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Review

Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update

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ABSTRACT

When peripheral neuropathy occurs due to chemotherapy treatment, it is referred to as chemotherapy-induced peripheral neuropathy (CIPN). Typically, symptoms are sensory rather than motor and include reduced feeling and heightened sensitivity to pressure, pain, temperature, and touch. The pathophysiology of CIPN is very complex, and it involves multiple mechanisms leading to its development which will be described specifically for each chemotherapeutic class. There are currently no approved or effective agents for CIPN prevention, and Duloxetine is the only medication that is an effective treatment against CIPN. There is an unavoidable necessity to develop preventative and treatment approaches for CIPN due to its detrimental impact on patients' lives. The purpose of this review is to examine CIPN, innovative pharmacological and nonpharmacological therapy and preventive strategies for this illness, and future perspectives for this condition and its therapies.

1. Introduction

Peripheral neuropathy is used to describe many disorders resulting from damage to peripheral nerves that can present in many different patterns [1,2]. The primary responsibility of peripheral nerves is to relay sensory and motor information of the extremities [2]. Therefore, damage to these nerves can result in both sensory and motor deficits. [1,3]. Sensory manifestations include paresthesias felt as a burning, tingling, or pins-and-needles [1,4]. It also encompasses mixed perceptions of hyperpathia and hypoesthesia [1,4]. Hyperpathia is increased sensitivity to stimuli in which normal touch can be painful (allodynia), whereas hypoesthesia is decreased sensitivity, feeling more like numbness [1,4]. Motor symptoms, although less common, can present as weakness, atrophy, and even decreased reflexes [1,4]. When peripheral neuropathy occurs due to chemotherapy treatment, it is termed Chemotherapy-induced peripheral neuropathy (CIPN) [1,2,5]. CIPN is a frequent adverse effect of anticancer agents most commonly presenting with sensory symptoms more than motor symptoms in a symmetrical "glove and stocking" distribution [3–6]. Patients will typically experience various pain, tingling, and numbness beginning at the fingers and toes that progress proximally to involve the arms and legs [4]. Some may even describe it as feeling like they are wearing stockings and gloves when they are not [4]. CIPN develops shortly after onset and continues through chemotherapy treatment [2,4]. Symptoms are dose-dependent, meaning they progress and worsen with continued treatment [2,4,6]. This can ultimately lead to premature cessation or reductions in

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treatment doses, potentially altering overall survival [3,6]. CIPN symptoms often diminish with time but, in some cases, can pursue for months after treatment discontinuation [1,2]. Patients with a more severe CIPN presentation experience a decreased quality of life physically, emotionally, and socially [7]. They also reported more pain, fatigue, and GI symptoms [7]. Furthermore, CIPN has been associated with interfering with patients' ability to work and a greater financial burden [7–9]. On average, healthcare costs of cases with CIPN were $17,344 higher when compared to a control group [9].

The pathophysiology of CIPN is rather complex, with multiple factors and processes leading to its development which varies with the different classes of chemotherapy drugs. What is well known is that larger doses and several courses of treatment correlate to patients being more likely to develop CIPN [2]. In addition, patients have an increased risk of CIPN if they have diabetes or already have peripheral neuropathy [2,10]. The treatments repeatedly shown to have an increased chance of causing peripheral neuropathy include taxanes, vinca alkaloids, platinum drugs, Bortezomib, and thalidomide [2,5,6,11]. The main mechanisms responsible for the development of CIPN are mitochondrial toxicity and oxidative stress, DNA damage, axonal transport disruption, and ion channel remodeling in peripheral nerves [12,13]. Taxanes and vinca alkaloids act on microtubules leading to their dysfunction [3,5,13]. While taxanes hyperstabilize the tubules, vinca alkaloids prevent polymerization [3,5,13]. The loss of normally functioning microtubules impairs axonal transport of cell products crucial to the function and structure of axons [13]. There is also evidence of taxane-induced CIPN sexual dimorphism in rodents, where Toll-like receptor 9 (TLR9) expression in macrophages infiltrating the dorsal root ganglion may play a role in the development of pathological, physiological, and behavioral changes in male mice but not females [14]. Platinum agents change the structure of DNA and appear to induce neural toxicity mainly through the dorsal root ganglion (DRG) [3,5]. They have been shown to reduce nucleolar size in the sensory DRG cells in which the degree of nucleolar size change correlated with the degree of neurotoxicity [15]. Oxaliplatin specifically induces acute neuropathy via alterations in axonal voltage-gated sodium channels [3,5]. Bortezomib is a proteasome inhibitor that seems to encourage apoptosis and prevent regular rates of cell division [13]. Pathogenesis of how Boretzomib promotes neuropathy is not completely understood [3,5,13]. One possibility is through its alterations on sphingolipid metabolism in astrocytes, which is involved in pain modulation and perception [16]. Thalidomide is another chemotherapeutic whose mechanism of causing CIPN is poorly understood [3,5]. It is thought to be related to immunomodulation, angiogenesis inhibition, and cytokine alteration [5]. Schwann cell damage, which myelinates peripheral nerves, is involved in the pathogenesis of CIPN, and drugs that inhibit anticancer agent-induced Schwann cell damage are expected to be therapeutic agents for CIPN [17].

Prevention and treatment of CIPN are tremendously challenging because of the varying underlying pathophysiological causes with differing chemotherapy agents [18,19]. While multiple hypotheses exist, no treatment based on these proposed mechanisms has led to acceptable intervention options [5,18]. According to ASCO and ESMO guidelines, there are no recommended or effective agents to prevent CIPN [20,21]. They suggest assessing patients regularly for the development of CIPN and to be aware of patients at high risk with factors predisposing them to develop CIPN [20,21]. In terms of treatment, the only recommended agent proven to be efficacious against CIPN is duloxetine [20,21]. Clinical trials support that duloxetine treatment reduces the pain, numbness, and tingling symptoms patients experience with CIPN, but only to a moderate degree [22]. However, duloxetine still has limited benefit.

It should be noted that it had the greatest effect on treating CIPN due to platinum-based drugs than other therapies like taxanes [21]. Other options such as tricyclic antidepressants or anti-seizure medications have been explored, but trials show mixed results [18,23]. ASCO currently makes no recommendations on these other therapies, but ESMO does endorse their consideration for treatment [20,21].

Additionally, rehabilitation via physical and/or occupational therapy may be helpful in CIPN patients with reduced function [2]. Therefore, there is still a need to explore and develop efficacious treatments for CIPN. This review aims to discuss CIPN, novel pharmacological and nonpharmacological treatment and prevention methods for CIPN, and future directions for this condition and its treatments.

2. Assessment, diagnosis, and epidemiology of chemotherapy-induced peripheral neuropathy

The epidemiology of CIPN is complicated because of the many different scales used to assess CIPN [24]. One study reports a CIPN aggregate prevalence of 48%, with rates starting at 68.1% within one month after the conclusion of chemotherapy treatment and steadily declining with the duration of treatment [19]. Another study shows a one-year cumulative prevalence rate of around 28.7% [24]. One of the main determinants of whether patients will develop CIPN is their type of cancer, establishing the type of treatment they will undergo [25]. Solid tumor cancers are the most likely to be treated with the neurotoxic chemotherapy drugs previously mentioned, therefore increasing the risk of these patients developing CIPN [25]. Furthermore, the cumulative dose of the chemotherapy agent is recognized as the most important factor in CIPN development [25].

Currently, there is no standardized approach for assessing and diagnosing CIPN, as this has proven to be very difficult to quantify definitively [18,26–28]. Broadly, assessment techniques can be divided into objective and subjective approaches [18]. One effective objective assessment that can be used is a neurophysiological examination [5,29]. Nerve conduction studies (NCS) can help distinguish between demyelination vs. axonopathy pathologies useful in assessing CIPN because almost all cases are related to axonopathy [6,30]. NCS will show reduced amplitudes of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CAMPs) with nearly unchanged conduction velocities in CIPN [3,5]. This contrasts with the decreased nerve conduction velocity you would see in a demyelinating disease [5]. An advantage to these tests is they are readily accessible in most hospitals. However, they only assess large myelinated fibers [30]. CIPN preferentially damages small fibers, limiting the use of NCS [30]. Group assessments that study these small fibers are quantitative sensory testing (QST), which evaluate pain and temperature [30].asw

One of the subjective assessments is the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), in which a medical professional uses a 1–5 scale to grade adverse events (including peripheral neuropathy) based on the severity of the symptoms [31]. Additional subjective tests include patient-reported assessments of their neuropathy, which, compared to physician-reported evaluations, generally reported more severe symptoms and effects on their daily lives [32]. Physicians underreporting and underestimating the severity of patients' CIPN shows a clear and needed importance of using patient-reported outcomes for assessing CIPN [32].

Given the limitations of both objective and subjective studies, composite studies have become progressively favorable for assessing CIPN [5,33]. These studies combine objective and subjective studies to evaluate CIPN, with the most common one being the Total Neuropathy Score (TNS) [5,34]. This allows simultaneous assessment of graded physician-reported severity with objective sensibility measures and NCS [34]. A pitfall to this method is that it is more time-consuming than other studies and requires instrumentation, leading to issues of availability and standardization [33,34]. It has proven to be more sensitive than the NCI-CTCAE, and it is proposed as a reliable source for assessing both severity and changes following CIPN [34].

Since CIPN symptoms are highly subjective, it leaves for a challenging diagnosis [26]. The first step in diagnosing CIPN is to exclude other potential neuropathy causes such as preexisting conditions, association with surgery, and any other factors that would come with an

increased risk of developing peripheral neuropathy [18,26,35]. Following exclusion of other potential causes, clinical examination is usually used to diagnose CIPN [30,35]. This greatly relies on the presence of sensory abnormalities, which can be evaluated and graded via several different assessments previously discussed [30,35]. However, a clinical examination can only endorse abnormalities in the nervous system but cannot prove their origin [36]. Despite its disadvantages, clinical examination for the diagnosis of CIPN is cost-effective with easy administration making it very appealing [30].

3. Treatments

3.1. Nerve-protective therapy

Erythropoietin (EPO) is a cytokine that is involved in hematopoiesis regulation. It also possesses neuroprotective effects, such as enhancing nerve regeneration and recovery following peripheral nerve injury [37,38]. As chemotherapeutic agents are thought to induce peripheral neuropathy through the impairment of the peripheral nerves, this neuroprotective effect makes EPO a seemingly ideal candidate for CIPN [39]. However, the utilization of EPO for the treatment of CIPN is highly contraindicated and should be approached with caution as EPO is associated with tumor cell growth [40].

3.2. Ion channel-targeted therapies

One of the many pathophysiological characteristics associated with CIPN is the alteration of ion channel expression in primary afferent sensory neurons [41]. Therefore, researchers have postulated that these ion channels may serve as a potential target in the treatment of CIPN. These ion channels can be targeted through substances that can bind to them, such as lidocaine, or through the direct administration of these ions, such as calcium and magnesium.

Lidocaine is a sodium channel blocker that prevents the flow of sodium ions through the channel pore [42]. It effectively relieves various causes of neuropathic pain, including CIPN [43,44]. Intravenous (IV) lidocaine produced a significant, moderate long-term (average of 23 days) analgesic effect in 8 out of 9 patients with CIPN [45]. These results are very promising, especially since the most common adverse effects associated with IV lidocaine include irritation at the injection site. To overcome this side effect and perhaps increase the intended duration of action, oral sodium channel blockers, such as mexiletine, may be administered instead of IV lidocaine [45].

These promising results demonstrate the need for larger clinical trials to further investigate the role of sodium channel blockers in the treatment of CIPN.

Magnesium infusion has also been postulated as a potential therapeutic option for CIPN. Researchers found a direct negative correlation between magnesium intake and CIPN severity. The magnesium supplementation during chemotherapy is proposed to decrease oxaliplatin-induced hyper-excitability of neurons and overall neuron damage. Increased magnesium administration levels were associated with a lower prevalence of CIPN and less severe symptoms in individuals who did experience CIPN [46]. However, other studies have failed to demonstrate any efficacy in using magnesium infusions to treat CIPN [47]. Similarly, calcium infusions failed to reduce CIPN in multiple studies, including those that combined calcium and magnesium infusions in hopes of achieving an additive effect [48].

Gabapentin is an anticonvulsant medication that inhibits the release of excitatory neurotransmitters. To achieve this, gabapentin crosses the blood-brain barrier and binds with high affinity to the alpha2-delta protein, a subunit to the presynaptic voltage-gated calcium channels of neurons[43]. Multiple studies have shown that gabapentin administration may alleviate the symptoms associated with CIPN, including neuropathic pain and neurologic deficits [49]. Furthermore, gabapentin has a mild side effect profile, making it a promising pharmacotherapeutic option for the management of CIPN [50]. Like gabapentin, pregabalin is an anticonvulsant medication that binds to the alpha2-delta protein, which inhibits the presynaptic, voltage-gated calcium channel and is thus considered a first-line treatment option for neuropathic pain [51]. Despite these drugs' seemingly identical mechanisms, a lower-cost generic version of gabapentin is available, making it more commonly prescribed than pregabalin in treating neuropathic pain. However, studies have shown that patients who respond poorly to gabapentin may experience a clinically significant improvement in pain when switching to pregabalin [52]. The varied response to these medications is likely due to their different pharmacokinetic profiles. Compared to gabapentin, pregabalin has a faster absorption rate, a higher maximum absorption rate, and a higher bioavailability [53]. Additional studies should further examine the varying efficacy of these medications to treat CIPN symptoms, especially pain.

3.3. Anti-inflammatory therapies

Some studies suggest that the best treatment approach for CIPN includes non-steroidal anti-inflammatory drugs (NSAIDs) that can reduce pain symptoms and the underlying inflammation associated with pain [54]. However, studies involving NSAIDs in the treatment of CIPN are limited and require further evaluation.

3.4. Neurotransmitter-based therapy

Venlafaxine (Effexor XR®) and duloxetine (Cymbalta®) belong to a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). These medications, primarily used to treat major depressive disorder (MDD), increase serotonin and norepinephrine levels in the neuronal synapse by blocking their subsequent reuptake [55]. SNRIs are also the first and only FDA-approved drug class for treating pain caused by diabetic peripheral neuropathy [56]. The side effects of venlafaxine and duloxetine are generally mild and include nausea, changes in sleeping patterns, constipation, sexual dysfunction, and increased heart rate and blood pressure. Additionally, these medications can cause an increase in bleeding risk among patients taking anticoagulants (e.g., warfarin and aspirin) [57].

A recent meta-analysis that included ten different studies (both controlled studies and observational studies) evaluated the potential use of SNRIs for the treatment of CIPN. SNRIs demonstrated substantial efficacy and excellent tolerability for the treatment of CIPN [58]. Although these studies emphasized the therapeutic potential of both venlafaxine and duloxetine in CIPN, further studies revealed that duloxetine possesses a higher efficacy in reducing the grade and severity of neuropathic pain [55,59,60]. Duloxetine is often considered a first-line treatment option for CIPN [61].

Despite these exciting results, other studies could not identify a significant reduction in acute or chronic CIPN symptoms following venlafaxine treatment [62]. However, these differences are likely due to alterations in venlafaxine dose, as lower doses (i.e., 37.5 mg once daily) were administered in these subsequent studies, and patients with neuropathy generally require higher doses of venlafaxine (i.e., 75 mg twice daily) [62,63]. A closer look at the underlying mechanisms of venlafaxine reveals a potential mechanism for this dose-related efficacy. Venlafaxine has a 30-fold greater affinity for serotonin transporters compared to norepinephrine transporters. Hence, venlafaxine acts primarily on serotonin reuptake at low doses, making it act similarly to a selective serotonin reuptake inhibitor (SSRI) rather than an SNRI. This key difference likely accounts for its ineffectiveness in treating CIPN at lower doses [62,64]. Additional studies should be done to determine the appropriate dose of SNRIs in the treatment of CIPN to ensure efficacy while minimizing adverse effects.

Tricyclic antidepressants (TCAs), which also block the reuptake of norepinephrine and serotonin, have long been recognized for their use in

treating neuropathic pain [65]. Although these drugs have demonstrated efficacy in reducing neuropathic pain, studies have found these drugs to be ineffective in treating pain associated with CIPN [66–68]. TCAs also present a high incidence of adverse effects and should be avoided until more conclusive studies can be conducted [69].

3.5. Antioxidants

The manganese chelates and superoxide dismutase mimetic mangafodipir is a widely used diagnostic tool that enhances contrast during magnetic resonance imaging (MRI). Its side effects, including cardiovascular effects and facial flushing, can be prevented with an adequate rate of intravenous injection [70]. Both preclinical and clinical studies have provided evidence for the use of mangafodipir in treating CIPN, where individuals experienced a significant reduction in pain [71]. Importantly, mangafodipir is an efficacious inhibitor of CIPN without interfering with the tumoricidal activity of chemotherapy [72].

One proposed mechanism of CIPN is the increased production of reactive oxygen species (ROS) in patients receiving chemotherapy, as an increase in ROS can cause direct damage to nerves through enhanced oxidative stress. Additionally, several chemotherapy agents cause a depletion of certain elements that make nerves more susceptible to injury (e.g., glutathione), therefore contributing to the observed neurotoxicity [73]. Although the underlying mechanisms responsible for the ability of mangafodipir to treat CIPN are not entirely elucidated, studies have suggested its antioxidant properties may be neuro- and/or myelin-protective and prevent this ROS-mediated injury [71,74]. Mangafodipir also acts as a superoxide dismutase (SOD) mimetic and possesses catalase-, and glutathione reductase–like properties, therefore targeting and preventing multiple steps of the ROS cascade that induce CIPN. Specifically, mangafodipir inhibits cellular oxidative stress by catalyzing the dismutation of superoxide and disarming redox-active iron [72]. Unfortunately, mangafodipir was removed from the U.S. market in 2003 and the European market in 2012 due to commercial reasons from the manufacturer [75].

3.6. Other drugs

Another proposed mechanism of CIPN is the ability of chemotherapy agents to sensitize neurons in the spinal cord responsible for receiving and analyzing pain signals. Cannabinoids activate both the 5-HT_{1A} receptor system and the CB1 receptors to suppress this mechanical sensitization and thus have been elucidated for the potential treatment of CIPN [76,77]. Studies have shown that endocannabinoid deficiencies are prevalent during CIPN, and researchers hypothesize that by replenishing this deficit with cannabinoids, patients may experience pain relief [78]. A pilot trial investigated nabiximols, which CIPN. Unfortunately, nabiximols did not significantly reduce CIPN. However, the researchers did emphasize that 5 out of 16 responders reported a significant reduction in CIPN that was far greater than anyone in the placebo group [79]. Therefore, further studies should be done to identify individuals who may benefit from cannabinoid treatment for CIPN, especially since side effects from these medications have been rarely reported [80].

Glutamine is an amino acid naturally produced by the body and plays an important role in our immune system and intestinal health [81]. Although studies have supported the efficacy of oral glutamine therapy in alleviating CIPN symptoms, these studies were limited by small sample sizes and the lack of a control group [82,83]. As oral glutamine lacks clear evidence to support its efficacy in treating CIPN, it is not recommended to treat CIPN symptoms in patients [84].

3.7. Topical treatments

Multiple studies have examined potential topical treatments, both alone and in combination, for the treatment of CIPN. However, most of these treatment regimens have only produced a modest effect, if any. When researchers applied a topical mixture of amitriptyline and ketamine to patients experiencing numbness, tingling, and/or pain associated with CIPN three times per day for three weeks, they did not see any significant improvement in symptoms compared to placebo [85]. In another similar study, a topical mixture of amitriptyline, ketamine, and baclofen was applied to the area associated with pain twice daily for four weeks. However, even with the addition of baclofen, patients only reported a slight improvement of symptoms [86].

Prior studies have shown that activating transient receptor potential melastatin 8 (TRPM8), the primary cold sensor in humans, can suppress the mechanical sensitization associated with CIPN [87]. Moreover, these molecular receptors are upregulated in neuropathic pain models, suggesting they may provide an easy and efficient target in the treatment of CIPN [88]. Although some studies have illuminated the possible benefits of menthol in treating CIPN, further studies need to be done to strengthen this very limited data [89].

The transient receptor potential (TRP) channel family is credited with being the most important ion channel family involved in detecting and transmitting noxious stimuli [90]. Among these TRP channels is the transient receptor potential vanilloid receptor (TRPV1), which initiates neurogenic inflammation and pain sensation and is thought to be involved in the CIPN-associated pain pathology [91]. Topical capsaicin is a TRPV1 agonist that has demonstrated efficacy in treating neuropathic pain, including that associated with CIPN [92–94]. Although capsaicin, which is the active component found in chili peppers, may cause a burning sensation, none of the patients within these studies found this side effect to be intolerable.

3.8. Non-drug treatments

A meta-analysis of 12 studies was conducted to evaluate the efficacy of non-pharmacologic interventions in treating CIPN. These studies found that acupuncture, massage, and foot bath independently produced a significant reduction in CIPN symptoms [95]. Another systemic review found that two out of three studies revealed acupuncture notably alleviated CIPN pain, although the third study did not reveal a significant effect [38]. Further studies have shown the effectiveness of acupuncture in treating CIPN-associated pain and numbness, all presenting with little to minimal side effects [96–99].

Physical therapy is an established and highly effective treatment option for neuropathic pain and thus has been evaluated for its potential use in the treatment of CIPN. A home physical therapy program that included exercise in patients with breast cancer revealed less pain and decreased pain over time in the treatment group compared to the sedentary group [100]. A systemic review that evaluated physical therapy for CIPN found similar results, whereas patients reported a significant reduction in CIPN symptoms, including pain and paresthesia [101].

Another promising noninvasive treatment strategy for CIPN includes scrambler therapy, whereby a machine is used to block the transmission of pain signals by emitting synthetic, non-pain information to C fiber surface receptors, which normally receive pain messages [102]. Pilot evaluations revealed a significant reduction in pain symptoms associated with CIPN, and these results were long-lasting as they were still present throughout ten weeks of follow-up [103,104]. Notably, no adverse events were reported in these studies. Unfortunately, these studies neglected to incorporate a control group for comparison. Randomized, double-blind clinical trials that included a sham group found no significant difference between CIPN patients receiving scrambler versus sham therapy [105]. Further studies should be conducted to determine if scrambler therapy is a viable treatment option for those suffering from CIPN symptoms, such as pain.

Neurofeedback (NF) is a non-invasive treatment that targets brain activity to reduce the severity and impact of chronic pain. NF therapy is performed in conjunction with an electroencephalogram (EEG) or

functional magnetic resonance imaging (fMRI), which allows for the accurate measurement of brain activity [106]. A randomized controlled trial found that EEG NF significantly reduced CIPN symptoms compared to control, suggesting NF may be a productive treatment option for patients suffering from CIPN [107].

3.9. Future directions in treatment of chemotherapy-induced peripheral neuropathy

Many prevention and treatment agents, both pharmacological and not, have been discussed throughout this paper. While several therapies look promising, few have proven to definitively prevent and/or treat CIPN. Currently, duloxetine is the only agent endorsed by the ASCO and ESMO guidelines for treatment for CIPN [20,21]. It is well tolerated and has recently been found to not interfere with the effects of chemotherapeutic agents resulting in it being supported as the first standardized drug to treat CIPN [20,108]. While no other agent has proven to treat and prevent CIPN with the same efficacy and safety as duloxetine, many have shown great promise and will be further discussed below.

One of the more recent pharmacological agents being explored is MR309, a selective antagonist of the sigma 1 receptor [109,110]. The sigma 1 receptor is found in the endoplasmic reticulum and modulates nociception and sensitization signaling pathways [109]. A phase II trial found patients treated with MR309 had a significant reduction in chronic neuropathic pain compared to the placebo group [109]. In addition, MR309 was found to be safe and allowed patients to receive a higher cumulative dose of the chemotherapeutic agent they were being treated with [109,110]. Scrambler therapy is another commonly studied technique to reduce CIPN symptoms. This treatment works by sending "non-pain" signals to replace "pain" signals perceived by the nerves [111–113]. The goal is to essentially block pain information's effects, thereby reducing the pain felt by the patient [112]. Scrambler therapy can drastically relieve acute and chronically CIPN pain with no toxicity [111,112]. Another treatment being tried is topical menthol [114]. Derived from mint, menthol activates the TRPM-8 receptor, responsible for detecting cold stimuli in peripheral nerves [114]. It was found to have a significant therapeutic response in CIPN when administered twice a day to affected skin areas and tolerated well [114].

Integrative and behavioral approaches focus on pain that deals with the complex processing of cognition and emotion to influence pain perception [115]. Studies have shown that patients' increased catastrophizing was associated with more severe pain symptoms [116]. The following complementary therapies focus on psychological and behavioral strategies and are all safe, inexpensive, and come without adverse effects [115]. Although there are mixed reviews, acupuncture may have its role in CIPN management [117]. Acupuncture stimulation suppresses nociception in peripheral sites by increasing endogenous opioid release [118]. While some studies report reduced pain and improved quality of life in CIPN patients, others have shown no benefit in either of these areas with acupuncture therapy [117]. Because this treatment is deemed safe and could alleviate some patients' symptoms, it can be considered at the clinician's discretion [117]. Another explored approach is massage therapy to manage cancer pain [115]. The basis of this is that calming the body calms the mind, which relaxes the body [115]. Massage therapy reduces pain, anxiety, nausea, and fatigue [115]. Lastly, mind-body techniques can manage cancer pain, including CIPN [115]. These combine educating the patient that psychological factors can influence pain (and vice versa) with training in cognitive (hypnosis, imagery, etc.) or behavioral coping skills [115].

4. Conclusion

CIPN is a possible adverse effect of chemotherapy. In addition to having to live with the pain, it also can affect patients' ability to work and is associated with a greater financial burden than in patients who do not experience CIPN. CIPN is not only hard to treat, but it is also difficult to assess and diagnose. There are several different assessments and diagnosis methods available, but currently, there is no standardization on which one to use. Part of the issue in finding a treatment for CIPN is that the pathophysiology is not well understood. This has led to many different pharmacological and non-pharmacological agents being used in trials to try and find prevention and treatment methods for CIPN. Many agents show great promise in their use but need larger studies conducted on them, such as IV lidocaine, cannabinoids, oral glutamine, cryotherapy, acupuncture, massage therapy, and exercise. In contrast, others were found to show no real efficacy or need for further trials because of the poor outcomes such as calcium, magnesium, TCAs, and nabiximols.

Furthermore, certain therapies can increase the risk and severity of CIPN and should be avoided, including EPO and acetyl-L-carnitine (ALC). The future direction for the treatment and prevention of CIPN is aiming to better understand the pathophysiology and, as a result, hopefully, find a therapy that can help treat this condition. Until then, duloxetine is currently the only recommended agent for CIPN treatment. Non-pharmacological therapies have proven to be helpful in some patients and may provide relief in certain individuals.

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CRediT authorship contribution statement

Elyse M. Cornett: Conceptualization, Methodology, Software, Writing – review & editing. **Alan David Kaye:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing. **Diana Cruz-Topete:** Conceptualization, Methodology, Software, Writing – review & editing. **Ivan Urits:** Conceptualization, Methodology, Software, Writing – review & editing. **Omar Viswanathb:** Conceptualization, Methodology, Software, **Omar Viswanat**. **Hemangini A. Dhaibar:** Data curation, Writing – original draft. **Allison D. Desforges:** Data curation, Writing – original draft, Writing – review & editing. **Chance M. Herbert:** Data curation, Writing – original draft, Writing – review & editing. **Allyson L. Spence:** Visualization, Investigation, Writing – review & editing. **Hemangini A. Dhaibar:** Software, Validation. **Bailey Reid:** Visualization, Investigation, Writing – review & editing. **Hemangini Dhaibar:** Writing – review & editing.

Conflict of interest statement

None

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