

DIABETIC NEUROPATHY MANAGEMENT – A REVIEW ARTICLE

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Abstract- Lifestyle and human behavioural changes in the last years have given a substantial rise in the occurrence of diabetes all over the world. Diabetic neuropathy is a persistent complication of diabetes mellitus with serious effects as it progresses and influences systems of the human body. The estimation shows that 371 million people in the age group 20-79 years worldwide suffer from diabetes mellitus, and half are unaware of the treatment. Diabetes mellitus can lead to several serious complications, among which diabetic neuropathy is the most prevalent. Diabetic neuropathy is a loss of sensory function starting distally in the lower extremities and characterised by pain and substantial morbidity. About 50% of people with diabetes develop diabetic neuropathy. This review discusses the classification, epidemiology, pathogenesis, sign and symptoms, causes, current treatment available and parameters for testing. The symptomatic treatment of sensory symptoms includes tricyclic antidepressants, serotonin & epinephrine reuptake inhibitors, gabapentin, pregabalin and opioids. Symptomatic treatment improves the quality of life of patients having diabetes. Diagnosis of diabetic neuropathy on time is important to avoid serious complications, including cardiac arrhythmias and lower limb amputations.

Keywords- Diabetic neuropathy, epidemiology, aetiology, pathogenesis

INTRODUCTION

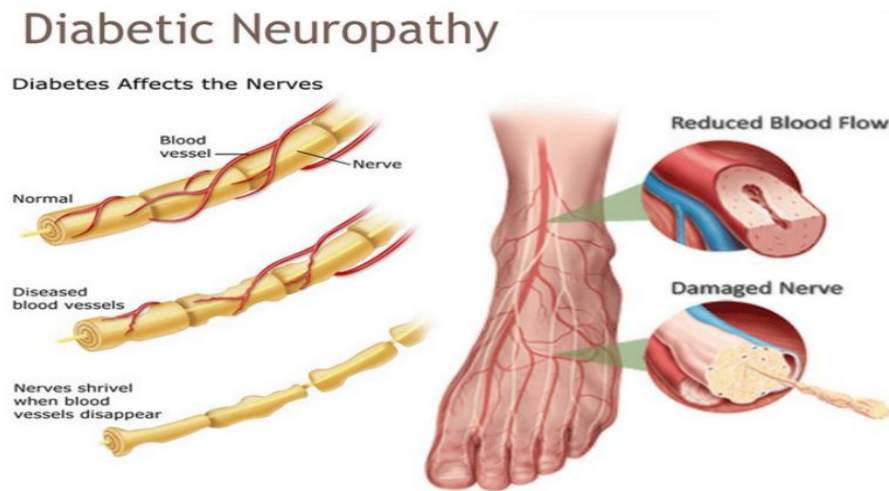
There are 425 million diabetics worldwide, per the International Diabetes Federation [1]. It is the largest worldwide epidemic of the 21st century [2]. As a result of changes in human behaviour and ways of life, the incidence of diabetes has skyrocketed during the past century.

The epidemic comprises mostly type 2 diabetes, obesity, and metabolic syndrome [3,4]. The most prevalent complication of diabetes is damage to the peripheral and autonomic nervous systems. The leading cause of neuropathy in diabetics is widespread and localised damage to the nerve system [5]. The complications of diabetes are classified as macrovascular, which includes cardiovascular disease, and microvascular, which includes retinopathy, nephropathy, and neuropathy [6]. In diabetic patients, diabetic neuropathy is a sign and symptom of peripheral nerve damage. Various causes of peripheral nerve dysfunction are also removed. Diabetic neuropathy is characterised by pain and substantial morbidity resulting from anomalies in the somatosensory nerve system.

Only glucose control and foot care are available to treat diabetic neuropathy [7]. Type 2 diabetes is primarily caused by a genetic predisposition, but it can also be caused by environmental and behavioural factors, such as a sedentary lifestyle, an excess of nutrient-dense foods, and obesity. To reduce diabetes morbidity and mortality, as well as manage microvascular and macrovascular effects, a comprehensive approach is required [8]. In contrast, diabetic neuropathy is a spectrum of clinical and subclinical symptoms affecting the peripheral nervous system and exacerbating diabetes [9]. The duration of diabetes and HbA1c levels are significant predictors [10]. The increase in diabetes complications is associated with the deterioration of hyperglycemia, indicating that an increase in glucose levels causes difficulties [11]. The most prevalent sign and symptom of diabetic peripheral neuropathy is symmetrical sensory pain in the lower extremities. Other symptoms include strange pain, numbness, pins-and-needles sensations, and blistering, scalding feelings.

Also frequent among patients are anxiety, melancholy, and sleep difficulties. Nerve motor dysfunction, such as muscle weakness, poor balance, and a tendency to fall, is one of the indications and symptoms [12].

Fig.1. Diabetic neuropathy is a progressive functional loss of nerve fiber, often damages legs and feet nerves. It is seen as common complication in 50% of diabetes mellitus patients



ETIOLOGY

Hyperglycemia contributes significantly to the initiation and progression of diabetic neuropathy [13]. A 2% rise in HbA1c has been linked to a 20% increase in the frequency of diabetic neuropathy [14], demonstrating the impact of high blood glucose levels on diabetic neuropathy. Hypertension is the most important and independent risk factor for diabetic neuropathy [15]. When diabetes and hypertension coexist, changes in nerve blood flow, conduction, and ischemia are found [16]. Because increasing levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol are linked with an increased risk of neuropathy, dyslipidemia is a risk factor for diabetic neuropathy. Triglycerides had the biggest influence on neuropathy among the characteristics above [17].

Diabetic neuropathy can also be caused by:[18]

- smoking,
- obesity,
- metabolic syndrome,
- insulin resistance,
- alcohol consumption,
- platelet activation and increased aggregability,
- low vitamin D
- subclinical inflammation,
- paraneoplastic syndrome in different cancers,
- related chemotherapy treatment,
- genetic factors and
- increased oxidative stress.

Sign & Symptoms (based on 19)

Symptom	Sign
Negative signs & symptoms :	
Hypoaesthesia	Decreased sensation too:
Pallhypoaesthesia	Non-painful stimuli
Hypoalgesia	Vibration
Thermohypoaesthesia	Painful stimuli
	Cold or warm stimuli
Spontaneous sensations or pain :	
Paraesthesia	Non-painful ongoing sensation
Paroxysmal pain	Painful, shooting electrical attacks for seconds
Superficial pain	Painful ongoing sensation

EPIDEMIOLOGY

Diabetic neuropathy is the most common condition affecting diabetics since it increases the risk of falling, causes discomfort, and lowers the quality of life [20]. Numerous research has shown that diabetic neuropathy is widespread worldwide, and various definitions of neuropathy have been used in various studies. Diabetes neuropathy affects 30% to 50% of diabetics. Additional risk variables include age, duration, smoking, hypertension, increased triglycerides, a higher BMI, alcohol use, and height [21, 22]. Neuropathy affects type 2 diabetes patients more commonly (6,500 per 100,000 person-years) than type 1 diabetes patients (3,000 per 100,000 person-years). Type 2 diabetes was present in 50% of those with silent neuropathy, compared to 57% of those with type 1 diabetes [23]. Over 10 years, the prevalence of diabetic neuropathy in type 2 diabetes patients rose from 10% to 45% [24]. The prevalence of painful or painless diabetic neuropathy varies depending on the demographic, type of diabetes, and selection criteria [25]. According to a population-based study, the number of persons suffering from neuropathy is increasing. It is most frequent in patients with type 1 diabetes, followed by those with impaired glucose tolerance, impaired fasting glucose, and normal glycemia [26].

TYPES OF DIABETIC NEUROPATHY

There are many different clinical signs of diabetic neuropathy, but the most common is distal, symmetrical, mostly sensory polyneuropathy, which affects the feet and legs over time. Acute ophthalmoplegia, which affects the third and sixth cranial nerves on one side; acute mononeuropathy of the limbs or trunk, including painful thoracolumbar radiculopathy; and an acute or subacute painful, asymmetrical, predominantly motor multiple neuropathies affecting the upper lumbar roots and proximal leg muscles are the others (diabetic amyotrophy).

After a subacute or chronic course, there is symmetrical, proximal motor weakness and wasting, often without pain and with irregular sensory loss, as well as autonomic neuropathy, which affects the bowel, bladder, sweating, and circulation [27].

Various types of diabetic neuropathy are as follows :

1. Sensorimotor Neuropathy
2. Autonomic Neuropathy
3. Distal symmetrical polyneuropathy
4. Painful diabetic neuropathy
5. Chronic painful diabetic neuropathy
6. Asymmetrical proximal diabetic neuropathy
7. Limb neuropathies
8. Mononeuropathy
9. Cranial neuropathy
10. Multiple neuropathies

SENSORIMOTOR NEUROPATHY

Distal Sensory Diabetic Polyneuropathy

It is the most prevalent kind of diabetic neuropathy. Burning sensations, discomfort, electrical or stabbing sensations, paraesthesia, hyperesthesia, and deep excruciating pain affect around 50% of individuals [28]. These symptoms are particularly intense at night and cause sleep disruption. Patients cannot do regular jobs and activities due to pain throughout the day [29]. Lower limb research often finds that people lose their sense of vibration, pain, pressure, and temperature and that their ankle reflexes do not work. Muscle weakness is often mild, but in certain instances, distal sensory neuropathy is accompanied by proximal weakness and wasting [30].

Acute Diabetic Neuropathy

In diabetics, the oculomotor nerve is the most affected, followed by the trochlear and facial nerves in that order. Diabetes has been linked to problems with all of the major nerves in the body's periphery, but the femoral, sciatic, and peroneal nerves are the ones that get hurt the most. Nerve entrapment outweighs nerve infarction [13].

Diabetic Multiple Mono-Neuropathies And Radiculopathies Are Conditions Caused By Diabetes.

This kind is related to mononeuropathies. In senior adults with modest or undiagnosed diabetes, a painful unilateral or multiple asymmetrical neuropathy condition is more likely. Many nerves are affected by this kind. Radiculoplexus neuropathies are different types of diabetic syndromes that cause pain and weakness in people with mild diabetes. Diabetic cervical radiculoplexus neuropathy, diabetic thoracic radiculoneuropathy, and diabetic lumbosacral radiculoplexus neuropathy can all be caused by diabetes [31].

Autonomic Neuropathy

Typically non-myelinated vegetative filaments and sympathetic and parasympathetic nervous system nerve fibres are destroyed in a group of diseases known as autonomic diabetic neuropathy [32]. Untreated autonomic diabetic neuropathy may harm the urinary, genital, digestive, and cardiovascular systems. It is a typical autonomic disorder of the adrenergic, cholinergic, and peptidergic fibres connected to diabetes and may manifest in the early years of diabetes mellitus.[33]

Cardiovascular Autonomic Neuropathy

An impairment in the autonomic control of the cardiovascular system is known as cardiovascular autonomic neuropathy. In the end, complex interactions between the degree of glucose management, length of the disease, age-related neuronal attrition, and systolic and diastolic blood pressure lead to cardiovascular autonomic neuropathy [34].

These symptoms include impaired heart rate variability, resting tachycardia, exercise intolerance, inconsistent blood pressure regulation, and orthostatic hypotension [35].

Gastrointestinal Autonomic Neuropathy

The basic rhythmicity created by Cajal interstitial cells located within smooth muscle controls the gastrointestinal motor, sensory, and secretory processes via the interplay of the autonomic (sympathetic and parasympathetic) and enteric neural systems. Constipation, diarrhoea, constipation, bloating, nausea, poor glycemic control, malnutrition, and a poor quality of life are also signs of diabetes [32, 35].

Bladder Dysfunction Associated with Diabetes

One research found that 27% of those with type 2 diabetes and 45–90% with type 1 diabetes had bladder impairment [36]. Bladder dysfunction develops due to peripheral and autonomic neuropathy brought on by diabetes mellitus [37]. The most typical indication that the lower urinary system is involved is damaged bladder sensation. Delay in micturition reflexes is caused by asymptomatic reduced bladder sensation, increased bladder capacity, and pee retention. Frequent warning indications include straining, hesitation, and stream weakening [29, 37].

Diabetic Sudomotor Dysfunction

Lack of thermoregulatory sweating in the glove and stocking distribution, which may also affect the upper limbs and the anterior abdomen, is the primary sign of diabetic autonomic neuropathy. Potentially, diabetic autonomic neuropathy might cause excessive sweating. *Gustatory sweating* is abnormal perspiration produced on the face, neck, head, shoulders, and chest that sometimes happens after eating non-spicy food [38].

Polyneuropathy Symmetric Distal

The most frequent form of diabetic neuropathy is distal symmetrical polyneuropathy (DSPN). It may be motor or sensory, with little or large fibres, or both. Due to the prolonged dependent dieback process, sensory issues develop at the knees before affecting the fingers [39]. There are two types of distal symmetrical polyneuropathy: large fibre neuropathy and small fibre neuropathy. Large fibre neuropathy is characterised by painless paraesthesia, impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. Large-fibre neuropathy affects nerve conduction, quality of life, and activities of daily living. Pain, burning, diminished pain perception, and perceptions of warmth are all signs of small fibre neuropathy, which are also present in autonomic neuropathy. Morbidity and mortality may result from small-fibre neuropathy [40].

Neuropathy in Diabetes

Around 10% to 12% of people with diabetes experience chronic pain [41]. In diabetic neuropathy, pain may be unrestrained or stimulated, acute or uncontrollable. Nighttime neuropathy pain associated with diabetes is often excruciating and may manifest as burning, pins and needles, shooting, arching, jabbing, sharp, cramping, tingling, freezing, or allodynia. When acute diabetic neuropathy pain is accompanied by weight loss and despondency, diabetic neuropathic cachexia ensues. This disorder is more prevalent in men [42].

Diabetic Neuropathy with Chronic Pain

Chronic painful neuropathy is discomfort that persists for longer than six months. Patients may develop medication tolerance or drug dependence. Neuropathy, also known as reduced glucose tolerance neuropathy, may occur before diabetes is clinically diagnosed. Patients who just discovered they have diabetes may have pain and tingle in their lower extremities which could be a sign of hyperglycemic neuropathy [43].

Asymmetrical Proximal Diabetic Neuropathy

Diabetic amyotrophy is another name for asymmetrical proximal diabetic neuropathy [44]. Other signs of proximal diabetic neuropathy, often known as diabetic polyradiculopathy, include thoracic radiculopathy and proximal diffuse lower limb weakness. People over 50 might gradually acquire weakening in the pelvifemoral muscles. The patients have discomfort in their low back, hip, and anterior thigh, which is usually unilateral but may be bilateral. The majority of patients lose weight [45].

Limb Neuropathies

Neuronal damage and entrapment are the dual foremost ways of limb neuropathies. Neuronal damage is linked with abrupt pain starting, trailed by inconstant feebleness and wasting. Recovery is slow for a few months. The most affected nerves are ulnar, median and peroneal [40].

Mononeuropathy

Nerve entrapment is more common than nerve infarction in diabetic patients. Entrapment neuropathies are characterised by a gradual onset and specific electrodiagnostic features in the entrapped nerve segment, such as conduction block or segmental nerve conduction deceleration. Neuropathies can also affect the radial, ulnar, lateral femoral cutaneous nerve of the thigh, peroneal, medial, and lateral plantar nerves in people with diabetes [40].

Neurotoxicity In The Brain

In diabetic cerebral neurotoxicity, the oculomotor nerve is the most often affected nerve, followed by the facial and trochlear nerves in order of prevalence. Due to nerve infarction, *diabetic oculomotor palsy* is defined as third nerve palsy with sparing of the pupil. The pupillary fibres are peripherally located [40].

Multiple Neuropathies

Several neuropathies affect multiple nerves. Since the disease in mononeuropathy develops rapidly in one nerve and sequentially or unevenly in the other nerves involved, Nerve infarction happens when the vasa nervosum gets blocked, and it needs to be set apart from extensive vasculitis [40].

Pathophysiology

The metabolic and ischemic components of diabetic neuropathy make up its pathogenesis. Hyperglycemia-related viscoelastic abnormalities raise endothelial vascular resistance and decrease neuronal blood flow. Through a "competitive absorption process," high blood sugar also causes nerve myoinositol to be used up [40].

Oxidative stress is the main cause of nerve damage in people with diabetes [8, 46, 47]. Most nerve damage in people is caused by problems with the blood vessels, which also cause oxidative stress and microangiopathy in the nerve [48, 8, 4]. Defensive reactions are started by neurons and Schwann cells, which need the activation of antioxidant pathways. Vascular damage in diabetic neuropathy has been connected to protein kinase C activation. Because of these changes, axonal transport is slowed down, and neuronal, axonal, and Schwann cell metabolism is changed.

Endoneural hypoxia is brought on by increased vascular resistance and decreased blood flow in the peripheral nerve. Hypoxia causes axonal atrophy and neuronal conduction that does not work right. It also decreases Na-K ATPase and causes capillary loss [22].

Pain Mechanism: Neuropathic pain is pain brought on by a somatosensory nerve system lesion or sickness. Neuropathic pain affects between 30 and 50% of diabetic neuropathy patients, with the majority reporting foot burning [49].

Treatment

Improvement of diabetes patients' risk of diabetic neuropathy (including diabetic peripheral neuropathy and autonomic neuropathy) can be reduced by improving blood glucose control and improving lipid and blood pressure indexes, as well as avoiding cigarette smoking and excessive alcohol consumption, which has been suggested for the prevention of other diabetes complications [50,51].

Pro-active Treatment

In pharmacological and genetic studies on animals, amplified levels of aldose reductase, protein kinase C, poly (ADP-ribose) polymerase, advanced glycation end products and their receptors, oxidative-nitrosative stress, growth factor imbalances are recorded, along with C-peptide deficiency and are linked to painful and unconscious neuropathy [52]. The powerful antioxidant alpha-lipoic acid reduces microvascular and macrovascular complications in diabetics [53]. It has been shown that three weeks of alpha-lipoic acid therapy is safe and permanently improves both positive neuropathic symptoms and neuropathic deficits [54].

People with diabetes often use angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers to control their blood pressure, treat or prevent cardiovascular disease, and treat or prevent nephropathy. A few studies show that ACE inhibitors are good for people with diabetes [4].

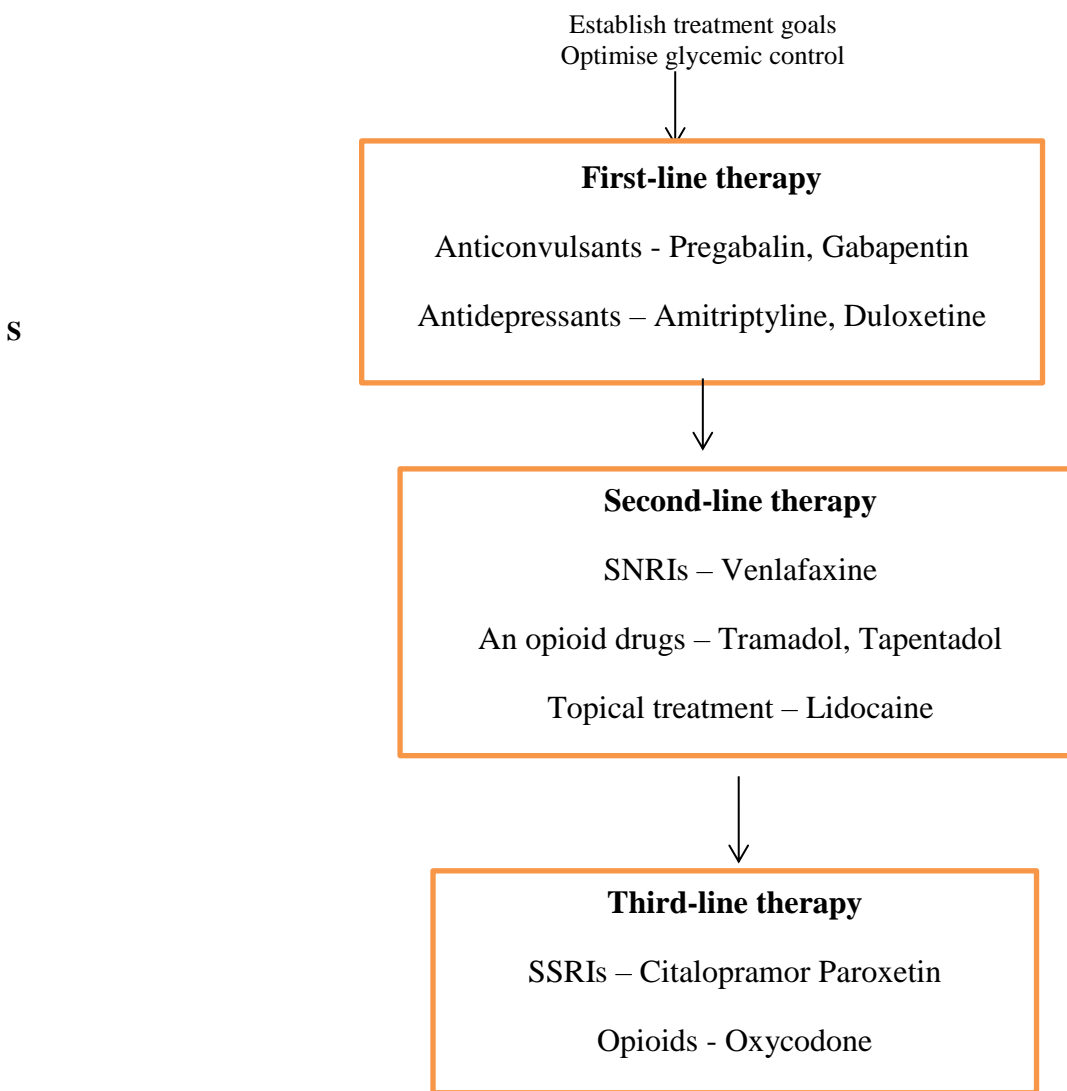
Symptomatic Treatment / Pharmacologic Treatment Options

Just two drugs, pregabalin (brand name Lyrica) and duloxetine (brand name Cymbalta), were granted approval by the Food and Drug Administration (FDA) in the United States for the management of diabetic neuropathy.

MANAGEMENT OF PAINFUL DIABETIC NEUROPATHY

Initial evaluation

Rule out other causes of neuropathy



Anticonvulsants

Painful diabetic neuropathy is treated with topiramate (Topamax), valproate (Depacon), oxcarbazepine (Trileptal), lamotrigine (Lamictal), and lacosamide (Impact), as well as a special class of calcium channel alpha-2-delta ligands (gabapentin and pregabalin) [55]. Pregabalin is helpful for people with neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia. [56]. Gabapentin can cause dizziness, sleepiness, swelling around the edges of the body and trouble walking [57, 58].

Tricyclic Antidepressants

First-generation antidepressants are tricyclic antidepressants. They are the first-line treatments for depression because they activate noradrenergic or increased serotonergic mechanisms. For neuropathic pain, they work best [59, 60]. TCAs have several side effects, including weight gain, dry mouth, constipation, drowsiness, and dizziness [59]. For younger adults, amitriptyline is an efficient first-line treatment. [56].

Selective Serotonin Reuptake Inhibitors

Venlafaxine, milnacipran, and duloxetine are the three medications that act as serotonin and norepinephrine reuptake inhibitors. These medications inhibit both serotonin and norepinephrine reuptake [61]. A daily dose of 60 mg of duloxetine effectively treats painful diabetic neuropathy for up to 12 weeks. It can potentially enhance the toxicity of CNS depressants, antiplatelet agents, alpha and beta-agonists, anticoagulants, and antipsychotics. It may also be incompatible with MAO inhibitors. [56].

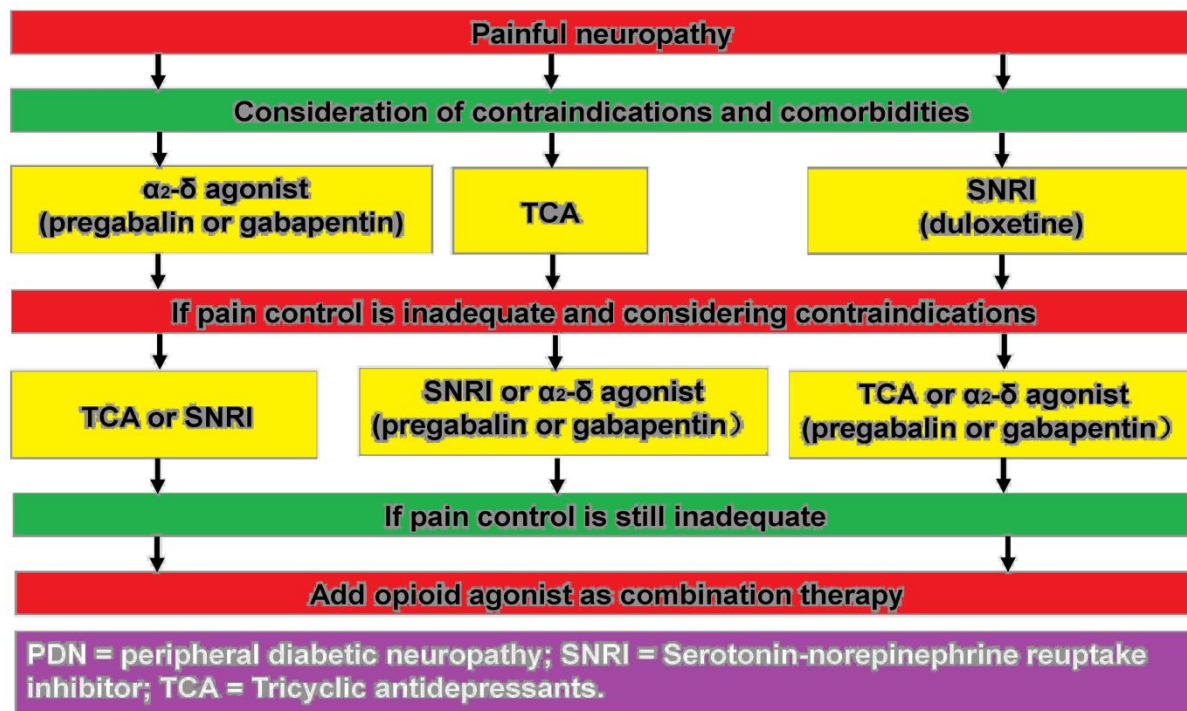


Fig 2. It showing the mechanism of pain full neuropathy and **Selective** Serotonin Reuptake Inhibitors to add opioid agonist as combination therapy

CONCLUSION

Because of the rising prevalence of diabetic neuropathy, there is an urgent need to focus on the various clinical manifestations and treatment options for diabetic neuropathy. First-line therapies include gabapentin and pregabalin, as well as SNRIs. The current management option for diabetic neuropathy is early detection and diagnosis to avoid further complications. With an accurate and timely diagnosis of diabetic neuropathy, clinical outcomes such as foot ulceration, amputation, and cardiovascular disease can be avoided.

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