

# Chemotherapy-Induced Peripheral Neuropathy in Pediatric Cancer Patients

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## Abstract

Chemotherapy-induced peripheral neuropathies (CIPNs) are an increasingly common neuropathic and pain syndrome in adult and pediatric cancer patients and survivors [1-69]. However, symptoms associated with CIPNs are often undiagnosed, under-assessed, and communications problems between clinicians, family members, and patients have been observed [70-73]. Less is known about the prevalence and impact of CIPNs on pediatric cancer populations [70-71]. This article aims to provide a brief understanding of CIPNs in pediatric populations, and to review the evidence for both its prevention and treatment.

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**Categories:** Pain Management, Pediatrics, Oncology

**Keywords:** chemotherapy induced peripheral neuropathy, cancer pain, communication, pediatric pain

## Introduction And Background

Chemotherapy-induced peripheral neuropathies (CIPNs) are an increasingly common neuropathic and pain syndrome in adult and pediatric cancer patients and survivors [1-69]. However, symptoms associated with CIPNs are often undiagnosed, under-assessed, and communication problems between clinicians, family members, and patients have been observed [70-73]. Less is known about the prevalence and impact of CIPNs on pediatric cancer populations [70-71]. The aim of this paper is to provide a brief understanding of CIPNs in pediatric populations, and review the evidence for both its prevention and treatment.

Chemotherapy-induced peripheral neuropathies (CIPNs) are common and serious complications of a patient's primary malignancy or its treatment, whether by surgery, radiation, or chemotherapy. CIPNs are sensory, dose-related, and cumulative. Briefly, drug-induced neurotoxicity can adversely affect the nerve fibers or the neuronal bodies (generally, the dorsal root ganglia (DRG)) of the primary sensory neurons [11, 70, 72-75]. The damage caused by chemotherapeutic agents can also cause subsequent and long-term functional abnormalities of structural lesions in both the peripheral and central nervous systems (CNS) [3-5]. The chemotherapeutic agents most often associated with CIPNs are the platinum-based compounds, taxanes, vinca alkaloids, thalidomide, and newer agents, such as bortezomib [3-10,70-73]. Although the incidence of peripheral neuropathy resulting from a single agent can be significant, the administration of multiple neurotoxic agents is not uncommon and can result in a higher grade of overall neurotoxicity. The impact may be immediate, delayed, or can appear weeks to months (or even years), after the initiation of therapy. Effects can range from motor, to sensory-motor, or almost exclusively sensory neuropathies, with or without autonomic impairment [70-75]. In severe damage, CIPNs can be partly reversible, and may sometimes be irreversible [75]. The majority of what is known about CIPNs is based on evidence from studies of animals and adult cancer patient and survivors [1-70]. Less is known about the prevalence

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and impact of CIPNs in pediatric cancer populations [70-71]. The aim of this paper is to provide a brief understanding of CIPNs in pediatric populations and review the evidence for both its prevention and treatment.

## Case study

Melissa R. is a 10-year-old undergoing therapy for high-risk pre-B cell acute lymphoblastic leukemia. She has completed her induction therapy with vincristine, dexamethasone, L-asparaginase, and doxorubicin. During the beginning of her consolidation therapy, she complains that she "can't walk right". Physical exam demonstrates mild weakness of the left lower extremity (decreased motor strength on dorsal and plantar foot flexion) and decreased tactile sensation and proprioception in both feet. Over subsequent days, her right foot and ankle develop similar motor findings. On ambulation, she demonstrates a bilateral foot drop. She begins to complain of "pinpricks" sensations in her feet.

## Review

### Epidemiology

#### *Prevalence and Incidence*

Similar to the prevalence of CIPNs in adult populations, the actual prevalence of CIPNs in pediatric cancer populations is not known, given a lack of adequate standardized assessment, measurement, and reporting mechanisms [3, 9, 11, 70-71]. What is known about CIPNs highlight the significant variation in the incidence of CIPNs, as symptoms that tend to depend on the type of drugs used, dosage, and treatment schedules employed [3-11,70-74]. The incidence of severe CIPN in adult cancer patients has been estimated to be between 3% to 7% in individuals treated with single agents, and upward of 38% in those treated with multiple chemotherapeutic agents [3-11]. Significantly less is known about the incidence of CIPNs in pediatric patients [70-71]. Moreover, although specific, standardized measures of CIPN are available for adults, such measures are limited for use in the pediatric populations [70-71]. The incidence of neurotoxicity has been reported from between 3-13% in studies of pediatric cancer patients, to about 35% in pediatric patients treated specifically for acute lymphoblastic leukemia (ALL). Patients in this specific study experienced one episode of neuropathic pain during treatment, with 16% experiencing at least one episode of recurrent pain [70-76]. A more recent study from India reported the highest CIPN incidence observed (50%) in a pediatric ALL patient [76].

#### *Pathophysiology*

The degree of neuronal damage from chemotherapy depends on a variety of factors, including the chemotherapeutic agent(s) used, duration of therapy, cumulative dose, and concomitant use of other neurotoxic agents [73]. Neural damage can also occur at multiple sites, including cell body, axon, and myline sheath. An overview of proposed mechanisms of damage in pediatric cancer patients are presented in Table 1.

Chemotherapeutic Agent	Type of Neuronal Damage	Use in Pediatric Cancers
Vincristine	Microtubule destabilization and axonopathy; sensory and motor	Acute lymphoblastic leukemias, lymphomas, brain tumors, solid tumors
Cisplatin	Binding to dorsal root ganglia cell DNA and inducing apoptosis; primarily sensory	Brain tumors, bone tumors, testicular cancer, other solid tumors
Taxanes	Microtubule destabilization; sensory damage more than motor	Rare, ovarian tumors
Epothilones	Microtubule polymerization agent; sensory involvement common, motor and autonomic can also occur	Refractory solid tumors
Bortezomib	mRNA, mitochondrial, and endoplasmic reticulum damage; sensory involvement with neuropathic pain	Refractory or recurrent cancers
Thalidomide	Unclear mechanism	Meduloblastoma and hepatocellular cancers

**TABLE 1: Adapted from: Gilchrist L. Chemotherapy-Induced Peripheral Neuropathy in Pediatric Cancer Patients. *Sem Ped Neurol*.2012; 19(1):9-17.**

#### *Risk Factors*

Comorbid conditions, such as diabetes, human immunodeficiency virus infection, alcoholism, preexisting neuropathies (diabetic neuropathy, small fiber neuropathies), prior treatment with platinum-based therapies, vitamin B, and other nutritional deficiencies, appear to place patients at greater risk for CIPN [3, 6, 11, 13-15, 77-78]. Although the incidence of peripheral neuropathy resulting from a single agent can be significant, the administration of two neurotoxic agents is not uncommon and can result in higher grades of overall neurotoxicity [11, 70, 73].

While the majority of studies which document risk factors associated with the development of CIPN have focused on adult populations; several important risk factors have also been observed in pediatric populations [70-72,77-82]. Anderson, et al. (2002) noted that one potential risk factor for CIPN in pediatric cancer patients is ventral nerve root vulnerability to intrathecal chemotherapy [70-71, 79]. Other studies indicate that a diagnosis of Guillain-Barre syndrome [80-81], Charcot-Marie-Tooth disease [82], prior treatment with platinum based therapies [70-73], or vitamin B and other nutritional deficiencies also place pediatric cancer survivors at greater risk for CIPNs [3, 6, 11, 13-15, 77-78]. Vincristine neurotoxicity may be aggravated by the following: a higher dosage regimen (>30–50 mg); hypersensitivity to the drug, pre-existing liver dysfunction; hereditary neuropathy; and concomitant use of other drugs, such as allopurinol, erythromycin, isoniazid, mitomycin C, phenytoin, and itraconazole [83]. Variation also exists in the symptoms associated with CIPNs. Little is known about what additional factors place pediatric patients at risk for CIPNs [70-71].

*Symptom Variation*

Cancer patients often experience concurrent symptoms in addition to pain. Common symptoms observed in pediatric CIPN patients include a lack of energy, pain, drowsiness, nausea, cough, and a lack of appetite [84]. Pain and fatigue are also associated with sleep disturbances, anxiety, depression, anorexia, nausea, and vomiting [84]. All these factors contribute to symptom burden, and more recent studies are beginning to identify and evaluate symptom clusters in pediatric cancer populations [84]. This work is in early in development [84]. In addition, many symptoms (e.g., depression or anxiety) might also not be voluntarily communicated by patients unless they are detected via systematic questioning, noted by either requests for information about symptoms by clinicians, or by observations from parents or caregivers [72]. These communication issues also contribute to the under-reporting of CIPNs. Also, even when neurophysiologic methods are used to diagnose CIPNs; the lack of gold-standard measures for CIPNs, and the wide variation in the resultant symptoms, further enhances the difficulty in predicting and potentially modeling which pediatric patients may be at the greatest risk for CIPNs (in either the short and long-term) [4-11, 70-73, 84].

Great heterogeneity in the underlying mechanism(s) of nerve injury caused by individual agents, may partly explain the wide variation in the symptoms that CIPN patients experience [3-11, 13-17, 29-31, 70-73]. Sex differences in symptoms have also been observed in adult CIPN patients [28], though less is known about such variation in pediatric populations [70-71, 73]. Chemotherapeutic toxicity is also influenced by multiple genetic factors and non-genetic factors, including age, gender, ethnicity, and drug-drug interactions [18-28, 73, 77]. The majority of patients report a gradual onset of neuropathic symptoms, although some develop symptoms more rapidly [3-11]. Symptoms can last from a few days to a lifetime [3-11].

Symptoms are described briefly below and include the following:

- The length dependent loss of innervation found in CIPNs can manifest as a stocking-and-glove distribution in the toes and fingers [3-11, 70-73].
- Physical examination may reveal tactile allodynia, cold allodynia, hypersensitivity, and loss of both vibration sensitizing and deep tendon reflexes [4, 8].
- Motor symptoms, including declines in muscle strength, can lead to muscle weakness and atrophy, precipitating functional impairment.
- Distant muscle weakness, balance deficits, gait abnormalities, and manual dexterity have also been observed in CIPN patient populations.
- Patient reported outcomes, including terms such as "burning," "tingling," "electric shock sensation," and "painful numbness," have all been used to describe symptoms and sensations associated with CIPNs [4, 8].
- Patients may also report increased pain during walking, with descriptions of sensations, such as "walking on shards of glass" or "stepping on razorblades" [4, 8].
- Patients may also experience a loss of proprioception, the unconscious perception of movement and spatial orientation within the body [7, 9, 13, 15]. Loss of proprioception can lead to significant safety issues, [8-9, 13]. Patients without proprioception are also at great risk for falls because they also tend to lose all sense of the position of their feet [7, 9, 15].

For instance, vincristine-induced neurotoxicity in pediatric populations is thought to be a consequence of its primary antineoplastic function as a mitotic spindle inhibitor. Experimental data suggest that this drug can also alter the structure of axonal transport. Axonal transport dysfunction is a major theory for the pathogenesis of a variety of toxic neuropathies, including vincristine-induced neurotoxicity [73]. It can also manifest as a loss of deep tendon reflexes, neuritic pain, paresthesias, and wrist and foot drop. Less frequently, cranial nerve palsies, transient cortical blindness, oculomotor nerve dysfunction, jaw pain, facial palsy, sensorineural hearing loss, and laryngeal nerve paresis have also been observed [78]. In this and in other CIPNs, symptoms can be severe and debilitating. Moreover, as symptoms develop and progress, they can also interfere with patients' ability to receive their full dose of cancer treatment, or receive doses at the frequency required for optimal outcomes [70-73]. Currently, no pharmacological agents have been proven to be effective for this indication [73].

### Prevention of CIPNs

Efforts to discover reliable preventative measures against CIPN remain elusive, for the most part. Research has focused on treating and preventing CIPNs in the setting of more commonly used cancer agents: the platinum-based compounds and the taxanes. To date, available evidence comes from small trials which fail to adequately discuss clear guidelines for prevention. Rather, the emphasis points to specific directions for future research, particularly in pediatric populations. Below is a general summary of specific agents researched, chemotherapy drug setting, and potential mechanisms associated with the prevention of CIPNs [32-37, 41, 43, 45, 73].

Chemoprotective Agent	Chemotherapy Setting of Study	Possible Mechanism of Protection	Comments
Vitamin E	Platinum compounds, taxanes	Protect against cellular oxidative damage	Promising small RCTs in adult populations
Amifostine	Platinum compounds, taxanes	Unknown; possibly enhancing intracellular DNA repair	
Ca <sup>2+</sup> /Mg <sup>2+</sup> infusion	Platinum compounds	Bind toxic metabolites of platinum agents	Some studies demonstrate concomitant antitumor activity
Glutathione	Platinum compounds	Decrease accumulation of platinum metals in dorsal root ganglion	
Glutamine	Platinum compounds, taxanes	Unknown; may enhance rapid healing of connective tissue damaged by chemotherapy	Some concern about tumor protective effects by glutamine needs to be elucidated
Carbamazepine	Platinum compounds	Delayed recovery of Na <sup>+</sup> gated channels	

**TABLE 2:** [32-34, 35-37, 41, 43, 45, 73]

### *Chemoprotectants*

Chemoprotectants, such as amifostine, have been tested as a means of detoxifying chemotherapy and facilitating DNA repair, while not interfering with the efficacy of chemotherapy. In studies testing the effect of amifostine on peripheral neuropathy associated with taxane-based chemotherapy regimens, no differences were found in sensory or motor neurotoxic symptoms in patients treated with amifostine. Amifostine was also shown to be ineffective in preventing or reducing the neurotoxic effects of high-dose paclitaxel [32-34]. A recent Cochrane review also noted that at present the data are insufficient to conclude that any of the purported chemoprotective agents prevent or limit the neurotoxicity of platinum based drugs in human patients [85].

### *Vitamin E*

Vitamin E supplementation has also been tested in the prevention of CIPNs [73]. Vitamin E is thought to be protective against cellular oxidative damage and side-effects, including numbness, tingling, burning, and or pain in peripheral extremities produced by cisplatin and other cytotoxic drugs. Three studies have examined the cytoprotective effect of vitamin E supplementation in the development of CIPNs following the administration of cisplatin, paclitaxel, or a combination regimen [35-37]. These studies showed that the incidence of neurotoxicity was lower in the group who received vitamin E, as compared to a control group. At present, the data are insufficient to conclude whether Vitamin E can prevent or limit the neurotoxicity of platinum-based drugs in either adult or pediatric populations [85].

### *Infusions of Calcium and Magnesium*

Calcium and magnesium infusions (Ca/Mg infusions) for oxaliplatin-associated neuropathy have been associated with positive preliminary data, but require further investigation [73]. Oxalate, an oxaliplatin metabolite, binds to calcium and magnesium [38, 73, 85]. Ca/Mg infusions and improvements in the clinical manifestations of acute neurotoxicity have been reported [38]. There is also additional evidence that Ca/Mg infusions could be a potentially safe and cost-effective means of preventing oxaliplatin-related peripheral neuropathy in adults [38, 73]. Ca/Mg infusions may offer a potentially safe, cost-effective means of preventing oxaliplatin-related peripheral neuropathy in adult populations [73]. The data, however, is insufficient to conclude the following: if infusions of calcium and magnesium provides benefit across other adult CIPNs populations; if such effects are only for the short-term, or become adverse in the long-term [73]. Finally, there is so substantial evidence that Ca/Mg infusion provides any benefit in the treatment or prevention of CIPNs in pediatric patients. Thus, additional studies in pediatric populations may be warranted [39-40, 85].

### *Carbamazepine*

Carbamazepine, an anticonvulsant drug, appears to protect against oxaliplatin-induced neurotoxicity by slowing the rate of recovery of voltage-activated sodium channels. Carbamazepine has been tested in the prevention of CIPN in a single non-randomized pilot study consisting of 10 previously treated patients with advanced colorectal cancer receiving oxaliplatin, leucovorin, and 5-fluorouracil. Results indicated the absence of World Health Organization Grade 2 to 4 neuropathy development in the patients treated with carbamazepine compared with 30% who experienced Grade 2 to 4 neuropathy in a historical control group [41]. In another randomized, controlled trial, von Delius and colleagues also tested the efficacy and safety of carbamazepine for the prevention of oxaliplatin-associated neuropathy in 36 patients with advanced colorectal cancer [42]. No differences were found between the groups on assessments of neurotoxicity. Additional studies are needed to clarify the role of carbamazepine

and oxcarbazepine in the prevention and treatment of CIPN in both adult and pediatric patient populations [73, 85].

#### *Glutamine*

Glutamine, a neutral gluconeogenic non-essential amino acid, is thought to have neuroprotective effects in patients receiving paclitaxel and oxaliplatin-associated neuropathy [43, 73]. Stubblefield and colleagues examined the neuroprotective effect of glutamine in 46 patients scheduled to receive high-dose paclitaxel before a stem cell transplant [43]. The results of neurologic symptom questions and electrodiagnostic testing indicate that those who received glutamine developed less weakness, loss of vibratory sensation, and toe numbness compared with those in the control group. In a non-randomized pilot study, Wang and colleagues tested the efficacy of glutamine for reducing the incidence and severity of peripheral neuropathy in colorectal patients receiving oxaliplatin [45, 73]. Study results suggest that glutamine supplementation may significantly reduce the incidence and severity of oxaliplatin-induced neuropathy [45, 73]. However, while glutamine is a potential neuroprotective agent, it must still be studied in larger sample of patients in a randomized, placebo-controlled trial. Also, concerns still exist about glutamine supplements protecting tumor cells from the cytotoxic effects of chemotherapy [45]. In summary, while glutamine has been associated with some positive preliminary data, additional investigation [73] is warranted in both adult and pediatric populations.

#### *Glutathione*

Several clinical trials have assessed the efficacy of glutathione in the prevention of CIPNs. It is thought that platinum drugs cause neurotoxicity via the accumulation of platinum in the dorsal root ganglion. Glutathione, a naturally occurring tri-peptide consisting of glutamyl-cysteinyl-glycine, has a high affinity for heavy metals, and may also prevent neurotoxicity induced by platinum compounds by preventing the initial accumulation of platinum adducts in the dorsal root ganglia [46,73]. This decrease in accumulation has been observed in both animal models and adult cancer patient populations. Additional studies are needed to further test the efficacy of this agent in pediatric patients [47-49, 73, 85-88].

## **Treatment**

Neuropathic pain management has generally been aimed at the reduction of symptoms [13, 50-51, 73]. Historically, treatments for CIPNs have been supportive and focused on controlling pain, when present [50]. At this time, no medications currently exist that can fully relieve the sensory and motor loss associated with advanced CIPNs [73]. Early intervention and management are essential. Still, the needs of patients with CIPNs are often unmet due to the absence of adequate assessment and evidence-based treatments that could be widely applied across both adult and pediatric patients with CIPNs [11, 70-73].

#### *Gabapentin*

Gabapentin, an antiepileptic medication with demonstrated efficacy for the treatment of neuropathic pain, has also been used in the treatment of CIPNs. The therapeutic action of Gabapentin on neuropathic pain is thought to involve voltage-gated calcium channels. Studies have failed to demonstrate the benefit of gabapentin in the treatment of CIPN-related symptoms [52, 77]. A related drug, pregabalin, is often used to treat adults with CIPNs. However, it has yet to be approved for use in pediatric CIPN patient populations.

#### *Pyridoxine and Pyridostigmine*



Pyridostigmine or analogues have been used to enhance intestinal motility in patients with bowel atony from various causes, including CIPNs. For example, Pyridostigmine has been used for vincristine-related neuropathy because reduction of gastrointestinal motility is one of the major symptoms of this neuropathy [78, 89]. A few case reports of full recovery of vincristine-associated bilateral ptosis (cranial polyneuropathy) after treatment with pyridoxine and Pyridostigmine are available [78, 89-91]. Because the pathophysiology of vincristine neuropathy is not fully understood, preventive and therapeutic approaches are still experimental. Additional studies are warranted in adult and pediatric populations.

#### *Nortriptyline*

Nortriptyline, a tricyclic antidepressant, works by blocking the reuptake of serotonin and norepinephrine in the pain-modulating system within the CNS [53]. Tricyclic antidepressant ingestion have also been shown to have a high potential for toxicity in pediatric patients. This case suggests, contrary to previous literatures, that toxicity may occur even with small doses [92].

#### *Opioids*

Multiple studies have demonstrated the efficacy of opioids to manage painful neuropathies [93]. Although such studies predominately focus on other etiologies of painful neuropathy (e.g. diabetic peripheral neuropathy, post-herpetic neuralgia), conclusions have been extrapolated to managing painful CIPN in adults. Traditional mu-receptor agonist analgesics, such as morphine, oxycodone, and fentanyl, can be useful as an initial therapy for managing pain in CIPN, particularly as a bridge therapy before other adjuvant drugs take effect. In more complex cases involving severe pain, opioids with NMDA receptor antagonist properties, such as methadone, may have a special role. As opposed to traditional mu-opioid agonists, such therapies should only be initiated in consultation with a pain or palliative care specialist with experience. Finally, tramadol, a mu-opioid agonist with weak norepinephrine and serotonin reuptake inhibition, has also been shown to be beneficial in neuropathic pain. However, it has not been approved for use in children [93].

#### *Acetyl L-carnitine*

Acetyl L-carnitine is an acetylated form of L-carnitine that has neuroprotective effects, and may be useful in treating peripheral nerve injury. While there is some evidence that adult patients who have received acetyl L-carnitine have shown improvement in neuropathy symptoms and in objective measures of sensory and motor neuropathy [54], small sample sizes and non-randomized one-group designs limit these studies. Randomized clinical trials in pediatric populations are necessary before acetyl L-carnitine can be recommended as a potential treatment for CIPN [94].

#### *Acupuncture*

Acupuncture is increasingly used to treat pain in both adults and pediatric patients [95]. One case series study tested the use of acupuncture in five patients with CIPNs. This modality was found to improve sensation and gait, resulting in decreased analgesic use. Control of symptoms persisted for six months for four of the five patients treated. A recent systemic review found that the majority of adverse events (AEs) associated with pediatric needle acupuncture were mild in severity. Many of the more serious AEs might have been caused by substandard practice. Similar to adult studies, this study also suggests that acupuncture is safe when performed by appropriately trained practitioners [95]. Additional studies of the efficacy of acupuncture in the



treatment of CIPNs in both adult and pediatric patients are warranted [55, 95].

#### *Transcutaneous Nerve Stimulation (TENS)*

TENS has been tested in adult patients with diabetic neuropathy, but rarely in cancer patient populations. In a randomized clinical trial of 19 patients with diabetic neuropathy, Forst and colleagues compared TENS with pseudostimulation by an electrically inactive device [62]. Significant subjective improvements in neuropathy symptoms, including numbness, pain, and allodynia, were demonstrated in 70% of treatment group participants compared with 29% in the control group. As an intervention, use of TENS in pediatric patients has been studied sparingly and sufficient data are lacking regarding its efficacy [96-97]. However, given its high tolerability in adults, it is likely a safe adjuvant therapy to offer pediatric CIPN patients [62, 96-97].

#### *Physical Rehabilitation*

Despite efforts to abate complications associated with CIPNs, sensorimotor deficits can be quite dramatic and unremitting. As early as possible, interdisciplinary involvement of psychiatry specialists is crucial to maintain and hopefully improve functional outcomes in pediatric patients. Physical and occupational therapists with experience treating pediatric populations can focus rehabilitative care on issues, such as fine motor dexterity and gait and balance stability, and continue to work to meet appropriate developmental milestones. Ongoing parent education (and involvement continuing prescribed therapies at home) through the course of cancer treatment and beyond are crucial to combating long-term complications of systemic chemotherapies, including CIPNs. These studies contain findings that should be interpreted with caution, as they have not been replicated in pediatric patients who either have, or are at risk for developing severe CIPNs [56-58].

## **Communication issues and prognosis**

As can be noted from the discussion above, CIPNs can certainly adversely impact lifestyle, potentially for an extended period of time. In plain language, frank communication with the patient and family – about symptom pathophysiology, surveillance, prevention, and therapy – is important to promoting improved function and enhanced quality of life. Children (to the extent they are able) and parents alike may need counseling about the impact of CIPNs on cancer treatment plans, disease prognosis, and delayed effects post-treatments. Additionally, families need to be educated as to the natural history of CIPNs that it can last for months, years, or beyond. Families also need to learn the signs and symptoms of new or worsening CIPNs – both sensory and motor manifestations – in order to alert healthcare professionals early. Sensorimotor neuropathy and neuropathic pain assessment should also be a component of routine follow-up, especially given its potential to become chronic.

Naturally, decisions about therapeutic interventions for CIPNs should be collaborative and made with patients and families. Specific pharmacotherapies should be elucidated, including potential dose-limiting side-effects, when indicated; opioid therapies should only be initiated after appropriate counseling, including differentiating tolerance, dependence, and addiction [98]. As with any chronic symptom, ongoing attention should be paid to the connection between intervention and improvement in function/independence; individual interventions (e.g. physical therapy, acupuncture, anticonvulsant pharmacotherapy) and symptoms should also be reevaluated at regular intervals in the context of quality-of-life assessments [98].

Finally, and perhaps most challenging to the clinician, patients and families will seek prognostic information about CIPN. To date, there is a lack of longitudinal studies of CIPNs in pediatric populations, leaving clinicians to speculate and observe over time. Due to the

comparatively large prevalence of pediatric ALL, available data on the natural history of and prognosis for CIPNs tend to focus mostly on what has been learned from this specific cancer. In one study, nearly 15% of childhood ALL survivors experienced long-dies of patients with childhood ALL, describe a subpopulation that experiences residual CIPN-related injury long after treatment conclusion [99]. Until additional and more complete studies are undertaken, clinicians must rely on observation and partnership with patients and families to manage CIPN-related symptoms.

## Conclusions

For children and adolescents diagnosed with cancer, advances in treatment often require intensive treatment regimens that have the potential to challenge and disrupt the psychosocial and physiological development of the child and of the family system [70-74]. Evidence supports the need for careful and ongoing assessment of CIPNs, especially in light of the limited information informing the diagnosis, treatment and assessment in pediatric populations. Specifically, clinical practice procedures need to be developed that address the need for standardized assessments of CIPN in pediatric populations [73-74], the frequency of CIPN evaluations while undergoing chemotherapy, and the length of assessments once treatment is completed. In addition, there is a need to determine the clinically significant amount of sensory and motor changes noted in either sensory or motor nerves that may warrant a dose reduction in the treatment drug and/or the need for a rehabilitation evaluation by physical or occupational therapy. In the absence of evidenced-based prevention or treatment modalities for CIPNs, clinicians must also educate patients and families about the functional changes they may expect to occur as a result of neurotoxic chemotherapies, and assist patients in developing strategies to manage limitations resulting from CIPNs [70-74, 95-100].

## Additional Information

### Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** The opinions expressed in this paper are those of the individual authors, and should not be attributed to either The Center for Tobacco Product at the United States Food and Drug Administration in Rockville, MD, or the Clinical Center of the National Institutes of Health in Bethesda, MD.

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