Published in final edited form as:

Crit Rev Oncol Hematol. 2020 January ; 145: 102831. doi:10.1016/j.critrevonc.2019.102831.

Prevention of Chemotherapy-Induced Peripheral Neuropathy: A Review of Recent Findings.

Eiman Y. Ibrahim, Barbara E. Ehrlich

Departments of Pharmacology and Cellular and Molecular Physiology, Yale University, New Haven, CT 06510, United States of America

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of chemotherapy that is frequently experienced by patients receiving treatment for cancer. CIPN is caused by many of the most commonly used chemotherapeutic agents, including taxanes, vinca alkaloids, and bortezomib. Pain and sensory abnormalities may persist for months, or even years after the cessation of chemotherapy. The management of CIPN is a significant challenge, as it is not possible to predict which patients will develop symptoms, the timing for the appearance of symptoms can develop anytime during the chemotherapy course, there are no early indications that warrant a reduction in the dosage to halt CIPN progression, and there are no drugs approved to prevent or alleviate CIPN. This review focuses on the etiology of CIPN and will highlight the various approaches developed for prevention and treatment. The goal is to guide studies to identify, test, and standardize approaches for managing CIPN.

Keywords

Chemotherapy; Neuropathy; CIPN; Taxanes; Paclitaxel; Cisplatin; Oxaliplatin; Vinca alkaloids

Introduction:

Systemic chemotherapy is a cornerstone in the management of various types of cancers. Recent progress in chemotherapeutic regimens has led to substantial improvements in the long-term outcome for cancer patients (1, 2). Unfortunately, administration of

Address for correspondence: Department of Pharmacology, 333 Cedar Street, New Haven, CT 06510-8022, USA, eiman.ibrahim@yale.edu, barbara.ehrlich@yale.edu.

AUTHOR CONTRIBUTIONS

EYI and BEE conceived the project, EYI wrote the first draft and both authors edited the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

COMPETING INTERESTS

BEE is a cofounder of Osmol Therapeutics, a company that is targeting NCS1 for therapeutic purposes.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

chemotherapeutic agents results in numerous changes to cellular structure and function that cause progressive, continuing, and oftentimes irreversible toxic side effects. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the common adverse events of several first-line chemotherapeutic agents (3, 4), affecting several million patients worldwide each year. CIPN is primarily associated with two types of sensory abnormalities. One mode appears as tingling and burning sensations, whereas the other presents as numbness and diminished touch sensation. In both modes, CIPN alters sensations in the hands and feet, often designated as a “glove and stocking” distribution. CIPN can also present as motor weakness or cranial nerve damage (5, 6), which can alter smell, taste, vision, face sensation and expression, hearing, balance, speech, swallowing, and muscles of the neck. Usually, pain symptoms occur early in the treatment cycles and the numbness and tingling develop later and can last years after cessation of treatment. There are some treatment for the neuropathic pain, but there are no preventive or curative strategies currently available. These neurological changes linked to pain, loss of sensation, and motor functionality lead to a decreased quality of life. Economically, CIPN puts a burden on both patients and the healthcare system, as it often leads to loss of jobs (7).

It is therefore crucial to find methods to manage the neurological complications of chemotherapy treatment. This task is no easy feat, however, because the consequences of CIPN vary during cancer treatment course, and because there are no current treatment strategies that prevent or effectively attenuate these symptoms. For many patients, when the signs of CIPN first appear, dose reduction or cessation of treatment is implemented, a strategy that ultimately may negatively affect overall survival (8). Long after the cessation of treatment, symptoms persist in more than half of all patients (9). More challenging still, the therapeutics available for neuropathy are generally ineffective, and there are no treatments for tingling and numbness, side effects that affect up to 70% of patients with CIPN (10, 11).

Recently, there has been an increase in the number of active collaborations between basic and clinical research teams aimed at providing a deeper understanding of the underlying mechanisms that initiate and cause the progression of CIPN (8, 9). With this knowledge, it will be possible to develop effective preventive methods and treatment plans. In this review, we outline the current understanding of how CIPN starts and progresses, discuss various approaches under development and ongoing studies for prevention and treatment, and suggest a design for standardized approaches to manage CIPN.

Incidence, epidemiology, and impact on quality of life:

CIPN is a side effect that is both cumulative and dose-dependent. Although patients tend to improve with time after course discontinuation, not all patients achieve pre-treatment status. Symptoms can be acute or chronic; nearly 90% of patients develop at least one symptom of acute neuropathy with the first treatment cycle (12). Chronic CIPN tends to have a broad scope of incidence ranging from 13% to 70% depending on the type and dose of chemotherapy (13-15). Data suggest that once the pain shifts from an acute to chronic state, it is more likely to be persistent (16, 17). In terms of quality of life, patients with chronic symptoms report having unsteady gait, putting them at higher risk of falling (18), and difficulty going back to work after treatment (19). They also report difficulty feeling tiny

objects, trouble buttoning clothing, and trouble walking (19). The overall problem is that patients may be cured of cancer, but they continue to suffer chronic debilitating neuropathy induced by their cancer treatment.

Clinical practice guidelines from the American Society of Clinical Oncology (ASCO) state that there is no preventative agent to be recommended, but early termination of the offending agent should be done prior to the development of disabling symptoms. However, currently used CIPN assessment strategies are insensitive and impractical for routine clinical monitoring (15, 20). It is therefore challenging to predict who will be at high risk of developing negative side effects, and which patients will have irreversible damage (21).

Clinical assessment:

Chemotherapy-related neuropathy manifestations most commonly develop in a “glove and stocking” distribution because anti-tumor agents tend to target longer axons located in the extremities (22). It is hypothesized that these are the primary site of action because nerve endings associated with longer axons are further from the neuronal cell body where the primary cell repair machinery is located.

Clinically, there are no standard tools for CIPN assessment. When CIPN is evaluated by a physician, objective assessment of neuropathic signs and symptoms is used. Nerve conduction studies and electromyography would be useful assessment tools, but these methods are costly and time consuming, and have therefore had limited use in clinical settings. Instead, web-based self-assessment tools have been introduced, and reports show high ratings of usability and satisfaction by patients (23, 24). There are numerous scales for evaluating CIPN severity; most commonly used are the common toxicity criteria of the National Cancer Institute (NCI-CTC) and the total neuropathy score (TNS). Additionally, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire along with the CIPN20 module is one of the most consistent tools for grading CIPN accurately and, as such, is often preferred for use in large oncology clinical trials (25).

There are no biomarkers available to assess and diagnose CIPN or predict the susceptibility or severity of neuropathy symptoms based on the chemotherapy duration or dosage. However, incorporation of both clinical and web-based methods has shown promising results (8). Further development of these measures will allow for early identification and will improve medical decisions about continuation or cessation of chemotherapy (26, 27). Continued research on and clinical management of the basic mechanisms and the clinical progression of CIPN will enhance identification of biomarkers, preventive agents, and appropriate treatments.

Pathogenesis and neurotoxic mechanisms of agents involved in CIPN development:

In this section, we summarize the current understanding of the mechanisms causing CIPN development as a consequence of treatment with a specific chemotherapeutic agent. Each

anti-tumor agent can generate specific symptoms that vary in clinical features, severity, and recovery (28), as shown in Figure 1.

1. Taxanes:

Anti-tumor mechanism—Taxanes are widely used in the treatment of multiple types of malignancies including breast, ovarian, prostate, gastric, and head-and-neck cancers, and non-small cell lung cancer (29). These drugs, which include paclitaxel and docetaxel, are microtubule-stabilizing agents. Docetaxel is more potent and more water soluble than paclitaxel. Taxanes promote the nucleation and elongation phases of tubulin polymerization. Because the dynamic assembly of microtubules is crucial for the formation of the mitotic spindle during cell division, taxane-induced stabilization of microtubules will lead to disturbance of interphase processes and eventually cell death.

CIPN mechanism—The mechanistic basis for taxane-induced CIPN development is less clear. Microtubule involvement may lead to neuropathy due to altering the track for axonal transport (30). Mitochondrial injury has also been implicated in the development of axonal dysfunction leading to CIPN. When compared to untreated nerve fibers, mitochondria appear enlarged or swollen, often with vacuolation (31, 32).

Intracellular calcium is an important modulator of both microtubule assembly and mitochondrial function. It is generally acknowledged that lack of calcium homeostasis is a major component in the induction of neuropathic pain such as CIPN (33, 34). An essential pathway for CIPN induction relies upon taxane binding to cytosolic neuronal calcium sensor 1 (NCS1)(35, 36), a calcium-binding protein that binds both taxanes and vinca alkaloids (described below). The interaction of these agents with NCS1 alters intracellular calcium signaling, resulting in the activation of calpain, a calcium-dependent enzyme (33, 37), and altered mitochondrial function. Activated calpain then catalyzes the degradation of several proteins, including NCS1, leading to neuronal dysfunction (36, 37).

Paclitaxel is primarily taken up by the liver via the organic anion transporting polypeptide B2 transporter (OATP1B2), which was recently identified as a mediator of taxane-induced neurotoxicity (38, 39). This finding suggests a novel pathway for paclitaxel-induced neuropathy. Pharmacologic inhibition or genetic knockout of OATP1B2 led to protection from allodynia, thermal hyperalgesia, and changes in digital maximal action potential amplitudes in mice (40).

Interestingly, the release of calcium by the NCS1-dependent pathway is inhibited by lithium (41) and the function of the OATP1B2 dependent transport system is noncompetitively inhibited by the tyrosine kinase inhibitor nilotinib (40). In both cases, inhibition occurs without compromising the chemotherapeutic function of paclitaxel. These findings can be used as the basis for future development of therapeutic management strategies.

Symptoms, severity, and recovery—Paclitaxel-induced peripheral neuropathy manifests with bilateral, symmetrical distal changes that are chiefly characterized by sensory symptoms such as tingling, numbness, and burning pain in a stocking-and-glove distribution. Deep tendon reflexes in lower limbs are usually low or absent (42).

Development of taxane-induced neuropathy depends on many predisposing factors, including: (1) advanced age, (2) treatment schedule and duration, (3) taxane dose for each cycle, (4) concurrent administration of neuropsychiatric drugs, and (5) the presence of pre-existing neuropathy or comorbidity as might be a consequence of long-standing diabetes mellitus (43). There are controversial results with regard to treatment regimens. Some report that weekly paclitaxel administration (80 mg/m²) leads to a higher rate of sensory symptoms when compared to tri-weekly administration (175 mg/m²) (44). In contrast, other reports state that with weekly paclitaxel regimens, the incidence of peripheral neuropathy was lower than in tri-weekly regimens (45, 46). An advantage of the weekly regimen is its superiority to the tri-weekly regimen in terms of tumor regression, whereas the tri-weekly regimen is associated with fewer musculoskeletal and hematologic side effects (45-47).

The genetic basis for vulnerability of patients to the neurotoxic effects of the taxanes was tested in two racially distinct patient cohorts (48). This result suggested that there is an increased risk of neuropathy associated with Cytochrome P450 2C8 (CYP2C8*3) variants. CYP2C8 is the main enzyme responsible for the metabolism of paclitaxel (49, 50). Heterozygosity for the CYP2C8*3 allele was also associated with decreased metabolism of paclitaxel and thus increase the risk of developing neuropathy (51). However, this result was not validated by the findings from a study on a large cohort of European breast cancer patients treated with paclitaxel or docetaxel (52), nor by retrospective series of ovarian cancer patients (53). Both studies failed to find a correlation between both CYP2C8*3 and CYP3A5*3 variants and any aspect of CIPN. Nonetheless, larger studies would be useful, especially if more consistent results could clear up the discrepancies (54).

2. Vinca alkaloids:

Anti-tumor mechanism—Vinca alkaloids are commonly used to treat lymphoma, non-small cell lung cancer, and testicular cancer. Vincristine, a type of vinca alkaloid, is known to produce the most severe neuropathy, whereas vinblastine and vinorelbine appear to be less neurotoxic (55). The primary mechanism of action for vinca alkaloid cytotoxicity is through binding to tubulin to disrupt polymerization and microtubular assembly. These compounds are cell cycle-specific agents, acting primarily in the M phase to arrest cell division (56, 57). The vinca alkaloid binding sites on tubulin are distinct from those of the taxanes, colchicine, and other drugs (56, 57). Although opposite to the effects of the taxanes on microtubule assembly, the destabilization of microtubules by vinca alkaloids also produces anti-cancer effects.

CIPN mechanism—Many of the effects of vinca alkaloids are similar to those described for the taxanes. Vinca alkaloids interfere with the neuronal cytoskeleton through their effect on tubulin, which leads to a loss of intact axonal microtubules and alterations in their length, arrangement, and orientation. These effects lead to the impairment of neuronal transport and axonal degeneration. As with taxanes, vincristine binds to NCS1, activates calpain, and degrades intracellular proteins (59), leading to neuronal dysfunction. Vincristine also alters mitochondrial function by changes in calcium homeostasis downstream of its binding to NCS1 and through its action on the mitochondrial membrane within Dorsal Root Ganglia (DRG) neurons. These changes in mitochondrial function lead to increased reactive oxygen

species generation and disruption of neuronal excitability (58). Vincristine appears to affect sensory fibers at earlier stages and more severely than motor fibers. In addition, vincristine targets cranial nerves, most commonly the oculomotor nerve (60-62).

Symptoms, severity, and recovery—Vincristine-induced neuropathy can be reversible with a moderately good long-term prognosis (57). Symptoms involve both peripheral sensory and motor nerves, autonomic nervous system, as well as the central nervous system. Patients usually complain of numbness, tingling and neuropathic pain in the upper and lower limbs. Autonomic neuropathy is typically presented by constipation, urine retention, and orthostatic hypotension (63). These symptoms sometimes worsen for a few months after cessation of vincristine, then improve with time in a phenomenon called “coasting” (57). Complete improvement over weeks to months is usually expected in mild cases, whereas incomplete resolution occurs over months to years in severe cases. Cranial nerve involvement and motor deficits can often be minimized by physical therapy (20, 64).

3. Platinum-based chemotherapeutics:

Anti-tumor mechanism—The use of platinum compounds such as cisplatin, carboplatin, and oxaliplatin has been essential to the practice of cancer treatment for the last 4 decades. These drugs are primarily used in the treatment of lung, breast, ovarian, and colon cancers. Platinum compounds are alkylating agents that exert their chemotherapeutic effects by binding to cellular DNA and creating intra-strand cross-links. If the DNA damage exceeds the capacity of the cellular repair, the cell undergoes apoptosis. The action of the platinum-based compounds is not cell cycle-specific (65).

CIPN mechanism: Platinum-based chemotherapeutics are notably toxic to neurons. These compounds lead to the impairment of neuronal membrane excitability, axonal transport dysfunction and disruption of neurotransmission, induction of inflammation via release of proinflammatory chemokines, and alteration of voltage-gated ion channels expression (64, 66). The DRG sensory neurons are particularly susceptible to neurotoxicity because they are not protected by the blood–brain barrier (67). The death of sensory neurons is considered as the primary responsible mechanism for permanent distal sensory loss (68).

Binding of platinum to mitochondrial DNA is the most probable mechanism of nerve cell necrosis (68). In some patients, the central dendrites of the DRG cells in the posterior columns are targeted to cause Lhermitte’s sign (an electric shock-like sensation that occurs when flexing the neck) (20).

Symptoms, severity, and recovery—Neuropathy symptoms differ among the platinum-based drugs (69). Cisplatin is clearly the most neurotoxic and carboplatin is relatively free from inducing peripheral neurotoxic side effects (70, 71). Symptoms also depend upon the dose and route of administration, where intra-arterial infusion may have improved outcomes and fewer side effects over intravenous infusions (20). Along with the sensory neuropathy, neurological symptoms such as encephalopathy, seizures, cerebral edema, laryngospasm-like condition, stroke, and severe ocular effects have been observed with platinum-based chemotherapy (71). Administration of calcium and magnesium salts

was found to improve oxaliplatin-induced neuropathy symptoms (72). For all of these agents, neurotoxicity may worsen after discontinuation of the drug (coasting). Oxaliplatin-induced neuropathy can eventually improve in a subset of patients, but relief of symptoms can take more than a year and recovery is usually incomplete (73).

4. Proteasome Inhibitors: Bortezomib, Carfilzomib, and Ixazomib

Anti-tumor mechanism: Three proteasome inhibitors have received regulatory approval and demonstrate great therapeutic efficacy in clinical settings: bortezomib, carfilzomib, and ixazomib. Bortezomib was the first proteasome inhibitor to be brought into clinical use. Carfilzomib is a novel selective proteasome inhibitor that is approved for treatment of relapsed and refractory multiple myeloma. Both agents have been used routinely in the treatment of multiple myeloma, mantle-cell lymphoma (MCL), and amyloidosis. They achieve their anti-tumor effects by inhibiting proteasome activity, which leads to the accumulation of misfolded protein in tumor cells, cell cycle arrest, and eventually apoptosis. Although it shows powerful antitumor activity in patients, bortezomib therapy is limited by treatment-induced peripheral neuropathy (74).

CIPN mechanism: Induction of oxidative injury within the mitochondria and endoplasmic reticulum (ER) has been shown to play a major role in the development of peripheral neuronal toxicity, as bortezomib can activate the mitochondrial intrinsic apoptotic pathway (75). Bortezomib also inhibits an ATP-dependent serine protease in mitochondria: HtrA2/Omi. HtrA2 is a stress-inducible mitochondrial protease that protects neurons from apoptosis, and its inhibition appears to be the cause of neuropathy in multiple myeloma (76). Additionally, a gene expression microarray using bortezomib-treated Schwann cells showed a substantial increase in ER stress proteins accompanied by dysregulation of the expressions of the myelin gene and increased secretion of macrophage chemoattractants (77, 78).

Symptoms, severity, and recovery: With patients receiving bortezomib, the development of peripheral neuropathy is dose-dependent and can lead to dose reduction. Despite the dramatically improved outcomes, up to 80% of patients with newly-diagnosed multiple myeloma treated with bortezomib develop neuropathy (all grades), and it increases with long-term exposure and/or higher doses (79). Changes in bortezomib route of administration, from intravenous to subcutaneous, or in the dosing schedule, from biweekly to weekly, have emerged as successful strategies to reduce the incidence of neuropathy while preserving anti-tumor efficacy (80).

Drug cessation or dose reduction resolved the neuropathy symptoms within three months in the majority of treated patients (64-85%) (72, 81).

5. Immunomodulatory Drugs: Thalidomide, Pomalidomide, and Lenalidomide

Anti-tumor mechanism: In the last 20 years, thalidomide has proven to be an effective agent for the treatment of multiple myeloma, and it significantly improves the response rate and survival rate of patients. This second generation of immunomodulators includes lenalidomide and pomalidomide, which are both more potent in anti-inflammatory activities than the first generation, thalidomide. Lenalidomide and pomalidomide are effective in

Chronic Lymphoid Leukemia, differentiated thyroid cancer, and myelodysplastic syndromes (82, 83).

These agents work by affecting both the cellular and humoral branches of the immune system. They modulate cytokine production in the bone marrow microenvironment, causing enhancement of cell growth, survival, and migration (84). This group of drugs also blocks angiogenesis by inhibiting basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) (85, 86). Through immunomodulation by these agents, the immune system becomes more able to alter the inflammatory environment that is favorable to tumorigenesis.

CIPN mechanism: The pathophysiology of thalidomide-induced peripheral neuropathy is poorly understood. Initially, it was thought that the anti-inflammatory effect of thalidomide would prevent neurotoxicity. However, nerve conduction studies have shown that thalidomide-induced neuropathy can be attributed to degeneration of sensory and motor nerves. As thalidomide has an anti-angiogenic effect, the loss of new blood vessels has also been proposed to be responsible for nerve fiber hypoxia and ischemia followed by irreversible injury of sensory neurons (87). It was shown that activation of the dihydroxy metabolite of thalidomide causes excessive release of reactive oxygen species and, in turn, DNA damage (88). However, it remains to be determined whether these metabolites are responsible for thalidomide treatment-induced peripheral neuropathy (88). Dysregulation of neurotrophin activity may also contribute to the pathogenesis of neurotoxicity through accelerated neuronal apoptosis (79).

Symptoms, severity, and recovery: The incidence of thalidomide neuropathy is between 21% and 50%. Genetic predisposition seems to be a more important risk factor than cumulative dose and duration of thalidomide therapy (89). Lenalidomide has lower rates of neuropathy related-treatment discontinuation and dose reduction compared with thalidomide (90).

Pharmacological strategies for management and protection against CIPN:

Due to the incomplete knowledge about the underlying pathophysiology of CIPN, symptomatic treatments are usually unsuccessful (15). As the success in identifying anti-tumor agents has increased, efforts have increased to develop approaches for prevention and management of CIPN, such that it will be possible to enhance quality of life for cancer survivors. There have been numerous clinical trials for CIPN prevention with small sample sizes, but none have produced valid evidence for CIPN prevention or treatment (15). Currently there are no established strategies to prevent or treat these toxic events.

Ongoing work, including work from our laboratory, provides hope that we are approaching some consensus on strategies to decrease the rate of developing and severity of CIPN. Here we discuss both pharmacological and non-pharmacological approaches for prevention of CIPN and suggest considerations for future research. As illustrated in Table 1, pharmacological management of CIPN is multifaceted, featuring serotonin-norepinephrine reuptake inhibitors, agents used to treat bipolar disorder, anticonvulsants, and analgesics.

Non-pharmacological approaches primarily use natural products (e.g., vitamins and herbal supplements), exercise and diet changes, or ice. Patient education and good doctor-patient communication are also crucial for CIPN management.

A) Established symptomatic treatment approaches:

1. Serotonin-norepinephrine reuptake inhibitors—Serotonin (5-HT) and norepinephrine (NE) are the main neurotransmitters that suppress pain sensation. They work through inhibiting painful peripheral stimuli input to the spinal dorsal horn neurons (91). Serotonin/norepinephrine reuptake inhibitors (SNRI) are effective in treating neuropathic pain and one drug, duloxetine, is useful in managing painful diabetic neuropathy (92). Similarly, duloxetine is the only drug shown to have any effectiveness for treatment of CIPN (93). Based on the results of one randomized, double-blind, crossover-controlled trial in 2014, the American Society of Clinical Oncology (ASCO) guidelines recommend duloxetine for CIPN treatment (15). Moreover, after the closure of a novel National Cancer Institute (NCI) clinical trial in 2013, ([ClinicalTrials.gov](https://clinicaltrials.gov) number,), it was found that use of duloxetine for 5 weeks resulted in a greater reduction in pain and lower limb numbness compared with placebo. Of the patients treated with duloxetine, fifty nine percent reported reduction in pain as compared to thirty eight percent of those who were treated with placebo (94).

An open-label, randomized, crossover study reported in 2014 found that duloxetine is effective for CIPN in Japanese patients (95). However, duloxetine does not provide complete attenuation of symptoms and there is no evidence that it helps to prevent acquisition of neurological side effects. It is important to point out that many cancer patients also suffer from anxiety, sleeping problems, and depression. Adjuvant antidepressants would improve these psychological symptoms, as well as pain control.

2. Anticonvulsants: Anticonvulsant drugs selectively bind to the $\alpha 2\delta$ subunit of the voltage-gated calcium channel (VGCC), decreasing the postsynaptic levels of both glutamate and other excitatory neurotransmitters. Traditionally, the primary anticonvulsant used has been gabapentin, but pregabalin, a successor of gabapentin using the same mechanism of action, is now also used in the clinic. In addition to the VGCC, these drugs affect other targets, including NMDA receptors, transient receptor potential channels, protein kinase C, and inflammatory cytokines, which are known to be important in pain and thermal sensation (96).

Gabapentin alone or in combination with opioids has been used to treat CIPN, based upon a few clinical trials (97, 98). However, despite robust efficacy against neuropathic symptoms of different etiologies, effectiveness against CIPN is very limited. In one randomized controlled trial testing patients with cancer-induced neuropathic pain, pregabalin was more effective than both gabapentin and amitriptyline, and a lower dose of a co-administered opioid was required (99). In contrast, pregabalin failed to reduce the chronic painful neuropathy associated with oxaliplatin therapy (100).

Gabapentinoids are generally useful in controlling anxiety and insomnia and can be beneficial in patients whose pain is unresponsive to opioids or for whom opioid reductions

are indicated. Carbamazepine, a sodium channel blocker validated to treat trigeminal neuralgia, has also been used by those with CIPN (101). To assess the clinical efficacy of gabapentin, a multicenter, double-blind, randomized trial was conducted on 115 patients with symptomatic CIPN. Patients were randomized to receive gabapentin (2700 mg/day in three divided doses) or a placebo, and CIPN symptoms were evaluated on weekly basis. CIPN scores were improved in both groups during the trial, but gabapentin failed to demonstrate any additional success in attenuating CIPN (101, 102). However, none of the anticonvulsant drugs have mechanisms of action that would suggest that they would be appropriate for use to prevent CIPN.

3. Analgesics: The analgesics act by various mechanisms to diminish peripheral neuropathy. Some members of this group work as opioid receptor agonists. Morphine mainly interacts with μ -opioid receptors, whereas oxycodone is a kappa agonist with relatively low affinity for μ -opioid receptors (103).

Currently, there are no data to suggest that one opioid agent is better than another for neuropathic symptoms management. This is especially true as the extensive use of opioids for neuropathic pain is not fully validated or accepted by most physicians. However, some patients benefit from combining neurotropic agents with an opioid (104). The best available trial that supports this combination was a multicenter, interventional, single-arm trial of oxycodone/naloxone added to gabapentin or pregabalin (98). The combination was significantly more effective in controlling CIPN than either agent alone (98). Although the results of this study are promising, there are some limitations. First, this study was conducted over a period of only 4 weeks, a relatively short time, and only on patients who were receiving pregabalin (300 mg/day) or gabapentin (900 mg/day). Thus, these findings must be repeated in a larger controlled trial of longer duration before final conclusions can be drawn (98).

Intravenous lidocaine has been extensively used in managing neuropathic symptoms of different etiologies and was recently tested in patients with CIPN (105). Although the study tested only nine patients, the results were promising; eight of nine patients displayed analgesic effect with more than 30% pain intensity difference. Lidocaine also decreased pain for prolonged periods of time, roughly 23 days after administration. This result suggests that lidocaine should be considered for additional tests for the management of refractory CIPN (105). Application of topical baclofen along with amitriptyline and ketamine for 4 weeks reduced hand tingling and burning sensation in patients who are treated with chemotherapy. (106)

There are only anecdotal studies that investigated the role of capsaicin patches and weak opioids, such as tramadol, for treatment for painful CIPN. Based on the theoretical advantages of these agents, tramadol, tapentadol, buprenorphine, or methadone may be considered but at the present time there are insufficient data to support this approach (107).

Targeting the endocannabinoid system has shown a certain level of efficacy and limited adverse effects in alleviating CIPN in preclinical and clinical studies and gives rise to considerations for future research (108).

4. Other agents and strategies: After exhausting many analgesic, psychiatric, or neurological drugs, studies investigating natural compounds and alternative approaches for treatment were initiated. Several nutraceuticals have demonstrated selective efficacy for treating CIPN related to specific chemotherapeutic agents. For example, there are promising reports using glutathione for oxaliplatin-induced neurotoxicity in cancer patients (109), vitamins E and B6 with cisplatin-induced neuropathy (110), and omega-3 fatty acids for taxane-induced peripheral neuropathy (111). In a small cohort acetyl-L-carnitine provided some efficacy as a protective option for taxanes and cisplatin-induced CIPN (112), but studies with large scale clinical trials are necessary.

B) Potential strategies for protection against CIPN:

1. Lithium—The ion lithium is the most effective treatment for bipolar disease. Although lithium has been prescribed for more than 50 years, there are still multiple proposed mechanisms of action for attenuating the mood swings of bipolar disorder, but no universally agreed upon mechanism. Long term daily treatment (>10 years) is associated with interstitial nephritis, which limits the use of lithium for the entire lifespan of a person with bipolar disorder. One of the proteins elevated in neuronal tissues of subjects with bipolar disorder is neuronal calcium sensor 1 (NCS1) (35, 113). When it was found that the taxanes bind to NCS1, lithium was tested to determine if it altered the interaction between NCS1 and paclitaxel. To summarize a number of studies, it was found that taxanes increase binding of NCS1 to the inositol 1,4,5-trisphosphate receptor (InsP3R), which increases intracellular calcium (37). The elevated calcium activates calpain, a calcium-dependent protease, degradation of a variety of cell proteins, and eventually, loss of cell functions related to the progression of peripheral neuropathy (37). The addition of lithium to taxane treatment prevents the initial increase of intracellular calcium, thus preventing calcium overload in the mitochondria and calpain activation, and subsequent loss of cell functions. Lithium only is needed in the cell when the taxane is present, which means prolonged administration, as used to treat bipolar disorder, is not required to prevent CIPN.

Promisingly, the addition of lithium in mice did not attenuate the anti-neoplastic effects of chemotherapy (41, 113). In fact, the correlation between high NCS1 expression and poor outcome, and the ability of lithium to attenuate NCS1 function suggests that lithium should be tested as an agent to slow cancer cell survival (114, 115). Interestingly, bipolar patients treated with lithium have a lower incidence of developing cancer, again suggesting that lithium may slow the transformation of normal cells to tumors (116).

Lithium is one of the few agents that appears to be effective in preventing CIPN (41). Taxane-induced peripheral neuropathy was prevented in mice when used as a pre-treatment and at a dose that would be considered subtherapeutic for treating bipolar patients. A retrospective study showed that patients treated for bipolar disorder while receiving chemotherapy had a lower risk for experiencing CIPN than patients who received chemotherapy alone (117). A well-designed clinical study is needed to validate these findings in cancer patients.

2. Other agents and strategies: As for treatment strategies, many studies investigating natural compounds and alternative approaches as neuroprotective agents were initiated to find effective therapies to prevent CIPN.

Ethoxyquin (an antioxidant and food preservative) appears to protect sensory neuron and dorsal root ganglia neurons in mice with cisplatin neuropathy (118), but there are no large scale controlled studies in humans (119). Multiple complementary therapies such as medicinal herbal formulas and regional cooling by applying ice on extremities have been used for decades. In a study of 40 female breast cancer patients receiving adjuvant paclitaxel, classical massage appears to have a positive outcome in preventing CIPN. This simple and cost effective intervention was reported to have reasonable success in improving patient quality of life (120).

More studies are still needed to optimize the use of these modalities to prevent the distressing symptoms of CIPN and put them into clinical practice. We still have much to consider about complementary approaches in terms of their safety, cross reaction, and cost-effectiveness.

Summary and conclusion:

Chemotherapeutic agents are widely used to treat common types of cancer, including breast, lung, gastrointestinal, hematological and gynecological malignancies. CIPN is one of the common adverse events that limits the use of prolonged or higher doses of anti-tumor agents. This limitation affects patients' survival and morbidity. It is especially a problem because many of the symptoms of CIPN are irreversible and there are no effective treatments for alleviating them.

Similarly, there are no conventional treatment modalities for preventing the occurrence of CIPN. Although the number of cancer survivors is increasing due to improved chemotherapeutic agents, survivors often need to re-adjust their lifestyle due to CIPN. Better knowledge into the various mechanisms of CIPN will significantly assist in developing neuroprotective drugs and to enhance cancer treatment in every cancer patient. It is time to utilize new hypotheses using well organized data leading to deeper understanding of the many cellular and biological processes causing CIPN with the aim to develop better treatment options. A strong translational approach involving research scientists and healthcare providers is needed.

ACKNOWLEDGEMENTS

We thank Allison Brill, Lien Nguyen, Tom Fischer and Edward Kaftan for helpful discussions and edits.

FUNDING SOURCES

Federal and NIH grant support is acknowledged: 5P01DK057751 and P30DK090744 (BEE).

References

1. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiology and Prevention Biomarkers*. 2010;19(8):1893–907.

2. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database of Systematic Reviews*. 2007(4). doi: 10.1002/14651858.CD004421.pub2. PubMed PMID: CD004421.
3. Argyriou AA, Koltzenburg M, Polychronopoulos P, Papapetropoulos S, Kalofonos HP. Peripheral nerve damage associated with administration of taxanes in patients with cancer. *Critical reviews in oncology/hematology*. 2008;66(3):218–28. [PubMed: 18329278]
4. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms? *Neuroscience letters*. 2015;596:90–107. Epub 2014/12/03. doi: 10.1016/j.neulet.2014.10.014. PubMed PMID: 25459280. [PubMed: 25459280]
5. Park S, Krishnan A, Lin C, Goldstein D, Friedlander M, Kiernan M. Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies. *Current medicinal chemistry*. 2008;15(29):3081–94. [PubMed: 19075655]
6. Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. *Toxicology*. 2012;291(1-3):1–9. [PubMed: 22079234]
7. Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemotherapy research and practice*. 2012;2012.
8. Dorsey SG, Kleckner IR, Barton D, Mustian K, O'Mara A, St. Germain D, Cavaletti G, Danhauer SC, Hershman DL, Hohmann AG, Hoke A, Hopkins JO, Kelly KP, Loprinzi CL, McLeod HL, Mohile S, Paice J, Rowland JH, Salvemini D, Segal RA, Smith EL, Stevens WM, Janelins MC. The National Cancer Institute Clinical Trials Planning Meeting for Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy. *JNCI: Journal of the National Cancer Institute*. 2019;111(6):531–7. doi: 10.1093/jnci/djz011.
9. Gadgil S, Ergün M, van den Heuvel SA, van der Wal SE, Scheffer GJ, Hooijmans CR. A systematic summary and comparison of animal models for chemotherapy induced (peripheral) neuropathy (CIPN). *PLOS ONE*. 2019;14(8):e0221787. doi: 10.1371/journal.pone.0221787. [PubMed: 31461480]
10. Mielke S, Sparreboom A, Mross K. Peripheral neuropathy: A persisting challenge in paclitaxel-based regimes. *European Journal of Cancer*. 2006;42(1):24–30. doi: 10.1016/j.ejca.2005.06.030. [PubMed: 16293411]
11. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*. 2014;155(12):2461–70. Epub 2014/09/28. doi: 10.1016/j.pain.2014.09.020. PubMed PMID: 25261162. [PubMed: 25261162]
12. Pachman DR, Qin R, Seisler DK, Smith EM, Beutler AS, Ta LE, Lafky JM, Wagner-Johnston ND, Ruddy KJ, Dakhil S, Staff NP, Grothey A, Loprinzi CL. Clinical Course of Oxaliplatin-Induced Neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(30):3416–22. Epub 2015/08/19. doi: 10.1200/jco.2014.58.8533. PubMed PMID: 26282635; PubMed Central PMCID: PMC4606060. [PubMed: 26282635]
13. Kelley MR, Fehrenbacher JC. Challenges and opportunities identifying therapeutic targets for chemotherapy-induced peripheral neuropathy resulting from oxidative DNA damage. *Neural regeneration research*. 2017;12(1):72. [PubMed: 28250749]
14. Song SJ, Min J, Suh SY, Jung SH, Hahn HJ, Im SA, Lee JY. Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. *Cancer*. 2017;25(7):2241–8. doi: 10.1007/s00520-017-3631-x. PubMed PMID: 28204996.
15. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(18):1941–67. Epub 2014/04/16. doi: 10.1200/jco.2013.54.0914. PubMed PMID: 24733808. [PubMed: 24733808]
16. Majithia N, Temkin SM, Ruddy KJ, Beutler AS, Hershman DL, Loprinzi CL. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons.

Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016;24(3):1439–47. Epub 2015/12/22. doi: 10.1007/s00520-015-3063-4. PubMed PMID: 26686859; PubMed Central PMCID: PMC45078987. [PubMed: 26686859]

17. Albers J, Chaudhry V, Cavaletti G, Donehower R. Interventions for preventing neuropathy caused by cisplatin and related compounds. The Cochrane database of systematic reviews. 2007(1):Cd005228. Epub 2007/01/27. doi: 10.1002/14651858.CD005228.pub2. PubMed PMID: 17253547. [PubMed: 17253547]
18. Kolb NA, Smith AG, Singleton JR, Beck SL, Stoddard GJ, Brown S, Mooney K. The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. JAMA neurology. 2016;73(7):860–6. Epub 2016/05/18. doi: 10.1001/jamaneurol.2016.0383. PubMed PMID: 27183099. [PubMed: 27183099]
19. Zanzillo NR, Nudelman KN, Smith DJ, Von Ah D, McDonald BC, Champion VL, Saykin AJ. Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016;24(11):4779–89. Epub 2016/07/30. doi: 10.1007/s00520-016-3329-5. PubMed PMID: 27470258; PubMed Central PMCID: PMC45031751. [PubMed: 27470258]
20. Albers J, Chaudhry V, Cavaletti G, Donehower R. Interventions for preventing neuropathy caused by cisplatin and related compounds. Department of Neurology, University of Michigan, 1C325/0032 University Hospital, 1500 E. Medical Center Drive, Box 0316. Ann Arbor, USA, MI. 48:109–0032.
21. McCrary JM, Goldstein D, Boyle F, Cox K, Grimison P, Kiernan MC, Krishnan AV, Lewis CR, Webber K, Baron-Hay S, Horvath L, Park SB. Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): a systematic review and Delphi survey. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2017;25(11):3485–93. Epub 2017/06/08. doi: 10.1007/s00520-017-3772-y. PubMed PMID: 28589310. [PubMed: 28589310]
22. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Critical reviews in oncology/hematology. 2012;82(1):51–77. Epub 2011/09/13. doi: 10.1016/j.critrevonc.2011.04.012. PubMed PMID: 21908200. [PubMed: 21908200]
23. Knoerl R, Dudley WN, Smith G, Bridges C, Kanzawa-Lee G, Lavoie Smith EM. Pilot Testing a Web-Based System for the Assessment and Management of Chemotherapy-Induced Peripheral Neuropathy. Computers, informatics, nursing : CIN. 2017;35(4):201–11. Epub 2016/12/22. doi: 10.1097/cin.0000000000000320. PubMed PMID: 28002115.
24. Toftagen C, Kip KE, Passmore D, Loy I, Berry DL. Usability and Acceptability of a Web-Based Program for Chemotherapy-Induced Peripheral Neuropathy. Computers, informatics, nursing : CIN. 2016;34(7):322–9. Epub 2016/04/27. doi: 10.1097/cin.0000000000000242. PubMed PMID: 27116414.
25. Cavaletti G, Cornblath D, Merkies I, Postma T, Rossi E, Frigeni B, Alberti P, Bruna J, Velasco R, Argyriou A. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. Annals of Oncology. 2012;24(2):454–62. [PubMed: 22910842]
26. Alberti P, Cavaletti G. Management of side effects in the personalized medicine era: chemotherapy-induced peripheral neuropathy Pharmacogenomics in Drug Discovery and Development: Springer; 2014 p. 301–22.
27. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology. 2014;32(18):1941–67. [PubMed: 24733808]
28. Boyette-Davis JA, Hou S, Abdi S, Dougherty PM. An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy. Pain management. 2018;8(5):363–75. Epub 2018/09/14. doi: 10.2217/pmt-2018-0020. PubMed PMID: 30212277; PubMed Central PMCID: PMC6462837. [PubMed: 30212277]

29. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *New England journal of medicine*. 1995;332(15):1004–14. [PubMed: 7885406]
30. Gornstein EL, Schwarz TL. Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. *Exp Neurol*. 2017;288:153–66. Epub 11/26. doi: 10.1016/j.expneurol.2016.11.015. PubMed PMID: 27894788. [PubMed: 27894788]
31. Matsumura Y, Yokoyama Y, Hirakawa H, Shigeto T, Futagami M, Mizunuma H. The prophylactic effects of a traditional Japanese medicine, goshajinkigan, on paclitaxel-induced peripheral neuropathy and its mechanism of action. *Molecular pain*. 2014;10:61. Epub 2014/09/23. doi: 10.1186/1744-8069-10-61. PubMed PMID: 25240613; PubMed Central PMCID: PMC4176860. [PubMed: 25240613]
32. Zheng H, Xiao WH, Bennett GJ. Functional deficits in peripheral nerve mitochondria in rats with paclitaxel- and oxaliplatin-evoked painful peripheral neuropathy. *Exp Neurol*. 2011;232(2):154–61. Epub 08/30. doi: 10.1016/j.expneurol.2011.08.016. PubMed PMID: 21907196. [PubMed: 21907196]
33. Boehmerle W, Splittgerber U, Lazarus MB, McKenzie KM, Johnston DG, Austin DJ, Ehrlich BE. Paclitaxel induces calcium oscillations via an inositol 1, 4, 5-trisphosphate receptor and neuronal calcium sensor 1-dependent mechanism. *Proceedings of the National Academy of Sciences*. 2006;103(48):18356–61.
34. Boeckel GR, Ehrlich BE. NCS-1 is a regulator of calcium signaling in health and disease. *Biochimica et biophysica acta Molecular cell research*. 2018;1865(11 Pt B):1660–7. Epub 2018/05/11. doi: 10.1016/j.bbamcr.2018.05.005. PubMed PMID: 29746899; PubMed Central PMCID: PMC6224314. [PubMed: 29746899]
35. Schlecker C, Boehmerle W, Jeromin A, DeGray B, Varshney A, Sharma Y, Szigeti-Buck K, Ehrlich BE. Neuronal calcium sensor-1 enhancement of InsP3 receptor activity is inhibited by therapeutic levels of lithium. *The Journal of clinical investigation*. 2006;116(6):1668–74. Epub 2006/05/13. doi: 10.1172/jci22466. PubMed PMID: 16691292; PubMed Central PMCID: PMC1459068. [PubMed: 16691292]
36. Benbow JH, DeGray B, Ehrlich BE. Protection of neuronal calcium sensor 1 protein in cells treated with paclitaxel. *Journal of Biological Chemistry*. 2011;286(40):34575–82. [PubMed: 21808066]
37. Boehmerle W, Zhang K, Sivula M, Heidrich FM, Lee Y, Jordt S-E, Ehrlich BE. Chronic exposure to paclitaxel diminishes phosphoinositide signaling by calpain-mediated neuronal calcium sensor-1 degradation. *Proceedings of the National Academy of Sciences*. 2007;104(26):11103–8.
38. de Graan A-JM, Lancaster CS, Obaidat A, Hagenbuch B, Elens L, Friberg LE, de Bruijn P, Hu S, Gibson AA, Bruun GH, Corydon TJ, Mikkelsen TS, Walker AL, Du G, Loos WJ, van Schaik RHN, Baker SD, Mathijssen RHJ, Sparreboom A. Influence of Polymorphic OATP1B-Type Carriers on the Disposition of Docetaxel. *Clinical Cancer Research*. 2012;18(16):4433–40. doi: 10.1158/1078-0432.ccr-12-0761. [PubMed: 22711709]
39. Smith NF, Acharya MR, Desai N, Figg IHW, Sparreboom A. Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel. *Cancer Biology & Therapy*. 2005;4(8):815–8. doi: 10.4161/cbt.4.8.1867. [PubMed: 16210916]
40. Leblanc AF, Sprowl JA, Alberti P, Chiorazzi A, Arnold WD, Gibson AA, Hong KW, Pioso MS, Chen M, Huang KM, Chodisetty V, Costa O, Florea T, de Bruijn P, Mathijssen RH, Reinbolt RE, Lustberg MB, Sucheston-Campbell LE, Cavaletti G, Sparreboom A, Hu S. OATP1B2 deficiency protects against paclitaxel-induced neurotoxicity. *The Journal of clinical investigation*. 2018;128(2):816–25. Epub 2018/01/18. doi: 10.1172/jci96160. PubMed PMID: 29337310; PubMed Central PMCID: PMC5785270. [PubMed: 29337310]
41. Mo M, Erdelyi I, Szigeti-Buck K, Benbow JH, Ehrlich BE. Prevention of paclitaxel-induced peripheral neuropathy by lithium pretreatment. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2012;26(11):4696–709. Epub 2012/08/15. doi: 10.1096/fj.12-214643. PubMed PMID: 22889832; PubMed Central PMCID: PMC3475250. [PubMed: 22889832]
42. Balayssac D, Ferrier J, Descoeur J, Ling B, Pezet D, Eschalier A, Authier N. Chemotherapy-induced peripheral neuropathies: from clinical relevance to preclinical evidence. *Expert opinion on drug safety*. 2011;10(3):407–17. [PubMed: 21210753]

43. Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. *Current neuropharmacology*. 2006;4(2):165–72. [PubMed: 18615126]
44. Seidman AD, Berry D, Cirincione C, Harris L, Muss H, Marcom PK, Gipson G, Burstein H, Lake D, Shapiro CL. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *Journal of Clinical Oncology*. 2008;26(10):1642–9. [PubMed: 18375893]
45. Mauri D, Kamposioras K, Tsali L, Bristianou M, Valachis A, Karathanasi I, Georgiou C, Polyzos NP. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer treatment reviews*. 2010;36(1):69–74. [PubMed: 19945225]
46. Tan Q-W, Luo T, Zheng H, Tian T-L, He P, Chen J, Zeng H-L, Lv Q. Weekly taxane–anthracycline combination regimen versus tri-weekly anthracycline-based regimen for the treatment of locally advanced breast cancer: a randomized controlled trial. *Chinese journal of cancer*. 2017;36(1):27. [PubMed: 28270181]
47. Budd GT, Barlow WE, Moore HC, Hobday TJ, Stewart JA, Isaacs C, Salim M, Cho JK, Rinn K, Albain KS. S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. *American Society of Clinical Oncology*; 2013.
48. Hertz DL, Roy S, Motsinger-Reif AA, Drobish A, Clark LS, McLeod HL, Carey LA, Dees EC. CYP2C8*3 increases risk of neuropathy in breast cancer patients treated with paclitaxel†. *Annals of Oncology*. 2013;24(6):1472–8. doi: 10.1093/annonc/mdt018. [PubMed: 23413280]
49. Dai D, Zeldin DC, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI, Goldstein JA. Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. *Pharmacogenetics*. 2001;11(7):597–607. Epub 2001/10/23. PubMed PMID: 11668219. [PubMed: 11668219]
50. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. *Pharmacogenomics*. 2009;10(9):1489–510. [PubMed: 19761371]
51. Green H, Söderkvist P, Rosenberg P, Mirghani RA, Rymark P, Lundqvist EÅ, Peterson C. Pharmacogenetic studies of Paclitaxel in the treatment of ovarian cancer. *Basic & clinical pharmacology & toxicology*. 2009; 104(2):130–7. [PubMed: 19143748]
52. Rizzo R, Spaggiari F, Indelli M, Lelli G, Baricordi OR, Rimessi P, Ferlini A. Association of CYP1B1 with hypersensitivity induced by taxane therapy in breast cancer patients. *Breast cancer research and treatment*. 2010;124(2):593–8. [PubMed: 20632082]
53. Bergmann TK, Gréen H, Brasch-Andersen C, Mirza MR, Herrstedt J, Hølund B, Du Bois A, Damkier P, Vach W, Brosen K. Retrospective study of the impact of pharmacogenetic variants on paclitaxel toxicity and survival in patients with ovarian cancer. *European journal of clinical pharmacology*. 2011;67(7):693–700. [PubMed: 21327421]
54. Cavaletti G, Alberti P, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. *The Lancet Oncology*. 2011;12(12):1151–61. Epub 2011/07/02. doi: 10.1016/s1470-2045(11)70131-0. PubMed PMID: 21719347. [PubMed: 21719347]
55. Moudi M, Go R, Yien CY, Nazre M. Vinca alkaloids. *International journal of preventive medicine*. 2013;4(11):1231–5. Epub 2014/01/10. PubMed PMID: 24404355; PubMed Central PMCID: PMC3883245. [PubMed: 24404355]
56. Downing KH. Structural basis for the interaction of tubulin with proteins and drugs that affect microtubule dynamics. *Annual review of cell and developmental biology*. 2000;16(1):89–111.
57. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treatment Reviews*. 2014;40(7):872–82. doi: 10.1016/j.ctrv.2014.04.004. [PubMed: 24830939]
58. Canta A, Pozzi E, Carozzi VA. Mitochondrial Dysfunction in Chemotherapy-Induced Peripheral Neuropathy (CIPN). *Toxics*. 2015;3(2):198–223. PubMed PMID: doi:10.3390/toxics3020198. [PubMed: 29056658]
59. Benbow JH, Mann T, Keeler C, Fan C, Hodsdon ME, Lolis E, DeGray B, Ehrlich BE. Inhibition of paclitaxel-induced decreases in calcium signaling. *The Journal of biological chemistry*. 2012;287(45):37907–16. Epub 2012/09/19. doi: 10.1074/jbc.M112.385070. PubMed PMID: 22988235; PubMed Central PMCID: PMC3488062. [PubMed: 22988235]

60. Nazir HF, AlFutaisi A, Zacharia M, Elshinawy M, Mevada ST, Alrawas A, Khater D, Jaju D, Wali Y. Vincristine-induced neuropathy in pediatric patients with acute lymphoblastic leukemia in Oman: Frequent autonomic and more severe cranial nerve involvement 2017;64(12). doi: 10.1002/pbc.26677. PubMed PMID: 28623857.
61. Batta B, Trechot F, Cloche V, George JL, Angioi K. [Vincristine-induced unilateral ptosis: case report and review of the literature]. *Journal francais d'ophtalmologie*. 2013;36(8):683–6. Epub 2013/07/31. doi: 10.1016/j.jfo.2013.03.007. PubMed PMID: 23896211.
62. Dixit G, Dhingra A, Kaushal D. Vincristine induced cranial neuropathy. *The Journal of the Association of Physicians of India*. 2012;60:56–8. Epub 2012/07/18. PubMed PMID: 22799120.
63. Starobova H, Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Front Mol Neurosci*. 2017;10:174–. doi: 10.3389/fnmol.2017.00174. PubMed PMID: 28620280. [PubMed: 28620280]
64. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. *Annals of neurology*. 2017;81(6):772–81. Epub 2017/05/10. doi: 10.1002/ana.24951. PubMed PMID: 28486769; PubMed Central PMCID: PMC5656281. [PubMed: 28486769]
65. Scagliotti GV, Vokes EE. 51 - Adjuvant and Neoadjuvant Chemotherapy for Early-Stage Nonsmall Cell Lung Cancer. In: Pass HI, Ball D, Scagliotti GV, editors. *IASLC Thoracic Oncology (Second Edition)* Philadelphia: Content Repository Only!; 2018 p. 512–24.e4.
66. Fukuda Y, Li Y, Segal RA. A Mechanistic Understanding of Axon Degeneration in Chemotherapy-Induced Peripheral Neuropathy. *Frontiers in Neuroscience*. 2017;11(481). doi: 10.3389/fnins.2017.00481.
67. Jamieson SMF, Liu J, Hsu T, Baguley BC, McKeage MJ. Paclitaxel induces nucleolar enlargement in dorsal root ganglion neurons in vivo reducing oxaliplatin toxicity. *Br J Cancer*. 2003;88(12):1942–7. Epub 06/10. doi: 10.1038/sj.bjc.6601012. PubMed PMID: 12799641. [PubMed: 12799641]
68. Kanat O, Ertas H, Caner B. Platinum-induced neurotoxicity: A review of possible mechanisms. *World J Clin Oncol*. 2017;8(4):329–35. Epub 08/10. doi: 10.5306/wjco.v8.i4.329. PubMed PMID: 28848699. [PubMed: 28848699]
69. Newton HB. Neurological complications of chemotherapy to the central nervous system. *Handbook of clinical neurology*. 2012;105:903–16. Epub 2012/01/11. doi: 10.1016/b978-0-444-53502-3.00031-8. PubMed PMID: 22230541. [PubMed: 22230541]
70. McKeage MJ. Comparative adverse effect profiles of platinum drugs. *Drug safety*. 1995;13(4):228–44. [PubMed: 8573296]
71. McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. *Molecular cancer therapeutics*. 2009;8(1):10–6. [PubMed: 19139108]
72. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nature Reviews Clinical Oncology*. 2009;6:596. doi: 10.1038/nrclinonc.2009.128.
73. Beijers A, Jongen J, Vreugdenhil G. Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies. *Neth J Med*. 2012;70(1):18–25. [PubMed: 22271810]
74. Broyl A, Corthals SL, Jongen JL, van der Holt B, Kuiper R, de Knecht Y, van Duin M, el Jarari L, Bertsch U, Lokhorst HM. Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *The lancet oncology*. 2010;11(11):1057–65. [PubMed: 20864405]
75. Pei XY, Dai Y, Grant S. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2004;10(11):3839–52. Epub 2004/06/03. doi: 10.1158/1078-0432.ccr-03-0561. PubMed PMID: 15173093. [PubMed: 15173093]
76. Arastu-Kapur S, Anderl JL, Kraus M, Parlatti F, Shenk KD, Lee SJ, Muchamuel T, Bennett MK, Driessen C, Ball AJ, Kirk CJ. Nonproteasomal Targets of the Proteasome Inhibitors Bortezomib and Carfilzomib: a Link to Clinical Adverse Events. *Clinical Cancer Research*. 2011;17(9):2734–43. doi: 10.1158/1078-0432.ccr-10-1950. [PubMed: 21364033]

77. Shin YK, Jang SY, Lee HK, Jung J, Suh DJ, Seo S-Y, Park HT. Pathological adaptive responses of Schwann cells to endoplasmic reticulum stress in bortezomib-induced peripheral neuropathy. *Glia*. 2010;58(16):1961–76. doi: 10.1002/glia.21065. [PubMed: 20830808]
78. Filosto M, Rossi G, Pelizzari AM, Buzio S, Tentorio M, Broglio L, Mancuso M, Rinaldi M, Scarpelli M, Padovani A. A high-dose bortezomib neuropathy with sensory ataxia and myelin involvement. *Journal of the neurological sciences*. 2007;263(1-2):40–3. Epub 2007/07/07. doi: 10.1016/j.jns.2007.05.023. PubMed PMID: 17612569. [PubMed: 17612569]
79. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, Avigan DE, Xie W, Ghobrial IM, Schlossman RL. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116(5):679–86. [PubMed: 20385792]
80. Manasanch EE, Orlowski RZ. Proteasome inhibitors in cancer therapy. *Nature Reviews Clinical Oncology*. 2017;14:417. doi: 10.1038/nrclinonc.2016.206.
81. Carozzi VA, Renn CL, Bardini M, Fazio G, Chiorazzi A, Meregalli C, Oggioni N, Shanks K, Quartu M, Serra MP, Sala B, Cavaletti G, Dorsey SG. Bortezomib-induced painful peripheral neuropathy: an electrophysiological, behavioral, morphological and mechanistic study in the mouse. *PloS one*. 2013;8(9):e72995–e. doi: 10.1371/journal.pone.0072995. PubMed PMID: 24069168. [PubMed: 24069168]
82. Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, Orlopp K, Schmidt-Wolf I, Gorschlüter M. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *British Journal of Haematology*. 2006;132(5):584–93. doi: 10.1111/j.1365-2141.2005.05914.x. [PubMed: 16445831]
83. Ibrahim EY, Busaidy NL. Treatment and surveillance of advanced, metastatic iodine-resistant differentiated thyroid cancer. *Current opinion in oncology*. 2017;29(2):151–8. Epub 2017/02/01. doi: 10.1097/cco.0000000000000349. PubMed PMID: 28141684. [PubMed: 28141684]
84. Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, Verma A. Mechanism of action of lenalidomide in hematological malignancies. *Journal of Hematology & Oncology*. 2009;2(1):36. doi: 10.1186/1756-8722-2-36. [PubMed: 19674465]
85. Zhu YX, Kortuem KM, Stewart AK. Molecular mechanism of action of immune-modulatory drugs thalidomide, lenalidomide and pomalidomide in multiple myeloma. *Leukemia & lymphoma*. 2013;54(4):683–7. Epub 2012/09/13. doi: 10.3109/10428194.2012.728597. PubMed PMID: 22966948; PubMed Central PMCID: PMC3931443. [PubMed: 22966948]
86. Bolonsky A, Schreder M, Meissner T, Hose D, Ludwig H, Pfeifer S, Zojer N. Immunomodulatory drugs thalidomide and lenalidomide affect osteoblast differentiation of human bone marrow stromal cells in vitro. *Experimental hematology*. 2014;42(7):516–25. Epub 2014/04/08. doi: 10.1016/j.exphem.2014.03.005. PubMed PMID: 24704163. [PubMed: 24704163]
87. Jongen JL, Broijl A, Sonneveld P. Chemotherapy-induced peripheral neuropathies in hematological malignancies. *Journal of neuro-oncology*. 2015;121(2):229–37. Epub 2014/10/20. doi: 10.1007/s11060-014-1632-x. PubMed PMID: 25326770. [PubMed: 25326770]
88. Wani TH, Chakrabarty A, Shibata N. The Dihydroxy Metabolite of the Teratogen Thalidomide Causes Oxidative DNA Damage. *ACS Chem Neurosci*. 2017;30(8):1622–8. doi: 10.1021/acs.chemrestox.7b00127. PubMed PMID: 28745489.
89. Ochonsky S, Verroust J, Bastuji-Garin S, Gherardi R, Revuz J. Thalidomide Neuropathy Incidence and Clinicoelectrophysiologic Findings in 42 Patients. *JAMA Dermatology*. 1994;130(1):66–9. doi: 10.1001/archderm.1994.01690010070009.
90. Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S, Dispenzieri A, Mikhael JR, Bergsagel PL, Dingli D, Reeder CB, Lust JA, Russell SJ, Roy V, Zeldenrust SR, Witzig TE, Fonseca R, Kyle RA, Greipp PR, Stewart AK, Rajkumar SV. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. *Blood*. 2010;115(7):1343–50. Epub 2009/12/17. doi: 10.1182/blood-2009-08-239046. PubMed PMID: 20008302; PubMed Central PMCID: PMC2826759. [PubMed: 20008302]
91. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *The Cochrane database of systematic reviews*. 2007(4):Cd005454. Epub 2007/10/19. doi: 10.1002/14651858.CD005454.pub2. PubMed PMID: 17943857. [PubMed: 17943857]

92. Bril V, England JD, Franklin GM, Backonja M, Cohen JA, Del Toro DR, Feldman EL, Iverson DJ, Perkins B, Russell JW, Zochodne DW. Evidence-based guideline: treatment of painful diabetic neuropathy--report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation. *Muscle & nerve*. 2011;43(6):910–7. Epub 2011/04/13. doi: 10.1002/mus.22092. PubMed PMID: 21484835. [PubMed: 21484835]
93. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL. 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):1359–67. Epub 2013/04/04. doi: 10.1001/jama.2013.2813. PubMed PMID: 23549581; PubMed Central PMCID: PMC3912515. [PubMed: 23549581]
94. Smith EML, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL, Alliance for Clinical Trials in O. 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):1359–67. doi: 10.1001/jama.2013.2813. PubMed PMID: 23549581. [PubMed: 23549581]
95. Hirayama Y, Ishitani K, Sato Y, Iyama S, Takada K, Murase K, Kuroda H, Nagamachi Y, Konuma Y, Fujimi A, Sagawa T, Ono K, Horiguchi H, Terui T, Koike K, Kusakabe T, Sato T, Takimoto R, Kobune M, Kato J. Effect of duloxetine in Japanese patients with chemotherapy-induced peripheral neuropathy: a pilot randomized trial. *International Journal of Clinical Oncology*. 2015;20(5):866–71. doi: 10.1007/s10147-015-0810-y. [PubMed: 25762165]
96. Kukkar A, Bali A, Singh N, Jaggi AS. Implications and mechanism of action of gabapentin in neuropathic pain. *Archives of pharmacol research*. 2013;36(3):237–51. Epub 2013/02/26. doi: 10.1007/s12272-013-0057-y. PubMed PMID: 23435945. [PubMed: 23435945]
97. Magnowska M, Izycka N, Kapola-Czyz J, Romala A, Lorek J, Spaczynski M, Nowak-Markwitz E. Effectiveness of gabapentin pharmacotherapy in chemotherapy-induced peripheral neuropathy. *Ginecologia polska*. 2018;89(4):200–4. Epub 2018/05/22. doi: 10.5603/GP.a2018.0034. PubMed PMID: 29781075. [PubMed: 29781075]
98. Kim BS, Jin JY, Kwon JH, Woo IS, Ko YH, Park SY, Park HJ, Kang JH. Efficacy and safety of oxycodone/naloxone as add-on therapy to gabapentin or pregabalin for the management of chemotherapy-induced peripheral neuropathy in Korea2018;14(5):e448–e54. doi: 10.1111/ajco.12822. PubMed PMID: 29280313. [PubMed: 29280313]
99. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhyay SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *The American journal of hospice & palliative care*. 2012;29(3):177–82. Epub 2011/07/13. doi: 10.1177/1049909111412539. PubMed PMID: 21745832. [PubMed: 21745832]
100. de Andrade DC, Jacobsen Teixeira M, Galhardoni R, Ferreira KSL, Braz Mileno P, Scisci N, Zandonai A, Teixeira WGJ, Saragiotto DF, Silva V, Raicher I, Cury RG, Macarenco R, Otto Heise C, Wilson Iervolino Brotto M, Andrade de Mello A, Zini Megale M, Henrique Curti Dourado L, Mendes Bahia L, Lilian Rodrigues A, Parravano D, Tizue Fukushima J, Lefaucheur JP, Bouhassira D, Sobroza E, Riechelmann RP, Hoff PM, Valerio da Silva F, Chile T, Dale CS, Nebuloni D, Senna L, Brentani H, Pagano RL, de Souza AM. Pregabalin for the Prevention of Oxaliplatin-Induced Painful Neuropathy: A Randomized, Double-Blind Trial. *The oncologist*. 2017;22(10):1154–e105. Epub 2017/06/28. doi: 10.1634/theoncologist.2017-0235. PubMed PMID: 28652279; PubMed Central PMCID: PMC5634769. [PubMed: 28652279]
101. Hu LY, Mi WL, Wu GC, Wang YQ, Mao-Ying QL. Prevention and Treatment for Chemotherapy-Induced Peripheral Neuropathy: Therapies Based on CIPN Mechanisms. *Current neuropharmacology*. 2019;17(2):184–96. Epub 2017/09/20. doi: 10.2174/1570159x15666170915143217. PubMed PMID: 28925884; PubMed Central PMCID: PMC6343206. [PubMed: 28925884]
102. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, Warner DO, Novotny P, Kutteh LA, Wong GY. 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):2110–8. Epub 2007/09/14. doi: 10.1002/cncr.23008. PubMed PMID: 17853395. [PubMed: 17853395]
103. Ong EC. Controlled-Release Oxycodone in the Treatment of Neuropathic Pain of Nonmalignant and Malignant Causes. *Oncology*. 2008;74(suppl 1)(Suppl. 1):72–5. doi: 10.1159/000143223. [PubMed: 18758202]
 104. Majithia N, Loprinzi CL, Smith TJ. New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment. *Oncology (Williston Park, NY)*. 2016;30(11):1020–9. Epub 2016/11/18. PubMed PMID: 27854104.
 105. van den Heuvel SAS, van der Wal SEI, Smedes LA, Radema SA, van Alfen N, Vissers KCP. Intravenous Lidocaine: Old-School Drug, New Purpose-Reduction of Intractable Pain in Patients with Chemotherapy Induced Peripheral Neuropathy 2017;2017:8053474. doi: 10.1155/2017/8053474. PubMed PMID: 28458593.
 106. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr, Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2011;19(6):833–41. Epub 05/25. doi: 10.1007/s00520-010-0911-0. PubMed PMID: 20496177. [PubMed: 20496177]
 107. Maayan F, Ron B, Shiran E, Ronen D, Pamela S, Moshe S, Noam A. Management of Peripheral Neuropathy Induced by Chemotherapy. *Current Medicinal Chemistry*. 2019;26:1–10. doi: 10.2174/0929867326666190107163756.
 108. Romero-Sandoval EA, Asbill S, Paige CA, Byrd-Glover K. Peripherally Restricted Cannabinoids for the Treatment of Pain. *Pharmacotherapy*. 2015;35(10):917–25. Epub 2015/10/27. doi: 10.1002/phar.1642. PubMed PMID: 26497478. [PubMed: 26497478]
 109. Milla P, Airoidi M, Weber G, Drescher A, Jaehde U, Cattel L. Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. *Anti-cancer drugs*. 2009;20(5):396–402. [PubMed: 19287306]
 110. Wiernik PH, Yeap B, Vogl SE, Kaplan BH, Comis RL, Falkson G, Davis TE, Fazzini E, Chevart B, Horton J. Hexamethylmelamine and low or moderate dose cisplatin with or without pyridoxine for treatment of advanced ovarian carcinoma: a study of the Eastern Cooperative Oncology Group. *Cancer investigation*. 1992;10(1):1–9.
 111. Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, Hashemzade S, Jafarabadi MA, Montazeri V, Keshavarz SA. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial. *BMC cancer*. 2012;12(1):355. [PubMed: 22894640]
 112. Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crinò L. A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy. *Tumori*. 2005;91(2):135–8. [PubMed: 15948540]
 113. Koh PO, Undie AS, Kabbani N, Levenson R, Goldman-Rakic PS, Lidow MS. Up-regulation of neuronal calcium sensor-1 (NCS-1) in the prefrontal cortex of schizophrenic and bipolar patients. *Proc Natl Acad Sci U S A*. 2003;100(1):313–7. Epub 12/20. doi: 10.1073/pnas.232693499. PubMed PMID: 12496348. [PubMed: 12496348]
 114. Schuette D, Moore LM, Robert ME, Taddei TH, Ehrlich BE. Hepatocellular Carcinoma Outcome Is Predicted by Expression of Neuronal Calcium Sensor 1. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2018;27(9):1091–100. Epub 2018/05/24. doi: 10.1158/1055-9965.epi-18-0167. PubMed PMID: 29789326.
 115. Moore LM, Wilkinson R, Altan M, Toki M, Carvajal-Hausdorf DE, McGuire J, Ehrlich BE, Rimm DL. An assessment of neuronal calcium sensor-1 and response to neoadjuvant chemotherapy in breast cancer patients. *NPJ breast cancer*. 2018;4:6. Epub 2018/03/22. doi: 10.1038/s41523-018-0057-7. PubMed PMID: 29560416; PubMed Central PMCID: PMC5847580 Bethyl Labs, Biocept, BMS, Cell Signaling Technology, Cepheid, ClearSight, Genoptix/Novartis, Merck, OptraScan, Perkin Elmer, and Ultivue. D.L.R. has received grant funding from Cepheid, Genoptix, Gilead Sciences, Pierre Fabre, Perkin Elmer and Nantomics.

None of these interactions are related to this work. The remaining authors declare no competing interests. [PubMed: 29560416]

116. Ge W, Jakobsson E. Systems Biology Understanding of the Effects of Lithium on Cancer. *Front Oncol.* 2019;9:296-. doi: 10.3389/fonc.2019.00296. PubMed PMID: 31114752. [PubMed: 31114752]
117. Wadia RJ, Stolar M, Grens C, Ehrlich BE, Chao HH. The prevention of chemotherapy induced peripheral neuropathy by concurrent treatment with drugs used for bipolar disease: a retrospective chart analysis in human cancer patients. *Oncotarget.* 2018;9(7):7322–31. Epub 2018/02/28. doi: 10.18632/oncotarget.23467. PubMed PMID: 29484113; PubMed Central PMCID: PMC5800905. [PubMed: 29484113]
118. Zhu J, Carozzi VA, Reed N, Mi R, Marmioli P, Cavaletti G, Hoke A. Ethoxyquin provides neuroprotection against cisplatin-induced neurotoxicity. *Scientific reports.* 2016;6:28861. [PubMed: 27350330]
119. Zhu J, Chen W, Mi R, Zhou C, Reed N, Hoke A. Ethoxyquin prevents chemotherapy-induced neurotoxicity via Hsp90 modulation. *Annals of neurology.* 2013;74(6):893–904. Epub 2013/08/21. doi: 10.1002/ana.24004. PubMed PMID: 23955554. [PubMed: 23955554]
120. Izgu N, Metin ZG, Karadas C, Ozdemir L, Cetin N, Demirci U. Prevention of chemotherapy-induced peripheral neuropathy with classical massage in breast cancer patients receiving paclitaxel: An assessor-blinded randomized controlled trial. *European journal of oncology nursing : the official journal of European Oncology Nursing Society.* 2019;40:36–43. Epub 2019/06/24. doi: 10.1016/j.ejon.2019.03.002. PubMed PMID: 31229205. [PubMed: 31229205]

Highlights:

- Chemotherapy-induced peripheral neuropathy (CIPN) is a common progressive, and often irreversible, adverse effect of many chemotherapeutic agents.
- Currently, there are no effective treatments to prevent or control CIPN, and there is limited evidence of effective treatments for chronic CIPN.
- There are new mechanisms that need to be highlighted and examined in depth for use in developing effective therapies.

Fig. 1.
Illustration demonstrating sites of action of agents involved in chemotherapy induced peripheral neuropathy (CIPN) development.

Table 1.

Pharmaceutical agents used for CIPN management.

Agent	Effect	Outcome	Study
Serotonin-norepinephrine reuptake inhibitors	Symptomatic treatment	- Duloxetine is only approved drug for treatment of CIPN. However, it is not confirmed whether duloxetine is more effective than a placebo. -No protective role.	Hershman et al (27) Smith et al (94) Hirayama et al (95)
Anticonvulsants	Symptomatic treatment	-Gabapentin: No major decrease in neuropathic symptoms. -Pregabalin: partially effective to reduce neuropathic symptoms if combined with opioids. -No protective role.	Magnowska et al (97) Kim et al (98) Mishra et al (99)
Analgesics	Symptomatic treatment	-Oxycodone/naloxone: partially effective to reduce neuropathic symptoms when combined with anticonvulsants. -No protective role.	Kim et al (98)
Acetyl-L-carnitine	Symptomatic treatment	-Acetyl-L-carnitine showed positive results for treatment of paclitaxel- and cisplatin-induced neuropathy. -Results need to be confirmed in larger double-blind, placebo-controlled studies.	Maestri et al (118)
Lithium	Protective	-Prevents CIPN symptoms induced by taxanes and vinca alkaloids without impairing the chemotherapeutic response. -Retrospective study supports human use.	Boehmerle et al (37) Mo et al (41) Wadia et al (112)
Ethoxyquin	Protective	-Protect sensory neuron and dorsal root ganglia neurons in mice with cisplatin neuropathy. -No evidence in human studies.	Zhu et al (113) Zhu et al (114)
Glutathione	Protective	-Associated with reduction of oxaliplatin-induced neurotoxicity. -Initial clinical trial in humans failed.	Milla et al (115)
Vitamin E Vitamin B6 Omega 3	Protective	- CIPN incidence was lowered with Vitamin E and B6 administration but vitamin B6 should not be administered with DDP or HMM chemotherapy regimens *. -Omega 3 administration showed positive results with taxane-induced neuropathy.	Wiernik et al (116) Ghoreishi et al (117)
Classical massage/ Regional cooling	Protective	-These modalities can prevent CIPN. -Patient reports support human use.	Izgu et al (119)

* cisplatin (DDP)-hexamethylmelamine (HMM) regimens