycemia activates aldose reductase pathway. The enzyme aldose reductase (AR) reduces glucose to sorbitol and sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose. Formation of fructose promotes glycation as well as depletes NADPH which is required for regeneration of glutathione(an important scavenger of reactive oxygen species). This could contributes to redox imbalance and lead to excess formation of ROS and results in neuronal dysfunction and death[15]**.**

Hexosamine Pathway-

Hyperglycemia contributes to the pathogenesis of diabetic complications by increasing the flux of fructose 6-phosphate into the hexosamine pathway [16]**.** Here fructose-6 phosphate is converted to glucosamine-6phosphate by glutamine fructose-6 phosphate amidotransferase[17]**.** Glucosamine-6 phosphate is then converted to uridine diphosphate-N-acetyl glucosamine (UDPGlcNAc). This causes increase in activation of sp1, transcription factor which is responsible for expression of many glucose induced "house keeping"genes i.e TGF-β1 and PAI1. Overexpression of TGF-β1 leads to increased collagen matrix production which promotes endothelial fibrosis and decreases proliferation in mesangial cells[18]**.** Over expression of PAI-1 promotes vascular smooth muscle cell

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mitosis which plays a role in atherosclerosis. Thus hexosamine pathway is implicated in multiple diabetic complications.

Protein Kinase Pathway-

The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycemia causes injury in complications-prone tissues. Elevated glucose level stimulates diacylglycerol (DAG), which in turn activates PKC. Increased production of the PKC, PKC-β-isoform in particular has been implicated in overexpression of the angiogenic protein vascular endothelial growth factor (VEGF), PAI-1, NF-κB, TGF-β and the development of diabetic complications such as retinopathy, nephropathy, and cardiovascular disease[19,20]. PKC activation also alters function of the Na^+K^+ ATPase pump and other enzymes crucial to proper nerve conduction. Activation of different PKC isoforms has been shown to decrease Na+–K+ ATPase activity in smooth muscle cells and normalize activity in peripheral nerves[21].

AGE Pathway

Advanced glycatd end products (AGEs) are formed by the non-enzymatic reaction of glucose and other glycating compounds derived both from glucose and from increased fatty acid oxidation in arterial endothelial cells and most likely heart (e.g. dicarbonyls such as 3-deoxyglucosone, methylglyoxal and glyoxal) with proteins[22]. In diabetes, AGEs are found in increased amounts in extracellular matrix[23]. AGE precursor by intracellular production can damage cells by three general mechanisms. AGEs modify intracellular proteins and alter the function. Secondly, extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and with matrix receptors (integrins) that are expressed on the surface of cells. Finally, modified plasma proteins by AGE precursors bind to AGE receptors on cells such as macrophages, vascular endothelial cells and vascular smooth muscle cells and RAGE binding further induces the production of ROS, which in turn activates the pleiotropic transcription factor, nuclear factor kappa B (NFκB), causing multiple pathological changes in gene expression [24].

Poly (ADP Ribose) Polymerase Pathway:

PARP found in Schwann, endothelial cells, and sensory neurons is also implicated in glucotoxicity. PARP is a nuclear enzyme closely associated with oxidative–nitrosative stress: free radicals and oxidants stimulate PARP activation. Recent evidence also suggests that the two act in concert: PARP both causes and is activated by oxidative stress [25]. PARP acts by cleaving nicotinamide adenine dinucleotide (NAD+) to nicotinamide and ADP ribose residues attached to nuclear proteins [26]. The results of this process include NAD+ depletion, changes in gene transcription and expression, increased free radical and oxidant concentration, and diversion of glycolytic intermediates to other pathogenic pathways such as PKC and AGE formation[27]. Such PARP-

implicated abnormalities manifest clinically as decreased nerve conduction velocity (NCV), small fiber neuropathy, neurovascular abnormalities, retinopathy, thermal and mechanical hyperalgesia, and tactile allodynia.[28, 29].

Oxidative Stress: The hypothesis of oxidative stress causing microvascular complications is based on the evidence that many biochemical pathways are strictly associated with hyperglycaemia (glucose autooxidation, polyol pathway, prostanoid synthesis, protein glycation) and can increase the production of free radicals[30]. Recently clinical trial has been shown that intravenous alpha lipoic acid, a potent antioxidant, is effective in improving neuropathic symptoms and other neuropathic end points[31].

Other Factors: Apart the major role of hyperglycemia, additional risk factors for diabetic polyneuropathy (DPN) are represented by increasing age, alcohol consumption or other drug abuse and classic cardiovascular risk factors including hypertension, dyslipidemia, obesity, cigarette smoking and albuminuria[32]. In addition, genetic susceptibility has an important contribution in determining the global risk for DPN. Several of the cardiovascular risk factors reported to be associated with DPN are markers of insulin resistance. The potential link between insulin resistance and diabetes microvascular complications including DPN is their association with oxidative stress and endothelial dysfunction. In addition, one of the most important links between the metabolic and vascular mechanisms of DPN was reported to be the depletion of nitric oxide and failure of antioxidant protection, both resulting in increased oxidative stress[33].

Management of Diabetic Neuropathy: Treatment of Diabetic polyneuropathy DPN can be viewed as approaches aimed at modifying the disease process or strategies aimed at alleviation of symptoms. Neuropathic pain is difficult to treat, and patients rarely experience complete pain relief[37]. The pain is often chronic and can be debilitating. There are no treatments that will relieve the pain completely; prevention remains the best strategy.

Prevention: Strict glycemic control is perhaps the single greatest prevention measure for neuropathy[34]. Also, controlling hyperlipidemia and hypertension, taking daily aspirin, ceasing smoking, and consuming alcohol only in moderation may also be important in the prevention of PDN.

Symptomatic treatment:

Treatment: The first step in the management of painful diabetic neuropathy(PDN) is glycemic control and correction of any other metabolic dearrangements. Strict glycemic control not only decreases the incidence of neuropathy but also slow down its progression by 57%[35]. In addition, patients often require management of their pain symptoms. Several agents, predominantly

antidepressants and antiepileptics, have been used with varying degrees of success in the treatment of PDN.

Medications for Treatment of Painful Diabetic Neuropathy(PDN): The major classes of drugs used to treat PDN are antidepressants (primarily tricyclic antidepressants [TCAs] and antiepileptics. The first medication studied in a randomized, controlled trial for the treatment of PDN was carbamazepine in 1969[36]. Amitriptyline was the first drug studied in an open-label study in 1977[37]**.** Since that time, many drugs have been found to have possible efficacy in the treatment of PDN.

Tricyclic Antidepressants (TCAs): TCAs were introduced in the late 1950s. This class is the most studied of all agents in the treatment of PDN. TCAs inhibit the reuptake of the biogenic amines, mostly norepinephrine (NE), as well as serotonin (5HT). The analgesic effect of TCAs appears dependent on inhibition of the re-uptake of norepinephrine and serotonin, which each agent does to various degrees.). Amitriptyline was the first TCA to be studied in 1977[38]**.** Amitriptyline and Imipramine are balanced serotonin and noradrenaline reuptake inhibitors. They also block a-adrenegic, H1-histamine, muscarinic cholinergic, and N-methyl-D-aspartate receptors[39]**.** Nortriptyline and desipramine are the metabolites of amitriptyline and imipramine, respectively and are primarily noradrenaline reuptake inhibitors. They also block a-adrenegic, H1-histamine, muscarinic cholinergic, and NMDA receptors which is also responsible for several severe side effects[40]**.** TCAs act centrally to reduce the perception of pain**.** In a placebo-controlled, double-blind, randomized, cross-over trial comparing amitriptyline, desipramine, and fluoxetine with placebo, both TCAs were equally effective and superior to fluoxetine or placebo. The beneficial effect was seen within 2 weeks and continued to increase at 6 weeks[41,42]**.**

TCAs should be used with caution in patients who have a history of cardiovascular disease or are > 65 years of age. Amitriptyline and nortriptyline are relatively contraindicated in patients with a history of ischemic cardiovascular disease, whereas doxepin is thought to be the least cardiotoxic of the TCAs[43]**.** TCAs have been associated with orthostatic hypotension and should be used cautiously in patients with a history of orthostasis or frequent falls. Some side effects, such as dizziness and sedation, can be lessened by careful titration[44]**.**

Other Antidepressants:

Selective Serotonin Reuptake Inhibitors (SSRIs): Selective serotonin reuptake inhibitors (SSRIs) inhibit presynaptic reuptake of serotonin but not norepinephrine and lack postsynaptic receptor blocking effects. These agents can be considered in patients who cannot tolerate TCAs. However, they should be used with caution, especially with Aspirin and Nonsteroidal anti-inflammatory drugs (NSAIDs), as a case-control study showed moderately increased risk of upper gastrointestinal

bleeding[45]. In a randomized, double-blind, crossover study, Paroxetine 40 mg/day significantly reduced neuropathic symptoms compared to placebo but was less effective than Imipramine[46]. Paroxetine was also shown to be effective in relieving both steady and lancinating type of pain and the therapeutic effect was seen within 1 week. Citalopram but not fluoxetine has been reported to have beneficial effects on pain relief[49,47]. Fluoxetine, 40mg/day, is not different from placebo[48]. Citalopram 40 mg/day has also been shown to be better than placebo for treating DPN[49].

Selective Serotonin Noreinephrine Reuptake Inhibitors (SSNRI): These agents are effective in treatment of pain based on the significant role of norepinephrine in endogenous pain modulation through the descending norepinephrine inhibitory pathway. SSNRIs work by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and, therefore, an increase in neurotransmission. Most SNRIs including venflaxine, desvenflaxine, and duloxetine, are several fold more selective for serotonin over norepinephrine, while milnacipran is three times more selective for norepinephrine than serotonin. Elevation of norepinephrine levels is thought to be necessary for an antidepressant to be effective against neuropathic pain, a property shared with the older tricyclic antidepressants (TCAs), but not with the SSRIs. Selective serotonin reuptake inhibitors such as duloxetine and venflaxine have shown to be effective in relieving neuropathic pain by increasing the the synaptic availabilty of 5HT and norepinephrine in the descending pathways that inhibit pain impulse[50].

Venflaxine has been studied in the treatment of PDN in three separate trials[51-53]. Venflaxine and its active metabolite are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venflaxine is also thought to work centrally by decreasing the perception of pain[54]. Adverse events are less frequent with venlflaxine than with the TCAs and include somnolence, nausea and sweating. Venflaxine 150–225 mg/day alleviates DPN but produces unacceptable cardiac side effects with increased risk of electrocardiographic changes[55].

Duloxetine was the first agent approved by the FDA for the treatment of PDN. Duloxetine inhibits both serotonin and norepinephrine transporters[50]. The efficacy and safety of duloxetine were evaluated in three controlled studies using doses of 60 and 120 mg/day over 12 weeks[56]. In all three studies, the average 24-hour pain intensity was significantly reduced with both doses compared to placebo treatment, the difference between active and placebo achieving statistical significance after 1 week. The pooled data from the three trials confirmed that efficacy was maintained throughout the treatment period of 12 weeks and that approximately 50% of patients had achieved at least 50% pain reduction[57]. The medication was, in general, well-tolerated with only 20% discontinuation due to

side effects. The most common side effects were nausea, somnolence, dizziness, decreased appetite, and constipation. Duloxetine is licensed for treatment of neuropathy at a dose of 60 mg/day[58].

Antiepileptics: Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, and zonisamide), potentiation of γ-aminobutyric acid activity (tiagabine and topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate, and zonisamide), antagonism of glutamate at *N*-methyl-D-aspartate receptors (felbamate), or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (felbamate, topiramate). Although the mechanisms of action of gabapentin, pregabalin, and levetiracetam remain to be fully determined, evidence suggests they act on subunits of voltage-gated calcium channels. An understanding of the mechanisms of action of the various drugs leads to the concept of rational polytherapy, where drugs with complementary mechanisms of action can be combined for synergistic effect.Carbamazepine was the first agent studied in the treatment of PDN[59]. Since then, there have been three additional trials investigating the efficacy of carbamazepine in the treatment of PDN[52-54]. Carbamazepine works peripherally by blocking the sodium channels on the Ad nerve fibers. Although carbamazepine has good efficacy in the treatment of PDN, it is also associated with serious adverse events, including aplastic anemia.

Lamotrigine also acts peripherally as a sodium channel blocker. The efficacy of lamotrigine has been evaluated in two studies one parallel placebo controlled[58] and one open label. Lamotrigine is less efficacious than carbamazepine and is associated with aplastic anemia and toxic epidermal necrolysis.

Valproate has been studied in three placebo-controlled trials. Valproate was found to be efficacious in two studies[60,61] but equivalent to placebo in the other[62]. Patients taking valproate must be monitored with liver function tests and complete blood count with platelets.

Topiramate is one of the few agents used in the treatment of PDN that is associated with weight loss[60]. Topiramate has many adverse effects, such as cognitive slowing, dizziness, and a small risk of kidney stones and closed-angle glaucoma, and it is often not tolerated by patients [61].

Gabapentin is commonly used in the treatment of neuropathic pain. Like the other antiepileptics, it acts peripherally to decrease pain perception. There have been two randomized, placebo-controlled studies of gabapentin in the treatment of painful diabetic neuropathy. The first study demonstrated a small but significant decrease in mean daily pain score in patients treated with gabapentin (titrated from 900 to 3,600 mg/dl or maximum tolerated dose), compared with placebo. The second, smaller study did not show a significant difference in pain scores between patients treated with gabapentin (900 mg/d) and placebo[65].Significant weight gain has been described with long-term use of gabapentin in the treatment of seizure disorder, typically starting 2–3 months after initiation.[62].

Pregabalin is the second agent approved by the FDA for the indication of PDN. It acts peripherally at the GABA receptor to block the perception of pain. Pregabalin has been evaluated in three parallel, placebo-controlled studies in the treatment of PDN [63-65]. Pregabalin is relatively well tolerated. However, it is associated with other rare but serious adverse events, including rhabodmyolysis ,acute renal failure, central nervous system effects, hyperthermia and secondary acute-angle glaucoma. Patients on pregabalin therapy must be monitored closely for myopathy and ocular complaints.

Other Agents: Capsaicin is an alkaloid derived from chillies. It acts peripherally by depleting the neurotransmitter substance P from sensory nerves. It is applied topically and is not absorbed significantly into the systemic circulation. The only adverse effects are local stinging and burning and sneezing or coughing during application. It must be applied while wearing gloves, and patients must be careful not to touch their face until after carefully washing their hands[65,66-70]**.** The pain with application decreases after the 1st week of use.

Tramadol acts through both monoaminergic (like the TCAs) and opioid mechanisms and acts centrally to block pain perception. It has lower abuse potential than other opioids. It has been evaluated in the treatment of PDN in two placebo-controlled studies[71,72]**.** Tramadol has side effects common to opioids, such as constipation, urinary retention, and central nervous system effects. It should be avoided in patients with substantial alcohol use or a history of opioid abuse.

Mexilitine is an oral analog of lidocaine. It is a class IB anti-arrhythmic agent and acts peripherally as an ion channel blocker to prevent the perception of pain. It has been evaluated in five placebo trials and was found to be efficacious in all[72-77]**.** Mexilitine has the fastest onset of pain relief, which is usuall within 1–4 days. Patients on mexilitine therapy should be monitored with complete blood count with platelet measurement electrocardiogram, and liver enzyme tests.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used in the treatment of PDN. NSAIDS inhibits cyclo-oxygenases, and thus prevent the formation of prostaglandins. Usually these are not recommended for the treatment of DPN due to their detrimental effects to GI, renal and cardiac functions[78]**.** In case of severe pain certain agents may be used in combination (eg. Antidepressant and anticonvulsant) or combined with a topical or nonpharmacolgical treatment[79]**.**

Treatment Of Autonomic Neuropathy:

Treatment of autonomic neuropathy is only palliative. With the help of pharmacological and non-pharmacological means the quality of life can be improved in these patients.

Orthostatic Hypotension: Nonpharmacological treatment should be the initial approach to increase venous return. Supportive stockings should be worn during the day and removed at bed time. Patients should be advised to avoid hot baths, to get out of bed or stand up slowly and if their

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diabetes is being treated with insulin, patients should administer insulin injections while lying down. Pharmacological approaches include mineralocorticoids, fludocortisone together with supplementary salt increase plasma volume. Unfortunately, it is generally ineffective until edema develops[80]. The mixed adrenergic agonsist, ephedrine, the α-1 adrenergic agonist, midodrine and the α- 2 adrenergic agonist, clonidine have each been found to be effective in some patients[80].

Gastroparesis: Diabetic gastroparesis can be treated with a variety of prokinetic agents and recommended dose regimens are shown below.

TABLE:-

Treatment	Dose regimen	Possible side effects
Behavioural advice		
Improve glycemic control		
Eat frequent small meals		
Reduce dietary fat (b40 g/day)		
Reduce dietary fiber		
Metoclorpramide	10 mg, 30–60 min ac	Galactorrhea, extrapyramidal symptoms
Erythromycin	250 mg, 30 min ac	Abdominal cramps, nausea, Diarrhea,rash Jujunostomy and liquid diet

Diabetic Diarrhoea: A broadspectrum antibiotic such as metronidazole can be used to treat diarrhoea resulting from bacterial overgrowth. Clonidine may improve diarrhoea by reversing adrenergic overactivity.. Loperamide can be used, but it should be used with caution due to risk of toxic megacolon.

Bladder Dysfunction: Treatment of neurogenic bladder should begin with scheduled voiding, often coupled with manual pressure on the bladder to initiate urination. The para sympathomimetic agent, bethanechol (10 mg,QID) may be helpful, and extended sphincter relaxation can be achieved with the α-1 adrenergic antagonist, doxazosin (1–2 mg, BID or TID) [81].

Erectile Dysfunction: It is one of the most common and distressing manifestations of DAN. Erectile dysfunction may be the presenting symptom of diabetes, and importantly, it is a marker for the development of generalized vascular disease and for premature death from myocardial infarction [84]. Treatment of erectile dysfunction should begin with optimization of glucose control and abstinence from alcohol and tobacco. Sildenafil (50 mg, 60min before sexual activity)or tadalafil (5 to 20 mg, 60 min before sexual activity) are effective in treating erectile dysfunction in men with diabetes .However, all of these agents are contraindicated in patients being treated with nitroglycerine or other nitrate-containing drugs. Injection of prostacyclin into the corpus cavernosum produces satisfactory erections, and surgically implanted penile prostheses are also available. Thus there are now several effective approaches to treating erectile dysfunction in men with diabetes.

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Pathogenic Treatment: Various pathogenic pathways are responsible for diabetic neuropathy. They contribute to oxidative stress and sometimes one pathway can stimulate other pathway which leads to further nerve damage and results in diabetic neuropathy. Therapies that are under investigation are as follows:-

1. Aldose reductase inhibitors
2. Antioxidants
3. AGE inhibitors
4. Protein kinase inhibitors
5. Glycemic control with insulin
6. Myoinositol
7. Agents increasing nerve blood flow
8. Growth factors.

Aldose Reductase Inhibitors: Sorbitol ,the first metabolic product of the polyol pathway is the most common target of diabetic neuropathy therapies. Elevated sorbitol levels are thus indicators of hyperglycemia and good therapeutic targets for reducing oxidative strss resulting from excessive glucose metabolism. Aldose reductase inhibitors reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose[82].

The past and ongoing ARI trials and investigations are described in the table below[88].

Compounds	Trial/notes
Sorbinil	Only slight improvement in NCV; high rate of skin rash, trial withdrawn
Tolrestat	Halted mild diabetic neuropathy progression; no significant improvements in NCV, trial withdrawn
Ponalrestat	No effect due to poor pharmacokinetics & pharmacodynamics, trial withdrawn
Zopolrestat	Low levels: slight NCV improvement High levels: significant improvement in NCV; elevated liver enzymes trial withdrawn
Zenarestat	Dose-dependent improvement of NCV
Lidorestat	Withdrawn at phase 2 clinical trial
Fidarestat	Similar to Sorbinil, suspended in phase 3 due to resource consolidation
AS-3201/Ranirestat	Promising phase 2 trials; phase 3 underway. High placebo effect complicating study
Epalresta	Delayed progression of diabetic neuropathy, study not replicated
Myo-inositol	Animal studies indicate beneficial effects, human studies needed

Hexosamine Pathway: Activation of the Hexosamine pathway generates UUDPGIcNAc, which modulates transcription factors and ultimately induces neurovascular insult .The modualtion of hexosamine pathway can redirect glycolytic flow away from subsequent deleterious pathways.

Benfotiamine: The increased formation of advanced glycation endproducts (AGEs) constitutes a potential mechanism of hyperglycaemia-induced micro and macrovascular disease in diabetes. In vitro and animal experiments have shown that various interventions can inhibit formation and/or actions of AGEs, in particular the specific AGE inhibitor aminoguanidine and the AGEs crosslink breaker alagebrium, and the B vitamins pyridoxamine and thiamine, and the latter's synthetic derivative, benfotiamine[83]**.** It was observed that 10mM concentration of benfotiamine and 5mM and 1mM concentrations of thiamine-hydrochloride produced fairly good response to decreased glycation[84]**.**

AGE Inhibitors: Numerous compounds have been investigated for anti-glycation activity but their use in humans is still debatable. The following section describes compounds that have been assessed for the ability to decrease activity of the RAGE axis in diabetic neuropathy[88].

Compounds	Trials/notes
Coenzyme Q10	Cofactor that improves metabolism but also a potent antioxidant
Nicotinamide	(AKA vitamin B3) is a weak PARP inhibitor, antioxidant, and calcium modulator. Effective in experimental diabetes and currently in a type 1 diabetes patient trial.
Eugenol.	From clove oil; both anti-inflammatory and antioxidant. Improves vascular and neural deficits in STZ-treated rats
Taurine	Plasma taurine is depleted in diabetic rats and replacement decreases hyperalgesia and other neural and vascular deficits.
U83836E	A synthetic ROS scavenger, effective against oxidative stress, and neurovascular deficits in rats.
Oleuropein)	From olive leaf, decreases blood glucose as well as oxidative stress in alloxan-treated rabbit.
Minerals	Metal ions including vanadium, chromium, magnesium, zinc, selenium, and copper contribute to antioxidant defense. They may become depleted in diabetic patients and should be included in the diet
Vitamin C	While vitamin C does not improve diabetes complications when given alone, it is used in combination with vitamin E or other antioxidants, since it facilitates effective antioxidant recycling.
Quercetin	A flavonoid that attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats.

Melatonin	Plasma levels decrease in diabetic patients with complications, supplementation reverses antioxidant status deficits and prevents complications. May both activate antioxidant response and scavenge ROS.
Apocynin	Decreases oxidative stress by inhibition of NAD(P)H oxidase .
Rutin	A polyphenol that may activate the antioxidant response. Prevents oxidative stress in diabetic rats.
Evening primrose oil	Initially used for therapeutic benefit of polyunsaturated fatty acids, also decreases oxidative stress.Efficacy further enhanced by conjugation with an antioxidant.
Nitecapone	Catechol-O-methyltransferase inhibitor with potent antioxidant properties. Had some ability to prevent diabetic Mechanical hyperalgesia, but essentially ineffective in preventing the development of diabetic neuropathy.
Troglitazone	Used as an insulin sensitizer in diabetic patients, but also operates as an antioxidant. May improve peripheral neuropathy in STZ-induced diabetic rats irrespective of blood-glucose concentrations.
N-acetylcysteine	Precursor of GSH that increases tissue GSH improves motor nerve conduction velocity and decreases oxidative stress in STZ-treated rats.

Protein Kinase Inhibitors:

Ruboxistaurin: It has been useful in reducing the progression of diabetic retinopathy, endothelial vasodilation and to a lesser extent diabetic nephropathy[85]**.** Ruboxistaurin, an orally active protein kinase C beta (PKC beta) inhibitor, is a macrocyclic bisindolylmaleimide compound under development by Eli Lilly with potential as a therapy for diabetic macular oedema and other diabetic angiopathies, including diabetic retinopathy, diabetic peripheral neuropathy and diabetic nephropathy[86]**.**

Myoinositol: There is a depletion of myoinosotol with the activation of polyol pathway. Myoinositol given from outside can restore the level of nerve myo-inosoitol.

Poly(ADP-Ribose) Polymerase Inhibitors: PARP inhibitors such as 1,5-isoquinolinediol and 3-aminobenzamide have successfully improved PARP-mediated dysfunctions in STZ-induced diabetic rats [87]**.** Nicotinamide has been shown to act as a PARP inhibitor and an antioxidant in animals that improves complications of early DN[88]**.** Currently a combination therapy for diabetic neuropathy including nicotinamide, the xanthine oxidase inhibitor, allopurinol, and the antioxidant DL-α-lipoic acid is under trial. (PARP) inhibition has emerged as a new therapeutic approach for peripheral diabetic neuropathy using clinically relevant animal model and endpoints, and nitrotyrosine (NT), TNF-alpha, and nitrite/nitrate as potential biomarkers of the disease[89]**.**

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Antioxidants: So many studies that report positive effects of antioxidants in both animal models and patients. Although, it is impossible to review all the antioxidants that can be effective to prevent or delay the onset of DN, some can be listed such as acetyl-L-carnitine, taurine, vitamin E, β-carotene, free amino acids, curcumin, ascorbic acid, and lipoic acid [90].

Taurine - Taurine is an antioixidant having effects on neuronal calcium signaling. It improves electrophysiological parameters and nerve blood flow and exhibits analgesic properties in patients with DN [91].

Acetyl-L-Carnitine - Acetyl-L-carnitine (ALC), the acetylated ester of the amino acid L-carnitine, as an antioxidant has shown significant reduction in pain of patients with DN.

Alpha Lipoic Acid - D-L-α-lipoic acid (ALA) is a potent antioxidant, which has been extensively evaluated in subjects with DN and has shown good effects but, there is insufficient evidence to recommend it in treatment of DN[91,92].

Targetting Vascular Disease That Increase Blood Flow: In experimental diabetes, enalapril, an ACE inhibitor, or L-158809, an angiotensin II receptor blocker, decreases neurovascular deficits including blood flow and motor nerve conduction velocity. Another ACE inhibitor, Perindopril, prevents photoreceptor loss, an indicator of neuropathy. In a small clinical study, the ACE inhibitor trandolapril produced a significant improvement in peripheral neuropathy. Another study treated long-term diabetic patients with DAN but not high blood pressure or arterial disease with the ACE inhibitor Quinapril and/or the ARB Losartan[89].

Neurotrophic Factors: There is growing interest in exploring the potential utility of NGFs, insulin, IGFs and others neurotrophic factors in the treatment of diabetic neuropathy.

Insulin-deficient rat models of diabetes appear to have more severely progressive neuropathy compared to T2DM models, suggesting insulin deficiency itself contributes to the development of neuropathy. Local delivery of insulin to the spinal cords of STZ-treated rats improves nerve condition velocity measurements.

C-peptide deficiency is concomitant with insulinopenia in T1DM. When C-peptide is replaced in diabetic rats, a number of measures of peripheral nerve function improve.

Insulin-like growth factors (IGFs) I and II have profound effects on nervous system development and survival, mediated through activation of the IGF-I receptor (IGF-IR). A number of preclinical studies in diabetic rats suggest systemic or intrathecal IGF therapy can improve neuropathy . The system of neurotrophins is critical for the development and maintenance of the PNS and CNS and includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), and neurotrophins (NT) 3–6. Preclinical studies of NGF in diabetic rats resulted in improvements in both signaling outcomes of the NGF system and PNS function, as well as positive effects on myelination[89].

Non Pharmacological Treatments:Patients not responsive to pharmacological therapy may be referred to physical or invasive treatments like central neurostimulation. In diabetic patients, physical therapy is found to be effective[90]. This is an alternate to reduce dependency on pain relieving drug treatment. Certain physiotherapy techniques are helpful in relieving symptoms in diabetic patients such as deep pain in extrimities, tingling or burning sensation, muscle cramps, sexual dysfunction and diabetic foot [91].

Electric stimulation- A painless low frequency electric current is passed through transcutaneous electrical nerve stimulation (TENS) and interferntial current(IFC), to relieve neuropathic pain, reduce oedema, relieve stiffness, improve mobility and heal resistant foot ulcers. Patients with foot ulcers are trained through gait training or posture training, and teaching the basic principles of off-loading can help prevent and stabilize foot complications. Muscle strengthening exercises can maintain muscle strength and reduce muscle wasting. Aerobic exercise such as swimming and riding a stationary bicycle have impact in peripheral neuropathy. Various other methods including heat, therapeutic ultrasound and short wave diathermy have been useful in for treating diabetic neuropathy [92]. Sexual function can be improved through pelvic floor musce exercises[93,94].

Now a days, Photo Energy Therapy devices are frequently used to treat neuropathic symptoms. These devices emit near infrared light of wavelength 880 nm. This wavelength stimulates the release of nitric oxide and results in vasodilation of capillaries and venuoles in the microcirculatory system. This increase in circulation contributes to decrease pain intensity in diabetic and non diabetic patients.

Electric spinal cord stimulation- In one reterospective cohort study, it is concluded that after 1 year of spinal cord stimulation (scs), 50% pain relief occurred in 63% of patients and analgesics usage was reduced in most SCS treated patients. Pain relieving effects of SCV is shown in many studies and promising results were reported[93].

Diet and Lifestyle Interventions: Glucose-modifying drug therapy is typically not appropriate for patients with impaired glucose regulation because of its cost and the potential for serious adverse effects such as hypoglycemia. A more suitable approach for these patients is a lifestyle intervention that could arrest the underlying process that leads to neuropathy. Lifestyle changes in patients with impaired glucose regulation, who are at the earliest definable stages of hyperglycemia, may also be effective in preventing diabetes-associated complications such as peripheral neuropathy.

It is advised to patient to maintain a healthy weight, quit smoking and use of natural remedies for diabetes. Patient should be encouraged to daily inspection of the feet, regular pedicure and awareness to trivial injuries. Proper care is also advised in patients with cutaneous sensory loss,

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impaired sweating and vascular disease. All these measures will decrease risk of developing foot ulceration to some extent [93].

New Therapeutic Approaches For DN: Despite relative lack of success of interventional agents to reverse or slow established DN, there is still hope to find some good agents. Some of the new approaches are described in the table below [94]

Endpoint	**Study populations**	**Compound**
Improvement of peripheral nerve function	Diabetic rats	Salvianolic acid A
Improvement of DN	Animal model of T2D	High-fat diet with menhaden oil
Improvement of DN	Patients with T2Dand neuropathy	Tai Chi exercise
Improvement of DN	T2DM patients	Beraprost sodium
Improvement of DN	STZ-diabetic rats	Anandamide
Improvement of peripheral nerve Function	Mouse model of DPN	Thymosin $\beta 4$
Improvement of chronic pain,including PDN	Rat model of STZ-induced PDN	Gastrodin
Prevention of progression of DN	Patients enrolled in the aldose reductase inhibitor-diabetes complications	Epalrestat
Improvement of DN	STZ-diabetic rats	Gliclazide with curcumin
Improvement of DN	STZ-diabetic rats	Bone marrow-derived mononuclear cells
Neuroprotection effect	In vitro model of high glucose-treated DRG neurons in culture	Galanin
Improvement of DN	———————	Baicalein

Improvement of pain	Animal models of neuropathic pain	Brazilian armed spider venom toxin
Neuroprotection effect Improvement of DN	STZ-diabetic rats	Magnesium-25 carrying porphyrin-fullerene nanoparticles
Maintaining health in diabetes	STZ-diabetic rats	Phosphodiesterase inhibitors
Improve transplant outcome and graft function in diabetes	Isolated rat pancreatic islets	IMOD
Improve islet transplantation in diabetes	Isolated rat pancreatic islets	Cerium and yttrium oxide nanoparticles

Other Drugs In Clinical Trials

SB-509- It is recently in phase 2 trials for treatment of diabetic neuropathy. This drug contains the gene (DNA) for a protein. After injecting in to the legs, it was found to enter the muscle and nerve cells around the injection site and promotes these cells to make a protein. This protein further increased the production of VEGF which improves the structure and function of nerves.

Quigley QR333- In a phase 2 double blinded placebo-controlled, clinical trial of diabetic peripheral neuropathy it was demonstrated that there is a significant improvement in two key measures of distal sensory nerve function in the group treated with QR333 which was applied topically to the feet of the subjects suffering from painful diabetic neuropathy. Over the course of 12 weeks ,it significantly improved maximal conduction velocity[93].

CONCLUSION:

Diabetic Neuropathy is a chronic condition of hyperglycemia and associated with metabolic imbalance. It is a most common condition of Diabetes, leading to substantial pain, morbidity and reduced quality of life. Neuropathy is a common complication of diabetes, affecting up to 50% of patients**.** Several biochemical mechanisms have been identified for nerve and neurovascular damage. The pathogenesis is also heterogenous, with different causative factors, including persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, and autoimmune mediated nerve destruction. Various therapies are available as a symptomatic treatment but therapies to eradicate the root cause of disease are less available. Treatment should emphasize on optimizing glycaemic control and patient education. Till date

suitable treatment for diabetic neuropathy still awaits. Several drugs have been declined in clinical trials due to intolerable side effects and some are yet to be in some phase of clinical trial which will have great impact in diabetic neuropathy.

Treatment of diabetic neuropathy should always begin with optimization of glycemic control. Now, there are numerous pharmacological approaches to treat the condition of diabetic neuropathy but disease modifying treatment await a more complete understanding of underlying mechanism behind diabetic neuopathy. Some positive results have been reported at preclinical level with inhibitors implicating in pathogenesis. Discovery of these targets will require biochemistry, bioinformatics, cellular biology and physiology. With further progress, development of agents to prevent mitochondrial oxidative damage will be the core focus of intense study.

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