REVIEW ARTICLE

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What Is New in Peripheral Neuropathy? Recent Advances in Diagnosis and Management

ABSTRACT

Peripheral neuropathy represents one of the most common neurological disorders encountered in clinical practice and includes a heterogeneous group of conditions affecting sensory, motor, and autonomic nerves. Traditional classification based primarily on etiology often provides limited guidance in the early diagnostic evaluation of patients presenting with neuropathic symptoms. Recent advances in neurophysiology, imaging, molecular diagnostics, and targeted therapeutics have significantly transformed the approach to peripheral neuropathy. A phenotype-based clinical framework emphasizing pattern recognition, fiber type involvement, and biomarker-guided investigations can facilitate more efficient identification of treatable neuropathies. Novel diagnostic modalities such as skin biopsy for quantification of intraepidermal nerve fiber density, corneal confocal microscopy for assessment of small fiber pathology, and next-generation sequencing for hereditary neuropathies have expanded the diagnostic armamentarium. At the same time, the therapeutic landscape has evolved substantially with the development of disease-modifying therapies for hereditary transthyretin amyloidosis, advances in immunotherapy for immune-mediated neuropathies, and emerging neuromodulation strategies for refractory neuropathic pain. Recognition of antibody-mediated nodo-paranodopathies and the development of RNA-based therapies illustrate the growing role of precision medicine in peripheral nerve disorders. This review provides a practical overview of contemporary advances in peripheral neuropathy with emphasis on clinical pattern recognition, modern diagnostic evaluation, and current as well as emerging therapeutic strategies relevant to day-to-day clinical practice.

Key words: Peripheral neuropathy; Small fiber neuropathy; Precision medicine

INTRODUCTION

Peripheral neuropathies are a diverse group of disorders resulting from damage to peripheral sensory, motor, or autonomic nerves. They are among the most common neurological conditions encountered in clinical practice and represent a frequent cause of neurological consultation. The global prevalence of peripheral neuropathy is estimated to be approximately 1% in the general adult population, rising with age to 6–10% among individuals older than 60 years.[1] Because of their chronic course and associated complications, peripheral neuropathies contribute substantially to disability, impaired mobility, and reduced quality of life.

Patients typically present with symptoms such as numbness, paresthesias, burning pain, distal weakness, and gait imbalance, reflecting involvement of different peripheral nerve fiber types. These symptoms often develop gradually and may initially be nonspecific, which can delay diagnosis and appropriate management. Early identification is nevertheless important because several neuropathies are potentially treatable, and timely therapy may prevent irreversible nerve damage and long-term neurological disability.

The etiological spectrum of peripheral neuropathy is remarkably broad. More than one hundred potential causes have been described, including metabolic, toxic, inflammatory, hereditary, infectious, and paraneoplastic disorders. Diabetes mellitus remains the most common cause worldwide and accounts for a large proportion of distal symmetric polyneuropathy cases.[1] Despite extensive investigations, however, a significant proportion of patients are ultimately classified as having idiopathic neuropathy, highlighting the diagnostic complexity of these conditions.

Traditionally, peripheral neuropathies have been classified according to their underlying etiology or pathological mechanism, such as axonal versus demyelinating neuropathies. Although useful for pathological categorization, this approach may be less practical during the initial clinical evaluation when the cause of neuropathy is still unknown. Increasingly, clinicians adopt phenotype-based approaches that incorporate clinical pattern recognition, fiber-type involvement, and disease tempo to guide diagnostic testing and narrow the differential diagnosis.[2,3]

Jharna Mahajan[1], Satish Khadilkar[2], Shamisha Khade[3], Ankur Bhoot[3]

[1]Associate Consultant, [2]Dean, Professor and Head of the Department, [3]Senior Resident
Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

Corresponding Author:
Jharna Mahajan, Associate consultant,
Department of Neurology,
Bombay Hospital and Medical Research Centre, Mumbai, Maharashtra, India.
E mail: bhanushali.jharna@gmail.com

In parallel, advances in neurophysiology, imaging, and molecular diagnostics, including skin biopsy for small-fiber neuropathy, magnetic resonance neurography, nerve ultrasonography, and genetic testing, have significantly improved the evaluation of peripheral nerve disorders. These developments, together with emerging disease-modifying therapies, are driving a shift toward precision neurology in peripheral neuropathy.[4,5]

In this review, we propose a clinically oriented 4-Axis Precision Neuropathy Model that integrates modern diagnostic tools with targeted therapeutic strategies to guide the evaluation and management of peripheral neuropathies.

Concept of the 4-Axis Precision Neuropathy Model

Given the marked heterogeneity of peripheral neuropathies and the rapid expansion of diagnostic technologies and targeted therapies, a structured clinical framework can facilitate a more systematic evaluation. We propose a 4-Axis Precision Neuropathy Model, which organizes the assessment of neuropathy into four clinically relevant dimensions: nerve fiber type involvement, pattern of nerve injury, etiologic biomarkers, and precision therapy.

1. The first axis identifies whether large or small nerve fibers are predominantly affected using tools such as nerve conduction studies, skin biopsy, and corneal confocal microscopy.
2. The second axis evaluates the pattern of neuropathic involvement, including length-dependent or non–length-dependent processes, through clinical examination and supportive investigations such as quantitative sensory testing.
3. The third axis focuses on detecting treatable etiologies through biomarker identification, including autoantibody and genetic testing.
4. Finally, the fourth axis links diagnosis to precision therapy, highlighting disease-specific treatments that may modify disease progression.

This model integrates clinical phenotype, modern diagnostics, and targeted management into a practical framework for the evaluation of peripheral neuropathies (Table 1) and figure 1

Axis	Clinical Question	Key Diagnostic Tools	Clinical Relevance
Axis 1 – Fiber Type	Which nerve fibers are affected?	NCS, skin biopsy, corneal confocal microscopy	Distinguishes large-fiber vs small-fiber neuropathy
Axis 2 – Pattern of Injury	What is the pattern of nerve injury?	Clinical examination, quantitative sensory testing (QST), newer evaluation tools	Identifies length-dependent neuropathy vs ganglionopathy
Axis 3 – Etiologic Biomarkers	Is there a treatable cause?	Autoantibody testing, genetic testing	Detects immune-mediated or genetic neuropathies
Axis 4 – Precision Therapy	What targeted treatment exists?	Disease-specific therapies	Enables precision-based management

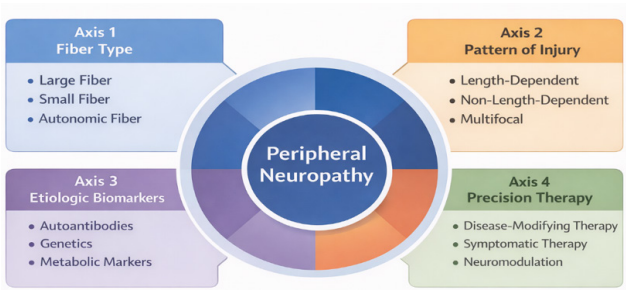

Fig. 1: 4-Axis Precision Neuropathy Model

AXIS 1 – FIBER TYPE: DETERMINING WHICH NERVE FIBERS ARE AFFECTED

A key step in evaluating peripheral neuropathy is identifying which nerve fiber populations are predominantly involved. Peripheral nerves contain large, myelinated fibers responsible for vibration, proprioception, and motor function, and small myelinated or unmyelinated fibers that mediate pain, temperature, and autonomic function. Recognizing the pattern of fiber involvement helps narrow the differential diagnosis and determine appropriate diagnostic testing.[2,6]

Large-Fiber Neuropathies

Large-fiber neuropathies involve large myelinated sensory and motor fibers. Clinically, patients present with numbness, loss of vibration and position sense, reduced reflexes, and sensory ataxia, sometimes accompanied by distal weakness.

Nerve conduction studies (NCS) are typically abnormal and remain the primary diagnostic test, showing reduced amplitudes or slowed conduction depending on whether the neuropathy is axonal or demyelinating.

Common conditions affecting large fibers include

- diabetic distal symmetric polyneuropathy,
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP),
- Charcot–Marie–Tooth disease,
- vitamin B12 deficiency,
- monoclonal gammopathy–associated neuropathy, and
- amyloid neuropathy.[1,3]

Small-Fiber Neuropathies

Small-fiber neuropathies involve thinly myelinated A-delta fibers and unmyelinated C fibers, which mediate pain,

temperature, and autonomic functions. Patients typically present with burning pain, dysesthesias, and allodynia, often beginning in the feet. Autonomic symptoms such as orthostatic dizziness, abnormal sweating, or gastrointestinal dysfunction may occur.[7]

Unlike large-fiber neuropathies, nerve conduction studies are usually normal, making diagnosis more challenging.

Common causes include

- diabetes and impaired glucose tolerance,
- amyloidosis,
- Fabry disease,
- Sjögren syndrome,
- sarcoidosis, and
- celiac disease,
- although many cases remain idiopathic.

Autonomic Neuropathies

- Autonomic neuropathies result from involvement of small autonomic fibers that regulate cardiovascular, gastrointestinal, genitourinary, and sudomotor functions. Clinical manifestations may include orthostatic hypotension, abnormal sweating, gastrointestinal dysmotility, bladder dysfunction, and erectile dysfunction.
- Autonomic involvement is commonly seen in diabetic autonomic neuropathy, amyloid neuropathy, autoimmune autonomic ganglionopathy, paraneoplastic neuropathies, and hereditary conditions such as familial amyloid polyneuropathy.8

Emerging Diagnostic Tools

Recent advances have improved the detection of small-fiber neuropathy.

1. Skin biopsy- A small punch biopsy is typically obtained from the distal leg and processed using immunohistochemical staining to visualize nerve fibers.
2. Reduced intraepidermal nerve fiber density confirms the presence of small fiber neuropathy and correlates with clinical symptoms.[9]
3. Corneal confocal microscopy (CCM)- It is a non-invasive imaging technique that allows visualization of corneal nerve fibers. The cornea contains a dense network of small sensory nerves, making it an ideal site for evaluating small fiber pathology. Studies have demonstrated that corneal nerve fiber density correlates with intraepidermal nerve fiber density measured by skin biopsy. This technique may therefore allow early detection of neuropathy, particularly in diabetic patients.[10,11]
4. Sudomotor testing, including QSART or electrochemical skin conductance, assesses autonomic small-fiber function.[12]

Together, these tools allow more accurate identification of fiber-type involvement, forming the first axis of the precision neuropathy framework. Figure 2

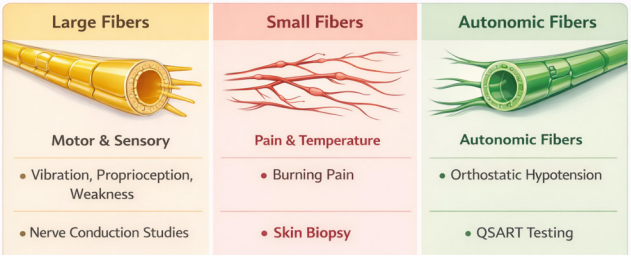

Fig. 2: Peripheral Nerve Fiber Types

AXIS 2 – PATTERN OF NERVE INJURY

Beyond fiber-type involvement, the anatomical pattern of nerve injury provides another crucial diagnostic clue in peripheral neuropathy. Careful recognition of whether neuropathy follows a length-dependent, non–length-dependent, or multifocal pattern can significantly narrow the differential diagnosis even before extensive investigations are performed. Clinical examination remains central to identifying these patterns, supported by investigations such as quantitative sensory testing (QST), electrodiagnostic studies, and nerve imaging.

Careful physical examination often provides important diagnostic clues to the underlying type of neuropathy. Severe axonal neuropathies may produce marked distal wasting and clawing of the hands, as seen in paraproteinemic neuropathy (Figure 3A). Certain hereditary neuropathies, particularly Charcot–Marie–Tooth disease, are associated with characteristic skeletal deformities including pes cavus and hammer toes resulting from chronic motor imbalance (Figure 3B–C). In contrast, mononeuritis multiplex typically presents with asymmetric focal deficits due to involvement of individual peripheral nerves; an example is wrist drop due to radial nerve involvement (Figure 3D). Long-standing severe axonal neuropathies may also lead to trophic skin changes and painless ulcers due to sensory loss and impaired protective mechanisms (Figure 3E). Recognition of these characteristic bedside findings can substantially narrow the differential diagnosis and guide targeted investigations.

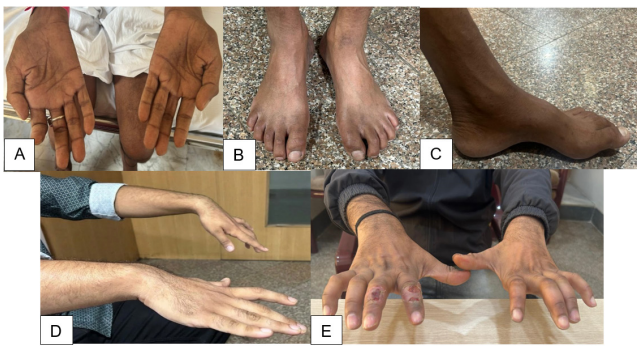

Figure 3: Various clinical signs of peripheral neuropathy (A) – Severe wasting and weakness of bilateral distal muscles-patient with axonal neuropathy in paraproteinemic neuropathy (hands) (B–C) Hammer Toes and Pes Cavus in hereditary neuropathy (D) Left wrist-drop in a patient with mononeuritis multiplex (E) Trophic ulcers in a patient with severe sensorimotor hereditary axonal neuropathy

Length-Dependent Polyneuropathy

Length-dependent polyneuropathy is the most common pattern of peripheral nerve injury. Symptoms typically begin in the distal feet and progress proximally in a "stocking–glove" distribution, reflecting the vulnerability of the longest axons. Patients usually present with distal sensory symptoms such as numbness, tingling, burning pain, or reduced vibration sense, with later involvement of the hands as the disease progresses.

Common causes include diabetes mellitus, which represents the leading cause worldwide, as well as toxic neuropathies related to alcohol, chemotherapeutic agents, and certain medications. Metabolic disorders, nutritional deficiencies, and chronic kidney disease may also produce this pattern. Recognition of a classic distal symmetric pattern often allows clinicians to focus the evaluation on a limited group of common etiologies.[2,13,14]

Non–Length-Dependent Neuropathies

In contrast, non–length-dependent neuropathies do not follow the typical distal gradient. Sensory symptoms may involve proximal limbs, trunk, or face early in the course, suggesting pathology affecting the dorsal root ganglia or proximal nerve segments rather than distal axons.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variants may also present with a non–length-dependent distribution, reflecting involvement of proximal nerve roots and segments. Classic CIDP causes progressive proximal and distal weakness with sensory deficits and demyelinating features on electrophysiology. Recognized variants include distal acquired demyelinating symmetric neuropathy (DADS), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis–Sumner syndrome), and pure sensory or pure motor CIDP.[15,16,31]

Another classic example is sensory neuronopathy (sensory ganglionopathy), in which sensory loss may be patchy or asymmetric and often accompanied by prominent sensory ataxia. This pattern is seen in conditions such as Sjögren syndrome, paraneoplastic neuropathies, and certain toxic or immune-mediated disorders.[17] Another example is autoimmune autonomic ganglionopathy, where autonomic dysfunction predominates due to involvement of autonomic ganglia. Figure 4 demonstrates various patterns of non-length dependent and length dependent neuropathies

Multifocal or Asymmetric Neuropathies

Multifocal or asymmetric neuropathies involve discontinuous or patchy nerve involvement and often present as mononeuropathy multiplex. Patients may develop stepwise deficits affecting different nerves over time.

Important causes include vasculitic neuropathy, in which ischemic injury to peripheral nerves produces painful asymmetric deficits. Multifocal motor neuropathy (MMN) is another key example, characterized by asymmetric distal weakness and conduction block on nerve conduction studies. Infectious neuropathies such as leprosy may also produce asymmetric nerve involvement due to direct infection of peripheral nerves.[18–20]

DIAGNOSTIC TOOLS

Recognition of neuropathic patterns relies primarily on clinical examination, but several investigations help confirm the pattern and underlying mechanism.

1. **Electromyography and Nerve Conduction Studies (EMG/NCS):** EMG and NCS remain the cornerstone of neuropathy evaluation. These studies help distinguish length-dependent axonal neuropathies, which typically show distal amplitude reduction, from non–length-dependent or demyelinating neuropathies, where conduction slowing, conduction block, or proximal involvement may be evident.[21]
2. **Nerve Imaging:** High-resolution nerve ultrasonography can demonstrate nerve enlargement or focal thickening, which is useful in inflammatory neuropathies and conditions such as leprosy. Magnetic resonance imaging (MRI), including MR neurography, can identify nerve root or plexus thickening and contrast enhancement, particularly in immune-mediated neuropathies such as CIDP.[22,23]
3. **Nerve Biopsy:** Nerve biopsy may be helpful in selected cases, particularly when vasculitis or infiltrative neuropathies are suspected. Histopathology may show characteristic findings such as onion bulb formations, reflecting repeated demyelination and remyelination, which can occur in hereditary neuropathies and CIDP.
4. **Autoantibody Testing:** Recent advances have identified antibodies targeting nodal and paranodal proteins (e.g., neurofascin, contactin, Caspr1), collectively referred to as nodopathies. Detection of these antibodies can identify specific immune-mediated neuropathies with distinct clinical features and potential implications for targeted immunotherapy.[24,25]

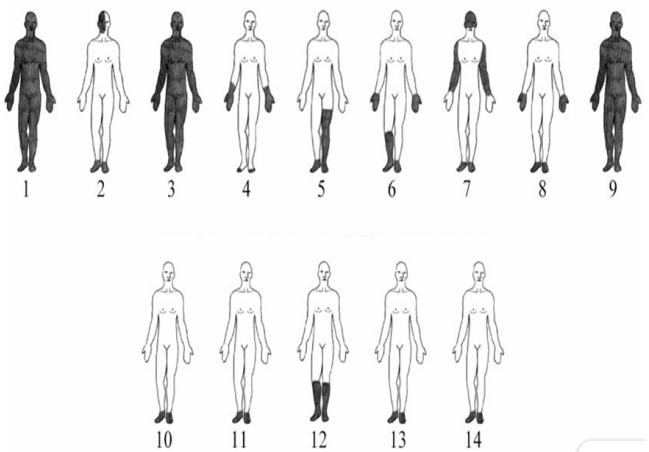

Figure 4: Image 1 to 9 suggestive of various non-length dependent polyneuropathy like seen in CIDP and its variants and sensory ganglionopathy. Image 10 to 11 suggestive of various length dependent polyneuropathy

AXIS 3 – ETIOLOGIC BIOMARKERS: IDENTIFYING TREATABLE CAUSES

Once the fiber type and pattern of nerve injury are defined, the next step is to identify etiologic biomarkers that may reveal a treatable cause. Advances in immunology, genetics, and laboratory diagnostics have significantly improved the ability to detect immune-mediated, hereditary, and systemic causes of neuropathy. Identification of these biomarkers is critical because many of these conditions are potentially disease-modifying or treatable, making early recognition clinically important.[5]

Autoimmune Biomarkers

Several peripheral neuropathies are now recognized to be immune-mediated, and the identification of disease-specific antibodies has refined their diagnosis. Antibodies against gangliosides (GM1, GD1a, GQ1b) are associated with disorders such as multifocal motor neuropathy and variants of Guillain–Barré syndrome. More recently, antibodies targeting nodal and paranodal proteins—including neurofascin-155, contactin-1, and Caspr1—have been described in a subset of CIDP patients. These conditions, often termed nodopathies, demonstrate distinct clinical features and may respond differently to immunotherapies. (Eg Nf155 antibody related CIDP responds better to Rituximab as compared to conventional IVIG/ Steroids)[24,26]

Genetic Diagnostics

Genetic testing has transformed the evaluation of hereditary neuropathies, particularly with the availability of next-generation sequencing panels. These tools allow identification of mutations responsible for disorders such as Charcot–Marie–Tooth disease, hereditary sensory neuropathies, and transthyretin (TTR) amyloid neuropathy. Early genetic diagnosis is increasingly important because disease-modifying therapies, including RNA-silencing treatments, are now available for certain hereditary neuropathies.[27,28]

Systemic and Metabolic Biomarkers

Several systemic disorders may present with neuropathy, and targeted laboratory evaluation can identify these treatable causes. Screening tests often include serum protein electrophoresis for monoclonal gammopathy, vitamin B12 levels, glucose metabolism assessment, and evaluation for systemic diseases such as amyloidosis or autoimmune conditions. Recognition of these biomarkers can guide specific treatment strategies and prevent further neurological damage.[29,30]

Together, the identification of etiologic biomarkers represents the third axis of the precision neuropathy framework, linking clinical phenotype to specific underlying mechanisms and targeted therapy.

PRECISION THERAPY: TARGETED AND SYMPTOMATIC MANAGEMENT

The final axis of the precision neuropathy framework links diagnostic stratification to therapeutic decision-making. Management of peripheral neuropathy involves both disease-modifying therapies directed at the underlying cause and symptomatic treatment, particularly for neuropathic pain and autonomic dysfunction. Advances in immunotherapy, molecular medicine, and targeted pharmacology have expanded treatment options for several neuropathies, reflecting the broader shift toward precision neurology.[4]

Disease-Modifying Therapies

Immune-mediated neuropathies represent one of the most important treatable groups. In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), international guidelines recommend intravenous immunoglobulin (IVIG), corticosteroids, or plasma exchange as first-line therapy.

- IVIG is usually administered as an induction dose of 2 g/kg over 2–5 days, followed by maintenance doses of approximately 1 g/kg every 3–4 weeks depending on clinical response. The mechanism of action of IVIG is complex and includes modulation of Fc receptors, neutralization of pathogenic autoantibodies, inhibition of complement activation, and suppression of inflammatory cytokines.
- Corticosteroids such as prednisone are typically started at 0.75–1 mg/kg/day, and exert their effect by reducing immune activation, suppressing inflammatory cytokines, and inhibiting T-cell–mediated nerve injury.
- Plasma exchange is usually performed as five exchanges over one to two weeks and works by removing circulating pathogenic antibodies and immune complexes from the plasma.[31,32]
- In multifocal motor neuropathy (MMN), IVIG remains the treatment of choice and is administered using similar dosing regimens. Some patients with nodal or paranodal antibody–associated neuropathies may respond poorly to IVIG but may benefit from rituximab, a monoclonal antibody that targets CD20-positive B cells and reduces autoantibody production. In vasculitic neuropathy, treatment typically includes high-dose corticosteroids (around 1 mg/kg/day of prednisone) combined with immunosuppressive agents such as cyclophosphamide, which acts by inhibiting DNA replication in rapidly dividing immune cells, thereby suppressing the vasculitic inflammatory process.[33]

Hereditary Amyloid neuropathy: Significant therapeutic advances have also occurred in transthyretin (ATTR) amyloid neuropathy. The transthyretin stabilizer tafamidis, administered at 20–61 mg orally once daily, works by binding to the transthyretin tetramer and preventing its dissociation into amyloidogenic monomers, thereby reducing amyloid fibril

formation. RNA interference therapies such as patisiran, given intravenously at 0.3 mg/kg every three weeks, and vutrisiran, administered as a 25 mg subcutaneous injection every three months, act by silencing hepatic transthyretin gene expression and reducing circulating transthyretin protein levels. Another therapy, inotersen, an antisense oligonucleotide given as 284 mg subcutaneously once weekly, works by inhibiting transthyretin mRNA translation, thereby decreasing amyloid deposition.[28,34,35]

Metabolic neuropathies: Treatment focuses on correcting the underlying metabolic abnormality. In diabetic neuropathy, strict glycemic control reduces metabolic stress on peripheral nerves by limiting hyperglycemia-induced oxidative stress, polyol pathway activation, and microvascular injury.[36] In vitamin B12 deficiency, replacement therapy is usually administered as cyanocobalamin 1000 µg intramuscularly weekly for four to six weeks followed by monthly maintenance injections, restoring normal myelin synthesis and neuronal metabolism. In thiamine deficiency neuropathy, thiamine supplementation at 100–300 mg/day restores coenzyme activity in carbohydrate metabolism, improving neuronal energy production.[37]

Symptomatic Treatment of Neuropathic Pain

Neuropathic pain is one of the most disabling manifestations of peripheral neuropathy, and current guidelines recommend a stepwise pharmacologic approach.

First-line agents:

1. Gabapentinoids are widely used. Gabapentin is usually initiated at 300 mg daily and titrated to 1800–3600 mg/day, while pregabalin is typically started at 75 mg twice daily and increased to 300–600 mg/day. These drugs bind to the α2δ subunit of voltage-gated calcium channels in presynaptic neurons, reducing calcium influx and thereby decreasing the release of excitatory neurotransmitters such as glutamate and substance P.[38,39]
2. Serotonin–norepinephrine reuptake inhibitors (SNRIs) are also effective. Duloxetine is commonly prescribed at 60–120 mg/day, while venlafaxine is used at doses of 75–225 mg/day. These medications increase synaptic levels of serotonin and norepinephrine, enhancing descending inhibitory pain pathways within the central nervous system.[40]
3. Tricyclic antidepressants such as amitriptyline (10–25 mg nightly, titrated to 50–75 mg/day) and nortriptyline (25–75 mg/day) are also commonly used. Their analgesic effect results from inhibition of serotonin and norepinephrine reuptake as well as sodium channel blockade, which reduces ectopic neuronal firing.

Second-line therapies include:

1. topical treatments: Lidocaine 5% patches, applied for up to 12 hours daily, work by blocking voltage-gated sodium channels in peripheral nociceptive fibers, thereby reducing ectopic discharges. Capsaicin 8% patches, applied under medical supervision and repeated approximately every three months, produce analgesia by desensitizing TRPV1 receptors on nociceptive neurons and causing reversible defunctionalization of pain fibers.
2. Tramadol, typically prescribed at 50–100 mg every six hours (maximum 400 mg/day), provides analgesia through weak µ-opioid receptor agonism combined with inhibition of serotonin and norepinephrine reuptake. Tapentadol, used at 50–250 mg twice daily, acts through dual mechanisms of µ-opioid receptor activation and norepinephrine reuptake inhibition.
3. For refractory neuropathic pain, additional options include ketamine infusions, which act as NMDA receptor antagonists that reduce central sensitization, and botulinum toxin injections, which may decrease peripheral neurotransmitter release. Neuromodulation techniques, including spinal cord stimulation, provide analgesia by modulating dorsal column signaling and altering pain transmission pathways.[41,42]

Non-Pharmacological Management of Neuropathic Pain:

Non-pharmacological interventions are an important component of the multimodal management of neuropathic pain, particularly in patients with partial response or intolerance to medications.

1. Physical therapy and structured exercise programs can improve muscle strength, balance, and gait stability, thereby reducing functional impairment associated with neuropathy.
2. Transcutaneous electrical nerve stimulation (TENS) may provide adjunctive pain relief by stimulating large sensory fibers and activating inhibitory spinal pathways, consistent with the gate-control mechanism of pain modulation.
3. Psychological interventions such as cognitive behavioral therapy (CBT) and mindfulness-based approaches can help patients cope with chronic pain and associated anxiety or depression.
4. In patients with refractory symptoms, neuromodulation techniques including spinal cord stimulation or peripheral nerve stimulation may be considered to modulate pain transmission pathways.
5. In addition, lifestyle measures such as optimal glycemic control, avoidance of neurotoxins, weight management, and foot care remain important supportive strategies, particularly in metabolic neuropathies such as diabetic neuropathy.

Management of Autonomic Neuropathy

Autonomic neuropathies require targeted therapy based on the affected organ system. In orthostatic hypotension, non-pharmacological measures such as increased fluid intake, compression stockings, and gradual postural changes are combined with medications such as midodrine (2.5–

10 mg three times daily), an α_1-adrenergic agonist that increases peripheral vascular tone, and fludrocortisone (0.1–0.2 mg/day), a mineralocorticoid that expands plasma volume. Gastrointestinal dysmotility may be treated with metoclopramide (10 mg before meals), which enhances gastric emptying through dopamine receptor blockade and prokinetic activity.[43]

Urinary autonomic dysfunction may manifest as bladder overactivity, urinary urgency, or urinary retention. Overactive bladder symptoms can be managed with antimuscarinic agents such as oxybutynin (2.5–5 mg two to three times daily) or tolterodine (2–4 mg/day), which reduce detrusor muscle overactivity by blocking muscarinic receptors. Alternatively, β3-adrenergic agonists such as mirabegron (25–50 mg/day) may be used to promote bladder relaxation and increase bladder storage capacity. In patients with neurogenic urinary retention, intermittent self-catheterization is often recommended, while α-adrenergic blockers such as tamsulosin (0.4 mg/day) may help facilitate bladder emptying by reducing urethral sphincter tone.

FUTURE PERSPECTIVES

Gene-Targeted and RNA-Based Therapies

Recent advances in molecular medicine have opened new therapeutic possibilities for hereditary neuropathies. RNA-based therapies such as small interfering RNA (siRNA) and antisense oligonucleotides have already transformed the treatment of transthyretin amyloid neuropathy by reducing production of pathogenic proteins. Similar strategies are being explored for other inherited neuropathies, including certain forms of Charcot–Marie–Tooth disease. In the future, gene editing technologies such as CRISPR-based approaches may offer the possibility of correcting disease-causing mutations at the genomic level.

Targeted Immunotherapy

The discovery of antibodies directed against nodal and paranodal proteins has improved understanding of immune-mediated neuropathies and led to the recognition of distinct disease subtypes known as nodopathies. These conditions may respond to targeted therapies such as B-cell–directed

Table 2: summarizes all the treatment measures along with respective guidelines/recommendations

Clinical Category	First-Line Therapy	Alternative / Adjunct Therapy	Mechanism of Action	Key Guideline Sources
CIDP	IVIG 2 g/kg over 2–5 days, maintenance 1 g/kg every 3–4 weeks	Corticosteroids (prednisone 0.75–1 mg/kg/day), Plasma exchange	Immunomodulation, neutralization of pathogenic antibodies	EFNS/PNS CIDP Guidelines; EAN/PNS 2021[44]
Multifocal Motor Neuropathy (MMN)	IVIG 2 g/kg induction, maintenance dosing	Rituximab in refractory cases	Modulation of immune-mediated nerve injury	EFNS/PNS recommendations[44]
Vasculitic Neuropathy	Prednisone ~1 mg/kg/day	Cyclophosphamide, azathioprine	Immunosuppression of inflammatory vasculitis	AAN & rheumatology guidelines[46]
ATTR Amyloid Neuropathy	Tafamidis 20–61 mg/day	Patisiran 0.3 mg/kg IV every 3 weeks; Vutrisiran 25 mg SC every 3 months; Inotersen 284 mg weekly	Stabilization or suppression of transthyretin production	European guidelines for amyloidosis [46]
Diabetic Neuropathy (disease control)	Tight glycemic control	Lifestyle modification	Reduction of metabolic and oxidative nerve injury	ADA guidelines[47]
Neuropathic Pain – First Line	Duloxetine 60–120 mg/day; Pregabalin 300–600 mg/day; Gabapentin 1800–3600 mg/day	Amitriptyline 25–75 mg/day	Modulation of central pain pathways	NeuPSIG 2015; [48]
Second-Line Pain Therapy	Topical lidocaine 5% patch	Capsaicin 8% patch	Sodium channel blockade; TRPV1 desensitization	NeuPSIG recommendations[48]
Third-Line Pain Therapy	Tramadol 50–100 mg every 6 h	Tapentadol 50–250 mg twice daily	μ-opioid receptor activation + monoamine reuptake inhibition	NeuPSIG guidelines[48]
Autonomic Neuropathy – Orthostatic Hypotension	Midodrine 2.5–10 mg TID	Fludrocortisone 0.1–0.2 mg/day	Increased vascular tone; plasma volume expansion	AAN autonomic disorder guidelines[47]

monoclonal antibodies (e.g., rituximab).[49,50] In addition, complement inhibitors and other monoclonal antibody therapies are currently under investigation for immune-mediated nerve injury. Future treatment strategies may increasingly rely on biomarker-guided immunotherapy, allowing therapies to be tailored according to specific pathogenic mechanisms.

Advances in Diagnostic and Digital Technologies

Technological progress is also shaping the future of neuropathy care. Improved nerve imaging techniques, including high-resolution ultrasound and magnetic resonance neurography are enhancing the ability to detect structural nerve abnormalities. Emerging approaches such as digital phenotyping, wearable sensor technologies, and artificial intelligence–based diagnostic tools may enable earlier detection of neuropathy and more accurate disease classification.

Innovations in Neuromodulation and Pain Management

For patients with refractory neuropathic pain, advances in neuromodulation and bioelectronic medicine are expanding treatment options. Techniques such as spinal cord stimulation, dorsal root ganglion stimulation, and peripheral nerve stimulation are being refined with newer closed-loop systems that adjust stimulation based on neural feedback, potentially improving efficacy and reducing side effects.

Artificial Intelligence in Peripheral Neuropathy

Artificial intelligence (AI) is emerging as a promising tool for the early detection and phenotyping of peripheral neuropathy. Machine learning algorithms can analyze large datasets from clinical parameters, neurophysiology, and imaging to identify patterns that may not be easily recognized by conventional methods. For example, deep-learning models applied to corneal confocal microscopy images have shown high accuracy in detecting diabetic peripheral neuropathy by identifying small-fiber loss.[51] As these technologies advance, AI may support screening, risk prediction, and precision diagnosis in peripheral neuropathy.

CONCLUSION

Peripheral neuropathy comprises a diverse group of disorders with multiple etiologies and varied clinical presentations, often making diagnosis challenging. Advances in neurophysiology, imaging, genetic testing, and immunological biomarkers have significantly improved the ability to identify underlying causes and recognize treatable neuropathies.

The four-axis precision neuropathy framework proposed in this review—integrating fiber type involvement, pattern recognition, etiologic biomarkers, and targeted therapy—provides a practical approach to the evaluation and management of peripheral neuropathies. With the emergence of disease-modifying therapies, improved symptomatic treatments, and evolving technologies such as artificial intelligence, the field is progressively moving toward mechanism-based and personalized care in peripheral nerve disorders.

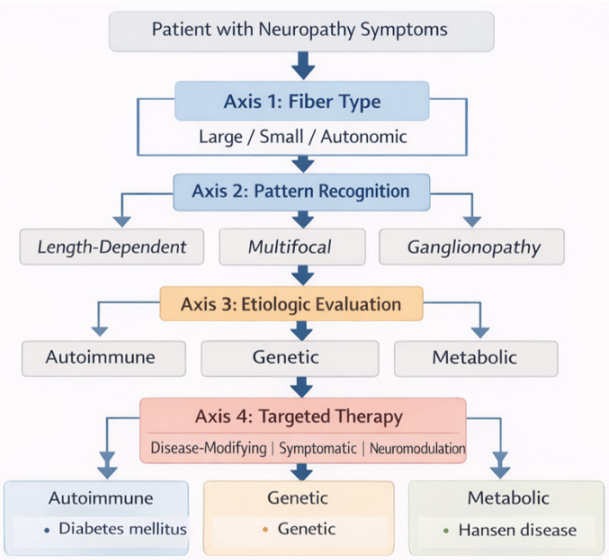

Figure 5: Clinical algorithm for peripheral neuropathy

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