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An Investigation On Novel Combination For Diabetic Neuropathy

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Abstract

Diabetes is a multifaceted metabolic illness. When it is a chronic ailment, it severely damages several organs, including the kidneys, heart, eyes, blood arteries, and nerves. This further leads to difficulties with the macro and microvascular systems. Although there are currently enough medications to manage diabetes, there is a significant danger and death rate associated with the disease. One of the biggest problems facing medical and healthcare professionals is the reported partial relief and ongoing pain of their patients. A parallel epidemic of complications from diabetes and prediabetes has been brought on by the global epidemics of these conditions.While the last ten years have seen a significant advancement in our knowledge of the intricacies of diabetic neuropathy, the unique processes behind neuropathy in type 1 and type 2 diabetes are still unknown. To effectively treat and prevent diabetic neuropathy, further research on the disease's pathophysiology will be essential. People with diabetic peripheral neuropathy (DPN) have a much lower quality of life when they have painful diabetic neuropathy. The development of tolerance is a constraint and the efficacy of currently available pharmaceutical medicines is restricted. We shall talk about an Investigation on Novel Combination for Diabetic Neuropathy in this paper.

Keywords – Investigation, Novel, Combination, Diabetic Neuropathy, Diabetes, Metabolic Disorder, Chronic Condition, Painful Autonomic Neuropathy, Insulin Neuritis, High Blood Sugar, Metabolic Factors.

Introduction:

Diabetic Neuropathy:

Diabetes can cause neuropathy, a condition that can cause issues all over the body. Nerves that regulate sensation, movement, and other processes can be impacted by diabetes. [1]

Patients with diabetic neuropathy experience severe suffering and a marked decline in quality of life. It is evident that hyperglycemia plays a significant role in the development of nerve injury. Recent research indicates that in individuals with impaired glucose tolerance (IGT), even minor blood glucose variations may be responsible for the development of neuropathic pain and damage to both tiny and large nerve fibers. [2]

Researchers in neurosurgery, neurology, and neuroscience at The Ohio State University Wexner Medical Center and College of Medicine will be able to test a novel diagnosis and therapy combination for excruciating diabetic neuropathy thanks to a $3.6 million grant from the National Institutes of Health. The method uses a patent-pending device called Detecting Early Neuropathy (DEN) to assess tiny fiber nerve activity in conjunction with spinal cord stimulation. [3]

Globally, diabetes is becoming a more significant health issue. In the US, the condition affects about 37 million people, or around 1 in 10 people, as per the Centers for condition Control and Prevention. Peripheral neuropathy is one of the many health issues linked to diabetes, and it can cause excruciating agony. [4]

The loss of nerve endings that supply our tissues and organs is known as peripheral neuropathy, and it can exacerbate diabetes management by impairing neural transmission between the brain and peripheral tissues and organs. Peripheral neuropathy is thought to affect around 30 million Americans. [5]

Distal symmetric sensorimotor polyneuropathy has been associated primarily with novel systemic biomarkers of oxidative stress, inflammation, and vascular activation; however, prospective studies and hypothesis-free approaches involving novel omics technologies should be the focus of future research in order to identify biomarkers that can be used to better understand and predict the development of diabetic neuropathies. [6]

One of the most common noncommunicable diseases affecting people of all racial and geographic backgrounds is diabetes mellitus. The incidence of diabetic complications, such as diabetic peripheral neuropathy (DPN), has increased in recent years due in part to an increased prevalence of diabetes. Peripheral neuropathy affects half to two thirds of diabetic individuals, depending on the diagnostic technique used. When other etiologies including persistent alcoholism, vitamin B-12 insufficiency, uremia, hypothyroidism, and malnutrition are taken into account, DPN is a diagnosis of exclusion. Out of all the presentations, distal symmetrical polyneuropathy (DSPN) accounts for 90% of cases of diabetic neuropathy. [7]

Clinical classifications of diabetic neuropathies:

Symmetric

- Diabetic polyneuropathy
- Painful autonomic neuropathy
- Painful distal neuropathy with weight loss “diabetic cachexia”
- Insulin neuritis
- Polyneuropathy after ketoacidosis
- Polyneuropathy with glucose impairment
- Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus [8]

Asymmetric

Radiculoplexoneuropathies

a. Lumbosacral
b. Thoracic
c. Cervical

- Mononeuropathies
- Median neuropathy at wrist
- Ulnar neuropathy at the elbow
- Peroneal neuropathy at the fibular head
- Cranial neuropathy [9]

Causes Diabetic Neuropathy:

Even though the precise causes of diabetic neuropathy are unknown, a number of things could be involved, such as:

- Elevated glucose (blood sugar). Elevated blood glucose alters the chemical composition of nerves and reduces their signaling capacity. Additionally, it may harm blood arteries that supply the nerves with nutrition and oxygen.
- Metabolic elements. Apart from glucose, elevated levels of triglycerides and cholesterol are linked to a higher chance of developing neuropathy. Additionally, those who are fat or overweight have a higher chance of acquiring neuropathy.

- Factors inherited. Certain individuals may be more prone to nerve illness than others due to certain hereditary characteristics. [10]

Review of Literature:

More importantly, as the 10g monofilament can only identify severe big fiber neuropathy, it should not be used to diagnose "neuropathy." Therefore, a "normal test" could deceitfully soothe doctors when the patient really has little fiber involvement or mild neuropathy. Furthermore, it's critical to accurately measure tiny fiber damage since successful intervention needs to be targeted at a stage in the subclinical or mild neuropathy where the nerve still has the ability to heal.When used to determine therapeutic efficacy in clinical intervention trials, quantitative sensory testing (QST)—which includes a thermal threshold assessment for warm sensation (c fibres) and cold sensation (A-δ fibres)—assesses small fiber dysfunction and can therefore detect early neuropathy. However, it is highly subjective and has low reproducibility [Boulton et al. 2004]. [11]
Treatment of Diabetic Neuropathy: An optimal treatment plan should minimize adverse effects while preventing or stopping the progressive loss of nerve function and improving symptoms. The fundamental cause of nerve injury is not addressed by the available therapeutic options, though. Moreover, new results emphasize that the absence of a discernible worsening of neuropathy in the placebo group poses the primary obstacle to any further clinical trials evaluating improvement in diabetic neuropathy [Dyck et al. 2007]. Currently, the only approved treatment for diabetic neuropathy is to improve glycaemic control. We have concentrated on three areas that are still being actively researched rather than providing a thorough evaluation of all treatments. [12]
In patients with diabetic neuropathy, determining the presence and intensity of painful symptoms accurately is crucial for both confirming the diagnosis and evaluating the efficacy of treatment—particularly given the possibility of a significant placebo effect, as this review has already covered in detail. To quantify neuropathic pain, numerous questionnaires and scoring systems have been created or used. The most widely used questionnaire, the McGill Pain Questionnaire, was not initially designed with diabetic neuropathic pain in mind. The Brief Pain Inventory short form for peripheral diabetic neuropathy (BPI-PDN) is one of the more recent and targeted ratings for diabetic painful neuropathy that have been created [Sorensen et al. 2006b]. [13]

Neuropathic pain (NP) is a major cause of the worldwide illness burden. Its frequency in the general population ranges from 6.9 to 10%, and it is predicted to rise by 2-3% a year as the number of elderly people rises and the incidence of diabetes and cancer rises. NP places a significant financial strain on society expenses and healthcare resources. According to estimates, the annual direct medical expenditures of NP in the US would surpass 635 billion. The majority of NP patients report having ongoing or sporadic spontaneous discomfort. Somatosensory nerve system disorders or lesions can cause spontaneous pain and increased sensitivity to pain in addition to function loss (Scholz et al., 2019).Additionally, severe anxiety, despair, sleep difficulties, and even suicide are frequently linked to NP patients. Nonetheless, NP treatment is still difficult and unsatisfying. [14]
PDN, also known as "pain as a direct consequence of abnormalities in the peripheral somatosensory system of diabetes patients," is a common subtype of painful diabetic neuropathy. One of the excruciating polyneuropathies is PDN. PDN prevalence in patients with diabetes mellitus varied from 13 to 35 percent. According to Rosenberger et al. (2020), PDN is a common consequence of long-term diabetes and one of the main causes of morbidity and disability. PDN has received a lot of interest as a result of rising diabetes prevalence and improved living standards; thus far, it has had the second-highest number of studies (132/914, 14.4%). The FDA recommends tapentadol as a supplement together with pregabalin and duloxetine as the current first-line therapy for PDN (Rosenberger et al., 2020).Mainly, unwanted side effects are the problem. Novel molecular targets and physical methods are the main focus of the ongoing PDN therapeutic trials. [15]
Boulton, A.J.M. Diabetes-related neuropathy (2012) Nowadays, diabetes ranks as the 4th most prevalent metabolic disease worldwide. It comes with a host of problems that could lower one's quality of life. Diabetics have higher blood glucose levels because either the pancreas produces insufficient insulin or the target cells are unable to absorb glucose from the blood. According to the International Association for the Study of Pain, "pain caused by a lesion or disease of the somatosensory nervous system" is referred to as neuropathic pain (IASP). Diabetic neuropathy (DN) is a side effect of diabetes that affects one-third of diabetic people. It raises the risk of brain, peripheral, and cardiovascular diseases.Right now, no medication exists that specifically blocks the pathogenic pathways causing DN, despite the fact that it is incredibly painful. An optimal treatment for diabetic neuropathy could be defined as one that minimizes side effects, enhances symptoms, and prevents the loss of nerve function. Clinical studies have demonstrated that anticonvulsant and antidepressant drugs are useful in treating DN-related pain. [16]

There are a number of drug combinations that have shown some promise in managing the symptoms of DN. Not all drugs under testing are those that have been taken off the market due to significant health risks when taken over an extended period of time. At the moment, there are very few FDA-approved therapies for painful diabetic nerve pain. The FDA has approved a spinal cord stimulation system for the treatment of diabetic nerve pain. Various different drugs and medicine combinations have been recommended by other regulatory organizations. The use of these medications has certain negative consequences in addition to their restricted efficacy. Treatment and medication discovery for DN are difficult tasks because the mechanism of the disease is still poorly understood. It can be challenging to treat DN for both patients and medical professionals. (Z. Qureshi, 2022). [17]

Oxidative stress: In addition to the overproduction of mitochondrial superoxide, increased enzymatic activity, changed proteins, and endothelial dysfunctions, hyperglycemia enhances the production of ROS directly through autoxidation. Furthermore, endothelial vascular damage results in a hypoxic state, disrupts neurological processes, and reduces the neural support system. The nervous system's microvasculature is harmed by oxidative and nitrosative stress because they damage the lipid layer of a nerve's myelin sheath. Furthermore, injury to the peripheral nerves causes a hyperexcitable state that results in the axon and dorsal root ganglia developing spontaneous impulses, which causes neuropathic pain. Casellini, C. M. (2006). [18]

Papanas N. (2012), Since there aren't many prospective research that have looked into this, the natural history of DPN is still not well known. Standardized procedures for DPN diagnosis are lacking, which is the primary cause of this. A significant difficulty in assessing neuropathy, in contrast to diabetic retinopathy and nephropathy, is the absence of straightforward, reliable, and easily repeatable techniques. Moreover, DPN is frequently diagnosed after it is already well established due to the subjective nature of the currently employed procedures, which also depend on the examiner's interpretation. All the same, it seems that the most rapid decline in nerve function happens shortly after type 1 diabetes is diagnosed; after two to three years, the decline slows down and the dysfunction curve slopes less steeply. Conversely, slowing of nerve conduction velocities (NCVs) is typically observed even at diagnosis in type 2 diabetes and may be among the initial neuropathic abnormalities. As a matter of fact, there is mounting data suggesting that people with prediabetes are at higher risk for DPN. The prevalence of DPN was found to be 28% in people with recognized diabetes, 13% in those with impaired glucose tolerance (IGT), 11% in those with impaired fasting glucose, and 7% in those with normal glucose tolerance in a sizable population study carried out in Augsburg, Southern Germany. Following diagnosis, NCV slows down at a consistent pace of about 1 m/sec/year, and the length of diabetes is positively connected with the degree of impairment. [19]

The pathogenesis, risk factors, and clinical manifestations of diabetic neuropathies vary widely. The nerve type affected (sensory, motor, or autonomic), the place of nerve injury (focal, multi-focal, or widespread), and the disease history (acute versus chronic) can all be used to categorize neuropathic disorders. The two main categories of neuropathic syndromes are atypical diabetic neuropathies (which are not covered in this review) and typical diabetic neuropathies (DPN). Typically DPN affects both motor and sensory nerves in a peripheral distribution and is by far the most common kind of neuropathy in people with diabetes. Individual differences exist in the relative influence on motor fibers and small and large sensory fibers. DPN is described as "a symmetrical, length dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (DM) and cardiovascular risk covariates" by the Toronto Diabetic Neuropathy Expert Group. Tesfaye S. (2010) [20]

Objectives:

- Diabetic neuropathy (DN) is a chronic complication of diabetes with extremely complex mechanism.
- Drug repurposing (DR) offers a promising approach in developing novel therapies with existing drugs for the treatment of DN.
- Mechanism and screening-based approaches can be employed for the identification of novel therapies against DN.

Research Methodology:

This study's overall design was exploratory. The research paper is an endeavor that is founded on secondary data that was obtained from reliable online resources, newspapers, textbooks, journals, and publications. The research design of the study is mostly descriptive in nature. [21]

Result and Discussion:

A set of clinical symptoms resulting from injury to the peripheral and autonomic nerve systems are by far the most common consequences associated with diabetes. These symptoms, which are sometimes referred to as distinct types of neuropathy, affect up to half of all diabetics and are brought on by localized and diffuse nervous system injury. [22] This primer focuses on distal symmetric polyneuropathy, the most prevalent type of diabetic neuropathy; henceforth, it will be referred to as diabetic neuropathy. Distal symmetric polyneuropathy typically affects the hands and lower limbs, with a "stocking and glove" distribution.A constellation of autonomic neuropathies, including cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cystopathy, and impotence, are examples of other diffuse neuropathies that can result from diabetes (FIG. 1). Though less frequent, focal neuropathies might result in isolated mononeuropathies from malfunctioning peripheral nerves or, less frequently, from radiculopathy or polyradiculopathy from malfunctioning nerve roots (FIG. 1). [23]

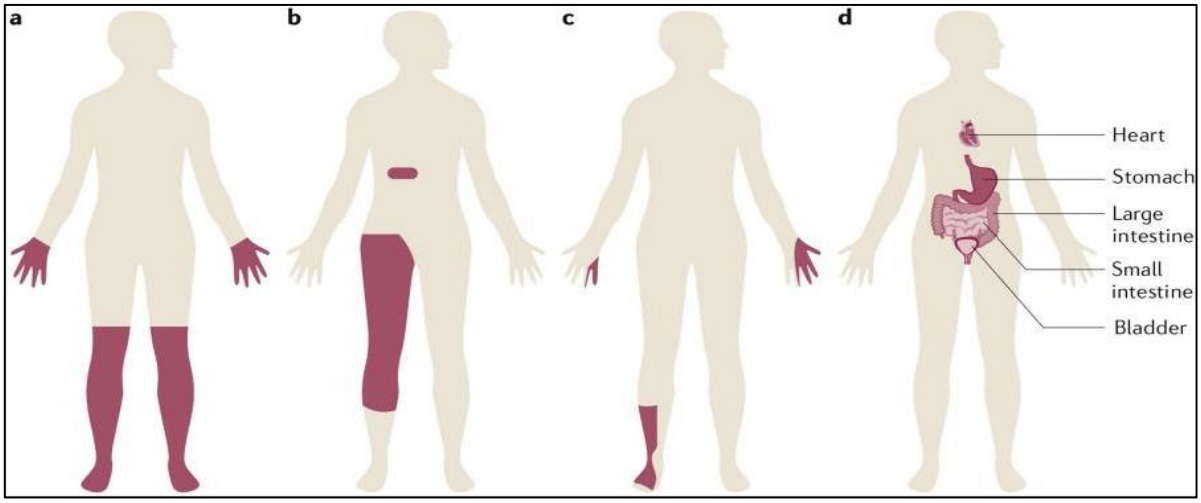

Figure 1: Patterns of nerve injury in diabetic neuropathy. [24]

Diabetic Autonomic Neuropathy:

Diabetic autonomic neuropathy impairs a number of body organs, including the heart, gastrointestinal tract, urine, sweat glands, and metabolism. Due to the wide range of symptoms, autonomic DN is frequently overlooked by doctors and patients alike. After DM diagnosis, autonomic nerve involvement may manifest as soon as a year later. [25] The severity of somatic neuropathy is typically correlated with diabetic autonomic neuropathy. It can range from severe cardiovascular, gastrointestinal, or genitourinary dysfunction to mild functional impairment of sudomotor and cardiovascular responses. Diabetic autonomic neuropathy is characterized by orthostatic hypotension, resting tachycardia, and insensitive heart rate to breathing. The clinical signs and symptoms of autonomic diabetic neuropathy are listed in Table 1. [26]

Table 1: Clinical manifestations of autonomic diabetic neuropathy:

Cardiovascular	Gastrointestinal	Genitourinary	Miscellaneous
Tachycardia	Oesophageal dysfunction	Erectile dysfunction Retrograde ejaculation	Hypoglycaemia unawareness
Exercise intolerance	Gastroparesis	Cystopathy Neurogenic bladder	Miosis Argyll Roberson pupil
Painless myocardial infarction	Diarrhoea Constipation		Heat intolerance
Orthostatic hypotension	Incontinence		Sweating disturbance, Gustatory sweating

Conventional Targets in Diabetes:

Conventional targets are the medications that have been available for a long time to treat diabetes; however, their supply is restricted, and they come with a lot of drawbacks, such as weight gain and hypoglycemia. Additionally, they are limited to managing the illness and postponing problems. Like biguanides, which reduce glucose production and promote glucose consumption in the liver and skeletal muscles, they function by preserving blood glucose levels. SGLT-2 inhibitors, which cause the kidneys to excrete more glucose. [27] A-Glucosidase inhibitors aid in reducing the intestinal absorption of glucose and free fatty acids. Sulphonyl ureas stimulates the pancreas to release more insulin and to become more sensitive. FFA production from fat cells is reduced by 2,4-thiazolidinediones (Fig. 2).

Novel targets for potential therapeutic use in Diabetes mellitus[28]

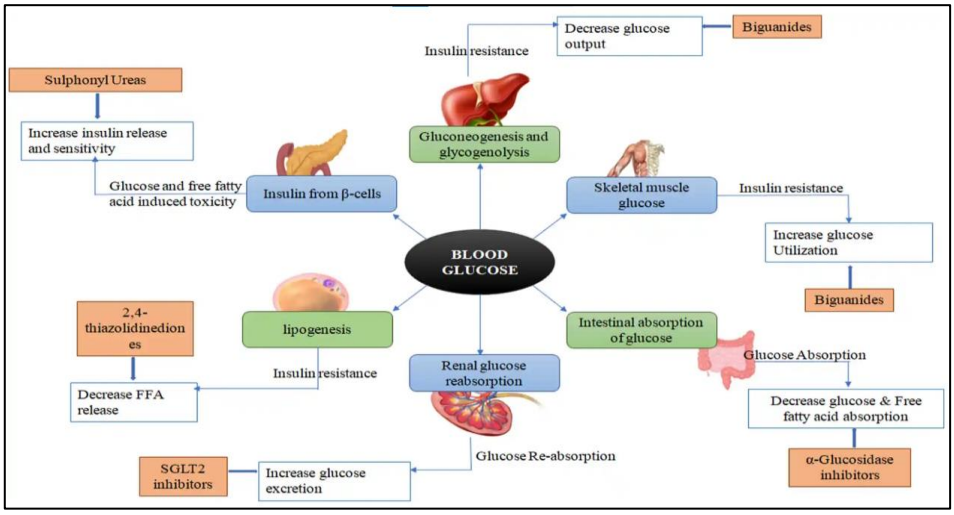

Figure 2: Roles of different conventional targets in diabetes mellitus [29]

Novel point of care device for monitoring diabetic peripheral neuropathy:

Peripheral neuropathy (DPN) is the most frequent consequence of diabetes, impacting over 50% of patients with the disease1. In addition, diabetes or a diabetogenic metabolic state might have a protracted asymptomatic precursor phase before the disease manifests itself because these conditions are necessary for DPN. [30]
By measuring the sural nerve's conduction velocity and the action potential's amplitude, new point-of-care devices (POCD) that are intuitive enough for non-specialist staff to use are aiding in the early detection of peripheral DPN symptoms. [31]
A POCD specifically made for automatic orthodromeneurography of the sural nerve is the NC-stat®/DPN Check™ (DPN Check) (Fig. 3). [32]. There is no need for any further human calculations because nerve conduction is determined automatically for both the height of the sensory nerve action potential (SNAP) and the nerve conduction velocity (NCV). For NCV and SNAP, the results are shown in m/s and µV, respectively. [33]

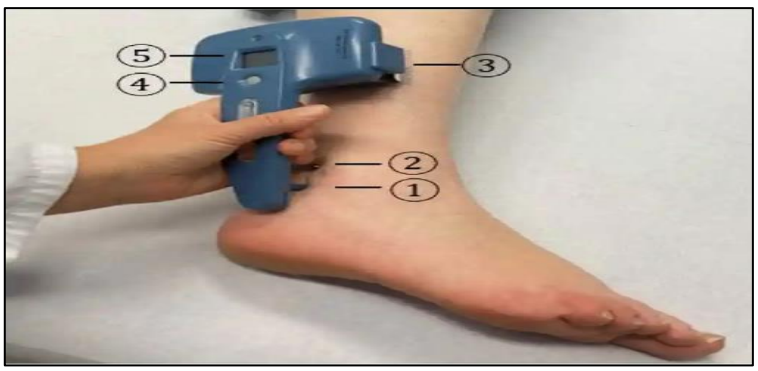

Figure 3: The NC-stat®/DPNCheck™ device in situ. 1: infrared thermometer, 2: stimulating probe, 3: biosensor, 4: test button, 5: display screen. [34]

When compared to measurements made using the traditional approach carried out by electromyography technicians, the studies have demonstrated that the N. Suralis´ amplitude potential obtained by non-technical staff utilizing the DPN Check has a high validity. Additionally, it has been demonstrated that the POCD has high specificity (86.11%) and sensitivity (90.48%) when used to identify DPN, as well as great intra-rater reliability (ICC≥ 0.79) and inter-rater interclass correlation coefficient (ICC ≥ 0.94). [35] The POCD has only been demonstrated to be reliable in establishing the diagnosis of diabetic peripheral neuropathy (DPN) in one randomized controlled study (RCT). As a result, it was uncertain whether or not its reliability was sufficient for consecutive assessments and clinical follow-up of DPN progression.[36]

Novel therapies in the treatment and management of diabetic neuropathy:

It seems that the field of DN is lacking in innovative therapies. While there is a number of pathogenic therapy choices (Table 2) that are recommended for the management of DN, they do not offer total relief. Neuromodulation techniques, including low-intensity laser therapy, monochromatic infrared light therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, and percutaneous electrical nerve stimulation (PENS), are employed only in cases where evidence-based therapies fail to control diabetic neuropathy. 37] In addition, dietary supplements and lifestyle modifications involving food and exercise are suggested nonpharmacological therapies. Acupuncture and yoga are examples of holistic therapies that are used. There are published reports on the advantages of acupuncture and yoga for the treatment of DN.The treatment's long-term effectiveness is unclear, though. As a result, finding a novel treatment for DN is critically important. [38]

Table 2. List of pathogenic treatment options for DN. [39]

Drug	Mechanism of action (s)	Side-effect (s)
Epalrestat, Fidarestat, Sorbitol, Zenarestat, Tolrestat,	Alleviates oxidative stress and inhibits polyol pathway (Aldose reductase inhibitors)	Hepatic dysfunction, nausea, vomiting, gastric discomfort, exacerbation of renal function, exacerbation of systemic numbness, edema,diarrhea
Benfotiamine	Inhibits hexokinase pathway	Nausea, dizziness, stomach ache and weight gain
Tocotrienol	Attenuates oxidative-nitrosative stress and inflammatory cascade	No significant side effects
Pyridoxamine	Inhibits AGEs	No significant side effects
Vitamin D	Inhibits AGEs	No significant side effects
Alpha Lipoic Acid	Inhibits NF-kB, ROS and TRPV1	No significant side effects
Nimeuslide, Celeoxib, Meloxicam.	Inhibits COX-2, allodynia and hyperalgesia	Diarrhea, vomiting, skin rash, itchiness, dizziness, bitterness in mouth
Acetyl L-carnitine	Inhibits COX-2 and ROS	No significant side effects
1,5 – Isoquinolinediol	Inhibits PARP	No significant side effects

Pathogenesis of Diabetic Neuropathies:

There has been a lot of research done, but the cause of diabetic neuropathy is still unknown. This is one of the reasons that the development of disease-modifying therapies has not advanced all that much, even after multiple clinical studies. [40] Numerous causal factors have been discovered in the past, such as autoimmune-mediated nerve damage, microvascular insufficiency, oxidative and nitrosative stress, faulty neurotrophism, and prolonged hyperglycemia. Our present understanding of the etiology of DPN is summed up in Figure 4. It is outside the purview of this Chapter to analyze the various theories in detail, however there are a number of very good contemporary evaluations. [41]

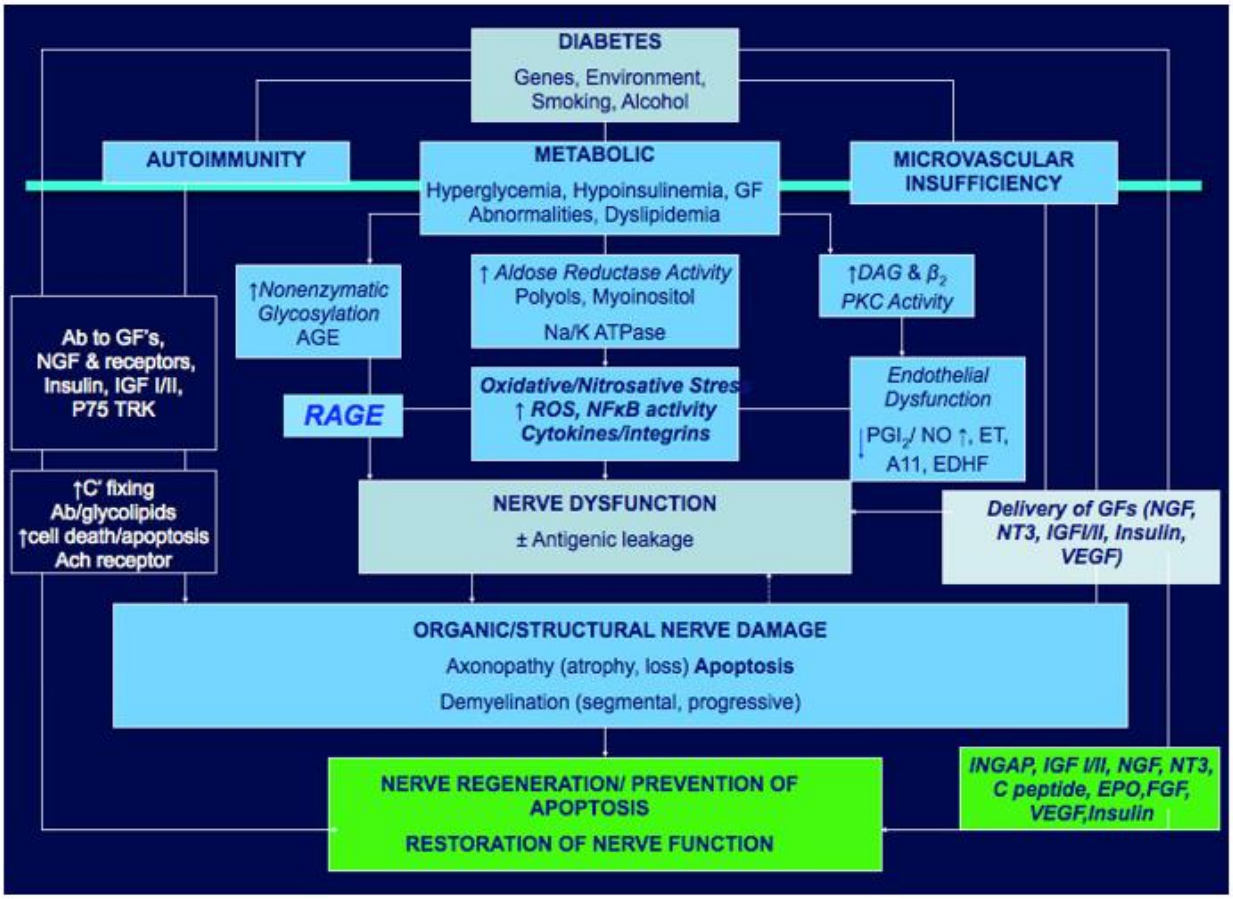

Figure 4: Pathogenesis of diabetic neuropathies. [42]

Ab, antibody; AGE, advance glycation end products; C', complement; DAG, diacylglycerol; ET, endothelin; EDHF, endothelium-derived hyperpolarizing factor; GF, growth factor; IGF; insulin-like growth factor; NFkB, nuclear factor kB; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotropin 3; PKC, protein kinase C; PGI2, prostaglandin I2; ROS, reactive oxygen species; TRK, tyrosine kinase. [43]

Treatment of Diabetic Neuropathy:

- **Prevention**

The underlying nerve injury that causes DPN cannot be reversed by current treatments. Thus, an important aspect of diabetic therapy is DPN prevention. To avoid or delay the onset of diabetic peripheral neuropathy (DPN), the American Diabetes Association advises establishing optimal glucose control in both type 1 and type 2 diabetes. In [44] But with type 1 diabetes rather than type 2, there is a lot more data supporting improving glycemic control in the prevention of DPN.Optimizing glucose control in type 1 diabetes has been proven to be beneficial, according to meta-analyses of sizable, well-conducted randomized controlled trials. For instance, intensive therapy was observed to dramatically lower the incidence of DPN in the Diabetes Control of Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study. In type 2 diabetes, the advantages for glucose and multifactorial risk factor control on DPN are unclear. [45]

- **Pathogenetic Treatments:**

In order to enhance neuronal function, pathogenetic treatments for DPN focus on the underlying illness mechanisms. While certain randomized controlled trials have demonstrated the effectiveness of pathogenetic therapy, pre-clinical study results have not always translated into results that are clinically significant. [46]

- **Symptomatic Treatment of Painful-DPN:**

In DPN, symptomatic therapy is the cornerstone of neuropathic pain management. Unfortunately, neuropathic pain has not been demonstrated to improve with pathogenetic therapies or with adequate glycemic management. [47] The only medications for the treatment of painful DPN that have FDA regulatory approval are duloxetine and pregabalin. On the other hand, the National Institute of Clinical Excellence in the United Kingdom suggests gabapentin, pregabalin, duloxetine, and amitriptyline as first-line treatments for neuropathic pain. An approach for treatment is displayed in Figure 5.

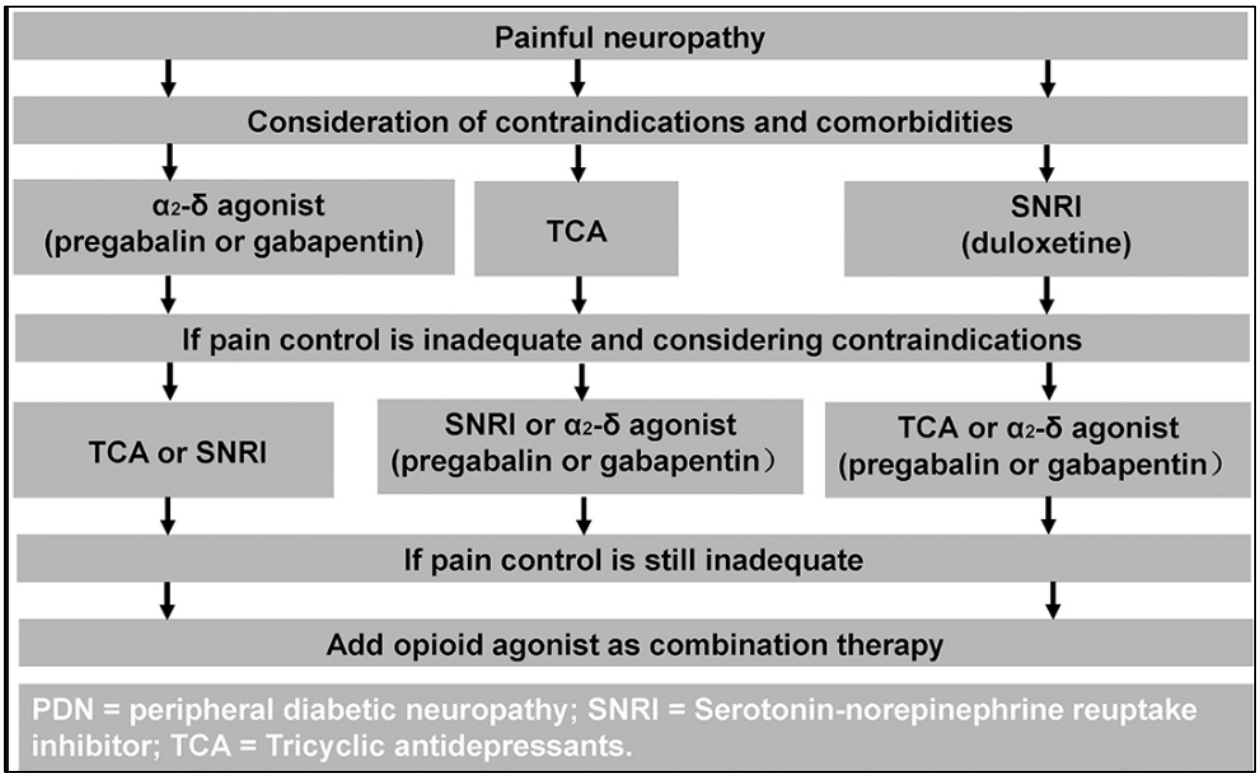

Figure5. Treatment algorithm for painful-DPN. [48]

The α2δ agonists, such as pregabalin and gabapentin, are often prescribed medications for painful DPN. [49] The regulation of voltage-sensitive calcium channel α2δ-1 and α2δ-2 subunits is how these medicines achieve their analgesic effect. Although gabapentin has a high frequency of adverse effects, the most prevalent of which are somnolence and dizziness, it is effective in treating pain and sleep disturbance in painful-DPN patients. 5.9 (4.6–8.3) is the stated number that must be treated in order to have at least 50% pain alleviation. Furthermore, gabapentin was discovered to be the most effective and secure treatment for painful DPN in a network meta-analysis. [50]

Conclusion:

The most crippling issue affecting the quality of life of those with diabetes is still neuropathic pain related to diabetic peripheral neuropathy. Drug therapy is the mainstay of NP treatment, while physical methods are also gaining traction. It is noteworthy that new physical approaches, fresh perspectives on traditional therapy, and innovative medication targets can all be effective approaches to treating NP. The difficulties in integrating research findings into clinical practice, however, require additional focus. While more research is necessary before any of these variables can be taken into account for stratification in clinical practice, doing so could potentially improve patient outcomes for those with painful DPN.

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