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Mechanisms, Predictors, and Challenges in Assessing and Managing Painful Chemotherapy-induced Peripheral Neuropathy

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Abstract

Objective: To describe the known predictors and pathophysiological mechanisms of chronic painful chemotherapy-induced peripheral neuropathy (CIPN) in cancer survivors and the challenges in assessing and managing it.

Data Sources: PubMed/Medline, CINAHL, Scopus, and PsycINFO.

Conclusion: The research on chronic painful CIPN is limited. Additional research is needed to identify the predictors and pathophysiological mechanisms of chronic painful CIPN to inform the development of assessment tools and management options for this painful and possibly debilitating condition.

Implications for Nursing Practice: Recognition of the predictors of chronic painful CIPN and proactive CIPN assessment and palliative management are important steps in reducing its impact on physical function and quality of life.

Keywords

chemotherapy-induced peripheral neuropathy; neuropathic pain; polyneuropathy; cancer; chronic pain; centralized pain

Chemotherapy-induced peripheral neuropathy (CIPN), often described as numbness, tingling, and neuropathic (burning, freezing, zapping, or shock-like) pain in the hands and feet, is experienced by 20% to 85% of individuals who receive neurotoxic chemotherapy.[1] Common preclinical manifestations of CIPN, primarily a sensorimotor axonal neuropathy, are loss of vibration and temperature sensation, proprioception, and deep tendon reflexes.

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Individuals may also report difficulty with balance, impaired fine and gross motor skills, and muscle cramps and weakness. However, autonomic symptoms such as orthostatic hypotension, loss of bladder control, constipation, hearing loss, and difficulty obtaining an erection have also been reported.[2,3] The effect of CIPN on individuals' ability to perform activities such as buttoning a shirt, typing or writing, climbing stairs, and avoiding falls in turn affects their occupational and social role performance.[4–8] Some individuals report a sense of isolation, a lost sense of purpose, and depression.[9–11] Because no curative treatments for CIPN are known,[12] it is a leading chemotherapy dose-limiting factor.[13–16]

Neuropathic pain caused by CIPN is generally chronic and often refractory to treatment. The chronic central nervous system (CNS) changes that underlie chronic painful CIPN may also increase an individual's susceptibility to or exacerbate other centrally mediated symptoms (eg, fatigue, emotional distress, insomnia).[17–21] While research on nonpainful CIPN is fairly abundant,[12,22–31] few reviews focus specifically on chronic painful CIPN. The purpose of this review is to raise awareness of this under-recognized chronic pain condition by summarizing the known predictors, pathophysiological mechanisms, assessment methods, and treatments of chronic painful CIPN in cancer survivors.

CIPN Patterns and Pathophysiology

Table 1 lists the various classes of neurotoxic chemotherapy—proteasome inhibitors, platinums, taxanes, vinca alkaloids, and thalidomides—known to most commonly cause CIPN.[2,3,14,29,32–44] Ifosfamide, epothilones, and topoisomerase inhibitors are excluded from the table because less evidence supports their association with high-grade CIPN. Table 1 also includes the specific CIPN-causing agents and the CIPN manifestations, pain incidence, and pain-causing mechanisms associated with each agent.

Acute CIPN

Specific types of neurotoxic chemotherapy (ie, oxaliplatin and bortezomib) induce acute painful CIPN. In 85% to 95% of individuals, oxaliplatin causes reversible painful cold hypersensitivity in the face, throat, hands, and feet, and muscle cramps.[36,45] Painful CIPN can manifest quickly, even before the third chemotherapy cycle, in up to 47% of individuals receiving bortezomib.[46]

With the exception of acute CIPN pain patterns, nonpainful manifestations of CIPN generally precede painful symptoms.[45,47] Nonpainful numbness and tingling generally progress distally to proximally, affecting the toes and fingertips first, then advancing up the extremities.[27,28,48] Nonpainful CIPN is sometimes called *cumulative CIPN* because its severity and duration usually increase with each additional dose of neurotoxic chemotherapy.[45,49] Even after completion of treatment, nonpainful and painful CIPN symptoms can develop or worsen in individuals who have received platinums[49] and vinca alkaloids.[50]

Acute CIPN pathophysiology.—Various mechanisms underlying CIPN development have been proposed: primarily, disruption of neuron cell metabolism (mitochondrial[51] and enzyme[33,52] function) and ion channel function; alteration of gene and protein expression;

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upregulation of N-methyl-D-aspartate (NMDA) and transient receptor potential (TRP) receptors; and inflammation. Neuron dysfunction that leads to an increase in the neurotransmitters serotonin and glutamate may also facilitate the development of painful CIPN. These changes can contribute to oxidative stress[53,54] and neuron hyperexcitability, demyelination, and apoptosis (cell death). The primary sites directly or indirectly affected by neurotoxic chemotherapy are the dorsal root ganglia, intraepidermal neurons, c-fiber sensory neuron axons and cell bodies, wide dynamic range neurons (WDRN) in the spinal cord, and the thalamus and hypothalamus.[26,52,55–57] The dorsal root ganglia are collections of peripheral sensory neuron cell bodies near each spinal cord nerve root that relay sensory information. The sensory intraepidermal neurons include pain-signaling c-fibers that extend into the skin. The WDRN in the spinal cord dorsal horn and the thalamus in the brain process information from various painful and nonpainful sensory inputs and inhibitory signals, then relay information to appropriate areas of the brain. The mechanisms of acute nonpainful CIPN may differ based on the type of neurotoxic chemotherapy; however, acute CIPN may advance to chronic painful CIPN via shared mechanisms.

Chronic painful CIPN

Up to 40% of individuals who receive neurotoxic chemotherapy develop chronic painful CIPN,[1,14,36,47] which has previously been defined as *centralized* pain caused by pathologic changes or disturbances in function of one or several nerves that persists (a) for at least 3 months or (b) after the visible somatic and/or nerve tissue has healed.[58] The persistence of pain is generally understood to result from chemotherapy-induced neuronal changes (ie, sensitization) in the CNS.

Chronic painful CIPN pathophysiology.—Sensitization can result in increased peripheral and/or central neuron excitability—magnitude and duration of response to received pain signals—and constant or spontaneous neuron activation initiating in abnormal sites (outside the axon hillock) of the neuron. It manifests with allodynia (pain elicited by normally nonpainful, low-intensity stimuli), hyperalgesia (heightened pain-severity response to painful stimuli), dysesthesia (abnormal painful sensation, such as burning and pins-and-needles sensations), and continuous or shooting pain.[59] Peripheral sensitization can cause persistent uncontrolled pain signaling to and sensitization of the WDRN and supportive (ie, satellite, Schwann, and glial) cells in the spinal cord dorsal horn, and in the thalamus and primary somatosensory cortex of the brain.[26,60,61]

Central sensitization may also result from direct chemotoxic damage[62–64] and/or dysfunction of the CNS descending pain-modulating pathways.[65–68] Very few studies have reported chemotherapy effects on descending pain-modulating pathways; however, emerging evidence suggests that analgesia through the descending pain-modulating pathway, particularly involving the lateral hypothalamus and orexinergic system, may be key in combatting CIPN pain.[65–68] The longer CIPN goes unmanaged, the more central sensitization progresses; painful CIPN then becomes chronic.

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Predictors and Comorbidities of Painful CIPN

Research is now beginning to uncover the predictors of chronic painful CIPN. Some evidence suggests that individuals who have more severe CIPN during chemotherapy treatment[35,49,69] experience preclinical sensory changes during chemotherapy (eg, thermal hyperalgesia)[35] or have a pre-existing diagnosis of osteoarthritis[69,70] may be at higher risk for developing chronic painful neuropathy following treatment with neurotoxic chemotherapy. In addition, being born premature, and having a lower income, a higher number of comorbidities, and/or back pain have also been shown to be associated with chronic painful CIPN.[70] Evidence is mixed for the role of age,[35,69–72] cumulative neurotoxic chemotherapy dose,[14,35,69,70] diabetes,[69,70] alcohol consumption,[14,70] body mass index,[14,70] and type of neurotoxic chemotherapy[14,49,70,73] in the development of chronic painful CIPN. Indicators that have not been associated with chronic painful CIPN development include gender;[35,70,71] educational,[70] marital,[70] and smoking[14] status; and ethnicity.[70,72] Finally, mindfulness has been linked to less severe chronic painful CIPN.[71] Overall, the described potential predictors of chronic painful CIPN must be interpreted cautiously because the reviewed studies used varying measures of pain and/or CIPN and definitions of chronic neuropathy (eg, did not specifically measure pain separately).

Various chronic pain conditions are known to co-occur with other physical and psychological symptoms that contribute to reductions in physical function and/or quality of life.[74–76] However, research on the comorbidities associated with chronic painful CIPN is particularly scant. Increased fatigue, insomnia,[77] and anxiety and/or depression severity[14,77] are commonly observed in patients with chronic painful CIPN. Most recently, Knoerl and colleagues[18] examined the prevalence of the sleep impairment, pain, anxiety, depression, and low energy/fatigue (SPADE) symptom cluster and its association with pain-related interference in a sample of patients with chronic painful CIPN ($n = 59$). Frequencies of moderate to severe SPADE symptoms were characterized based on predefined cut-off scores on the 0 to 10 average pain intensity numerical rating scale and the Patient-Reported Outcome Measurement Information System (PROMIS)[78] subscales. Participants frequently experienced moderate levels of average pain (67.8%), fatigue (62.7%), sleep-related impairment (69.5%), and anxiety (30.5%), while depression (10.2%) was less prevalent. Clusters of SPADE symptoms were common: 54.2% of participants experienced at least three SPADE symptoms concurrently. Further, the number of SPADE symptoms reported by participants (0–5) was moderately correlated with pain interference scores ($r = 0.48$).[18] Additional research is needed to elucidate predictors of and symptoms that co-occur with chronic painful CIPN so that clinicians can identify those at greatest risk of developing painful CIPN. During chemotherapy, proactive referral for individualized therapy for CIPN-associated SPADE symptoms may help to mitigate the effects of chronic painful CIPN on physical function after completion of chemotherapy.

Assessment of Painful CIPN

Several clinical evaluation and patient-reported outcome (PRO) measures are available to assess painful CIPN in the clinical and research settings. Methods of clinical evaluation of painful CIPN include quantitative sensory testing (QST), skin biopsy, and several variants of

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the Total Neuropathy Score (ie, TNSc, TNSr, TNS-PV, Ped mTNS).[79–82] QST methods utilize different sensory stimuli such as heat, cold, and pressure to test for pain sensitivity (ie, hyperalgesia and allodynia).[83–85] Skin biopsy may be used to measure intraepidermal nerve fiber density (IENFD) to evaluate for reduced c-fiber (pain-sensing nerve) density, which may be associated with painful CIPN.[86,87]

Several PRO measures subjectively evaluate the incidence and severity of CIPN. Some examples of these measures are the Oxaliplatin-Associated Neurotoxicity Questionnaire,[88] the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-CIPN 20-item scale (QLQ-CIPN20),[89] and proposed variants of the QLQ-CIPN20.[90]

While measuring specific symptoms like numbness and tingling is vital to understanding the presentation of CIPN, many of these PRO measures do not operationalize painful CIPN using the word *pain*. To our knowledge, the following seven measures assess painful CIPN, among other symptoms: the Neuropathic Pain Scale for Chemotherapy-Induced Neuropathy (NPS-CIN),[91] the QLQ-CIPN20,[89] the Oxaliplatin-Associated Neurotoxicity Questionnaire, [88] the Scale for Chemotherapy-Induced Long Term Neurotoxicity (SCIN),[92] the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane),[93] the Treatment-induced Neuropathy Assessment Scale (TNAS),[94] and the Patient Neurotoxicity Questionnaire (PNQ).[95] These scales ask only a few questions regarding painful CIPN, except the NPS-CIN, which includes six neuropathy-specific pain items.[91] The QLQ-CIPN20, Oxaliplatin-Associated Neurotoxicity Questionnaire, and SCIN each include two questions about painful CIPN symptoms; the FACT-Taxane and TNAS each ask one question about pain. [88–90,92,94]

Limitations of painful CIPN measurement

Both clinical evaluation methods and PRO measures of painful CIPN have limitations, whether from inadequate psychometric properties or poor feasibility. The TNS and its variants, QST, and skin biopsy are psychometrically strong measures; however, the feasibility of these methods within clinical and research settings is limited by equipment expense and time and testertraining requirements.[84] Further, none of the clinical evaluation methods comprehensively assess the CIPN symptom experience because of their limited number or absence of subjective and pain-specific items.[80,96–100] While many studies use clinician-graded scales like the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)[101] to quantify neuropathy severity, they do not evaluate painful CIPN. Thus, research studies often use CIPN PRO measures in addition to QST and/or the TNS.[102–104]

Given the dearth of pain-specific CIPN PRO measures, previous randomized controlled trials investigating treatments for painful CIPN have used both CIPN- and non-CIPN–specific pain PRO measures to operationalize pain outcomes. Some examples of pain measures commonly coupled with validated CIPN measures include the Brief Pain Inventory (BPI), the Numeric Rating Scale (NRS), and the Neuropathic Pain Symptom Inventory (NPSI).[81,102,105–109]

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The lack of a comprehensive gold-standard measure of painful CIPN is detrimental to randomized controlled trials that attempt to evaluate various interventions for painful CIPN. Additionally, the use of multiple modes of CIPN assessment—clinical evaluation, PRO, and/or sensory function tests—can increase participant burden. Thus, future research is needed to develop comprehensive measurement tools that include questions about painful CIPN to improve intervention research testing prevention and management strategies for painful CIPN.

CIPN Management

No curative treatments for CIPN have been discovered. This section summarizes the strongest evidence supporting the use of pharmacologic and complementary treatments, as well as preliminary results from preclinical studies of promising new treatments.

Pharmacologic interventions: clinical studies

Duloxetine is the only drug recommended by the American Society of Clinical Oncology to treat established, painful CIPN caused by oxaliplatin or paclitaxel.[81,110] This recommendation is based on a systematic review of 48 randomized controlled trials that were designed to test 22 different pharmacologic interventions.[12] seven[81,105,106,111–114] of the 48 studies included in the review specifically tested drug interventions for painful CIPN (ie, duloxetine,[81] nortriptyline,[113] gabapentin,[106] amitriptyline,[114] lamotrigine,[105] or topical amitriptyline ketamine and baclofen combinations [111,112]); only one of the seven studies revealed an effective treatment: duloxetine.[81] However, it should be noted that, in the other six pain studies, none of which demonstrated an effect, limitations because of suboptimal pain measurement, lack of control for confounding factors, high attrition, and low statistical power could have resulted in an inability to detect truly effective treatments.[115]

The study that provides evidence of duloxetine efficacy for painful CIPN was a double-blind, randomized, placebo-controlled, crossover trial exploring whether duloxetine 60 mg taken orally once daily would decrease CIPN pain severity (primary aim) following paclitaxel or oxaliplatin treatment.[81] Participants (N = 231) had > grade-1 sensory CIPN (per the NCI-CTCAE v4.0) and an average CIPN neuropathic pain score ≥ 4 (0–10 scale) for ≥ 3 months after chemotherapy. Patients were randomized to receive either placebo or duloxetine 60 mg daily. Individuals receiving duloxetine had a larger mean decrease in average pain score than did those in the placebo group (P = .003) (es = 0.513). Further, 33% and 21% experienced a clinically significant reduction in pain score: 30% and 50%, respectively. Side effects were generally mild and occurred infrequently. Duloxetine- and placebo-related fatigue (7%/5%), insomnia (5%/7%), and nausea (5%/3%) were the most commonly reported adverse events. Also, a secondary data analysis suggested that duloxetine worked better for pain induced by oxaliplatin than by paclitaxel.[9]

Given that chronic painful CIPN is a centralized pain condition, it is not surprising that a centrally acting drug (ie, duloxetine) is effective. Serotonin (5-HT) and norepinephrine (NE) dual reuptake inhibitors (SNRI) such as duloxetine work by increasing the amounts of key pain-inhibiting neurotransmitters—5-HT and NE—within the CNS descending pain-modulating pathways.[116] These neurotransmitters suppress the transmission of painful

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stimuli arising from the periphery by inhibiting input to the WDRN in the spinal cord.[117–119] Duloxetine exerts its analgesic action by blocking serotonin (SLC6A4) and norepinephrine (SLC6A2) transporters that are responsible for reuptake in the pre-/post-synaptic cleft.[120]

Drugs that target peripheral nerve function would not be expected to have a significant effect on chronic centralized CIPN pain. However, preliminary evidence suggests that peripherally acting drugs may in fact work to *prevent* chronic CIPN pain if administered before neurotoxic chemotherapy begins. Specifically, in addition to its central effects in the CNS/spinal cord, duloxetine exhibits a local effect by blocking Nav1.7 sodium channel currents,[121,122] thereby inhibiting the transmission of spontaneous nerve impulses from the periphery to the CNS. Thus, drugs that target peripheral mechanisms could subsequently prevent central sensitization and chronic painful CIPN. Because the effect of peripherally acting drugs to prevent chronic painful CIPN has not yet been demonstrated, more well-designed clinical studies are needed in this area.

Given that duloxetine is the only treatment option recommended for painful CIPN, clinicians often prescribe drugs with efficacy in other neuropathic pain conditions (eg, tricyclic antidepressants, venlafaxine, gabapentin, pregabalin). This practice is cautiously supported by American Society of Clinical Oncology and other experts because duloxetine may be ineffective, contraindicated, or poorly tolerated in some patients.[12,123,124] Although opioids are frequently used to treat neuropathic pain,[125–127] they should not be used as first-line treatment for chronic CIPN pain because of the risk of addiction, overdose-associated mortality,[128] and opioid-induced hyperalgesia—a condition whereby opioids make pain worse.[129]

Several other promising pharmacologic agents might be effective for painful CIPN but require further testing. Cannabis has demonstrated efficacy for neuropathic pain from peripheral neuropathy caused by HIV and diabetes,[130–136] but cannot be recommended for CIPN because of a lack of studies for this specific indication. Small quasi-experimental studies provide preliminary evidence that high-dose 8% capsaicin patches[137] and intravenous lidocaine[138] may ameliorate painful CIPN. However, larger studies with control group comparisons are needed to confirm or refute these preliminary findings.

Natural products and complementary treatments

Some patients will not benefit from pharmacological treatments because of lack of efficacy (eg, 41% experienced no effect from duloxetine) and drug interactions.[139–144] For these patients, non-drug treatment options are sorely needed. Two systematic literature reviews reveal that several natural products and complementary therapy interventions have been tested for CIPN.[12,145] Based on the findings of these systematic reviews, the following treatments cannot be recommended to treat painful CIPN: vitamin E, glutamate, goshajinkigan, acetyl-L-carnitine, alpha-lipoic acid, and omega-3 fatty acids. Studies of these products either were significantly biased because of small sample sizes and poor outcome measures, or showed detrimental (in the case of acetyl-L-carnitine) or insignificant effects on CIPN.[12,145] Furthermore, pain was not the primary outcome in any of the studies.

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Several experimental and quasi-experimental studies have tested complementary treatments for painful CIPN, such as acupuncture [108,109,146] electrocutaneous nerve stimulation (scrambler therapy)[147–149], and exercise [150–152]. Results from studies of acupuncture are mixed, and only quasi-experimental scrambler studies provide preliminary evidence of efficacy. Although exercise interventions have been tested to reduce CIPN, their effects on painful CIPN as the primary outcome have not been adequately explored. Given the threats to the external and internal validity of these studies—small samples, lack of blinded placebo control comparisons, and high drop-out rates—none of these complementary treatments can be recommended to treat CIPN pain.

Cognitive behavioral therapy (CBT), a complementary therapy with demonstrated efficacy for chronic pain conditions (eg, fibromyalgia, migraine headaches, arthritis)[153] and cancer pain,[154–156] often leads to larger improvements in pain-related outcomes than does pharmacologic therapy.[157] The CBT approach involves educational strategies that teach about causes and treatment of pain, modify inaccurate beliefs about pain control, and provide practical approaches for improving problem-solving and coping. One small randomized wait-list controlled pilot study provides preliminary evidence that CBT—specifically, a self-guided online cognitive and behaviorally based pain management intervention —may be effective to reduce chronic CIPN pain severity.[158] Patients ($N = 60$) with chronic CIPN pain rated as ≥ 4 on a 0–10 numeric rating scale were randomized either to an 8-week Web-based CBT intervention or a wait-list control. The Web-based CBT program included self-guided modules about late effects, patient/provider communication, exercise, sleep, goal setting, activity pacing, strategies to encourage participation in enjoyable activities, and peripheral neuropathy management. Individuals who received the CBT intervention had significantly greater improvements in averaged 7-day pain scores when compared with the wait-list controls ($P = .046$, $d = .58$). The main study limitations were lack of blinding and high attrition (22%). Despite these limitations, the positive findings justify the need for a larger, placebo-controlled trial of CBT for painful CIPN.

Preclinical studies of CIPN preventive interventions

Although no evidence has emerged from well-designed randomized controlled trials that anything prevents CIPN, painful or otherwise, several preclinical studies provide information that could lead to new treatments in the future. Researchers at the University of Michigan explored the effect of duloxetine to prevent oxaliplatin-induced hyperalgesia in male and female rats. When compared with vehicle/water-treated animals, duloxetine-treated animals demonstrated less hyperalgesia following 5 days of oxaliplatin treatment (unpublished). These preliminary findings provide the foundation for a pending multi-site National Cancer Institute-funded Phase 2/3 trial testing the comparative effectiveness of 30 mg or 60 mg daily duloxetine versus placebo as prevention for painful and nonpainful CIPN.

Several preclinical studies also suggest potential benefits of other agents, such as enzymes, nutritional supplements, opioid agonists, and neuropeptides, for painful CIPN. One exciting new approach to preventing painful CIPN involves the use of poly ADP-ribose polymerase (PARP) inhibitors. PARP—a nuclear enzyme found in nerve cells—plays a role in DNA damage. Although the precise mechanisms of action are not fully understood, PARP

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inhibitors can turn off DNA-damaging processes, such as oxidative stress, and thus might prevent painful neuropathy caused by neurotoxic drugs.[159] This premise has been supported in a preclinical study of vincristine-induced neuropathy: three different PARP inhibiters attenuated mechanical allodynia in vincristine-treated male mice.[160] Studies have also evaluated another enzyme, histone deacetylase 6 (HDAC6), a microtubule-associated deacetylase that is involved in α-tubulin-dependent intracellular mitochondrial transport in sensory nerves.[161] Because HDAC6 inhibitors improve nerve function in animals with peripheral neuropathy caused by Charcot-Marie-Tooth disease,[162] these novel agents might help to prevent CIPN. This idea is supported by a recent study showing that a HDAC6 inhibitor, ACY-1083, was more effective than a control vehicle to mitigate mechanical allodynia, spontaneous pain, and numbness in cisplatin-treated male rodents.[161] Flavonoids —compounds found in fruits and vegetables—have been tested in animal models of oxaliplatin- and cisplatin-induced neuropathy.[163,164] In a recent study, several dose levels of the flavonoid 6-Methoxyflavone (6-MF) were compared with a control vehicle and gabapentin.[164] After receiving 4 weekly cisplatin injections, 6-MF–treated male rats demonstrated significantly less cisplatin-induced mechanical allodynia than animals receiving the control vehicle. While the antinociceptive effects of the highest 6-MF dose and gabapentin were similar, only gabapentin caused motor dysfunction. Another preclinical study showed that cebranopadol, an opioid receptor agonist that binds to many different types of opioid receptors in the peripheral and CNS, decreased cold-induced allodynia in male mice following oxaliplatin administration.[165] Orexin A, an endogenous neuropeptide that facilitates descending pain modulation in the CNS, was compared with duloxetine and a control vehicle in another preclinical study of oxaliplatin-induced neuropathy.[68] One group of male mice was injected with Orexin A into the cerebral ventricles; another group of male mice was injected with duloxetine into the peritoneum. Mechanical allodynia tests suggested that orexin may be more effective than duloxetine in preventing oxaliplatin-induced painful neuropathy. These highlighted studies, and many others not described here, provide hope for new treatments that might prevent or attenuate painful CIPN for millions of cancer survivors.

In conclusion, limited high-level evidence supports the use of anything other than duloxetine for the treatment of established painful CIPN, and numerous clinical trials have failed to identify effective preventive treatments. However, preclinical studies provide evidence for promising new agents that may be examined in future clinical studies. Rigorous placebo-controlled studies of natural products and complementary interventions are also needed. Our understanding of the pathophysiological mechanisms underlying painful CIPN is limited but expanding. As our knowledge of CIPN pain pathophysiology increases, future mechanism-targeted interventions will emerge.

Conclusion

Impact and implications for the nursing practice

Distressing CIPN often leads to reductions in potentially life-saving chemotherapy treatment. Most patients receive inadequate education about CIPN before initiating chemotherapy and have difficulty describing their symptoms when they manifest. [4,82,166]

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Additionally, clinicians often lack the time, knowledge, and resources for adequate assessment of CIPN.[167] Although individuals may adjust to CIPN, it might never resolve. While no curative treatments for CIPN are known, several nursing and pharmacologic interventions may help to manage CIPN and lessen resulting functional limitations. Duloxetine is the only drug that is recommended for the palliative treatment of chronic painful CIPN. However, treatments (eg, nortriptyline, gabapentin, amitriptyline) for other chronic pain conditions that exhibit chronic painful CIPN-like manifestations and pathophysiological mechanisms may also be recommended. Further research will help to identify which of these chronic pain treatments are effective for chronic painful CIPN.

Ultimately, nurses play a vital role in assessing for early signs and existing manifestations of CIPN, providing CIPN education, and assisting patients with CIPN management. Nurses can advocate and suggest referrals to CIPN and co-occurring symptom management resources for patients. Finally, nurses can provide emotional support to individuals who are experiencing the scary, painful, isolating, and functionally debilitating manifestations of CIPN.

Future directions in research

Further research is needed to explore the specific mechanisms and predictors of chronic painful CIPN and to evaluate interventions to prevent and treat each type of CIPN. Several classes of neurotoxic agents may induce CIPN through varying mechanisms; thus, the intervention must be tailored to the type of CIPN. Many of the more than 75 trials that have tested CIPN interventions were limited by poor CIPN measurement and lack of intervention specificity to the type of CIPN studied. Most importantly, few studies have focused specifically on interventions for chronic painful CIPN. Additional studies of nonpharmacologic interventions and preclinical studies of pharmacologic agents and supplements are needed to inform larger and more rigorous clinical research testing mechanism-specific interventions for chronic painful CIPN.

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Table 1

Agents that cause chronic painful CIPN.

Drug Class	Specific Agents	Prominent Manifestations	Pain Incidence	Sensitization Mechanism
Proteasome inhibitors	Bortezomib	*Neuropathic pain and allodynia[32,33] Hypoesthesia Loss of fine motor function Cramps[2,3]	Up to 47%[3,34]	TRPV, TRPA1, and NMDA receptor up-regulation Inflammation (cytokine release and macrophage infiltration) Altered enzyme activity (reductions in phosphoglycerate dehydrogenase and L-serine; protein kinase C → NMDA receptor upregulation and increased glutamate release)
Platinums	Oxaliplatin, cisplatin, carboplatin	Acute cold hyperalgesia (oxaliplatin alone) *Sensory Loss of vibration sensation and sensory ataxia	5%–50%[14,33,36]	TRPV, TRPA1, and NMDA receptor upregulation Ion channel (sodium, calcium, and potassium) dysfunction
Taxanes	Paclitaxel, docetaxel	*Sensory[14] Muscle weakness	Up to 30%[14]	TRPV, TRPA1, and NMDA receptor upregulation Ion channel (sodium, calcium, and potassium) dysfunction Inflammation (cytokine release and macrophage infiltration)
Vinca alkaloids	Vincristine, vinblastine, vinorelbine, vindesine	*Sensory and motor[29,37,38] Autonomic	11%–44%[29,39–41]	Serotonin increase and channel upregulation
Thalidomides	Thalidomide, lenalidomide	*Autonomic[42] *Hypoesthesia[43,44]	Uncommon[44]	Inflammation (cytokine release, and macrophage infiltration)

*Indicates the most prominent manifestations. *Sensory* refers primarily to numbness and tingling.

Abbreviations: NMDA, N-methyl-D-aspartate; TRP, transient receptor potential.