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Novel Combination for Diabetic Neuropathy

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Diabetic Neuropathy, Diagnostic, Nerve Injury, Metabolic Risk, Treatment, Diabetes Mellitus, Dorsal Root Ganglia, Nervous System, Diabetic Amyotrophy, Chronic Course.

Abstract:
Diabetic neuropathy is common, under or misdiagnosed, and causes substantial morbidity with increased mortality. Defining and developing sensitive diagnostic tests for diabetic neuropathy is not only key to implementing earlier interventions but also to ensure that the most appropriate endpoints are employed in clinical intervention trials. This is critical as many potentially effective therapies may never progress to the clinic, not due to a lack of therapeutic effect, but because the endpoints were not sufficiently sensitive or robust to identify benefit. The global epidemic of prediabetes and diabetes has led to a corresponding epidemic of complications of these disorders. The most prevalent complication is neuropathy, of which distal symmetric polyneuropathy (for the purpose of this Primer, referred to as diabetic neuropathy) is very common. Diabetic neuropathy is a loss of sensory function beginning distally in the lower extremities that is also characterized by pain and substantial morbidity. Over time, at least 50% of individuals with diabetes develop diabetic neuropathy. Glucose control effectively halts the progression of diabetic neuropathy in patients with type 1 diabetes mellitus, but the effects are more modest in those with type 2 diabetes mellitus. Novel In This Paper We Will Discuss Combination for Diabetic Neuropathy.

Introduction:

Neuropathy is nerve injury that starts with the longest nerves that innervate the toes and progresses proximally. Common symptoms are numbness, tingling, pain and/or weakness starting in the distal lower extremities. Diabetes is well established as the most important metabolic risk factor for neuropathy, but treatment of hyperglycemia is not enough to prevent neuropathy in those with type 2 diabetes. The prevalence of neuropathy is 8–45% in those with type 2 diabetes, with about a quarter of patients experiencing pain. Disease-modifying treatments for diabetic neuropathy remain elusive, but

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recent evidence has identified new metabolic risk factors, mechanisms and potential disease-modifying therapies. [1]

Diabetic peripheral neuropathy (DPN) is a symmetrical, length-dependent sensorimotor poly-neuropathy related to metabolic and microfossil alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. Despite the advances in knowledge of the pathos-genesis of neuropathy, there are still few causal therapeutic options. [2] Alpha-lipoic acid (ALA) is suggested as a pathogenesis-oriented treatment option, targeting underlying causes of neu-real lesions. The efficacy of ALA in patients with diabetes mellitus (DM) is attributed to its anti-inflammatory, anti-hyperglycemic, and antioxidant properties, as well as its role in endothelial function, insulin sensitivity, and lipid metabolism parameters. [3]

Diabetic neuropathy is one of the most prevalent chronic complications in adults with type 1 or type 2 diabetes while also affecting individuals with prediabetes and young people with diabetes, with an estimated lifetime prevalence exceeding 50%. Although the term “diabetic neuropathy” encompasses a broad spectrum of different neuropathic conditions, diabetic peripheral neuropathy (DPN) is the most common and most studied among them and has the strongest available evidence regarding therapeutic approaches. [4]

The early diagnosis and staging of the severity of diabetic neuropathy using patient questionnaires, determining thermal and mechanical sensitivities, and examining nerve conduction velocities require standardization. Whilst recent studies have established good diagnostic utility and reproducibility for sensory nerve evaluation in the skin and cornea, there has been limited application of these techniques in the clinic. For patients with painful diabetic neuropathy, underdiagnosis and adequate control of symptoms remain challenging. [5]

The investigated whether in vivo corneal confocal microscopy could detect improvement of corneal nerve parameters following improved glycemic control in patients with type 2 diabetes. 32 patients with DPN and 12 age-matched control subjects underwent nerve conduction studies and assessment of corneal nerve morphometry at baseline and after approximately one year. [6] At follow-up, 1/2 of the diabetic subjects had improved HbA1c whilst the other 1/2 continued to have elevated HbA1c. In the subjects with improved glycemic control, corneal nerve fiber density and corneal nerve fiber length increased significantly compared to baseline, whilst those with poor HbA1c showed a significant reduction in sural sensory nerve conduction velocity, corneal nerve fiber density, and corneal nerve fiber length. The authors concluded that corneal nerve fiber repair can be detected when glycemic control improves and that in vivo corneal confocal microscopy could be a sensitive method to assess nerve repair in future longitudinal or interventional studies of DPN. [7]

Review of Literature:

Diabetes mellitus is a metabolic and multifactorial disorder which is characterized by chronically hyperglycemia and develops due to alteration in secretion and/or function of insulin. The different organs of the body such as kidneys, eyes, nerve, blood vessels and heart are affected by chronic hyperglycemic condition of diabetes (Kodikonda M&Naik PR, 2017). Diabetic neuropathy is a common complication of both type 1 and type 2 diabetes, which affects more than 90% of the diabetic patients. [8]

In the clinical practices various synthetic drugs such as antioxidants, selective serotonin reuptake inhibitors, antidepressants, anti-arrhythmics, polyphenols, anticonvulsants and opioids are being used alone and or in combination to treat neuropathic patients (Courteix C et al, 1994). [9]

Thour A & Marwaha R 2023 reported the sever side effect of amitriptyline such as neurological, cardiac, and anticholinergic adverse reactions in patients. Therefore, there is a need to decrease its dose by opting synergism concept and/or use of herbal therapy. Many researchers have suggested the benefits of co-administration drug treatment over the drug alone. Combination treatment at lower doses than either drug alone results in greater therapeutic effects, lessen the side effects and increases the compliance (Kalra, S et al, 2010). [10]

Antidepressant drugs are widely recommended for treating neuropathic pain at lower doses than the doses used for treating depression. Amitriptyline is one of tricyclic antidepressant commonly used to treat patients suffered from neuropathic pain. amitriptyline relives the neuropathic pain through the inhibition of serotonin and noradrenaline reuptake, however it’s exact mechanism of action is yet unknown (Onghena P & Houdenhove B 1992; Moore AR et al 2015). [11]

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Galer BS (2000) DPN may present with a wide range of clinical symptoms and signs. Some people may be entirely asymptomatic, where a foot ulcer can be the first presentation. However, other patients may experience one or a number of different symptoms such as paresthesia (tingling/pins and needles), numbness and neuropathic pain (often described as burning, lancinating, shooting, or aching) which can range from mildly troublesome to intractable, causing great suffering. These symptoms may be sporadic or constant, and their natural history varies among patients. Sensory symptoms may be present for only a short period of time before they disappear entirely, or they may become chronic. Sensory symptoms and clinical examination signs begin in the toes/distal foot symmetrically. On physical examination, light touch and pin-prick of the distal foot is commonly impaired first, followed by more advanced sensory (i.e., vibration and proprioception loss) and motor (i.e., weakness, clawing of the toes, ankle reflex loss, and loss of muscle bulk) abnormalities. [12]

Tesfaye S (2010) Routine biochemical assay should be performed to determine the quality of glycemic and cardiovascular risk factor control and rule out other causes of peripheral neuropathy (e.g., coeliac disease, vitamin B12 deficiency, hypothyroidism, infectious/inflammatory disease). When the clinical features are atypical or the diagnosis is unclear then patients should be referred for specialist assessment. Nerve conduction studies remain the gold standard measure of large fiber function, but QST and skin biopsy may be used for diagnosing small fiber neuropathy. [13]

Pop-Busui R (2017) The diagnosis of DPN is often made during diabetic foot screening. Type 2 diabetes is often diagnosed after it has been present for some time; therefore, patients with type 2 diabetes should be screened for DPN from diagnosis. However, the risk of DPN is low at diagnosis of type 1 diabetes, so foot screening should commence 5 years after diagnosis. Subsequently, all patients should be assessed on an annual basis for lower limb sensory and vascular deficits. Once there is a clinical suspicion of DPN, a thorough clinical assessment must exclude other causes of neuropathy, and should involve a comprehensive history and examination including: temperature/pinprick sensation testing to assess small-fiber function; vibration sensation testing with 128-Hz tuning fork and assessment of ankle reflexes to assess large fiber function; and 10-g monofilament for the assessment of protective sensation. [14]

Neuropathic pain is defined by International Association for the Study of Pain (IASP) as “pain caused by a lesion or disease of the somatosensory nervous system”. Diabetes mellitus (DM) is a complex metabolic disorder which is characterized by high blood glucose levels, due to inadequate insulin secretion by the pancreas or inability of target cells to reuptake glucose from the blood (M. N. Piero, 2015). [15]

Diabetic neuropathy can be classified into two broad categories: diffuse and focal neuropathies. Diffuse neuropathies branch into diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy (DAN). Peripheral neuropathies usually affect the nerves present in the extremities. Both small and large nerve fibers are affected by DPN. Damage to large nerve fibers interferes with the body movement and body position whereas demyelination of smaller nerve fibers in the peripheral region causes dysesthesias and paresthesia linked with neuropathic pain (G. Said, 2007). [16]

These agents may also contribute to preventing DPN complications, since co-existing peripheral vascular disease can contribute to long-term diabetic complications such as foot ulcerations. Although DPN is not an outcome in studies addressing these comorbid conditions, they may be described as important comorbidities in studies of glucose control that report on diabetic neuropathy outcomes. We will not include statins and antihypertensives in this review, because they are prescribed for other indications (hypercholesterolemia, hypertension and/or periperhal vascular disease) and not for the treatment of diabetic peripheral neuropathty. (Wu S, 2012). [17]

Wang X (2020) There is an unmet need for alternative treatment options for patients with DPN. Considering the bothersome and dangerous adverse effects that occur with existing treatment options for DPN patients, the identification, development, and incorporation of novel non-pharmacological treatment options that include nanotechnology formulated delivery systems will add important safe and effective options for patients and clinicians. Reductions in addiction, abuse, GI and other systemic side effects, toxicity issues, cardiovascular and renal implications may be able to be lessened through the use of these non-pharmacological approaches. [18]

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DPN is a neurodegenerative disorder, character-sized by morphological changes and lesions mainly to the peripheral nerves. The major pathomecha-nisms include demyelination and thickening of the axon, contraction, and diminishment of Schwann cell as well as distortion of Ranvier nodes. An overall decrease in unmyelinated fibers which innervate organs of the abdominal cavity is usual-ly present, however negative changes in peripheral nerves are observed more frequently. The patho-genesis of this disease has a complex mechanism. Nevertheless, two potential mechanisms of DPN are proposed: metabolic and ischemic. Hypergly-cemia is considered a major factor causing disor-ders of the nervous system in DM (Vinik AI, 1999). [19]

Vinik A.I. et al (2013) Peripheral neuropathy is the most common complication of both type 1 (T1DM) and type 2 diabetes (T2DM), with more than one half of all patients developing nerve dysfunction in their lifetime. Both chronic and acute diabetic neuropathies are seen, but distal length-dependent symmetrical polyneuropathy is the most common and generally referred to as diabetic peripheral neuropathy (DPN). DPN is the primary cause of diabetic foot disease, including ulceration and nontraumatic amputations. [20]

A major unmet need for patients with DPN is the ability to predict whether a particular drug is likely to be efficacious. A more “personalized” and mechanistically based approach to identify the pain generator or modulatory site(s) would enable greater selectivity and targeting of drug therapy, which would limit side effects and improve overall efficacy. Neuropathic pain drugs work in specific locations, as defined by the receptors that they target. For instance, gabapentin and pregabalin exert their analgesic effect through high-affinity binding and modulation of the calcium channel α2-δ proteins in the dorsal root ganglion. (Taylor C.P, 2009) [21]

Based on the definition of neuropathic pain by IASP (International Association for the Study of Pain), painful diabetic neuropathy may be defined as pain arising as a direct consequence of abnormalities in the somato-sensory system in people with diabetes. The epidemiology of painful diabetic neuropathy has not been studied and also diabetic neuropathy. It is estimated that around half of patients with chronic diabetic neuropathy experience pain and the majority have features of chronic sensorimotor peripheral neuropathy. A community-based population study in the UK reported that around one-third of all diabetic patients have pain. It is also reported that 12% of patients with painful symptoms have never volunteered this to their doctors and ~40% never receive treatment. The prevalence of painful neuropathy in Type 2 diabetes is more than twice that seen in Type 1 diabetes. (Abbott CA, 2011) [22]

Ziegler D (2008) Pain in combination with physical disability because of other long-standing complications of diabetes substantially impairs the quality of life. Patients with neuropathic pain have markedly lower scores on quality-of-life domains, including enjoyment of life, sleep, physical mobility, self-care, and energy levels. It is not surprising that the majority of patients reporting neuropathic pain suffer from anxiety and depression. The natural history of painful diabetic neuropathy varies from unpredictable fluctuations in pain severity to complete resolution. Pain can develop at any stage of diabetes. Up to one in four patients suffer from pain with no signs of neuropathy. [23]

Diabetic neuropathy is the most common long-term complication of the condition and a leading cause of neuropathy in the developed world. Both duration of diabetes and degree of glycaemic control are important predictive factors for the development of neuropathy. (Tesfaye S, 2005) [24]

Young MJ (1993) The prevalence of diabetic neuropathy varies considerably among clinical studies because of differences in the study population, design, and diagnostic criteria. Prevalence increases predictably with the duration of diabetes from 10% at diagnosis to as much as 53% after 25 yr of diabetes. There is also a proportional increase with age. It is estimated that around half of the patients with chronic diabetic neuropathy experience pain and the majority of them have features of chronic sensorimotor peripheral neuropathy. [25]

In 2016, Morel et al. studied the efficacy of memantine in the prevention of post-mastectomy pain in 40 patients. Patients in the intervention arm (n =20) of this pilot study received memantine 5-20 mg daily for 2 weeks prior to mastectomy surgery for a total of 4 weeks. The intensity of pain was evaluated on a numerical rating scale (0–10) 3 months after mastectomy surgery. Based on the results, memantine significantly decreased the severity of post-mastectomy pain (5% vs 30% in the placebo group) and decreased analgesic requirements in patients. The mentioned study supports our idea regarding the

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beneficial effect of memantine in neuropathic pains; however, in our study, memantine demonstrated a beneficial effect in a prolonged period of treatment (8 weeks) compared to the mentioned study (4 weeks). Moreover, our study is focused on the treatment of neuropathic pains rather than prevention. [26]

Pop-Busui R (2017) Patients with PDPN present with neuropathic pain that has distinct presentations as burning, sharp, aching, electric shock like, and evoked pains. The pain can be mild or intractable; sporadic or constant; transient (disappear completely after some time) or chronic. Regardless of the presence of pain, these patients may also develop numbness, tingling, and pins and needle sensations. The DPN symptoms begin with asymmetrical involvement of distal lower limbs, and progress to involve proximal lower limbs, before finally involving the upper limbs. Physical signs in early DPN include impairment of light touch, pinprick, and temperature sensation. The signs in advanced DPN include loss of vibration, proprioception, 10-g monofilament sensation, ankle reflexes, and motor involvement (muscle weakness, muscle wasting, and clawed toes) [27]

Objectives:

- Diabetic peripheral neuropathy (DPN) is a common chronic complication of diabetes mellitus.
- Diabetic neuropathies are heterogenous in their clinical presentation, risk factors and pathophysiology.
- Monofilament evaluation is a good tool to assess the loss of protective sensation related to diabetic neuropathy.
- In present situation sufficient drugs are available for the treatment of diabetes but risk and rate of mortality of a patient suffering from diabetes is very high.

Research Methodology:

The overall design of this study was exploratory. we reviewed the pathogenesis, clinical manifestations diagnosis and treatment of diabetic neuropathies. [28] New diagnostic techniques may aid the clinical assessment in detecting clinical and subclinical DPN, but further research is required to determine whether clinical outcomes such as foot ulceration, amputation and cardiovascular disease can be prevented with their routine use and whether they may be used as surrogate end points for DPN. further validation is required before any of these factors can be considered for stratification in clinical practice but there is potential that it may improve patient outcomes in painful-DPN. [29]

Result and Discussion:

Diabetic neuropathy is a unique neurodegenerative disorder of the peripheral nervous system that preferentially targets sensory axons, autonomic axons and later, to a lesser extent, motor axons. [30] How diabetes mellitus targets sensory neurons remains debated. Progressive diabetic neuropathy involves retraction and 'dying back' of terminal sensory axons in the periphery, with relative preservation of the perikarya (cell bodies).

Its 'stocking and glove' pattern of involvement reflects damage to the longest sensory axons first with, for example, loss of distal leg epidermal axons preceding loss in more proximal limbs; for this reason, diabetic neuropathy is considered a length-dependent neuropathy. [31]

Substantial experimental evidence supports the notion that the entire neuron, from the perikaryon to the terminal, is targeted by diabetes. However, whether damage first targets peripheral axons and their associated Schwann cells or the neuron perikarya that reside in the dorsal root ganglia (DRG) and act to support the axons are debated (Fig. 1). [32]

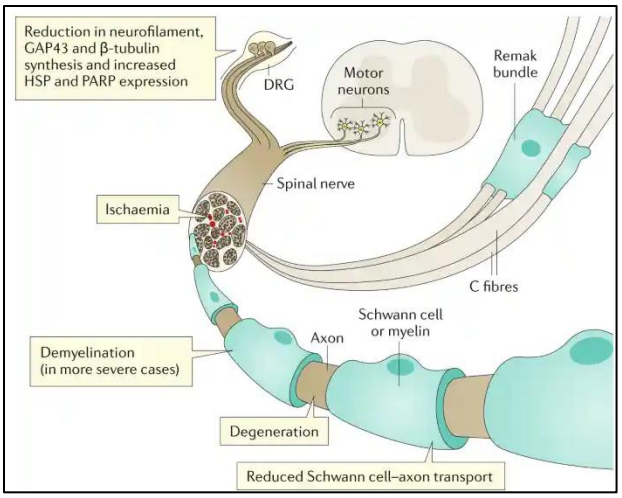

Figure 1: The peripheral nervous system and alterations in diabetic neuropathy. [33]

Sensory neurons relay sensory information from their nerve terminals (which are located throughout the

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periphery) to the dorsal horn of the spinal cord. The cell bodies of these sensory neurons are located in the dorsal root ganglia (DRG). Conversely, the cell bodies of motor neurons reside in the spinal cord ventral horn and transmit information from here to the periphery. [34] Thin and unmyelinated sensory axons (C fibres or small fibres) are grouped together by non-myelinating Schwann cells into Remak bundles and represent a large portion of neurons of the peripheral nervous system. By comparison, other sensory axons are myelinated by associated Schwann cells, which have an important role in preserving axonal function. The precise order of cellular injury (whether, for example, damage to Schwann cells or axons occurs before damage to neuronal cell bodies) in diabetes is currently unknown. These changes include alterations in Schwann cell–axon transport, alterations in protein expression in the DRG, demyelination and degeneration. [35]

Table 1: Conventional drugs for the treatment of painful diabetic neuropathy. [36]

Drug Name	Class	Dose and route
First Line agents		
Pregabalin	αδ2 calcium ligand	150–300 mg/day, PO
Duloxetine	Norepinephrine and Serotonin reuptake Inhibitor	60–120 mg/day, PO
Amitriptyline	Tricyclic antidepressant	10–25 mg/day, PO
Nortriptyline	Tricyclic antidepressant	25–50 mg/day, PO
*No response to first choice agents over a period of 12 weeks; Shift to second line agents or add to first line agents		
Second Line agents		
Tramadol	μ-opiod receptor agonist	37.5–75 mg/day, PO
Gabapentin	αδ2 calcium ligand	1200–3600 mg/day, PO
Pregabalin+ Nortriptyline (FDC)	Gabapentinoid + Tricyclic Antidepressant	75 mg + 10 mg
Third line agents		
Topiramate	Potentiates GABA action	200–400 mg/day
Venlafaxine	Norepinephrine and Serotonin reuptake Inhibitor	75–225 mg/day
Carbamazepine	Reduces Na channel conductance	200–600 mg/day, PO
Topical agents (Non-response/add on to oral drugs)		
Capsaicin Cream and Patch (8%)	Depletes substance P at nerve endings	Topical 2–3 times/day
Lidocaine Patch (5%)	Blocks sensory afferent nerve fibre	Topical 2–3 times/day

FDC: Fixed dose combination.

Table 2 Novel therapeutic agents for symptomatic pain relief in diabetic peripheral neuropathy. [37]

S. No.	Drug	Drug class/Mechanism Of Action	Doses	Side effects	Usage
A	**Completed phase 3 studies**				
1.	Tapentadol ER	μ-opioid receptor agonist and norepinephrine reuptake inhibitor (MOR-NRI)	50–100 mg 4-6 times/day PO	Nausea, headache, dizziness, somnolence	Approved, In clinical use, Limited clinical efficacy
2.	Desvenlafaxine	Serotonin-norepinephrine reuptake inhibitor (SNRI)	200 & 400 mg/day PO	Nausea, dry mouth, hyperhidrosis, insomnia.	Not approved, Limited clinical efficacy
3.	Nabilone	Synthetic cannabinoid (CB1 predominant) receptor agonist	1–4 mg/day PO	Drowsiness, dizziness, euphoria, dry mouth, agitation and paranoid ideation	Not approved
5.	Nabiximol	Synthetic cannabinoid receptor agonist	4-10 sprays	Drowsiness, dizziness, euphoria, dry mouth, agitation and paranoid ideation	Not Approved
4.	Dronabinol	Synthetic cannabinoid receptor agonist	2.5–10 mg (daily dose) PO	Drowsiness, dizziness, euphoria, dry mouth, agitation and paranoid ideation	Not Approved
6.	Palmitoylethanolamide (PEA)	*N*-acylethanolamine Family	300 or 600 mg daily PO	Drowsiness, dizziness, euphoria, dry mouth, agitation and paranoid ideation	Not approved
7.	Alpha Lipoic acid	Selectively inhibit neuronal T-type calcium channels	600 mg/day, oral or IV	None	In clinical use. Limited clinical efficacy
8a.	Benfotiamine	Anti-oxidant	600 mg/day, PO	Allergic reaction, Gastrointestinal discomfort	In clinical use, Limited efficacy
8b.	Alpha Lipoic acid + Benfotiamine	–	100 mg + 100 mg, PO	–	In clinical use, Limited efficacy
9.	Calcitonin	Sodium channel modulation	75–300 IU/day, Nasal spray or subcutaneous	–	Not Approved Limited efficacy
B	**Phase 1 and 2 Human Trials**				
10.	Pooled human Immunoglobulin	Immunomodulatory agent	IV	Allergic reaction	–
11.	EMA401	Angiotensin Receptor 2 Antagonist	100 mg BD	Nausea, abdominal pain, cholecystitis, nasopharyngitis, headache	–
–12.	PF-05089771	Sodium Channel v1.7 subtype blocker	150 mg BD	Headache, pneumonia, upper respiratory tract infections	–
13.	Tanezumab	Humanized monoclonal IgG2 antibody	20 mg sc (day 1 and day 48)	Peripheral edema, paraesthesia	–
14.	Ruboxistaurin	Beta protein kinase inhibitor	32 mg/day	Nausea, vomiting, diarrhea	–
15.	KAI-1678	Epsilon protein Kinase inhibitor	25 mg, SC	Infusion site pain, headache	–
16.	VM202	Hepatocyte growth factor	8 or 16 mg, IM	–	–

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In addition to pharmacological agents, certain interventional therapies have been considered in select patients with refractory neuropathic pain, including spinal cord stimulation, electrical stimulation therapy through stocking electrodes, pulsed magnetic field therapy, trans-cutaneous nerve stimulation (TENS), acupuncture, laser therapy and monochromatic infra-red-light therapy (MIRE). [38] Experience with MIRE has seen mixed results with initial few studies showing improvement in pain intensity measured by 10 cm visual analogue scale (VAS), sensation assessed with 10 gm monofilament and balance.

A small study of nineteen patients with low level laser therapy irradiated through scanning mode with dosage of 3.1J/cm2 on the plantar and dorsum of the foot and 3.4j/ cm2 with contact method for 10 days showed a significant reduction in neuropathic pain using VAS scale and Michigan Neuropathy Screening Instrument (MNSI). [39]

Several fairly distinct clinical syndromes of diabetic neuropathy have been delineated. [40] The most common, as noted, is a distal, symmetrical, primarily sensory polyneuropathy affecting feet and legs in a chronic, slowly progressive manner. The others are as follows: acute ophthalmoplegia that affects the third, and less often the sixth, cranial nerve on one side; acute mononeuropathy of limbs or trunk including a painful thoracolumbar radiculopathy; an acute or subacute painful, asymmetrical, predominantly motor multiple neuropathy affecting the upper lumbar roots and the proximal leg muscles (‘diabetic amyotrophy'); [41] a more symmetrical, proximal motor weakness and wasting, usually without pain and with variable sensory loss, pursuing a subacute or chronic course, and an autonomic neuropathy involving bowel, bladder, sweating and circulatory reflexes. These forms of neuropathy often coexist or overlap, particularly the autonomic and distal symmetrical types and the subacute proximal neuropathies (tables 3 and 4). [42]

Table 3 Signs, diagnosis and treatment of diabetic autonomic neuropathies: [43]

	Cardiac	Gastrointestinal	Sexual dysfunction	Bladder dysfunction	Sudomotor (sweating) dysfunction	Pupillomotor
Symptoms	Exercise intolerance, early fatigue and weakness with exercise Postural hypotension, dizziness, light-headedness, weakness, fatigue, syncope	Gastroparesis, erratic glucose control Abdominal pain or discomfort, early satiety, nausea, vomiting, belching, bloating Constipation Diarrhoea, often nocturnal alternating with constipation and incontinence	ED Vaginal dryness	Frequency, urgency, nocturia, urinary retention, incontinence	Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Visual blurring, impaired adaptation to ambient light, impaired visceral sensation
Tests	HRV, multigated angiography (MUGA) thallium scan, 123I-metaiodobenzylguanidine (MIBG) scan, measure blood pressure standing and supine, measure catecholamines	Gastric emptying study, barium study Endoscopy, manometry, electrogastrogram	History and physical examination, HRV, penile-brachial pressure index, nocturnal penile tumescence	Cystometrogram, post-void sonography	Quantitative sudomotor axon reflex, sweat test, skin blood flow	Pupillometry, HRV
Treatments	Graded supervised exercise, ACE inhibitors, β-blockers Mechanical measures, clonidine, midodrine, octreotide	Frequent small meals, prokinetic agents (metoclopramide, domperidone, erythromycin) Antibiotics, antiemetics (Phenergan, Compazine, Tigan, scopolamine), bulking agents, tricyclic antidepressants, pancreatic extracts, pyloric Botox, gastric pacing, enteral feeding	Sex therapy, psychological counseling, sildenafil, vardenafil, tadalafil, prostaglandin E1 injection, device or prosthesis Vaginal lubricants	Bethanechol, intermittent catheterization	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators	Care with driving at night, recognition of unusual presentations of myocardial infarction

HRV = Heart rate variability; ACE = angiotensin-converting enzyme.

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Table 4: The main features of different patterns of disabling neuropathies in patients with diabetes [44]

Pain	Distal symmetrical sensory loss	Weakness	Sensory ataxia	Autonomic dysfunction	Progression	CSF Protein	Electro-physiological test	Nerve biopsy
Length-dependent polyneuropathy								
Frequent in distal limbs	Length dependent – predominates on pain and temperature sensations	Minor, distal symmetrical	Rare	Common	Years	Variable	Axonal pattern, distal symmetrical	Massive axonal loss
CIDP in diabetic patients								
Occasional	Variable – predominates on proprioception	Common, often severe proximal and distal	Common	Uncommon	Weeks or months	Increased	Mixed axonal and demyelinative	Variable axon loss and demyelination
Focal/multifocal diabetic neuropathy								
Present in most cases	Variable	Common – asymmetrical – nerve or root territory	Uncommon	Uncommon	Weeks or months	Increased	Axonal pattern, multifocal	Variable

CIDP = Chronic inflammatory demyelinating polyneuropathy; CSF = cerebrospinal fluid.

Diagnosis of DPN:

The diagnosis of DPN is often made during diabetic foot screening. Type 2 diabetes is often diagnosed after it has been present for some time; therefore, patients with type 2 diabetes should be screened for DPN from diagnosis. However, the risk of DPN is low at diagnosis of type 1 diabetes, so foot screening should commence 5 years after diagnosis. Subsequently, all patients should be assessed on an annual basis for lower limb sensory and vascular deficits. Once there is a clinical suspicion of DPN, a thorough clinical assessment must exclude other causes of neuropathy, and should involve a comprehensive history and examination including: temperature/pinprick sensation testing to assess small-fiber function; vibration sensation testing with 128-Hz tuning fork and assessment of ankle reflexes to assess large fiber function; and 10-g monofilament for the assessment of protective sensation. [45] Clinical scoring systems may also be used to aid in diagnosing DPN e.g., Toronto Clinical Scoring System.

Routine biochemical assay should be performed to determine the quality of glycemic and cardiovascular risk factor control and rule out other causes of peripheral neuropathy (e.g., coeliac disease, vitamin B12 deficiency, hypothyroidism, infectious/inflammatory disease). When the clinical features are atypical or the diagnosis is unclear then patients should be referred for specialist assessment.

Nerve conduction studies remain the gold standard measure of large fiber function, but QST and skin biopsy may be used for diagnosing small fiber neuropathy. [46]

In this study, 500 patients were assessed for eligibility, of whom 143 were enrolled. Patients were assigned to memantine (n = 72) and the control groups (n = 71). Forty patients discontinued the study during the follow-up period. Therefore, 103 patients were analyzed (Figure 1). The baseline demographic and clinical characteristics of 103 patients are summarized in Table 1. The mean age of patients was 55.8 ± 7.4 and 54.67 ± 5.3 years in the memantine and control groups, respectively.

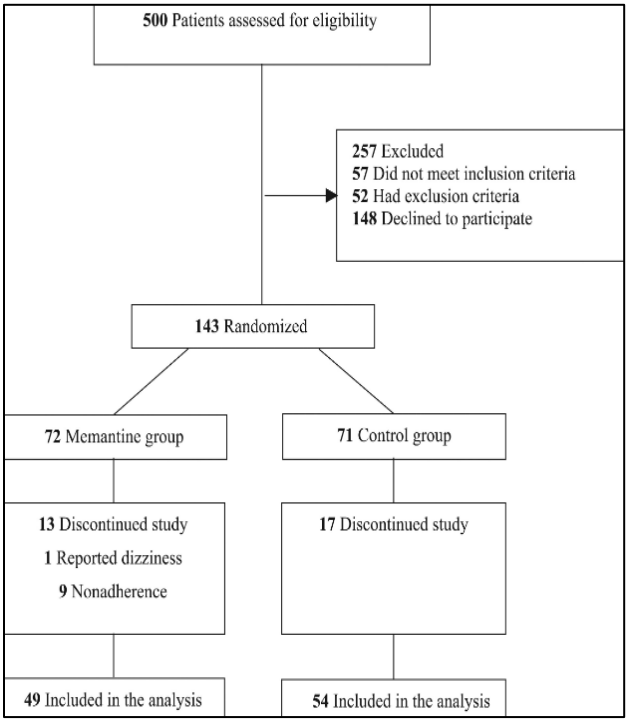

Figure 2: Consort diagram of the study.

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Table 5: Baseline demographic and clinical characteristics of patients in both groups.

Parameters	Memantine (*n* = 49)	Control (*n* = 54)	*p*-value
Gender (female %)	35 (71.4%)	29 (53.7%)	.064
Age (year)	55.8 ± 7.4	54.67 ± 5.3	.09
Comorbidities			
Renal disorders	13 (26.5%)	17 (31.5%)	.58
Hyperlipidemia	26 (53.1%)	40 (74.1%)	.03
BPH	2 (4.1%)	7 (13.1%)	.16
IHD	8 (16.1%)	20 (37%)	.02
Medications			
Metformin	36 (66.7%)	44 (81.4%)	.06
Insulin	18 (33.3%)	15 (27.7%)	.8
Antihypertensive agent	49 (100%)	54 (100%)	1
Statin	49 (100%)	54 (100%)	1
Aspirin	46 (93.8)	50 (92.5%)	1

Data were described as mean ± standard deviation (SD) or number (%). BPH: benign prostatic hyperplasia; IHD: ischemic heart disease. *p*-value ≤ .05 is significant.

With a few exceptions, the two study groups were well-balanced for baseline parameters (p-value > .05). There was a significant difference between the groups in terms of the DN4 questionnaire score at baseline (p-value = .03), presence of ischemic heart disease (IHD) (p-value = .02), and presence of hyperlipidemia (p-value = .03). In the final analysis, data were adjusted based on gender, hyperlipidemia, IHD, and DN4 questionnaire score at baseline.

Conclusion:

Diagnosis and treatment of DN are still elusive because of problems associated with the efficacy and safety of current therapies. If it is taken into account the difficulties of discovering new drugs by traditional methods and generating new drugs using computational methods, repurposing old drugs sounds like a good option. For this purpose, we have concentrated on the molecular pathways that contribute to DN progression, as well as the existing pharmacological and non-pharmacological treatments for DN patients. Finally, improved treatment of neuropathic pain will require increased utilization of guideline-recommended medications and decreased use of opioids. Novel MONRI, SNRI and cannabinoid receptor agonists have shown some promise for neuropathic pain relief in human trials, but await regulatory approvals.

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