

Chemotherapy-induced peripheral neuropathy in patients with breast cancer treated with taxanes (Review)

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Abstract. Breast cancer is the most common malignancy among women worldwide and is frequently treated with taxane-based chemotherapy. Despite their therapeutic efficacy, taxanes are associated with a high incidence of chemotherapy-induced peripheral neuropathy (CIPN), a disabling condition that impacts the quality of life of patients. CIPN primarily affects the sensory nerves, leading to symptoms such as numbness, tingling, pain and motor dysfunction, which can persist long after treatment completion. The pathophysiology of taxane-induced CIPN involves direct neurotoxic effects on the dorsal root ganglia, a disruption of microtubule dynamics and neuroinflammatory responses. Given the limited efficacy of current pharmacological treatments, such as duloxetine, lidocaine or topical agents, alternative approaches, including cryotherapy and other non-pharmacological interventions, are being explored. The present literature review provides an updated synthesis of the epidemiology, mechanisms and management strategies of taxane-induced CIPN among patients with breast cancer. Identifying efficacious interventions

remains a critical challenge in oncology. By specifically addressing this underexplored, yet clinically relevant, issue, the present review aims to promote future improvements in patient care and quality of life.

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1. Background

Breast cancer is the first cancer among women worldwide (1), and is treated with different therapeutic strategies, including chemotherapy. Among all the agents available, taxanes are commonly used at every stage of breast cancer therapy: in adjuvant therapy for early-stage cancer patients, in neoadjuvant therapy for those with locally advanced disease, and in palliative care for patients facing advanced stages of the disease (2). However, despite its therapeutic advantages, this type of agent is often associated with neurological toxicities, particularly peripheral neuropathy (3).

Chemotherapy induced Peripheral Neuropathy (CIPN) is characterized by a primary effect on the sensory nerves during chemotherapy, with potential impacts on motor and autonomic functions. The symptoms include numbness, tingling, pain, mechanical allodynia, and loss of motor function in the limb extremities, ranging from mild to severe, and potentially impairing daily activities. The severity is often dose-dependent, requiring clinical adjustments of the treatment (4). Despite these modifications and the available therapies, 44% of patients report persistent symptoms two years after CIPN diagnosis (5).

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Abbreviations: ASCO, American Society for Clinical Oncology; CIPN, chemotherapy-induced peripheral neuropathy; EANO, European Association of Neuro-Oncology; EONS, European Oncology Nursing Society; ESMO, European Society for Medical Oncology; FACT-NTX, Functional Assessment of Cancer Therapy Neurotoxicity; nab-PTX, albumin-bound paclitaxel; NCV, nerve conduction velocity; QoL, quality of life; SNRI, serotonin and norepinephrine reuptake inhibitor; ST, scrambled therapy

Key words: peripheral neuropathy, chemotherapy, taxanes, side effects, neuropathic pain, treatments, prevention, quality of life, breast cancer

CIPN poses a significant clinical challenge for breast cancer patients undergoing taxane treatment, complicating treatment adherence and negatively affecting long-term outcomes. A better understanding of the mechanisms and prevalence of CIPN could enhance prevention strategies and improve patients' quality of life (QoL).

This review thus aims to provide an up-to-date synthesis of the epidemiology, mechanisms, and therapeutic strategies for managing taxane-induced peripheral neuropathy among breast cancer patients. Unlike previous reviews that address CIPN more broadly (6,7), focus on specific approaches such as pharmacogenetics (8) or cryotherapy (9), or explore CIPN specifically in breast cancer without focusing on taxanes (10), this work offers a clinically oriented perspective specifically on taxane-induced peripheral neuropathy in the context of breast cancer. Moreover, while some recent reviews focus exclusively on the psychological impact and quality of life of patients (11), the present review offers a novel and comprehensive overview of both current and emerging therapeutic strategies, including pharmacological and non-pharmacological therapies, supported by completed and ongoing clinical trials. By addressing this significant toxicity, this review aims to support more effective and personalized care for breast cancer patients undergoing taxane-based chemotherapy, with the goal of reducing side effects such as peripheral neuropathy.

2. Methodology

An initial bibliographic exploration was conducted using references cited in summary articles available on the UpToDate database. This served as a starting point to identify the main themes addressed in recent literature. A complementary search was then carried out on PubMed using combinations of the following keywords: 'taxane-induced neuropathy', 'chemotherapy-induced peripheral neuropathy', 'breast cancer AND taxanes AND neuropathy' and 'CIPN AND paclitaxel OR docetaxel'.

Articles were selected manually based on their relevance and contribution to the topic. Particular attention was paid to literature reviews, clinical studies, practice guidelines, and publications from the last ten years.

While the primary focus was on taxane-induced neuropathy in breast cancer patients, some studies involving other types of cancer or chemotherapies were also included when they offered transferable insights, such as mechanistic explanations, common risk factors, or management strategies. Only articles published in English were included in this review.

3. Taxane chemotherapy in breast cancer

Breast Cancer comprises various subtypes identified by molecular and histological characteristics (12). Consequently, treatment approaches and prognoses vary across different breast cancer subtypes. However, chemotherapy, particularly taxane-based regimens, is widely and frequently used in early-stage, locally advanced, and metastatic breast cancer (8).

Taxanes are chemotherapy agents that target cell division by stabilising microtubules, essential components of the cellular skeleton involved in various functions, such as cell shape, mitochondrial activity, and cell signalling. In oncology,

their primary interest lies in their ability to interfere with chromosome separation during mitosis (13). Taxanes bind to tubulin, a key component of microtubules, preventing their disassembly and thereby inhibiting cell cycle progression, and ultimately inducing apoptosis (14,15). Although taxanes have enhanced disease-free and overall survival among breast cancer patients (16), they also cause significant toxicities, particularly peripheral neuropathies.

4. Incidence and impact of CIPN

CIPN affects approximately 60% of patients receiving taxane-based chemotherapy, with symptoms including numbness, tingling, and pain predominantly in the hands and feet (17). Neurotoxicity is a well-recognized side effect of adjuvant chemotherapy with taxanes, with peripheral neuropathy generally limited to distal paraesthesia, often partially reversible after treatment discontinuation. However, in a meta-analysis, neuropathic symptoms persisted among 11% to over 80% of the patients, one to three years following treatment (18). A clinical trial showed that 41.9% of patients receiving anthracycline and taxane-based chemotherapy were still experiencing peripheral neuropathy two years after treatment initiation. In some cases, the neuropathy can be permanent and interfere with daily activities (19).

Taxanes, such as paclitaxel and docetaxel, are frequently used in early-stage breast cancer (2). Both are associated with motor and sensory neuropathy, which is dose and schedule-dependent, and cumulative. One study demonstrated that in a sample of 4,950 patients treated with taxanes, a significant percentage developed neuropathy. Patients treated with paclitaxel experienced grade 2 to 4 neuropathies in 20 to 27% of cases, depending on the treatment regimen, with an incidence of 5 to 8% for grade 3 or 4 neuropathies. Similarly, patients treated with docetaxel developed grade 2 to 4 neuropathies in 16% of cases, with 4 to 6% presenting grade 3 or 4 neuropathies (20).

CIPN typically occurs during the first two months of treatment, progresses during active treatment, and then usually stabilizes shortly after treatment ends (7). However, it sometimes persists in the long term, with only partial remission of the symptoms, which prevents patients from achieving a good QoL (5,21). It is therefore important to understand the action mechanisms of taxanes and their impact on CIPN in order to offer solutions for patients.

5. Mechanisms of taxane-induced CIPN

Taxanes induce neuropathy through several mechanisms, including direct neurotoxic effects on the dorsal root ganglia neurons, a disruption of microtubule dynamics, and the triggering of inflammatory response in the peripheral nervous system. Paclitaxel, in particular, promotes tubulin polymerization, leading to cell cycle arrest. However, microtubules are also vital for critical cellular processes such as motility, intracellular transport, and neuronal growth (22,23). In-vitro studies and animal models have shown that paclitaxel inhibits neurite outgrowth and damages neurons and peripheral glial cells, resulting in demyelination and nerve degeneration (24-27). It has also been demonstrated that in-vitro paclitaxel blocks the G2/M

phase of cell mitosis, preventing the cells from achieving correct mitotic spindle formation and successful cell division (28).

Research using animal models has found that both paclitaxel and docetaxel predominantly damage large myelinated fibres in the peripheral nerves (29). A rare human nerve biopsy study following long-term paclitaxel treatment showed fibre loss, axonal atrophy, and secondary demyelination, suggesting that ganglionopathy, rather than axonopathy, is the primary mechanism behind paclitaxel-induced peripheral neuropathy (30). The accumulation of paclitaxel in the dorsal root ganglia is particularly implicated in axonal degeneration and impaired nerve function.

Several taxanes are used in the treatment of breast cancer, each with a similar mechanism of action, but distinct pharmacological properties. Paclitaxel is the most commonly used molecule, and works by binding to the β -tubulin subunit on microtubules. It thus promotes and stabilizes their polymerized state, thereby preventing normal microtubule depolymerization, an essential process for mitotic spindle function during cell division. As a result, paclitaxel induces mitotic arrest at the G2/M phase of the cell cycle, leading to apoptosis in rapidly dividing cancer cells (31). However, some mechanisms remain incompletely understood, such as its effects on neuronal mitochondrial dysfunction, calcium signalling, and macrophage-mediated neuroinflammation (32,33).

Docetaxel acts similarly by stabilizing microtubules, but differs in its chemical structure (34). This structural difference increases its solubility and enhances its efficacy (35). Moreover, due to its increased affinity for β -tubulin, docetaxel can target a broader range of the cell cycle, including the S/G2/M phases, whereas paclitaxel primarily affects the G2 and M phases. Docetaxel also promotes the phosphorylation of Bcl-2, an anti-apoptotic gene frequently overexpressed in several solid cancers, including breast cancer, thereby enhancing cancer cell apoptosis and contributing to its therapeutic efficacy (36).

Cabazitaxel is also a taxane, but as a second-generation semisynthetic molecule (37). It works by stabilizing microtubules like other taxanes, but has a more favourable pharmacokinetics with higher lipophilicity, a safer profile and induces less resistance (38). It can therefore be used in patients who are resistant to docetaxel (38,39).

Additionally, Ortataxel is the first orally taxane developed in order to overcome multidrug resistance, and has shown great activity against both drug-sensitive and resistant cancer models, including those resistant in paclitaxel and docetaxel (37,40). It differs from paclitaxel by inducing abnormal tubulin polymers, suggesting a distinct binding mode and polymerization mechanism. This unique interaction with tubulin may explain their ability to overcome resistance typically seen with conventional taxanes like paclitaxel (41). Currently, ortataxel is being developed for various advanced cancers.

Among the taxanes, paclitaxel and docetaxel are widely used as standard-of-care treatments for breast cancer. Cabazitaxel, although primarily approved for metastatic castration-resistant prostate cancer, has shown clinical activity in breast cancer patients previously treated with taxanes, as demonstrated in phase II trials (42,43). Ortataxel has completed phase II trials in patients with taxane-resistant metastatic breast cancer (44), demonstrating promising antitumor activity and the ability to overcome multidrug resistance mechanisms. While only

paclitaxel and docetaxel are currently approved for breast cancer treatment, cabazitaxel and ortataxel represent potential alternatives under investigation, particularly for patients refractory to first-line taxane therapy.

The mechanisms by which taxanes exert their anticancer effects are central to their therapeutic efficacy in breast cancer treatment. This ability to interfere with the cell cycle makes taxanes highly effective against proliferative tumour cells. However, the same mechanisms also impact healthy, non-dividing cells, which rely on microtubules for essential functions (6). In the peripheral nervous system, microtubules are critical for axonal transport, neuronal integrity, and regeneration. When taxanes accumulate in structures like the dorsal root ganglia, they interfere with these processes, leading to axonal degeneration, demyelination, and neuronal damage (45). This explains the emergence of CIPN.

Understanding the mechanisms of taxanes is essential to guiding the development of targeted strategies that could effectively counteract CIPN without compromising their anticancer activity. In the following section, we will explore the various strategies currently available to decrease taxane-induced neuropathies, as well as those with potential future relevance.

6. Prevention and management strategies

Pharmacological interventions. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) that blocks the reuptake of these neurotransmitters, which are essential for transmitting signals to the brain and the nervous system. Because of its mechanism of action, duloxetine is currently recommended in clinical guidelines as the only agent with moderate efficacy for managing established symptoms of CIPN (7,46), as it does not fully resolve the neuropathy. For instance, a large double-blind, randomized and placebo-controlled trial showed that duloxetine reduced pain for only 59% of the 231 patients with CIPN, without significantly improving other symptoms, but no serious adverse events were reported (47).

In addition, studies have shown duloxetine to be more efficacious in treating CIPN caused by platinum-based chemotherapy than that caused by taxanes (7). Indeed, a double-blind, randomized, placebo-controlled trial found no significant effect on paraesthesia, numbness, sensitivity to cold, or other nerve conduction velocity (NCV) measurements among breast cancer patients receiving paclitaxel chemotherapy (48).

While duloxetine is the primary treatment for CIPN, other options are available when duloxetine proves inefficacious or unsuitable. Although anticonvulsants and tricyclic antidepressants offer some potential for symptom relief, their efficacy is less well-established (7). Given their general use in managing neuropathic pain, membrane-stabilizing agents such as anticonvulsants (pregabalin and gabapentin for instance) or tricyclic antidepressants could be considered as alternatives for managing CIPN symptoms (7). These agents should be used only when duloxetine fails, as numerous double-blind, randomized studies, including placebo-controlled trials, have demonstrated no significant improvement in CIPN symptoms with tricyclic antidepressants (49,50) or gabapentinoids (51,52).

A randomized placebo-controlled trial also explored the potential of lithium in preventing CIPN. The neuroprotective effects of lithium are thought to stem from its ability to

modulate the neuroinflammatory pathways. This hypothesis led to the elaboration of a placebo-controlled randomized clinical trial aiming to assess the efficacy of lithium to prevent chemotherapy-induced peripheral neuropathy among breast cancer patients. Unfortunately, the results were non-significant (53).

A recent randomized controlled study also investigated the efficacy of lidocaine in preventing and managing taxane-induced peripheral neuropathy in breast cancer patients. Intravenous saline infusion was administered to the control group (54). Lidocaine, an amino-amide local anaesthetic, provides rapid and prolonged effects. It blocks the nerve signals by binding to specific sodium channel receptors in the nerve fibre membrane, thereby preventing nerve impulses (55). The study found that lidocaine was as efficacious as duloxetine in reducing both the incidence and the severity of neuropathy caused by taxane-based chemotherapy. Both lidocaine infusion and oral duloxetine were shown to minimize axonal damage and demyelination of the peripheral nerves, thus mitigating the adverse impact on QoL among breast cancer patients (54).

These findings underline the critical need for targeted strategies to mitigate taxane-induced neurotoxicity. While duloxetine remains a recommended option, its limited efficacy, especially for taxane-induced neuropathy, highlights the need to explore alternative pharmacological treatments (Table I). The comparable efficacy of lidocaine suggests potential new avenues for managing this condition, emphasizing the importance of continued research to optimize therapeutic approaches and improve patient outcomes and QoL.

Topical applications. Topical treatments have also been investigated for their potential to alleviate or prevent CIPN. Among these, capsaicin stands out as a promising option given its widespread use in treating peripheral neuropathies (56–58). To investigate the potential benefits of this treatment for CIPN, a British clinical trial was conducted with 16 patients with chronic CIPN, who were given 8% capsaicin patches applied to their feet for 30 min. The patients experienced significant reductions in spontaneous, touch-sensitive, and cold-sensitive pain, along with improvements in overall pain. Skin biopsies also showed a regeneration of the nerve fibres after treatment, with a normalization of key biomarkers. Among these patients, 10 out of 16 had developed CIPN as a result of taxane chemotherapy, but none was a breast cancer patient. The control group consisted of healthy volunteers (59). Therefore, further studies with more specific criteria are required to determine whether capsaicin could be beneficial for breast cancer patients experiencing taxane-induced peripheral neuropathies. This is also in line with the recommendations from the ASCO guidelines (46), while the ESMO-EONS-EANO Clinical Practice Guidelines adopt a more flexible stance, suggesting that its use could be considered (7).

Other molecules have also been investigated in topical applications. A study involving 208 patients with CIPN evaluated a compounded topical organogel containing baclofen, amitriptyline, and ketamine vs. a placebo. While the treatment group showed an improvement in sensory neuropathy, the result was not statistically significant. However, the same group experienced a significant improvement in motor symptoms, particularly related to tingling, cramping, and pain in

the hands. No significant differences in adverse events were observed between the treated group and placebo groups, with similar rates of mild to moderate side effects and rare severe cases in both arms. No information on the cancer type was given for the patients included in this trial (60). In contrast, a second trial, randomized and placebo-controlled, on a cream containing ketamine and amitriptyline (without baclofen) failed to demonstrate any benefit in reducing CIPN symptoms. Among the 461 patients included, 40% (n=184) had breast cancer, and 53% (n=246) had received taxanes for cancer treatment (61).

Given the inconclusive results, the 2020 ASCO guidelines do not recommend the use of topical baclofen, amitriptyline and ketamine to treat CIPN (46), and the 2020 ESMO/EONS/EANO guidelines even specifically issued a recommendation against their use for this indication (7).

Menthol has also been explored as a topical application to treat CIPN in breast cancer. A Turkish randomized controlled clinical trial showed significant improvements in CIPN symptoms following the application of 1% menthol to limb extremities twice a day, suggesting its potential efficacy in treating CIPN (62). Similar findings were observed in a 2015 proof-of-concept study, which highlighted the potential use of 1% menthol as an analgesic for CIPN. However, this study included only two patients who had received taxane-based chemotherapy, and only 23% of the participants had breast cancer (63). Therefore, further research is needed to validate these findings in breast cancer patients and to confirm the results observed in the Turkish trial. In the meantime, the ESMO guidelines suggest that menthol should be considered, given its low cost and the absence of reported side effects (7).

Non-pharmacological interventions. In the absence of truly efficacious pharmacological treatments for taxane-induced chemotherapy neuropathies, alternative methods have been studied to relieve patients. These alternative methods are non-pharmacological (Table II), implying lower treatment costs and easier implementation. In this section, we will discuss the various non-pharmacological techniques studied to reduce taxane-induced chemotherapy neuropathies in breast cancer patients.

Cryotherapy for example, has emerged as a potential intervention for preventing CIPN. It involves applying cold garments or ice bags to the hands and feet during chemotherapy administration, to prevent or reduce treatment-related neuropathy symptoms. The hypothesis is that continuous flow-limb hypothermia during chemotherapy administration decreases the occurrence and severity of CIPN by reducing the delivery of the neurotoxic drug to the peripheral nerves.

One self-controlled trial investigated the use of cryotherapy among breast cancer patients receiving paclitaxel. Patients who wore refrigerated gloves and socks during their chemotherapy sessions experienced a significantly lower incidence of CIPN than the control group. No patients discontinued due to cold intolerance. Only 28% of patients experienced a loss of hand sensitivity on the treated side, compared to 81% on the untreated side (64). However, a meta-analysis involving 17 trials, including 13 with patients with breast cancer, showed no significant difference in the preventive effects of cryotherapy (65).

Table I. Summary of pharmacological interventions for the treatment of CIPN and their outcomes.

First author/s, year	Molecule	Total number of patients with breast cancer treated, n	Results	(Refs.)
Jordan <i>et al</i> , 2020; Smith <i>et al</i> , 2013	Duloxetine	130	Recommended for managing established CIPN symptoms, with moderate efficacy. Showed improved efficacy in platinum-based chemotherapy compared with taxane-based chemotherapy (59% pain reduction).	(7,47)
Aghili <i>et al</i> , 2024			No significant effect on paraesthesia, numbness or other NCV measurements in paclitaxel-treated patients with breast cancer.	(48)
Hammack <i>et al</i> , 2002; Kautio <i>et al</i> , 2008; Rao <i>et al</i> , 2007; Shinde <i>et al</i> , 2016	Anticonvulsants (gabapentin and Pregabalin) or tricyclic antidepressants	26	No significant improvement in CIPN symptoms compared with duloxetine; however, further studies are needed in patients with breast cancer.	(49-52)
Najafi <i>et al</i> , 2021	Lithium (prevention)	36	Showed some neuroprotective effects by modulating neuroinflammation, but without significant prevention of CIPN.	(53)
Abouelmagd <i>et al</i> , 2023	Lidocaine	60	Lidocaine infusion was as effective as duloxetine in reducing the incidence and severity of taxane-induced neuropathy.	(54)
Clifford <i>et al</i> , 2012; Webster <i>et al</i> , 2011; Anand <i>et al</i> , 2019	Topical capsaicin (8% patch)	Unknown	Reductions in pain and nerve fiber regeneration; however, further studies needed in patients with breast cancer.	(56,58, 59)
Barton <i>et al</i> , 2011	Topical baclofen + amitriptyline ketamine	Unknown	Sensory neuropathy improvement but not statistically significant, and motor symptoms improved; however, further studies are needed in patients with breast cancer.	(60)
Gewandter <i>et al</i> , 2014	Topical ketamine + amitriptyline	184	No significant benefit in terms of CIPN symptom reduction.	(61)
Ozdemir <i>et al</i> , 2024; Fallon <i>et al</i> , 2015	Topical menthol (1%)	72	Improvement in CIPN symptoms in a Turkish trial; promising for patients with breast cancer.	(62,63)

CIPN, chemo-induced peripheral neuropathy; NCV, nerve conduction velocity.

Given the mixed results from previous studies, cryotherapy has not yet been standardized (4) and remains a controversial approach for preventing CIPN among breast cancer patients receiving taxane chemotherapy despite a recent recommendation by the American Society for Clinical Oncology (ASCO) in their 2020 guidelines (46). However, considering its low cost and minimal risk of toxicity, the use of ice bags during treatment could be a reasonable strategy.

In addition to cryotherapy, compression therapy has also been explored to determine whether or not it is efficacious on CIPN. The objective is the same as with cryotherapy: to reduce the amount of neurotoxic drug reaching the peripheral nerves. A recent Colombian randomized clinical trial analysed the efficacy of compression therapy ('too small' gloves/socks) and compared it to cryotherapy and placebo

('loose' gloves/socks). The results showed that compression therapy was not only more efficacious, but also more popular among patients. Indeed, among the 63 patients included, compression therapy was more efficacious (64.7% success at 12 weeks) and provided greater patient adherence (72.7%) compared to cryotherapy (41.1% success, 35.0% adherence) and placebo (41.1% success, 76.2% adherence). Success was defined by a less than 5-point decrease in the Functional Assessment of Cancer Therapy Neurotoxicity (FACT-NTX) score, which measures the severity of the chemotherapy-induced neuropathy (9).

Another self-controlled clinical trial also reported that surgical glove compression therapy was efficacious in reducing albumin-bound-paclitaxel (nab-PTX)-induced peripheral neuropathy among breast cancer patients, from 76.1% of grade 2 or higher occurrence neuropathy to 21.4%. No patient

Table II. Summary of non-pharmacological interventions for the treatment of CIPN and their outcomes.

First author/s, year	Procedure	Total number of patients with breast cancer treated, n	Results	(Refs.)
Tandon <i>et al</i> , 2024	Cryotherapy	Unknown	Cryotherapy may help prevent neuropathy during taxane chemotherapy for breast cancer; however, the results were mixed and inconsistent.	(4)
Hanai <i>et al</i> , 2018		40	Patients wearing frozen gloves and socks during chemotherapy experienced a lower incidence of CIPN compared with the control group.	(64)
Tai <i>et al</i> , 2024		Unknown	Meta-analysis of 17 trials showed no significant difference in the preventive effects of cryotherapy.	(65)
Accordino <i>et al</i> , 2024	Compression therapy	63	More effective and better adhered to by patients compared with cryotherapy and placebo, with 64.7% success at 12 weeks.	(9)
Tsuyuki <i>et al</i> , 2016; Tsuyuki <i>et al</i> , 2019		100	Surgical glove compression reduced nab-PTX-induced neuropathy occurrence from 76.1 to 21.4%.	(66,67)
Bandla <i>et al</i> , 2020	Cryocompression	11	Cryocompression was well-tolerated and may help preserve neuronal function, suggesting potential improved efficacy in alleviating taxane-induced neurotoxicity. Further studies are needed in breast cancer.	(68)

CIPN, chemo-induced peripheral neuropathy; nab-PTX, albumin-bound paclitaxel.

discontinued the study due to intolerance to the compression (66). The same team conducted another clinical trial and reinforced this conclusion (67).

Given these results, it would be reasonable to wonder whether the combination of cryotherapy and compression therapy could benefit patients. This was the focus of a pilot study by the Sundar team, in which 13 cancer patients undergoing taxane chemotherapy received cryo-compression therapy alongside their treatment. The study concluded that cryo-compression was well tolerated and helped preserve neuronal function, suggesting a potentially improved efficacy in alleviating taxane-induced neurotoxicity, though larger studies are needed to confirm these findings. Overall, limb hypothermia caused no serious or long-lasting adverse events. For context, these results were retrospectively compared to patients receiving continuous-flow cooling or no hypothermia (68). The team also developed an ergonomic cryo-compression device in the form of a glove, to reduce taxane-induced peripheral neuropathy (69).

Cryotherapy, compression, and cryo-compression techniques appear promising. Given their cost-effectiveness and ease of implementation, these strategies seem to be an interesting option for the prevention of CIPN.

Alternative therapies. Alternative therapies have also been explored (Table III). Acupuncture, a traditional Chinese medicine technique, has been studied as an alternative therapy for reducing CIPN. It is believed to work by influencing neurotransmitters and neurohormones (70). Numerous studies

have indicated that acupuncture could help alleviate peripheral neuropathy symptoms among patients with other conditions such as diabetes (71), and its effects on CIPN have also been explored.

Regarding CIPN prevention through acupuncture, the results are contrasted. One randomized, sham-controlled trial with breast cancer patients treated with taxanes showed no benefit from electro-acupuncture (72) while another with a similar population demonstrated a reduction in the incidence of high-grade CIPN (70). These are the only studies specifically focused on breast cancer patients, thus highlighting the need for further research.

These mixed results have also been observed in the treatment of CIPN. While several controlled studies have shown the benefits of acupuncture in reducing CIPN (73-76), one four-arm randomized study found no benefit from electroacupuncture (77), and a systematic review demonstrated that there was not enough evidence to support the use of acupuncture for CIPN treatment (78).

These studies often involve a small number of patients, raising concerns about their reliability. To provide a more comprehensive analysis, a recent meta-analysis examined the effects of acupuncture-related interventions on CIPN improvement in a total of 33 studies involving 2,027 participants. The conclusion suggests that acupuncture-based treatments could offer benefits by alleviating CIPN symptoms, pain, and improving quality of life (79). These trials were not limited to breast cancer patients treated with taxanes. Today, it is unclear whether these methods could

Table III. Summary of alternative interventions for the treatment of CIPN and their outcomes.

First author/s, year	Procedure	Total number of patients with breast cancer treated, n	Results	(Refs.)
Bao <i>et al</i> , 2018	Acupuncture (prevention)	104	Decrease in the incidence of high-grade CIPN, but more research needed on breast cancer.	(70)
D'Alessandro <i>et al</i> , 2022	Acupuncture (treatment)	Unknown	Benefits observed in reducing CIPN, but results were limited by the small number of subjects, and the study was not specific to patients with breast cancer.	(73)
Iravani <i>et al</i> , 2020		18	Decrease in the grading scale of CIPN in the acupuncture group, but the study was not specific to patients with breast cancer.	(74)
Lu <i>et al</i> , 2020		40	Adjuvant taxane therapy for breast cancer improved neuropathic symptoms. However, further larger studies are required to validate these results.	(75)
Molassiotis <i>et al</i> , 2019		37	Improvements were observed in pain, clinical neurological assessment, quality of life and symptom distress, but the study was not specific to patients with breast cancer.	(76)
Li <i>et al</i> , 2019	Acupuncture	40	Systematic review showed no sufficient evidence to recommend acupuncture to prevent or treat CIPN.	(78)
Yeh <i>et al</i> , 2024		Unknown	Meta-analysis demonstrated that acupuncture-based treatments may help alleviate CIPN symptoms, reduce pain and enhance quality of life.	(79)
Greenlee <i>et al</i> , 2016	Electro-acupuncture (prevention)	63	No benefit observed.	(72)
Rostock <i>et al</i> , 2013	Electro-acupuncture (treatment)	21	No benefit observed and the study was not specific to patients with breast cancer.	(77)
Coyne <i>et al</i> , 2013; Pachman <i>et al</i> , 2015; Smith <i>et al</i> , 2010 Smith <i>et al</i> , 2020	Scrambler therapy	Unknown	Evidence of pain reduction, but the studies were outdated and not specific to breast cancer. Further studies are needed in breast cancer.	(80-82)
		Unknown	No clear benefit in this randomized controlled trial. Further studies are needed in breast cancer.	(83)
Loprinzi <i>et al</i> , 2020		Unknown	Improvement in neuropathy symptoms compared with TENS therapy. Further studies are needed in breast cancer.	(84)
Chung <i>et al</i> , 2024		2	Improvement in pain relief and quality of life, but further trials needed because of the small number of participants. Further studies are needed in breast cancer.	(85)

CIPN, chemo-induced peripheral neuropathy; TENS, transcutaneous electrical nerve stimulation.

help reduce or alleviate symptoms in breast cancer patients with CIPN.

Another alternative therapy has been studied: scrambled therapy (ST). ST is an innovative device that delivers non-invasive skin electrostimulation in order to replace pain signals

with 'no-pain' signals. Three single-arm clinical trials have shown that this type of treatment could decrease pain induced by CIPN (80-82), but these studies are ten years old, they were not randomized or controlled, and none was specific to breast cancer patient treated with taxane-based chemotherapy.

Among more recent trials, results have been mixed. A pilot randomized sham-controlled trial conducted on 35 patients found no benefit using ST (83), whereas another conducted on 50 patients found that patients treated with ST showed a significantly greater improvement in neuropathy symptoms than those treated with TENS (Transcutaneous Electrical Nerve Stimulation) (84).

More recently, a pilot study with a 6-month follow-up investigated the long-term efficacy of ST for CIPN. The findings suggested that ST improved pain relief and quality of life. No adverse events with ST treatment were reported. However, as the study was conducted on only 10 patients and with a single-arm design, further trials are needed to confirm these results (85).

Vitamin-D. Another way of preventing taxane-induced peripheral neuropathy could be to screen patients for vitamin-D deficiency as it has been shown to increase the severity of this condition. Indeed, one controlled study demonstrated that among breast cancer patients receiving paclitaxel weekly, those with a vitamin-D deficiency presented more peripheral neuropathy than the others (86). This conclusion was also validated in another trial conducted on 1191 breast cancer patients, a third of whom presented pre-treatment vitamin-D deficiency. Patients with vitamin-D deficiency experienced a higher rate of grade ≥ 3 CIPN than those with adequate vitamin-D levels (20.7% vs. 14.2%) (87).

Vitamin-D could easily be measured before the start of taxane treatment in women with breast cancer to plan for supplementation if needed and counteract CIPN. However, prospective clinical trials are required to verify the efficacy of this approach.

7. Future perspectives

Ongoing research is seeking a better understanding of the pathophysiology of CIPN and is aiming to develop more efficacious prevention and treatment strategies. However, despite some promising results, the lack of large cohorts and problems of study quality have prevented the full validation of these findings and the formulation of concrete recommendations. To address this gap, conducting large-scale clinical trials focused specifically on breast cancer patients treated with taxanes appears to be a necessary next step. These trials would provide more robust evidence regarding the efficacy of various therapeutic approaches.

A promising perspective is the development of early diagnostic biomarkers, enabling patients at higher risk of developing CIPN to be identified and the instatement of earlier and more personalized interventions. Moreover, combining pharmacological and non-pharmacological treatments, such as the integration of cryotherapy or acupuncture with drugs, could offer enhanced efficacy in managing CIPN.

Investigating the role of vitamin D supplementation in preventing neuropathy is another area of interest, particularly given its easy implementation in clinical practice and its low cost.

Beyond breast cancer, broader strategies are also being explored, such as the development of a carbazole-based compound designed to protect nerves during chemotherapy and reduce the overall incidence of CIPN (88). In France, a

study is about to begin recruitment to assess the efficacy and safety of photo-biomodulation for the treatment of neuropathic pain related to CIPN (NCT06834685).

In addition to the previously discussed interventions, several ongoing clinical trials could provide new insights for treating breast cancer patients who have CIPN. For example, an Austrian study is currently recruiting breast cancer patients receiving taxane-based chemotherapy to evaluate the efficacy of HiToP® 191 PNP, a certified device already used in conditions such as diabetic neuropathy (NCT06132776). Similarly, a Swedish study is investigating whether an orthopaedic silicone orthosis can alleviate CIPN symptoms in the feet of breast cancer patients (NCT06904989).

An Egyptian study completed in 2024 explored the potential benefits of pentoxifylline (PTX) against CIPN among breast cancer patients treated with paclitaxel-based chemotherapy (NCT06562998). Pentoxifylline is a xanthine derivative and phosphodiesterase inhibitor, which improves microcirculation by reducing blood viscosity and increasing red blood cell flexibility (89), which could help alleviate taxane-induced chemotherapy neuropathy by enhancing nerve perfusion and reducing inflammation. In this study of 72 patients (35 pentoxifylline, 37 placebo), peripheral neuropathy (grade 2-3) at week 12 was significantly lower with pentoxifylline (28.6%) than placebo (64.9%, $P=0.016$), and quality of life was better in the pentoxifylline group (FACT/GOG-NTx score: 98.18 vs. 81.43, $P<0.001$). These findings are encouraging and support further investigation of pentoxifylline as a potential strategy to prevent CIPN in breast cancer patients receiving taxane-based therapy.

Another upcoming trial will assess the neuroprotective effect of hesperidin and diosmin in breast cancer patients undergoing paclitaxel-based chemotherapy (NCT06811220).

Additional trials are actively recruiting breast cancer patients to further evaluate some of the therapeutic strategies previously discussed, such as cryotherapy (NCT06020222), surgical gloves (NCT05771974), lidocaine (NCT04732455), and exercise interventions (NCT05641571).

Together, these studies reflect the growing interest in identifying effective strategies to prevent and treat CIPN among breast cancer patients treated with taxanes. Ultimately, further comprehensive clinical studies are essential to establish standardized, evidence-based guidelines for the prevention and management of CIPN among breast cancer patients treated with taxanes, improving both outcomes and quality of life.

8. Limitations

This review has several methodological limitations that must be acknowledged. First, the selection of studies was not conducted through a systematic review process, which could introduce a selection bias and limit the comprehensiveness of the literature included. As the review focuses exclusively on breast cancer patients treated with taxanes, the findings cannot be generalized to patients with other cancer types or to those receiving different chemotherapeutic agents. Additionally, much of the data on emerging interventions and ongoing clinical trials reports preliminary or incomplete results, which limits our ability to draw definitive conclusions about their efficacy.

Finally, the review is inherently dependent on the quality, design, and heterogeneity of existing studies, which vary widely in methodology, endpoints, and sample sizes, thereby affecting the overall strength of the evidence presented.

9. Conclusion

Chemotherapy-induced peripheral neuropathy (CIPN) caused by taxanes is common among breast cancer patients during treatment and can persist even after therapy ends. These symptoms are debilitating and significantly affect patients' quality of life, making it crucial to understand and manage them effectively. Unfortunately, current treatment strategies, both pharmacological and non-pharmacological, remain insufficiently efficacious, with duloxetine being the only moderately effective agent recommended in Clinical Guidelines.

Recent studies have explored several alternative or complementary options, such as lidocaine infusions, topical menthol or capsaicin, cryotherapy, compression therapy, acupuncture, vitamin D supplementation and pentoxifylline. These approaches have shown preliminary promising results. However, the available evidence is often heterogeneous, inconclusive or based on small samples, especially among breast cancer patients treated specifically with taxanes.

Continuing research is essential, not only to understand the mechanisms of CIPN, but also to identify early biomarkers (e.g. vitamin D deficiency), and develop targeted, efficacious preventive and therapeutic interventions. Future studies with rigorous designs and larger cohorts focused on taxane-induced neuropathies are necessary to validate existing treatments and establish clear, evidence-based guidelines for clinical practice, thus avoiding premature clinical recommendations. Ultimately, improving the management of CIPN could substantially improve patients' quality of life and the overall efficacy of cancer treatments.

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MG conducted the literature research and wrote the review. XD, JPJ and CA reviewed the manuscript and made amendments. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an artificial intelligence tool (ChatGPT, developed by OpenAI, version: GPT-4-turbo) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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