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Review Article

Diabetic Neuropathy: Current Pharmacological Management

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Abstract

Diabetic mellitus play an enormous role in evolving neuropathy results in pain and decreased motility and is a manifested disorder. Type 2 Diabetes mellitus is the dominant root of neuropathic pain. Neuropathic pain is most common and costly complication of both Type 1 Diabetes mellitus and Type 2 Diabetes mellitus. Neuropathic pain represents a devastate disease which has currently increased the incidence rate of panoramic implications for mutiny the health care costs. Pain has been considered to play a primary role in alteration of normal physiology of patients worldwide. Neuropathic pain is a persistent chronic pain resulting from damage to the central or peripheral pain signaling pathways. Neuropathic pain proceeds as a result of lesions or disease affecting the somato-sensory nervous system either peripherally or centrally. Neuropathic pain is characterized by spontaneous ongoing or shooting pain and invokes intensify pain response after noxious responses or non-noxious stimuli. There have been a number of pharmaceutical therapies which are reported to show beneficial effects in Diabetic Neuropathy; which includes selective serotonin reuptake inhibitors, analgesics, serotonin-norepinephrine reuptake inhibitors, atypical anti-depressants, anti-convulsants, anti-epileptic medications .The objective of this review article is to represent the functioning of pathways and various mechanisms involved in the development of diabetic neuropathy and current therapeutic approaches employed in Diabetic Neuropathy.

1. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disease characterized by chronic hyperglycemia resulting from defects in insulin action, insulin secretion, or both resulting in impaired metabolism of carbohydrate, lipid and protein[1-2]. DM is a disease in which homeostasis of carbohydrate, protein and lipid is improperly regulated by insulin hormone resulting in elevation of the fasting and postprandial blood glucose levels. As the condition of hyperglycemia progresses, increases in tissue or vascular damage may lead to obesity, hypertension, advancing age, accumulation of harmful agents in the vascular endothelium causing development of microvascular complications. The complications of DM are microvascular (neuropathy, nephropathy, cardiomyopathy and retionopathy) as well as macrovascular (e.g. atherosclerosis, hypertension, coronary artery disease (CAD), and stroke) pathologies with more than 17.5 million peoples attributable to cardiovascular complications and may cause death[3].

2. ALARMING EPIDEMIOLOGY OF DIABETES MELLITUS

Long considered a disease of minor significance, in the 21st century, DM is now considered one of the main threats to human health in the 21st century[2]. The prevalence of DM is rapidly increasing all over the world due to stress, food, habits, obesity and decreased physical activity [4]. India is the diabetic capital in the world and predicted to have 57.2 million people suffering from DM by the year 2025. Currently, 77 million people are suffering from DM in India. Diabetes affects the people worldwide and its prevalence is expected to increase up to 592 million by the year 2035[5]. According to International Diabetes Federation (IDF) Diabetes Atlas 6th Edition-2013 update, about 382 million people have diabetes as IDF report 2013. The number of people with type 2 diabetes is increasing in every country; the greatest numbers of people with diabetes are between 40 and 59 years of age. Diabetes caused 5.1 million deaths in 2013. Also 175 million people with diabetes are undiagnosed with a rate of a person dies from diabetes in six seconds and more than 21 million live births were affected by diabetes during pregnancy in 2013. In accordance to the latest IDF publication, it is clear that the incidence and prevalence of diabetes are increasing at an alarming rate both in developed and in developing countries but the largest proportional and absolute increase will occur in developing countries, particularly India[6]. The World Health Organization (WHO) estimated a worldwide prevalence of DM is about 347 million people; the incidence of T2DM is increasing at an alarming rate both nationally and worldwide[7].

2.1 Clinical Sign and Symptoms of Diabetes Mellitus

Individual can experience different sign and symptoms of diabetes like increased hunger, weight loss, tiredness, frequent urination, excessive thirst, a tingling sensation or numbness in the hands or feet, frequent infections, slow-healing wounds, blurred vision, vomiting and stomach pain.[8]

2.2 Risk Factors and Associated Diabeteic Complications

There are various risk factors for the micro vascular complication of diabetes mellitus; generally associated with neuropathy development has been suggested such as overweight and obesity, poor glycemic control, high cholesterol levels, hypertension, chronic hyperglycemia, dyslipidaemia, smoking, excess alcohol intake, diet, older age and male sex and tall height[9-12].

T2DM and related complications are associated with many pathological conditions which are responsible for reduced quality of life and increased risk factors for mortality and morbidity. The long-term chronic hyperglycemia is an important factor in the development and progression of micro (diabetic nephropathy, neuropathy and retinopathy) and macro (peripheral arterial disease, coronary artery disease, and stroke) vascular complications[13-16].

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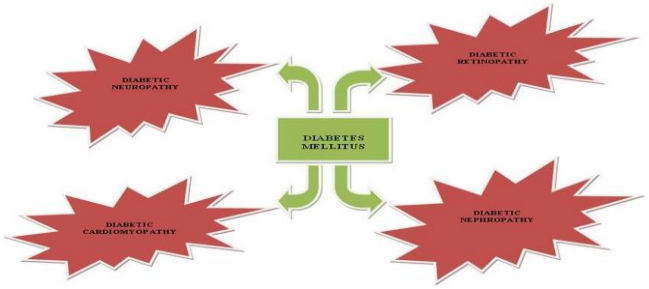

Fig. 1: Main complications of diabetes mellitus

3. DIABETIC NEUROPATHY

T2DM is the primary cause of neuropathic pain. Neuropathic pain is most common and costly complication of both T1DM and T2DM[17]. Neuropathic pain is a persistent chronic pain resulting from damage to the central or peripheral pain signaling pathways[18]. Diabetic neuropathy (DN) results in pain and increased mortality either subclinical or clinically evident, that occurs in both the peripheral and autonomic nervous system. Neuropathy is the most common complication of T2DM affecting upto 50% of patients. Examples of neuropathic pain include the postherpetic neuralgia, trigeminal neuralgia, painful polyneuropathy and post stroke pain. Neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain response after noxious responses or non-noxious stimuli[19]. DN is a heterogeneous disorder with high morbidity and can be classified as a number of different syndromes ranging from sub-clinical to clinical manifestations, depending on the classes of fibers involved[20]. Symptoms associated with Diabetic peripheral neuropathy (DPN) involve poor gait and balance associated with large sensory fibers, on the hand abnormal cold and/or heat sensations associated with the small sensory fibers. DN is represented by; Hyperalgesia (increased pain perception/response to painful stimuli), Allodynia (pain in response to stimuli that does not normally provoked pain), Paresthesias (Unpleasant abnormal sensation), and Spontaneous pain[24-26].

4. EPIDEMIOLOGY OF DIABETIC NEUROPATHY

DN is the most common complication of T1DN and T2DM, which affects approximately 20% of adult diabetic patients and 50% of all diabetic patients, will develop DN in their lifetime[21]. The prevalence of DN is estimated to be about 8% in newly diagnosed patient and greater than 50% in patient with long standing disease[22]. DN occurs in persons with diabetes at a rate of 11.6% in those who are insulin dependent and 32.1% in those who are not. According to an epidemiological study which reported that diabetic patients shows tingling, shooting, or burning pain in the community[23]. Prevalence of pain was greater in patients with T2DM, greater in females with diabetes than in males, and showed variability between ethnic groups as per the cohort study.

5. CLASSIFIACTION OF DIABETIC NEUROPATHY

DN has been classified as into various types which are shown in table-1[27-28].

Table 1: Classification of diabetic neuropathy

Autonomic neuropathy	Sensorimotor neuropathy
▪ Hypoglycemic unawareness	▪ Distal symmetric polyneuropathy
▪ Abnormal papillary function	▪ Focal neuropathy
▪ Cardiovascular autonomic neuropathy	➢ Diabetic mononeuropath
▪ Vasomotor neuropathy	➢ Mononeuropathy multiplex
▪ Sudomotor neuropathy (sweet gland)	▪ Diabetic amyotrophy
▪ Gastrointestinal autonomic neuropathy	
➢ Diabetic diarrhea or constipation	
➢ Fecal incontinence	
▪ Genitourinary autonomic neuropathy	
➢ Bladder dysfunction	
➢ Sexual dysfunction	

6. PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

The factors which precipitate the development of diabetic neuropathy are not clearly understood, and several hypotheses have been proposed[29]. A bunch of pathways involved in pathophysiology of DN. Extensive research has implicated four major pathways of glucose metabolism in the development of microvascular complication of DM;

1. Increase polyol pathway activity leading to accumulation of sorbitol and fructose and change in signal transduction
2. Non-enzymatic glycation of protein and yielding advanced glycation end product (AGEs)
3. Activation of protein kinase C (PKC) pathway
4. Increase in hexosamine pathway flux[24].

While each pathway may be injurious alone collectively these pathways cause an imbalance in the mitochondrial redox state of the cell and lead to excess formation of reactive oxygen species (ROS). Development of symptoms depends upon many factors, such as total hyperglycemia exposure, elevated lipids, blood pressure, smoking, increased height and exposure to neurotoxic agents such as ethanol[30]. Long term hyperglycemia elicits enhanced polyol pathway, increased non-enzymatic glycation of structural proteins, enhanced oxidative stress as well as altered PKC and poly ADP-ribose polymerase (PARP) activity that are all interrelated for the cause and development of DN[31] .

6.1 Polyol pathway in diabetic neuropathy

Hyperglycemia causes increased level of intracellular glucose in nerves which leads to the saturation of normal glycolytic pathway. Excess level of glucose shunted to polyol pathway and converted it into sorbitol and fructose by the enzyme aldose reductase and sorbitol dehydrogenase respectively with the accumulation of sorbitol and fructose leads to decreased membrane Na+/K+-ATPase activity, reduced myoinositol, impaired axonal transport and structural breakdown of nerves. Fructose and sorbitol both being osmotically active compounds lead to an increase in water content in the nerves. Further the oxidation/reduction status of the cell is altered with loss of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) and glutathione stores.

NADPH is consumed by aldose reductase mediated reduction of glucose to sorbitol and NADPH is required for regeneration of reduced glutathione (GSH) this contributes to oxidative stress[1, 32]. Reduced NADPH, a cofactor for the enzyme nitric oxide synthase, reduces nitric oxide formation leading to decreased vasodilatation that impairs blood supply to the nerve. ATPase in peripheral nerve of the galactosaemic animals showed a reduction in the myoinositol level[24]. The second step of polyol pathway oxidized sorbitol to fructose via sorbitol dehydrogenases. Fructose formation promotes AGE formation and increase formation of diacylglycerol (DAG), which activate PKC pathway and cause oxidative stress[33].

6.2 Advanced glycation end products (AGEs) in diabetic neuropathy

Excess glucose in hyperglycemia can lead to non-enzymatic glycation of proteins, nucleotides and lipids resulting in production of AGEs that may have role in disrupting neuronal integrity and repair mechanisms. AGEs are modified heterogeneous, intracellular and extracellular bio molecules[24, 34]. Inside cells, both protein and DNA adducts alter function and cellular transport. Extracellular protein AGEs include plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGEs (RAGE). AGE –RAGE interaction activates the transcription factor i.e. nuclear factor kappa B (NF-κ B). NF-κB regulates a number of activities including inflammation and apoptosis. Activation of neuronal RAGE induces oxidative stress through NADPH oxidase activity[35]. Increased levels of AGE and RAGE are found in human diabetic tissue. Collectively, the biochemical damage induced by AGEs results in impaired nerve blood flow and diminished neurotrophic support[24].

6.3 Protein kinase C (PKC) activity in diabetic neuropathy

PKC pathway is an additional mechanism by which hyperglycaemia causes injury in complication prone tissues. Elevated glucose levels stimulate DAG, which in turn activates PKC enzyme. Increased production of the PKC β-isoform in particular has been implicated in over expression 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[36]. PKC pathway activation alters vasoconstriction and capillary permeability, which cause hypoxia, angiogenesis, basement membrane thickening, and endothelial proliferation. These changes in neurovascular blood flow are the likely source of PKC's role in DN. PKC activation also alters function of the $Na\text{-}K^+$ ATPase pump and other enzymes crucial for proper nerve conduction. The link of PKC with DN is supported by studies in HFD/STZ induced diabetic rats, where PKC inhibition normalizes both nerve conduction velocity and sciatic nerve blood flow. Over expression of PKC isoforms can also directly induce insulin resistance[24, 37].

6.4 Hexosamine pathway in diabetic neuropathy

Hexosamine pathway was implicated as an additional factor in the pathophysiology of DN. Fructose-6-phosphate is a metabolic intermediate to glycolysis. During glucose metabolism some Fructose-6-phosphate is shunted from the glycolytic pathway to the hexosamine pathway. The fructose-6-phosphate is converted to glucosamine-6-phosphate by an enzyme glutamate fructose-6-phosphate amidotransferase[38]. Glucosamine-6-phosphate is then converted to uridine diphosphate-N-acetyl glucosamine (UDP GIcNAc), a molecule that attaches to the serine and threonine residue of transcription factor[39]. Hyperglycemic conditions create additional flux through the hexosamine pathway, resulting in excess GlcNAc and abnormal modification of gene expression[39-40]. The reduced fructose-6 phosphate input decreases flux through the hexosamine pathway (as well as flux through the AGEs, DAG and PKC pathway.

6.5 Poly (ADP-ribose) polymerase pathway in diabetic neuropathy

PARP activation plays an important role in the pathogenesis of diabetic complications including painful diabetic neuropathy (PDN). PARP is a neuclear enzyme found in Schwann and endothelial cells and sensory neurons is also implicated in glucotoxicity, which is activated by free radicals and oxidative stress[41]. PARP acts by cleaving nicotinamide adenine dinucleotide (NAD^+) to nicotinamide and ADP-ribose residues attached to nuclear proteins. 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 AGEs formation[41-42]. PARP inhibitors such as 1, 5-isoquinolinediol and 3-aminobenzamide have successfully improved these PARP-mediated dysfunctions in STZ-induced diabetic rats[41-44]. It is a nuclear enzyme toxic to β-cells and involved in the development of brain dysfunction in diabetic neuropathy[21]. Activation of PARP is an important affector of oxidative-nitrosative injury, which further causes motor and sensory nerve conduction deficits, neurovascular dysfunctions and myelinated fibre atrophy which are characteristics of PDN[43].

6.6 Oxidative Stress in diabetic neuropathy

The increased production of free radicals in diabetes may be detrimental via several mechanisms. They may directly damage small blood vessels, supplying nerves, leading to nerve ischemia. DN is consequence of multiple mechanistic changes occurring within both peripheral and central nervous system. It is best viewed as a group of disorder of nervous system[45]. Unexpected pathophysiology of neuropathic pain involves role of oxidative stress and nitrate oxide mechanism and their interaction[46]. There are many inflammatory mediators released from neutrophils and macrophages after peripheral injury that impairs tissue in normal condition and permit accumulation of free oxygen radicals that accelerate tissue destination. Oxidative stress is critically involved in the development and progression of neuropathic pain and related condition[46-47]. Axons are susceptible to hyperglycemia damage both due to their direct access to nerve blood supply and nerve supply overloads the metabolic capacity of the mitochondria producing oxidative stress[39].

6.7 Cytokines (Inflammation) in diabetic neuropathy

Cytokines plays an injurious role in the pathophysiology of neuropathic pain and evidence suggest that interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) both may be involved. These mediators are released and modulate neuronal homeostasis independent of the metabolic stimulus[48]. Hyperglycemia accelerates the production of endogeneous TNF-α in microvascular and neuronal tissue. There is strong linkage of release of various other pro-inflammatory cytokines like IL-6 and NF-κB and anti-inflammatory role of IL-10 in DN[49]. Increase in COX-2 expression and PGE2 was found to be a mediator of TNF –α action. COX-2 is an enzyme that is upregulated by NF- κB[50].

6.8 Nitric oxide in diabetic neuropathy

Nitric oxide (NO) is a key regulatory molecule with broad metabolic, vascular, and cellular effects[51]. Activation of NO synthase (NOS) is under insulin control through the Akt pathway, regulation of NO metabolism is important in diabetics. Hyperglycemia play a key role in the decreased NO production in T2DM because high glucose per se inhibit endothelial NOS activity through PKC associated mechanism. T2DM induces endothelial dysfunction by reducing the bioavailability of endothelial cell-derived NO. Endothelial nitric oxide synthase (eNOS) is an important target for high glucose adverse effects on endothelial progenitor cells number and activity. eNOS deactivation in diabetic endothelial progenitor cells resulted in excessive superoxide anion production and in reduced NO. Inducible nitric oxide synthase (iNOS) is induced by NF- κB and leading to a vicious cycle of inflammation[52]. NO is synthesized from L-arginine by enzyme NOS. There are three different isoform of NOS which differ in the structure enzymes, such as eNOS, neuronal NOS (nNOS), and a calcium independent enzyme i.e. iNOS. The iNOS is expressed at high levels only after induction by cytokine or other inflammatory agents[53].

6.9 Role of calcium in diabetic neuropathy

Specific antagonist for neuronal N-type calcium channels have been shown to reduced heat hyperalgesia and mechanical allodynia in the chronic constriction injury (CCI) model when administration directly to the site of nerve injury[54]. An increase in excitatory amino acid and calcium were observed to occur in an NMDA receptor contribute receptor dependent manner[55]. NMDA receptor activation contributes to the increased level of glutamate and aspartate. The increase in calcium could also form a positive feedback loop through indirect activation of PKC, a hypothesis supported by the anti-allodynic effect of a PKC inhibitor in the sciatic nerve ligation model of neuropathic pain[56]. Increase in intracellular calcium can contribute to depolarizing membrane current initiate transmitter release by promoting the activation of membrane docking proteins[57] initiate increased transcription (by activation of kinases) and initiate phosphorylation of membrane proteins (eg, Nmethyl- D-asparate and AMPA receptors) that can enhance channel efficacy[58] or activate a variety of intracellular enzymes (eg, phospholipase A2). Blockage of L-type calcium channels in vascular smooth muscle at concentration blocks sympathetic neurones overactivity[59]. Calcium influx through presynaptic voltage gated calcium channel triggers to release of pro-nociceptive neurotransmitter and neuromodulators such as substance P, calcitonin, cGRP and glutamate[60]. L/N-type channels can be used as targets for therapeutic interventions in different disorders of sensory neurons characterized by intractable pain. Blockage of N- type calcium channels might reduce H_20_2-induced neuronal damage and show antioxidant action[61]. Neuro-protective effect of L-type and N-type calcium channel blocker shown in rat focal brain ischemia model[62].

7. CURRENT CLINICAL PHARMACOTHERAPY FOR THE MANAGEMENT OF DIABETIC NEUROPATHY

Pharmacologic and non-pharmacologic treatments address the efficacy to reduce pain and improve physical function and quality of life in patients with PDN. The pharmacological management of DN is complex as the unique pathophysiology of this neuropathic pain syndrome and there are common links of pathogenesis to other neuropathic syndromes. Currently, only duloxetine and pregabalin are Food and Drug Administration (FDA) approved for the treatment of DN. The drugs are largely included within the classifications of antidepressants, anticonvulsants, antipsychotics, anesthetics/anti-arrythmics, vasodilators, anti-dementia agents, and opioids. In a review of randomized controlled trials of antidepressants and anticonvulsants for the treatment of pain associated with T2DM and post-therapeutic neuropathies, one third of patients achieved at least 50% pain relief with either category of drug[63].

Choices for pain regulation are tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and antiepileptic medicines. First-line treatments for neuropathic pain include the tricyclic anti-depressant amitriptyline, the selective serotonin and noradrenaline reuptake inhibitor duloxetine, and calcium channel α-2 delta ligands such as pregabalin and gabapentin[64-65]. A systematic review reported that oral TCAs and traditional anticonvulsants were better than the newer generation anticonvulsants for the short-term pain relief. Carbamazepine (CBZ) is a traditional anticonvulsant having pain relief and improved symptoms of PDN[66].

7.1 Anti-depressants medications for the management of DN

Antidepressants largely exert their activity by modulation of serotonin, nor-epinephrine, and dopamine and research findings much attention their use in DN. These includes Amitriptyline (75mg/day), Imipramine, Nortriptyline, Clomipramine, Protriptyline, Trimipramine, Doxepin, Amoxapine, Desipramine and are effective in decreasing painful symptoms but suffer from multiple side effects that are dosage dependent. A 2014 Meta analysis found the antidepressant duloxetine effective for treatment of DN[67]. The same group reviewed data for amitryptyline in the treatment of neuropathic pain and found limited trial data for the successful use in neuropathic pain[68]. Antidepressants and anticonvulsants have suppressive effects on neuropathic pain and antidepressants are widely used for the treatment of neuropathic pain. Indeed, antidepressants, particularly TCAs, are regarded as first-line drugs for the treatment of neuropathic pain[69].

7.2 Selective serotonin reuptake inhibitors (SSRI's) for the management of DN

The mechanism of these drugs involves the inhibition of histamine (5-HT) reuptake back to the presynaptic neurons. SSRIs differ from TCAs and selectively inhibit serotonin rather than norepinephrine. Beside inhibition of SSRI, some SSRI like trazodone, nafezodone and venalafaxime have been reported to cause down regulation of 5-HT auto-receptor present in presynaptic neurons[70]. The SSRI medication class (e.g., citalopram, escitalopram oxalate, fluoxetine, paroxetine, sertaline) is efficacious in the treatment of neuropathic pain. The SSRI antidepressants have largely been disappointing in clinical trials of DN with the exception of paroxetine and citalopram[71]. In other studies of patients with PDN, paroxetine and citalopram were associated with statistically significant greater pain relief as compared to fluoxetine[64].

7.3 Serotonin-norepinephrine reuptake inhibitors (SNRIs) for the management of DN

SNRIs (e.g., duloxetine and venlafaxine) act as dual inhibitors of both serotonin and nor-epinephrine[72]. These SNRIs are also used clinically as a treatment modality for neuropathic pain[73-74].The anti-nociceptive effects of SNRIs have been examined using a variety of animal models of pain. The SNRI duloxetine is licensed for DN, at the same time as venlafaxine is also regularly used. Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran or SNRIs. For example, duloxetine is a potent, balanced inhibitor of serotonin and norepinephrine reuptake[75]. It was demonstrated that milnacipran significantly attenuated late phase paw licking behavior in the formalin test[76]. Venlafaxine inhibits serotonin reuptake at lower dosages and inhibits both serotonin and norepinephrine reuptake at higher dosages[64]. It has shown therapeutic effects for the management of chronic and neuropathic pain[77], particularly in patients with DM. On current evidence, duloxetine is probably the most effective drug for DN[78]. Among patients with diabetic PDN, continuous treatment with duloxetine was associated with a reduction in opioid use[79]. Venlafaximne modified 38 analgesic effect of morphine depended on the mode of the administration (single or long-term) in STZ-induced neuropathic pain model[80].

7.4 Anti-convulsants medications for the management of DN

The anticonvulsants have more recently become considered first-line for the treatment of PDN due to a reduced side effect profile compared to antidepressants and the generic availability of gabapentin[81]. Anticonvulsants has more drug interactions, with the exception of the gabapentinoids (pregabalin and gabapentin), compared to their antidepressant counterparts. A mixture of these medications (gabapentin and nortriptyline) will also be superior to a single agent. The only three drugs authorized by the FDA for the DN are duloxetine, pregabalin and tapentadol[82]. Prior to making an attempt a few medications, medical doctors suggested treating localized DN with lidocaine patches.

These medications include carbamazepine (CBZ) and valproic acid salts. CBZ is the first anticonvulsant to receive FDA approval for the treatment of neuropathic pain syndrome (trigeminal neuralgia) and is a potent sodium channel antagonist[83]. CBZ is valuable but not essentially safe for DN. Valproic acid and divalproex both possess data from randomized controlled trials (RCT) to support use in the treatment of DN[84].

The second generation anticonvulsants are much more widely used in practice today and are supported by a large clinical database of experience with positive data to support use in PDN includes gabapentin, felbamate, topiramate, lamotrigine, zonisamide, oxcarbazepine, levetiracetam, pregabalin, lacosamide[81]. Gabapentin (Neurontin) and pregabalin (Lyrica) are the two anticonvulsants used most frequently to treat neuropathic pain. These agents are derivatives of the inhibitory neurotransmitter GABA; they do not have a direct pharmacological effect on GABA uptake or metabolism. They reduce synaptic neurotransmitter release into hyper-excited neurons by diminishing calcium intake at nerve terminals[86].

7.5 Anti-epileptic medications for the management of DN

Anti-epileptic medications includes the gabapentinoid group of drugs, gabapentin and pregabalin appear to offer the most evidence-based data for the treatment of DPN[81]. Gabapentin blocks the tonic phase of nociception induced by formalin and it exerts a potent inhibitory effect in several animal modes of neuropathic pain such as mechanical allodynia, thermal hyperalgesia, mechanical hyperalgesia and thermo-allodynia[87]. Carbamazepine (Tegretol) is chemically related to the TCAs. The effect of CBZ on pain suppression is probably mediated via central and peripheral mechanisms. CBZ, the first anticonvulsant studied in clinical trials for DN may alleviate pain by decreasing conductance of Na^+ channels and inhibiting ectopic neural discharges. CBZ is valuable but not essentially safe for DN[66, 85].Oxcarbazepine (Trileptal) is keto-analogue of carbamazepine. The therapeutic window for the treatment of pain conditions with this drug has yet to be established[88]. In a multicenter, placebo-controlled trial, the efficacy of oxcarbazepine in patients with PDN was evaluated using VAS scores as a primary efficacy variable[89].

7.6 Analgesics medications for the management of DN

Opioids are effective analgesics used for treating both acute and chronic pain. Several controlled and sustained released opiates such as oxycodone, tapentadol, and tramadol, have shown clinical efficacy in the treatment of DPN[90-91]. These are used as second or third line agent for treatment of DN. Oxycodone, tramadol, fentanyl and morphine have been shown in placebo control studies to be effective in treating neuropathic pain. The use of these drugs can be associated with a poor side effect. Opioids such as tramadol and oxycodone are used to treat neuropathic pain[92]. Opioid produces analgesic effect by blocking opioid nociceptors in central nerves system[93]. Opioids inhibit the high voltage gated calcium current in DRG neurons that lead to reduce the neuronal excitability by inhibiting excitatory neurotransmitter release. Effective dose of oxycodone ranges between 10-20 mg/day, while for morphological ranges 15-300 mg/day. Tramadol (200-400mg/day) is a centrally acting, synthetic analgesic that likely acts as a weak opoids agonist and also has properties of serotonin and nor epinephrine agonists. Combination of acetaminophen (paracetamol) with tramadol is also found to be effective in PDN[92].

7.7 Miscellaneous drugs used for the management of DN

Ketamine is an NMDA receptor antagonist used for the treatment of PDN but having side effects includes psycho mimetic effects which can limit its usefulness. Some statin drugs (Alrestatin, epalrestat, ponalrestat, tolrestat, zenarestat, and zopolrestat) represents the acetic acid compounds. Sorbinil and fiderestat are spirohydantoins, ranirestat is a succinimide which are useful in treatment of DN. Ruboxistaurin is a bis-indolylmaleimide that inhibits PKC pathway in the pathogenesis of DN[94]. Benfotiamine is a lipid-soluble thiamine derivative with improved bioavailability[95]. A patch containing 8% capsaicin has yielded encouraging results in treating PDN and painful HIV-associated sensory polyneuropathy[96].

8. NON-PHARMACOLOGICAL TREATMENTS FOR DIABETIC NEUROPATHY

These steps may prevent or slow the progression of diabetic neuropathy like control hyperglycemia, normal blood pressure, regular Exercise, no smoking, limited amount of alcohol intake, healthy diet and normal weight. Non-pharmacological approaches and non-conventional treatment into management of PDN patient: acupuncture, electro-stimulation, traditional Chinese medicine, exercise, tight glucose control, transcutaneous nerves system (TENS) and physical therapy[97]. TENS and interferential current use as a painless electrical current and the physiological effects from low frequency electrical stimulation to relieve stiffness, improve mobility, relieve neuropathic pain, reduce oedema and heal resistant foot ulcer, gait training, posture training and teaching these patients the basic principle of off-loading can help prevent foot ulcer. General exercise and muscle strengthening exercises will help to maintain muscle wasting[98]. Aerobic exercise such as swimming and using a stationary bicycle can help peripheral neuropathy but activates the pressure on feet[99]. Heat, therapeutic ultrasound, hot wax and short wave diathermy are also useful for treating DN. Tight glucose control treatment of early manifestation of sensory motor polyneuropathy comes to bettering glycemic control[100]. Keep regulation of blood glucose can reverse the changes of DN.

Table 2: Recent medicines under clinical trials for the management of diabetic neuropathy

Product name	Sponser	Development phase
AS-3201 (ranirestat)	Eisai *Woodcli Lake, NJ*	Phase II/III
ARA 290	Araim Pharmaceuticals *Yorktown*	Phase I/II
BMS-813160(CCR2/CCR5 chemokine receptor antagonist)	Bristol-Myers Squibb *Princeton, NJ* diabetic nephropathy	Phase II
AVP-923(dextromethorphan /quinidine fixed-dose combination)	Avanir Pharmaceuticals *Aliso Viejo, CA*	Phase III
AZD5213 (histamine-3 receptor antagonist)	AstraZeneca *Wilmington, DE*	Phase II
CBX129801 (long-acting C-peptide)	Cebix *San Diego, CA*	Phase II
d-methadone	Relmada Therapeutics *New York*	Phase I/II
NP-1998	Acorda Therapeutics *Ardsley, NY*	Phase II
SKL-NP	SK biopharmaceuticals *Fair Lawn,NJ*	Phase II
topical clonidine gel	BioDelivery Sci. Int. *Raleigh, NC*	Phase II
VM202 (modified hepatocyte growth factor gene therapy)	*South Korea* VM BioPharma *Atlanta, GA*	Phase II

9. CONCLUSION

In the 21st century, Diabetes is undoubtedly one of the most challenging health problems and represents one of the main life-threatening health problems to humans. Currently, Diabetes and its complications (micro and macrovascular) are the leading cause of morbidity and mortality worldwide. And also it is the leading cause of cardiovascular, renal and other serious health problems in humans. Diabetes Neuropathy represents a convoluted disease affecting people globally that can be well defined as a disease which is continuous in onset but ruthless in progression. Crucial care has been required in order to treat the patients by maintaining the daily lifestyle. The development of agents which block upgraded pain transmission through these mechanisms is an important therapeutic order for research and treatment of the disease. Huge number of probable therapies has been suggested for the treatment of DN, but other novel targets are still to be investigated in order to completely treat and prevent the patients presented with DN. This current study is to represent the functioning of various pathways and mechanisms involved in the development of diabetic neuropathy and current therapeutic approaches employed in Diabetic Neuropathy.

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