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IMPACT OF COGNITIVE-BEHAVIORAL THERAPY ON PAIN AND ASSOCIATED SYMPTOMS IN CANCER SURVIVORS WITH CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW OF DIFFERENTIAL EFFECTS ON PAIN, PSYCHOLOGICAL DISTRESS, AND QUALITY OF LIFE.

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Abstract
Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and debilitating adverse effect of neurotoxic agents, characterized by chronic pain, sensory disturbances, and significant psychological distress, for which effective treatments are limited. Cognitive-Behavioral Therapy (CBT) offers a non-pharmacological approach by targeting the central cognitive-affective mechanisms that modulate pain perception. This systematic review aimed to evaluate the efficacy of CBT compared to control conditions in reducing pain, improving sensory symptoms, functional ability, quality of life, and psychological distress in adult cancer survivors with CIPN. A systematic literature search was conducted following PRISMA guidelines across six electronic databases, resulting in the qualitative synthesis of four studies. The findings demonstrate that CBT consistently produces significant, clinically relevant reductions in neuropathic pain intensity and associated distress, though it has minimal effect on objective sensory deficits. Improvements in function and quality of life were observed as secondary benefits. Critically, the intervention format was a key moderating factor, with therapist-led protocols yielding broader improvements across psychological and quality-of-life domains compared to self-guided programs, which were primarily effective for pain reduction. The therapeutic mechanism was identified as top-down cognitive-affective regulation, involving reduced catastrophic thinking and improved perceived control. In conclusion, CBT is an effective intervention for managing the pain and distress of CIPN, with its benefits being most comprehensive when delivered through a structured, therapist-led format, supporting its integration as a core component of a multimodal management strategy.
Categories: Medicine and Pharmacology, Neuroscience, Oncology, Psychology, Public Health and Epidemiology.
Keywords: Cognitive-Behavioral Therapy, Chemotherapy-Induced Peripheral Neuropathy, CIPN, Neuropathic Pain, Cancer Survivors, Pain Management, Psychological Distress, Quality of Life, Non-Pharmacological Intervention.

INTRODUCTION AND BACKGROUND

Chemotherapy often leads to acute and chronic pain, including neuropathic pain syndromes such as chemotherapy-induced peripheral neuropathy (CIPN), which can persist for years after treatment and substantially burden cancer survivors' daily functioning. Persistent pain is strongly associated with higher levels of psychological distress, including anxiety, depression, and fear about disease progression, and these emotional

reactions can in turn heighten pain perception through bidirectional mind–body pathways(Juliana Martins Izzo et al., 2019; Rahman et al., 2025).

CIPN is affecting approximately 68% of patients receiving neurotoxic chemotherapy and often presenting with numbness, tingling, and pain in a characteristic "stocking-glove" distribution (Kwekkeboom et al., 2018a; Knoerl et al., 2018). In a substantial number of cases, these symptoms become chronic, with up to 40% of survivors experiencing persistent pain that can last for months or even years after treatment cessation, significantly interfering with fine-motor control, gait, and overall independence (Kwekkeboom et al., 2018; Feldman et al., 2019). This persistent neuropathic pain originates from a complex pathophysiology involving neurotoxic injury from agents like platinum compounds and taxanes, which disrupt axonal transport and mitochondrial integrity, leading to a "dying-back" axonopathy (Brewer et al., 2016; Lee et al., 2024).

Critically, the experience of chronic CIPN is not solely a peripheral phenomenon but is also maintained and amplified by central nervous system mechanisms, including central sensitization and maladaptive cortical plasticity, which amplify nociceptive signaling (Schreiber et al., 2015; D'Souza et al., 2025). Recent meta-analyses confirm that chronic painful CIPN affects 38–40% of survivors, establishing it as a complex neuro-sensory disorder involving both peripheral and central pathways (D'Souza et al., 2025).

Studies of patients undergoing or having completed chemotherapy consistently show that greater pain intensity correlates with worse health-related quality of life across physical, emotional, and social domains, limiting mobility, sleep, work, and social participation. Longitudinal research further indicates that distress and reduced quality of life can remain elevated for years in survivors with ongoing pain symptoms, underscoring the need for integrated approaches that address both physical and psychological consequences of chemotherapy(Bellali et al., 2020; Boekhoudt et al., 2025; Papadopoulou et al., 2022; Poço Gonçalves et al., 2020).

The clinical and psychological burden of CIPN is profound, extending beyond sensory impairment to generate significant psychological distress, with up to 30% of patients reporting persistent symptoms that interfere with daily function and are linked to increased anxiety and depression (Knoerl et al., 2018). This multifaceted suffering is compounded by the limited efficacy of pharmacological management, where duloxetine remains the only guideline-recommended agent, yet its use is often hampered by side effects and modest efficacy, leading to poor adherence (Nudelman et al., 2016; Wang et al., 2023). The heterogeneity in CIPN's clinical presentation, driven by differences in chemotherapeutic mechanisms and assessment tools, further complicates the development of universally effective treatments (Lee et al., 2024; D'Souza et al., 2025).

These collective challenges underscore the urgent need for safe, multimodal, non-pharmacological strategies that can address both the physical and emotional dimensions of CIPN (Antoni et al., 2001). It is within this context that Cognitive-Behavioral Therapy (CBT) presents a compelling mechanistic rationale, as it directly targets the central cognitive-emotional processes that maintain chronic pain.

The rationale for CBT in CIPN is grounded in its ability to target the maladaptive thoughts, hypervigilance, and low self-efficacy that reinforce central sensitization and prolong the perception of pain (Bean et al., 2020). By employing techniques such as cognitive reframing, stress regulation, and behavioral activation, CBT modulates the top-down processing of nociceptive signals. Neuroimaging evidence supports this, demonstrating that CBT can normalize hyperactivity in brain regions like the anterior cingulate and prefrontal cortices, which are critical for the affective and cognitive evaluation of pain ((Zeidan et al., 2011); Bean et al., 2020).

Consequently, a growing body of evidence has begun to demonstrate the promise of CBT for cancer survivors with CIPN, showing reductions in pain intensity, improved emotional regulation, and enhanced overall quality of life (Kwekkeboom et al., 2018; Jelvehzadeh et al., 2022). Narrative and meta-analytic reviews further consolidate these findings, emphasizing that CBT alleviates the overall symptom burden by modulating cognitive-affective networks involved in pain perception (Li et al., 2022; Lee et al., 2024). However, the existing evidence base remains limited by methodological inconsistencies and small sample sizes, necessitating a systematic evaluation to clarify the differential effects of CBT on the distinct domains of pain, psychological distress, and quality of life for this patient population (Abbas et al., 2022).

This systematic review aimed to critically evaluate and synthesize the existing evidence on the efficacy of CBT in managing CIPN in cancer survivors, with a specific focus on its differential impact on pain perception, psychological distress, and quality of life.

METHODOLOGY

Design

The review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive and transparent reporting process (Page et al., 2021), and the study protocol was prospectively registered on PROSPERO (ID: CRD420251242820) to ensure methodological rigor and transparency. This review did not require review or approval by the ethics committee as it used previously published data.

Research Question

The primary research question, structured using the PICO framework, was: **How effective is CBT compared to control conditions in reducing pain, improving sensory symptoms, quality of life, and psychological distress in adult patients with CIPN?

Population (P): Adult patients (≥18 years) with a diagnosis of CIPN.

Intervention (I): Any form of CBT, including therapist-led, self-guided, or online formats, incorporating

techniques such as cognitive restructuring or relaxation.
Comparator (C): Control conditions, including usual care, wait-list, education, or attention-control interventions.
Outcomes (O):
Primary: Pain intensity (e.g., worst/average pain scores).
Secondary: Sensory symptoms (numbness, tingling), quality of life (physical, emotional, social domains), and psychological distress (anxiety, depression).

Search Strategy and Selection Criteria

The eligibility criteria were defined to include both observational and experimental studies published in English in peer-reviewed journals. Studies were excluded if CIPN was not specific to chemotherapy, or if they were conference abstracts, reviews, editorials, or case reports. A systematic literature search was executed across multiple electronic databases (EMBASE, Medline, Web of Science, Scopus and PubMed) from inception to [Insert Search Date]. The search strategy utilized a combination of keywords and Boolean operators related to three core concepts: (1) "cognitive behavioral therapy*" OR "CBT"; (2) "pain" OR "quality of life" OR "psychological distress"; and (3) "chemotherapy-induced peripheral neuropathy" OR "CIPN". Screening process was then undertaken by two independent reviewers. First, titles and abstracts were screened for relevance, followed by a full-text assessment of potentially eligible articles against the predefined inclusion and exclusion criteria. Any disagreements were resolved through consensus, and the reference lists of included studies were manually searched for additional relevant publications.

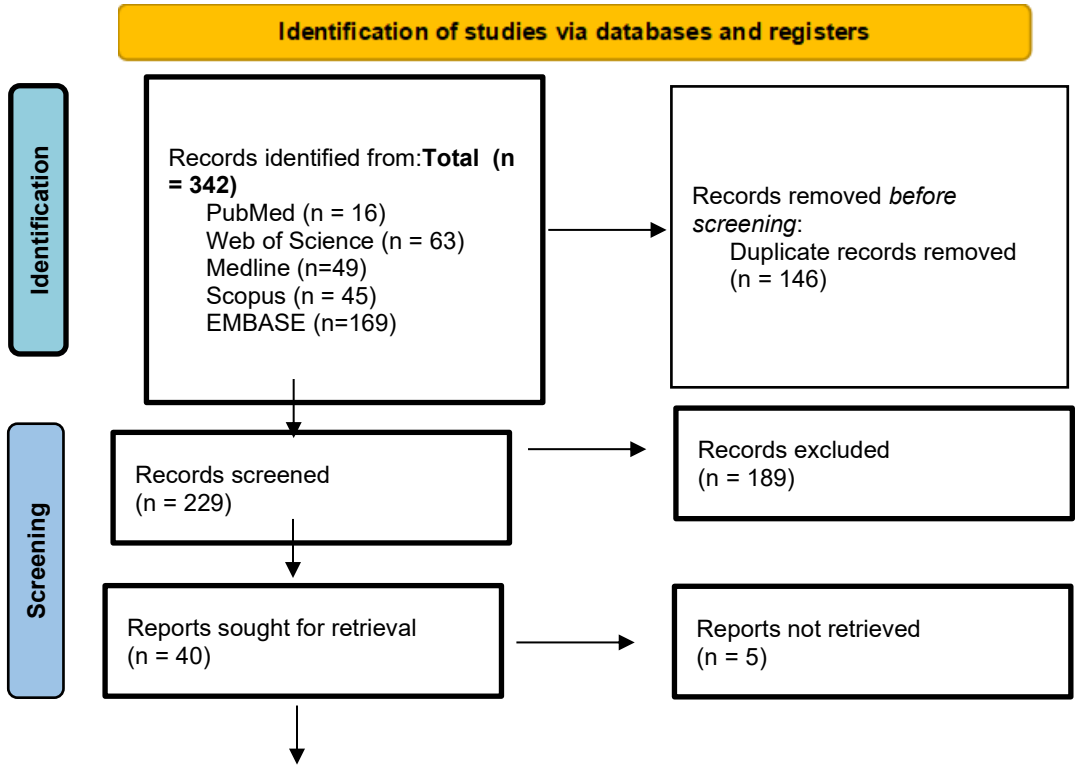
Data Extraction and Risk of Bias Assessment

Data from the final set of included studies were extracted independently by two reviewers into a standardized Excel spreadsheet. The extracted data included key study characteristics (e.g., author, design, participant demographics), details of the CBT and control interventions, and all relevant outcome measures and results pertaining to pain, sensory symptoms, function, quality of life, and psychological distress.The methodological quality of the included randomized trials was critically appraised using the Cochrane Risk of Bias tool (RoB 2)(Sterne et al., 2019). This tool was used to evaluate bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. This assessment was conducted to gauge the overall strength and validity of the synthesized evidence.

RESULTS

Search Results

The systematic literature search and selection process are detailed in the PRISMA flow diagram (Figure 1). Initial searches across six electronic databases yielded 342 records. After the removal of 146 duplicates, 196 records underwent title and abstract screening. Of these, 35 studies were deemed relevant for full-text review. Upon detailed assessment, 31 studies were excluded for not meeting the eligibility criteria, resulting in four studies that were included in the final qualitative synthesis.



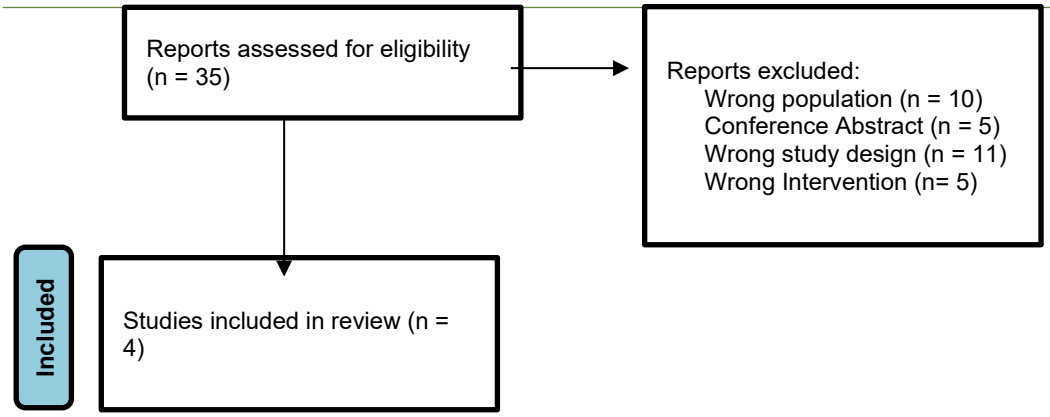


Figure 1: PRISMA flow diagram.PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Characteristics

The key characteristics of the four included studies are summarized in Table 1. The studies, published between 2018 and 2021, were conducted in the United States (n=3) and Iran (n=1). The total sample size across all studies was 334 participants, with individual study sizes ranging from 50 to 164. Most participants were female (76%), and the mean age of participants ranged from 46.3 to 61.15 years. All studies included patients with chronic, painful CIPN, and the interventions were delivered either via therapist-led sessions or self-guided online platforms over 6 to 8 weeks.

Table 1: Summary of Study Characteristics.

Study ID	Design	Participants	Intervention	Control
Kwekkeboom et al. (2018)	Randomized Controlled Trial	164 patients with metastatic/recurrent cancer	Daily imagery/relaxation (CBS)	Cancer education
Elyasi et al. (2021)	Pretest-Posttest Trial	50 breast cancer patients	8 therapist-led CBT sessions	No treatment
Knoerl, Barton, et al. (2018)	Wait-list Controlled Trial	60 patients with chronic painful CIPN	Self-guided online (PROSPECT)	Treatment as usual
Knoerl, Smith, et al. (2018)	Randomized Controlled Trial	60 patients with chronic painful CIPN	Self-guided online (PROSPECT)	Wait-list control

Quality Assessment

The methodological quality of the included studies was appraised using the Cochrane Risk of Bias (RoB 2) tool. Among the four studies, two (50%) were rated as having a low risk of bias, demonstrating robust methodology. The remaining two studies (50%) were judged to have some concerns, primarily due to issues in the randomization process and potential biases arising from missing outcome data (Figure 2).

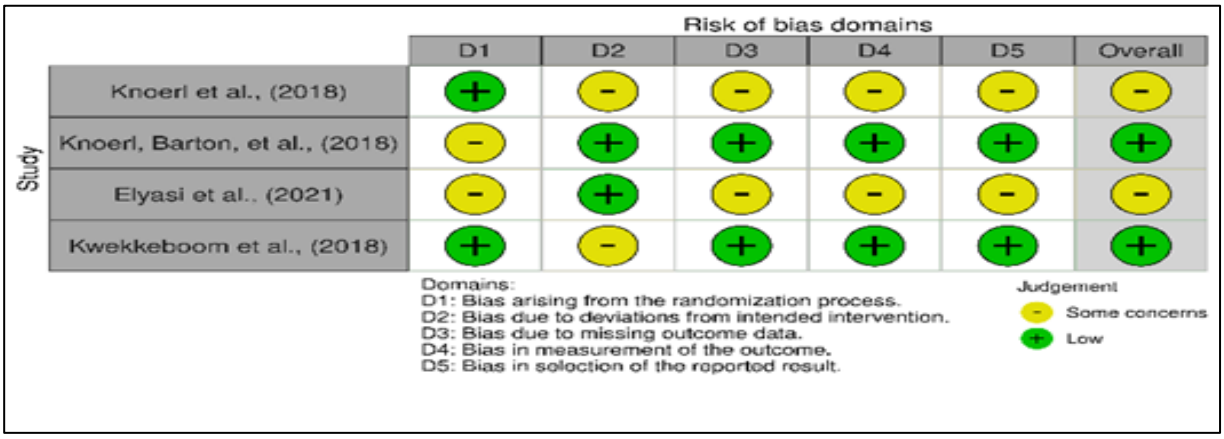


Figure 2: Risk of bias analysis of the included studies

Key Findings

The synthesized evidence from the four studies investigated the effects of CBT on pain intensity, sensory symptoms, functional ability, quality of life, and psychological distress in patients with CIPN. A summary of key findings by outcome domain is presented in Table 2.

A synthesis of the four included studies reveals a consistent pattern: CBT-based interventions demonstrate efficacy in reducing the subjective experience of cancer-related neuropathic pain, particularly its intensity and associated distress. However, the evidence does not support a direct effect on the underlying neuropathic sensory

deficits. The benefits on broader outcomes like function and quality of life appear to be secondary, mediated by improvements in pain and coping.

Table 2:Summary of Key Findings by Outcome Domain.

Outcome Domain	Overall Conclusion	Supporting Evidence
Pain Intensity & Distress	**Consistent, significant improvement.** Most robust finding across studies.	• Knoerl, Smith et al.: Significant reduction in worst pain ($p=0.046$). • Elyasi et al.: ~25% pain reduction. • Kwekkeboom et al.: Reduced pain distress ($p<0.05$).
Sensory Symptoms	**Minimal to no improvement.** CBT does not reverse peripheral nerve damage.	• Knoerl, Barton et al. & Knoerl, Smith et al.: No significant improvement in numbness/tingling ($p>0.3$).
Function & Quality of Life	**Modest, secondary improvement.** Gains are mediated by better coping.	• Knoerl, Smith et al.: Better daily activity performance. • Elyasi et al.: Improved physical function and body image. • Kwekkeboom et al.: Reduced symptom interference.
Psychological Distress	**Improvement dependent on intervention format.**	• **Therapist-led (Elyasi; Kwekkeboom):** Significant reductions in stress, anxiety, depression. • **Self-guided (Knoerl et al.):** Small or non-significant effects on mood.
Intervention Mechanism	**Top-down cognitive-affective regulation.**	• Effects are mediated by reduced stress, improved outcome expectancy, and enhanced perceived control (Kwekkeboom et al.).

Primary Outcome: Effects on Pain Intensity and Distress

All four studies consistently reported that CBT interventions led to significant reductions in neuropathic pain intensity and associated distress. Knoerl, Smith et al. (2018) found a statistically significant improvement in worst CIPN pain intensity compared to a wait-list control ($p = 0.046$), while Elyasi et al. (2021) observed an approximately 25% reduction in pain from baseline in their therapist-led CBT group. Kwekkeboom et al. (2018) specifically highlighted a significant reduction in pain-related distress ($p < 0.05$), underscoring CBT's role in modulating the affective component of pain. Overall, CBT was associated with a 10–25% reduction in pain metrics, primarily mediated through improved self-management and cognitive reframing (Sikorskii et al., 2006).

Sensory Symptoms

In contrast to its effects on pain, CBT demonstrated minimal to no impact on the objective sensory deficits characteristic of CIPN. Both PROSPECT trials (Knoerl, Barton et al., 2018; Knoerl, Smith et al., 2018) reported no significant improvement in non-painful symptoms such as numbness and tingling ($p > 0.3$). This confirms that CBT's therapeutic action is centered on the central processing and interpretation of sensory signals rather than the restoration of peripheral nerve function.

Secondary Outcomes: Effects on Function, Quality of Life, and Psychological Distress

Function and Quality of Life

Functional and quality-of-life outcomes showed modest, secondary improvements. Participants in the PROSPECT study demonstrated better daily activity performance, and both Elyasi et al. (2021) and Kwekkeboom et al. (2018) reported reduced interference of symptoms with daily living and enhanced role performance ($p < 0.05$). Gains in quality of life were most pronounced in therapist-led interventions, which showed significant enhancements in physical functioning, body image, and future perspective (Elyasi et al., 2021). These functional improvements appear to be driven by enhanced coping and self-efficacy rather than direct physiological change.

Psychological Distress

The effects on psychological outcomes were influenced by the intervention format. Therapist-led CBT consistently produced significant reductions in stress, anxiety, and depression (Elyasi et al., 2021; Kwekkeboom et al., 2018). In contrast, self-guided programs like PROSPECT yielded smaller or non-significant effects on mood, indicating that structured therapist guidance is crucial for achieving robust emotional benefits. Mediation analyses supported that decreased stress and improved outcome expectancy were key mechanisms driving symptom relief (Kwekkeboom et al., 2018).

Exploration of Intervention Characteristics and Mechanisms

The format and content of the CBT interventions were identified as critical factors influencing their effectiveness. The key characteristics and their relationship to outcomes are summarized in the table below.

Table 3: Influence of Intervention Characteristics on Outcomes.

Characteristic	Description & Example	Impact on Outcomes	Proposed Mechanism

Therapist-Led, Multi-Session CBT	• Structured, therapist-guided sessions (Elyasi et al., 2021). • Includes cognitive restructuring and emotional processing.	Broadest efficacy: Significant improvements in pain, psychological distress (anxiety, depression), and multiple QoL domains (e.g., physical function, body image).	The therapeutic relationship and guided cognitive work facilitate deeper cognitive-affective change and emotional regulation.
Self-Guided / Symptom-Focused Tools	• Self-administered, online or audio-based (Knoerl et al., 2018; Kwekkeboom et al., 2018). • Focuses on behavioral exercises like relaxation and distraction.	Targeted efficacy: Effective for primary targets of pain intensity and distress but shows limited to no effect on general mood (anxiety, depression) or sensory function.	Provides skills for symptom management but lacks the depth to significantly reshape underlying cognitive schemas or provide therapeutic support.
Cognitive-Affective Mechanism	• The consistent, overarching process identified across all effective interventions.	Drives improvement across domains: Mediates changes in pain, distress, and function.	Works by modifying the patient's relationship to symptoms through increased perceived control, reduced catastrophizing, and enhanced coping skills (Kwekkeboom et al., 2018).

DISCUSSION

This systematic review synthesized evidence from four studies examining the effects of cognitive-behavioral therapy (CBT) on pain, sensory symptoms, function, quality of life (QoL), and psychological distress in patients with chemotherapy-induced peripheral neuropathy (CIPN). Across 334 participants in these studies, the results consistently demonstrated that CBT significantly reduces pain intensity and pain-related distress, while effects on sensory symptoms, functional ability, and QoL were variable. These findings indicate that CBT primarily alleviates the affective and cognitive components of pain perception rather than directly reversing neuropathic deficits.The findings align with previous literature supporting CBT as an effective approach for chronic pain and psychological distress (Jordan Maccora et al., 2022; Hofmann et al., 2012). Techniques such as relaxation, distraction, and guided imagery have been shown to attenuate both pain intensity and the emotional burden of cancer pain (Anderson et al., 2006; Kwekkeboom et al., 2003). The moderate effectiveness observed in CIPN mirrors this evidence, reinforcing the role of cognitive-affective modulation in pain management.

Variability in outcomes among the reviewed studies likely reflects differences in intervention design, delivery format, and participant population.(Hughes et al., 2020) Self-guided programs such as PROSPECT (Knoerl, Smith et al., 2018) demonstrated modest but significant reductions in pain. In contrast, therapist-led CBT (Elyasi et al., 2021) achieved broader benefits, including improved QoL and decreased psychological distress. This suggests that therapist guidance and structured cognitive restructuring may enhance engagement and therapeutic depth. These findings are consistent with prior findings in cancer-related fatigue and mood disorders ((Malouff et al., 2008); Kangas et al., 2008).The inconsistency in outcomes for sensation and function highlights a critical mechanistic insight: CBT does not appear to restore peripheral nerve function but instead modulates central pain-processing pathways. By reducing catastrophizing and enhancing cognitive control over pain signals, CBT influences prefrontal-limbic circuitry responsible for emotional regulation and symptom perception (Wiech & Tracey, 2013(Ferguson et al., 2012)). This neurocognitive mechanism explains the consistent improvement in pain and psychological domains, even when sensory measures remain unchanged.(Phillips et al., 2011).

The integration of CBT with other therapeutic modalities may enhance outcomes. Combining CBT with physical therapy, sensory re-education, or pharmacological treatments could produce synergistic effects by concurrently addressing central and peripheral contributors to neuropathic pain.(Pouwer et al., 2024) Recent studies in multimodal pain management support this integrative approach (Wang et al., 2023).

LIMITATIONS

There are some limitations to this review that should be noted. Firstly, heterogeneity in the intervention formats (self-guided, online, or in-person) limits comparability and generalization. Secondly, most studies involved small sample sizes and predominantly female participants, particularly breast cancer cohorts, restricting representativeness. Thirdly, variability in outcome measures and short follow-up durations have hindered the evaluation of long-term efficacy. Lastly, few studies have controlled for confounding factors such as chemotherapy type, comorbidities, and concurrent treatments, which may have influenced results.

FUTURE DIRECTIONS

Future research should develop standardized CBT protocols specifically tailored to CIPN, including structured

modules for pain coping, sensory awareness, and fatigue management. (Getu et al., 2021).Large-scale randomized controlled trials with longitudinal follow-up (≥6 months) are required to determine sustained efficacy. Neurophysiological and neuroimaging studies should explore CBT's central modulatory mechanisms and potential interaction with neuroplastic recovery. Additionally, hybrid interventions combining CBT with sensory rehabilitation, pharmacologic agents, or neuromodulation should be tested for synergistic benefits. Digital and telehealth CBT, potentially enhanced by AI-based personalization, may improve accessibility for patients in remote or mobility-limited settings.

CONCLUSION

This systematic review provides convergent evidence that Cognitive Behavioral Therapy (CBT) offers measurable benefits for neuropathic pain and psychological distress in patients with chemotherapy-induced peripheral neuropathy (CIPN). While CBT consistently reduced pain intensity and improved emotional well-being, effects on sensory function and daily activity were limited. The findings indicate that CBT acts through cognitive and emotional regulation pathways, normalizing pain perception and enhancing patients' coping capacity rather than producing direct physiological recovery. The integration of CBT into multidisciplinary oncology care is supported by its safety, adaptability, and patient-centered focus. Nonetheless, current evidence is constrained by small sample sizes and heterogeneous protocols. Future research should employ standardized CBT frameworks, multimodal designs combining sensory rehabilitation and behavioral therapy, and longer follow-up to strengthen clinical recommendations and mechanistic understanding.

AUTHOR CONTRIBUTIONS

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work

DISCLOSURES

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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