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Updates in the treatment of chemotherapy-induced peripheral neuropathy

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Opinion statement

Chemotherapy-induced peripheral neuropathy (CIPN) is a common toxicity associated with treatment with platinum-based agents, taxanes, vinca alkaloids, and other specific agents. The long-term consequences of this condition can result in decreased patient quality of life and can lead to reduced dose intensity, which can negatively impact disease outcomes. There are currently no evidence-based preventative strategies for CIPN and only limited options for treatment. However, there are several strategies that can be utilized to improve patient experience and outcomes as more data are gathered in the prevention and treatment setting. Before treatment, patient education on the potential side effects of chemotherapy is key, and although trials

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have been limited, recommending exercise and a healthy lifestyle before and while undergoing chemotherapy may provide some overall benefit. In patients who develop painful CIPN, our approach is to offer duloxetine and titrate up to 60mg daily. Chemotherapy doses may also need to be reduced if intolerable symptoms develop during treatment. Some patients may also try acupuncture and physical therapy to help address their symptoms, although this can be limited by cost, time commitment, and patient motivation. Additionally, data on these modalities are currently limited, as studies are ongoing. Overall, approaching each patient on an individual level and tailoring treatment options for them based on overall physical condition, their disease burden, goals of care and co-morbid health conditions, and willingness to trial different approaches is necessary when addressing CIPN.

Keywords

Chemotherapy-induced peripheral neuropathy; duloxetine; acupuncture; exercise therapy

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious potential side effect of treatment with a number of chemotherapeutic agents, including taxanes, platinum-based compounds, vinca alkaloids, epothilones, and bortezomib, and CIPN affects between 30 to 40% of patients treated with these agents [1, 2]. Symptoms of CIPN result from damage to dorsal root ganglion neurons or their axons, leading to physical findings of a sensory peripheral neuropathy including sensory loss, paresthesia, ataxia, and allodynia [2, 3]. Nerve conduction studies in patients with CIPN show that both small and large motor and sensory nerve fibers undergo axonal degeneration, leading to these often debilitating symptoms [4].

CIPN can result in a significant dose reduction in chemotherapy. For example, in patients receiving oxaliplatin at cumulative doses of more than 540–850mg/m^2, CIPN symptoms required dose reductions in oxaliplatin by up to 62.5% [5, 6]. CIPN also reduces patient quality of life, increasing the long-term risk of falls and functional impairments [3, 7–11]. The incidence of CIPN is highest within the first two years following exposure to cytotoxins, making it a common concern for recent cancer survivors [12]. Additionally, symptom severity can vary widely among patients [2]. In spite of the severity of the impact of CIPN, evidenced-based management options are limited, with current approaches aimed at either preventing the development of CIPN or managing symptoms once they develop.

The 2020 ASCO guideline update does not recommend any specific agents for the treatment of CIPN other than the potential limited benefit of duloxetine for painful CIPN [1]. In information provided to patients who develop CIPN, home safety measures like using handrails and burn prevention are recommended, and the potential permanent nature of symptoms are discussed, but treatment options continue to be described as limited [13]. Additionally, patient-reported symptom severity may be even higher than neuropathy grades given by physicians based on standard scoring mechanisms [14–16]. Patient outcome measures, including the patient-reported outcome (*PRO*) measure and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of

Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy scale (QLQ-CIPN20), are questionnaires that focus on physical, emotional, and cognitive function and provide benefit in identifying better CIPN intervention trials in finding successful strategies for CIPN prevention and treatment [17–19]. The EORTC-CIPN20 [20–23] and FACT/GOG NTx [22, 24, 25] are the most commonly utilized Patient-Reported Outcome Measures (PROMs) in published studies of CIPN. The discrepancy between patient-reported outcomes and physician scoring highlights the urgency with which continued multimodal, evidence-based treatment regimens are needed for this condition and shows that patient-reported outcomes will be the gold standard in effectively managing this condition

In a 2019 National Cancer Institute clinical trials planning meeting, CIPN was demonstrated as a high priority for symptom management that warrants further exploration [17]. Given the limited management guidelines available, this article will summarize current treatment methods available for CIPN symptoms and highlight potential emerging therapies with the goal of assisting those treating patients suffering from CIPN in developing multimodal strategies to address this disorder.

Treatment options

Diet and lifestyle

Diet—In general, there is no evidence that specific foods or diets will prevent or treat CIPN, and studies examining dietary patterns have not elucidated clear results. For example, analysis of patients enrolled in the Pathways study, which used a population-based prospective cohort of 4,505 women with newly diagnosed invasive breast cancer, showed that patients with a higher intake of fruits, vegetables, and dietary fats actually experienced more neuropathy symptoms, although their self-reported physical well-being scores were higher [26]. Studies relying on patient-reported data show that multivitamin and magnesium use before and during treatment may be associated with a lower risk of CIPN or with less severe symptoms, although the data varies widely from patient to patient and is subject to recall bias in some cases [27–29]. Studies examining supplement use remain small and require additional testing, although some have reported positive results in the reduction of pain and neuropathic impairment in initial trials [30]. In general, however, the use of supplements other than a multivitamin in cancer patients requires additional study to determine both safety and efficacy, and ASCO guidelines currently recommend against the use of supplements due to the lack of evidence supporting their benefit [1, 31]. Additionally, recent trial data highlights that some supplements can be associated with poorer disease-free survival and, in the case of acetyl-L-carnitine, can even worsen CIPN symptoms [31, 32].

In a recent study using a mouse model of paclitaxel-induced peripheral neuropathy, a fenofibrate-enriched diet did show promise in that it had some ability to prevent the development of mechanical hypersensitivity, prevented cold hypersensitivity, and prevented a reduction in sensory nerve action potential in mice treated with four intraperitoneal injections of paclitaxel [33]. This will obviously take time to extrapolate to human studies of CIPN. Theoretically, flavonoids are another potential option for managing CIPN based on their mechanism of action and animal models, but human studies are again needed [34]. Additionally, the use of any supplement during chemotherapy must be shown to be

safe in terms of potential interactions with chemotherapy agents and must not decrease the effectiveness of chemotherapy.

Exercise—Exercise is the most common intervention for CIPN with a varied combination of sensorimotor exercise, yoga, aerobic, strength, balance training and physical activity [35–39]. Overall, there is a lack of high-quality evidence to support specific interventions in CPIN [39], but exercise and exercise rehabilitation strategies play important roles in improving the strength, balance, and lessening symptom progression in CIPN patients [40].

Recent trials suggest that balancing and muscle strengthening exercises can improve quality of life and reduce CIPN pain; however, the trial sample sizes were small, and it should be noted that patients in the intervention group had a larger body surface area and received higher doses of chemotherapy than the placebo group in initial studies [21, 37, 41, 42]. A randomized controlled trial also determined that, although patients reported higher quality of life scores on assessment, there was no significant difference in their sensory or motor symptom scores after completing a dedicated exercise program [23].

Several potential mechanisms that may explain the beneficial effects of exercise on CIPN symptoms include the ability of exercise to reduce chronic inflammation and to change how sensations are processed by the brain to the hands, feet, and the rest of the body [43]. Recent growing evidence also suggests that exercise can prevent CIPN [20, 23, 37, 44], although we need larger phase II and phase III studies to minimize the limitations of the current available data. Overall, ASCO does not have any formal recommendations regarding the benefit of exercise in preventing or treating CIPN, although a general consensus appears to agree that exercise is in no way detrimental to the management of this disease [45].

Pharmacologic treatment

Class of drugs

Specific drugs

Antidepressants

Serotonin-norepinephrine reuptake inhibitors: Duloxetine and venlafaxine: The agent with by far the most evidence behind its efficacy in the treatment of CIPN and the only agent currently recommended by ASCO for the treatment of CIPN is duloxetine, a SNRI. Smith *et al.'s* 2013 phase III trial showed a significant improvement in pain control between patients taking duloxetine versus placebo after just five weeks [46]. This does not appear to be completely unique among the SNRIs, as comparative studies examining duloxetine versus venlafaxine showed that duloxetine was more effective in decreasing overall motor neuropathy and neuropathic pain grade scores after four weeks in patients suffering from CIPN [47]. Interestingly, venlafaxine did have some reduction in pain compared to a placebo group, and it was suggested that the least expensive agent should be trialed first prior to changing to a more expensive agent on an individual basis [47]. Of note, however, the doses used in this trial were 37.5mg venlafaxine and 30mg duloxetine, where previous studies, including Smith *et al.*'s, have determined that 60mg duloxetine is the most effective dose to treat CIPN, so further trials should be pursued to test different therapeutic doses of the

two agents instead of comparing the efficacy of the two agents to one another [46–49]. In a current ongoing trial through Alliance for Clinical Trials in Oncology, Dr. Ellen M. Lavoie Smith is examining the best dose of duloxetine for CIPN prevention in colorectal cancer patients undergoing treatment with oxaliplatin.

In general, the side effects of duloxetine are mild, and most commonly include mild nausea, poor appetite, constipation, drowsiness or insomnia, and sexual side effects [47, 50]. Although laboratory monitoring is not required, it can cause transient elevations of liver enzymes and can increase serum cholesterol, and it should not be given to patients with a creatinine clearance of less than 30 mL/min. The use of SSRIs and SNRIs is also cautioned in patients taking tamoxifen, as these medications can decrease the hepatic metabolism of tamoxifen into its active metabolite [47]. In general in the U.S., if duloxetine is not covered by a patient's insurance, the high monthly cost of therapy may preclude treatment, as well.

Tricyclic antidepressants: amitriptyline, despiramine, and nortriptyline: Tricyclic antidepressants are not recommended for the treatment of CIPN, and two small double-blind, placebo-controlled trials examining amitriptyline and nortriptyline did not show any benefit of these agents in treating patients with CIPN symptoms [51, 52]. Given the vast side effect profile and potential for overdose, the routine prescription of these medications is not recommended [53].

Gabapentinoids: gabapentin and pregabalin: Gabapentin and pregabalin are commonly used to treat neuropathic pain, but they are not useful in CIPN and have the risk of side effects and, in the case of pregabalin, high cost. A phase three double-blind placebo-controlled trial failed to show any benefit from the use of gabapentin to treat CIPN symptoms in patients who received vinca alkaloid, platinum-based, or taxane chemotherapy [54]. A placebo-controlled trial addressing the utility of pregabalin in preventing CIPN also showed no difference in neuropathy symptoms or pain between treatment and control groups in patients undergoing treatment with paclitaxel [55]. We should note, however, that the use of these medications in patients with neuropathic cancer-related pain, not CIPN, can be effective, with pregabalin having the most significant improvement in cancer-related pain scores and sparing the use of opioids in patients with active malignancy [56].

Opioid analgesics: Although often medically necessary to treat active cancer-related pain, opioids are not recommended for the treatment of CIPN and risk unnecessary side effects, potential addiction, and increased cost to the healthcare system [57–59]. As a salvage option, however, the European Society for Medical Oncology (ESMO) does note that opioids may be an option for CIPN, with no specific opioid being better than another [60].

Additional agents: Table 1 details additional agents occasionally used to treat CIPN. It should be noted that none of these agents are recommended by ASCO or have shown statistically significant efficacy in the treatment of CIPN in clinical trials.

Interventional procedures

The majority of available interventional procedures aim to prevent CIPN and will be described briefly here, but three procedures in particular, acupuncture, neurofeedback

therapy, and botulinum toxin injections have limited evidence suggesting their roles in treatment of this condition and warrant further investigation.[68]

Specific interventional procedures

Acupuncture: After an initial case series involving five patients treated with acupuncture showed improvement in CIPN symptoms [78], additional trials sought to show the benefits of this therapy in CIPN patients. A small pilot study showed improvement in five of six patients with CIPN treated with acupuncture [79], and a small retrospective study of breast cancer patients also suggested the benefit of this practice for improving CIPN symptoms [80]. A recent randomized controlled pilot trial of forty women treated with taxanes for breast cancer who developed CIPN showed that those who underwent an eight-week acupuncture treatment regimen had significant improvement in neuropathic pain and sensory symptoms [81]. In general, the availability and cost of acupuncture may be challenging for patients seeking treatment, but the overall positive nature of these studies indicates that larger randomized controlled trials are needed to assess the effectiveness of acupuncture as a treatment for CIPN, especially given the limited options for medical management of this condition. Larger randomized studies in acupuncture are currently ongoing, with Dr. Ting Bao from Memorial Sloan Kettering Cancer Center currently leading a trial examining the benefits of acupuncture and acupressure for CIPN.

Cryotherapy and compression therapy: Cryotherapy involves cooling the skin surface in an attempt to limit local effects of chemotherapy. This can involve limb-induced hypothermia or cooling gloves or socks, and it is often combined with compression therapy, a process that utilizes elastic stockings or surgical gloves to apply diffuse pressure to the skin surface [82]. Used for the prevention of CIPN, prophylactic cryotherapy has been shown to reduce the risk of dose reduction of taxane-based chemotherapy [83]. Additional studies have sought to determine its ability to prevent CIPN symptoms. Compression therapy can be used with or without cryotherapy for prevention of CIPN, although it is much less expensive than cryotherapy when used alone. Prospective and phase II trials have shown the benefit of cryotherapy in preventing peripheral neuropathy in patients undergoing neurotoxic chemotherapy [84, 85], although it should be noted that studies of cryotherapy and compression therapy showed that compression therapy alone appears to be just as effective as cryotherapy [82]. All of these studies were limited by sample size and warrant further investigation with multi-institution, randomized controlled trials in the future. These studies are currently under development.

Neurofeedback: Electroencephalogram (EEG) neurofeedback involves a brain/computer interface and provides auditory and visual feedback to help participants modify the source of their pain perception in real time [86, 87]. This effectively allows patients to change the interpretation of their neurological pain signals. In a randomized controlled trial in which the treatment group of cancer survivors underwent twenty sessions of neurofeedback therapy, patients in the treatment group showed a statistically significant reduction in pain scores with corresponding EEG changes that predicted improvement of symptoms [86]. Follow up with the same patient cohort at four months showed continued effectiveness of neurofeedback [87]. Although this study had a small sample size, and will require longer-

term follow up, the overall improvement in symptoms of CIPN and duration of improvement suggests that neurofeedback warrants further investigation. Of note, this procedure requires both a significant time and cost commitment from patients and the healthcare system, so systemic administration of neurofeedback therapy may be limited in the future regardless of long-term outcomes.

Physical therapy and other specific therapies

Physical therapy—In a recent RCT examining the utility of physical therapy for the treatment of CIPN, the authors found improved grip dynamometry and pain pressure thresholds as well as decreased pain over time in the treatment group (of note, this study only examined a small cohort of patients up to six months post-chemotherapy) [88]. It should be noted, however, that patients who reported more exercise in general also had improved heat pain thresholds and vibratory sensation compared to more sedentary individuals [88]. It may be, therefore, that physical therapy can be considered for patients with specific functional mobility deficits at risk of developing CIPN, but there may be more evidence for the benefit of general exercise and strength training compared to physical therapy alone.

Specific therapies

Sensorimotor training and whole-body vibration training: In a promising prospective RCT, patients in the intervention groups reported subjective improvement of CIPN symptoms and also had objective improvement in tendon reflexes and pain control in the sensorimotor training and whole-body vibration training groups, respectively [89]. The benefit of this study is that patients with known CIPN were targeted verses other studies examining patients undergoing chemotherapy at risk of developing CIPN. With a small sample size (forty patients), the potential benefits of sensorimotor training and whole-body vibration therapy warrant further investigation, especially since, as the authors note, both therapies require relatively little time and effort to complete.

Other treatments

Scrambler therapy: Scrambler therapy involves the use of a device that delivers electrocutaneous stimulation to the skin and is designed to replace endogenous pain signals. In single arm trials, scrambler therapy seemed to effectively treat painful CIPN [90, 91]; however, data from randomized controlled trials has been mixed and is less promising [92, 93]. Additional studies in this area are needed.

Surgical management: There are not currently any recommended surgical management options for CIPN.

Emerging therapies

Several emerging therapies are under evaluation seeking a novel approach to the prevention or treatment of CIPN. Hu *et al.* assembled a comprehensive review of such therapies in 2019 [3].

Axonal Degeneration—Axonal degeneration has been implicated in the development of CIPN symptoms. There are several proposed mechanisms of axon destruction, and trials evaluating their inhibition are ongoing.

One source of axonal degeneration is the expression of sterile alpha and TIR motif-containing protein (SARM-1). When activated, SARM-1 leads to rapid breakdown of nicotinamide adenine dinucleotide (NAD^+) which ultimately results in axonal destruction. The primary suggested therapy to counteract the destructive activity of SARM-1 is driving increased NAD^+ synthesis in vivo [94]. Another proposed source of axonal degeneration is an aggregation of cis-platinum in dorsal root ganglion (DRG) neurons. Ethoxyquin (EQ) is an antioxidant that has been used as a food preservative for decades [95]. EQ has been found to mitigate CIPN symptoms in mice via modulation of HSP90 without obstructing the anti-tumor effect of cisplatin [95]. A third source of axonal destruction results from inhibition of BCL-w translation by paclitaxel. When active, BCL-w binds IP_3R1 and preserves axonal integrity. It has been proposed that a BCL-w mimetic in sufficient concentration could overcome the effects of paclitaxel [96].

Botulinum Toxin Injections—Although not yet studied in humans, a botulinum toxin-neuropeptide conjugate was tested in a murine model of taxol-induced neuropathy [97]. In this study, an injection of the conjugate molecule decreased pain, suggesting that the use of botulinum toxin-neuropeptide conjugates may be a potential future therapy for humans suffering from CIPN [97].

Ganglioside-Monosialic Acid—Ganglioside-monosialic acid (GM1) is a glycosphingolipid involved in nerve development, differentiation, and repair. In CIPN studies, patients were provided with oxaliplatin and GM1 concurrently or oxaliplatin alone. Patients that received GM1 experienced neuropathy symptoms at levels near to the control group; however, the severity of their symptoms was significantly lower [98]. Clinical trials evaluating GM1 utility are ongoing.

Mitochondrial Enzyme—Mitochondrial injury has been identified as a possible correlative with CIPN. It has been proposed that injury stems from oxidative stress, and possible treatments are currently being evaluated in clinical trials. One promising study is assessing the activity of a manganese superoxide dismutase mimic known as calmangafodipir, which combats reactive oxygen species and thereby prevents nerve injury [99].

Immunomodulation—Taxanes, platinum-based agents, and proteasome inhibitors have been known to dysregulate sphingolipid metabolism. The result is an increase of Sphingosine 1-Phosphate (S1P), which binds and activates the sphingosine-1-phosphate receptor (S1PR1). This CIPN-causing pathway seems to be inhibited by the immunomodulating drug fingolimod. Fingolimod is FDA-approved for the treatment of multiple sclerosis and has known adverse side effects including bradycardia and hypotension [100].

Another medication with a similar downstream effect to fingolimod is nicotine. Nicotine may promote the nicotinic acetylcholine receptor-mediated pathway, ultimately resulting in prevention or treatment of CIPN. However, the possibility that nicotine may also encourage tumor growth supports the need for further study [101].

Neuronal Transporter Inhibition—Two types of transporters allow for accumulation of chemotherapy agents in the dorsal root ganglia: organic anion transporting polypeptides (OATP), and organic cation transporters (OCT). Knockout of these transporters in mice has been found to protect against symptoms of CIPN [102].

Targeting Endonuclease Function—Nerve injury can also occur when sensory neuron DNA is damaged by chemotherapeutic agents. When this occurs, apyrimidinic endonuclease/redox effector factor (APE1) clears the damaged DNA. Studies show that reduction in APE1 levels in neuronal samples treated with cisplatin or oxaliplatin lead to increased neurotoxicity [103]. Studies evaluating the efficacy of an APE1 targeting agent, APX2009, are ongoing [104].

Conclusions

CIPN presents numerous challenges: it can lead to dose reductions in chemotherapy and can significantly affect patient quality of life. Our treatment options for CIPN remain limited in spite of numerous trials assessing the utility of different medications and multimodal treatment strategies. Research in the field, however, remains promising, with both *in vivo* studies and early-stage clinical trials showing the potential benefit of a number of different treatment methods. As studies begin to incorporate larger sample sizes and gain greater power, our hope is that we will soon have a better regimen of treatment options and preventative strategies for this debilitating condition.

References and Recommended Reading

1. Loprinzi CL, et al. , Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol, 2020. 38(28): p. 3325–3348. [PubMed: 32663120]
2. Staff NP, et al. , Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol, 2017. 81(6): p. 772–781. [PubMed: 28486769]
3. Hu S, et al. , Recent Developments of Novel Pharmacologic Therapeutics for Prevention of Chemotherapy-Induced Peripheral Neuropathy. Clin Cancer Res, 2019. 25(21): p. 6295–6301. [PubMed: 31123053]
4. Krøigård T, et al. , Characterization and diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin and docetaxel comparing skin biopsy to quantitative sensory testing and nerve conduction studies. Eur J Neurol, 2014. 21(4): p. 623–9. [PubMed: 24460946]
5. Gamelin E, et al. , Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol, 2002. 29(5 Suppl 15): p. 21–33.
6. Leonard GD, et al. , Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. BMC Cancer, 2005. 5: p. 116. [PubMed: 16168057]

7. Bonhof CS, et al. , Course of chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer patients: A longitudinal study. Gynecol Oncol, 2018. 149(3): p. 455–463. [PubMed: 29605500]
8. Zajączkowska R, et al. , Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. Int J Mol Sci, 2019. 20(6).
9. Gewandter JS, et al. , Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. Support Care Cancer, 2013. 21(7): p. 2059–66. [PubMed: 23446880]
10. Schneider BP, Hershman DL, and Loprinzi C, Symptoms: Chemotherapy-Induced Peripheral Neuropathy. Adv Exp Med Biol, 2015. 862: p. 77–87. [PubMed: 26059930]
11. Speck RM, et al. , Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients. Support Care Cancer, 2012. 20(10): p. 2433–9. [PubMed: 22231480]
12. Shah A, et al. , Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort. J Neurol Neurosurg Psychiatry, 2018. 89(6): p. 636–641. [PubMed: 29439162]
13. Brown TJ, Sedhom R, and Gupta A, Chemotherapy-Induced Peripheral Neuropathy. JAMA Oncol, 2019. 5(5): p. 750. [PubMed: 30816956]
14. Nyrop KA, et al. , Patient-reported and clinician-reported chemotherapy-induced peripheral neuropathy in patients with early breast cancer: Current clinical practice. Cancer, 2019. 125(17): p. 2945–2954. [PubMed: 31090930]
15. Paice JA, et al. , AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions. J Pain, 2017. 18(3): p. 233–246. [PubMed: 27884691]
16. Tan AC, et al. , Chemotherapy-induced peripheral neuropathy-patient-reported outcomes compared with NCI-CTCAE grade. Support Care Cancer, 2019. 27(12): p. 4771–4777. [PubMed: 30972648]
17. Dorsey SG, et al. , The National Cancer Institute Clinical Trials Planning Meeting for Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy. J Natl Cancer Inst, 2019. 111(6): p. 531–537. [PubMed: 30715378]
18. Gewandter JS, et al. , Trial designs for chemotherapy-induced peripheral neuropathy prevention: ACTTION recommendations. Neurology, 2018. 91(9): p. 403–413. [PubMed: 30054438]
19. Smith EML, et al. , In Search of a Gold Standard Patient-Reported Outcome Measure for Use in Chemotherapy- Induced Peripheral Neuropathy Clinical Trials. Cancer Control, 2018. 25(1): p. 1073274818756608. [PubMed: 29480026]
20. Chen SC, et al. , Non-randomized preliminary study of an education and elastic-band resistance exercise program on severity of neuropathy, physical function, muscle strength and endurance & quality of life in colorectal cancer patients experiencing oxaliplatin-induced peripheral neuropathy. Eur J Oncol Nurs, 2020. 49: p. 101834. [PubMed: 33120223]
21. McCrary JM, et al. , Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. Support Care Cancer, 2019. 27(10): p. 3849–3857. [PubMed: 30756229]
22. Kneis S, et al. , It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. BMC Cancer, 2019. 19(1): p. 414. [PubMed: 31046719]
23. Bland KA, et al. , Effect of Exercise on Taxane Chemotherapy-Induced Peripheral Neuropathy in Women With Breast Cancer: A Randomized Controlled Trial. Clin Breast Cancer, 2019. 19(6): p. 411–422. [PubMed: 31601479]
24. Streckmann F, et al. , Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-a randomized controlled pilot trial. Support Care Cancer, 2019. 27(7): p. 2471–2478. [PubMed: 30382392]
25. Galantino ML, et al. , Impact of Somatic Yoga and Meditation on Fall Risk, Function, and Quality of Life for Chemotherapy-Induced Peripheral Neuropathy Syndrome in Cancer Survivors. Integr Cancer Ther, 2019. 18: p. 1534735419850627. [PubMed: 31131640]

26. Shi Z, et al. , Distinct trajectories of fruits and vegetables, dietary fat, and alcohol intake following a breast cancer diagnosis: the Pathways Study. Breast Cancer Res Treat, 2020. 179(1): p. 229–240. [PubMed: 31599394]
27. Zirpoli GR, et al. , Supplement Use and Chemotherapy-Induced Peripheral Neuropathy in a Cooperative Group Trial (S0221): The DELCaP Study. J Natl Cancer Inst, 2017. 109(12).
28. Wesselink E, et al. , Dietary Intake of Magnesium or Calcium and Chemotherapy-Induced Peripheral Neuropathy in Colorectal Cancer Patients. Nutrients, 2018. 10(4).
29. Mongiovi JM, et al. , Associations between self-reported diet during treatment and chemotherapy-induced peripheral neuropathy in a cooperative group trial (S0221). Breast Cancer Res, 2018. 20(1): p. 146. [PubMed: 30486865]
30. Desideri I, et al. , Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera. Med Oncol, 2017. 34(3): p. 46. [PubMed: 28205185]
31. Ambrosone CB, et al. , Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221). J Clin Oncol, 2020. 38(8): p. 804–814. [PubMed: 31855498]
32. Hershman DL, et al. , Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol, 2013. 31(20): p. 2627–33. [PubMed: 23733756]
33. Caillaud M, et al. , A Fenofibrate Diet Prevents Paclitaxel-Induced Peripheral Neuropathy in Mice. Cancers (Basel), 2020. 13(1).
34. Siddiqui M, et al. , Flavonoids Alleviate Peripheral Neuropathy Induced by Anticancer Drugs. Cancers (Basel), 2021. 13(7).
35. Clark PG, Cortese-Jimenez G, and Cohen E, Effects of Reiki, Yoga, or Meditation on the Physical and Psychological Symptoms of Chemotherapy-Induced Peripheral Neuropathy:A Randomized Pilot Study. Journal of Evidence-Based Complementary & Alternative Medicine, 2012. 17(3): p. 161–171.
36. Bao T, et al. , Yoga for Chemotherapy-Induced Peripheral Neuropathy and Fall Risk: A Randomized Controlled Trial. JNCI Cancer Spectr, 2020. 4(6): p. pkaa048. [PubMed: 33225208]
37. Kleckner IR, et al. , Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer, 2018. 26(4): p. 1019–1028. [PubMed: 29243164]
38. Courneya KS, et al. , A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy. Cancer Epidemiol Biomarkers Prev, 2014. 23(5): p. 857–64. [PubMed: 24599578]
39. Kanzawa-Lee GA, et al. , Exercise Effects on Chemotherapy-Induced Peripheral Neuropathy: A Comprehensive Integrative Review. Cancer Nurs, 2020. 43(3): p. E172–e185. [PubMed: 32187026]
40. Andersen Hammond E, et al. , An Exploratory Randomized Trial of Physical Therapy for the Treatment of Chemotherapy-Induced Peripheral Neuropathy. Neurorehabilitation and Neural Repair, 2020. 34(3): p. 235–246. [PubMed: 31976819]
41. Dhawan S, et al. , A Randomized Controlled Trial to Assess the Effectiveness of Muscle Strengthening and Balancing Exercises on Chemotherapy-Induced Peripheral Neuropathic Pain and Quality of Life Among Cancer Patients. Cancer Nurs, 2020. 43(4): p. 269–280. [PubMed: 30888982]
42. Schwenk M, et al. , Interactive Sensor-Based Balance Training in Older Cancer Patients with Chemotherapy-Induced Peripheral Neuropathy: A Randomized Controlled Trial. Gerontology, 2016. 62(5): p. 553–63. [PubMed: 26678611]
43. Holschneider DP, et al. , Reorganization of functional brain maps after exercise training: Importance of cerebellar-thalamic-cortical pathway. Brain Res, 2007. 1184: p. 96–107. [PubMed: 17964551]
44. Zimmer P, et al. , Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Supportive Care in Cancer, 2018. 26(2): p. 615–624. [PubMed: 28963591]

45. Duregon F, et al. , Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol, 2018. 121: p. 90–100. [PubMed: 29198853]
46. Smith EM, et al. , Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA, 2013. 309(13): p. 1359–67. [PubMed: 23549581]
47. Farshchian N, et al. , Comparative study of the effects of venlafaxine and duloxetine on chemotherapy-induced peripheral neuropathy. Cancer Chemother Pharmacol, 2018. 82(5): p. 787–793. [PubMed: 30105459]
48. Piccolo J and Kolesar JM, Prevention and treatment of chemotherapy-induced peripheral neuropathy. Am J Health Syst Pharm, 2014. 71(1): p. 19–25. [PubMed: 24352178]
49. Smith EM, et al. , Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial - CALGB/alliance 170601. Eur J Cancer Care (Engl), 2017. 26(2).
50. Aziz MT, Good BL, and Lowe DK, Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. Ann Pharmacother, 2014. 48(5): p. 626–32. [PubMed: 24577146]
51. Hammack JE, et al. , Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain, 2002. 98(1–2): p. 195–203. [PubMed: 12098632]
52. Kautio AL, et al. , Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. J Pain Symptom Manage, 2008. 35(1): p. 31–9. [PubMed: 17980550]
53. Kerr GW, McGuffie AC, and Wilkie S, Tricyclic antidepressant overdose: a review. Emerg Med J, 2001. 18(4): p. 236–41. [PubMed: 11435353]
54. Rao RD, et al. , Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer, 2007. 110(9): p. 2110–8. [PubMed: 17853395]
55. Shinde SS, et al. , Can pregabalin prevent paclitaxel-associated neuropathy?--An ACCRU pilot trial. Support Care Cancer, 2016. 24(2): p. 547–553. [PubMed: 26155765]
56. Mishra S, et al. , A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care, 2012. 29(3): p. 177–82. [PubMed: 21745832]
57. Ulker E and Del Fabbro E, Best Practices in the Management of Nonmedical Opioid Use in Patients with Cancer-Related Pain. Oncologist, 2020. 25(3): p. 189–196. [PubMed: 31872911]
58. Paice JA, Managing Pain in Patients and Survivors: Challenges Within the United States Opioid Crisis. J Natl Compr Canc Netw, 2019. 17(5.5): p. 595–598. [PubMed: 31117028]
59. Paice JA, Pain in Cancer Survivors: How to Manage. Curr Treat Options Oncol, 2019. 20(6): p. 48. [PubMed: 31062182]
60. Jordan B, et al. , Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol, 2020. 31(10): p. 1306–1319. [PubMed: 32739407]
61. Li Y, et al. , DRG Voltage-Gated Sodium Channel 1.7 Is Upregulated in Paclitaxel-Induced Neuropathy in Rats and in Humans with Neuropathic Pain. J Neurosci, 2018. 38(5): p. 1124–1136. [PubMed: 29255002]
62. Gewandter JS, et al. , A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. Support Care Cancer, 2014. 22(7): p. 1807–14. [PubMed: 24531792]
63. Mercadante S, Topical amitriptyline and ketamine for the treatment of neuropathic pain. Expert Rev Neurother, 2015. 15(11): p. 1249–53. [PubMed: 26488799]
64. Besson M, et al. , GABAergic modulation in central sensitization in humans: a randomized placebo-controlled pharmacokinetic-pharmacodynamic study comparing clobazam with clonazepam in healthy volunteers. Pain, 2015. 156(3): p. 397–404. [PubMed: 25687539]

65. Barton DL, et al. , A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer, 2011. 19(6): p. 833–41. [PubMed: 20496177]
66. Hartrick CT, Noradrenergic reuptake inhibition in the treatment of pain. Expert Opin Investig Drugs, 2012. 21(12): p. 1827–34.
67. Rao RD, et al. , Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer, 2008. 112(12): p. 2802–8. [PubMed: 18428211]
68. Saif MW and Hashmi S, Successful amelioration of oxaliplatin-induced hyperexcitability syndrome with the antiepileptic pregabalin in a patient with pancreatic cancer. Cancer Chemother Pharmacol, 2008. 61(3): p. 349–54. [PubMed: 17849118]
69. Waissengrin B, et al. , Effect of cannabis on oxaliplatin-induced peripheral neuropathy among oncology patients: a retrospective analysis. Ther Adv Med Oncol, 2021. 13: p. 1758835921990203. [PubMed: 33613702]
70. Masocha W, Targeting the Endocannabinoid System for Prevention or Treatment of Chemotherapy-Induced Neuropathic Pain: Studies in Animal Models. Pain Res Manag, 2018. 2018: p. 5234943. [PubMed: 30147813]
71. Alkislar I, et al. , Inhaled Cannabis Suppresses Chemotherapy-Induced Neuropathic Nociception by Decoupling the Raphe Nucleus: A Functional Imaging Study in Rats. Biol Psychiatry Cogn Neurosci Neuroimaging, 2021. 6(4): p. 479–489. [PubMed: 33622657]
72. Ward SJ, et al. , Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. Br J Pharmacol, 2014. 171(3): p. 636–45. [PubMed: 24117398]
73. Maihöfner C, et al. , Chemotherapy-induced peripheral neuropathy (CIPN): current therapies and topical treatment option with high-concentration capsaicin. Support Care Cancer, 2021.
74. Privitera R and Anand P, Capsaicin 8% patch Qutenza and other current treatments for neuropathic pain in chemotherapy-induced peripheral neuropathy (CIPN). Curr Opin Support Palliat Care, 2021. 15(2): p. 125–131. [PubMed: 33905384]
75. Fradkin M, et al. , Management of Peripheral Neuropathy Induced by Chemotherapy. Curr Med Chem, 2019. 26(25): p. 4698–4708. [PubMed: 30621553]
76. Fallon MT, et al. , Cancer treatment-related neuropathic pain: proof of concept study with menthol--a TRPM8 agonist. Support Care Cancer, 2015. 23(9): p. 2769–77. [PubMed: 25680765]
77. Storey DJ, et al. , Reversal of dose-limiting carboplatin-induced peripheral neuropathy with TRPM8 activator, menthol, enables further effective chemotherapy delivery. J Pain Symptom Manage, 2010. 39(6): p. e2–4.
78. Wong R and Sagar S, Acupuncture treatment for chemotherapy-induced peripheral neuropathy--a case series. Acupunct Med, 2006. 24(2): p. 87–91. [PubMed: 16783284]
79. Schroeder S, Meyer-Hamme G, and Epplée S, Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): a pilot study using neurography. Acupunct Med, 2012. 30(1): p. 4–7. [PubMed: 22146780]
80. Ben-Horin I, et al. , Acupuncture and Reflexology for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer. Integr Cancer Ther, 2017. 16(3): p. 258–262. [PubMed: 28150504]
81. Lu W, et al. , Acupuncture for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Survivors: A Randomized Controlled Pilot Trial. Oncologist, 2020. 25(4): p. 310–318. [PubMed: 32297442]
82. Kanbayashi Y, et al. , Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial. Breast, 2020. 49: p. 219–224. [PubMed: 31901783]
83. Rosenbaek F, et al. , Effect of cryotherapy on dose of adjuvant paclitaxel in early-stage breast cancer. Support Care Cancer, 2020. 28(8): p. 3763–3769. [PubMed: 31828491]
84. Shigematsu H, et al. , Cryotherapy for the prevention of weekly paclitaxel-induced peripheral adverse events in breast cancer patients. Support Care Cancer, 2020. 28(10): p. 5005–5011. [PubMed: 32036471]

85. Hanai A, et al. , Effects of Cryotherapy on Objective and Subjective Symptoms of Paclitaxel-Induced Neuropathy: Prospective Self-Controlled Trial. J Natl Cancer Inst, 2018. 110(2): p. 141–148. [PubMed: 29924336]

86. Prinsloo S, et al. , Randomized controlled trial of neurofeedback on chemotherapy-induced peripheral neuropathy: A pilot study. Cancer, 2017. 123(11): p. 1989–1997. [PubMed: 28257146]

87. Prinsloo S, et al. , The Long-Term Impact of Neurofeedback on Symptom Burden and Interference in Patients With Chronic Chemotherapy-Induced Neuropathy: Analysis of a Randomized Controlled Trial. J Pain Symptom Manage, 2018. 55(5): p. 1276–1285. [PubMed: 29421164]

88. Andersen Hammond E, et al. , An Exploratory Randomized Trial of Physical Therapy for the Treatment of Chemotherapy-Induced Peripheral Neuropathy. Neurorehabil Neural Repair, 2020. 34(3): p. 235–246. [PubMed: 31976819]

89. Streckmann F, et al. , Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-a randomized controlled pilot trial. Support Care Cancer, 2019. 27(7): p. 2471–2478. [PubMed: 30382392]

90. Coyne PJ, et al. , A trial of Scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. J Pain Palliat Care Pharmacother, 2013. 27(4): p. 359–64. [PubMed: 24143893]

91. Pachman DR, et al. , Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. Support Care Cancer, 2015. 23(4): p. 943–51. [PubMed: 25245776]

92. Loprinzi C, et al. , Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. Support Care Cancer, 2020. 28(3): p. 1183–1197. [PubMed: 31209630]

93. Smith TJ, et al. , A Pilot Randomized Sham-Controlled Trial of MC5-A Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN). J Palliat Care, 2020. 35(1): p. 53–58. [PubMed: 30714486]

94. Gerdts J, et al. , SARM1 activation triggers axon degeneration locally via NAD,Äö√Ö,à´ destruction. Science, 2015. 348(6233): p. 453–7. [PubMed: 25908823]

95. Zhu J, et al. , Ethoxyquin provides neuroprotection against cisplatin-induced neurotoxicity. Sci Rep, 2016. 6: p. 28861. [PubMed: 27350330]

96. Pease-Raissi SE, et al. , Paclitaxel Reduces Axonal Bclw to Initiate IP(3)R1-Dependent Axon Degeneration. Neuron, 2017. 96(2): p. 373–386.e6. [PubMed: 29024661]

97. Mustafa G, et al. , Anti-nociceptive effect of a conjugate of substance P and light chain of botulinum neurotoxin type A. Pain, 2013. 154(11): p. 2547–2553. [PubMed: 23933181]

98. Zhu Y, et al. , Ganglioside-monosialic acid (GM1) prevents oxaliplatin-induced peripheral neurotoxicity in patients with gastrointestinal tumors. World J Surg Oncol, 2013. 11: p. 19. [PubMed: 23351188]

99. Glimelius B, et al. , Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx(¬¨√Ü)): a placebo-controlled randomised phase II study (PLIANT). Acta Oncol, 2018. 57(3): p. 393–402. [PubMed: 29140155]

100. Szepanowski F, et al. , Fingolimod promotes peripheral nerve regeneration via modulation of lysophospholipid signaling. J Neuroinflammation, 2016. 13(1): p. 143. [PubMed: 27283020]

101. Kyte SL, et al. , Nicotine Prevents and Reverses Paclitaxel-Induced Mechanical Allodynia in a Mouse Model of CIPN. J Pharmacol Exp Ther, 2018. 364(1): p. 110–119. [PubMed: 29042416]

102. Fujita S, et al. , Identification of drug transporters contributing to oxaliplatin-induced peripheral neuropathy. J Neurochem, 2019. 148(3): p. 373–385. [PubMed: 30295925]

103. Kelley MR, et al. , Role of the DNA base excision repair protein, APE1 in cisplatin, oxaliplatin, or carboplatin induced sensory neuropathy. PLoS One, 2014. 9(9): p. e106485. [PubMed: 25188410]

104. Kelley MR, et al. , Identification and Characterization of New Chemical Entities Targeting Apurinic/Apyrimidinic Endonuclease 1 for the Prevention of Chemotherapy-Induced Peripheral Neuropathy. J Pharmacol Exp Ther, 2016. 359(2): p. 300–309. [PubMed: 27608656]

Table 1:

Additional medication treatment options for CIPN

Mechanism	Drugs	References
Sodium channel blockers	Lacosamide, mexiletine, tocainide, parenternal lidocaine	[3, 61]
NMDA receptor antagonists	Ketamine (topical)	[62, 63]
$GABA_A$ receptor agnoists	Clonazepam (and other benzodiazepines)	[64]
$GABA_B$ receptor agonists	Baclofen	[62, 65]
Alpha-2 adrenergic agonists	Tizanidine	[66]
Anticonvulsants	Oxcarbazepine, lacosamide	[67, 68]
Cannabinoids	Nabiximols, dronabinol	[69] Animal models: [70–72]
Topical agents	Capsaicin	[73, 74]
	Lidocaine	[75]
	Menthol	[76, 77]