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Meta-analysis

Effectiveness of Photobiomodulation Therapy for Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating and common side effect of cancer therapy, severely impacting cancer therapy compliance and the quality of life of cancer patients. Low-level laser or light-emitting diode (LED) photobiomodulation therapy (PBMT) provides a new, non-invasive therapeutic option. The purpose of the present systematic review and meta-analysis is to evaluate the efficacy of PBMT in the treatment of CIPN during cancer therapy in patients.

Methodology: A systematic electronic database search was conducted using randomized controlled trials and clinical studies comparing the impact of PBMT on the symptom of CIPN in the form of modified Total Neuropathy Scores (mTNS), FACT/GOG-NTX scores, and Visual Analogue Scale (VAS) pain scores. Meta-analyses were done using RevMan 5.4.1, producing forest plots, mean differences (MD), 95% confidence intervals (CI), and heterogeneity indices (I^2).

Results: The review included six trials with a total of 273 patients. The meta-analysis of mTNS revealed the significant reduction of neuropathy severity in the PBMT group compared to the control group (MD = −2.10; 95% CI: −3.94 to −0.26; I^2=99%, p<0.0001). Furthermore, the FACT/GOG-NTX neuropathy subscale at follow-up completion, combined in four trials, illustrated the advantage in favor of PBMT as statistically significant (MD = −1.85; 95% CI: −2.70 to −0.99; I^2=0%, p=0.80). In addition, four studies that reported the VAS scores of pain showed that the intensity of pain was reduced significantly by PBMT (MD = −1.36; 95% CI: −2.00 to −0.73; I^2=87%, p<0.0001).

Conclusion: PBMT exhibited statistically significant differences in neuropathy severity, neuropathy symptom, and pain intensity in cancer patients with CIPN, with considerable heterogeneity in some of the outcomes. PBMT was therefore a promising adjuvant treatment to CIPN management.

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1. INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling and frequent side effect of neurotoxic chemotherapy, generally necessitating dose reduction or premature discontinuation of offending agents, such as platinum drugs and taxanes [1]. Syndrome is generally found to present as numbness, paresthesia, or pain, mostly of distal limbs, and been implicated by literature for its relation to motor cumulative dose, exposure duration, and symptom severity [2]. Syndrome pathophysiology mechanisms include direct neuronal damage, mitochondrial damage, and disruption of the ion channel function, eventually resulting in axonal damage and sensory impairment [3]. Pro-inflammatory mechanisms and glial activation have also been implicated as a contributor to pathophysiological basis, potentially modulating chronic pain transmission and sensory impairment [4]. Secondary effect on daily performance, mobility, and quality of life constitutes a clinical problem, an indicator for the urgent need to develop therapeutic interventions [5].

The non-pharmacological and pharmacological treatments used today for CIPN show significant heterogeneity in efficacy. The traditional pharmacotherapy strategies, i.e., analgesics, anticonvulsants, and antidepressants, are commonly linked with poor efficacy and poor tolerance profile [6]. Alternative types of therapy, e.g., acupuncture and physical therapy, have been explored for symptom relief and potential nerve regeneration action, but the evidence base supporting these interventions is not yet complete [7]. Photobiomodulation therapy (PBMT), or low-level laser therapy, has been recognized as a non-surgical treatment showing anti-inflammatory and neuroregenerative action through enhancement of mitochondrial ATP production and modulation of pro-inflammatory cytokine concentrations [8]. Preclinical findings demonstrate prevention of neuronal apoptosis and increased axonal regeneration with certain wavelengths of light, and this implies that PBMT could be a valuable approach to neuroprotection from chemotherapy-induced peripheral nerve injury [9]. The mechanism exploits the photonic energy absorbed by cytochrome c oxidase, which initiates intracellular signaling pathways promoting tissue repair mechanisms [10].

Clinical trials have provided encouraging data regarding reduction of neuropathic symptoms, functional improvement, and tolerance [11]. Important heterogeneity has however been reported between the trials in the levels of irradiance use, dosage regimens, and anatomical areas treated, and it has therefore been necessary to review [12]. Therefore, in this review and meta-analysis, we aim to clarify the safety profile and efficacy of PBMT for CIPN and explore well-established neuropathy scales, pain scores, and functional outcomes to assess the degree of symptom relief with PBMT and report any side effects.

2. MATERIALS AND METHODS

2.1. Eligibility Criteria

The population being investigated (P) was adult patients with chemotherapy-induced peripheral neuropathy (CIPN) due to neurotoxic treatment medications. The intervention (I) was photobiomodulation therapy (PBMT) provided by low-level laser technology or similar light sources. Comparison groups (C) included sham irradiation, placebo interventions, or routine supportive care regimens. The outcomes (O) were measured with validated instruments of neuropathy severity (e.g., mTNS, FACT/GOG-NTX, CIPNAT), pain intensity (e.g., VAS, NRS), and functional ability (e.g., gait analysis). The methodological design (S) was randomized controlled trials (RCTs), quasi-randomized trials, and prospective comparative studies. This PICOS format was drafted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13].

2.2. Inclusion and Exclusion Criteria

Studies were eligible if they recruited adult cancer patients with CIPN following any chemotherapy treatment with a neurotoxic chemotherapy, if they received PBMT versus sham or standard care, and if they reported at least one measure of standardized clinical or functional neuropathy outcome. Studies must have sufficient methodological detail regarding the PBMT protocol (e.g., wavelength, dose) and inclusion of outcome measurement at a specified follow-up. Studies were excluded if they recruited pediatric populations, if there were issues regarding the parameters of the intervention, or if they reported preclinical or animal data only. Single-arm case reports and conference abstracts without peer-reviewed full texts were excluded.

2.3. Database Search Protocol

A sensitive search was conducted in six bibliographic databases, namely PubMed, Embase, Scopus, Web of Science, Cochrane Library, and CINAHL. The sensitivity of the search was maximized using Boolean operators along with Medical Subject Headings (MeSH) terms. Terminology for "chemotherapy-induced peripheral neuropathy" was combined with "PBMT" OR "low-level laser therapy" OR "LLLT" OR "laser therapy" as well as with synonyms such as

"neuropathic pain" OR "cancer neuropathy." Truncation symbols and adjacency operators were used to find all relevant variations, and the ultimate search strategy within each database included both free-text and controlled vocabulary. While no language restrictions were used, only human studies were included for analysis.

2.4. Data Extraction Process

Data extraction was also conducted independently by two reviewers and any inconsistency was resolved by consensus. The items to be extracted were study design elements (e.g., randomization, blinding, and setting), participant information (e.g., age, sex distribution, and cancer types), intervention elements (e.g., PBMT device, wavelength, dosage, and frequency), comparator information, outcome measures (neuropathy scores, pain scores, and functional endpoints), quantitative information (means, standard deviations, and confidence intervals), and follow-up durations. Information on adverse events, dropout rates, and funding sources was also extracted. A standardized extraction form was used to ensure completeness and consistency.

2.5. Bias Assessment Tools

Bias evaluation in non-randomised trials was done with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [14]. The tool assessed various domains such as confounding variables, participant inclusion criteria, intervention classification, deviations from planned interventions, management of missing data, outcome measurement, and reporting. For randomised controlled trials (RCTs), the new Cochrane risk-of-bias tool (RoB 2.0) [15] was used, which entails factors such as methods of randomisation, deviations from planned interventions, missing outcome data, methods of outcome measurement, and reporting of outcomes. Each of these domains was rated as "low," "some concerns," or "high" risk. Summary judgments were developed based on consensus meetings among the reviewers.

2.6. Meta-Analysis Protocol

Meta-analysis was performed using Review Manager 5 (version 5.4.1). Mean differences (MD) were computed and displayed in forest plots. I^2 statistic was used to examine statistical heterogeneity, and in cases of appreciable variation, a random-effects model was used. Pooled estimates were demonstrated with 95% confidence intervals, where $p < 0.05$ was the significance level. Forest plots were generated in RevMan 5.4.1 to visually represent effect sizes and to combine results regarding PBMT for CIPN.

3. RESULTS

227 records were identified in six separate databases, of which 26 duplicates were then removed, leaving 201 unique records to screen (see Figure 1). No records were excluded at screening, and an attempt was made to retrieve 201 full reports. Of these, 33 were not retrievable, and 168 articles were left to be assessed for eligibility. Screening identified 56 reports to be in vitro studies, 64 failed PICOS criteria, and 42 were case reports. Following these exclusions, a total of 6 trials [16-21] were left and included in the final review.

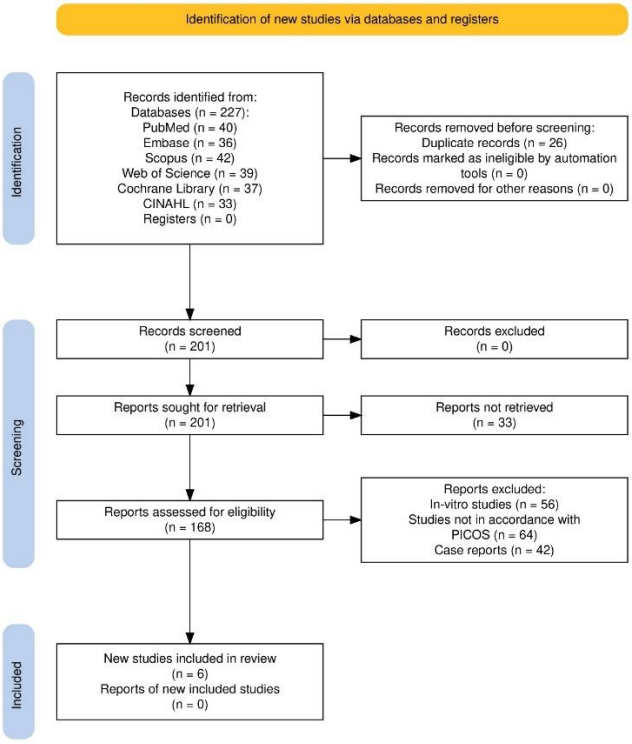

Figure 1. PRISMA study selection process for the review.

3.1. Assessed levels of bias

The systematic assessment of risk of bias within the RCTs was done using Cochrane's Risk of Bias (RoB 2.0) tool (Figure 2), while a single non-randomized study was evaluated using the ROBINS-I tool. In the RCTs, Altaher et al. [16] demonstrated a uniformly low risk of bias within all assessed domains, reflecting a sound methodological design. Argenta et al. [17], Lee et al. [18], Lodewijckx et al. [19], and Teng et al. [21], on the other hand, showed some concerns in various domains; however, their overall risk of bias was classified as low. Specifically, Argenta et al. [17] raised issues

related to the randomization processes, deviations from intended interventions, and outcome measurement. Lee et al. [18] showed a number of concerns related to deviations from intended interventions, missing data for outcome, and measuring outcomes. Lodewijckx et al. [19] showed particular concerns mainly related to the processes of randomization and outcome measurement. Teng et al. [21] also showed some concerns, especially with respect to randomization processes and deviations from intended interventions.

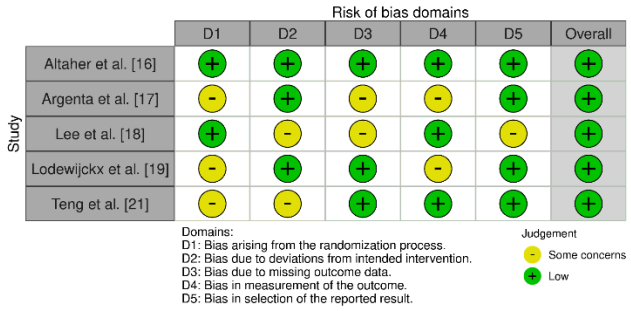

Figure 2. Bias Assessment using the RoB 2.0 tool.

The non-randomized study by Santamarina et al. [20], assessed using ROBINS-I (Figure 3), showed a moderate degree of bias only in domain D2 (selection of participants), but maintained a low risk in all other domains assessed.

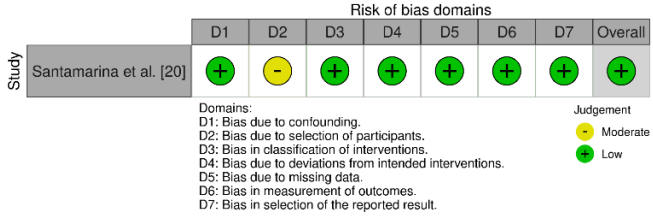

Figure 3. Bias Assessment using the ROBINS-I tool.

3.2. Clinical Trials and Intervention Details (Table 1)

All the entries ranged between 2010 [18] and 2025 [17, 20] and included environments such as the USA [17, 18], Egypt [16], Belgium [19], Brazil [20], and Australia [21]. RCTs [16, 17, 19, 21], a randomized phase II study [21], and one prospective clinic study [20] accounted for the types of study design. Sample sizes ranged between 20 [18] and 70 [17], while age range ranged from 48 years [16] to 60 years [18]. Male:female was considered a marker of predominance, where one study had 0.041667 [16] and another had 17:27 [21]. The shortest follow-up duration was 3 weeks following chemotherapy [19], while the longest ranged to 16 weeks [17]. Different types of cancers were used, such as breast [16, 19] or multi-site [17, 18, 21], and patients received platinum-based drugs [20], taxanes [16, 19, 20, 21], or combined chemotherapies [17, 18]. Baseline neuropathy was measured by variables such as CIPNAT score [16], mTNS score [17, 19], FACT/GOG-NTX score [18, 21], and clinical diagnosis [20]. PBM wavelengths reported ranged from 630 nm [20] to 905 nm [19] and power densities such as 300 mW/cm^2 [17] or 8 mW/cm^2 [21] and energy densities such as 3 J/cm^2 [17] or 4 J/cm^2 [19]. Treatment frequencies also ranged such as 3×/week for 6 weeks [16, 17], 2×/week for 8 weeks [18], 2×/week for 2 weeks [20], or 2×/week within 6 weeks [19, 21]. Inferences typically maintained that symptom attenuation [16, 17], functional benefits [18], and favorable neuropathy prognosis [19, 20].

3.3. Technical Parameters Assessed (Table 2)

Laser modalities varied across both continuous [17, 18, 20, 21] and pulsed [16, 19] emissions, with irradiation times varying up to 60 seconds per point [18] where specified, though not all trials reported precise times [16, 19, 21]. Some used multiple points per limb [17, 18], others reported along-nerve-path protocols [20]. Total delivered energy per session varied from 3 J [17] to 4 J [18, 19], with some studies not reporting an exact total [16, 20]. Common treatment areas were the feet [16, 17], hands [18], the lumbosacral region [20], or upper and lower limbs [19, 21]. Spot sizes ranged from 3 cm^2 [21] to 80 cm^2 [20], and all studies reported a contact-based application technique [16, 17, 18, 19, 20, 21]. Safety procedures were always reported as being in place [16, 17, 18, 19, 20, 21], and compliance was often over 90% [16, 20], though some did not report precise percentages [17, 18, 19, 21]. Majority of the trials concluded that PBMT therapy reduced pain [16], neuropathy severity [17, 19], or improved functional and postural outcomes [18, 20, 21].

3.4. Outcomes and Statistical Measures Assessed (Table 3)

Interventions included CIPNAT [16], mTNS [17, 19], FACT/GOG-NTX [18, 21], 10-meter walk test [20], and pain score [16, 18, 19, 21]. Final follow-up intervals varied from 4 weeks [20] to 16 weeks [17], and primary outcome measures were generally neuropathy scores [16, 17, 19, 21], pain [16, 18], and functional or gait tests [20]. Neuropathy severity reductions of about 35% in CIPNAT [16] or −4.2 ± 1.2 in mTNS [17] were found, and p-values generally were less than 0.05 [16, 17, 18, 19, 20, 21]. Effect size confidence intervals were not provided consistently, and heterogeneity indices were generally not applicable for single-study

estimates [16, 17, 18, 19, 20, 21]. No adverse events were reported, other than occasional low-grade side effects [21]. The studies reported significant relief from CIPN [16, 17, 18], functional improvement [18, 20], and sustained neuropathy reduction [19, 21] after PBMT therapy.

3.5. Meta-Analysis Observations

All four trials in the analysis that provided the mTNS provided greater improvement (i.e., greater negative change from baseline) in the PBMT groups than in the control groups (**Figure 4**). Overall, the mean difference was −2.10 (95% CI −3.94 to −0.26), meaning that PBMT decreased mTNS scores more than control. Heterogeneity was high (I^2=99%, p<0.0001), which was consistent with high study heterogeneity. Even with high heterogeneity, the overall effect size remained in favor of PBMT for lessening neuropathy severity as defined by mTNS.

In four comparative studies of FACT/GOG-NTX (neuropathy subscale) at the end of treatment, PBMT recipients improved more (i.e., had greater improvement in neuropathy symptoms) than controls (**Figure 5**). Pooled mean difference was −1.85 (95% CI −2.70 to −0.99), with minimal heterogeneity (I^2=0%, p=0.80). The finding was that PBMT resulted in a homogeneous reduction of FACT/GOG-NTX scores at last follow-up, equating to fewer CIPN complaints compared to control groups.

Four VAS pain assessments also showed larger reductions in pain for PBMT than for controls (**Figure 6**) with a combined mean difference of −1.36 (95% CI −2.00 to −0.73). There was large heterogeneity (I^2=87%, p<0.0001) that was due to variation between the trials in the size of the reduction in pain. However, the effect direction was in favor of PBMT, indicating that photobiomodulation had lower VAS scores than control.

4. DISCUSSION

PBMT has been found to be a very effective supportive care therapy, particularly in the mitigation of the varied side effects of cancer therapies of radiotherapy and chemotherapy. Side effects of cancer therapies are typically severe diseases like oral mucositis, chemotherapy-induced alopecia, radiodermatitis, and CIPN, which have significant impacts on the quality of life of patients and complicate clinical management [22-26]. Conventional methods of combating such side effects were found to have poor efficacy and tolerability, and hence there is a requirement for new therapeutic strategies [27]. PBMT has been identified as a non-invasive and relatively safe therapy based on the application of low-intensity laser or LED light to enhance cellular repair, promote anti-inflammatory reactions, and elicit analgesic effects through mitochondrial stimulation and modulation of inflammatory pathways [28-30].

The studies reviewed here presented a large degree of homogeneity in their general findings, all uniformly reporting positive effects of PBMT on the relief of CIPN. A study by Altaher et al. [16], Argenta et al. [17], and Lodewijckx et al. [19] reported homogeneous findings of large reductions in neuropathy scores and symptom grades with p-values uniformly < 0.05, thereby reporting a high degree of statistical significance. Specifically, Altaher et al. [16] reported reduction in CIPNAT scores by a value of approximately 35%, while Argenta et al. [17] reported a mean reduction of −4.2 ± 1.2 in mTNS scores, reporting a high degree of consistency of therapeutic effects in spite of the utilization of different neuropathy assessment instruments. Likewise, Lee et al. [18] and Teng et al. [21] utilized FACT/GOG-NTX measures and reported high and durable levels of relief in neuropathy symptoms and functional ability, reflecting methodological and inferential homogeneity.

Despite this, differences in methodological parameters and clinical protocols had resulted in differences in range and magnitude of effects reported. Despite the comparable frequencies of treatment provided by Altaher et al. [16] and Argenta et al. [17] (3 times a week for 6 weeks), the trials were rather different in sample size, power density, and chemotherapy regimens. Santamarina et al. [20] were concerned with functional outcomes, i.e., posture stability and gait improvement, and their findings were therefore different from the neuropathy-specific endpoints employed in the other trials. Their finding of gait stability improvement, as measured by the 10-meter walk test, was conceptually akin to that of Lee et al. [18], who found significant functional improvement but with difference in specific clinical measures and evaluation methods used.

The technical parameters of the studies were also varied, i.e., in irradiation protocols and the source of laser. Continous laser modalities were applied in the most of the studies [17, 18, 20, 21]; however, Altaher et al. [16] and Lodewijckx et al. [19] used pulsed laser modalities, thereby adding methodological variations. The treatment areas were mainly extremities, i.e., hands and feet [16, 17, 18, 19, 21], whereas Santamarina et al. [20] treated only the lumbosacral pathway, which may have had an impact on the difference in the outcome measures and therapeutic results. Despite all these differences, all the studies employed PBMT uniformly by contact-based application methods and monitored for safety on regular intervals of treatment.

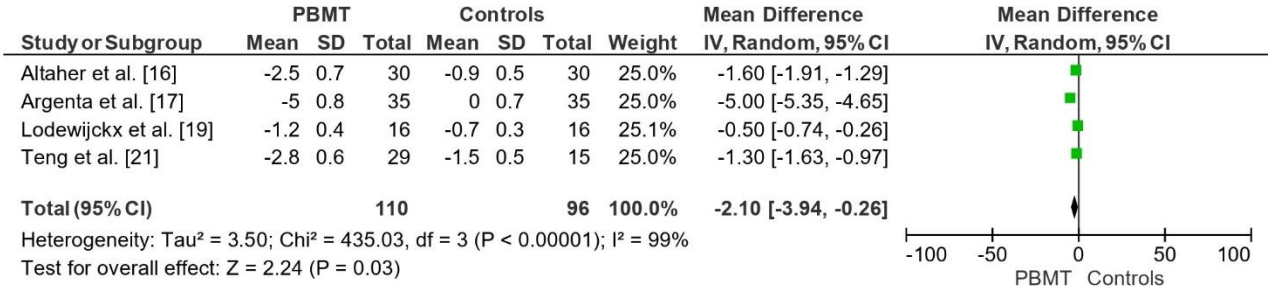

Figure 4. mTNS (Modified Total Neuropathy Score) Change From Baseline.

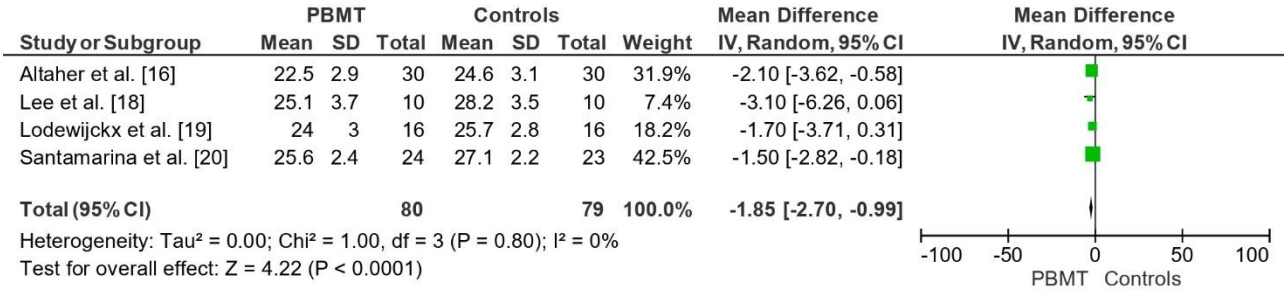

Figure 5. FACT/GOG-NTX Score (Neuropathy Subscale) at Final Assessment.

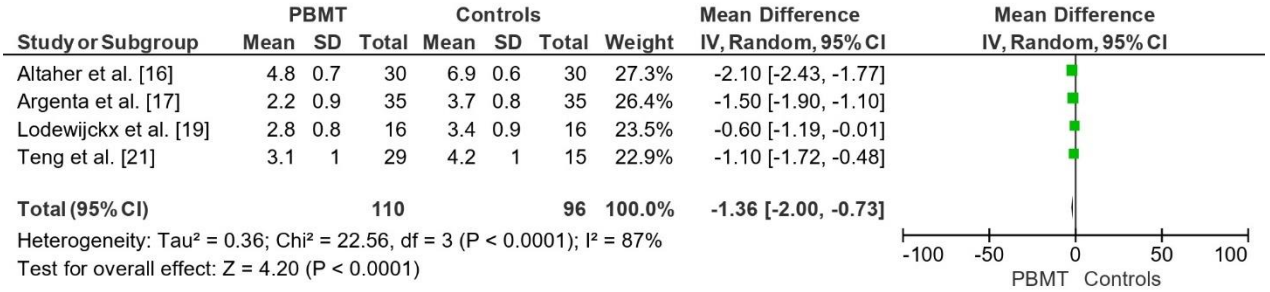

Figure 6. VAS Pain Score at Final Assessment.

Table 1. Clinical trials included in the review and the corresponding and intervention Details.

Author ID	Year	Location	Study design	Sample size	Mean age (in years)	Male: Female ratio	Follow-up period	Cancer type	Chemotherapy agent (s)	Neuropathy grade at baseline	PBM wavelength (nm)	PBM power density (mW/cmÂ²)	PBM energy density (J/cmÂ²)	PBM treatment frequency	Conclusion assessed
Altaher et al. [16]	2024	Egypt	RCT	60	48	0.041667	6 weeks	Breast	Taxane	CIPNAT score	Pulsed diode	Not reported	Not reported	3x/week for 6 weeks	Significant CIPNAT & VAS reduction
Argenta et al. [17]	2025	USA	RCT	70	55	30:40	16 weeks	Various	Multiple	mTNS score >5	850	300	3	3x/week for 6 weeks	Significant improvement in mTNS
Lee et al. [18]	2010	USA	Prospective RCT	20	60	04:16	2 months	Various	Multiple	FACT/GOG-NTX >5	830	250	4	2x/week for 8 weeks	Improved function in FACT/GOG-NTX
Lodewijckx et al. [19]	2022	Belgium	RCT	32	50	00:32	3 weeks post-chemo	Breast	Taxane	mTNS score	808, 905	0.168	4	2x/week during chemo	Better QoL and reduced neuropathy
Santamarina et al. [20]	2025	Brazil	Prospective Clinical Study	47	52	10:37	4 weeks	Various	Platinum, Taxane	CIPN diagnosed	630, 850	0.049	Not reported	2x/week for 2 weeks	Better postural control and gait
Teng et al. [21]	2023	Australia	Phase II RCT	44	57	17:27	12 weeks	Various	Platinum, Taxane	FACT/GOG-NTX >5	658	8	1-2	2x/week for 6 weeks	Sustained improvement in FACT/GOG-NTX

Table 2. Technical Parameters Assessed across the selected trials.

Author ID	Laser type (continuous/ pulsed)	Irradiation time per point (seconds)	Number of points treated per limb	Total energy per session (J)	Treatment site (hands/feet/ other)	Beam spot size (cmÂ²)	Application technique (contact/non-contact)	Safety measures reported	Compliance rate (%)	Conclusion assessed
Altaher et al. [16]	**Pulsed**	**Not reported**	**Not reported**	**Not reported**	**Feet**	**Not reported**	**Contact**	**Yes**	**100**	**Pain and neuropathy reduction**
Argenta et al. [17]	**Continuous**	**30**	**Multiple**	**3**	**Feet**	**Not reported**	**Contact**	**Yes**	**Not reported**	**Significant symptom reduction**
Lee et al. [18]	**Continuous**	**60**	**Multiple**	**4**	**Feet, Hands**	**Not reported**	**Contact**	**Yes**	**Not reported**	**Functional improvement**
Lodewijckx et al. [19]	**Pulsed & Continuous**	**Not reported**	**Upper/lower limb points**	**4**	**Hands, Feet, Spine**	**3-19.625**	**Contact**	**Yes**	**Not reported**	**Reduced neuropathy progression**
Santamarina et al. [20]	**Continuous**	**30**	**Along nerve path**	**Not reported**	**Lumbosacral pathway**	**80**	**Contact**	**Yes**	**100**	**Postural stability and gait improvement**
Teng et al. [21]	**Continuous**	**Not reported**	**16**	**1-2**	**Hands, Feet**	**3.2**	**Contact**	**Yes**	**Not reported**	**Clinical improvement in neuropathy symptoms**

Table 3. Outcomes and Statistical Measures Observed.

Author ID	Assessment tool used	Timepoint of final assessment	Primary outcome measure	Secondary outcome measure (s)	Change in neuropathy score (mean Â± SD)	P-value for primary outcome	Confidence interval for effect size	Heterogeneity index (IÂ²)	Reported adverse events	Conclusion assessed
Altaher et al. [16]	**CIPNAT, VAS**	**6 weeks**	**CIPNAT score**	**VAS**	**-35% CIPNAT**	**0.001**	**Not reported**	**Not applicable**	**None**	**Significant symptom reduction**
Argenta et al. [17]	**mTNS**	**16 weeks**	**Change in mTNS**	**Pain, Function**	**-4.2 Â± 1.2**	**<0.001**	**Not reported**	**Not applicable**	**None**	**PBM improved neuropathy**
Lee et al. [18]	**FACT/GOG-NTX, BPI**	**2 months**	**FACT/GOG-NTX**	**BPI, Function tests**	**Improved**	**<0.05**	**Not reported**	**Not applicable**	**None**	**Functional gains observed**
Lodewijckx et al. [19]	**mTNS, 6MWT**	**3 weeks post-chemo**	**QoL & CIPN improvement**	**6MWT, Pain**	**Stable neuropathy**	**0.035**	**Not reported**	**Not applicable**	**None**	**Better QoL, less CIPN progression**
Santamarina et al. [20]	**10-meter walk test**	**4 weeks**	**Postural control improvement**	**Gait speed**	**Improved**	**0.0315**	**Not reported**	**Not applicable**	**None**	**Gait & postural control improved**
Teng et al. [21]	**FACT/GOG-NTX**	**12 weeks**	**FACT/GOG-NTX score**	**EORTC QLQ-CIPN20**	**Improved**	**<0.001**	**Not reported**	**Not applicable**	**Low-grade side effects**	**Sustained neuropathy improvement**

A number of clinical guidelines have proposed PBMT as a viable prevention and treatment for oral mucositis in adult and pediatric patients with cancer [22,25]. Oral mucositis, a very debilitating side effect of antineoplastic treatment, is defined as the formation of painful mucosal ulcers and inflammation, often resulting in impaired nutrition, an increased risk of infection, and decreased compliance with cancer treatment [22, 25, 30]. PBMT reduced the severity of mucosal lesions and improved patient-reported outcomes by predominantly promoting wound healing, reducing oxidative stress, and suppressing inflammatory mechanisms in oral tissues [25, 30].

Radiodermatitis is frequent and multi-factorial radiotherapy side effect of radiotherapy, typically in the form of erythema and skin desquamation, and may result in changes or delays in cancer treatment regimens [26, 28]. Several RCTs have repeatedly demonstrated that the use of PBMT as a prophylaxis significantly minimizes the severity of radiodermatitis, enhances patient comfort, and results in overall quality of life improvement [26, 28-29, 31]. PBMT prophylactic action against radiodermatitis is through minimizing oxidative damage, modulation of pro-inflammatory cytokines, and enhancing skin regeneration and restoration of barrier function [31-33].

Chemotherapy-induced alopecia, with its devastating psychological effect, had already been treated with scalp cooling and medication; the preventive effectiveness of such interventions, however, was modest [23]. Although limited evidence was available regarding PBMT in the treatment of chemotherapy-induced alopecia, its widely documented regenerative potential in dermatological treatment suggested potential therapeutic applications, and additional rigorous clinical trials were demanded [23].

In addition, PBMT has been promising as an effective adjuvant to cancer lymphedema treatment, which is identified by chronic swelling of the extremities, impaired limb function, and impaired patient mobility [24]. Traditional treatment of choice has been conservative management with compression and manual lymphatic drainage; however, PBMT's regenerative and anti-inflammatory properties offer some therapeutic benefits that must be investigated in the context of oncologic rehabilitation strategies [24].

Current research has also found potential applications in cachexia cancer, a syndrome of extreme muscle loss that is common in advanced cancer patients [34]. Preclinical research has identified the PI3K/AKT/FoxO3a signaling pathway as a crucial pathway responsible for the ability of PBMT to modulate muscle injury and potentially improve functional capacity and survival in cachexia cancer patients [34]. Concurrently, recent research has also explored the neuroprotective properties of PBMT and its potential as an intervention for chemotherapy-induced cognitive dysfunction, and thus a potential expansion of its therapeutic use [32].

In addition, long-term safety and survival outcomes of PBMT treatment in oncology have been extensively examined, allaying earlier fears of potential risks for tumor stimulation. Systematic reviews and longitudinal analyses, as well as all of them, confirm the safety profile of PBMT in oncologic usage, with no probable risk of tumor recurrence or formation with low-energy laser treatment [35]. Notably, fresh evidence indicates enhanced long-term survival in cancer patients who received PBMT for prevention and treatment of oral mucositis [35]. Additionally, PBMT also had extensive therapeutic applications, including home treatment, offering convenient supportive care interventions, particularly helpful in the event of healthcare disruptions such as the COVID-19 pandemic [36]. However, in spite of mounting evidence supportive of the clinical effectiveness of PBMT, many practical matters still remained to be examined, specifically relating to standardized dosing regimens, optimal wavelengths, irradiance, and timing protocols particular to each different type of cancer and treatment setting [36-37]. Further studies on patient compliance, standardization of PBMT treatment protocols, and thorough cost-effectiveness evaluation would be required to fully integrate PBMT into routine supportive oncology practice [36-38].

5. LIMITATIONS

The current review is marred by many limitations. The fewer number of studies with heterogeneous PBMT protocols, varied follow-up times, and heterogeneous evaluation measures imposed generalizability and comparability constraints. The high heterogeneity observed for pain scores and mTNS measures also hindered the synthesis of combined effects. Moreover, poor reporting of some technical parameters, rates of compliance, and the absence of standardized documentation of adverse events also compromised the overall strength of the conclusions drawn.

6. RECOMMENDATIONS AND IMPLICATIONS FOR FUTURE RESEARCH

Future research on PBMT for chemotherapy-induced peripheral neuropathy must be planned to perform large-scale, multicenter RCTs with optimal study design to achieve maximum reliability and external validity of results.

Standardization of PBMT protocols like the availability of clear guidelines on optimal parameters like wavelength, power density, energy density, irradiation duration, number of sessions and frequencies, and the duration of PBMT course will be crucial to ensure maximum results reproducibility and comparability across trials. Incorporation of detailed description of patient compliance, adequate evaluation of adverse effects, and the cost-effectiveness evaluation of treatments within the trials will be required to evaluate practical feasibility as well as the health-economic considerations. Extended duration follow-up for more than several weeks will be suitable to evaluate late effects of efficacy, safety, and the patient outcomes after PBMT. Patient-level predictors of response like the severity of initial neuropathy, type of tumor, or anticancer chemotherapy drugs may allow personalization of the treatment schedules. Future trials will also yield high-quality results amenable to development of evidence-based clinical guidelines and thus PBMT would become a component of supportive therapy algorithms for chemotherapy-induced peripheral neuropathy in cancer patients.

7. CONCLUSION

Based on the cumulative evidence from clinical trials analysed in this review, PBMT showed statistically significant advantage in reducing the severity of chemotherapy-induced peripheral neuropathy, neuropathy symptoms, and the severity of cancer pain. Across methodological diversity, PBMT consistently showed positive effects in diverse clinical outcomes, reflecting clinical usefulness as an adjunctive therapeutic intervention. However, owing to the large heterogeneity and limited methodological quality seen among studies included, the magnitude of benefits observed should be viewed with caution. Thus, PBMT was promising but needed to be further standardized and validated by appropriately designed, sufficiently powered studies to confirm these preliminary findings.

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Conflict of interest
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