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Neuromuscular Disorders (C Fournier, Section Editor)

Complementary and Alternative Medicine for Painful Peripheral Neuropathy

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Abstract

Purpose of review The purpose of our manuscript is to review the current evidence supporting the use of complementary and alternative medicine (CAM) in neuromuscular disease, specifically in painful peripheral neuropathy (PPN). We outline the therapeutic challenges of this debilitating condition and describe the best evidence for incorporating such therapies into clinical practice. The most studied modalities include lifestyle modifications with diet and exercise, supplements, and acupuncture. CAM therapies such as yoga, meditation, electrical stimulation, neuromodulatory devices, and cannabis are mentioned as emerging therapies.
Recent findings Current data suggests that targeted lifestyle modifications, including aerobic exercise and diet modifications that promote weight loss, may improve the natural course of diabetic painful neuropathy and potentially other types of neuropathy. A number of studied dietary supplements and vitamins including B vitamins, vitamin D, alpha-lipoic acid, and acetyl-L-carnitine improve both subjective and objective neuropathic measures. A wide range of neuromodulatory devices and electrical stimulation modalities demonstrate mixed results, and further studies are needed to confirm their benefit. Finally, acupuncture and yoga both demonstrate benefit in a variety of PPNs.

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Summary Multiple CAM therapies show efficacy in the treatment of PPN. From the strongest level of evidence to the least, lifestyle modifications including exercise and diet; supplements including B12, alpha lipoic acid, acetyl-L-carnitine, and vitamin D in deficient patients; followed by acupuncture and yoga may alleviate symptoms of PPN.

Introduction

Diseases of the nerve and muscle are negatively impacting the function and quality of life in a growing number of individuals as our population ages and lives longer. One of the most common and debilitating neurologic conditions is painful peripheral neuropathy (PPN) mainly as a consequence of diabetes but also associated with blood dyscrasias, physical injury to a nerve, malignancy, alcoholism, kidney failure, autoimmune responses, nutritional deficiencies, vascular disorders, and idiopathic neuropathies [1]. More than 2 out of every 100 persons are estimated to have peripheral neuropathy, and the incidence rises to 8 in every 100 people for ages 55 or older [2]. Prevalence of neuropathic pain was found to be as high as 17.9% in one surveyed population [3]. In diabetic patients, the prevalence of neuropathy is a function of disease duration, and can range from 25 to 50%, with up to 70% of cases associated with pain [4–6]. Additional neuropathies that are notoriously refractory to treatment include chemotherapy-induced peripheral neuropathy (CIPN) and HIV peripheral neuropathies (HIV-PN). CIPN is a common side effect of taxane- and platinum-based chemotherapy, with prevalence rates ranging from 12 to 96%. Risk factors for developing CIPN include older age, previous history of neuropathy, symptom burden, alcohol intake, and number of chemotherapy cycles [6]. HIV-PN is also the most common neurological disorder among people living with HIV/AIDS and is a result of damage to the nerves by both the virus and the antiretroviral therapy. A number of studies show that HIV-PN is experienced by 30–60% of people living with HIV/AIDS, affecting several millions worldwide [7].

Clinically, PPN is associated with a burning discomfort, typically in the feet and subsequently in the hands, that ranges from mild discomfort to crippling pain. Accompanying symptoms of imbalance, weakness, and dysautonomia can cause significant functional impairment. Diabetic neuropathy also results in substantial morbidity, including recurrent lower extremity infections, ulcerations, and subsequent amputations [4]. As patients increasingly develop diseases that predispose them to PPN (i.e., type 2 diabetes), clinicians face the challenge of managing symptoms that are often refractory to monotherapy [8] with side effects limiting dose titrations [9]. First-line therapy for neuropathic pain includes three drug classes: tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and the calcium channel alpha-2-delta ligands [10••]. Unfortunately, patients who are prescribed opioids or who find temporary relief with their use may later experience dependence and inadequate pain relief [11].

Due to the various presentations of PPN, the inherent challenges in treatment and patient interest in non-pharmacologic options, complementary and alternative medicine (CAM) is ripe for investigation and implementation in this field. In order to clarify varying terminologies, CAM is defined as non-allopathic treatment that focuses on holistic, individual, and preventative healthcare [12]. Alternative medicine is used in place of prescriptions or traditional medicine, while complementary medicine is used in addition to other treatments. Integrative medicine and therapies is a broad term that encompasses all such therapies with a focus on tailoring treatment and maximizing lifestyle modifications. We will review the evidence for lifestyle, supplements, cannabinoids, acupuncture, and mind body practices in PPN.

Etiology of pain in PPN

The pathology of the peripheral disorders that cause neuropathic pain predominantly involves the small unmyelinated C fibers and the myelinated Aβ

and Aδ fibers [8]. Peripheral neuropathy alters the electrical properties of sensory nerves, leading to an imbalance between central excitatory and inhibitory signaling and creating a state of hyperexcitability. Alterations in ion channels within the affected nerves lead to increased expression and function of sodium channels and a loss of potassium channels that normally modulate neural activity [13]. This increased excitability causes pain hypersensitivity such that innocuous stimuli, including light touch and warm or cool temperatures, are perceived as painful, while stimuli that are usually slightly painful such as a pinprick are sensed as extremely painful [14]. Additionally, inflammation after a nerve lesion leads to the activation and migration of macrophages into the nerve and dorsal root ganglion, causing pain hypersensitivity by releasing proinflammatory cytokines such as tumor necrosis factor α [15].

In patients with diabetes mellitus, methylglyoxal plasma levels are increased due to excessive glycolysis and decreased degradation by the glyoxalase system. Methylglyoxal activates peripheral nerves by changing the function of Nav1.7 and Nav1.8 voltage-gated sodium channels. Animal studies have also shown that methylglyoxal slows nerve conduction, heightens calcitonin gene-related peptide release from nerves, and leads to thermal and mechanical hyperalgesia [13].

Treatment

Exercise, diet, and lifestyle

Dietary modification, exercise, and lifestyle optimization have become mainstay interventions for a large area of the healthcare spectrum due to emerging evidence in favor of these behavioral interventions for both primary and secondary prevention of chronic diseases. For those with PPN, these accessible, affordable, low-risk interventions may result in positive outcomes.

Exercise

As in other painful conditions, movement, specifically aerobic exercise, has been shown to alleviate pain perception and improve quality of life. Patients frequently ask about what type of exercise, if any, is beneficial for the symptoms of PPN. In a study by Yoo et al. in 2014, a significant improvement in quality of life after a sixteen-week supervised aerobic exercise program was demonstrated. The improved measures included decreased pain with walking, normal work relationship with others, sleep hygiene, and overall pain interference although there was not a significant difference in actual pain ratings [16]. A recent single-blind randomized controlled trial (RCT) in participants with DPN showed significant improvement in distal vibratory sensory thresholds after 8 weeks of a moderate intensity aerobic exercise program that consisted of training at 40–60% of heart rate reserve and perceived exertion scores [17••]. These findings highlight the ability of aerobic exercise intervention to reduce pain interference and neuropathic symptoms in painful DPN.

Physical therapy is recommended as a treatment option for comorbidities of PPN such as postural instability, falls, and fall-related injury. Balance training has been studied for individuals with DPN and found to be safe and effective in preventing falls in older adults in an analysis of three separate studies [18]. The studies indicate that patients with neuropathy can safely participate in and may

receive benefit from strength and balance training. Although no studies were identified that evaluated strength and balance training for treatment of PPN, the authors encourage this intervention for the unsteady patient given the significant risk for injury and the lack of other evidence-based therapies available [18].

Diet

Food choices are a popular and dynamic lifestyle intervention, and patients often want to know which "diet" would be most helpful to reduce symptoms of PPN. With the exception of gluten neuropathy due to celiac disease, there are not enough available studies to reach an evidence-based conclusion to determine a specific diet for neuropathy. Rather, one can advise that a series of healthy eating habits, choosing fresh food, and preparing more meals at home may prevent progression of chronic diseases that predispose to neuropathy. In the case of DPN, the progression can be prevented or slowed down by tight glycemic control, implying that food choice plays a vital role in addition to or in place of glucose-lowering medications [19].

Lifestyle modifications emphasizing strategies aimed at lowering blood sugar are effective at reducing symptoms of DPN. A well-designed RCT of individuals with type 2 diabetes and painful DPN compared patients on a low-fat, plant-based diet with vitamin B12 supplementation with a control group taking vitamin B12 without dietary intervention. The intervention group had statistically significant weight loss, improvement in electrochemical skin conduction, pain reduction (McGill pain questionnaire), and Michigan Neuropathy Screening instrument score [20].

Lifestyle (putting it all together)

Specific lifestyle strategies including increased physical activity, weight loss, diet modifications, and routine foot care demonstrated clinically significant reduction in subjective neuropathic pain after 12 weeks [21]. A 2017 Look AHEAD study investigated various intensive lifestyle modifications in obese patients with type 2 diabetes, largely aimed at weight loss and increased physical activity. Maximal weight loss achieved at 1 year was associated with significantly lower neuropathy scores, which persisted throughout study follow-up [22••]. In a well-designed pilot study by Tin et al., sensory nerve conduction parameters improved in patients with glycemic disorders and metabolic syndrome after a three-month lifestyle modification program including diet and physical activity counseling. However, the improvement was not noted in motor nerve conduction parameters [23].

Nutraceutical supplements and cannabinoids

Nutraceutical supplements have been studied for PPN with low to moderate efficacy and relatively good safety profiles. This area of research remains challenging due to the numerous products available for consumer purchase, different concentrations of active ingredients, and varying product quality based on brand. Amidst the confusion, clinicians are unclear on how to guide continued consumers on product label interpretation and brand selection of supplements that perform independent quality control testing. Therefore, studies that clearly define safety and efficacy of nutraceuticals and set purity and dosage standards are essential.

Cannabis (marijuana) for medicinal use has become popular in recent years (currently legal in some form in 32 US states). Aside from cumbersome prescribing issues, the lack of clear safety and quality standards for treatment with cannabis makes many clinicians give pause to this treatment for PPN (despite patients wholeheartedly embracing it). The following section summarizes the evidence for the use of supplements and cannabinoids in the treatment of PPN.

B vitamins and folate

It is well established that deficiency of the B vitamins can cause peripheral neuropathy; thus, B vitamins have been historically used as a therapeutic treatment in clear cases of vitamin deficiency neuropathies. Of note, in the case of B6 specifically, both deficiency and toxicity may cause a neuropathy so supplementation in non-deficient patients should be avoided. The use of B12 appears to reduce symptoms of diabetic neuropathy even in those with normal serum B-12 levels [24, 25]. Methylcobalamin (MC) has a more effective cellular uptake by neurons than cobalamin and is proposed to mitigate oxidative stress, abnormal cellular signaling, and glutamate-induced neurotoxicity in injured neurons [26•]. There have also been a number of retrospective and observational studies with varying methodologies, mostly conducted in Asian populations, demonstrating significant improvement in both subjective symptoms of painful neuropathy and objective outcome measures in DPN patients [24, 25, 26•, 28]. Intravenous (IV) therapies using MC combined with prostaglandin E1 (PE1) and/or lipoic acid have found evidence favoring combination therapy over MC alone in improving nerve conduction parameters in DPN patients [27, 29]. MC alone or in combination therapy via oral or IV routes is widely used in Asia for treatment of DPN. An effective oral regimen used in a small double-blind RCT was 500 mcg of MC three times daily [25]. While there are several examples of studied IV and IM regimens, the practicality and feasibility of recommending oral MC is preferred in the authors' clinical experience [24, 27].

A prescription medical food product for treatment of painful DPN containing L-methylfolate 3 mg, methylcobalamin 2 mg, and pyridoxal-5′-phosphate 35 mg (Metanyx®) demonstrated significant improvement in subjective symptoms and quality of life without a significant difference in vibratory sensory threshold in a 2013 multicenter, randomized, double-blind, placebo-controlled study [30]. Of note, the cost of this product may be prohibitive for many patients when compared with that of other B12 supplements, and as of yet, there are no studies comparing efficacy between Metanx and other B vitamin supplements.

Additionally, a recent study of DPN patients receiving oral folate supplementation 1 mg daily for 16 weeks compared with placebo showed increase in serum folate levels, decreased homocysteine levels, unchanged B12 levels, and significant increase in sensorimotor nerve response amplitudes [31•]. This early but limited evidence implies that folate supplementation could also have a role in the treatment of DPN symptoms.

Vitamin D

While vitamin D deficiency in and of itself does not appear to cause peripheral neuropathy, it has been shown to be an independent risk factor for the development of peripheral neuropathy in diabetic patients [32]. An open-label,

prospective study in 51 patients with painful DPN and vitamin D insufficiency showed that 2000 IU of cholecalciferol (vitamin D3) daily for 3 months resulted in a 50% decrease in the visual analog pain score [33]. A placebo-controlled study in patients with DPN and vitamin D deficiency randomized to 50,000 IU of vitamin D3 once weekly for 8 weeks showed improvement in the Neuropathy Disability Score [34]. Another study of painful DPN found that a single IM dose of 600,000 IU of vitamin D3 had a significant effect on reducing neuropathic pain symptoms and pain scores [35]. This therapeutic effect was maximal at 10 weeks, lasted the 20-week study period, and was independent of baseline vitamin D levels. Further studies are warranted to examine the use of vitamin D3 in those with normal serum vitamin D levels and to employ the use of objective measurements such as nerve conduction studies.

Magnesium

It has been observed that almost 25% of type 1 diabetic patients with or without DPN have low levels of circulating magnesium [36]. In type 2 diabetes patients, neuropathy was found to be more prevalent when magnesium depletion was present, though a direct causal relationship is not clear [37•]. Two studies have shown a correlation between low magnesium levels and abnormal nerve conduction study results [37•, 38•]. Long-term supplementation with 300 mg daily magnesium glycinate vs no supplementation for 5 years in type 1 diabetic patients restored a normal magnesium status and slowed down the natural progression of PN based on patient symptoms and neurologic exam [36]. Based on this preliminary information, more research investigating dosing, tolerability, and effectiveness of oral magnesium supplementation in patients with DPN will inform its clinical use.

Alpha-lipoic acid

Alpha-lipoic acid (ALA), also known as thioctic acid, is found in health supplement products due to its proposed antioxidant and blood glucose-lowering effects [39]. ALA is naturally synthesized in the mitochondria and utilized in mitochondrial energy metabolism. ALA has been used for years in Germany to treat DPN, mostly in the IV form. Studies of ALA in patients with DPN demonstrate variable but significant benefits in both subjective and objective outcomes, including neuropathy scores, vibratory sensory thresholds, and nerve conduction parameters [40, 41••]. A 2012 comprehensive meta-analysis of RCTs found statistically significant evidence from pooled data supporting the use of ALA in reducing the total symptom score (TSS) for DPN [42]. Doses greater than 600 mg showed no further improvement; however, they were associated with greater incidence of side effects such as nausea, vomiting, and dizziness. No upper limit for ALA has been established, but clinical trials have used oral ALA up to 2400 mg daily and IV 600 mg daily with no reported adverse effects compared with placebo [39, 40, 41••, 42]. In the authors' experience, an oral dose trial of ALA of 600 mg at night for 4–6 weeks is a reasonable, low-risk intervention for PPN.

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC) has been gaining popularity in recent years as a supplement for use in DPN due to the proposed mechanism for ALC

acting as a direct antioxidant to reduce mitochondrial DNA damage, modulation of nerve growth factors, and energy regulation in the mitochondria. ALC penetrates the blood-brain barrier, is effective when taken orally, and has a favorable safety profile [43]. Research is promising for the use of ALC in painful DPN and for antiretroviral toxic neuropathy in HIV patients [44].

There are multiple studies demonstrating both subjective and objective favorable outcomes in patients with PPN taking ALC [43–46]. In a systematic review of four RCTs (three for DPN and one for PPN associated with antiretroviral therapy), ALC intake reduced pain when compared with placebo [44]. Additionally, ALC supplementation was not inferior to methylcobalamin for patients with DPN, over 24 weeks, with significant benefits seen in both groups [47••]. Interestingly, there is a wide range of ALC doses used across studies, ranging from 500 to 3000 mg/day with minimal side effects, aside from rare gastrointestinal intolerance. The authors recommended a three-month trial of 1500 to 3000 mg of oral ALC for painful neuropathy as adjunctive treatment, divided into twice or three times daily.

Cannabinoids

Currently, the endocannabinoid system is being investigated for its role in the modulation of neuropathic pain. Understanding this pathway is an emerging area in the development of new pharmaceutical drugs to treat refractory PPN. Meanwhile, medicinal cannabis (i.e., medical marijuana) and its main chemical components tetrahydrocannabinol (THC) and cannabidiol (CBD) are currently available (where legal) and becoming popular for self-management of refractory chronic pain syndromes. THC is the component responsible for psychoactive symptoms but also with what appears to be dose-dependent analgesic effects [48, 49••, 50]. CBD is not psychoactive and has anti-inflammatory and antioxidant properties. Potential THC side effects of cognitive impairment and psychosis, among others, raise concerns regarding the safety and tolerability of high-dose THC preparations for treatment of refractory PPN. There are a small number of studies investigating different formulations of cannabis, including various THC concentrations in smoked whole plant, isolated THC+CBD, plant-derived THC, and synthetic THC. These studies suggest that patients can benefit from cannabis for neuropathic pain relief, however for now, that is still accompanied by expected dose-dependent side effects (largely psychiatric) [48, 49••, 50].

Devices

Whole-body vibration

Whole-body vibration (WBV) is a newer rehabilitation tool that involves the patient standing on a small platform that vibrates mechanically, transferring energy from the vibrating platform to the lower extremities. The proposed benefits of this device include improved strength, stability, glucose regulation, bone density, and even growth hormone production. The literature review by Verhulst et al. reveals conflicting reports of statistically significant benefit of WBV for CIPN [51]. Nevertheless, two small trials in DPN patients showed statistically significant benefit of WBV in

conjunction with balance and strength training compared with training alone [52], improved lower limb muscle strength, and reduced "timed up and go time" test [53].

One of the proposed mechanisms for the improvement observed in muscle strength following WBV is the "Tonic Vibration Reflex." In this reflex, the mechanical stimulation to muscle length is transferred through mono- and polysynaptic pathways from the muscle spindles to the central nervous system for response selection. This reflex is responsible for several peripheral responses including muscular contraction, leading to increased muscle strength. Additionally, the excitation of the Golgi tendon organs activates a reflex through which the agonist muscle is forced to relax while the antagonist muscle contracts, allowing for further movement [54].

In summary, the primary benefits of the WBV device seem to be ease of use, time efficiency, and availability to patients unable to fully participate in therapy regimens, with minimal adverse effects.

The scrambler

The scrambler therapy is a relatively new neuromodulatory device that is non-invasive and is designed to work through electrocutaneous stimulation of nerves, similar to a transcutaneous electrical nerve stimulation (TENS) unit, with the proposed mechanism of retraining the perception of pain via neuroplasticity. This type of stimulation is widely used for musculoskeletal pain syndromes including chronic low back pain [55•]. The limited studies available focus on the treatment of CIPN-related pain.

Although cost and access to this device may limit its use, the available studies show promising results. A pilot trial of 37 CIPN patients treated with scrambler therapy (ST) resulted in 53% reduction in pain scores as measured through the pain numerical rating scale, ranging from 0 to 10 [56]. Statistically significant pain reduction was also seen in another prospective trial of by Ricci et al. in 219 patients with chronic pain, 37% of whom had cancer-related pain [57]. In both studies, pain reduction was maintained during follow-up and minimal side effects were reported [56, 57].

Dorsal root nerve stimulation

Neurostimulation is a fairly common treatment modality for chronic back pain, particularly through surgically implanted dorsal column spinal cord stimulators. The dorsal root ganglion (DRG) is a target for PPN symptom relief using an implantable neurostimulator. Only recently, DRG neurostimulation has been investigated for PPN relief. In a small study of patients with DPN, peripheral stimulation between L2 and L5 spinal levels led to markedly reduced pain scores, and 70% of patients that permanent stimulator implants experienced continued pain relief over the 12-month follow-up period [53]. While early, this data suggests that DRG stimulation may be an effective method to treat PPN and is a relatively safe modality aside from procedural risks. Barriers to this treatment include complications of a minor surgical procedure and cost. Given this, a cost benefit analysis, prospective follow-up at 2 years, and control comparison with standard treatment would be helpful to assess feasibility and long-term outcomes.

Emerging therapies

Yoga

In addition to more traditional aerobic, resistance, and balance exercises, the practice of yoga is increasingly being incorporated into a healthy lifestyle. As a method for improving general wellness, balance, cardiovascular health, and mental health, yoga has also been shown to positively impact multiple health parameters in diabetic and pre-diabetic patients including reduction in BMI, waist circumference, systolic blood pressure, and fasting glucose [58]. Furthermore, some studies demonstrate reduction in oxidative stress parameters after yoga programs [59].

There have been limited studies investigating the effect of yoga on peripheral neuropathy although the opportunity exists. Research thus far has largely addressed patients with DPN and the results are promising. In one study of patients with early DPN, a yoga program comprising a daily 30–40-min asanas (yoga poses) routine over 40 days showed overall stability of nerve conduction velocity of the median nerves compared with deterioration of the control group, suggesting neuroprotective effects in these patients [60]. A more recent study of patients with DPN undergoing a daily, 60-min Hatha Yoga (relaxation or restorative) program over 8 weeks showed improvements in multiple holistic areas including functionality, balance, stress management, and sleep [61•].

Overall, yoga appears to be a promising modality for improving quality of life in patients with diabetic neuropathy, and there is limited data to suggest some degree of nerve protection and stability of nerve function in these patients. Although yoga is becoming more mainstream and available to different groups, access and cost continue to be barriers to its implementation. Further studies with larger patient populations would be needed to demonstrate duration and number of sessions needed for benefit and to investigate generalizability in non-diabetic neuropathy patients.

Meditation

Similar to yoga, meditation has been gaining popularity in recent years as a readily available method of improving mindfulness, stress reduction, mental health, and sleep. Mindfulness meditation practices are thought to reduce chronic pain by adjusting the amplification of nociceptive sensory processes [62]. Proposed neural mechanisms involved in the analgesic effects of meditation include bilateral thalamic deactivation and greater activation of the subgenual anterior cingulate cortex (sgACC), orbitofrontal cortex (OFC), and right anterior insula. The sgACC is involved in the cognitive and affective control of pain. The OFC has been associated with altering the contextual evaluation of sensory events, and the right anterior insula is implicated in afferent nociceptive modulation and interoceptive awareness [62]. While studies show promising results for the attenuation of chronic pain with meditation, the effects on peripheral neuropathy have not been well studied. In two studies investigating the effects of meditation on neuropathy, neither demonstrated a significant difference in quality of life, functionality, or pain scores after meditation [63, 64]. Data is limited and studies of larger populations and more regimented programs may be helpful to investigate benefit of meditation in

PPN. While patients may benefit from meditation's effects in their general health, the current data does not suggest any benefit specific to PPN.

Acupuncture

Although frequently met with hesitation, acupuncture is an established method of treating chronic and musculoskeletal pain as well as other conditions. The actual mechanisms behind acupuncture are poorly understood; proposed pathways include endorphin release, anti-inflammatory responses, and autonomic remodeling [65•]. There is supportive evidence for the use of acupuncture in chronic pain patients (particularly in CIPN when combined with reflexology) [66], and there is emerging data for its use in PPN. The specific use of acupuncture for certain peripheral neuropathies such as DPN, HIV-PN, and carpal tunnel syndrome has been well studied and is detailed as reviewed by Dimitrova et al. [67••].

Shin et al. investigated the efficacy of electro-acupuncture in DPN in 126 patients with at least a 6-month history of painful DPN. The treatment group received acupuncture twice a week for 8 weeks and demonstrated statistically significant improvement in pain scores when compared with the non-treatment group [68•]. Two studies of acupuncture in CIPN patients investigated the effect of acupuncture on the incidence of CIPN during paclitaxel chemotherapy suggesting that acupuncture may reduce incidence of CIPN in this population [69•]; acupuncture also improved subjective sensorimotor symptoms significantly in patients with established CIPN associated with bortezomib [70•].

Overall, current evidence suggests that acupuncture may be efficacious in treating PPN of various etiologies with minimal adverse effects. However, cost, insurance coverage, and availability may be a limitation in some communities. High-quality, sham-controlled studies are needed to demonstrate effectiveness and indication of acupuncture for PPN.

Other treatments

Besides the various modalities that have been studied more extensively discussed above, there are several approaches currently being investigated for various neuropathies, and those include essential oils and natural products, probiotics, high-intensity ultrasound therapy, and neurofeedback:

- Topical linseed oil is used in traditional Iranian medicine as an analgesic, anti-inflammatory, and antioxidant vs placebo was applied in addition to nightly wrist splinting, demonstrating significant improvement in Boston Carpal Tunnel Questionnaire (BCTQ)—a validated measurement, assessing symptom severity. Additionally, median nerve conduction velocities were significantly improved in the treatment group [71].
- Topical chamomile oil was investigated by Hashempur et al. through the use of topical chamomile oil vs placebo, plus nightly wrist splinting for 4 weeks, and found improvement in subjective symptoms and in median nerve compound latency [72•]. Both studies show promise and with fairly cheap and widely available compounds.
- Betulinic acid is being investigated as a non-opioid way to treat CIPN, largely aimed at pain alleviation. A recent in vivo study of betulinic acid (derived from a desert lavender) demonstrated reversal of mechanical allodynia in rat models of CIPN, HIV-PN, and partial sciatic nerve ligation

after intrathecal administration of the drug [73].

- Probiotics: An in vitro study of the probiotic DSF (high-concentration formulation) in the F11 neuron model demonstrated normalization of pain-associated receptors with paclitaxel exposure, suggesting a potential role of some probiotic formulations in the regulation of inflammation and pain remodeling in CIPN patients [74•].
- High-intensity ultrasound: The effectiveness of high-intensity ultrasound applied to the L5 dorsal root ganglia in vincristine-induced neuropathy rat models of CIPN demonstrated significantly improved innocuous and noxious mechanical thresholds and thermal thresholds compared with sham treatment rats suggesting potential effectiveness [75•].
- Neurofeedback is gaining popularity, showing promise in a variety of chronic conditions including chronic pain, headaches, and anxiety. A recent study in CIPN patients comparing 20 sessions of neurofeedback resulted in improvement in pain severity, numbness, functional interference, and fatigue, all of which persisted at 4-month follow-up [76•].

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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