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Review

The Future of Chemotherapy: The Mechanisms and Benefits of Exercise in Taxane-Induced Peripheral Neuropathy

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side-effect resulting from numerous neurotoxic chemotherapies that damages the peripheral nerves, alters sensations in the hands and feet, causes burning and shooting pains, and impairs a patient's quality of life (QoL). There are limited established interventions to help improve CIPN symptoms. There is only one pharmacological agent (Duloxetine) for treatment of CIPN; however, it only has mild benefit, signaling a critical need for alternative management options to manage patient symptoms. Multiple studies suggest therapeutic benefits of exercise in cancer care to improve physical and psychological functioning; however, the benefits regarding CIPN symptoms and physical function are less clear. This narrative review synthesizes research articles investigating the effect and mechanisms induced by different exercise programs for patients with taxane-induced peripheral neuropathy (TIPN) symptoms and function. The overall incidence, manifestations, characteristics, and mechanisms of CIPN are also discussed. While some studies in this narrative review demonstrated that exercise programs may have benefits on sensory and motor TIPN symptoms in some but not all patients, there are consistent benefits of improved QoL and physical function across most patients. This narrative review highlights the need for future research to confirm the effects of exercise for TIPN, with a focus on other important components, including the effect of exercise adherence, type, and supervision level.

Keywords: cancer; exercise: physical activity: rehabilitation; neuropathy; peripheral neuropathy; chemotherapy-induced peripheral neuropathy; taxane-induced peripheral neuropathy

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1. Introduction

Chemotherapy agents with new mechanisms of action have been developed since the 1940s, when nitrogen mustards and folic acid antagonist drugs were first used for cancer treatment [1]. These treatments have resulted in improved patient survival, with a projected 22.1 million cancer survivors by 2030 [2]. However, chemotherapy administration commonly leads to the development of comorbidities [1]. Numerous chemotherapies (e.g., taxanes, platinums, vinca alkaloids, thalidomide, and bortezomib) result in a side effect called chemotherapy-induced peripheral neuropathy (CIPN), which can affect between 50 and 90% of patients [3]. CIPN manifests as altered sensation (numbness, tingling, burning, and shooting pain) in the hands and feet and can subsequently impair quality of life (QoL) due to damages of nerves beginning in the peripheral nervous system (PNS) impacting on physical and daily function [3].

The PNS, a large network of neurons, sends signals from various parts of the body to the central nervous system (CNS) composed of the brain and spinal cord [4]. The PNS is divided into two main sections: the Autonomic Nervous System that controls involuntary bodily functions, such as blood pressure, rate of breathing, and glands, and the Somatic Nervous System, which controls muscle movement and relays information from the ears,

eyes, and skin to the central nervous system [5]. By damaging peripheral nerves, neurotoxic chemotherapy agents can affect a multitude of critical functions within the body, including sensory, motor, and autonomic nerve dysfunction.

Sensory symptoms usually develop first in a "glove and stocking" pattern, presenting as numbness, tingling, impaired vibration sensibility, paresthesias and dysesthesias to light touch and warm or cool temperatures (i.e., hyperalgesia and mechanical or thermal allodynia), spontaneous burning, and shooting or electric shock-like pain [6]. The most distal parts of the limbs exhibit the greatest deficits before progressing proximally [6]. Motor symptoms occur less frequently than sensory symptoms and present as gait and balance disturbances and decreased muscle strength and deep tendon reflexes [7]. Autonomic symptoms occur infrequently, presenting as orthostatic hypotension, constipation, altered sexual and urinary function, hearing, smell, taste, vision, face sensation, balance, speech, and swallowing [8]. In most instances, CIPN symptoms decline after chemotherapy treatment concludes; however, some chemotherapy agents have the potential to cause further progression or new development of CIPN after finishing treatment (a phenomenon known as "coasting") [9].

Recommendations are lacking regarding the treatment and management of CIPN, with only a single pharmacological agent available, Duloxetine, which does not provide a satisfactory level of relief for many patients [9]. Exercise is commonly recommended to manage the physical and psychological effects of chemotherapy, including fatigue, decreased physical fitness, and lower quality of life [10]. However, the evidence regarding the relationship between exercise and specific types of CIPN is less clear. Thus, this narrative review will explain the mechanisms of key CIPN types and potential effects of exercise on CIPN, then describe the literature exploring the associations between exercise and taxane-induced peripheral neuropathy (TIPN) symptoms and physical functioning in breast cancer survivors. The most common taxane agents include paclitaxel, docetaxel, and cabazitaxel [11]. TIPN-associated numbness in the feet and weakness in the limbs put patients at high risk of falling and having trouble sensing small or sharp objects [7,12]. Symptoms of TIPN typically start during the first 2 months, progress during treatment, and can persist or further worsen after the cessation of treatment [13]. Initial management of TIPN often consists of treatment delays, reducing treatment dosages, or discontinuing the chemotherapy regimen, which may affect cancer outcome [14].

2. Mechanisms of CIPN

The main mechanisms by which neurotoxic chemotherapy drugs lead to CIPN are interference in the activity of the Dorsal Root Ganglion (DRG), axonal degeneration, demyelination, CNS alterations, and various mechanisms of mitochondrial damage, microtubule disruption, ion channel activity alteration, DNA damage, and neuroinflammation. The DRG is a collection of sensory neurons that relay information from the periphery of the body (skin, muscles, and organs) to the CNS [15]. The neurons in the DRG are pseudobipolar, meaning they have a peripheral branch that extends out toward the periphery and a central branch that carries the somatosensory information to the spinal cord by creating synaptic connections with other neurons, including secondary sensory neurons, interneurons, and motor neurons [15]. Chemotherapy drugs can interfere with the neurons in the DRG because they are not protected by the blood–brain barrier [16].

2.1. Axonal Degeneration and Demyelination

Axonal degeneration and demyelination are key mechanisms by which various chemotherapeutic agents may cause CIPN. Axonal degeneration of both large (Aα and Aβ) and small (Aδ and c) fibers of peripheral nerves can be triggered by a wide variety of mechanisms, including direct insult to the nerves, neuroinflammation, damage to the glial cells, and capillary damage and accompanying nerve ischemia. Specifically, these mechanisms may cause CIPN through DNA damage and altered axonal transport, mitochondrial

functioning, ion channel functioning, and calcium homeostasis [17]. These mechanisms will be further discussed in relation to key CIPN types in subsequent sections.

Axonal demyelination most often occurs secondary to axonal degeneration and only occurs in large fiber peripheral nerves. Chemotherapy-induced damage to the Schwann cells that maintain the myelin sheath around large fiber axons may also contribute toward demyelination in CIPN [18].

Measurement of CIPN

Large fiber axonal degeneration and demyelination is measured using nerve conduction studies and physical assessments, such as vibration perception, deep tendon reflexes, proprioception, muscle weakness, and self-reported numbness and tingling [19]. Nerve conduction studies are utilized to quantify both the strength (amplitude) and velocity of compound sensory action potentials and compound motor action potentials [20]. Small fiber axonal degeneration is assessed based on temperature sensation, paresthesia, and self-reported neuropathic pain (allodynia and spontaneous shooting, burning, and electric-shock like pain), as well as a skin biopsy test to measure IENF density [21,22]. Neuropathic pain is often a sign of peripheral sensitization.

2.2. Central Nervous System Alterations in CIPN

Central sensitization may be responsible for chronic painful CIPN. Sensitization results from increases in membrane excitability and synaptic strength. Chronic CIPN due to changes within the CNS represents a functional shift in the somatosensory system from high-threshold nociception to low-threshold pain hypersensitivity [23]. Normally, sensitization and hyperactivity of the somatosensory peripheral nervous system helps prevent further damage by notifying the body of pain [23]. However, persistence beyond the point of danger causes irritability of the ascending nerves and decreased inhibition of the descending pain modulatory system in the CNS [23]. This hypersensitivity changes the CNS response even to normal (innocuous) sensory inputs, which manifests as allodynia (pain to non-painful stimuli) and hyperalgesia (excessive pain response to painful stimuli) [23]. Central sensitization causes changes to nociceptive pathways through inputs that usually do not affect the pathways. For example, large low-threshold mechanoreceptor myelinated fibers are used to produce Aβ fiber-mediated pain [23]. This results in mechanical sensitivity rather than heat sensitivity that is presented in peripheral sensitization [23].

There is also evidence that suggests that certain neurotoxic chemotherapies may have the ability to permeate through the blood–brain barrier (BBB) in small quantities and influence the astrocytes/glial cells in the spinal cord dorsal horn. For example, preliminary evidence suggests oxaliplatin might enter the endothelial cells of the BBB vessels and trigger a signaling pathway that induces disassembly of the tight junctions between the endothelial cells and allow oxaliplatin to leak through the BBB [24]. Specific molecular factors like TNF-α, IL-1β, IL-6, free radicals/oxidative stress, bradykinin, or angiogenic factors such as VEGF may play a role in the disassembly and leakiness of the BBB [24].

2.3. Mechanisms of Key CIPN Classes

2.3.1. Taxane-Based Compounds

Taxane-based chemotherapeutic agents (paclitaxel, docetaxel, and cabazitaxel) [11] are believed to cause CIPN by interfering with the normal cycling of microtubule depolymerization and repolymerization, causing mitochondrial dysfunction, axon degeneration, neuroinflammation, and altered Ca^{2+} hemostasis, and resulting in an increase in the production of pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines.

Paclitaxel binds to and stabilizes microtubules, resulting in neurotoxicity. Axons are rich in microtubules, which provide structural support and serve as tracks for axonal transport throughout the life of a neuron [25]. At high concentrations, paclitaxel binds to the β-tubulin subunit, which promotes the assembly of tubulin-enhancing microtubule polymerization [16]. This leads to the formation of altered mitotic spindles, preventing

normal mitosis and resulting in cell apoptosis [16]. The stabilization of the microtubule and disruption of microtubule function is another result of β-tubulin binding [26]. It is proposed that the inhibition of microtubule function affects the structure and function of neurons, resulting in clinically apparent neuropathy [27]. Furthermore, microtubule disruption and the consequently impaired axonal transport of essential cellular components cause the degeneration of distal nerve segments (Wallerian degeneration) and axonal membrane remodeling [28]. At small concentrations, however, paclitaxel does not increase microtubule polymerization; rather, it acts as a microtubule-stabilizing agent, blocking depolymerization, resulting in halted anaphase, and apoptosis mechanisms are activated [29].

Mitochondrial dysfunction is another mechanism by which taxane compounds result in CIPN. Taxanes do not bind directly to the mtDNA as platinum agents do to cause this dysfunction; rather, by impairing microtubule function, axonal transport of important cellular components is halted. This halt of axonal transport may have a significant role in the production of ROS that relates to mitochondrial dysfunction. Increased ROS levels, which have been detected in sensory neurons and the spinal cord [30–34], cause the activation of apoptotic processes, the disruption of cell structures, and demyelination. These events lead to the impairment of signal transmission and the activation of immune processes, including increased production of pro-inflammatory cytokines (TNF-α, IL-1β) and a decrease in anti-inflammatory cytokines (IL-4 and IL-10) [30–32].

Increased production of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines were found to cause the development of neuroinflammation, presenting as peripheral sensitization [35]. In the DRG, Paclitaxel induced the recruitment, activation, and accumulation of macrophages with a pro-inflammatory M1 phenotype, leading to pro-inflammatory cytokine and chemokines release that induced DRG and distal nerve ending damage [36–39]. When inflammatory cells accumulate around damaged peripheral nerves, they produce multiple cytokines and chemokines, such as TNF-α, IL-1β, IL-6, IL-8, CCL2, and the CXC family, resulting in peripheral sensitization [6].

Axonal degeneration also results from high systemic doses of paclitaxel or injections of paclitaxel directly into a peripheral nerve. In mature rats with two intravenous injections of paclitaxel 3 days apart, it was seen that severe axonal degeneration and hypomyelination resulted in sections of the DRG, whereas ventral roots remained intact [40]. In contrast, relatively low systemic doses of paclitaxel did not result in axonal degeneration in the peripheral nerve [41,42]. Degeneration of the sensory terminal arbors was found in adult male Sprague Dawley rats induced with Paclitaxel. The control rats (CCI) were those with painful peripheral neuropathy due to nerve trauma and rats with a sciatic nerve transection. The CCI rats had 343.1 ± 25.8 intraepidermal nerve fibers (IENF) per centimeter, whereas the paclitaxel-treated rats had 261.0 ± 25.2 IENFs per centimeter, a reduction of 23.9% relative to control [43].

Paclitaxel also alters calcium homeostasis, which has been shown to play a role in the pathogenesis of CIPN [44]. Specifically, paclitaxel has been shown to cause the release of calcium from mitochondria; the process is thought to be mediated by the activation of the mitochondrial permeability transition pore [44]. This release of calcium may result in heightened neuronal excitability and impaired glial function [44]. Reducing the availability of extracellular calcium, blocking calcium release from intracellular stores, or chelating cytoplasmic-free calcium would thus be expected to reverse some of the adverse consequences of impaired mitochondrial calcium regulation [44]. In an experiment with adult male Sprague Dawley rats treated with paclitaxel, data showed that the neuropathic pain produced by paclitaxel is significantly ameliorated by drugs that decrease the extracellular and intracellular availability of calcium (TMB-8, Quin-2, EGTA, and EGTA-am) [44]. Thus, there is significant evidence to suggest that altered calcium homeostasis is linked to neuropathic pain produced by paclitaxel administration.

Although chemically similar, docetaxel and paclitaxel show differences in mechanism of action [16]. Docetaxel has a higher affinity for the binding site in the β-tubulin subunit [45]. The tubulin polymers generated by docetaxel are structured differently than

those of paclitaxel, and docetaxel does not change the number of the protofilaments in the microtubules [16].

2.3.2. Platinum-Based Compounds

Platinum-based chemotherapeutic agents (oxaliplatin, cisplatin, and carboplatin) are believed to result in CIPN by impairing the electrophysiologic function of DRG neurons through the formation of platinum adducts and altering ion channel activity. The DRG is a collection of sensory neurons that relay information from the periphery of the body (skin, muscles, and organs) to the central nervous system (CNS) [15]. Chemotherapy drugs can interfere with the neurons in the DRG because they are not protected by the blood–brain barrier [16]. Once the platinum agent is administered intravenously, it binds preferentially to guanosine and adenosine in the nucleus of DRG neurons to form intrastrand and interstrand crosslinks [16]. This results in the formation of DNA adducts, which restrict DNA replication, transcription, cell cycle arrest, and apoptosis [16].

Platinum compounds can irreversibly alter mitochondrial activity in cells by binding to mitochondrial DNA (mtDNA) because there are no mtDNA repair systems in mitochondria [16]. Damage to the mtDNA leads to increases in the amount of reactive oxygen species and oxidative stress on the cell [16]. Oxidative stress damages neurons by causing demyelination, mitochondrial dysfunction, microtubular damage, and apoptosis [46]. Mitochondria are localized in the axons of peripheral neurons; therefore, platinum binding of the mtDNA results in alterations to axonal transport, which is thought to be involved in the onset of neuropathic pain [16]. Furthermore, platinum binding of mitochondria—internal storage units for calcium—leads to accumulation of intracellular calcium, resulting in altered neuronal excitability and axonal degeneration from altered activation of calpain [16].

Platinum-based compounds alter ion channel activity. Ion channels are responsible for generating and sustaining the different phases of action potentials, which are necessary for vesicle mobilization, fusion, and exocytosis [7]. One of the more prominent ion channels associated with CIPN is the sodium ion channel [47]. Voltage-gated sodium channels mediate the depolarization phase, but oxaliplatin has been seen to alter the activation and inactivation behavior of sodium channels; specifically, it leads to a slowdown of sodium channel inactivation kinetics [48]. The more than threefold increase in refractory time of the peripheral nerve proved that oxaliplatin led to a delay of inactivation of the sodium channels [48]. Refractory time is the time between action potentials when it is very difficult to generate another action potential [47]. The prolonged refractory period following oxaliplatin administration indicates that the ability of nerves to transmit signals accurately and efficiently might be compromised, possibly leading to altered sensory perception. It was found that early changes in the length of the median nerve action potential refractory period were a predictor of the development of chronic neuropathy after oxaliplatin treatment, where 78% of patients that had a prolonged refractory period of at least 4 ms (the normal duration is 3 ms) developed peripheral neuropathy [49].

Oxaliplatin also induces changes in voltage-gated potassium ion channels. This ion channel mediates the repolarization phase, which returns the cell's membrane potential to a negative potential (resting membrane potential) [47]. A single administration of oxaliplatin was seen to induce neuronal hyperexcitability, thereby decreasing the expression of TREK1 and TRAAK, potassium channels in DRG neurons [50]. This decreased expression led to a sustained thermal and mechanical hypersensitivity in naive animals tested [50].

Even within the platinum compound class, physiological effects can differ. For example, cisplatin may form more adducts in the DRG than oxaliplatin [51]. Additionally, carboplatin is less neurotoxic at conventional doses than cisplatin, which could be due to lower intracellular platinum accumulation and platination [52].

2.3.3. Vinca-Alkaloid Based Compounds

Vinca-alkaloid-based chemotherapeutic agents (vincristine, vinblastine, vinorelbine, and vindesine) are believed to result in CIPN by both inhibiting the assembly of micro-

tubules and promoting their disassembly, ultimately leading to cell cycle arrest, distal axonal degeneration, and immune system activation. Vinca-alkaloid agents inhibit the assembly of microtubules by binding to the β-tubulin subunit, preventing the straightening of the structure of the molecule, thus interfering with tubulin polymerization [53,54]. This interference promotes microtubule disassembly, which disrupts axonal transport [45]. Axonal transport is a key process that plays a role in nearly all activities of a nerve cell (neuron), from mitochondrial distribution within to neurogenesis, synaptogenesis, and plasticity of each neuron [55]. Neurogenesis and synaptogenesis are integral processes in the overall architecture of the nervous system, as they are responsible for forming neurons and synapses [55]. However, impairment of axonal transport by vinca-alkaloid agents may result in neuroinflammation, axonal degeneration, and apoptosis, which elicits further inflammation in response to the cell damage [45]. Interruption of axonal transport leads to the disruption of mitochondrial distribution, neurogenesis, synaptogenesis, and neural plasticity, which, in turn, leads to apoptosis of long fiber peripheral nerves in the DRG, leading to CIPN symptoms.

Vincristine also induces CIPN by inducing distal axonal degeneration. In an in vitro model of vincristine neuropathy in rat DRG, direct axonal toxicity at the distal terminals was observed [56]. The mechanism by which vincristine results in CIPN is through the activation of a multidomain protein, sterile alpha and toll/interleukin-1 receptor motif-containing 1 (SARM1) in the axon, causing a rapid decrease in NAD+ before local metabolic collapse and axon fragmentation is initiated [57,58].

Peripheral neuropathy was also found to result from vincristine administration through the activation of the immune system. After the administration of two consecutive cycles of vincristine, there was an increase in the number of monocytes expressing the CX3CR1 receptors in the sciatic nerve [59]. Macrophage infiltration, which increases CX3CR1 receptors, plays a role in the development of mechanical neuropathy. This can be seen by the reversal of allodynia—a type of painful hypersensitivity to non-painful stimuli—in CX3CR1-deficient mice that were treated with the CCR2 antagonist, which reduces the macrophage infiltration in the sciatic nerve [59].

2.4. CIPN Manifestations and Patterns

As established, there are many different mechanisms by which neurotoxic chemotherapy drugs lead to the incidence of CIPN, depending on the class of chemotherapy induced. The difference in mechanism leads to differing incidence, manifestations, onset, trajectory, and permanence of CIPN symptoms. The incidence of CIPN is a key difference between different chemotherapy agents. Paclitaxel administration leads to a 61–92% incidence of CIPN compared to a 20% incidence for vincristine, 12–85% for cisplatin, and 85–96% (acute) and 40–93% (chronic) for oxaliplatin [60].

2.4.1. Manifestations of CIPN

The symptoms that result from different chemotherapy agents, even within the same class, differ. In the platinum class, the main symptoms of acute OIPN include cold-related paresthesias of the hands and feet, pharyngolaryngeal dysesthesias, jaw spasms, fasciculations, and muscle cramps [61]. Cold-induced neuropathy after oxaliplatin is a unique feature of OIPN, and this is a major important difference in the symptoms between oxaliplatin and cisplatin CIPN [62]. Additionally, individuals receiving cisplatin tend to develop ototoxicity, which is not the case for oxaliplatin CIPN.

In the taxane class, the main symptoms are sensory. These include paresthesias, dysesthesias, numbness, altered proprioception, and loss of dexterity predominantly in the toes and fingers (stocking-and-glove distribution); however, motor and autonomic symptoms do develop as well [63]. Following paclitaxel administration, patients demonstrated reduced mechanical sensibility [64].

In the vinca-alkaloid class, the main initial symptoms are pain located in hands and feet. Other symptoms include muscle weakness, including wrist extensors and dorsiflex

or weaknesses and cramping [65]. When vincristine was administered, patients displayed impaired touch thresholds and deficits in pinprick perception [64].

2.4.2. Onset of CIPN

The onset of CIPN symptoms differs based on the chemotherapy drug used for treatment. While some agents result in neuropathic symptoms during or immediately after treatment, others result in symptoms either weeks or months after chemotherapy treatment was completed. Furthermore, some chemotherapy classes, such as platinums, induce a "coasting" phenomenon, where symptoms continue to worsen for months after cessation of the chemotherapy treatment [66].

In taxane-induced peripheral neuropathy, symptoms may start days after the first dose and typically occur during the first 2 months, progress during treatment, and may even worsen after cessation of therapy [67]. In vinca-alkaloid-induced peripheral neuropathy, symptoms usually appear within the first 3 months of treatment [68]. Vincristine may produce the most severe neuropathy, with symptoms of distal numbness and tingling commonly beginning approximately 4–5 weeks after treatment [45]. The onset of cisplatin-induced peripheral neuropathy is variable, with some patients reporting symptoms after the first dose, and some reporting onset after 12 cycles of therapy [69]. Cisplatin-induced peripheral neuropathy develops after cumulative doses above 350 mg/m^2 and at the cumulative dose of 500–600 mg/m^2 [70].Chronic cisplatin-induced peripheral neuropathy has been observed in 5–20% of patients at 12 months after therapy [20,71]. Even within a chemotherapy class, onset of CIPN is not the same. Acute, transient oxaliplatin-induced peripheral neuropathy develops in almost 65–98% of patients within hours of oxaliplatin infusion at a dose ranging from 85 to 130 mg/m [72]. Chronic oxaliplatin-induced peripheral neuropathy has been observed in 26–46% of patients at the 12-month follow-up, in 24% of patients at the 15–18-month follow-up, and in 84% of patients at the 24-month follow-up [73].

2.4.3. Intensity and Duration of CIPN

Symptoms of CIPN can range from acute, transient thermal sensations to permanent changes in peripheral nerves accompanied by chronic pain and irreversible nerve damage [74]. In general, most neurotoxic agents cause CIPN in a time- and dose-dependent manner, meaning the severity and likelihood of CIPN increase with higher cumulative doses and longer exposure times to the chemotherapy [75,76].

Platinum agents are the most neurotoxic, with oxaliplatin causing the highest prevalence of CIPN [77]. High-grade chronic OIPN occurs in approximately 10% of patients receiving accumulated doses ranging from 510 to 765 mg/m^2, while at doses higher than 1000 mg/m^2, this condition may be present in almost 50% of patients at doses higher than 1000 mg/m^2 [78]. Acute, transient OIPN may last up to 5–7 days, but symptoms may persist up to 21 days or longer in patients receiving 12 cycles of chemotherapy [79,80].

Symptoms of TIPN usually improve after stopping the treatment. In some patients, symptoms can continue up to 1–3 years after completion of the therapy or last lifelong [81]. Within the taxane class, the intensity of symptoms differs. Symptoms are most intense for paclitaxel, whereas the docetaxel intensity of symptoms is milder [82].

Vinca alkaloid CIPN symptoms and incidence increase with more frequent dosing in addition to increasing with higher cumulative doses [76]. Neurotoxicity can occur at doses of 1.4 mg/m^2 [72] per week with sensory symptoms and painful paresthesias arising first, and distal weakness typically occurring after doses above 6–8 mg/m [83]. Autonomic symptoms occur in up to $^1/_3$ of patients.

2.5. Limitations to Duloxetine Treatment for CIPN

Duloxetine, a serotonin–norepinephrine reuptake inhibitor, is the only agent currently recommended by the American Society of Clinical Oncology for the treatment of CIPN. In CIPN patients, neuropathic pain is a common symptom that decreases QoL. Duloxetine

increases the amount of serotonin and norepinephrine in the body, which are key pain-inhibiting neurotransmitters [84]. Recent research has found limitations to Duloxetine's effectiveness. One specific limitation is the factor of emotional functioning that plays a role in Duloxetine's effectiveness [84]. In patients treated with oxaliplatin or paclitaxel, those with better emotional functioning were four times more likely to respond well to Duloxetine [84]. This is a significant limitation, as not all CIPN patients have high emotional functioning. Another limitation is Duloxetine's low ineffectiveness in a large percentage of CIPN patients [84]. In a randomized, placebo-controlled trial, it was found that duloxetine was ineffective in 41% of the study participants [84]. Duloxetine's inconsistent effectiveness, which may depend on emotional functioning, makes it an unreliable choice for CIPN treatment, prompting the need for other treatment options.

2.6. Exercise Effects on CIPN and Potential Mechanisms

Exercise interventions, including strength, aerobics, and balance training, are a possible treatment to improve symptoms of CIPN, stabilize CIPN symptoms, and prevent symptom onset and CIPN-related injuries. In a secondary analysis of a trial conducted with 355 cancer patients treated with taxane, platinum, or vinca alkaloid-based chemotherapy, patients were randomized to either chemotherapy alone or chemotherapy and a 6-week home-based exercise program of progressive walking and resistance training. Numbness/tingling and hot/coldness increased more in the control group than the intervention group (by 0.58 and 0.77, respectively, in the control group vs. 0.38 and 0.38, respectively, in the exercise group ($p = 0.061$ and $p = 0.045$)) [85]. Moreover, unpleasant skin sensations and sensitivities related to neuropathic pain were found to be attenuated following chronic exercise training [86]. Another study looked at how a form of strength training (closed kinematic chain exercises) administered for a total of 15 sessions over 3 weeks affected CIPN symptoms and found that the exercises were effective in reducing symptoms in neuropathy and improving balance [87].

Exercise has been found to stabilize CIPN symptoms. A trial randomized 30 stage IV metastasized colorectal cancer patients receiving palliative chemotherapy (median of 23.5 chemotherapy cycles of various regimens prior to intervention) to either an 8-week supervised exercise program involving endurance, resistance, and balance training or a negative control group. The study found that symptoms of CIPN remained stable throughout the course of the study in the intervention group but significantly worsened in the control group [88].

Exercise has been found to possibly prevent CIPN symptom onset. In a trial conducted with 61 lymphoma patients undergoing unspecified chemotherapy, participants were randomized to either standard clinical care with physical therapy alone or in combination with a 36-week supervised exercise program involving sensorimotor (i.e., balance), strength, and endurance training. The study found that total incidence of peripheral neuropathy among the exercise group was 40% (8/20) and 71% (12/17) in the control group. Subsequent symptomatic improvement was significantly better and only demonstrated in the exercise group (87.5% vs. 0%, $p < 0.001$) [89].

2.6.1. Mitochondrial Function

Exercise may also prevent chemotherapy-induced mitochondrial dysfunction, which is a cause of CIPN from vincristine, paclitaxel, cisplatin, oxaliplatin, and other agents, including bortezomib [90]. Exercise has been shown to increase mitochondrial antioxidant capacity, electron transport chain efficiency, and biogenesis (production of mitochondria) and decrease oxidative stress and mtDNA damage [91]. Aerobic exercise provides oxygen to muscle cells, improving mitochondrial function, increasing the density of mitochondria in muscle tissue, and triggering angiogenesis, the growth of new blood vessels [92]. Furthermore, in improving mitochondrial function in mouse models, exercise was shown to promote both neurogenesis and hippocampal plasticity, processes that contribute to apoptosis of long fiber peripheral nerves in the DRG when impaired.

2.6.2. Axonal Integrity

Axonal degeneration is a major mechanism by which CIPN symptoms develop. Exercise has been shown to promote axonal outgrowth and protect against axonal degeneration. In a mouse model of paclitaxel-induced neurotoxicity, treadmill exercise was shown to protect against axonal degeneration and prevent reduction in IENF density (small fiber CIPN) [93].

2.6.3. Neurotrophic Factors

Exercise has been shown to increase the production of neurotrophic factors, which are proteins that support the development and survival of neurons [94]. Specifically, in a study assessing the relationship between treadmill use and neurotrophic factors, exercise was shown to enhance the production of the glial cell line-derived growth factor (GDNF), brain-derived neurotrophic factor (BDNF), and insulin-like growth factor 1 (IGF-1) in the blood, nerves, and muscles of exercising animals [94]. These neurotrophic factors are essential to axonal regeneration, which is important given that axonal degeneration is a main mechanism of CIPN [95]. However, the relationship between specific types and dosages of exercise and the upregulation of neurotrophic factors is not so well understood, however. Whether it has a correlation to neuropathic pain and its maintenance is still being understood and is a topic for further research [96].

2.6.4. Anti-Inflammatory Effects

The release of pro-inflammatory cytokines is a main mechanism by which neurotoxic chemotherapy leads to CIPN symptoms. These pro-inflammatory cytokines, which are released following peripheral nerve damage, include tumor necrosis factor-Alpha (TNF-A), interleukin-1Beta (IL-1B), IL-6, and IL-8 [97]. Although the cytokines lead to inflammation and oxidative stress, exercise reduces this effect by promoting the release of anti-inflammatory cytokines (IL-6, which subsequently increases IL-10 and IL-1RA) and reducing levels of oxidative markers [90,98,99]. The pro-inflammatory cytokine IL-1β increases after chemotherapy administration and leads to CIPN development, but exercise has been shown to decrease levels of IL-1β [100]. Moreover, exercise has been shown to increase levels of IL-10, an anti-inflammatory cytokine that reduces CIPN-associated inflammation [98].

2.6.5. Brain Hyperactivity

Brain hyperactivity in sensory regions of the brain (e.g., insula, which plays a major role in the process of bodily sensations called interoception) [101] has been found to be positively correlated with CIPN severity and a reduction in brain activity in the insula was found to be associated with a reduction in CIPN symptom severity [102]. There are several pathways related to or underlying brain hyperactivity that lead to CIPN symptoms, including reduced GABAergic inhibition, neuroinflammation, and overactivation of GPCR/MAPK pathways [102]. Although exercise has not been proven to improve brain hyperactivity, there is preliminary work that suggests a role for exercise in reducing functional connectivity in the interoceptive brain system, particularly rooted connections with the posterior cingulate cortex [103].

2.7. Measurement of CIPN in Exercise Rehabilitation Studies

Patient-reported outcome measurements are an established method for assessing the manifestations of CIPN [104]. In measuring CIPN symptoms, the main tools used are the European Organization for Research and Treatment of Cancer Chemotherapy Induced Peripheral Neuropathy Questionnaire, Functional Assessment of Cancer Therapy/Gynecologic Cancer Group Neurotoxicity Subscale, Numerical Rating Scale, CIPN Assessment Tool, and the Patient Neurotoxicity Questionnaire. In measuring pain symptoms, the main tools used are Brief Pain Inventory, Numerical Rating Scale, Pain Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs, and the PainDETECT questionnaire. These latter

two methods are designed to solely separate neuropathic pain from nocioceptive pain, not measure the intensity of the pain felt, whereas the Brief Pain Inventory assesses patients' pain on its severity and interference in their life [105].

Objective measures of neuropathy outcomes are focused in three main areas: Neurological Assessment, Neurophysiology, and Quantitative Sensory Testing [104]. The main tests in clinical neurological examinations are deep tendon reflexes, proprioception, vibration thresholds, light touches, and pinprick sensibilities. The Total Neuropathy Score is used to validate the combined results of the neurological exam and patient symptoms report. In a neurophysiology sense, nerve conduction studies are used to provide information regarding CIPN pathophysiology. Quantitative Sensory Testing is used to measure sensory fiber functionality, providing information on warm detection and pain pressure thresholds, aside from other parameters not mentioned.

Beyond objective and subjective measures, there are various measures to quantify the impact of CIPN on physical functioning, balance control, muscle strength, and QoL [104]. For physical functioning measurements, upper limb function tests are performed. For balance control measurements, either objective assessment, clinician-rated performance measures, or patient report tests are utilized, including the Berg Balance Scale, Fullerton Advanced Balance Scale, and postural sway testing. For muscle strength measurements, dynamometry, chair rise, and sit-to-stand tests are performed. For QoL assessment, the European Organization for Research and Treatment of Cancer Quality of Life questionnaire, Functional Assessment of Cancer Therapy–General, 36-item Short Form Health Survey, and the McGill scale are used.

2.8. Significance of Exercise for TIPN in Breast Cancer Survivors

Breast cancer is the most common malignant tumor in women, occurring in one out of every eight women in their lifetime [10]. TIPN is highly prevalent and exhibits distinct pathophysiologic mechanisms, onset, and symptom patterns from other CIPN types. TIPN-associated numbness in the feet and weakness in the limbs put patients at high risk of falling and injury from inability to sense extreme temperatures and sharp objects [11,12]. Symptoms of TIPN typically start during the first 2 months and progress during treatment, potentially persisting or worsening after cessation of treatment [7]. Initial management of TIPN often consists of treatment delays, reducing treatment dosages, or discontinuing the chemotherapy regimen, which may affect cancer outcome. In a retrospective cohort study of patients receiving docetaxel or paclitaxel for non-metastatic breast cancer, patients with TIPN received a significantly lower final cumulative taxane dose [13].

Recommendations are lacking regarding the treatment and management of CIPN, with only a single pharmacological agent available, duloxetine, which does not provide a satisfactory level of relief for many patients [9]. Exercise is commonly recommended to manage the physical and psychological effects of chemotherapy, including fatigue, decreased physical fitness, and lower overall quality of life [14]. However, the evidence regarding the relationship between exercise and TIPN is less clear.

3. Literature Review

The purpose of the following literature review is to explore the associations between exercise and physical functioning and TIPN symptoms in breast cancer survivors receiving taxane-based chemotherapy. Other outcomes of interest included balance control, muscle strength, and QoL.

3.1. Results

The search yielded 250 articles, from which 5 articles met full eligibility, presented in detail in Table 1. The results from the study are discussed in further detail in Table 2 and in the discussion.

Table 1. Literature Review Study Designs.

Citation	Participants	Design	Exercise Intervention
Bland et al., 2019 [106]	A total of 27 women with stage I–III breast cancer scheduled to receive taxane chemotherapy ($n_{PACLITAXEL}$ = 20; $n_{DOCETAXEL}$ = 7)	Participants were randomized to IG (exercise during chemotherapy) or waitlist CG (exercise after chemotherapy) group; were assessed with the EORTC QLQ C30 and CIPN20; assessed at baseline (before chemotherapy), pre-cycle 4 (before the final taxane cycle), the end of chemotherapy, and follow-up (10–15 weeks after chemotherapy)	Supervised aerobic, resistance, and balance training that was conducted 3 days a week for 8–12 weeks
Hammond et al., 2020 [107]	A total of 48 women with stage I-III breast cancer scheduled to receive adjuvant taxane chemotherapy ($n_{DOCETAXEL}$ = 48)	Participants were randomized to treatment (exercise during and after chemotherapy) or CG (treatment as usual) group; were assessed with QST and patient questionnaires: Numeric Pain Rating Scale (NPRS), Disability of the Arm, Shoulder, and Hand (DASH), and Self-report version of Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS); assessed prior to chemotherapy, mid-treatment, post-chemotherapy, 3 months post-chemotherapy, and 6 months post-chemotherapy	Home-based nerve gliding exercises were performed 3 times daily post-surgery to 6 months post-treatment; average duration was 8.25 months
Vollmers et al., 2018 [108]	A total of 36 women with breast cancer scheduled to receive paclitaxel chemotherapy ($n_{PACLITAXEL}$ = 36)	Participants were randomized to the IG (exercise during chemotherapy) or CG (informed of side effects but and were suggested to design their own physical activity plan) were assessed with EORTC, Multidimensional Fatigue Inventory (MFI-20), BR23, CIPN20, and Fullerton Advanced Balance Scale; assessed at T0 (before Paclitaxel treatment), T1 (12 weeks after last dose), and T2 (24 weeks follow-up)	General strength, endurance, and sensorimotor training were conducted 2 times per week throughout treatment and 6 weeks after chemotherapy treatment
Şimşek et al., 2021 [109]	A total of 90 women with stage II-IV breast cancer scheduled to receive taxane chemotherapy	Participants were randomized to exercise, cold application, or usual care; were assessed with Patient Identification Form and CIPN Assessment Tool at baseline (onset of CIPN during chemotherapy treatment) and week 12	Home-based progressive strengthening, stretching, and balance exercises occurred 5 times per week, starting the week when the first neuropathy symptom developed to 12 weeks late
Courneya et al., 2013 [110]	A total of 301 women with stage I-III breast cancer scheduled to receive herceptin or taxane chemotherapy ($n_{PACLITAXEL}$ = 38; ($n_{DOCETAXEL}$= 202)	Participants were randomized to participate in a standard aerobic exercise group (STAN), high dose aerobic group (HIGH), or combined aerobic and resistance training exercise group (COMB) throughout chemotherapy; were assessed with the Medical Outcomes Survey-Short Form (SF)-36, Functional Assessment of Cancer Therapy-Taxane, and fitness tests at baseline (within 1–2 weeks of starting chemotherapy), periodically during treatment ($^1/_3$ and $^2/_3$ through), and post-intervention (3–4 weeks post-chemotherapy completion)	STAN: 25 to 30 min of aerobic exercise HIGH: 50 to 60 min of aerobic exercise COMB: combined dose of 50 to 60 min of aerobic and resistance exercise Exercises were supervised 3 times weekly throughout treatment until 3–4 weeks after chemotherapy (mean length 16.4 weeks)

Table 2. Literature Review Article Results.

Citation	Design	Outcome			
		TIPN	**Balance Control**	**Muscle Strength**	**QoL**
Bland et al., 2019 [106]	RCT (n = 27) Supervised aerobic, resistance, and balance training (3 days/week for 8–12 weeks) compared to waitlist control	At cycle 4, significant differences were found in the number of people in the IG and waitlist CG who reported moderate to severe numbness in the toes or feet (nIG = 1 and nWaitlist = 7; p = 0.04) and had impaired vibration sense in the feet (nIG = 2 and nWaitlist = 10, p < 0.01). However, no differences were found at the end of chemotherapy	-	-	Overall quality of life was higher in IG than waitlist control at the end of chemotherapy (p = 0.05), but, by the end of exercise intervention for waitlist control, there were no significant differences between groups (p = 0.29)
Hammond et al., 2020 [107]	RCT (n = 48) Home-based nerve gliding exercises (3 times daily post-surgery to 6 months post-treatment for 8.25 months) compared to usual care	- Per the NPRS, 49% of the CG reported pain (1 + pain scores) and 30% of the IG reported pain (p = 0.053) - Compared to less active participants, physically active participants (who engaged in any form of moderate activity for 30 min at least 4 times a week on at least 3 out of 4 reassessment visits) had better vibration scores (pLEFT = 0.001, pRIGHT = 0.001) and a decrease in heat pain thresholds bilaterally in the hands (pLEFT = 0.021, pRIGHT = 0.039)	-	- Pain pressure thresholds (p = 0.034) and grip dynamometry (p < 0.000) were better in the IG vs. CG and did not decline over time	- The unilateral improvement in quality of life variables in intervention group (NPRS, DASH, S-LANSS, and functional grip strength tests) suggests a consistent effect

Table 2. *Cont.*

Citation	Design	Outcome			
		TIPN	**Balance Control**	**Muscle Strength**	**QoL**
Vollmers et al., 2018 [108]	RCT (n = 36) General strength, endurance, and sensorimotor training (2 times per week from chemotherapy treatment initiation to 6 weeks after chemotherapy completion) compared to standard care	-	- In monopedal stance, there was significantly smaller sway area in the IG than the CG at T1 and T2 in left ($p < 0.001$; $p = 0.003$) and right leg ($p < 0.001$; $p < 0.01$) - In bipedal stance, there was a significant improvement over time at T1 vs. T0 ($\bar{x}$IG = −0.49 $\bar{x}$CG = 1.14 ($p = 0.039$)) - Significant differences were found in balance, signifying improvement in postural stability [37.71 ± 2.73 (IG) vs. 34.47 ± 3.98 (CG) ($p = 0.004$)]	- There was a significant loss of strength in the CG and a slight improvement of strength in the IG ($\bar{x}$T1 to T2 = −1.60 (CG) vs. $\bar{x}$T1 to T2 = 0.60 (IG); $p = 0.029$)	- There was a lack of significant improvements in QoL
Şimşek et al., 2021 [109]	3-group RCT (n = 90) Strength, stretching, and balance training (5 times per week, starting the week when the first neuropathy symptom developed to 12 weeks later) compared to cryotherapy or usual care	- There was no increase in neuropathy rate of the patients in the exercise group when compared to the control group - Significant differences among groups were found at the followup time point in the severity of numbness in the hands ($p = 0.009$) and feet ($p = 0.005$), with the exercise group exhibiting the lowest means hand and foot numbness scores - CIPN symptoms remained stable in the IG despite the IG having received a higher mean chemotherapy dose	- The mean scores of all the symptoms in the CG except the loss of balance increased significantly ($p < 0.050$)	-	-

Table 2. *Cont.*

Citation	Design	Outcome			
		TIPN	Balance Control	Muscle Strength	QoL
Courneya et al., 2013 [110]	3-Group RCT (n = 301) STAN: 25 to 30 min of aerobic exercise; HIGH: 50 to 60 min of aerobic exercise; COMB: 50 to 60 min of combined aerobic and resistance exercise; (3 days per week throughout treatment until 3–4 weeks after chemotherapy; mean duration 16.4 weeks)	- Physical functioning scores were lower for and statistically similar among all groups post-treatment, meaning a higher dose of aerobic exercise and addition of resistance exercise did not improve the physical functioning - For the physical component summary, HIGH was superior to STAN (p = 0.04) - For bodily pain, HIGH was superior to both STAN (mean group difference = 2.3; p = 0.02) and COMB (mean group difference = 2.0; p = 0.04)	-	- COMB was superior to both HIGH and STAN for muscle strength and endurance (p < 0.01)	-

3.2. Methods

This review included articles retrieved from PubMed, Google Scholar, the National Library of Medicine, and ScienceDirect between 2013 and 2023 that were randomized control studies. Articles were searched using "taxane-induced peripheral neuropathy," "exercise," and "breast cancer" search terms as well as through hand-searching of recent systematic reviews and meta-analyses on the effects of exercise for CIPN. Studies were only included if they focused on breast cancer survivors who were treated with taxane-based agents. Articles were excluded if patients had received any other types of neurotoxic chemotherapies or focused on passive exercise interventions and other alternative medicine interventions, including massage, whole body vibration, herbal medicine, capsaicin ointment, and acupuncture.

4. Discussion

The narrative review suggested that among breast cancer survivors receiving taxane-based therapy, exercise interventions may preserve or improve physical functioning, QoL, and some TIPN symptoms. Specifically, combined aerobic, strength, resistance and balance/sensorimotor training led to improvements in muscular strength [107,108,110], TIPN symptoms [109], QoL [106], pain pressure thresholds [107], and vibration sensibility [106]. Additionally, interventions that were implemented at the start of chemotherapy or during/early on led to significantly improved CIPN outcomes, such as pain pressure thresholds and grip dynamometry [107], postural stability [108], the severity of numbness in the hands and feet [109] and muscle strength and physical functioning [110]. Depending on the level of intensity, there were differences found in CIPN outcomes. For light intensity exercise regimens consisting of progressive strengthening, stretching, and balance exercises performed five times per week, there were significant improvements in hand and foot numbness [109]. Comparably, nerve gliding exercises performed three times daily were found to result in increased pain pressure thresholds and grip dynamometry [107]. Moderate to vigorous exercise in the form of strength, endurance, and sensorimotor training conducted two times per week showed improvements in balance [106]. High intensity aerobic and resistance exercise for 50 to 60 min improved bodily pain, muscle strength, and endurance [110].

Three studies from this review provide moderate level evidence that exercise—particularly combined exercise interventions—helps preserve muscular strength during taxane-based chemotherapy treatment. Two RCTs (n = 48 and 36) showed that grip strength was preserved and significantly better (compared to usual care recipients) among individuals who received physical therapy (primarily a nerve-gliding exercise) [107] or combined strength, endurance, and sensorimotor training [108] throughout and until 6 weeks [108] and 6 months post-taxane treatment [106]. Nerve gliding is a type of physical therapy intervention that involves gentle positioning and stretching to improve nerve functioning. The Courneya et al. (2013) [110] randomized comparison study (n = 301) compared the effects of standard dose aerobic (25 to 30 min per session), high dose aerobic (50 to 60 min per session), and combined aerobic and resistance exercises (50 to 60 min per session) on outcomes, including muscle strength [110]. The study concluded that combined aerobic and strength exercise preserved muscular strength more than standard and high dose aerobic exercise alone [110]. Ultimately, the results were limited due to unreliable measurement of or discrepancies in exercise adherence [106,110], small sample size [107,108], lack of a control condition [110], and lack of blinding of participants and assessors. For example, varying exercise session completion rates (87.8% in the standard aerobic, 81.6% in the high dose aerobic, and 78.0% in the combined exercise groups) may have biased the results in the Courneya study [110]; a higher dropout rate could indicate attrition of the least-adherent individuals optimizing the results for that group.

The Şimşek et al. (2021) study looked at the effect of progressive strengthening, stretching, and balance exercises on the sensory functioning of 90 women with stage II-IV breast cancer receiving taxane chemotherapy [109]. Participants were randomized to either exercise, cold application, or control group. To assess the TIPN of patients, the

CIPN Assessment Tool—a Likert-type scale developed by Tofthagen et al. [111]—was utilized at baseline and 12 weeks. The CIPN Assessment Tool quantified sensory and motor issues such as numbness, itching, burning, cold sensitivity, pain, weakness, and balance disorder on a scale of 1 to 10, with a higher score indicating a higher level of neuropathy. The scale also evaluated and scored problems encountered in the daily life activities of patients, which indicated their sensory and motor abilities, such as dressing, walking, picking up objects, and holding onto objects. The study found that exercise reduced TIPN symptoms of numbness in hands and in the feet significantly compared to the control and cold application groups. This suggests that improved sensory functioning in patients with TIPN could be attributed to a combined strengthening, stretching, and balance exercise intervention. A limitation of the study was the tool used for data collection. Instead of a clinical assessment, only patient-reported measures of symptoms were collected, limiting the reliability of the differences seen pre- and post-test in TIPN symptoms.

Bland et al. (2019) showed improved QoL outcomes in patients who developed TIPN (n = 27) who participated in supervised aerobic, resistance, and balance training during taxane chemotherapy, compared to the waitlist control group [106]. The participants were separated based on the time period that they underwent exercise—the IG performed exercise during chemotherapy, and the waitlist CG performed exercise after chemotherapy. Specifically, the intervention appeared to prevent decline in QoL at the end of chemotherapy (before the waitlist CG started exercise) by a clinically meaningful amount in the IG relative to those receiving usual care on the waitlist. After the waitlist control group completed their exercise training, the QoL of participants in this group increased as well, more than the increase in QoL of the IG. The QoL of the IG stayed increased at the follow-up time point, which was 10–15 weeks after chemotherapy. This provides evidence that increased QoL may be sustained after exercise intervention and that completing exercise during and after taxane treatment can preserve and improve QoL among breast cancer survivors who developed TIPN. However, given the significant limitations of the study, including the small sample size and a lack of control on physical activity outside of the intervention, there is low to moderate evidence suggesting exercise improves QoL in patients with TIPN. Vollmers et al., 2018, showed no significant improvements in the QoL of TIPN patients [108]. There are significant limitations associated with the study that may be the cause of this finding. There were prominent variances in the subjective scales used to test QoL and a limited cohort size, making it challenging to ascertain the QoL effects of exercise.

One study from this review showed increased pain pressure thresholds of patients with TIPN undergoing an exercise intervention. The Hammond et al., 2020, exercise intervention [107], as outlined earlier, also tested the effect of nerve gliding exercises on pain pressure thresholds in 48 women with stage I–III breast cancer receiving adjuvant taxane chemotherapy. To test this outcome, pressure algometry, a hand-held device to measure pain thresholds, was used. Increasing pressure was applied to the quadriceps muscle until the participant determined that the sensation changed from a feeling of pressure to a feeling of pain (pressure at that point was recorded). They found that pain pressure thresholds were improved in the IG compared to the CG and did not decline over time. As mentioned earlier, the outside activity of the participants was not strictly monitored, so this may have been a confounding variable affecting the pain pressure thresholds, making this result low to moderately significant.

One study from this review showed improvement in the vibration sensibility of patients with TIPN undergoing an exercise intervention. The Bland et al., 2019, study [106], as outlined earlier, also tested the effect of supervised aerobic, resistance, and balance training on the vibration sensibility of 27 women with stage I-III breast cancer receiving taxane chemotherapy. To test this outcome, clinical sensory testing was conducted, including vibration sensation performed on the superior surface of the participant's right and left great toe proximal interphalangeal and the medial malleolus and inferior pole of the patella. The study found that more waitlist CG participants (n = 10) had impaired vibration sense before the last taxane cycle compared to the IG (n = 2). By the follow-up (10–15 weeks

after chemotherapy), there were no significant differences between groups, suggesting the exercise improved vibration sensibility in the TIPN patients. Vibration sensibility may have improved in the IG compared to the waitlist CG by the last taxane cycle because exercise was not yet performed in the waitlist CG by this point. By the time that the two groups underwent the exercise intervention, vibration sensibility improved in both. This suggests that exercise improved vibration sensibility in the groups. However, the study did not provide information on the vibration sensibility of a group receiving no exercise at all, making it unclear whether vibration sensibility by the follow-up was significantly improved with the exercise intervention.

The findings presented in this narrative review coincide with other recently published studies that investigate exercise interventions and CIPN, such as by Brownson-Smith et al., 2023 [112], and Kleckner et al., 2018 [85]. The meta-analysis by Brownson-Smith et al., 2023 [112], identified reduced levels of CIPN symptoms and higher HR-QoL in women with breast cancer who exercised before and/or during taxane-containing chemotherapy regimens compared with non-exercising control groups. When synthesizing evidence from one of the larger trials in this field by Kleckner et al., 2018 [85], 355 cancer patients receiving taxane-, platinum-, or vinca alkaloid-based chemotherapy were randomized to chemotherapy or chemotherapy plus Exercise for Cancer Patients, a standardized, moderate-intensity, home-based, six-week progressive walking and resistance exercise program. The study found that exercise reduced CIPN symptoms of hot/coldness in hands/feet (-0.46 units, $p = 0.045$) and numbness and tingling (-0.42 units, $p = 0.061$) compared to the control. These findings coincide with this narrative review's finding that exercise interventions can improve sensory functioning. However as this study focused on numerous chemotherapy types other than taxanes, this study was not included in this narrative review.

This literature review helps to fill the gap in the literature regarding how exercise affects physical functioning and other TIPN-related symptoms in patients specifically receiving taxane-based chemotherapy. Different chemotherapies have different mechanisms by which they contribute to peripheral neuropathy; therefore, this review aimed to summarize the current literature regarding TIPN only.

5. Conclusions

Based on findings, there is low-moderately strong evidence to suggest that exercise maintains or improves physical functioning, QoL and some TIPN symptoms in breast cancer patients receiving taxane chemotherapy. With the generation of higher quality evidence of the benefits of exercise for patients at risk of CIPN in addition to the other established physical and psychological benefits, future efforts may focus on the investigation of implementing exercise programs into oncology centers.

However, the studies presented had methodological limitations, including small sample sizes and lack of blinded assessors, which may impact the generalizability of the findings and make it difficult to make general conclusions about the true effect of exercise on TIPN until more rigorously conducted studies are performed. Lastly, future studies should monitor exercise adherence, which is an important factor contributing to the dose–response benefits of exercise, which can be challenging due the clinical and psychological difficulties presented to patients while trying to uptake and adhere to an exercise program during cancer treatment.

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