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Pharmacological and Non-Pharmacological Interventions for Diabetic Neuropathic Pain: Current Evidence and Clinical Applications

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ABSTRACT

Background: Diabetic neuropathic pain (DNP) is a common and debilitating complication of diabetes mellitus, primarily resulting from chronic hyperglycemia, induced peripheral nerve damage. It manifests as burning, stabbing, and electric shock-like sensations. This review aims to explore the underlying mechanisms, current management strategies, and emerging therapeutic interventions for DNP.

Method: An extensive review of existing literature was conducted to summarize the pathophysiology and treatment approaches for DNP. The study integrates findings from pharmacological and non-pharmacological research, focusing on oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired neurotrophic signaling as key pathological contributors.

Results: Pharmacological therapy remains the mainstay for symptom relief. First-line agents such as duloxetine, pregabalin, and gabapentin demonstrate significant efficacy, while topical treatments like capsaicin and lidocaine patches, along with second-line options including tramadol, tapentadol, and alpha-lipoic acid, provide additional benefit. Non-pharmacological interventions—such as glycemic control, exercise, psychological support, and lifestyle modifications—enhance overall management outcomes. Emerging therapeutic strategies include gene therapy, mesenchymal stem cell (MSC) transplantation, and targeted molecular therapies involving Nav1.7 sodium channel blockers, TRPV1 antagonists, and AT_2R blockers like Olodanrigan. Neuroregenerative approaches using growth factors (NGF, IGF-1, VEGF), along with antioxidant and anti-inflammatory agents (curcumin, resveratrol, N-acetylcysteine), and neuromodulation techniques (spinal cord stimulation, TENS), show promising preclinical and clinical outcomes.

Conclusion: Effective management of diabetic neuropathic pain requires a multidisciplinary and personalized approach, combining pharmacological and non-pharmacological therapies. Integration of conventional treatments with novel regenerative and molecular strategies offers significant promise for addressing both symptom relief and disease modification in DNP.

Keywords: Diabetic neuropathy, Neuropathic pain, Hypergylcemia, DNP Models..

1. INTRODUCTION

It is a chronic condition associated with diabetes and often a progressive condition that arises as a complication of diabetes mellitus disease, particularly in individuals with prevailing blood glucose levels. It is one of the most common and distressing manifestations of diabetic peripheral neuropathy and significantly impairs the quality of life of affected individuals [1]. DNP results from damage to the peripheral nerves caused by sustained hyperglycaemia, leading to abnormal nerve function and pain signalling. Patients typically describe the pain as burning, stabbing, tingling, or electric shock-like sensations, predominantly affecting the feet and lower extremities (Table 2) [2, 3]. The pathogenesis of DNP includes multifactorial, involving metabolic derangements, oxidative stress, mitochondrial dysfunction, inflammation, and microvascular damage (Table 3). Despite its prevalence, DNP remains underdiagnosed and undertreated [4] (Table 1).

Table 1: Types of neuropathic pain and symptoms in patients

S. No.	Type of neuropathic pain	Definition	Symptom
1.	Peripheral Neuropathy	Peripheral Neuropathy affects nerves in the extremities (hands, feet, arms, legs).	burning, throbbing, or electric shock-like pain, numbness, tingling ("pins and needles"), reduced sensitivity to touch, muscle weakness and lack of coordination, skin changes and itchiness [5].
2.	Autonomic Neuropathy	Autonomic Neuropathy impairs nerves controlling involuntary bodily functions (digestion, heart rate, etc.)	heat intolerance and abnormal sweating, digestive issues (e.g., bloating, diarrhoea) and bladder dysfunction, dizziness due to blood pressure fluctuations [2, 3].
3.	Focal Neuropathy (Mononeuropathy)	Focal Neuropathy affects a single nerve, often due to compression or injury. The examples include	Sudden, severe facial pain triggered by routine activities (e.g., brushing teeth), facial paralysis and pain [6].
4.	Diabetic Neuropathy	Diabetic Neuropathy is caused by diabetes- related nerve damage.	Burning or shooting pain in feet/legs, Tingling, numbness, and sensitivity to touch, Thoracic/lumbar radiculopathy (chest/abdominal wall pain) [7].
5.	Phantom Limb Syndrome	Phantom Limb Syndrome occurs after limb amputation	Pain or sensations (burning, prickling) in the missing limb, mixed signals from the brain/spinal cord causing prolonged discomfort [8].
6.	Postherpetic Neuralgia	Postherpetic Neuralgia follows shingles infection	persistent burning or stabbing pain in areas previously affected by shingles rash, hypersensitivity to touch (allodynia).

7.	Polyneuropathy	Polyneuropathy disease includes damaging multiple nerves.	Numbness, tingling, or weakness, progressive pain spreading from feet/hands to legs/arms [9].

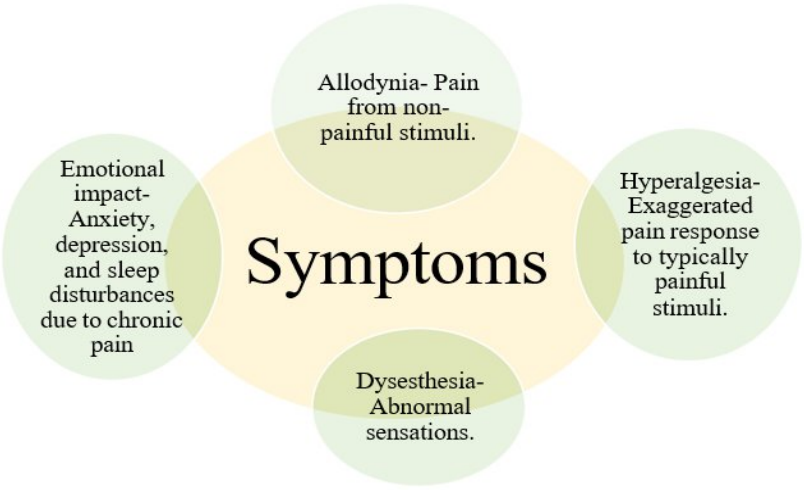

Fig. 1: Common symptoms of various Polyneuropathy [9]

Pathophysiology of Diabetic Neuropathic Pain

Prolonged elevated blood glucose levels lead to a cascade of biochemical changes that result in structural and functional damage to peripheral nerves. (Fig.1)

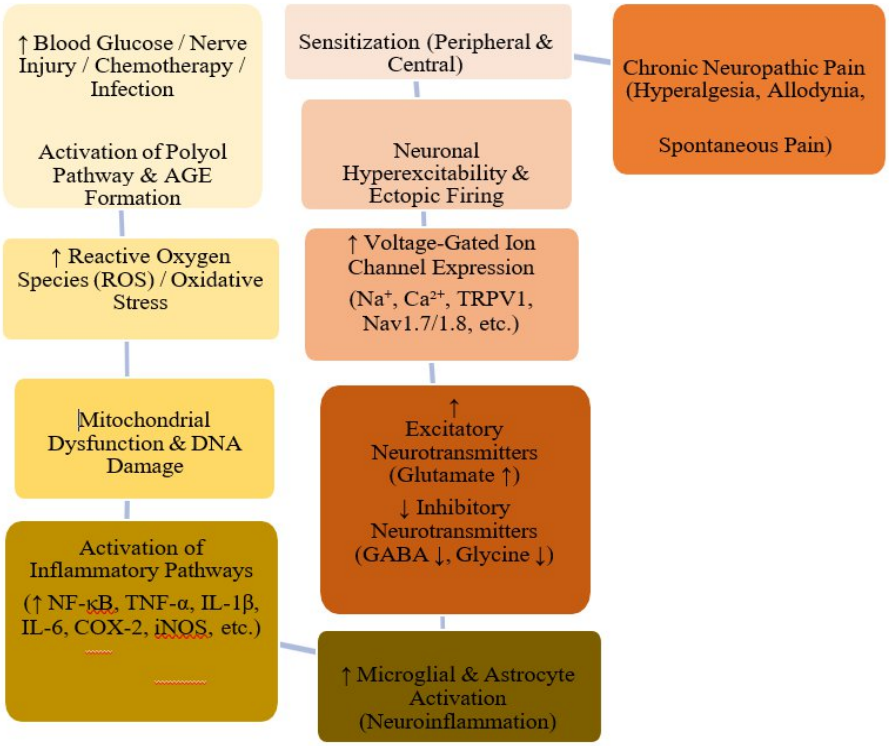

Fig 2: Cascade of biochemical changes that result in structural and functional damage to peripheral nerves.

The mechanism for DNP involves the activation of the polyol pathway, where excess glucose is converted into sorbitol and

fructose, leading to osmotic stress and depletion of essential cofactors such as NADPH, which impairs antioxidant defences and promotes oxidative stress [10]. This oxidative stress damages the endoneuria microvasculature and nerve tissue, contributing to axonal degeneration and demyelination.

Advanced glycation end-products (AGEs) also play a significant role. The non-enzymatic glycation of proteins and lipids forms AGEs, which bind to specific receptors (RAGE) on nerve and immune cells, triggering inflammatory responses and further oxidative damage which impair neuronal energy metabolism and further exacerbate nerve injury [11, 12].

Neuroinflammation is another critical component, chronic low-grade inflammation in diabetes activates immune cells such as macrophages and microglia, releasing pro- inflammatory cytokines (e.g., TNF-α, IL-1β) that sensitize nociceptors and alter pain signaling pathways [13]. This contributes to central sensitization and the perception of exaggerated pain responses.Moreover, impaired neurotrophic support—such as reduced levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) also leads to diminished nerve repair and regeneration capacity [14].

Clinical Manifestations of Diabetic Neuropathic Pain

Diabetic neuropathic pain (DNP) presents with a range of sensory symptoms that are typically chronic, progressive, and symmetrical in distribution.

DNP can also be accompanied by autonomic neuropathy, which affects various organ systems. Manifestations can include orthostatic hypotension, gastroparesis, urinary retention, erectile dysfunction, and abnormal sweating, depending on the nerves involved [15].

Diagnosis of Diabetic Neuropathic Pain

The diagnosis of diabetic neuropathic pain (DNP) is primarily clinical and involves a thorough patient history, physical examination, and exclusion of other potential causes of neuropathy.

Clinical History and Symptom Assessment- Diagnosis begins with a detailed history of the patient's symptoms, focusing on the quality, duration, and distribution of the pain. Typical features of DNP include burning, tingling, stabbing, or electric shock-like pain, often worse at night and commonly affecting the feet and lower limbs in a symmetrical pattern [1].

Physical and Neurological Examination-The neurological examination evaluates sensory, motor, and autonomic function. Common findings in DNP include reduced or absent ankle reflexes, loss of vibration and pressure sensation (tested using a 128-Hz tuning fork and monofilament), decreased pain and temperature perception, signs of allodynia or hyperalgesia [2].

Screening and Diagnostic Tools- Several standardized tools can assist in diagnosing and assessing the severity of DNP including Michigan Neuropathy Screening Instrument (MNSI), Toronto Clinical Neuropathy Score (TCNS), Neuropathy Disability Score (NDS), DouleurNeuropathique 4 (DN4) Questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[3].

Electrophysiological Studies-Although not routinely required for typical DNP, nerve conduction studies (NCS) and electromyography (EMG) are used to confirm peripheral neuropathy that rule out other conditions (e.g., radiculopathy, entrapment neuropathies), and assess the extent of nerve damage [16].

Laboratory Investigations- Blood tests are performed to rule out other causes of neuropathy (e.g., vitamin B12 deficiency, renal or hepatic dysfunction, thyroid abnormalities). Glycated haemoglobin (HbA1c) levels are also checked to assess long-term glycaemic control.

Quantitative Sensory Testing (QST) and Skin Biopsy- In research or specialized settings, QST can evaluate thresholds for temperature and vibration, and skin biopsy may assess intraepidermal nerve fibre density, useful for diagnosing small fibre neuropathy [17].

Preclinical models of Diabetic Neuropathic Pain

Preclinical animal models are fundamental for understanding the mechanisms of diabetic neuropathic pain (DNP) and for evaluating potential treatments before clinical trials. These models replicate key features of human diabetic neuropathy, including both type 1 and type 2 diabetes, and are essential for studying molecular, cellular, and behavioural aspects of the disease [18, 19, 21].

Common Preclinical Models

Streptozotocin (STZ)-Induced Models: STZ is a chemical that selectively destroys pancreatic β-cells, inducing type 1 diabetes in rodents (rats and mice). This model is widely used to study the onset and progression of DNP, particularly thermal and mechanical hyperalgesia and allodynia [19, 21].

Diet/Nutrition-Induced Models: High-fat or high-sugar diets are used to induce type 2 diabetes and metabolic syndrome in rodents, mimicking the gradual onset of neuropathy seen in human type 2 diabetes [18, 19].

Genetic Models: Examples include Zucker diabetic fatty rats, BB/Wor rats (type 1, insulinopenic), and BBZDR/Wor rats (type 2, hyper insulinemic). These models develop diabetes spontaneously due to genetic mutations and are valuable for

studying chronic DNP [19, 21].

Transgenic/Knock-out Models: These involve specific genetic modifications to study the contribution of particular genes or pathways to diabetic neuropathy and pain [19, 21].

Pain behaviours in animal models are assessed using Thermal hyperalgesia (increased sensitivity to heat), Mechanical allodynia (pain from normally non-painful stimuli), Spontaneous pain behaviours, Quantitative sensory testing [20, 21]

Treatment Approaches for Diabetic Neuropathic Pain

The management of DNP aims to reduce pain, improve quality of life, and prevent further complications such as foot ulcers and infections. Since DNP is a chronic condition, long-term management and patient education are essential.

Glycaemic Control

Tight and sustained glycaemic control is crucial for preventing the progression of neuropathy and potentially alleviating symptoms. Studies such as the DCCT (Diabetes Control and Complications Trial) have shown that improved glycaemic control can delay the onset and progression of diabetic neuropathy, particularly in type 1 diabetes [22]. However, in patients with type 2 diabetes, the benefit in reducing neuropathic pain is less pronounced and should be balanced against the risk of hypoglycaemia.

Pharmacological Interventions

First-Line Agents

Antidepressants: Duloxetine and amitriptyline are commonly used and effective for neuropathic pain. Mechanism includes inhibiting the reuptake of serotonin and norepinephrine in the central nervous system, thereby increasing their levels in the synaptic cleft. This dual action enhances descending inhibitory pain pathways in the spinal cord, which helps to modulate and reduce the transmission of pain signals. But the drug also does possess side effects including nausea, vomiting, dry mouth, dizziness, fatigue, somnolence, headache, increased blood pressure, sweating, constipation, decreased appetite, sexual dysfunction, Serotonin syndrome, urinary retention and increased urethral sphincter tone. Duloxetine is contraindicated in patients with a known hypersensitivity to the drug, those taking monoamine oxidase inhibitors (MAOIs), and patients with uncontrolled narrow-angle glaucoma [24].

Anticonvulsants: Pregabalin and gabapentin are effective in reducing pain and improving sleep and quality of life in patients with DNP. The drug act by binding specifically to the alpha-2-delta (α2δ) subunit of voltage-gated calcium channels (VGCCs) in the central nervous system [25]. This binding reduces calcium influx into presynaptic neurons, which in turn decreases the release of excitatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide (CGRP). By inhibiting the release of these neurotransmitters, pregabalin and gabapentin reduce neuronal hyperexcitability and synaptic transmission

thereby alleviating neuropathic pain [26, 27]. The common side effects of drug include dizziness, somnolence (drowsiness), peripheral oedema (swelling of extremities), weight gain, dry mouth, blurred vision, difficulty with concentration or attention [28].

Second-Line and Adjunctive Therapies

Topical agents: Capsaicin 8% patches and lidocaine 5% patches are used for localized pain. Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor, which is expressed on nociceptive (pain-sensing) C fibres and some Aδfibres. Upon topical application, capsaicin activates TRPV1, causing an influx of calcium and sodium ions, which initially leads to depolarization and a sensation of burning, stinging, or heat.With repeated or high-dose exposure, this activation results in desensitization and “defunctionalisation” of nociceptor fibres which involves depletion of neuropeptides (e.g., substance P), loss of receptor functionality, temporary degeneration or retraction of nerve fibre terminals, impaired local nociception for extended periods [29].The analgesic effect is due to this prolonged desensitization, which reduces the ability of nerves to transmit pain signals. Whereas the drug also have side effects that include initial burning, stinging, or itching at the site of application, erythema (redness) and swelling, rarely, blistering or local skin irritation[30]. Lidocaine is a local anaesthetic that blocks voltage-gated sodium channels on neuronal cell membranes. By inhibiting sodium influx, lidocaine prevents the initiation and propagation of action potentials in peripheral nerves, resulting in reversible loss of sensation (analgesia and anaesthesia) in the area of application. The side effects of drug include local skin reactions (redness, irritation, rash, or oedema) dizziness, drowsiness, confusion, or, in severe cases, cardiac arrhythmias and central nervous system toxicity [31].

Opioids (e.g., tramadol, tapentadol): This class of drug is considered only for short-term use in patients with severe pain unresponsive to first-line agents, due to risk of dependence and side effects. Tramadol and Tapentadol being an active metabolite (M1) bind to μ-opioid receptors in the central nervous system, producing analgesia similar to other opioids. Tramadol inhibits the reuptake of serotonin and norepinephrine, enhancing inhibitory effects on pain transmission in the spinal cord [32]. The side effect of drug includes nausea, vomiting, constipation, dizziness, drowsiness, headache, dry mouth, fatigue, and sweating, seizures, serotonin syndrome, respiratory depression, and risk of dependence or withdrawal

[33, 34]

Other options: Alpha-lipoic acid (ALA) being a potent antioxidant that directly scavenges reactive oxygen and nitrogen species and regenerates other antioxidants such as vitamins C and E and glutathione. It also enhances cellular antioxidant capacity by inducing genes involved in glutathione synthesis and redox regulation [35]. ALA acts as a metal chelator, binding to transition metals and reducing metal-induced oxidative stress. ALA improves glucose uptake, glycogen synthesis, and insulin sensitivity by activating the insulin receptor cascade, PI3K/Akt signalling pathway, and peripheral AMPK, while inhibiting hypothalamic AMPK [36]. ALA inhibits the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), reducing the expression of pro-inflammatory genes and cytokines [37, 38]. ALA modulates several signalling pathways, including the activation of protein kinase B (Akt), AMPK, and peroxisome proliferator-activated receptors (PPARs), contributing to its metabolic and anti-inflammatory effects. The side effect of drug include nausea, vomiting, abdominal pain, diarrhoea, rashes, itching, headache, hypoglycaemia[39].

Non-Pharmacological Interventions

Physical therapy and exercise that can improve blood flow, nerve function, and overall physical condition. Psychological therapies including cognitive-behavioural therapy (CBT) helps manage the emotional burden of chronic pain. By educating patients regarding their foot care education is critical to prevent ulcers and infections. And complementary therapies like Acupuncture, transcutaneous electrical nerve stimulation (TENS), and biofeedback may provide additional symptom relief for some patients [40].

Emerging Therapies

Gene therapy, stem cell therapy, and targeted molecular treatments-

Gene Therapy for Diabetic Neuropathic Pain

Gene therapy involves the delivery of genes encoding neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, ciliary neurotrophic factor, glial cell-derived neurotrophic factor, and hepatocyte growth factor (HGF) [41]. These factors support nerve survival, regeneration, and function, countering the neurodegenerative processes in diabetic neuropathy[42].It is advantageous because of its potential for long-lasting or disease-modifying effects, direct targeting of underlying nerve damage and regeneration pathways [43]

Stem Cell Therapy for Diabetic Neuropathic Pain

Stem cells, particularly mesenchymal stem cells (MSCs) modulate immune responses, reducing neuroinflammation by lowering pro-inflammatory cytokines and increasing anti- inflammatory cytokines, which is crucial in the pathogenesis of diabetic neuropathy [44]. Stem cells secrete neurotrophic and angiogenic factors that enhance blood flow, support nerve survival, and stimulate endogenous repair mechanisms [45]. Animal models of diabetic neuropathy have shown that transplantation of MSCs leads to improved nerve conduction, increased intra-epidermal nerve fibre density, enhanced sciatic nerve blood flow, and a reduction in pain behaviours such as hyperalgesia and allodynia [46].

Targeted Molecular Treatments for Diabetic Neuropathic Pain

Targeted molecular therapies for diabetic neuropathic pain (DNP) aim to address the underlying pathophysiological mechanisms rather than only providing symptomatic relief. For ex- Alpha-Lipoic Acid (ALA)is a potent antioxidant that reduces oxidative stress, a key contributor to diabetic neuropathy. It also improves glycaemic control and supports nerve function by scavenging free radicals and regenerating endogenous antioxidants [47]. Aldose Reductase Inhibitors (ARIs)such as epalrestat and ranirestat, inhibit the polyol pathway by blocking aldose reductase, thereby reducing sorbitol accumulation and preventing osmotic and oxidative damage to nerves [48]. Antioxidants and Anti-inflammatory Agents, for ex- Kaempferol and other flavonoids modulate oxidative and nitrosative stress, suppress pro- inflammatory cytokines, and reduce the formation of advanced glycation end products (AGEs), all of which are implicated in DNP [49, 50]. ALA in combination with Methyl cobalamin gives enhanced improvement in neuropathic symptoms and nerve conduction velocities compared to methyl cobalamin alone [51]

Fig.3: Treatment Strategy

Non Pharmacological intervention in the Management of Diabetic Neuropathic Pain

Lifestyle modifications play a pivotal role in the comprehensive management of DNP. While pharmacologic therapies target symptom control, lifestyle changes aim to improve metabolic health, prevent further nerve damage, and enhance overall quality of life.

Glycemic Control Through Diet and Monitoring

Maintaining blood glucose levels within target ranges helps prevent the progression of diabetic neuropathy. By emphasizing low-glycemic index foods, whole grains, lean proteins, and healthy fats supports glycemic control and regular monitoring of blood glucose and HbA1c is vital to assess control and make timely adjustments [52].

Physical Activity

Regular exercise improves insulin sensitivity, reduces inflammation, and may directly alleviate neuropathic symptoms including aerobics enhance circulation and glycemic

control, resistance training improves muscle strength and metabolic function, exercise has also been shown to reduce pain perception and improve mood [53].

Weight Management

Obesity is associated with increased inflammation and worsened insulin resistance, contributing to neuropathy progression. Weight loss through diet and exercise can decrease pain intensity and improve nerve function. Even modest weight reduction (5–10% of body weight) can lead to meaningful health benefits.

Smoking Cessation

Quitting smoking improves peripheral circulation and reduces the risk of foot ulcers and amputations [2].

Alcohol Moderation or Cessation

Chronic alcohol use is a known risk factor for neuropathy. Limiting or avoiding alcohol is essential to minimize additional nerve damage.

Foot Care and Daily Inspection

Due to sensory loss, patients are at high risk for unnoticed injuries and ulcers. Daily foot checks, moisturizing, proper footwear, and regular podiatric evaluations are critical.

Stress Management and Sleep Hygiene

Following stress reduction techniques (e.g., mindfulness, yoga, deep breathing) may help with pain modulation and establishing good sleep hygiene can reduce pain perception and fatigue.

Patient Education and Support

Educating patients on the importance of lifestyle choices empowers them to take an active role in managing their condition. Support from diabetes educators, nutritionists, and support groups enhances adherence and outcomes.

Emerging Therapies and Research Directions in Diabetic Neuropathic Pain

Despite current treatments, diabetic neuropathic pain (DNP) remains inadequately managed in many patients. Traditional pharmacological agents primarily address symptom relief rather than disease modification. As a result, significant research efforts are being directed toward identifying novel, more effective, and disease-modifying therapies.

Novel Pharmacologic Agents- Sodium Channel Blockers (Nav1.7, Nav1.8 inhibitors):

Voltage-gated sodium channels play a key role in nerve excitability. Selective blockers such as vixotrigine are under study for their ability to reduce neuropathic pain with fewer systemic side effects (Figure 4) [17, 55]

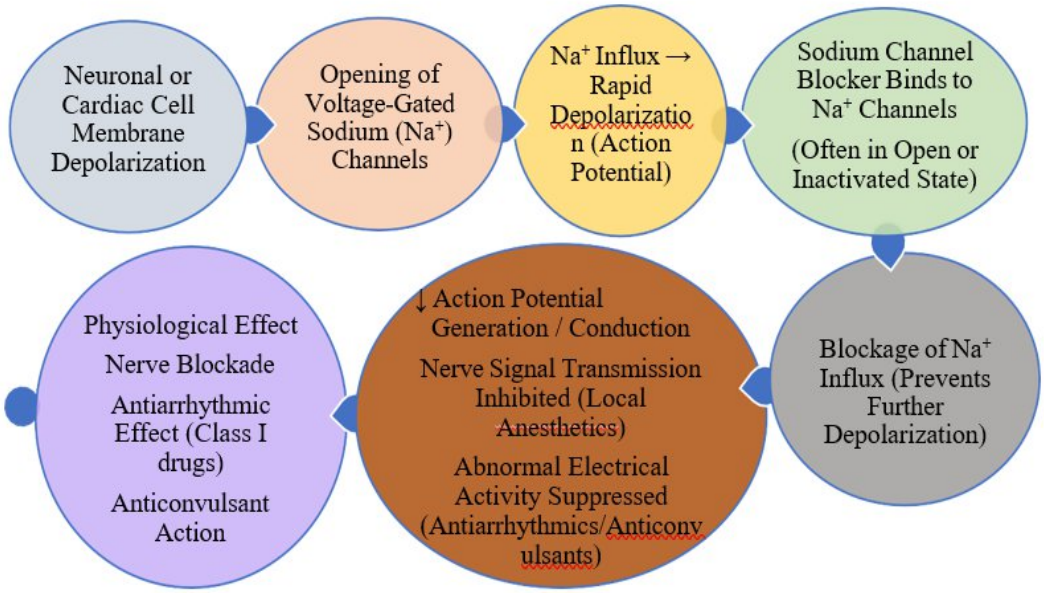

Figure 4: Mechanism of action of sodium channel blocker [56, 57]

Gene Therapy and Neurodegenerative Strategies

Gene therapy approaches aim to enhance expression of neurotrophic factors such as nerve growth factor (NGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) to promote nerve repair and regeneration [58].Stem cell therapy, uses mesenchymal stem cells (MSCs) for investigation for its ability to regenerate damaged peripheral nerves and improve microvascular function [59].Traditional therapies focus on symptom management, but recent advances aim at repairing and regenerating damaged nerve tissue through gene therapy and stem cell therapy [60].Gene therapy works by delivering specific genes into nerve cells or supporting tissues to promote axon regeneration, enhance neuronal survival, and improve vascular supply (Table 4) [61]. Methods of Delivery include viral vectors (e.g., AAV, lentivirus), non-viral vectors (liposomes, nanoparticles), local injections or implantable scaffolds [62].

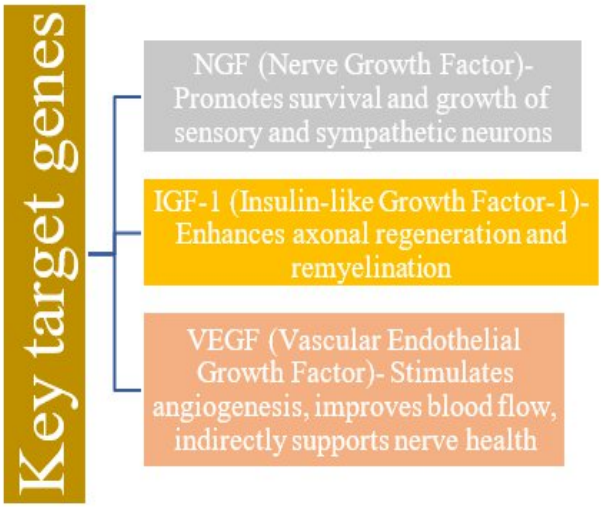

Figure 5: Key Target Genes

Stem Cell Therapy-Mesenchymal Stem Cells (MSCs) derived from bone marrow, adipose tissue, or umbilical cord, show promise in differentiating into neuron-like or glial cells, secreting neurotrophic and anti-inflammatory factors, promoting angiogenesis and extracellular matrix remodelling. Mechanism of MSCs include migration to injury site → release growth factors → reduce inflammation → support nerve remyelination → regenerate axons [63].

Combined approach of Gene + Cell Therapy include engineered stem cells overexpressing NGF, IGF-1, or VEGF can enhance neurodegeneration more effectively than either therapy alone(Figure 6) [64].

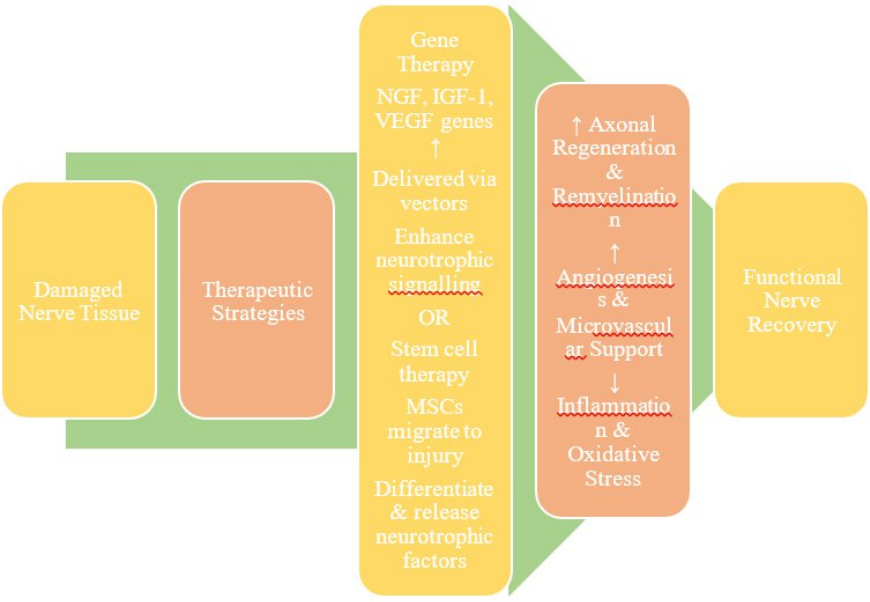

Figure 6: Neurodegenerative mechanism via Gene and Stem Cell Therapy

Antioxidants and Anti-inflammatory Agents

Oxidative stress and inflammation contribute to nerve injury in diabetes. Agents like alpha- lipoic acid, curcumin, and benfotiamine have shown antioxidant and anti-inflammatory effects (Table 2), and ongoing studies aim to clarify their efficacy as adjunct therapies [65].IL-1β and TNF-α inhibitors are being explored for targeting neuroinflammatory pathways in neuropathy.

Table 2: Antioxidants and Anti-inflammatory Agents in diabetic neuropathic pain

S. No.	Class	Mechanism of Action	Effects in Diabetic Neuropathic Pain
1	6-Hydroxyflavanone (6-HF)	Inhibits COX-2 and 5- LOX; modulates opioid and GABA-A receptors;	Reduces inflammation and neuropathic pain in animal models
		multi-target anti-inflammatory and anti-nociceptive	
2	Polyphenols (e.g., ginger)	Antioxidant, lowers blood glucose, reduces inflammation and oxidative stress	Decreased inflammation and oxidative stress in type II diabetes
3	Achillea extracts	Modulate inflammatory and oxidative pathways	Anti-diabetic neuropathic pain and anti-inflammatory effects
4	Tannins	Antioxidant, anti-inflammatory, antihyperalgesic; reduce IL-6, TNF-Î±, NO, MMP-9	Improve hyperalgesia/allodynia, reduce oxidative stress markers
5	Catechin, EGCG	Antioxidant, reduces MDA, increases GSH, SOD, catalase; reduces inflammatory markers	Neuroprotection, reduced nociceptive response in animal models
6	Naringin	Preserves antioxidants, reduces oxidative-nitrosative stress, apoptosis	Neuroprotection, reverses neuropathic pain (with or without insulin)
7	Resveratrol, Curcumin	Antioxidant, anti-inflammatory, modulate cytokines and glycation	Pain reduction, improved nerve function (alone or with insulin)
8	N-Acetylcysteine (NAC)	Antioxidant precursor, restores phospholipids, prevents cytochrome c release and caspase activation	Mitigates lipid peroxidation, prevents neuronal apoptosis

9	Quercetin	Inhibits TNF-Î±, IL-1Î², reduces inflammation, antioxidant	Reduces inflammation and neuropathic pain
10	Sulforaphane	Suppresses NF-ÎºB, reduces pro-inflammatory cytokines, enhancesNrf2 antioxidant response	Reduces oxidative and nitrosative stress, neuroinflammation

Neuromodulation Techniques

Spinal cord stimulation (SCS) and dorsal root ganglion stimulation are invasive but increasingly used methods for treatment-resistant neuropathic pain.These methods modulate pain signals and have shown sustained relief in some patients with refractory DNP [66].Non- invasive methods, such as transcranial magnetic stimulation (TMS) and transcutaneous electrical nerve stimulation (TENS), are also being evaluated for their effectiveness in modulating central pain pathways.

Microbiome and Gut-Brain Axis

Emerging evidence suggests that gut microbiota may influence pain perception and inflammation. Modifying the gut microbiome through diet, probiotics (Table 3), or fecal transplants is a novel area of research in managing neuropathy and other complications of diabetes [67].

Table 3: Role of Probiotics in Diabetic Neuropathic Pain

S. No.	Mechanism	Potential Benefit in DNP
1	Modulation of gut microbiota	Reduced systemic inflammation
2	Decreased oxidative stress	Neuroprotection, less nerve damage
3	Lowered pro-inflammatory cytokines	Reduced pain signaling
4	Improved metabolic control	Lower risk/severity of neuropathy

Personalized Medicine and Biomarkers

Identification of genetic, proteomic, and metabolomic biomarkers (Table 4) may allow for tailored treatment strategies based on individual risk profiles and response predictors. Pharmacogenomics could help identify patients who would respond better to certain medications with fewer side effects [68].

Table 4: Biomarkers in DNP [69]

S. No.	Biomarker Type	Example(s)	Role/Significance in DNP

1	Oxidative Stress Markers	Malondialdehyde (MDA)	Elevated in DNP, indicates lipid peroxidation and cellular damage due to oxidative stress
		Nitric oxide (NO)	Increased levels reflect nitrosative stress, contributing to neuronal injury.
		8-hydroxy-2'-deoxyguanosine (8-OHdG)	Marker of oxidative DNA damage, elevated in DNP
2	Antioxidant Enzymes	Superoxide dismutase (SOD)	Decreased levels indicate impaired antioxidant defence in DNP
		Glutathione (GSH)	Lowered in DNP, reflects reduced cellular protection against oxidative damage.
		Catalase	Decreased activity in DNP, indicating compromised antioxidant capacity
3	Pro-inflammatory Cytokines	TNF-α	Elevated in DNP, promotes neuroinflammation and pain signaling
		IL-1Î², IL-6	Increased levels are linked to nerve inflammation and pain hypersensitivity
4	Matrix Metalloproteinases	MMP-9	Elevated in DNP, associated with tissue remodeling and inflammation.
5	AGEs (Advanced Glycation End Products)	HbA1c, AGEs	Accumulate in DNP, contributing to nerve damage and dysfunction.

6	Neuroinflammation Markers	NF-κB, NLRP3	Activation reflects ongoing neuroinflammation and immune cell recruitment in nerves.
7.	Glial Activation Markers	Microglia, astrocyte markers	Increased glial activation is implicated in the maintenance of neuropathic pain.

Recent innovative therapeutic approaches for DNPincludes recent developments in the treatment of neuropathic pain and neurodegenerative diseases (Table 5) [69].

Table 5: Emerging Strategies categories with respect to the agents that cause them

S. No.	Category	Examples/Agents
1.	Novel Drugs	Nav1.7 inhibitors, TRPV1 antagonists, AT2R blockers
2.	Regenerative Therapies	NGF gene therapy, MSCs
3.	Antioxidants	Alpha-lipoic acid, benfotiamine, curcumin
4.	Neuromodulation	Spinal cord stimulation, TMS, TENS
5.	Microbiome Interventions	Probiotics, dietary modulation
6.	Personalized Medicine	Genomic biomarkers, individualized therapies

2. CONCLUSION

Diabetic neuropathic pain is a common and debilitating complication of diabetes mellitus that significantly impairs patients' quality of life. Its complex pathophysiology involves metabolic, vascular, and inflammatory mechanisms leading to nerve damage and altered pain processing. Despite advances in understanding the condition, effective management remains

challenging. Current treatment strategies emphasize strict glycemic control, pharmacologic interventions with antidepressants and anticonvulsants, lifestyle modifications, and comprehensive patient education. However, many patients continue to experience persistent pain, underscoring the need for novel therapeutic approaches.

Emerging research focusing on targeted molecular therapies, neuroregenerative techniques, and neuromodulation holds promise for improved outcomes. A multidisciplinary approach combining pharmacologic, non-pharmacologic, and lifestyle measures is essential for optimal care. Continued investigation into the underlying mechanisms, early diagnosis, and personalized treatment plans will be critical to reduce the burden of diabetic neuropathic pain and improve patient well-being

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P. Mahesh Kumar. Literature collection and analysis were carried out by the Ankita Raikwar. Manuscript writing and editing were completed by all Ankita Raikwar, P. Mahesh Kumar and Subhranshu Panda. Final approval was given by P. Mahesh

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