

## Non-Pharmacologic Care and Management of Neuropathy

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### Abstract

According to the International Association of the Study of Pain (IASP), neuropathic pain is caused by a primary lesion or dysfunction of the nervous system. The lesion may be peripheral, spinal, or supra-spinal and is differentiated from other types of pain due to sensory symptoms caused by a compromised peripheral or central nervous system. Neuropathic pain is further delineated as “evoked pain” or “rest pain”, the latter typically observed in spinal cord injury patients. Neuropathies can be cranial, autonomic, or focal.

The major types and categories of neuropathies include chronic degenerative neuropathy, post-traumatic neuropathy, diabetic neuropathy, stroke-related neuropathy, and peripheral neuropathy. Common comorbidities include Alzheimer’s disease and Parkinson’s disease. Neuropathic conditions are diagnosed by a patient’s medical history, examination, and when indicated, electromyography (EMG) and the nerve conduction velocity (NCV) test. This research explores non-pharmacologic care and management of specific neuropathies, particularly nutrition, and nutritional supplementation, and photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT). Comparisons are given regarding these modalities and conventional treatments. Although research into the efficacious applications of nutrition, nutritional supplements, and photobiomodulation therapy is in its relative infancy, these modalities seem promising when used alone or, in combination and or as conjunctive therapies with conventional treatments.

**Keywords:** Alzheimer’s Disease; Demyelination; Diabetic Neuropathy; Neuropathic Pain; Nutritional Supplements; Parkinson’s Disease; Vitamins

### Abbreviations

CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; EMG: Electromyography; IASP: International Association of the Study of Pain; LLLT: Low-Level Laser Therapy; NCV: Nerve Conduction Velocity; PBMT: Photobiomodulation Therapy; QoL: Quality-Of-Life; SLE: Systemic Lupus Erythematosus; TENS: Transcutaneous Electrical Nerve Stimulation; VAS: Visual Analog Scale

### Introduction

Neuropathy is caused by damage to the nerve cells and is characterized by pain, numbness, tingling sensation, swelling, and muscle weakness in various parts of the body. Neuropathic pains are often associated with poor prognosis and diminished quality-of-life (QoL). Significant advancement in techniques used to detect neuropathy has helped develop new multidisciplinary treatment strategies [1,2]. Research data regarding the prevalence of neuropathic pain differ due to the highly diverse disease types and etiologies [3].

The International Association of the Study of Pain (IASP) defines neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction of the nervous system”. The lesion may be located in the peripheral, spinal, or supra-spinal nervous system. Neuropathic pain

can be differentiated from other types of pain by the presence of sensory symptoms, being caused by damage either to the peripheral or central nervous system [4].

### Discussion

Neuropathic pain is classified as evoked pain or rest pain (pain at rest). The latter is observed commonly in patients with spinal cord injury. Symptoms of evoked pain include pressure hyperalgesia, allodynia, and heat hyperalgesia, whereas those of rest pain include numbness, burning and pricking pain, and electric-shock-like pain. Neuropathic pain intensity is often determined using a visual analog scale (VAS) scoring system [5].

### Cranial neuropathy

Cranial neuropathy, also known as multiple cranial neuropathies, is a common clinical neurological condition. Diagnosis of cranial neuropathy is challenging due to its complex etiology. Typically, dysfunction of or damage to any of the 12 cranial nerves can result in cranial neuropathy. Infections, autoimmune diverticulitis, and neoplasms can also lead to the condition [6,7].

### Autonomic neuropathy

Autonomic neuropathy is a condition in which involuntary nerve fibers are affected, in addition to peripheral nerve dysfunctions. Mostly, the conditions are mild and asymptomatic. In a few instances, myelinated nerve fibers are involved. These conditions are often associated with diabetes mellitus, metabolic alkalosis, immune-mediated autonomic neuropathy like para-neoplastic syndrome, various inherited autonomic neuropathies, autonomic neuropathies of infectious origin, and toxic autonomic neuropathies. The syndrome's clinical features include gastrointestinal, cardiovascular, urogenital, sudomotor, pupillomotor, and thermoregulatory impairments. Diagnostic procedures and physiological and laboratory tests help estimate autonomic function and monitor outcomes in most patients [8].

### Focal neuropathy

This neuropathy occurs when a single (or group of nerves) at a particular site is affected. The etiology is varied, ranging from acute traumatic nerve injuries to chronic compressions. Although differential diagnosis is challenging, an accurate diagnosis can be determined by a detailed medical history, clinical examination, and targeted physiologic examination. Imaging techniques, such as magnetic resonance imaging and monographs, provide essential information. Morphological data in complicated cases helps delineate the diagnosis. Further, the diagnostic process has become more direct due to the availability of state-of-the-art electrodiagnostic procedures [9,10]. Peripheral neuropathy is sometimes considered a category of focal neuropathy, which will be discussed in a later section.

### Major types/categories of neuropathies

#### Chronic degenerative neuropathy

Patients with chronic degenerative neuropathy, also known as chronic inflammatory demyelinating polyneuropathy (CIDP), often present with nerve swelling and irritation (inflammation), resulting in a loss of strength or sensation [11].

In this condition, nerves outside the brain and spinal cord are involved, commonly affecting both sides of the body. As damage to the nerve cell's myelin sheath leads to degeneration, the condition is considered autoimmune. Moreover, CIDP is associated with multiple disorders, such as chronic hepatitis, diabetes mellitus, bacterial infection, HIV, compromised immunity, inflammatory bowel syndrome, systemic lupus erythematosus (SLE), cancer of the lymph system, hyperthyroidism, and use of anticancer medications [11,12]. Although there are data on the disease pathogenesis, the exact triggering factors remain unclear.

The incidence and prevalence rates of CIDP were 1.6/100,000/year and 8.9/100,000, respectively, in a study conducted in the United States. The disease seems to affect individuals aged 40–60 years, having male predominance [11,12].

### Clinical presentation of chronic degenerative neuropathy

The symptoms are mostly symmetrical and progressive, starting from the feet and gradually moving to the arms and hands. Symptoms include weakness of limbs, burning, tingling, pain, and numbness. There may be fatigue, dyspnoea, slurred speech, hoarseness of voice (dysphonia), and uncoordinated movements (ataxia) in patients with advanced disease. It is crucial to differentiate CIDP from Guillain-Barré syndrome, especially in patients presenting with relapse [11,12].

### Post-traumatic neuropathy

Injury to the peripheral nerves is the primary cause of post-traumatic neuropathy. Accidental traumas, surgeries, and diseases can cause mild to severe neuropathic pain. As this condition affects the productive age group, it has a considerable negative effect on the patient's QoL. The incidence of peripheral nerve injury ranges from 2.8% to 5% [13].

Although various pathophysiological mechanisms can explain these types of pains, the differentiating factor is that post-traumatic neuropathy begins with a spontaneous or deranged activity in the injured sensory neurons [14].

Post-surgical neuropathy is a commonly encountered variant of post-traumatic neuropathy [15].

### Clinical presentation of post-traumatic neuropathy

The clinical picture revolves around pain, allodynia, dysesthesia, and hypersensitivity. Such pain and symptoms have been reported mostly after surgeries, such as mastectomy, thoracotomy, and hernia repair [13–15].

### Diabetic neuropathy

Signs and symptoms of neuropathy in diabetic patients often point to the presence of diabetic neuropathy. The condition can be either symmetrical or asymmetrical neuropathy, but most patients (75%) often present with distal symmetrical neuropathy. Asymmetrical neuropathies likely involve cranial, thoracic, or limb nerves, resulting from an acute ischemic episode of vasa nervosa causing infarction [16].

Diabetic neuropathy, under the symmetric variant, is further classified as diabetic polyneuropathy, painful autonomic neuropathy, painful distal neuropathy with weight loss (diabetic cachexia), insulin neuritis, polyneuropathy after ketoacidosis, polyneuropathy with glucose impairment, and CIDP. Under asymmetrical variants, there are radiculoplexic neuropathies (lumbosacral, thoracic, cervical), mononeuropathies, median neuropathy of the wrist, ulnar neuropathy of the elbow, peroneal neuropathy of the fibular head, and cranial neuropathy. The predisposing factors for diabetic neuropathy are hyperglycemia, dyslipidemia, and impaired insulin signaling [17,18].

### Clinical presentation of diabetic neuropathy

Clinically, diabetic neuropathy manifests with varied symptoms. Along with signs and symptoms of diabetes mellitus and classical signs of peripheral neuropathy (e.g., numbness, tingling, burning sensation), the condition involves symptoms related to the autonomic nervous system. Diabetic neuropathy of the digestive system is associated with nausea and vomiting, diarrhea or constipation, and heartburn; blood vessel aberrations are associated with heartbeat fluctuation (arrhythmia), low blood pressure, and blacking out on a sudden change of posture (postural syncope or postural hypotension); and the male urogenital system is associated with aspermia (dry ejaculation), incontinence, and difficulty in voiding the bladder (urinary retention) [19,20].

### Stroke-related neuropathy

About 8–10% of stroke survivors experience stroke-related neuropathy, also known as central post-stroke pain. Stroke-related neuropathy is a type of central neuropathy and is more common in a lesion of the thalamus. This type's unique feature is that pain is caused by minimal stimulation to peripheral pain receptors [21].

### Clinical presentation of stroke-related neuropathy

Stroke-related neuropathy is often associated with other post-stroke pains. The symptoms can appear even after 6 months, making diagnosis challenging. Symptoms include a burning sensation, stabbing and searing sensation, and pins-and-needles sensation—forms of paresthesia [21].

### Peripheral neuropathy

The most frequently encountered condition in the clinical setting is peripheral neuropathy, which encompasses a broad spectrum of neuropathies, leading to a challenging diagnosis. Peripheral neuropathy can be classified based on etiology (compressive or non-compressive), the number of nerves involved (mono or polyneuropathy), duration (chronic or acute), and pathology (axonal, demyelinating, or fixed) [22].

Although the incidence rate of peripheral neuropathy is considerably high, epidemiological data are scarce. About 2.4% of the population is affected by a peripheral nerve disorder, and the prevalence rate increases up to 8% in elderly individuals. Diabetic neuropathy is one of the most common types of peripheral neuropathy [23]. In Southeast Asia, leprosy is reported to be often associated with peripheral neuropathy. Charcot-Marie-Tooth syndrome is another rare genetic disorder associated with peripheral neuropathy [14].

Numerous factors—such as hypothyroidism, diabetes mellitus, nutritional deficiencies, alcoholism, infections and inflammation, autoimmune conditions, drug-induced conditions, direct trauma, neoplastic disorders, and genetic predisposition—may contribute to peripheral neuropathy.

The disease's pathophysiology depends on the underlying condition. Wallerian degeneration, where the neuron's axon degenerates following an injury or compression, causes mostly mononeuropathies—axonal degeneration or the dying-back phenomenon, manifested by symmetrical polyneuropathies. As the axon's distal portion to its distance from the cell body is more vulnerable to metabolic vulnerability, the axons start degenerating from distal to proximal [24].

Segmental demyelination spares the axon, but the myelin sheath degenerates, resulting in mononeuropathies, sensorimotor or motor neuropathies [23,24].

### Clinical presentation of peripheral neuropathy

In the early phase of the disease, the classical signs of numbness and tingling, pain, and burning sensations present in a “stocking and glove”-like manner in the distal limbs. These sensations gradually move to the proximal parts, and the symptoms intensify. Some degree of atrophy of muscles in distal parts is observed in advanced stages. A 128-Hz tuning fork can be used to confirm the loss of vibrational sensibility in extremities. The sensory loss also includes temperature and pinprick sensations [15,22–24].

### Prevalent comorbidities of neuropathy

### Alzheimer's disease

Alzheimer's disease is the most common type of dementia of old age. It is a progressive neurodegenerative disease, characterized by the deposition of abnormal neuritic plaques and neurofibrillary tangles. However, due to overlapping pathology, patients with Alzheimer's disease are found to have primary optic neuropathy due to retinal ganglion cells and axons of the optic nerve undergoing degenerative changes [25,26].

### Parkinson's disease

Parkinson's disease is the most common neurodegenerative movement disorder characterized by infarction in the nigra-striatal pathway, and accumulation of misfolded  $\alpha$ -synuclein in the substantia nigra, and loss of dopaminergic neurons in the pars compacta of the substantia nigra. Predisposing factors include advanced age and male gender, in addition to hereditary traits. It is posited that the underlying neurodegenerative process in the peripheral nervous systems causes peripheral neuropathy in patients with Parkinson's disease [27-29].

### Principles of diagnosis of a neuropathic condition

Clinical diagnosis requires a thorough physical examination and medical history of the patient. Clinical, physiologic testings can narrow the diagnosis and help determine the etiology and underlying pathology. Electromyography (EMG) and nerve conduction velocity (NCV) tests are definitive, regarding the diagnoses of specific conditions [30,31].

### Non-pharmacologic care and management of neuropathy

#### Nutrition and nutritional supplementation

As stated by Hippocrates, "Let food be your medicine and medicine be your food". Nutraceuticals (inadequate intake or supplemental intake) play a significant role in developing and treating neuropathies, respectively. Nutritional supplements have emerged as a highly effective treatment modality due to their various benefits. These treatments involve multiple physiological pathways with limited, negligible, or absent adverse effects. Prominent nutraceutical agents are as follows:

1. Vitamin B12 plays a vital role in the peripheral and central nervous systems. Its deficiency leads to specific neurological manifestations and peripheral neuropathy—supplementation of the same results in a reversal of the conditions, leading to clinical improvement. The vitamin is readily found in eggs, meat, fish, and low-fat dairy products [32,33].
2. Alpha-lipoic acid is an antioxidant found abundantly in various foods. Historically, it was used to treat nerve damage, effectively delaying or reversing diabetic peripheral neuropathy symptoms by preventing nerve hypoxia and the glycation process [16].
3. Acetyl L carnitine is a naturally occurring amino acid with a potent antinociceptive effect, and is an established neuroprotective agent. Although its mechanisms are not entirely understood, it seems to alleviate specific neuropathic pain [17,32].
4. Curcumin, also known as turmeric, is known for its numerous medicinal benefits. It has a time-tested reputation in alleviating symptoms in several neurological disorders. Studies have demonstrated its action on delaying neuropathic pain and specifically benefiting patients with post-chemotherapeutic neuropathies [34,35].
5. Fish oil, rich in omega-3 fatty acids, is effective in alleviating symptoms of diabetic peripheral neuropathy. These acids are abundant in walnut, flaxseed, sardine, and salmon. A few preclinical studies have indicated that fatty acids slow the progression of and reverse the neuropathy to a certain extent. Metabolites, such as docosahexaenoic acid and eicosapentaenoic acid, are resolvins and neuroprotectants that promote neuron growth *in vitro* [18,23,36].

### Photobiomodulation therapy

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), is a therapeutic modality in which infra-red spectrum, light-emitting diodes are used to provide treatment. This electromagnetic technology is believed to act by a phenomenon called tissue biostimulation. Therapeutic effects are elicited by photoelectric, photoenergetic, and photochemical reactions [23,24].

PBMT has proven efficacy in the peripheral nerve repair process. PBMT has also shown nerve regeneration capabilities. The rise in myelinated fibers and improved lamellar organization of myelin sheath enhances activity, functionality, and interactivity. A decrease in pain and inflammation is also observed. Better alignment of vascular and collagen networks augments the release of growth factors and facilitates neural regeneration [23].

### Specific conditions and corresponding managements

#### Chronic degenerative neuropathy

Nutraceutical management consists of alpha-lipoic acid and curcumin, two of the most potent nutraceutical agents due to their antioxidant properties—alleviating nerve cells' degenerative process by decreasing oxidative stress, enhancing endogenous antioxidant levels, and stabilizing mitochondrial activity. Other nutraceutical agents that have a potential in the management of the disease are coenzyme Q10 (ubiquinone),  $\beta$ -carotene, lycopene, and astaxanthin [33].

PBMT contributes to myelin sheath recovery, active recovery of the nerve cells where the degeneration has begun, and the rapid reduction of neuropathic pain [37,38].

#### Post-traumatic neuropathy

Nutraceutical management with vitamin B12 promotes axons' growth after a nerve injury and is, therefore, used to treat peripheral nerve damages. Post-traumatic nerve injury can be managed using vitamin B12 due to its beneficial role in the axon regeneration process. Vitamin B12 contributes to microtubule stabilization, remyelination, and myelin reparation by rescue [33].

PBMT has a more or less a similar action as in chronic degenerative neuropathy owing to its regenerative properties [37].

#### Diabetic neuropathy

Nutraceutical management involves replacing or replenishing vitamins D and B12—effective in patients with a deficiency of these factors. However, their benefits to individuals with normal vitamin D and B12 levels have not been determined. Alpha-lipoic acid is another nutraceutical agent that may play a beneficial role in diabetic neuropathy, although its efficacy in this regard remains debatable [39].

PBMT appears to benefit patients with diabetic peripheral neuropathy, although conclusive evidence is lacking. However, PBMT has been found highly useful in treating diabetic foot ulcers [39,40].

#### Stroke-related neuropathy

There are scant data and evidence-based research suggesting the efficacious use of nutraceuticals in managing stroke-related neuropathy. Also, there are scant data and evidence-based research suggesting the efficacious use of PBMT in managing stroke-related neuropathy.

### Peripheral neuropathy

Regarding nutraceutical management, vitamin B12 deficiency is one of the prime predisposing factors for peripheral neuropathy; hence, replacement therapies have proven useful. Vitamin B1, B6, and E deficiencies are also associated with peripheral neuropathy. Logically, in a condition such as peripheral neuropathy with multiple components, different nutraceutical agents have various and distinct roles regarding the underlying pathology. Foods rich in antioxidants and vitamins will promote the repair of damaged nerves and help maintain general nerve health [16-18,22,23,32,34-37].

PBMT, due to its property of reviving damaged nerve cells, is a promising therapy for managing peripheral neuropathy. PBMT is specifically seen to be more effective in managing chemotherapy-induced peripheral neuropathy, and seems poised to become a prime treatment modality in the future. However, current evidence to support such is limited [24].

### Comparison of non-pharmacologic vectors with more traditional treatment modalities

#### Medicaments

Conventionally, the pharmacologic agents used to treat neuropathic pains are categorized as first-line, second-line, and third-line. First-line drugs include serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants, and gabapentin and pregabalin. Second-line drugs include lidocaine, tramadol, and capsaicin 8%. Third-line drugs include opioids. Long-term use of these drugs results in multiple side effects, often resulting in secondary discomfort for patients. Alternative treatment strategies could be safe and effective, supporting the emergence of novel non-pharmacologic treatment modalities [41,42].

#### Transcutaneous electrical nerve stimulation

Another method to reduce neuropathic pain is transcutaneous electrical nerve stimulation (TENS). In advanced cases, psychotherapeutic drugs might also be required [43].

### Conclusion

The causes of neuropathologies are numerous and varied. Conventional treatments are typically drugs, physiotherapy and electrotherapy, with mixed results and none, for the most part, addressing the condition's root cause. Nutraceuticals and photobiomodulation therapy (low-level laser therapy) are promising therapies for the care and management of neuropathies—used alone, in combination and or as conjunctive therapies with conventional neuropathic treatments. Nutritional augmentation, nutraceuticals, and PBMT help alleviate and manage neuropathic pain through multiple pathways. Nutraceuticals and photobiomodulation therapy (low-level laser therapy) appear to have no significant adverse effects when used correctly and with an understanding of their mechanisms of action. Also, they may eliminate or ameliorate the need for opioids, lessening the opioid crisis.

### Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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