Emerging Therapeutic Strategies for Chemotherapy-Induced Peripheral Neuropathy: Current Evidence and Future Directions

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a condition where the sensory system deteriorates due to unintended negative consequences of chemotherapy medications such as cisplatin, oxaliplatin, paclitaxel, vincristine, and bortezomib. CIPN, affecting up to 80% of patients, is among the most common and debilitating side effects of chemotherapy that can manifest in diverse manners, with the severity and the specific chemotherapeutic agent playing a crucial role in influencing the illness. Individuals suffering from (CIPN) encounter atypical sensory perception, difficulties with balance, unsteady gait, and sensations such as warmth, burning or discomfort in the limbs. While it is possible for symptoms to ultimately subside, it is important to note that many individuals may experience them indefinitely. Because CIPN is mechanistically heterogeneous, treatment selection should be individualized according to symptom phenotype, pain severity, tolerability, comorbidities, and prior response. Duloxetine remains the best-supported pharmacological option for painful established CIPN, while add-on gabapentin or amitriptyline should be framed as individualized or investigational strategies rather than routine superior therapy. This review critically summarizes pharmacological options, mechanistic rationale, patient-reported outcome measures, and evidence gaps to guide future comparative trials.

Keywords: chemotherapy-induced peripheral neuropathy; duloxetine; gabapentin; amitriptyline; pharmacotherapy; patient-reported outcomes; neurotoxicity; oncology supportive care.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy, also known as CIPN, is primarily a sensory degeneration for nerves these can additionally manifest as changes in autonomic and motor function[1].

The most prominent adverse effects caused by several chemotherapy drugs, including cisplatin, oxaliplatin, paclitaxel, vincristine, and bortezomib, are off-target in nature (CIPN) is the most prevalent among these negative consequences[2]. A significant loss of primary afferent sensory axonal fibers is one of the defining characteristics of CIPN, which ultimately results in sensory abnormalities in patients. It is estimated that up to 75 percent of patients acquired CIPN while they were undergoing chemotherapy[3].

The lack of neuroprotective measures and the limited treatment choices frequently necessitate a reduction in the amount of life-saving chemotherapy or even an early termination of the treatment, which has an impact on the Therapeutic efficacy and the patient's ability to survive[4]. (CIPN) can occur in a variety of ways, with the overall dosage and type of medication used having a major impact. In general, between around 60 % to 80% of patients documented having CIPN symptoms in the month following the end of neurotoxic chemotherapy[1]. CIPN is mainly characterized by sensory axonal peripheral neuropathy[5]. This condition often manifests in a pattern resembling a stocking and glove. The distribution of the condition primarily affects longer axons, with the longer axons being impacted[6].

Patients with this condition primarily experience abnormal sensory perception, which can lead to balance issues and unstable walking in addition to sensations including a lack of sensation, heat, tingling, or pain in the extremities[7]. While the symptoms may eventually go away, many individuals often have them for the rest of their lives[8]. It was

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believed until a few years ago that CIPN seldom resulted in substantial restrictions on individuals impacted[9].

Unfortunately, neuropathy has the potential to have this negatively impacts the patient's general well-being and standards of life as well as quality of their life[10]. CIPN has been associated with several adverse consequences, including fatigue, psychological distress, and a reduction in physical independence, according to research[11,12]. CIPN is associated with dramatically higher health care costs (an additional $18,000 per patient) and increased utilization of healthcare services compared to patients without CIPN[13]. It is also possible that it will have an impact on how well patients are able to work[14].

According to the recommendations for clinical practice that were recently issued by the American Society of Clinical Oncology (ASCO), there are no therapeutic Options that are strongly recommended for the purpose of avoiding or dealing with chemotherapy-induced peripheral neuropathy (CIPN) that has already occurred[15].

The only suggested method of reducing neurotoxicity is still dose reduction because there are few neuroprotective and therapeutic options. As a result, clinical and survival outcomes may be impacted by the tolerance of an effective anti-cancer medication being decreased impacting clinical and survival outcomes. Given that neurotoxic therapies for malignancies sometimes include Considering the rising rates of survival, many cancer survivors are probably going to long-term results of CIPN. Better understanding the pathophysiological pathway of the disease and mechanism of actions of medications will give us better insights in treatment and whether using combinations in CIPN would be effective or not. In this review we will explore a more comprehensive of drugs that may provide us with valuable insights into the effectiveness of employing combinations in CIPN.

Clinical presentation of CIPN

Patients with (CIPN) commonly experience sensory problems that manifest in a stocking-and-glove pattern affecting both hands and feet. Symptoms consist of abnormal sensations, heightened sensitivity to physical stimuli, numbness, and persistent discomfort that can significantly hinder everyday tasks[5].

These symptoms are present and affecting mainly small fibers have a substantial influence on patients' quality of life (Figure1). Patients experience challenges such as difficulty in grasping objects and performing tasks that require fine finger movement due to numbness. They also struggle with tasks like removing items from the fridge and enduring cold weather due to hypersensitivity. Additionally, they may face issues with balance and walking due to hypersensitivity and numbness in the feet. Patient's experience impacts on emotional and social functions, including feelings of loneliness, loss of independence, changes in social and familial interactions, and difficulty performing specific work duties. CIPN can manifest at any point throughout treatment, even after stopping therapy, signs and symptoms might continue for a number of months or years following chemotherapy it is a phenomenon referred to as 'coasting'[18] .

The progression of (CIPN) varies depending on the kind of chemotherapy and the length of treatment. CIPN is usually dose-dependent, with

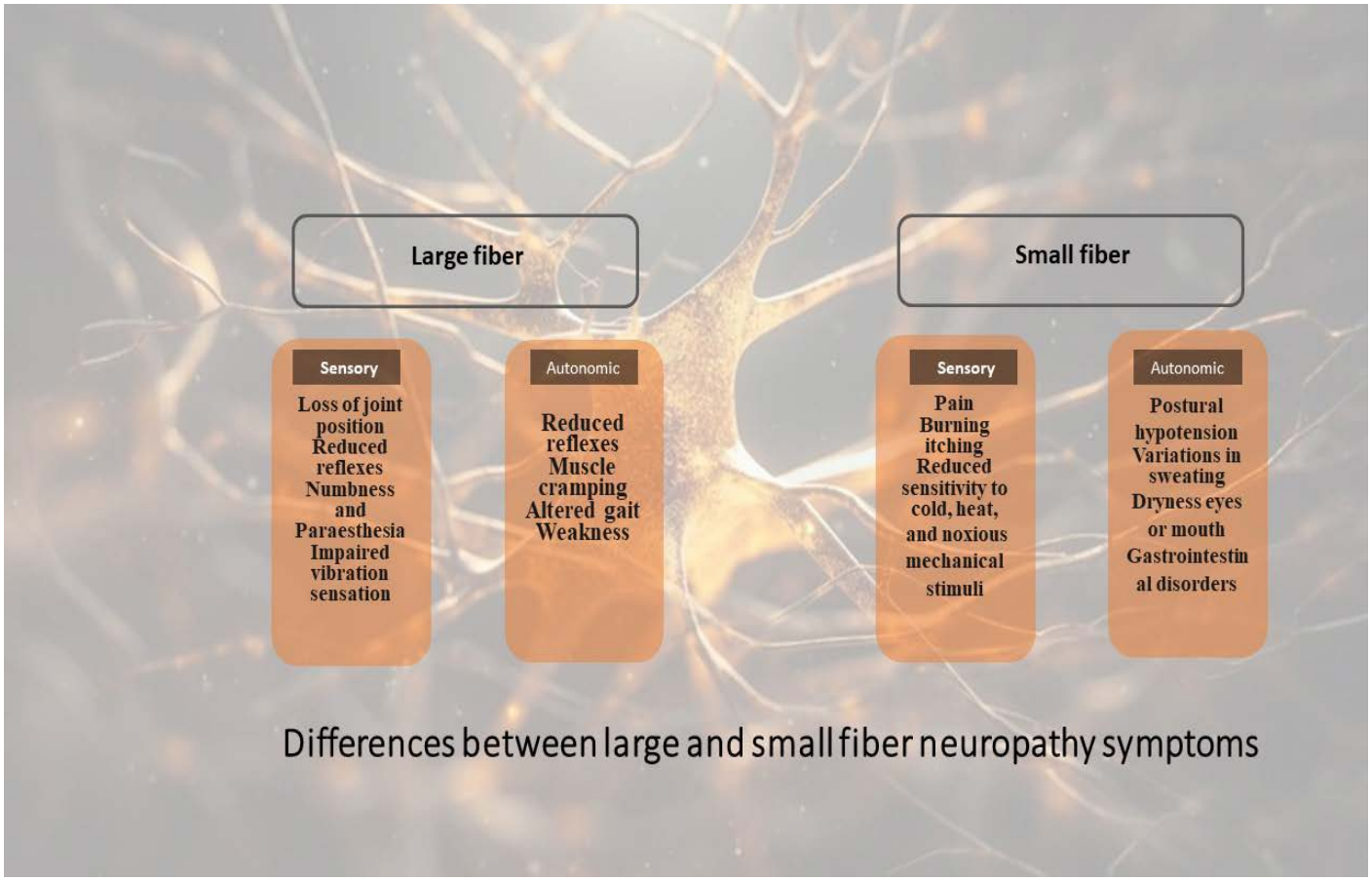

Figure 1. Large- and small-fiber manifestations of chemotherapy-induced peripheral neuropathy. The figure differentiates large-fiber involvement, which may impair vibration sense, proprioception, gait, and balance, from small-fiber involvement, which may present with burning pain, allodynia, thermal hypersensitivity, and dysesthesia.

symptoms emerging after the accumulation of chemotherapy doses, typically during the 3rd or 4th cycle[19]. A recent systematic review and meta-analysis analyzed data from 31 studies involving over 4,000 patients who were treated with various chemotherapy drugs to determine the average prevalence of chemotherapy-induced peripheral neuropathy (CIPN)[1]. The authors noted a significant level of variability among trials, which was attributed to factors such as the timing and technique of assessment, dosage administered, and kind of chemotherapy in which sixty percent within one month of abandoning chemotherapy and thirty percent within six months or beyond[20].

Pathophysiology of CIPN

CIPN is best interpreted as a convergent neurotoxicity syndrome rather than a single pathological entity. Neurotoxic anticancer agents differ in their dominant targets, but most ultimately produce distal sensory axonal injury, dorsal-root-ganglion vulnerability, abnormal excitability, and impaired communication between the peripheral and central nervous systems. Organizing the mechanisms into clinically interpretable pathways improves the link between pathogenesis, symptom phenotype, and therapeutic rationale (Table 1 and Figure 2).

Oxidative stress and DNA injury: Platinum compounds and several other neurotoxic agents increase reactive oxygen species and may produce DNA injury, particularly in dorsal-root-ganglion neurons, which are relatively vulnerable because of their exposure outside the conventional blood-nerve barrier. Oxidative stress contributes to nociceptor sensitization, axonal degeneration, and persistent sensory symptoms.

Mitochondrial dysfunction: Mitochondrial swelling, impaired adenosine-triphosphate generation, and altered calcium handling have been implicated in taxane-, platinum-, and bortezomib-associated neurotoxicity. Energy failure is clinically relevant because long

Table 1. Mechanistic pathways in chemotherapy-induced peripheral neuropathy and therapeutic relevance.

Mechanistic pathway	Dominant biological process	Commonly implicated agents	Clinical/therapeutic relevance
Oxidative stress / DNA injury	Reactive oxygen species, DNA adducts, dorsal-root-ganglion neuronal injury	Platinum agents; taxanes; bortezomib	Supports antioxidant and neuroprotective research; explains persistent sensory injury
Mitochondrial dysfunction	ATP depletion, calcium dysregulation, mitochondrial swelling	Taxanes; platinum agents; bortezomib	Contributes to axonal energy failure and chronic neuropathic symptoms
Ion-channel alterations	Voltage-gated sodium-channel remodeling and neuronal hyperexcitability	Oxaliplatin, especially acute toxicity	Explains cold-triggered paresthesia and early dysesthesia
Neuroinflammation	Cytokine signaling, macrophage/glial activation, neuroimmune amplification	Taxanes; platinum agents; bortezomib	Potential target for mechanism-directed analgesic or anti-inflammatory strategies
Axonal transport disruption	Microtubule stabilization or depolymerization with impaired cargo transport	Taxanes; vinca alkaloids; bortezomib	Explains length-dependent stocking-and-glove axonopathy
Schwann-cell injury	Impaired myelin support, repair signaling, and Schwann-cell inflammatory mediators	Taxanes; platinum agents; bortezomib	Potential target for nerve repair and persistent CIPN prevention strategies

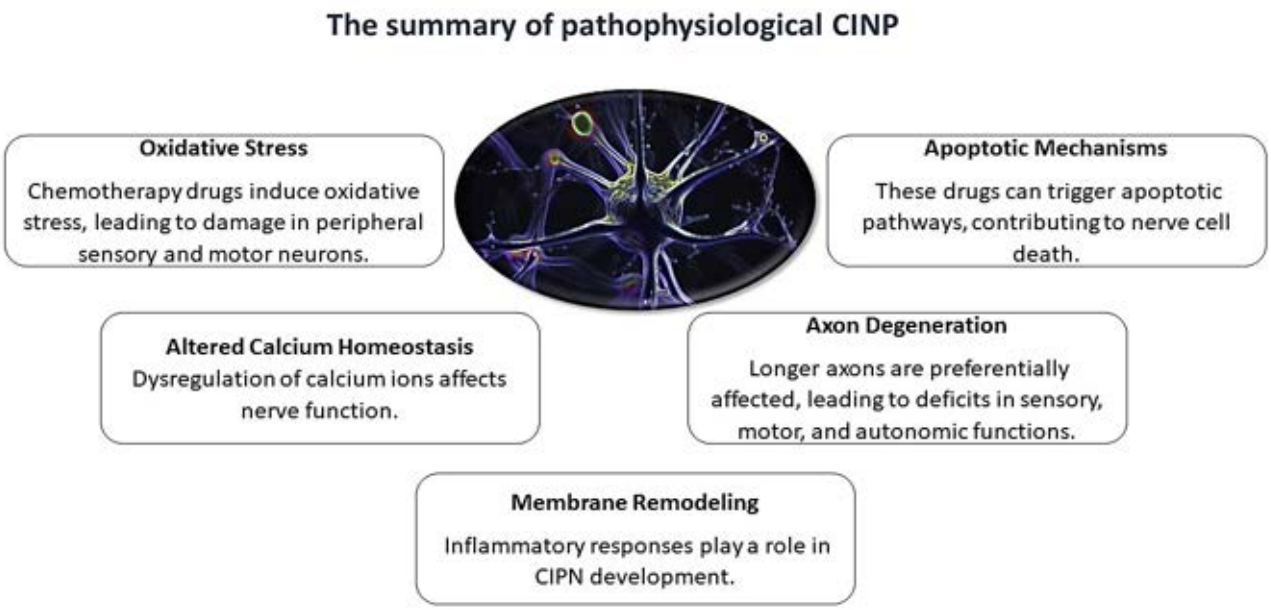

Figure 2. Mechanistic pathways implicated in chemotherapy-induced peripheral neuropathy. The diagram summarizes converging pathways including oxidative stress, mitochondrial injury, ion-channel remodeling, neuroinflammation, axonal transport disruption, and Schwann-cell/myelin injury.

peripheral axons require high metabolic support for axonal transport, membrane repolarization, and regeneration.

Ion-channel alterations: Oxaliplatin is strongly associated with acute cold-triggered paresthesia and dysesthesia through altered voltage-gated sodium-channel function and neuronal hyperexcitability. Ion-channel remodeling may help explain the rapid onset of acute symptoms that can occur before structural axonal loss is clinically evident.

Neuroinflammation: Neuroimmune activation, cytokine signaling, macrophage infiltration of dorsal-root-ganglia, and glial signaling may amplify peripheral and central sensitization. These inflammatory mechanisms support why pain intensity may persist even when electrophysiological abnormalities are modest.

Axonal transport disruption: Taxanes stabilize microtubules, whereas vinca alkaloids inhibit microtubule polymerization. Both mechanisms disrupt axonal transport of organelles, proteins, and trophic factors, causing length-dependent axonal degeneration and the characteristic stocking-and-glove distribution of CIPN symptoms.

Schwann-cell injury and myelin support: Schwann cells maintain peripheral nerve integrity, myelination, and repair. Schwann-cell injury, altered myelin support, and Schwann-cell-derived inflammatory mediators such as galectin-3 may contribute to persistent symptoms and represent potential future therapeutic targets.

Patients who experience chemotherapy-induced peripheral neuropathy (CIPN) are advised to take certain precautions at home, such as utilizing handrails and taking steps to prevent burns. They are also informed about the possibility of symptoms becoming permanent. However, it is noted that the available treatment options for CIPN are still considered to be limited[29]. In addition, patients may report experiencing more severe symptoms than what physicians determine based on accepted rating systems for neuropathy grades[29-31] .

Measuring neurotoxicity in CIPN

The measurement of (CIPN) continues to be a difficulty, as there is no agreement on the most effective clinical procedures. At present, there is no a generally recognized approach to assessing and diagnosing peripheral neuropathy brought on by chemotherapy (CIPN), as accurately measuring its severity has proven to be extremely challenging[5]. This continued constraint hinders progress in this field of research. Although there is no agreement on diagnostic standards and evaluation methods[32], several instruments have been created to aid in the measurement of nerve function and the quantification of damage in clinical settings. In most cases, assessment procedures can be categorized into objective and subjective methods[33].

Physician grading scales

Furthermore, extensive clinical trials on a broad scale have been conducted by Salgado et al. . Nevertheless, the NCI-CTCAE, despite its widespread usage, if compared to other negative events, (CIPN) is especially susceptible to the shortcomings of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), primarily because it lacks clear benchmarks and consistent grading for assessing the severity of CIPN. Despite the potential improvement in dependability through clinician training, there is still only a moderate level of agreement among different observers. Additionally, there are considerable differences in the reports of patients and clinicians. The extensive utilization of the NCI-CTCAE poses a constraint on the research sector because it is insufficient as a dependable and responsive technique for assessing CIPN (Table 2).

Patient-reported outcome measures: clinical relevance and integration
Patient-reported outcome measures (PROMs) should be retained in the manuscript, but their role should be narrowed to their clinical and therapeutic relevance. In CIPN, PROMs capture symptoms that are frequently underestimated by clinician grading, including pain, numbness, tingling, cold sensitivity, functional interference, sleep disruption, and quality-of-life impairment.

For treatment-focused CIPN studies, disease-specific tools such as the EORTC QLQ-CIPN20 and FACT/GOG-NTx are most useful for characterizing sensory, motor, and functional symptom burden. Pain-specific instruments such as the Brief Pain Inventory-Short Form (BPI-SF) are complementary when painful CIPN is the target outcome, because BPI-SF distinguishes pain severity from pain-related interference and uses patient-completed 0-10 ratings across clinically meaningful domains.

In line with SPIRIT-PRO principles, studies using PROMs should prespecify the PRO rationale, target domains, assessment time points, instrument selection, scoring approach, handling of missing items or missing assessments, and whether patient responses are monitored to inform clinical care. This is particularly important in CIPN trials because repeated assessments across multiple domains can increase multiplicity risk and selective reporting if the primary PRO domain and time point are not defined a priori.

Therefore, PROMs should not be presented as a lengthy standalone methodological subsection. They should be integrated into the therapeutic interpretation: whether an intervention reduces pain, improves sensory symptoms, preserves function, improves quality of life, or merely changes a numerical score without clear clinical relevance.

Pharmacological treatment of CIPN

A structured literature search was conducted to identify clinical studies evaluating pharmacological treatment strategies for established CIPN. PubMed/MEDLINE, EMBASE, and Cochrane were searched from database inception to January 30, 2024. The search combined CIPN terms with pharmacological treatment terms, including: ("chemotherapy-induced peripheral neuropathy" OR "chemotherapy induced peripheral neuropathy" OR CIPN OR "chemotherapy-induced neurotoxicity") AND (duloxetine OR venlafaxine OR pregabalin OR gabapentin OR amitriptyline OR nortriptyline OR lamotrigine OR opioid* OR ketamine OR baclofen OR "topical treatment" OR pharmacologic* OR treatment OR therapy) AND (clinical trial OR randomized OR randomised OR placebo OR prospective OR observational OR case report) (Figure 3).

Table 2. NCI-CTCAE grading framework for peripheral sensory neuropathy. The table should be interpreted as a clinician-reported toxicity grade and should be complemented by patient-reported outcome measures because clinician grading may underestimate symptom burden and functional impact.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	Asymptomatic	neuropathy Moderate, limiting activity daily life	symptoms; limiting self-care ADL	symptoms; Severe Life-threatening An immediate intervention is necessary.	Not applicable

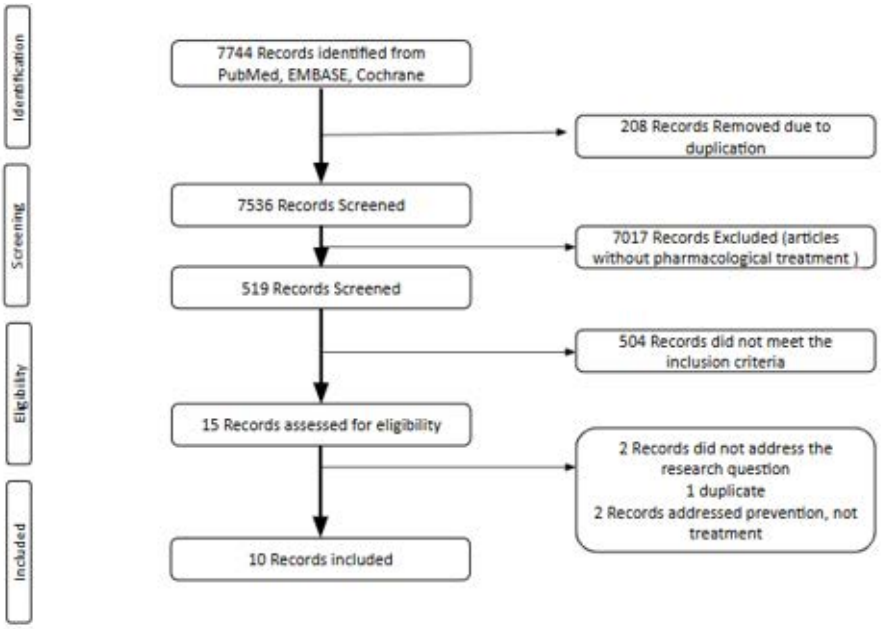

Figure 1. Flowchart of the selection process.

Figure 3. PRISMA flow diagram of the study selection process. Records were identified from PubMed/MEDLINE, EMBASE, and Cochrane, deduplicated, screened, assessed for eligibility, and narrowed to 10 included pharmacological-treatment studies.

Eligible studies included human participants with established CIPN after neurotoxic anticancer therapy and reported at least one clinical outcome related to neuropathic pain, neuropathy severity, sensory symptoms, functional impairment, quality of life, or tolerability. Prevention-only studies, preclinical studies, non-pharmacological interventions alone, reviews/editorials, and studies in which CIPN outcomes could not be separated from other neuropathic pain conditions were excluded. Two reviewers screened titles/abstracts and full texts, with disagreements resolved by senior review. Ten studies met the final eligibility criteria[34-55].

Study quality was interpreted according to design, using randomized-trial risk-of-bias domains for controlled trials and critical appraisal principles for non-randomized or case-based evidence. Owing to heterogeneity in interventions, comparators, follow-up duration, dose intensity, and outcome measures, the evidence was synthesized narratively rather than pooled quantitatively.

DULOXETINE

Duloxetine's effectiveness in alleviating CIPN symptoms was examined in many of randomised controlled trials conducted by Smith et al.[56], Hirayama et al.[57], Avan et al.[58], Farshchian et al. , and Salehifar et al.[59]. Duloxetine was successful in treating chemotherapy-induced peripheral neuropathy in all five explanations. The total of these investigations was conducted head-to-head trials comparing duloxetine with pregabalin[58.59] , VB12[57], and Venlafaxine [60].

Smith et al.[51] were the first to demonstrate the effectiveness of duloxetine in treating CIPN. Duloxetine alleviated discomfort from CIPN when compared to the placebo group. Duloxetine proved more beneficial for) produced by platinum compounds compared to taxanes drugs. Phase III research conducted by Smith et al. in 2013 demonstrated that patients who were given duloxetine as opposed to a placebo saw a significant increase in their ability to control their pain after only five weeks[51]. Among the selective serotonin reuptake inhibitors (SNRIs), it appears that this is not an altogether and not typical occurrence. Research evaluating duloxetine and venlafaxine revealed that duloxetine was greater in effectiveness in lowering peripheral neuropathy and neuropathic pain evaluations after twenty-eight days of administration in patients with (CIPN)[60]. In contrast, venlafaxine was found to have limited benefits in this regard. It was suggested that starting with the most cost-effective option would be a good approach before considering a pricier alternative on a case-by-case basis[60]. The real-world results demonstrated a noteworthy reduction in pain for those taking venlafaxine when weighed against those receiving a placebo. This outcome is quite intriguing. However, it is important to note that the research study analyzed doses of venlafaxine and duloxetine at 37.5 mg and 30 milligrams, respectively. Based on previous research, like the study conducted by Smith et al., it has been determined that the most effective dosage of duloxetine for treating CIPN is sixty mg. Therefore, instead of just comparing the effectiveness of the two agents, it is advised to conduct additional trials to assess the efficacy of each of the ingredients at different the recommended dosage for therapeutic applications. Ellen M. Lavoie Smith is currently overseeing a trial that is being carried out by the Alliance for Clinical Trials in Oncology. The objective of this investigation is to ascertain the most effective dosage of duloxetine for avoiding the development of (CIPN) in patients with colorectal cancer[60-62]. The use of duloxetine led to a notable improvement in peripheral neuropathy caused by oxaliplatin, while still maintaining a manageable level of side effects. In addition, Duloxetine also showed improvement in depression and pain scores[63].

In general, the adverse effects of duloxetine are not severe. The most common adverse effects include mild nausea, low appetite, constipation, drowsiness or sleeplessness, and sexual side effects. There is no requirement for laboratory monitoring of this medication. It is particularly important to exercise caution when prescribing SSRIs and SNRIs to patients who are taking tamoxifen since these drugs have the potential to reduce the amount of tamoxifen that is metabolized by the liver into its active metabolite. Symptoms associated with sensory along with motor neuropathy in the individuals with chemotherapy-induced peripheral neuropathy (CIPN). In addition, venlafaxine has demonstrated improvements in hypertension. The occurrence of hypertension was 51.9% in the group receiving venlafaxine, 86.5% in the group receiving duloxetine, and 81.4% in the group receiving

placebo at week 4. There was a significant difference between the groups (p less than 0.001). Moreover, venlafaxine decreased the occurrence of hypertension significantly (p less than 0.05). Venlafaxine may be advantageous for patients with CIPN that have another comorbidity of hypertension. Duloxetine generally showed greater effectiveness as opposed to venlafaxine.

SODIUM CHANNEL BLOCKERS

Lamotrigine: A 10-week double-blinded randomised controlled trial (RCT) was undertaken in the United States in 2008 to explore the effects of lamotrigine. The study included a total of 125 participants[67-71]. Lamotrigine was used to treat (CIPN) symptoms that lasted for at least one month these symptoms were likely a result of the medications prescribed. The dosage of lamotrigine was gradually increased from 25 mg to 150 mg. However, the use of lamotrigine did not result in any positive changes in discomfort, depressive disorders, or quality of life for patients with CIPN, suggesting that it is not an effective treatment option. There was no notable difference in negative events between the groups. The most common side effects observed were ataxia, rash, constipation and other joint pain, digestive problems. Discomfort, pruritus, drowsiness and headache that they have.

GABAPENTINOIDS: GABAPENTIN AND PREGABALIN

Tricyclic Antidepressants (TCA): Antidepressants that belong to the tricyclic class include amitriptyline, desipramine, and nortriptyline. The use of TCA class is not indicated for the management of CIPN. Furthermore, two short trials that examined amitriptyline and nortriptyline and were controlled by a placebo did not demonstrate any advantage of these medicines in the treatment of patients who were experiencing symptoms of CIPN[72-74]. Prescription of these medications regularly is not suggested because of the extensive list of adverse effects and the possibility of taking an excessive amount of them[75,76].

Opioids

Opioid analgesics include: Opioids are not advised for the management of (CIPN) because they carry the danger of unneeded side effects, the possibility of Substance dependence, and escalating expenses for the health care sector[77-80] . However, opioids are frequently required by medical professionals to manage active pain associated with cancer. However, the European Society for Medical Oncology (ESMO) does emphasize that opioids may be a choice for CIPN as a salvage option, although there is no particular opioid that is superior to another[81].

Topical treatments

Several studies have investigated various topical therapies, either alone or in combination, for the management of chemotherapy-induced peripheral neuropathy (CIPN). Nevertheless, the majority of these therapy regimens have yielded just a limited impact, if any at all. Researchers administered a topical combination of amitriptyline and ketamine to patients suffering from numbness, tingling, and/or pain related to CIPN. The treatment was given three times daily for a

Table 3. Pharmacological therapies for established CIPN: mechanism, evidence, guideline position, and clinical role.

Therapy/class	Mechanistic rationale	Clinical evidence signal	Guideline/clinical position	Practical role
Duloxetine	SNRI; descending inhibitory pain modulation; analgesic effect in painful neuropathy	Strongest pharmacological evidence; benefit is statistically significant but clinically modest in RCTs	Only pharmacological agent with guideline-supported evidence for painful established CIPN	Preferred first-line option for painful CIPN if no contraindication
Duloxetine + amitriptyline	SNRI plus TCA mechanisms; serotonin/norepinephrine modulation with additional receptor and sodium-channel effects	Recent RCT by Salah et al. showed within-group improvement but no clear between-group superiority after multiplicity adjustment[90]	Not a routine standard; individualized option pending larger multicenter confirmation	Consider only for inadequate response and acceptable anticholinergic/cardiac risk profile
Duloxetine + gabapentin	SNRI plus alpha-2-delta calcium-channel modulation	Recent RCT showed within-group improvement but no superiority over duloxetine monotherapy[90]	Individualized option; evidence insufficient for routine add-on use	Consider if mixed neuropathic pain phenotype, insomnia, or duloxetine partial response; adjust for renal function
Gabapentin / pregabalin	Alpha-2-delta calcium-channel modulation; reduced excitatory neurotransmitter release	Mixed or weak CIPN-specific evidence; gabapentin phase III evidence is not clearly positive	Not equivalent to duloxetine for painful CIPN	Use selectively when duloxetine is unsuitable or for comorbid neuropathic pain indications
Tricyclic antidepressants	Monoamine reuptake inhibition; sodium-channel and receptor effects	Limited and generally inconclusive/negative CIPN evidence	Not recommended for routine CIPN treatment	Avoid in frail or older patients; consider only selected cases with careful monitoring
Lamotrigine	Sodium-channel blockade and reduced glutamate release	Negative randomized evidence in CIPN	Not recommended for routine CIPN management	No routine role
Topical amitriptyline/ ketamine/baclofen combinations	Local NMDA, sodium-channel, and GABAergic mechanisms with lower systemic exposure	Small studies with limited or modest benefit and heterogeneous formulations	Adjunctive/investigational rather than standard therapy	May be considered when systemic toxicity limits oral options, if available and monitored
Opioids	Mu-opioid receptor analgesia; not disease-modifying	May relieve severe cancer pain but not CIPN-specific evidence	Salvage option only; no preferred opioid for CIPN	Reserve for severe refractory pain or concurrent cancer pain with opioid stewardship

duration of three weeks. However, there was no notable improvement in symptoms when compared to a placebo group[82]. In a separate research with comparable conditions, a combination of amitriptyline, ketamine, and baclofen was topically administered to the specific region linked to pain twice a day for a duration of four weeks. Nevertheless, despite the use of baclofen, patients only saw a marginal amelioration of symptoms[83].

Comparative effectiveness and evidence interpretation

The evidence hierarchy should be presented explicitly. Duloxetine remains the best-supported pharmacological treatment for painful established CIPN, but the expected benefit is modest and not all patients tolerate or respond to treatment. Evidence for gabapentinoids, tricyclic antidepressants, lamotrigine, opioids, and topical combinations is weaker, inconsistent, or limited by small samples, short follow-up, heterogeneous outcome measures, and incomplete safety reporting. These agents should therefore not be described as equivalent alternatives to duloxetine.

Combination therapy is mechanistically plausible because CIPN involves multiple pathways, including mitochondrial injury, ion-channel remodeling, neuroinflammation, and axonal transport disruption. However, clinical evidence remains insufficient to establish superiority over optimized duloxetine monotherapy. The recent randomized trial by Salah et al. compared duloxetine monotherapy with duloxetine plus amitriptyline or gabapentin in 160 patients with CIPN; all groups improved, but between-group differences were not statistically significant at Week 4 or Week 8 after adjustment, and responder rates were comparable by Week 8[90-94]. This supports a cautious conclusion: combination regimens may be reserved for individualized use in patients with inadequate response or specific symptom profiles, while larger multicenter comparative trials are needed before routine adoption (Table 3).

Future directions

Future CIPN research should move from drug-by-drug descriptive evaluation toward mechanism-directed, phenotype-informed trials. Patients should be stratified by neurotoxic agent, symptom phenotype (painful versus predominantly numbness/sensory loss), baseline neuropathy risk, diabetes or pre-existing neuropathy, cumulative chemotherapy exposure, and objective neuropathy findings.

Trial design should prioritize adequately powered, multicenter, head-to-head comparative studies using duloxetine as the active evidence-based comparator when painful CIPN is studied. Add-on therapy should be tested against optimized monotherapy with predefined escalation rules, adverse-effect stopping criteria, and deprescribing plans for non-response.

Outcome assessment should combine PROMs and objective measures. At minimum, trials should prespecify a primary pain or CIPN-specific PROM domain, principal time point, clinically meaningful response threshold, missing-data approach, and safety endpoints. BPI-SF is appropriate when pain is the therapeutic target, whereas EORTC QLQ-CIPN20 or FACT/GOG-NTx better capture sensory, motor, and functional symptom burden.

Safety, tolerability, falls, sedation, anticholinergic effects, cognitive impairment, renal-dose adjustment, drug-drug interactions, opioid exposure, treatment persistence, and cost-effectiveness should be reported systematically. This is particularly important in oncology populations where polypharmacy, frailty, comorbidity, and concurrent anticancer therapy may alter the risk-benefit balance.

CONCLUSIONS

CIPN remains a clinically important, dose-limiting, and quality-of-life-limiting complication of neurotoxic anticancer therapy. Its pathophysiology is multifactorial, involving oxidative injury, mitochondrial dysfunction, ion-channel remodeling, neuroinflammation, axonal transport disruption, and Schwann-cell/myelin injury. This biological complexity explains why single-agent pharmacotherapy often provides incomplete relief and why prevention and reversal remain unmet needs.

The current pharmacological evidence supports duloxetine as the most evidence-based option for painful established CIPN, although the magnitude of benefit is modest and tolerability may limit use in routine practice. Evidence for gabapentinoids, tricyclic antidepressants, lamotrigine, opioids, topical agents, and combination regimens remains weaker or inconsistent. The available randomized evidence, including the recent trial by Salah et al. [90], supports individualized add-on therapy only for selected patients rather than routine superiority of combination treatment.

Clinically, CIPN management should combine symptom phenotype assessment, patient-reported outcomes, functional evaluation, medication-safety review, and shared decision making. Future studies should prioritize adequately powered comparative trials, standardized PROMs, objective neuropathy measures, longer follow-up, robust safety reporting, and mechanism-based patient stratification. Until stronger evidence emerges, treatment decisions should emphasize realistic goals: pain reduction, preservation of function, minimization of toxicity, and avoidance of unnecessary long-term polypharmacy.

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