

# Photobiomodulation Therapy for Chemotherapy-Induced Peripheral Neuropathy: Targeted Mechanisms and Optimized Strategies for Sensory Symptom Relief

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doi: 10.53011/JMRO.2025.01.03  
ISSN: 2784 – 0131

Received May 22, 2025

Revised June 18, 2025

Accepted July 5, 2025

Available online July 31, 2025

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## ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a widespread and often disabling effect of neurotoxic cancer therapies. Patients frequently experience sensory abnormalities such as numbness, tingling, heightened sensitivity to mechanical or cold stimuli (allodynia), and disrupted proprioception. These symptoms can persist long after treatment, significantly impairing daily function and quality of life. Photobiomodulation (PBM), which uses specific wavelengths of low-level red or near-infrared light, has recently emerged as a viable non-pharmacologic option for reducing these sensory disruptions.

Evidence from both laboratory and clinical research shows that PBM can enhance mitochondrial activity, facilitate axonal repair, and suppress oxidative stress and inflammatory responses within nervous tissue. In particular, PBM administered in the 780–850 nm wavelength range with fluences between 3 and 48 J/cm<sup>2</sup> has demonstrated the ability to relieve allodynia mediated by transient receptor potential (TRP) channels and restore proprioceptive function via nerve regeneration. Clinical implementation is hampered by inconsistencies in reported treatment parameters such as wavelength, dosage, and session frequency, making it challenging to replicate findings or compare studies. Furthermore, many existing PBM protocols do not tailor treatments to specific sensory symptoms or differentiate by chemotherapy type.

This review consolidates current mechanistic and clinical data, evaluates PBM's effects across various CIPN symptom categories, and highlights the need for standardization and patient-specific protocol development. Future progress should include the integration of biomarkers for response prediction, the use of quantitative sensory testing (QST), and rigorous long-term safety assessments. Adopting an approach that matches PBM parameters to sensory symptom patterns and underlying chemotherapeutic mechanisms may significantly enhance its therapeutic impact in treating CIPN.

**KEYWORDS:** *chemotherapy, low-level laser therapy, peripheral neuropathy, photobiomodulation*

## 1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-limiting side effect of many frontline chemotherapeutic agents, with an

estimated incidence ranging from 30% to 90% depending on drug type, cumulative dose, and assessment timing (1). Sensory dysfunction—including numbness, tingling, cold and mechanical allodynia, and impaired proprioception—is the

hallmark of CIPN and persists for months or years post-treatment, significantly affecting the quality of life and functional capacity of cancer survivors (2). The mechanistic underpinnings of CIPN are multifactorial and agent-specific (3). Platinum-based agents, such as oxaliplatin and cisplatin, accumulate in the dorsal root ganglia and induce DNA adducts, mitochondrial dysfunction, and oxidative stress, preferentially affecting large myelinated fibers responsible for touch and proprioception (3). Conversely, taxanes and vinca alkaloids primarily impair small unmyelinated and thinly myelinated fibers, disrupting microtubule function, and promoting inflammatory responses, which predominantly result in painful dysesthesias and thermal hyperalgesia (4,5).

Currently, pharmacological treatments for CIPN offer limited efficacy (6). Duloxetine remains the only guideline-recommended drug for painful neuropathy, with only modest benefits (6). As such, there is increasing interest in non-pharmacological approaches such as exercise therapy, acupuncture, and most recently, photobiomodulation (PBM) (7). PBM involves the application of low-intensity red or near-infrared light, which activates cytochrome c oxidase in mitochondria, enhancing ATP production and modulating cellular stress responses (8). These effects probably promote nerve repair, reduce neuroinflammation, and improve sensory function (9). In vitro, PBM has increased GAP-43 and synapsin I expression—markers of axonal regeneration and synaptic plasticity—while in vivo animal studies reveal reduced cold allodynia and improved nerve conduction velocities following PBM (9).

Argenta et al. demonstrated that PBM therapy using 800–970 nm wavelengths reduced modified Total Neuropathy Scores (mTNS) by over 50% in treated patients compared to sham controls (10). Similarly, the NEUROLASER trial showed that twice-weekly PBM during taxane-based chemotherapy helped preserve sensory function and quality of life, suggesting a preventive role for PBM (11). Laser acupuncture, a variation using focused light at acupuncture points, also demonstrated improved cold pain thresholds and touch-detection sensitivity in oxaliplatin-treated patients (12).

Despite these promising results, significant barriers to PBM clinical translation remain (13). Chief among them is the lack of standardized treatment

protocols (14). Clinical studies employ a wide range of wavelengths (630–970 nm), fluences (0.5–48 J/cm<sup>2</sup>), and treatment schedules (daily to weekly), often without symptom-specific rationale (13). Moreover, outcome assessments vary, with inconsistent use of validated measures such as the mTNS, FACT/GOG-Ntx, or quantitative sensory testing (15). There is also a paucity of stratified analyses based on the type of chemotherapy, neuropathy severity, or patient comorbidities (15).

This review aims to systematically evaluate PBM's efficacy for specific CIPN sensory symptoms, including numbness, tingling, and allodynia. It also explores the mechanistic basis of PBM effects and the challenges associated with optimizing treatment protocols. By integrating evidence from basic science, clinical trials, and guideline reviews, we propose a framework for the symptom- and mechanism-driven application of PBM, highlighting the need for personalized approaches that align with the underlying pathology of the neuropathy. The ultimate goal is to support the development of standardized, evidence-based PBM protocols that can be broadly implemented to mitigate the burden of CIPN and improve patient outcomes.

## 2. Review of Literature

### 2.1. PBM Parameters and Mechanisms

Photobiomodulation (PBM) is a form of therapy that utilizes red to near-infrared light in the 630–970 nm range to target peripheral nerve tissues (14). This therapy mainly revolves around the absorption of photons by mitochondrial cytochrome c oxidase, an enzyme that plays a crucial role in the electron transport chain (16). When it becomes activated, it causes a surge in ATP synthesis, changes calcium signaling within the cell, and controls reactive oxygen species (ROS) generation (15). These molecular events decrease apoptotic and inflammatory responses, particularly against neuropathic CIPN pathology (14,15).

Specifically, in CIPN, PBM acts against mitochondrial aberrancies arising from neurotoxic chemotherapeutics (14,17). PBM restores mitochondrial membrane potential, downregulates caspase-mediated apoptosis, and stimulates neurotogenic pathways for axon growth and repair (17). Especially, neurotrophic pathways are reactivated,

such as Brain-derived neurotrophic factor (BDNF) and neuronal growth factor (NGF), which help maintain axonal integrity (17). Preclinical studies show that PBM mitigates axonal loss and supports the functional restoration of axons when damaged by chemotherapy (18).

## 2.2. Role of Wavelength

Tissue penetration depths achieved by photobiomodulation mainly depend on the wavelength parameters of the light used (16). Red light (usually 630–670 nm) is absorbed through superficial tissues, and therefore, it serves primarily to target small sensory fibers associated with tingling, mild numbness at the surface level (19). On the other side, near-infrared light (780–850 nm) will penetrate deeper and will target deep nerve structures

responsible for pain hypersensitivity and proprioception (19).

In animal model experiments, PBM at 670 nm is linked to enhanced expression of GAP-43, which is involved in axonal sprouting (20). Wavelengths in the 780–850 nm range exhibit suppressive effects on cold-sensitive Transient Receptor Potential (TRP) channels like Transient Receptor Potential Melastatin 8 (TRPM8) and Transient Receptor Potential Ankyrin 1 (TRPA1), which are central to cold and mechanical allodynia, respectively (21). These wavelength-specific actions clarify the necessity of matching PBM parameters to specific symptom targets (20,21).

## 2.3. Symptom-Specific Effects of PBM

The symptoms are detailed below and also summarized in Table 1.

**Table 1:** Photobiomodulation parameters and their effect on specific chemotherapy-induced peripheral neuropathy symptoms

Study	CIPN symptom	Targeted PBM wavelength	Optimal fluence	Mechanism of action
Santamarina et al. (2025)	Numbness	630–670 nm (red light)	3–12 J/cm <sup>2</sup>	Stimulates axonal regeneration, restores proprioception
Hsieh et al. (2016)	Tingling	630–670 nm (red light)	0.5–6 J/cm <sup>2</sup>	Enhances small-fiber function, reduces inflammation
Hsieh et al. (2016)	Cold allodynia	780–850 nm (near-infrared)	12–48 J/cm <sup>2</sup>	Reduces TRP channel-mediated pain, neuroinflammation
Lodewijckx et al. (2020)	Mechanical allodynia	780–850 nm (near-infrared)	24–48 J/cm <sup>2</sup>	Modulates TRP channels, reduces central sensitization
Teng et al. (2022)	Proprioceptive deficits	630–850 nm (both)	6–12 J/cm <sup>2</sup>	Enhances axonal conduction and central neural pathways

*PBM – Photobiomodulation, CIPN – Chemotherapy-induced peripheral neuropathy, TRP – transient receptor potential.*

### 2.3.1. Numbness

CIPN-associated numbness is mainly due to damage to large myelinated fibers, probing sensory discrimination, and proprioceptive feedback (22). Many works reported that PBM within 630–850

nm wavelengths can ameliorate numbness by stimulating axonal regrowth and signal conduction restoration (22). More recently, Santamarina et al. found PBM treatment directed toward spinal reflex centers resulted in striking improvements in proprioceptive balance scores (23).

### 2.3.2. *Tingling*

Tingling sensations are largely due to dysfunction in small fiber pathways and often represent an early CIPN symptom (22,24). It seems that PBM reduces tingling by supporting synaptic stability and inhibiting pro-inflammatory cytokines within the affected nerves (18,22). Clinical evidence by Hsieh et al. suggests that repair of superficial sensory fibers implicated in tingling can be effectively stimulated by shorter wavelengths (630-670 nm) acting on superficial nerve endings (13).

### 2.3.3. *Allodynia*

Cold and mechanical allodynia come into being when damaged small fibers become hypersensitized with overactivation by TRP channels (11). PBM between 780 and 850 nm was shown to cause desensitization by Lodewijckx et al. (14). Clinical research by Hsieh et al. concluded that 780 nm PBM at 48 J/cm<sup>2</sup> significantly reduced the severity of pain (12). The beneficial effects had been shown in both pulsed and continuous light formats (12).

### 2.3.4. *Proprioceptive Impairment*

The proprioceptive impairment arises when there is demyelination or loss of large fiber carrying spatial positioning information (25). PBM expedites conduction in spinal pathways through enhanced speed and precision of nerve signal transmission (25). As far as studies of Teng et al. are concerned, there were significant improvements in proprioceptive function with effects lasting for 12 weeks after the treatment (26). These results give further proof of the potential of PBM in addressing large fiber dysfunction-related sensorimotor deficits (24,25). Teng et al. showed statistically significant improvements in proprioceptive function in a Phase II trial, with effects lasting up to 12 weeks post-treatment as measured by balance test scores and gait parameters (26).

## 2.4. Dosimetry Considerations

The administered dose of light is the most critical factor in determining the clinical effectiveness of PBM, usually related in terms of fluence (J/cm<sup>2</sup>) (16). Treatment protocols vary considerably across studies: low-dose treatments at approximately 0.5–3 J/cm<sup>2</sup> tend to be anti-inflammatory, while higher doses (greater than 12 J/cm<sup>2</sup>) would favor axonal regeneration and tissue repair (27).

For example, Argenta et al. implemented a protocol with variations in pulsed and continuous waveforms having power outputs ranging from 6 to 12 watts throughout six weeks, delivering targeted PBM in the areas of the most significant symptom burden (10). On the other hand, Hsieh et al. used daily treatments of 48 J/cm<sup>2</sup> over four weeks and reported a marked improvement in sensory function (13). These results seemingly indicate that total energy delivery should be optimized depending upon the clinical severity of neuropathy to reap clinical benefits (27). The therapeutic window must be carefully dosed to maximize adherence and efficacy while avoiding overstimulation or a decrease in returns. Fluence, frequency, and application site may all interrelate in order to isolate the application and investigate consistent, measurable improvements (16,27,28).

## 2.5. Treatment Planning

The number of sessions, or session frequency, also varies significantly in clinical applications (11). Some protocols (Table 2) may prefer daily treatment while in the acute symptom phase, whereas others propose or prefer treatment once a week or twice a week for maintenance (11,28). Preventive strategies, such as those used in the NEUROLASER trial, apply PBM simultaneously with chemotherapy to decrease the probability of symptom development. If a specific frequency of therapy is best adapted to the patient, it depends on the precise mode of chemotherapy, neuropathy progression, and overall tolerance (11). When cases display an intense or cumulative neurotoxic exposure, more frequent sessions may be advisable; maintenance schemes should be adequate in less severe cases or follow-ups throughout the long term (11,14).

**Table 2:** Comparison of photobiomodulation treatment protocols in chemotherapy-induced peripheral neuropathy clinical trials

Study	ChT Regimen	PBM Wave-length	PBM Fluence	PBM Frequency	Primary Outcome	Results
<b>Argenta et al. (2016)</b>	Taxane-based ChT	800–970 nm	6–12 J/cm <sup>2</sup>	2 sessions per week	mTNS	>50% reduction in mTNS score
<b>Hsieh et al. (2016)</b>	Oxali-platin-based ChT	780 nm	48 J/cm <sup>2</sup>	Daily for 4 weeks	Pain thresholds, sensory sensitivity	Improved cold pain thresholds and touch sensitivity
<b>Lodewijckx et al. (2020)</b>	Taxane-based ChT	780–850 nm	12 J/cm <sup>2</sup>	Twice-weekly during ChT	Preservation of sensory function, QoL	Improved quality of life, preserved sensory function
<b>NEURO-LASER Trial (2022)</b>	Taxane-based ChT	630–670 nm	0.5–3 J/cm <sup>2</sup>	Biweekly during ChT	Prevention of CIPN onset	Significant delay in CIPN onset

*PBM – Photobiomodulation, ChT – chemotherapy CIPN – Chemotherapy-induced peripheral neuropathy, mTNS – Total Neuropathy Score, QoL – Quality of Life.*

## 2.6. Multisite Application Strategy and Role of Biomarkers

PBM needs to be applied to several anatomical sites containing elements of the peripheral and central nervous system (29). This further augments recovery by hitting the affected nerve endings and their higher centers (fingers/toes: dorsal root ganglia or paraspinal regions) concurrently (29). Dual-site protocols, which employ short wavelengths (around 630 nm) on the hands and feet and longer wavelengths (up to 850 nm) along the spine, have demonstrated a synergistic effect in negating local and referred symptoms (7,27). In Lodewijckx et al.'s study, this strategy led to preserved sensory function and improved patient-reported outcomes compared to placebo, indicating the clinical value of combining anatomical target points (14). This elaborated approach takes care of the entire neuro-anatomical extent of CIPN and enhances the capacity of the therapy in pain modulation and sensorimotor restoration (7,24).

The ongoing advancements in the identification of biomarkers are instrumental in ushering in highly exigent and tailored PBM therapy (30). Methods like quantitative sensory testing (QST), epidermal nerve fiber density analysis from skin biopsies, and measurement of circulating neurofilament light chain (NFL) levels provide innovative directions in evaluating treatment response and disease progression (30). These resources can be employed in neuropathy severity and symptom phenotype stratification, so that they render clinicians capable of setting PBM parameters with finer precision (30,31). For instance, those with minor fiber damage could require superficial light applications, whereas considerable fiber damage with proprioceptive loss would ask for a deep, high-fluence intervention (30,32). Moreover, using biomarkers to observe responses over time could lead to adapting the therapy accordingly, thus improving reproducibility between studies and marking pathways toward establishing criteria to measure actual therapeutic gains (33). This type of profiling will be critical to highlighting PBM as more than

an experimental concept and as a standard treatment technique in integrative neuropathy care (33).

## 2.7. Safety Profile of PBM

Safe use has been demonstrated in patient populations treated with PBM, which have good safety records, including those undergoing active cancer treatment (14,16). In these clinical trials, such as NEUROLASER and Argenta, there has been no report of serious adverse events, complications from treatment, or suggestive indications that PBM might be associated with an increase in cancer recurrence or progression (10,11).

Generally, patients tolerate PBM well, but its use should be carefully evaluated in patients with an established diagnosis of photosensitivity or those concurrently undergoing radiotherapy where light exposure may interfere with treatment fields (34). Using standard and accepted protocols would help reassure safety and help achieve smooth incorporation into oncologic care (16,34). Noninvasiveness and lack of drug interactions particularly make LLLT an attractive option with patients taking multiple drugs or unable to tolerate neuropathic medication. These features, coupled with its safety and symptom alleviation, make PBM an attractive option in supportive care treatments (35).

## 3. Discussion

The purpose of this review was to evaluate the efficacy of PBM for chemotherapy-induced peripheral neuropathy (CIPN) and explore its potential as a non-pharmacological intervention for symptom-specific optimization. Our review highlights the diverse sensory manifestations of CIPN and underscores the need for targeted approaches. The results of the present review highlight that the effectiveness of PBM appears to vary by sensory phenotype, with distinct mechanistic pathways underlying its benefits.

PBM demonstrates distinct effects on the physiological substrates underlying each sensory deficit, but optimization remains hindered by a lack of standardization across wavelength, dosage, and treatment schedules (36). Clinical trials have reported encouraging quantitative outcomes (10,11). Argenta et al. conducted a randomized, sham-controlled trial showing >50% reduction in

mTNS scores among PBM-treated patients with taxane-induced neuropathy (10). The NEUROLASER trial, using biweekly PBM during chemotherapy, observed statistically significant delays in the onset of CIPN, preservation of touch-detection thresholds, and improvements in quality-of-life scales (EORTC QLQ-CIPN20) (11). Hsieh et al. demonstrated that 48 J/cm<sup>2</sup> PBM at 780 nm significantly improved cold pain thresholds and mechanical sensitivity in oxaliplatin-treated patients (12,13).

The evidence highlights that PBM's effectiveness varies by sensory phenotype, for example, PBM demonstrates pronounced efficacy in addressing numbness and proprioceptive deficits, likely due to its influence on large myelinated fibers and central neural structures (30,36). This pattern of results is consistent with previous studies employing 630-850 wavelengths, which report improvement in balance and sensory discriminations (36). However, studies such as Santamarina et al. and Teng et al. have small sample sizes and require replication in larger, stratified cohorts (24,26). In contrast, cold and mechanical allodynia appear more responsive to higher fluences (e.g., 48 J/cm<sup>2</sup>) and deeper-penetrating wavelengths (780-850 nm), which more effectively target dorsal root ganglion hyperexcitability and TRP channel sensitization (12,21). Hsieh et al. provide compelling evidence through both subjective and quantitative sensory testing metrics (12). However, direct comparisons across wavelength ranges are limited, and trials often fail to isolate single sensory symptoms, which impedes protocol refinement (24,28).

The incorporation of personalized dosimetry, as demonstrated by Argenta et al., represents a significant advancement in PBM research, enabling tailored interventions based on neuropathy distribution and intensity (10). Several randomized controlled trials have evaluated the efficacy of PBM in CIPN. In the study by Argenta et al., patients receiving 800-970 nm PBM twice weekly for 6 weeks experienced over a 50% reduction in mTNS scores compared to the sham group (10). The NEUROLASER trial, a randomized placebo-controlled study, demonstrated that biweekly PBM during taxane-based chemotherapy delayed the onset of CIPN symptoms and preserved sensory thresholds and quality of life (11). In a separate randomized phase II trial by Teng et al., PBM

resulted in significant improvements in proprioceptive function with effects lasting up to 12 weeks (26). These trials provide critical high-quality evidence supporting PBM's potential in both therapeutic and preventive settings.

In comparison, past researchers focused primarily on post-neurotoxicity rehabilitation (23,26). The present review extends this work by advocating for preventative PBM integrating into chemotherapy regimens, as evidenced by the NEUROLASER trial (11). Notably, PBM's effects persist for 10 to 12 weeks post-treatment (26,37). These results suggest a paradigm shift toward early intervention to mitigate chronic symptom progression (31,37).

Despite these advancements, there are several potential limitations concerning the results of this study. One limitation of this study is that the diversity of assessment tools used to evaluate PBM results, e.g., Modified Total Neuropathy Score (mTNS), FACT/GOG-Ntx, EORTC QLQ-CIPN20, and quantitative sensory testing (QST), all provide valuable data but differ in sensitivity and focus, which complicate cross-study comparison (38). The variability in PBM devices and calibration standards poses barriers to replication (7,27). An additional limitation is the small sample sizes in key studies, necessitating a larger, stratified cohort for validation (23,26). Future research should prioritize standardized outcome measures to facilitate robust meta-analysis. While multiple studies suggest positive outcomes with PBM, the overall quality of evidence remains mixed. Many studies suffer from small sample sizes, short follow-up durations, and heterogeneous treatment protocols, which limit generalizability. Only a few randomized controlled trials, such as those by Argenta et al. and the NEUROLASER group, provide high-level evidence (10,11). Future research must address these limitations through multicenter, well-powered trials with standardized PBM protocols and consistent outcome measures.

These data have several intervention implications. For example, Biomarker integration, such as serum NFL levels or skin nerve fiber density, could enhance objective monitoring of PBM efficacy (33). Additionally, granular dose-finding studies are needed to delineate therapeutic windows, particularly when stratified by neuropathy type, and chemotherapy class (18). In terms of future

research, it would be helpful to explore the maintenance PBM cycle post-chemotherapy to assist long-term neuroprotection (31,32). Furthermore, mechanistic studies investigating PBM's pleiotropic effects, such as mitochondrial ATP synthesis and cytokine modulation, could clarify its role in addressing both neurodegeneration and neuroinflammation (33).

The current literature contributes to a growing body of evidence supporting PBM's safety and efficacy in cancer survivors, with no increased recurrence rates associated with PBM. However, multi-year follow-ups remain limited (19). Education for oncology providers and therapists on PBM's indications, application, and contraindications is also crucial (39). Despite these limitations and concerns, the present study has enhanced our understanding of PBM's potential as a precision intervention for CIPN. World Association of Laser Therapy (WALT) advises the use of transcutaneous LED or laser devices emitting near-infrared light (wavelength range: 800-1100), with an irradiance of 10-150 mW/cm<sup>2</sup>. The recommended energy dose is 2 Einstein per treatment area, corresponding to a photon fluence of 9 pJ/cm<sup>2</sup> at 810 nm. These treatments should be administered 3 to 4 times per week throughout 4 to 6 weeks to observe clinically meaningful benefits (28). We hope that the current review will stimulate further investigation into standardized protocols, cost-effectiveness, and clinical guideline integration to optimize patient outcomes.

#### 4. Conclusion

PBM emerges as a promising, non-invasive intervention for managing the complex sensory disturbances associated with chemotherapy-induced peripheral neuropathy. Unlike conventional pharmacological strategies, PBM targets underlying pathophysiological mechanisms such as mitochondrial dysfunction, oxidative stress, and neuroinflammation, aligning with the diverse neurotoxic pathways activated by different chemotherapeutic agents. Clinical and preclinical evidence supports the efficacy of PBM in alleviating both large fiber-mediated symptoms such as numbness and proprioceptive loss, and small fiber-mediated pain syndromes like cold and mechanical allodynia.

The effectiveness of PBM is closely tied to the optimization of treatment parameters, including wavelength, fluence, and treatment frequency. Multicenter, stratified trials using consistent sensory endpoints and incorporating both patient-reported outcomes and objective metrics are needed to validate and refine current approaches. PBM has

the potential to become a cornerstone of CIPN management, offering durable symptom relief and neuroprotection. When applied with precision and informed by evolving evidence, PBM can significantly improve patient quality of life and support the broader movement toward integrative and personalized cancer care.

## ABBREVIATIONS

ChT – chemotherapy

CIPN – Chemotherapy-induced peripheral neuropathy

LLL – Low-Level Laser Therapy

mTNS – Modified Total Neuropathy Score

NFL – Neurofilament Light chain

QoL – Quality of Life

QSL – Quantitative Sensory Testing.

PBM – Photobiomodulation

TRP – Transient Receptor Potential

WALT – World association of laser therapy

## STATEMENTS

**Authors' contributions:** MN wrote the manuscript and revised the text.

**Consent for publication:** As the corresponding author, I confirm that the manuscript has been read and approved for submission.

**Conflict of interests:** The authors declare no conflict of interest.

**Funding Sources:** None

**Ethical Approval:** This study was not subject to ethical review and approval due to its format.

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