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Review

Neuropathic pain in diabetes mellitus: Challenges and future trends

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ABSTRACT

Neuropathy, or damage to the nerves of the peripheral nervous system, is a debilitating yet surprisingly common and complex condition. Diabetic peripheral neuropathy (DPN) is a prevalent, disabling condition. The damage of the central or peripheral nervous system results in neuropathic pain and which is also triggered by primary lesion and dysfunction of the nerves system. **There is still limited knowledge about the factors that initiate and maintain neuropathic pain. It poses a significant challenge for clinicians as it is often diagnosed late when patients present with advanced consequences**. The chronic hyperglycaemia activates various downsream cascasdes like polyol pathway, increasing glycation in non-enzymatic with several structural proteins that further alter Protein Kinase C activity, increases oxidative stress as well as alteration in Peroxisome proliferator-activated receptor gamma (PPAR-γ) activation that all are interrelated for the development and cause of neuropathy. **Multifactorial risk factor reduction, targeting glycaemia, blood pressure and lipids can reduce the progression of DPN.** Different therapies are also used for managing diabetic neuropathy and neuropathic pain includes anticonvulsants, opioids, antidepressants, aldose reuptake inhibitors. **The current treatment of DPN is largely symptomatic. A number of novel potential candidates, including erythropoietin analogues, angiotensin II receptor type 2 antagonists, and sodium channel blockers are currently being evaluated in phase II clinical trials.** Future studies are needed to further explore this relationship with implications for new treatments for this common disease.

1. Introduction

Daibetic mellitus (DM) is a long lasting metabolic syndrome also characterized by chronic hyperglycaemia, hyperlipidemia, negative nitrogen balance and glycosuria and also sometimes ketonaemia occurs due to impaired insulin action and secretion, or resulting in both the impaired functioning in the carbohydrate, lipid and protein metabolism (Choby, 2017; Siddique et al., 2020; Murillo and Fernandez, 2017). According to the International Diabetes Federation (IDF), diabetic people in India are anticipated to rise to 101.2 million by 2030. And within 20 years that will be rise to 438 million. Each year about 7 million peoples develop diabetes mellitus (Ahamed and Banjii, 2012). The various complications like, neuropathy, nephropathy, retinopathy and cardiovascular disease leads to the increased prevalence of the disease which represents a problem in the health of the human because of its chronic effectives (Iqbal et al., 2018). The neuropathic pain and neuropathy are the hotline complications associated with both types Diabetes that is type 1 and type 2 which has afftected upto 50% patients (Boulton et al., 2005; Jain et al., 2014). The damage of the centralor peripheral nervous system results in neuropathic pain and which is also triggered by primary lesion and dysfunction of the nerves system (Vinik et al., 2016). Remarkably, upto 25 to 62 percent of patients are informed to suffer from pre-diabetes who have idiopathic peripheral neuropathy, 12–25 percent have peripheral neuropathy and 13–21 percent have pain due to neuropathic complications (Feldman et al., 2019) (Figs. 1–3).

The Various signs of neuropathy caused by diabetes comprise of abnormal walking by either irregular cold or heat sensation with small small sensory fibers, big sensory fibers (Muthuraman and Singh, 2012; Edwards et al., 2008). Chronic pain includes hyperalgesia, allodynia, paresthesias, and spontaneous pain (Farmer et al., 2012). Furthermore, various mechanisms like polyol pathway, AGE's, oxidative stress, PKC is involved in the pathophysiology of neuropathy caused due to diabetes. The chronic hyperglycaemia increases polyol pathway, increasing glycation in non-enzymatic with several structural proteins that further alter PKC activity, increases oxidative stress as well as alteration in PARP activation that all are interrelated for the development and cause of neuropathy (Said, 2007). In response, they activate or restrain the PKC activity or either activates MAP kinase activity, resulting in functional and structural disturbance in nerve in the peripheral nervous

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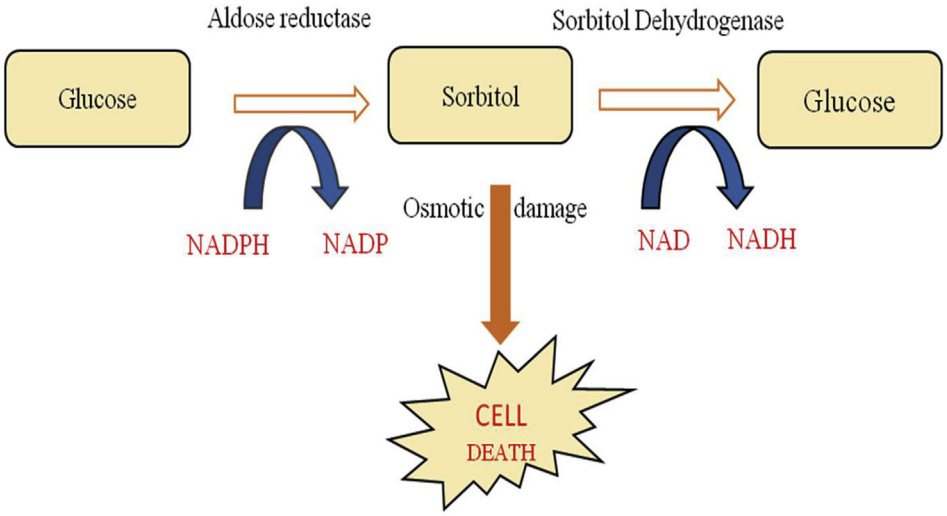

Fig. 1. Polyol pathway in diabetic nephropathy.

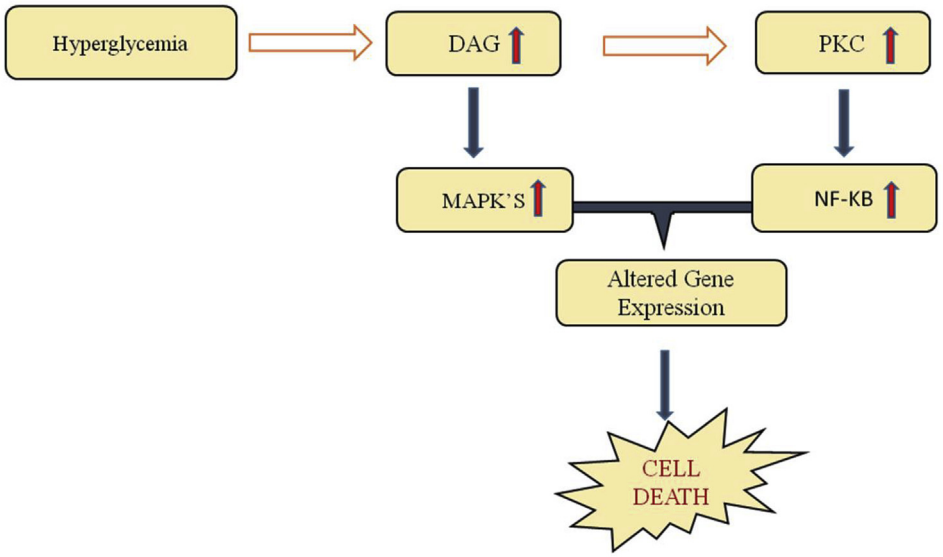

Fig. 2. Activity of Protein kinase C (PKC) in diabetic neuropathy.

system (Yagihashi et al., 2007). Other factors for neuropathy are lifestyle factors, cigarette smoking, environmental toxins, alcoholism, and tumors to the nerve (Koike et al., 2008; Callaghan et al., 2012). Different therapies are also used for managing diabetic neuropathy and neuropathic pain includes anticonvuslants, opioids, antidepressants, aldose reuptake inhibitors (Mu et al., 2017). Antidepressants are the class of management which includes TCAs and SSRI. TCAs are the first choice of treatment in pain such as neuropathy and also painful neuropathy caused by diabetes (Koltezenburg and Scadding, 2001). Drugs include Amitriptyline, nortriptyline, impramine, desipramine, maprotiline, and clomipramine. The symptoms that occurs the most are visual blurring, drying of mouth, cognitive impairment, tachycardia, hypotension caused due to standing or lying down, sedation and weight gain. For the symptomatic relief of these pain SSRIs like fluoxetine, paroxetine, citalopram, and venlafaxine are used and for the management of these pain, anticonvulsants such as carbamazepine, phenytoin, gabapentin, pregabalin, clonazepam, lamotrigine, valproic acid are used. They can be used as first line or add-on therapy. Pregabalin decreases the synthesis of excitatory neurotransmitter by binding to voltage gated calcium channels. The other drug used for the treatment for the pain is Gabapentin. Aldose reductase inhibitors decrease the glucose flux via polyol pathways that inhibits the buildup of fructose and sorbitol, and inhibiting redox reduction potential. It includes tolrestat, alreastat, zopolrestat, epalrestat (Tavakoli et al., 2017).

1.1. Potential causes of diabetic neuropathy

There are different causes for various type of diabetic neuropathy. The study has been initiated by the investigators as to how high glucose level in the blood are exposed that results in the nerve damage. Nerve damage is caused by the combination factors like:

- lifestyle factors and genetics (Ripsin et al., 2009),
- alcohol consumption and cigarette smoking (Duarte et al., 2019),
- Obesity (CDC, 2004)
- environmental toxins
- metabolic factors like elevatation in cholesterol, hypertension and metabolic syndrome like Reaven's syndrome, Syndrome X, (Alberti et al., 2005),
- inflammation in nerves due to autoimmune factors
- The causes of neuropathy in diabetic patient are acromegaly, chronic pancreatitis, Cushing's syndrome, thyrotoxicosis,

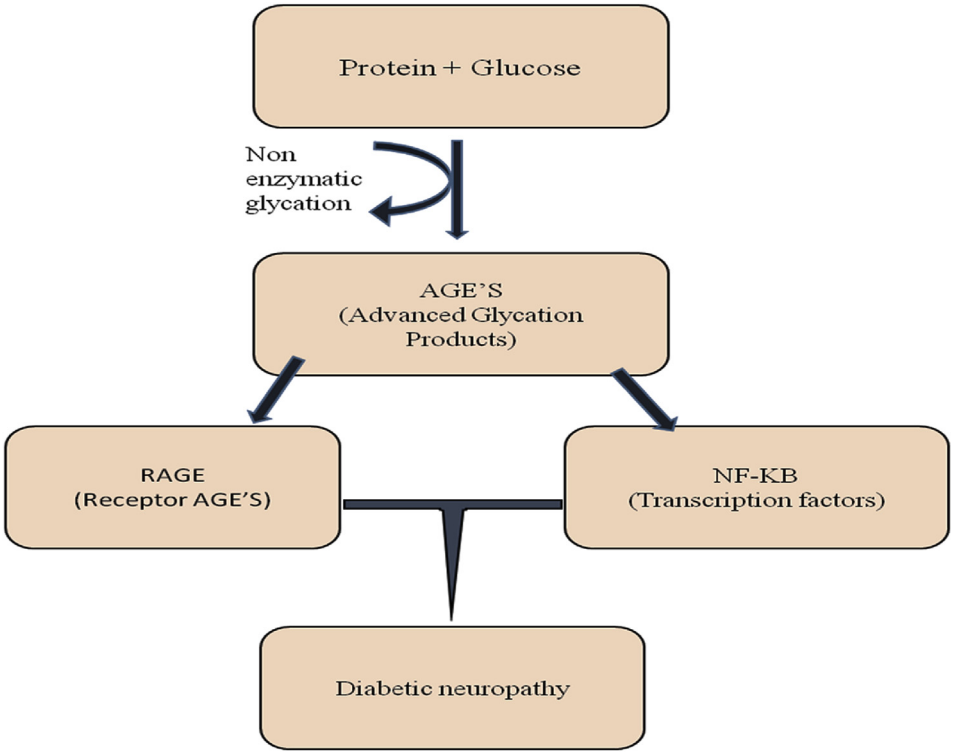

Fig. 3. Advanced glycation end products (AGEs).

pheochromocytoma, cancer (Fauci et al., 2008).

1.2. Pathophysiology

There are many pathological factors which lead to the diabetic neuropathy complication but there are many hypotheses which have been proposed (Papanas et al., 2011; Malik et al., 2013), but still not well understood. There are various pathways and mechanisms which defines pathogenesis of diabetic neuropathy which is as follows:

- Polyol pathway
- PKC activity
- Hexosamine pathway
- AGEs
- Oxidative Stress
- Nitric oxide

Hyperglycemia increases the levels of glucose intra cellularly in nerves, which leads to conversion of the increased glucose into fructose and sorbitol with the help of enzyme such as aldose reductase and sorbital dehydrogenase (Vinik et al., 2003). Then further leads to decreased myoinositol, which decreases the membrane Na+/K+ ATPase activity. The aldose reductase Nicotinamide-adenine dinucleotide phosphate (NADPH) and which helps in regenerating glutathione reduction (GSH) and this leads to oxidative stress (Alter et al., 2012). Reduced NADPH, decreases the activity of K+ Na+ ATPase membrane which results in breakdown in structure of the nerves. The second step is oxidization of sorbitol, polyol pathway, into fructose by sorbitol dehydrogenases (Yamagishi et al., 2012).

PKC is a pathway which increases glucose level causing injury to the prone tissues. Excess glucose concentration activates PKC pathway through increased synthesis of DAG, it further activates the MAPKs causing alterations in gene expression and transcription factors like PAI-1, TGF-ß, VEGF, NF-κB, which results in progression of conditions such as diabetic neuropathy, retinopathy, nephropathy, and CVS disease (Arikawa et al., 2007).

1.3. Hexosamine pathway in diabetic neuropathy

Hexosamine pathway is also one of the factor for causing diabetic complication. Fructose −6 phosphate forms in between the process of glycolysis process. In this pathway Fructose −6 phosphate is transformed to glucosamine-6 phosphate through the glutamate fructose- 6 phosphate amidotransferase enzyme (Thornalley, 2005). Uridine diphosphate- N-acetyl glucosamine is formed after the conversion of Glucosamine-6 phosphate (UDP, GIcNAc). Excess glucose levels create extra flux resulting in increased GlcNAc and modifications in gene expression (Feldman et al., 2017; Goldberg et al., 2006).

AGE are formed from excess proteins, lipids and nucleotides by non-enzymatic reaction of glucose, which results in interference of transport of axons and nerve cell metabolism (Eichberg, 2002) and so disrupts the neuronal integrity and repair mechanisms (Edwards et al., 2008). Extracellular protein AGEs like matrix proteins and plasma that disrupts the cell adhesion and activates the AGE Receptor. Further activating the transcription factor i.e. NF-κB, causing complication like cell apoptosis and inflammation (Ramasamy et al., 2007).

1.3.1. Oxidative stress

The excess free radicals production in diabetes may cause diabetic neuropathy via many mechanisms occurring in both central and peripheral nervous system. It shows that this causes disorders of nervous system (Dellamea et al., 2014). After peripheral injury inflammatory mediators are released from macrophages and neutrophils which impairs normal condition of tissue and allows accumulation of free radicals which further causes oxidative stresses and other complications like neuropathic pain (Kim et al., 2004). Due to Hyperglycemia Axons are more prone to damage both due to nerve blood supply and so it gets overloaded with mitochondrial producing oxidative stress (Feldman et al., 2017).

1.3.2. Nitric oxide

NO is an endogenous mediator which is secreted from many cells like endothelial, smooth, neuronal cells and macrophages of the central

and peripheral nervous system (Kleinbongard et al., 2007). Excess glucose produces less NO in T2DM because it inhibits endothelial NOS activity via protein kinase C mechanism (Bauser-Heaton et al., 2008), inducing endothelial dysfunction. Endothelial-NOS deactivate in diabetic endothelial progenitor cells which results in the elevation in production of superoxide anion. The decrease in NO level, leads to increased oxidative stress damaging the signaling pathways in protein (Cohen and Tong, 2010). The Inducible nitric oxide induced by NF-κB synthase (iNOS resulting in neuropathic pain and inflammation (Kim et al., 2004).

1.3.3. Classification of diabetic neuropathy

The two main types of neuropathy in diabetic patient are autonomic and Sensorimotor and Autonomic which is further classified according to the part or system affected e.g gastrointestinal, bladder whereas sensorimotor neuropathy is further classified as diabetic amyotrophy, focal neuropathy and distal symmetric polyneuropathy (Ropper and Samuels, 2019).

1.3.4. Sensorimotor neuropathy

It is the commonest classification in diabetic neuropathy, and as per the studies, 50% of diabetic patients are suffering and experiencing symptoms like: deep aching pain, burning pain, paraesthesia, hyperaesthesia, stabbing or electrical sensations (Boulton et al., 2005) These mainly starts from long axons like lower and patient may feel pressure pains, pin pricks, temperature perception, sensory loss of vibration (Boulton et al., 2005; Ropper and Samuels, 2019).

1.3.5. Distal symmetrical polyneuropathy

Polyneuropathy is the type of DN which is common and up to 75% of DNs, and characterised by both sensory or motor (Kimura, 2013). Polyneuropathy is then divided into large and small fiber neuropathy. In large fibre type of neuropathy symptom such as loss of reflex of ankle, joint position, painless paraesthesia, touch and pressure sensation. Small fibre neuropathy is composed of impairment of pain and temperature sensation, burning, pain (Tavakoli et al., 2017).

1.3.6. Diabetic amyotrophy

It is also called as diabetic proximal neuropathy (Pasnoor et al., 2013). The weakness occurs in pelvifemoral muscles stepwise in the age above 50 years the patients have problem like pain in low back, hip, thigh. It was thought that Diabetic amyotrophy occurs due to metabolic changes, but later due to biopsy changes it is now due to immunological abnormality (Tracy et al., 2009). Patients may take many months (6–12) to recover.

1.3.7. Focal neuropathy

It is asymmetric type of diabetic neuropathy, it involves trochlear and facial nerve followed by oculomotor nerves. The other type of neuropathies in diabetic patients are lateral, radial,cutaneous nerve of thigh, medial, lateral, ulnar femoral, peroneal popliteal nerves (Tavakoli et al., 2017).

1.3.8. Autonomic neuropathy

It is a slow progress type of neuropathy which is a prevalent disorder found in the diabetes without other causes. The disorder includes the adrenergic, peptidergic and cholinergic fibers. This affects the cardiovascular, gastrointestinal, bladder and erectile dysfunction. It affects both sympathetic and parasympathetic enteric nerves. Autonomic Neuropathy is diagnosed by both subclinical and clinical form which includes tests and signs and symptoms respectively (Spallone et al., 2011).

1.3.9. Cardiovascular autonomic neuropathy

Due to parasympathetic denervation there is damage to cardiovascular. The signs of CVS Autonomic Neuropathy are tachycardia, bradycardia, orthostatic hypotension, impaired heart rate exertion intolerance like exercise, abnormal blood pressure. The evaluation of this type of neuropathy is measured by orthostatic blood pressure (Tesfaye et al., 2010; Bessac et al., 2018; Gandhi et al., 2016).

Erectile Dysfunction: Almost 30–40% of men are affected by Erectile dysfunction (ED) due to diabetes. It occurs because of autonomic neuropathy and endothelial dysfunction. In diabetic patient there is no example of treating borderline hypogonadism but is limited (Gandhi et al., 2016).

Bladder Dysfunction: Bladder dysfunction occurs in 43–87% and it occurs in 25% in type I and type II diabetes (Boulton et al., 2005; Tesfaye et al., 2010; Kisozi et al., 2017). Due to diminished bladder sensation micturition reflexes get delayed due to increment in capacity of bladder and retention of urine usually that occurs symptomatically (Tracy et al., 2009; Tesfaye et al., 2010; Burakgazi et al., 2012).

1.3.10. Extra manifestations (Tracy et al., 2009)

Eyes: autonomic neuropathy affects eyes (pupils) due to which they become unresponsive when there is any change of light and difficulty in driving.

Sweat Glands: diabetic neuropathy affects the sweat glands which controls sweating due to which sweat glands do not work properly and so body temperature do not get regulated. At night it may cause sweating and while eating.

Face: neuropathy may affect the face on one side causing paralysis known as Bell's palsy.

Foot: it may cause blisters and pain in the foot.

Sex Organ And Urinary Tract: the complete bladder emptying is prevented by nerve damage, that allows the growth of bacteria in the cell which causes urinary tract infections (UTI), decrease in sexual response in males and females, even if the sex drive can be unchanged.

Digestive System: The most common causes of the nerve damage to the digestive system are gastroparesis, constipation (too slow to empty stomach) which may further cause loss of appetite, bloating and vomiting.

Heart Blood Vessels: The damage in the nerve of the heart and blood vessels tend to interfere in the adjustment blood pressure according to body's ability, due to which a person can faint.

Thighs: pain in the thighs due to nerve damage.

1.4. Diagnosis

The signs of DPN may vary according to the type of the involvement of the fibres. In disease with fibre that are small such as polyneuropathy disease, it weakens perception such as pain and temperature which results in paraesthesia, dysaesthesia and/or neuropathic pain whereas disease such as polyneuropathy large fibre weakens light touch and proprioception. In an asymptomatic neuropathy it may cause conditions like neuroarthropathy (Charcot's joints) and ulceration as a late complication, of the foot (Edwards et al., 2008). For diagnosis of DPN, there are many bedside examinations like muscle power assessment, joint position, touch and temperature, sensations of pinprick. Only results of the test and different neurological indications can help to screened out diabetic neuropathy.

Diagnosis of Diabetic Neuropathy-

- pallesthesia
- abnormal electrophysiological tests
- symptoms like (pain, paraesthesia, dysaesthesia)
- increased HbA1c for long term
- symptoms of autonomic neuropathy
- skin biopsy test

Assessment of Aδ pathway dysfunction among laboratory tests is done by the best tool known as the laser-evoked potential for biopsy of skin that assesses neuropathies along with distal loss of nerve fibres

which are unmyelinated as well as small fibre neuropathy (Cruccu et al., 2010).

Important signs which are objectively detected in diabetic peripheral neuropathy are compiled below:

Pallesthesia: refers to the sensation of mechanical vibration on body using aaluminium tuning fork with 128-Hz. The test is first done at the big toe. The tuning fork is positioned bilaterally at the big toe's dorsum. The patient is asked to indicate when he/she senses the tuning fork vibration. A trial is to be initiated so that patient should response to the vibration not to the pressure of the tuning fork (Rinkel et al., 2017; Moghtaderi et al., 2006).

Monofilament: 10 g of monofilament is used when the patient feels loss of light touch on both the toes. In this the patient foot is supported and filament is prestressed.In between the nail fold and the DIP joint at the dorsum of the big toe, the filament is then applied with pressure. 10 g of filament is applied and when filament bends the patient is asked whether he/she feels the filament (Rinkel et al., 2017; Moghtaderi et al., 2006).

Reflexes seen in Ankle: This examination must be done with the help of suitable reflex hammer (e.g., Queen square and tromner square). The foot is dependent and the patient must be in relaxed position. In order acquire the stretching of the muscles the foot must be positioned passively. The tendon called Achilles is tapped gently, if the result shows reflex, it is categorized as present and if the reflex is absent the patient is asked to hook the fingers together and pull and if the reflex is still absent, even after hooking fingers, the reflex is categorized as absent (Rinkel et al., 2017; Moghtaderi et al., 2006).

Quantitative sensory testing: It may be used in detection of small fibre neuropathy when other examinations are found to be normal, (Jia et al., 2014).

Visual Analog Scale (VAS)– VAS helps in the measurement of pain intensity. VAS is a scale of 10 cm (100 mm) in measurement of length. The scale is fixed by 'no pain' (0 score) in order to show pain intensity and "worst imaginable pain" (score of 100).

Quessionaires– It includes various types of quessionaires which are used for the diagnosis of DPN. It involve health related quessionaires, DN4 quessionaires, SF-36 quessionaires and many more which is used to diagnose the health of the patient.

Differential Diagnosis (Tracy et al., 2009).

In patients having diabetes about 10–26% suffers from neuropathy but the cause for the neuropathy may be different, hence careful evaluation of diagnosis is required. The differential diagnosis may vary with the type of neuropathy.

The different diagnosis involves:

- Deficiency of Vitamin B12
- hypothyroidism
- chronic high alcohol intake
- drug induced neuropathy
- heavy metal poisoning
- amyloidosis
- uraemia
- chronic inflammatory demyelinating neuropathy

The differential diagnosis may vary with the type of neuropathy.

1.4.1. Management

Early treatment, prevention is very important but the exact cause and effective treatment should be known. Hyperglycaemia is the most important factor in controlling the progression of neuropathy.

1.4.2. Major groups consider while treatment of neuropathy

Glycemic control: The onset of diabetic neuropathy is prevented or delayed by good blood sugar (Tesfaye et al., 2005), Diabetes Control and Complications Trial Research Group 1995 & United Kingdom Prospective Diabetes Study Group 1998). The symptoms seen in painful neuropathic are also improved by improving metabolic control with insulin usage therapy in type 2 diabetes (Javed et al., 2015a). It is a first step for managing the painful neuropathy aimed at improving glycemic control (Azmi et al., 2019).

Aldose reductase inhibitors (ARIs). It is an enzyme that plays a significant role in the polyol pathway that is used to inhibit the conversion of glucose to sorbitol. The prevention of DSPN has been done by ARIs. Most of the ADRs have been detected and are found to be less efficacious after the test (Boulton et al., 2013). A 3-year randomized trial concluded a preventative role of DSPN with epalrestat and these epalrestat helps in curing the patient who has been reported neuropathic symptoms with an acceptable safety profile (Hotta et al., 2012; Singh et al., 2014).

α-Lipoic acid: An increased free-radical production along with defective antioxidant mechanisms can generate oxidative stress that has been linked to the development of DSPN (Kawanami et al., 2016). ALA is found to be well tolerated.

Incretin: Incretin (glucose-dependent insulinotropic polypeptide GIP and glucagon-like peptide-1: GLP-1) was discovered as a new antidiabetic drug, which has useful effects on diabetic complications, that is independent of glucose-lowering abilities mediated by anti-oxidative stress and anti-inflammatory (Simpson et al., 2017).

Capsaicin: The application of topical capsaicin (0.075%) on the affected area for three to four times per day has been found to relieve neuropathic pain. The Topical capsaicin stimulates unmyelinated C-fibers to deplete substance "P" from nerve terminals, and for the 2–4 weeks of application there may be worsening of symptoms (Sandireddy et al., 2014).

Symptomatic treatment - In diabetic neuropathy, pain generation is one of the most common issues and it may be deep, superficial, or aching. Pain treatment is a very important goal yet difficult and often disappointing. Treatment often prescribed will be from anticonvulsants to antidepressants and other modes (Cohen et al., 2015).

Intravenous Lignocaine: Theseanaesthetic antiarrhythmic drugs are indicated in severe neuropathic. Intravenous lignocaine is effective in relieving neuropathic pain (Javed et al., 2015b).

1.4.3. Anticonvulsants

Anticonvulsants are the first-line drugs used for many years in diabetic neuropathy. Anticonvulsants, like carbamazepine, phenytoin, gabapentin, sodium valproate (Lesser et al., 2004), more recently pregabalin (Boyle et al., 2012) have been found effective in severe neuropathic pain. Due to the side effects of this class, the treatment is complicated so treatment must be started from a low dose to then further increase to high dose by taking care of side effects. So, gabapentin and pregabalin have appeared are found to be better tolerated with fewer side effects (Lesser et al., 2004; Boyle et al., 2012). Gabapentin is a calcium channel blocker and reduces the effects of excitatory neurotransmitters. As the starting dose will be 300 mg daily and increasing the dose with 100–300 mg daily. It only decreases 11% of overall pain. Side effects may be weight gain with long term use. Pregabalin is the analog of neurotransmitter γ-aminobutyric acid and central nervous system active compound. Recent studies recommend pregabalin is the first choice drug as it markedly improves a 50% reduction in pain with diabetic neuropathy and also improves mental health, social functioning, and decreased sleep patterns. The dose recommended will be 150 mg daily and raise to 300 mg daily over one week is important (Cohen et al., 2015) (Table 1). Sodium valproate is different from both pregabalin and gabapentin in the mechanism of action as it acts by affecting GABA. It shows the only moderate reduction in pain of approximately 30% (Table 2).

1.4.4. Antidepressants

Tricyclic anti-depressants (TCA) are a very important class of drugs in diabetic neuropathy as it helps to reduce the pain that is sharp, throbbing, burning, and aching. TCA works mainly by inhibiting the

Table 1
List of Anticonvulsants used in DN.

Generic Name	Brand Name	Mechanism of Action	Recommended Dosage
Pregabalin	Lyrica	Central calcium channel modulator inhibits neuroexcitation	300–600 mg/day
Gabapentin	Neurontin	Inhibits the release of excitatory neurotransmitters	900–3600 mg/day
Sodium valproate	Depacon, Depakote	Increases GABA activity	500–1200 mg/day

reuptake of the biogenic amines from the brainstem to the spinal cord, commonly nor-epinephrine along with serotonin (5HT).TCA's are classified as amitriptyline, nortriptyline, desipramine, and imipramine causing side effects like sedation, dry mouth, dizziness, sweating (Siddique et al., 2020). Amitriptyline in some studies gives a large response in pain relieves up to 60%.side effects like blurred vision, urinary incontinence, dry mouth, etc. Desipramine is also recommended and has similar pain-reducing effects like amitriptyline. Some are selective serotonin reuptake inhibitor (SSRI) family are desipramine and imipramine are also given but generally disappointing results are noticed (Chong and Hester, 2007).

Opioid analgesic: For the effect of descending inhibitory pathways, modulating nociception, tramadol has been suggested (Christoph et al., 2013). The MOA of tramadol involves the opioid spinal – supraspinal synergy and effect of intrinsic spinally mediated μ-opioid receptor agonist-norepinephrine reuptake inhibitors (Bahari and Meftahi, 2019) opioids analgesics classified as tramadol, morphine, oxycodone used to treat pain but when get addicted it causes nausea and constipation like side effects (Table 3).

Table 3
List of analgesics used in DN.

Generic name	Brand Name	Mechanism of Action	Recommended Dosage
Morphine	MS Contin	Binds opiate receptors	Up to 120 mg/day
Oxycodone	Oxycontin	Binds opiate receptors	Up to 120 mg/day
Tramadol	Ultram	Changes serotonin and norepinephrine by binding with opiate receptors	210 mg/day

1.4.5. Currently the most widely used drugs in diabetic neuropathy

Duloxetine: Duloxetine falls under the classification of antidepressant drug SNRI - selective serotonin-norepinephrine reuptake inhibitor which possesses central pain inhibitory actions, as it has the ability of noradrenergic and serotonergic activity in the Central Nervous System. In the descending pain inhibition pathways of the brainstem and spinal cord, Serotonin and Norepinephrine show neurotransmission action. Moreover, for the reduction of the transmission of pain signals in the CNS from the periphery, the neurotransmitters work in a synergistic manner (Minami et al., 2018). In the stomach where the environment is acidic, this type of medicine gets deteriorated, these drugs are coated such that the compound is primarily absorbed in the small intestine. So, it is necessary to be careful that the duloxetine capsule should not be chewed as it removes the coating before entering into the digestive system (Farshchian et al., 2018). Duloxetine is acid-labile when the enteric coating is present and does not let the drug get deteriorated in the stomach. After the intake of a 60 mg dose of this drug, almost 50% of oral bioavailability is attained. After 6 h post-dose, there is almost a 2-h delay until the kinetic of absorption starts with maximum plasma drug concentration. Food delays the time of the duloxetine absorption and takes up to 6–10 h to reach its peak concentration but does not affect C_{max} (Wang et al., 2010). It highly binds with the protein around > 90%such as albumin and α1-acid glycoprotein. The V_D of Duloxetine is around 1640 L. It gets metabolized by the enzyme such as CYP2D6 and CYP1A2 present in the liver. The metabolites formed after metabolism circulates in the blood and are inactive pharmacologically. Its elimination half-life is about 12 h. The pharmacokinetics dose of Duloxetine is proportional to its therapeutic range. Steady-state is attained after 3 days. The drug dose is excreted as metabolites in urine (70%) as well as in the liver (20%) and about 1% are found in unchanged form in the urine. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial months of a course of drug therapy or at times of dose increases or decreases** (Stahl, 2013).

MOA of Duloxetine: It works by inhibiting serotonin and norepinephrine (NE) reuptake in the CNS.In the prefrontal cortex, it gives rise to the dopamine by inhibiting NET in places where there are less DA reuptake pumps (Sansone and Sansone, 2014). The affinity of the duloxetine for cholinergic, dopaminergic, opioid, glutamate, histaminergic, and GABA reuptake transporters and could be considered as a selective 5-HT reuptake inhibitor and NE transporters. It metabolizes extensively, but no circulating metabolites play a role in pharmacological action (Berardis et al., 2010). The elevation in pro-inflammatory cytokines within CNS is because of the presence of depressive disorders. The antidepressant drugs which have similar moa as that of duloxetine, such as serotonin metabolism inhibition, cause an increase in anti-inflammatory cytokines and reduction in pro-inflammatory cytokine activity; Even if this process may be useful to duloxetine for its effect on depression, it is found that duloxetine therapy that is cytokine specific is lacking (Dussaule and Bouilleret, 2018). The main cause of the analgesic properties of the duloxetine in the treatment of central pain syndromes like fibromyalgia, neuropathy due to diabetes has been found and the reason for this is the sodium channel blockade (Stahl, 2013).

Pregabalin: It acts centrally and is one of the novel neuro modulating medicine that has been indicated for the cure of painful diabetic neuropathy and postherpetic neuralgia. The drug was approved by the FDA in 2004. The indication such as adjunctive therapy with partial seizure in adults was approved in 2005 and approved for the cure of fibromyalgia, lately. It has also been accepted by the European Medicine Agency as adjunctive therapy in adults with partial seizure and GAD for curing the central and neuropathic pain. When taken on an empty stomach it gets rapidly absorbed. Its peak plasma concentration is attained in about 1 h. The oral bioavailability of this drug is high and is not dependent on its dose. The absorption rate, C_{max} (approx

Table 2
Antidepressants drugs used in the treatment of DPN (Cohen et al., 2015).

Generic Name	Brand Name	Mechanism of Action	Recommended Dosage
Amitriptyline	Elavil	Increases the availability of serotonin and norepinephrine	25–100 mg/day
Duloxetine	Cymbalta	Serotonin/norepinephrine reuptake inhibitor elevates the availability of norepinephrine and serotonin.	60–120 mg/day
Venlafaxine	Effexor	Serotonin/norepinephrine reuptake inhibitor elevates the availability of norepinephrine and serotonin.	75–225 mg/day

25–30%) of the drug is reduced when taken along with the food. Moreover, there is a lag in T_{max} (about 2.5 h s) but it does not affect the absorption extent. It does not metabolize extensively. As per the experiment performed with the use of the nuclear medicine method, the recovery of the 98% radioactivity in the urine was found to be an unchanged form of pregabalin. *N*-methyl pregabalin is the primary metabolite. The elimination of this drug takes place from the systemic circulation via renal as an unchanged form of the drug. Pregabalin's renal clearance value is 73 mL/min. **Treatment with pregabalin at dosages greater than 300 mg per day (100 mg three times daily) is not recommended because of the potential for dose-dependent AEs Treatment with pregabalin may lead to physical or psychological dependence, so the drug is classified as a Schedule V controlled substance** (Toelle et al., 2012).

Mechanism of action: It has been chosen as the first-line drug for treating neuropathic pain Neu PSIG of the International Association for the Study of Pain (Niture et al., 2014). The drug is bound to the alpha2-delta auxiliary subunit present in the voltage-gated calcium channels. If these channels are blocked, it blocks the calcium-dependent release of many neurotransmitters. It neither binds directly to benzodiazepine $GABA_a$, GABA receptors, it is a structural derivative of the GABA, an inhibitory neurotransmitter. It also does not increase GABA responses in neurons that are cultured and does not change short term effects on GABA uptake/degradation. The prolonged use of pregabalin gives rise to the GABA transporter protein density and elevated the function of the GABA transport rate in the case of cultured neurons. The antinociceptive or antiseizure activity of the drug is not obtained by the activation of opioid receptors, the effect on noradrenaline reuptake, serotonin, dopamine activity, sodium channels, cyclooxygenase changes of the enzyme (Yang et al., 2019).

Epalrestat: It has been approved in Japan and is an aldose reductase inhibitor. It is indicated for the subjective neuropathy symptoms treatment, heartbeat abnormality that is related to vibration sense and diabetic peripheral neuropathy. It can most. Likely effect or lag the development of the underlying disease process unlined the most recent treatment option for neuropathy in the diabetic patient (Varkonyi et al., 2017). It works by inhibiting aldose reductase, a rate-limiting enzyme of the polyol pathways as it is a carboxylic acid derivative (Iyer et al., 2019). It is administered in 50 mg effective dose, 3 times a day before meals. It reduces the glucose flux via the polyol pathway, inhibiting tissue build-up of fructose as well as sorbitol. The elevation of the sorbitol concentration leads to organ and cellular injury. The accumulated sorbitol leads to reduce myoinositol in peripheral nerves. When my-inositol is decreased, there is a resulting decrease in The Na + K + -ATPase activity decreases as the Myo-inositol decreases that help in the conduction of the nerves. Due to the over usage of NADPH and elevated polyol pathway action by aldose reductase, many homeostatic processes are adjusted. Reduced nitric oxide and impaired glutathione production are due to NADPH depletion. Decreased in nitric oxide can result in reduced vasodilation whereas reduction in glutathione results in elevated reactive oxygen species, results in damaged function of the endothelial cell (Wang et al., 2018). The most commonly reported ADRs of this drug are levels of liver enzyme, GI problems such as vomiting and nausea. It has been recommended as a new therapeutic drug for the prevention and in a decrease in the progression of diabetic neuropathy. For the use in clinical areas, comparative studies in a diversified population of the patient should be done for the long term [83].

2. Conclusion

Numerous pharmacological treatments—both approved and off-label—have been used to reduce the pain associated with DPN and to improve patients' quality of life. Diabetic neuropathy is a highly prevalent and disabling condition associated with significant healthcare costs. Although diabetic neuropathies differ in clinical course, distribution, fiber involvement, and pathophysiology. Rigid glucose control along with preventive management helps to prevent diabetic complications. Newer advances still in the developmental stage include glutamate antagonists, cytokine inhibitors, vanilloid-receptor agonists, catecholamine modulators, ion-channel blockers, acetylcholine modulators, adenosine receptor agonists. **A 30% reduction in pain intensity, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with DPN**. Pharmacotherapeutic strategies are the cornerstone of neuropathy treatment but still, results are inconclusive, hence vigorous research should be directed towards these aspects to find improved counterparts and **identifying the best combinations of treatments for diabetic neuropathy. The goal of current pharmacotherapy is to provide an updated grading system that is scientifically effective, appropriate, internally reliable, and in the face of uncertainty, allows for appropriate treatment choices**.

First line of pharmacotherapy includes TCAs, gabapentanoids, SNRIs, topical lignocaine, and capsaicin. These should be lasts over four to six weeks. When satisfactory results in the form of pain score and quality of life are not to be expected with the first line of therapy than the next step, turn to the second line of treatment which involves tramadol and combination therapy. Combination therapy is common in the treatment of neuropathic pain. It is advised that patients who do not respond to first- and second-line of treatments be referred to a specialist pain clinic. In this condition a combination of SSRIs, anticonvulsants, or NMDA receptor antagonists may be used. Third-line treatment includes interventional therapies such as pulsed radiofrequency, epidural injection, sympathetic blockade, and adhesiolysis.

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Declaration of competing interest

There are no conflicts of interest.

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References

Ahamed, M., Banjii, O., 2012. A review on diabetic neuropathy and nephropathy. Int. Natl. J. Pharm. Sci. Res. 3 (2), 300–304.
Alberti, K.G., Zimmet, P., Shaw, J., 2005. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome a new worldwide definition. Lancet 366 (9491), 1059–1062.
Alter, M.L., Ott, I.M., Websky, K., Tsuprykov, O., Sharkovska, Y., 2012. DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for diabetic nephropathy. Kidney Blood Pres. Res. 36, 119–130.
Arikawa, E., Ma, R.C., Isshiki, K., Luptak, I., He, Z., Yasuda, Y., Maeno, Y., Patti, M.E., Weir, G.C., Harris, R.A., Zammit, V.A., Tian, R., King, G.L., 2007. Effects of insulin replace-ments, inhibitors of angiotensin, and PKC beta's actions to normalize cardiac gene expression and fuel metabolism in diabetic rats. Diabetes 56 (5), 1410–1420.
Azmi, S., Ferdousi, M., Kalteniece, A., Al-Muhannadi, H., Al-Mohamedi, A., Hadid, N.H., Mahmoud, S., Bhat, H.A., Gad, H.Y.A., Khan, A., Ponirakis, G., Petropoulos, I.N., Alam, U., Malik, R.A., 2019. Diagnosing and managing diabetic somatic and autonomic neuropathy. Ther. Adv. Endocrinol. Metab. 10 2042018819826890.
Bahari, Z., Meftahi, G.H., 2019. Spinal α2-adrenoceptors and neuropathic pain modulation; therapeutic target. Br. J. Pharmacol. 176 (14), 2366–2381.
Bauser-Heaton, H.D., Song, J., Bohlen, H.G., 2008. Cerebral microvascular nNOS responds to lowered oxygen tension through a bumetanide-sensitive cotransporter and sodium-calcium exchanger. Am. J. Physiol. Heart Circ. Physiol. 294 (5), 166–173.
Berardis, D., Conti, C.M., Serroni, N., Moschetta, F.S., Olivieri, L., Carano, A., Salerno, R.M., Cavuto, M., 2010. The effect of newer serotonin-noradrenalin antidepressants on cytokine production: a review of the current literature. Int. J. Immunopathol. Pharmacol. 23 (2), 417–422.
Bessac, A., Cani, P.D., Meunier, E., Dietrich, G., Knauf, C., 2018. Inflammation and gut-brain axis during type 2 diabetes: focus on the crosstalk between intestinal immune

cells and enteric nervous system. Front. Neurosci. 12, 725.
Boulton, A.J., et al., 2005. Diabetic neuropathies. A statement by the American diabetes association. Diabetes Care 28, 956–962.
Boulton, A., Kempler, P., Ametov, A., Ziegler, D., 2013. Whither pathogenetic treatments for diabetic polyneuropathy. Diabetes Metab Res Rev 29, 327–333.
Boyle, J., Eriksson, M.E., Gribble, L., Gouni, R., Johnsen, S., Coppini, D.V., Kerr, D., 2012. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 35, 2451–2458.
Burakgazi, A.Z., Alsowaity, B., Burakgazi, Z.A., Unal, D., Kelly, J., 2012. Bladder dysfunction in peripheral neuropathies. Muscle Nerve 45, 2–8.
Callaghan, B., Cheng, H., Stables, C., Smith, A., Feldman, E., 2012. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 11, 521–534.
Choby, Beth, 2017. Diabetes update: prevention and management of diabetes complications. FP essentials 456, 36–40.
Chong, M., Hester, 2007. Current and future treatment options. J. Diabetic Painful Neuropathy 67, 569–585.
Christoph, T., Schroder, W., Tallarida, R., De Vry, Tzschentke, T., 2013. Spinal-supraspinal and intrinsic mu-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI) synergy of tapentadol in diabetic heat hyperalgesia in mice. J. Pharmacol. Exp. Therapeut. 347, 794–801.
Cohen, R.A., Tong, X., 2010. Vascular oxidative stress: the common link in hypertensive and dia-betic vascular disease. J. Cardiovasc. Pharmacol. 55 (4), 308–816.
Cohen, K., Shinkazh, N., Frank, J., Israel, I., Fellner, C., 2015. Pharmacological treatment of diabetic peripheral neuropathy. Pharm. Therapeutics 40 (6), 372.
Cruccu, G., Sommer, C., Anand, P., Attal, N., Baron, R., Garcia-Larrea, L., Haanpaa, M., Jensen, T.S., Serra, J., Treede, R.D., 2010. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur. J. Neurol. 17, 1010–1018.
Dellamea, B.S., Leitão, C.B., Friedman, R., Canani, L.H., 2014. Nitric oxide system and diabetic nephropathy. Diabetol. Metab. Syndrome 6 (1), 17.
Duarte, I.A., Botelho, R.B., Akutsu, R.D., 2019 Mar 4. Regional food consumption in the northeast of Brazil by the low-income population. J. Culin. Sci. Technol. 17 (2), 155–169.
Dussaule, C., Bouilleret, V., 2018. Psychiatric effects of antiepileptic drugs in adults. Geriatr. Psychol. Neuropsychiatr. Vieil. 16 (2), 181–188.
Edwards, J.L., Vincent, A.M., Cheng, H.T., Feldman, E.L., 2008. Diabetic neuropathy: mechanisms to management. Pharmacol. Ther. 120, 1–34.
Eichberg, J., 2002. Protein kinase C changes in diabetes: is the concept relevant to neuropathy? Int. Rev. Neurobiol. 50, 61–82.
Farmer, K., Li, C., Dobrowsky, R.T., 2012. Diabetic peripheral neuropathy: should a chaperone accompany our therapeutic approach. Pharmacol. Rev. 64, 880–900.
Farshchian, N., Alavi, A., Heydarheydari, S., Moradian, N., 2018. Comparative study of the effects of venlafaxine and duloxetine on chemotherapy-induced peripheral neuropathy. Canc. Chemother. Pharmacol. 82 (5), 787–793.
Fauci, A.S., Braunwauld, E., Kasper, D., Hauser, S.L., Longo, D.L., Jameson, J.L., Loscalzo, J., 2008. Diabetes mellitus. Harrison's Principles of Internal Medicine, seventeenth ed. McGraw-Hill, New York, pp. 2275–2304.
Feldman, E.L., Nave, K.A., Jensen, T.S., Bennett, D.L.H., 2017. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron 93 (6), 1296–1313.
Feldman, E.L., Callaghan, B.C., Pop-Busui, R., Zochodne, D.W., Wright, D.E., Bennett, D.L., Bril, V., Russell, J.W., Viswanathan, V., 2019 Jun 13. Diabetic neuropathy. Nat. Rev. Dis. Primers 5 (1), 41.
Gandhi, J., Dagur, G., Warren, K., 2016. Effect of diabetes mellitus on sexual arousal and intercourse. Transl. Biomed. 7 (2).
Goldberg, H.J., Whiteside, C.I., Hart, G.W., Fantus, I.G., 2006. Posttranslational, reversible O-glycosylation is stimulated by high glucose and mediates plasminogen activator inhibitor-1 gene expression and Sp1 transcriptional activity in glomerular mesangial cells. Endocrinology 147 (1), 222–231.
Hotta, N., Kawamori, R., Fukuda, M., Shigeta, Y., 2012. Aldose Reductase Inhibitor–Diabetes Complications Trial Study Group. Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on progression of diabetic neuropathy and other microvascular complications: multivariate epidemiological analysis based on patient background factors and severity of diabetic neuropathy. Diabet. Med. 29 (12), 1529–1533.
Iqbal, Z., Azmi, S., Yadav, R., Ferdousi, M., Kumar, M., Cuthbertson, D.J., Lim, J., Malik, R.A., Alam, U., 2018. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin. Therapeut. 40 (6), 828–849.
Iyer, S., Sam, F.S., DiPrimio, N., Preston, G., Verheijen, J., Murthy, K., Parton, Z., Tsang, H., Lao, J., Morava, E., Perlstein, E.O., 2019. Repurposing the aldose reductase inhibitor and diabetic neuropathy drug epalrestat for the congenital disorder of glycosylation PMM2-CDG. Disease Model. Mech. 12 (11).
Jain, D., Bansal, M.K., Dalvi, R., Upganlawar, A., Somani, R., 2014. Protective effect of diosmin against diabetic neuropathy in experimental rats. J. Integr. Med. 12 (1), 35–41.
Javed, S., Alam, U., Malik, R.A., 2015a. Treating diabetic neuropathy: present strategies and emerging solutions. Rev. Diabet. Stud.: Reg. Dev. Stud. 12 (1–2), 63.
Javed, S., Alam, U., Malik, R.A., 2015b. Treating diabetic neuropathy: present strategies and emerging solutions. Rev. Diabet. Stud. 12 (1–2), 63–83.
Jia, Z.R., Wang, T.T., Wang, H.X., 2014. Significance of quantitative sensory testing in the diagnosis of diabetic peripheral neuropathy. J. Clin. Neurophysiol. 31 (5), 437–440.
Kawanami, D., Keiichiro, Matoba, Sango, K., Utsunomiya, K., 2016. Incretin-Based therapies for diabetic complications: basic mechanisms and clinical evidence. Int. J. Mol. Sci. 17, 1223.
Kim, H.K., Park, S.K., Zhou, J.L., Taglialatela, G., Chung, K., Coggeshall, R.E., Chung, J.M., 2004. Reactive Oxygen species plays an important role in a rat model of neuropathic pain. Pain 11, 116–124.
Kimura, J., 2013. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. Oxford university press.
Kisozi, T., Mutebi, E., Kisekka, M., Lhatoo, S., Sajatovic, M., Kaddumukasa, M., Nakwagala, F.N., Katabira, E., 2017. Prevalence, severity and factors associated with peripheral neuropathy among newly diagnosed diabetic patients attending Mulago hospital: a cross-sectional study. Afr. Health Sci. 17 (2), 463–473.
Kleinbongard, P., Keymel, S., Kelm, M., 2007. New functional aspects of the L-arginine nitric oxide metabolism within the circulating blood. ThrombHaemost 98 (5), 970–974.
Koike, H., Kawagashira, Y., Iijima, M., Yamamoto, M., Hattori, N., Tanaka, F., Hirayama, M., Ando, Y., Ikeda, S.I., Sobue, G., 2008 Oct 1. Electrophysiological features of late-onset transthyretin Met30 familial amyloid polyneuropathy unrelated to endemic foci. J. Neurol. 255 (10), 1526.
Koltezenburg, M., Scadding, J., 2001. Neuropathic pain. Neuromuscular diseases: nerve. Curr. Opin. Neurol. 14, 641–647.
Lesser, H., Sharma, U., LaMoreaux, L., Poole, R.M., 2004. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 63 (11), 2104–2110.
Malik, Z.A., Tabassum, N., Sharma, P.L., 2013. Attenuation of experimentally induced diabetic neu-ropathy in association with reduced oxidative-nitrosative stress by chronic administration of Mo-mordicacharantia. Adv. Biosci. Biotechnol. 4, 356–363.
Minami, K., Tamano, R., Kasai, E., Oyama, H., Hasegawa, M., Shinohara, S., Asaki, T., 2018. Effects of duloxetine on pain and walking distance in neuropathic pain models via modulation of the spinal monoamine system. Eur. J. Pain 22 (2), 355–369.
Moghtaderi, A., Bakhshipour, A., Rashidi, H., 2006. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. Clin. Neurol. Neurosurg. 108, 477–481.
Mu, A., Weinberg, E., Moulin, D.E., Clarke, H., 2017. Pharmacologic management of chronic neuropathic pain: review of the Canadian Pain Society consensus statement. Can. Fam. Physician 63 (11), 844–852.
Murillo, A.G., Fernandez, M.L., 2017. The relevance of dietary polyphenols in cardiovascular protection. Curr. Pharmaceut. Des. 23 (17), 2444–2452.
Muthuraman, A., Singh, N., 2012. Neuroprotective effect of saponin rich extract of Acoruscalamus in vincristine-induced painful neuropathy in rats. J. Nat. Med. 65, 480–487.
Niture, N.T., Patil, D.G., Somani, R.S., Sahane, R.S., 2014. Effect of rutin on early diabetic neuropathy in experimental animals. J. Nat. Prod. Plant Resour. 4, 1–9.
Papanas, N., Katsiki, N., Papatheodorou, K., Demetriou, M., Papazoglou, D., Gioka, T., Maltezos, E., 2011 May. Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. Angiology 62 (4), 291–295.
Pasnoor, M., Dimachkie, M.M., Barohn, R.J., 2013. Diabetic neuropathy part 2: proximal and asymmetric phenotypes. Neurol. Clin. 31 (2), 447–462.
Ramasamy, R., Yan, S.F., Schmidt, A.M., 2007. Arguing for the motion: yes, RAGE is a receptor for advanced glvcation end product. Mol. Nutr. Food Res. 51, 1111–1115.
Rinkel, W.D., Castro Cabezas, M., Setyo, J.H., Van Neck, J.W., Coert, J.H., 2017. Traditional methods versus quantitative sensory testing of the feet at risk: results from the rotterdam diabetic foot study. Plast. Reconstr. Surg. 139 (3), 752e–763e.
Ripsin, C.M., Kang, H., Urban, R.J., 2009. Management of blood glucose in type 2 diabetes mellitus. Am. Fam. Physician 79 (1), 29–36.
Ropper, A.H., Samuels, M.A., 2019. Adams and Victor's Principles of Neurology. McGraw-Hill, New York 11.
Said, G., 2007. Diabetic neuropathy a review. Nat. Clin. Pract. Neurol. 3, 331–340.
Sandireddy, R., Yerra, V.G., Areti, A., Komirishetty, P., Kumar, A., 2014. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int. J. Endocrinol. 2014.
Sansone, R.A., Sansone, L.A., 2014. Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. Innov. Clin. Neurosci. 11 (3–4), 37.
Siddique, N., Durcan, R., Smyth, S., Tun, T.K., Sreenan, S., McDermott, J.H., 2020. Acute diabetic neuropathy following improved glycaemic control: a case series and review. Endocrinol. Diabetes Metab. Case Rep. 2020.
Simpson, D.M., Robinson-Papp, J., Van, J., Stoker, M., Jacobs, H., Snijder, R.J., Schregardus, D.S., Long, S.K., Lambourg, B., Katz, N., 2017. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled study. J. Pain 18 (1), 42–53.
Singh, R., Kishore, L., Kaur, N., 2014. Diabetic peripheral neuropathy: current perspective and future directions. Pharmacol. Res. 80, 21–35.
Spallone, V., Bellavere, F., Scionti, L., Maule, S., Quadri, R., Bax, G., Melga, P., Viviani, G.L., Esposito, K., Morganti, R., Cortelli, P., 2011. Diabetic Neuropathy Study Group of the Italian Society of Diabetology: recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr. Metabol. Cardiovasc. Dis. 21, 69–78.
Stahl, S., 2013. Stahl's Essential Pharmacology. Cambridge University Press, New York, pp. 305–309.
Tavakoli, M., Gogas Yavuz, D., Tahrani, A.A., Selvarajah, D., Bowling, F.L., Fadavi, H., 2017. Diabetic neuropathy: current status and future prospects. J. Diabetes Res. 5825971.
Tesfaye, S., Chaturvedi, N., Eaton, S.E.M., Witte, D., Ward, J.D., Fuller, J., 2005. Vascular risk factors and diabetic neuropathy. N. Engl. J. Med. 352, 341–350.
Tesfaye, S., Boulton, A.J., Dyck, P.J., Freeman, R., Horowitz, M., Kempler, P., Lauria, G., Malik, R.A., Spallone, V., Vinik, A., Bernardi, L., Valensi, P., 2010. Toronto Diabetic Neuropathy Expert Group: diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 33, 2285–2293.
Thornalley, P.J., 2005. The potential role of thiamine (vitamin B (1)) in diabetic complications. Curr. Diabetes Rev. 1 (3), 287–298.
Toelle, T.R., Varvara, R., Nimour, M., Emir, B., Brasser, M., 2012. Pregabalin in

neuropathic pain related to DPN, cancer and back pain: analysis of a 6-week observational study. Pain 5, 1–11.
Tracy, J.A., Engelstad, J.K., Dyck, P.J., 2009. Microvasculitis in diabetic lumbosacral radiculoplexus neuropathy. J. Clin. Neuromuscul. Dis. 11 (1), 44.
Varkonyi, T., Korei, A., Putz, Z., Martos, T., Keresztes, K., Lengyel, C., Nyiraty, S., Stirban, A., Jermendy, G., Kempler, P., 2017. Advances in the management of diabetic neuropathy. Minerva Med. 108 (5), 419–437.
Vinik, A.I., Maser, R.E., Mitchell, B.D., Freeman, R., 2003. Diabetic autonomic neuropathy. Diabetes Care 26 (5), 1553–1579.
Vinik, A.I., Casellini, C., Nevoret, M.L., 2016 Jan 1. Alternative quantitative tools in the assessment of diabetic peripheral and autonomic neuropathy. Int. Rev. Neurobiol. 127, 235–285 Academic Press.
Wang, S.Y., Calderon, J., Kuo Wang, G., Wang, Calderon Kuo, 2010. Block of neuronal Na + channels by antidepressant duloxetine in a state-dependent manner. Anesthesiology 113 (3), 655–665.
Wang, X., Shen, L., Bailin, H.E., Zhang, L., Gou, A., 2018. Clinical study of alprostadil combined with epalrestat and methylcobalamin in the treatment of type 2 diabetic peripheral neuropathy. Chin. J. Primary Med. Pharm. 25 (13), 1700–1703.
Yagihashi, S., Yamagishi, S., Wada, R., 2007. Pathology and pathogenetic mechanisms of diabetic neuropathy: correlation with clinical signs and symptoms. Diabetes Res. Clin. Pract. 77 (1), 184–189.
Yamagishi, S., Maeda, S., Matsui, T., Ueda, S., Fukami, K., 2012. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes Biochemistry. Biophysiology 1820, 663–671.
Yang, J., Zhao, Z., Yuan, H., Ma, X., Li, Y., Wang, H., Ma, X., Qin, G., 2019. The mechanisms of glycemic variability accelerate diabetic central neuropathy and diabetic peripheral neuropathy in diabetic rats. Biochem. Biophys. Res. Commun. 510 (1), 35–41.