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REVIEW

The Efficacy of Neuromodulation Interventions for Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis

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Purpose: To determine the efficacy and safety of a neuromodulation intervention regimen in the treatment of chemotherapy-induced peripheral neuropathy (CIPN).

Patients and Methods: Systematic searches were conducted in seven English databases. Randomized controlled trials of all neuromodulation interventions (both invasive and non-invasive) for the treatment of CIPN were selected. Group comparisons of differences between interventions and controls were also made. We divided the outcomes into immediate-term effect (≤3 weeks), short-term effect (3 weeks to ≤3 months), and long-term effect (>3 months).

Results: Sixteen studies and 946 patients with CIPN were included. Among immediate-term effects, neuromodulation interventions were superior to usual care for improving pain (SMD=−0.77, 95% CI −1.07~ 0.47), FACT-Ntx (MD = 5.35, 95% CI 2.84~ 7.87), and QOL (SMD = 0.44, 95% CI 0.09~ 0.79) (moderate certainty); neuromodulation loaded with usual care was superior to usual care for improving pain (SMD=−0.47, 95% CI −0.71 ~ −0.23), and QOL (SMD = 0.40, 95% CI 0.12 ~ 0.69) (moderate certainty). There were no statistically significant differences between the neuromodulation interventions regimen vs usual care in short- and long-term outcomes and neuromodulation vs sham stimulation from any outcome measure. There were mild adverse events such as pain at the site of stimulation and bruising, and no serious adverse events were reported.

Conclusion: Neuromodulation interventions had significant immediate-term efficacy in CIPN but had not been shown to be superior to sham stimulation; short-term and long-term efficacy could not be determined because there were too few original RCTs. Moreover, there are no serious adverse effects of this therapy.

Keywords: chemotherapy, peripheral neuropathy, neuromodulation, systematic review, meta-analysis

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common dose-limiting side effect during cancer therapy. Various conventional cytotoxic drugs can cause CIPN, such as paclitaxel, platinum, periwinkle alkaloids, proteasome inhibitors, thalidomide and so on.[1,2] The symptoms of CIPN commonly occur in the hands and feet, while the symptoms are more severe in the lower extremities than the upper extremities. The typical clinical features include tingling, numbness, burning, symmetrical "socking type", and other paresthesias and dysesthesias.[3,4] Meanwhile, some

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patients may experience ataxia and other motor symptoms.[5,6] CIPN seriously affects the quality of life for cancer patients, and symptoms may continue for extended periods. The treatment's efficacy may be compromised if the chemotherapy dose is lowered or stopped too soon due to a severe adverse effect.[7,8]

The conventional CIPN treatments are pharmacological interventions and non-pharmacological interventions.[4,9] According to the American Society of Clinical Oncology and the European Society for Medical Oncology guidelines, duloxetine is recommended for CIPN pain management with moderate evidence.[2–4] However, a recent meta-analysis shows that duloxetine's efficacy in treating CIPN is not considerably more remarkable than the placebo effect, and caution should be used concerning its side effects.[10,11] Based on the above discussion, the search for a proven treatment is critical.

Non-pharmacological interventions for CIPN have become a research hotspot. Neuromodulation interventions, as a rapidly evolving multidisciplinary non-pharmacological therapy, are now widely applied in pain management.[12,13] The International Neuromodulation Society defines it as: "The alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body".[13,14] Common neuromodulation interventions include invasive and non-invasive ways, with invasive interventions including spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), and acupuncture.[15–17] Non-invasive interventions include neurofeedback (NF), scrambler therapy, and TENS.[18–20]

Current research on the mechanisms of CIPN involves the peripheral nerve, spinal nerve, and brain levels.[21–23] Neuronal overexcitation, imbalance of nerve cell metabolic homeostasis, as well as brain hyperactivity, reduced GABAergic inhibition, neuroinflammation, and overactivation of the GPCR/MAPK pathway may all contribute to the onset and development of CIPN.[23] Therefore, neuromodulation interventions based on the nerve or brain level are promising, and these interventions act directly or indirectly on the nerves and the brain through various stimulation modalities to improve their functions and enhance peripheral nerve regeneration processes.[22]

The benefits of neuromodulation interventions in pain alleviation and improved quality of life have recently been demonstrated by several high-quality RCTs.[24–26] Neuromodulation interventions have shown promise in the management of CIPN, according to several guidelines[2,4] and reviews.[3,9] However, the efficacy of neuromodulation therapy is still unknown because there are not many large-scale clinical trials, there are contradicting findings in the present research, and the methodologies are not all of high quality (eg, some studies did not report the details of the random grouping process; small sample sizes; no blinding was used in the intervention process or in assessing outcomes, etc.). The majority of the original research included in previous systematic reviews of neuromodulation treatment for treating CIPN lacked quantitative analysis.[18,27] Therefore, this study provided a comprehensive assessment of the therapeutic effects of neuromodulation interventions for CIPN through a systematic review and meta-analysis utilizing neurophysiological tests and patient-reported outcome measures (PROMs). The aim was to in order to fill the gaps in existing studies and to determine the efficacy and safety of neuromodulation as a stand-alone treatment or in combination in reducing pain, relieving symptoms, and improving the quality of life of patients with CIPN.

Materials and Methods

We had registered on PROSPERO with the number CRD42023413430. This review was reported adhering to the PRISMA guidelines (Supplementary Material, Table S1).[28]

Data Sources and Literature Search

We searched PubMed, Embase, Cochrane, Web of Science, PsyclNFO, and CINAHL from the database inception to February 2023. The search language is limited to English, and the search term is shown in Supplementary Material, Table S2. Two authors (Xu and Yu) independently screened the title, abstract, and full-text articles in turn. Disputes are resolved by third parties (Yan).

Inclusion Criteria

The inclusion criteria are formulated from five aspects: ①population (P): Patients with CIPN, ②interventions measures (I): Neuromodulation Interventions Program, ③control group (C): Usual care and sham stimulation, ④outcome (O):

Patient-reported Outcomes Measures and neurophysiological examinations, ⑤study design (S): RCTs. (see Supplementary Material, Table S3 for specific details)

Exclusion Criteria

The exclusion criteria included: (1) the participant with cause peripheral neuropathy due to other diseases; (2) Cross-over trials; (3) non-English published articles; (4) Repeated publication or inability to obtain literature in full text (If there were duplicates, the most recent/comprehensive paper was selected for inclusion in the study).

Data Extraction

Two investigators (Zhang and Jia) independently extracted the literature data. Disputes are resolved by third parties (Jiang). Information was extracted as follows: (1) Characteristics information: authors, publication year, patients' characteristics (age, chemotherapy drug, chemotherapy status, etc.), sample size, details of interventions/control measures; (2) outcome data: pain intensity, FACT-Ntx, EORTC QLQ-CIPN20, quality of life, and NCS; (3) risk of bias assessment required for key elements.

We divided the outcomes into immediate-term effect (≤3 weeks), short-term effect (3 weeks to ≤3 months), and long-term effect (>3 months).[29–31] In research with multiple time points, we chose data for the point closest to 3 weeks and the third month. The point longer than 3 months was also extracted.

Risk of Bias Assessment

The Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2)[32] was conducted to assess the methodological quality of each study in five aspects: (1) randomization process, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) the selection of the reported result. For each included study, three determinations, "high risk", "unknown risk", and "high risk", were made. This process was assessed independently by two researchers (Zhang and Li).

Statistical Methods

Statistical analysis was performed using Review Manager 5.4.1. The types of data in this study were measurement data, which were expressed using standardized mean differences (SMD) or mean differences (MD), and 95% confidence intervals (CIs) were calculated. Subgroups were analyzed according to follow-up time or intervention protocol (e.g, use of neuromodulation interventions alone, neuromodulation loaded with usual care). The statistical heterogeneity of the results for different groups was analyzed using the Q test, combining the P value with the judgment of heterogeneity: $P>0.10$ and $I^2\leq 50\%$ represent good homogeneity within the group, so the fixed-effect model was used for meta-analysis; $P\leq 0.10$ and $I^2>50\%$ represent greater statistical heterogeneity within the group, so the random-effect model was used.[33] When heterogeneity is high, subgroup analysis was implemented to trace the sources. The publication bias was performed by funnel plots with Egger's test.

Level of Evidence

Use the Grading of Recommendations Assessment Development and Evaluation (GRADE) to evaluate the level of evidence for outcome indicators.[34] Five factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) that may lower the level of evidence were evaluated using GRADEpro GDT (https://gradepro.org/). The final results will be divided into four levels: high, moderate, low, or very low.

Results

Literature Search

The initial database search obtained 1449 publications, and 16[25,26,35–48] RCTs were finally included in the literature for meta-analysis. The details are shown in Figure 1.

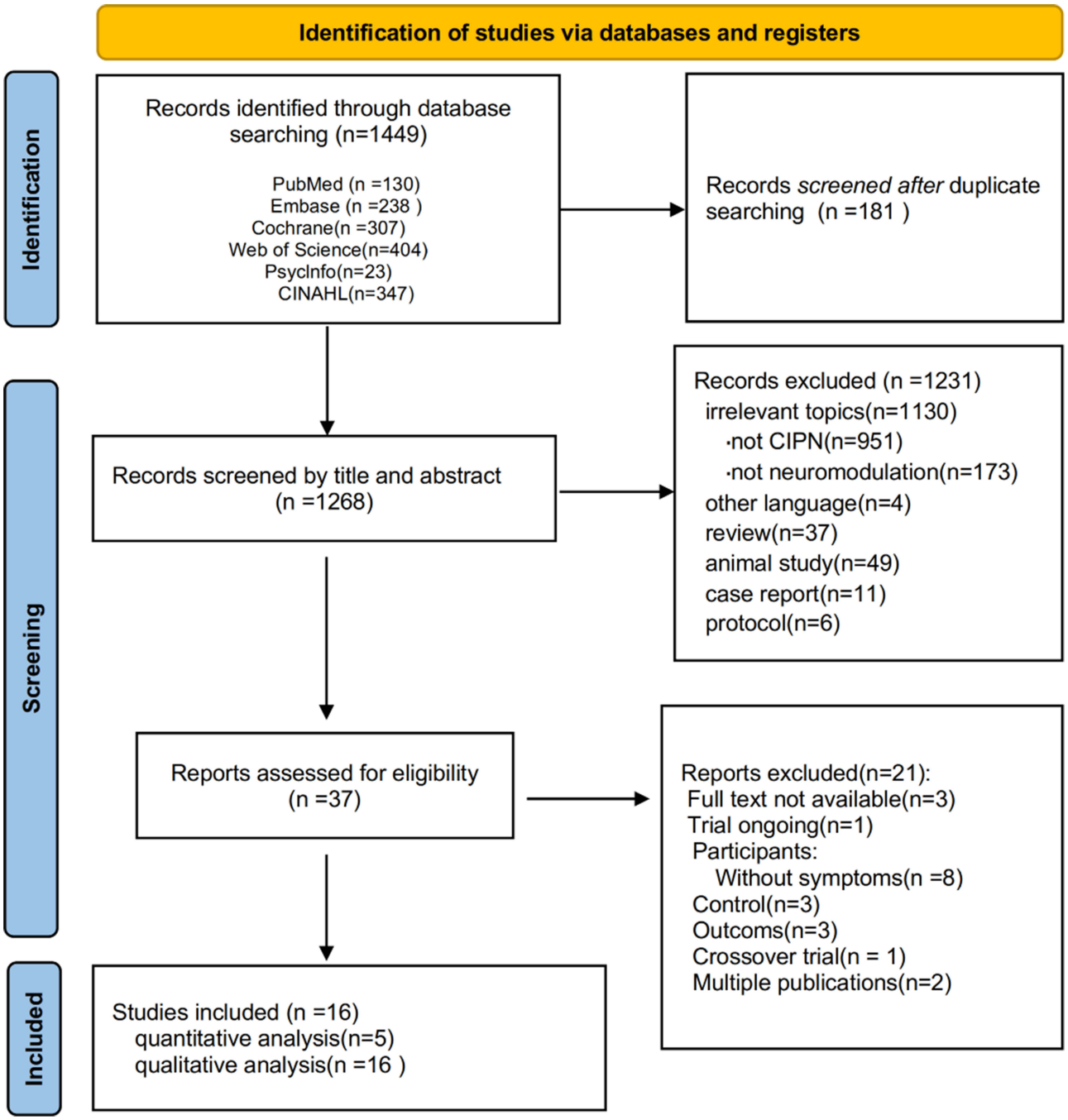

Figure 1 Flowchart of systematic review.

Characteristics of Included Literature

Sixteen studies were included from the United States,[25,38,46,48] China,[26,37,40,42] Canada,[49] Germany,[41,47] the United Kingdom,[35] South Korea,[36] Australia,[44] Sweden,[45] and Brazil.[43] One of the studies was a three-arm study,[46] so there were 17 comparisons in the review. A total of 946 patients were involved, including 461 patients in the experimental group and 465 patients in the control group. According to the variations in interventions between the experimental and control groups, the aforementioned 17 comparisons were classified into three categories: Neuromodulation interventions in comparison to usual care (including standard care and usage of medicines advised by guidelines);[38,41,42,48,49]

Neuromodulation interventions versus sham stimulation,[25,36,40,43–47] and Neuromodulation interventions combined with usual care versus usual care.[26,35,37,46]

Outcome indicators for these RCTs include: 1. pain level (scales including NRS, VAS, BPI-SF) 2. quality of life (scales including SF-36, EORTC QLQ-C30, FACT-G, WHOQOL-BREF) 3. scales for the evaluation of symptoms and functions in patients with CIPN: the Functional Assessment of Cancer Therapy Neurotoxicity (FACT-NTX);[50] European Organization for Research and Treatment of Cancer Chemotherapy Induced Peripheral Neuropathy Questionnaire (EORTC QLQ-CIPN20).[51] A total of 10 RCTs[25,35–37,40,42,43,45,46,48] measured pain intensity, 8 RCTs[26,35,38,40,41,44,48,49] reported quality of life, 7 RCTs[26,37,38,40,44,46,49] measured FACT-Ntx, 5 RCTs[25,35,36,44,49] reported EORTC QLQ-CIPN20 and 5 RCTs[26,37,41,42,47] reported NCS. All RCTs had immediate effect measures for outcomes at the end of the last interventions; a total of 8 RCTs[27,28,38,41,42,44,46,49] reported short-term effect outcomes ranging from 4 weeks to 80 days; a total of 1 RCT[45] reported long-term effects. The details are shown in Table 1.

Quality Assessment

Among the included studies, 6 RCTs[25,26,36,40,46,49] were evaluated as low risk, 7 RCTs[35,41–45,47] were evaluated as unknown risk, and 3 RCTs[37,38,48] were evaluated as high risk. Selection bias: 3 studies[37,45,47] did not report details of the random grouping process, while the grouping method of the rest of the studies was by computer-generated random numbers, and 5 studies[36,40–42,48] did not report details of allocation concealment methods. Implementation bias: Because of the characteristic of the neuromodulation interventions, trial performers and participants are difficult to blind to the interventions (eg, needling). Six studies[26,38,46–49] did not blind trial performers and participants, and 3 studies[26,46,47] blinded subjects only. No bias occurred due to the study setting in the included studies. Three studies[37,42,48] were evaluated as high risk or some concern because of inappropriate methods for intervention effect analysis. Withdraw bias: 2 studies[38,48] were evaluated as high risk because many cases were lost to follow-up, and no reasonable reason was given. Measurement bias: 6 studies[35,37,38,41,44,48] did not clearly report assessor blindness. Given that the outcomes were mostly subjective, it is possible that the outcome assessors were impacted by the absence of blindness (details in Figure 2).

Immediate-Term Effect

Four outcomes of CIPN pain intensity, FACT-Ntx, EORTC-CIPN20 and quality of life were meta-analyzed. NCS outcomes were quantitatively described in the three groups according to the inclusion of RCT interventions and outcomes. The results of the GRADE evaluation are shown in Supplementary Material, Figure S1.

Nerve conduction study (ncs)

The 5 studies[26,37,41,42,47] revealed the results for immediate-term effect of nerve conduction studies involving the common peroneal nerve, sural nerve, median nerve, ulnar nerve, and tibial nerve. Among them, 3 studies[26,41,42] fully reported distal nerve latency, amplitude, and conduction velocity, while the other two[37,47] only reported nerve conduction velocity.

For neuromodulation with usual care, the results of one study[26] showed that the included population was in the normal range of neurophysiological examinations at baseline, and there was no significant difference for endpoints compared to baseline. However, another study[37] showed a significant improvement in nerve conduction velocities of peroneal nerve sensory at the end of the treatment when neuromodulation interventions with usual care compared to usual care ($P<0.01$), and this intervention regimen was also statistically significant in a within-group comparison of MCV in the bilateral median nerve and the peroneal nerve.

For the use of neuromodulation alone, one study[42] showed significant differences in the improvement of the amplitude of the sural nerve, MCV of the peroneal nerve, and the amplitude and the MCV of the tibial nerve when compared to usual care. However, another study showed[41] that at the end of the treatment, all outcomes were not statistically significant when compared to the usual care. Rick showed that[47] there was no statistically significant improvement in NCV of the peroneal nerve with neuromodulation compared to sham groups, and there was a significant difference in conduction velocities of peroneal nerve after 3 weeks of interventions ($P=0.021$), whereas the difference was not statistically significant after 3 months of interventions.

Table 1 Characteristics of the Included Studies

Literature		Number of Cases	Chemotherapy		Interventions			Treatment/ Week	Outcome	Follow-Up Time	Adverse Events
Author, Publish Time	Country	Interventions Group/Control Group	Drugs	Status	Interventions Group		Control Group				
					Interventions Details	Stimulation Site					
Al Onazi 2021[49]	Canada	16/15	Platinum	Chemotherapy in progress or completed	Ultrasound therapy; 5min/point, 3Hz, 0.7~0.8w/cm2, 10 times	Fingers and toes/soles	Usual Care	2 weeks	②③④	6 weeks	None
Bao 2021(1)*[46]	USA	24/23	Platinum, taxane	Completed chemotherapy ≥ 3 months	Acupuncture + Usual care; 30 min/time, 2~5Hz, 2 times/week (1~2 weeks), 1 time/week (3~8 weeks)	(1) Auricular points: HT7, HX1 (2) Acupoints: LI4, PC6, SI03, LR03, GB43, ST40, EX-LE10, EX-UE9	Usual Care	8 weeks	①③	4 weeks	6/0
Bao 2021(2)[46]	USA	27/24	Platinum, taxane	Completed chemotherapy ≥ 3 months	Acupuncture + Usual care; 30 min/time, 2~5Hz, 2 times/week (1~2 weeks), 1 time/week (3~8 weeks)	(1) Auricular points: HT7, HX1; (2) Acupoints: LI4, PC6, SI03, LR03, GB43, ST40, EX-LE10, EX-UE9	Placebo	8 weeks	①③	4 weeks	6/0
Han 2017[37]	China	52/52	Not reported	Chemotherapy in progress	Acupuncture + Usual care; 30min/time, 3 times/day; 2 days/session;	LR03, ST43, GB41, SP6, ST36, SP10, ST25, CV14, DU12, DU11, DU09, BL13, BL17, BL58	Usual Care	12 weeks	①③⑤	None	Not reported
Huang 2021[40]	China	10/10	Platinum, taxane	Completed	Acupuncture; 30min/time, 2 times/week (1~6 weeks); 1 time/week (7~9 weeks)	CV5, LI11, PC6, LI4, ST36, SP6	Placebo	9 weeks	①②③	None	None
Iravani 2020[42]	China	20/20	Platinum, Taxane, ADM/CTX	Completed	Acupuncture; 20min/time, 3 times/week;	(1) Main acupoint: CV5, DU20, ST36, SP6, LI4, LI11, LR03; (2) additional acupoints: upper limbs: EX-UE9, lower limbs: EX-LE10	Usual Care	4 weeks	①⑤	4 weeks	0/1
Lindblad 2016[45]	Sweden	34/33	Platinum, Taxane, VLB, Bortezomib, Capecitabine	Completed	High-powered interferential electrotherapy and long-wave transthermal therapy (ITH); Interferential electrotherapy: 15 min/session, 0 ~ 100 Hz, ITH: 6 min/session, 1 time/week	CIPN symptomatic areas in both lower extremities	Placebo	12 weeks	①	25 weeks	Not reported
Lu 2020[38]	USA	20/20	Taxane	Completed chemotherapy ≥ 1 week	Electroacupuncture; 30min/time, 2~10Hz, 3 times/week (1–2 weeks), 2 times/week (3~8 weeks);	EX-LE12, LR03, KI3, ST36, SP6, LI11, EX-HN3, EX-UE9, TW-5	Usual Care	8 weeks	②③	8 weeks	1/1
Molassiotis 2019[26]	China	44/43	Platinum, Taxane, Bortezomib, Capecitabine	Chemotherapy in progress or ending chemotherapy	Acupuncture+ Usual Care; 30min/time, 2 times/week;	(1) Upper limbs: LI4, LI11, PC07/TE5/EX-UE9 (2) Lower limbs: SP6, ST36, LR03/ST41/EX-LE10	Usual Care	8 weeks	②③⑤	6 weeks / 12 weeks	None
Prinsloo 2018[48]	USA	30/32	Platinum, Taxane	Completed chemotherapy ≥ 3 months	EEG neurofeedback; 45min/time,≥2 times/week	Scalp	Usual Care	20 times/ ≤10 weeks to complete	①②	None	None

Rick 2017[47]	Germany	21/23	Platinum, Taxane, VLB, Bortezomib, Thalidomide, etc.	Completion of chemotherapy	Magnetic therapy; 5min/time, 2 times/day, 6 times/week, 4 ~ 12 Hz, 420 mT	CIPN symptomatic areas	Placebo	12 weeks	⑤	None	Not reported
Rostock 2013[41]	Germany	14/15	VLB, Platinum, Taxane	Completion of chemotherapy	Electroacupuncture; 15min/time, 50Hz, 9 times;	(1) Lower limbs: LR03, GB34, GB41 (2) Upper limbs: LI4, LI11, SI03, HT3	Usual Care	3 weeks	②⑤	9 weeks	Not reported
Smith 2020[25]	USA	17/18	Platinum, Taxane	Completed chemotherapy ≥ 3 months	Scrambler therapy: 30min/session, 10 sessions	CIPN symptomatic areas	Placebo	2 weeks	①④	18 days/ 50 days/ 80 days	Not reported
Song 2020[36]	Korea	36/36	Taxane, Anthracycline, nitrogen mustards	Completion of chemotherapy	Low-frequency electrical stimulation therapy; 120 min/time, 2 times/day, 100 μA, 40 Hz;	PC6	Placebo	2 weeks	①④	None	10/9
Stringer 2021[35]	UK	61/59	Platinum, Taxane, Thalidomide	Chemotherapy in progress or completed	Acupuncture + Usual care; 40min/time, 1 time/week;	(1) Lower limbs: LR03, SP6, ST36, EX-LE10, BL60 (2) Upper limbs: EX-UE9, LI4	Usual Care	10 weeks	①②④	None	16/0
Teng 2023[44]	Australia	29/15	Platinum, Taxane	Completed chemotherapy ≥ 3 months	Photobiomodulation therapy; 2 times/week, 12 times; Wavelength 658μm, power density 8mW, intensity: maximum tolerance for degrees	EX-LE10, EX-UE9, C–6 - T1, L–5 - S1 nerve roots bilaterally	Placebo	6 weeks	②③④	6 weeks	19/8
Tonezzer 2017[43]	Brazil	11/13	Platinum, Taxane	Chemotherapy in progress	TENS; 60 min/time, 7~65 Hz, pulse width 200 μs, intensity: maximum tolerance to degree;	CIPN symptomatic areas	Placebo	45 days	①	None	Not reported

Notes: *One study (Bao 2021) with two comparisons in our review; Outcomes: ① represented Pain intensity; ② represented Quality of life; ③ represented FACT-Ntx (Functional Assessment of Cancer Therapy/Gynecologic Cancer Group Neurotoxicity Subscale); ④ represented EORTC-CIPN20 (European Organization for Research and Treatment of Cancer Chemotherapy Induced Peripheral Neuropathy Questionnaire); ⑤ represented Nerve conduction study (NCS); Adverse Events: None: no adverse events; Not reported: adverse events not mentioned.

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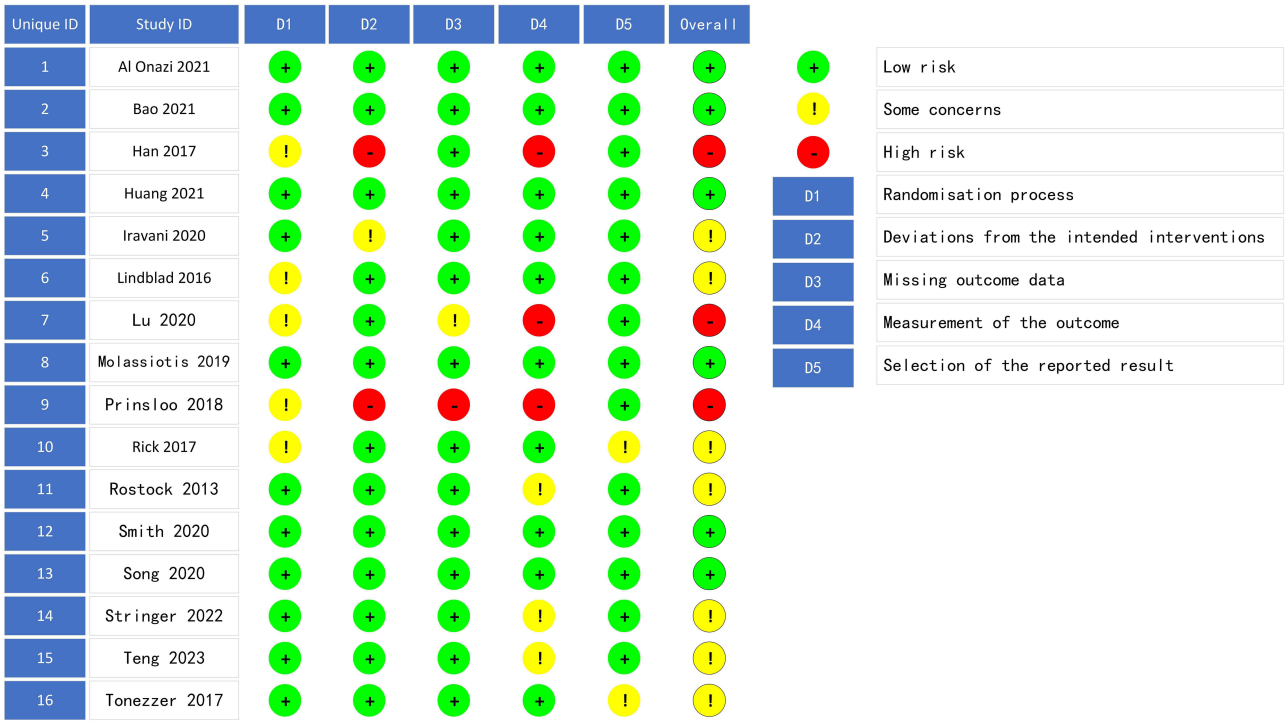

Figure 2 Risk of bias summary.

Pain Intensity

Twelve studies reported the immediate effect on the improvement of CIPN pain intensity, including 734 patients. Because the included studies had different scales for assessing pain intensity but the same purpose and tendency, the results are combined using standardized mean differences (details in Figure 3A).

Four studies[38,42,46,48] compared neuromodulation interventions with usual care and showed that there was a significant difference in the reduction of pain intensity with neuromodulation interventions compared with usual care (moderate evidence; fixed-effect model; N = 187; SMD = −0.77, 95% CI −1.07~ 0.47, P<0.00001; I^2=0%).

The combined results of the 6 studies[25,36,40,43,45,46] showed that there is no difference between neuromodulation interventions and sham stimulation in interventions (high evidence; fixed-effects model; N = 265; SMD = −0.21, 95% CI −0.45~ −0.04, P = 0.1; I^2 = 36%).

Three studies[26,35,37] showed that the difference between neuromodulation interventions combined with usual care and usual care in terms of pain reduction was statistically significant (moderate evidence; fixed-effects model; N = 282; SMD = −0.47, 95% CI −0.71~ −0.23, P = 0.0001; I^2= 41%).

FACT-Ntx

Six studies reported the immediate effect on the improvement of the FACT-Ntx neurotoxicity index, including 734 patients. Only two groups were included in the number of studies, and the results were analyzed in the form of descriptive analysis combined with meta-analysis (details in Figure 3B).

Three studies[38,46,49] compared neuromodulation interventions with usual care and showed that there was a significant difference in the improvement of FACT-Ntx neurotoxicity index with neuromodulation interventions compared with usual care (moderate evidence; fixed-effect model; N = 122; MD = 5.35, 95% CI 2.84~ 7.87, P < 0.0001; I^2= 48%).

The combined results of the 2 studies[40,46] showed that the difference between neuromodulation interventions and sham stimulation in terms of sham stimulation was not statistically significant (low evidence; fixed-effects model; N = 71; MD = 1.23, 95% CI −1.70~ 4.16, P = 0.41; I^2= 0%). Only 1 study[26] showed that there was a significant difference in the improvement of FACT-Ntx neurotoxicity indexes between neuromodulation interventions combined with usual care compared with usual care (MD = 0.55, 95% CI 0.12~0.97, P = 0.01).

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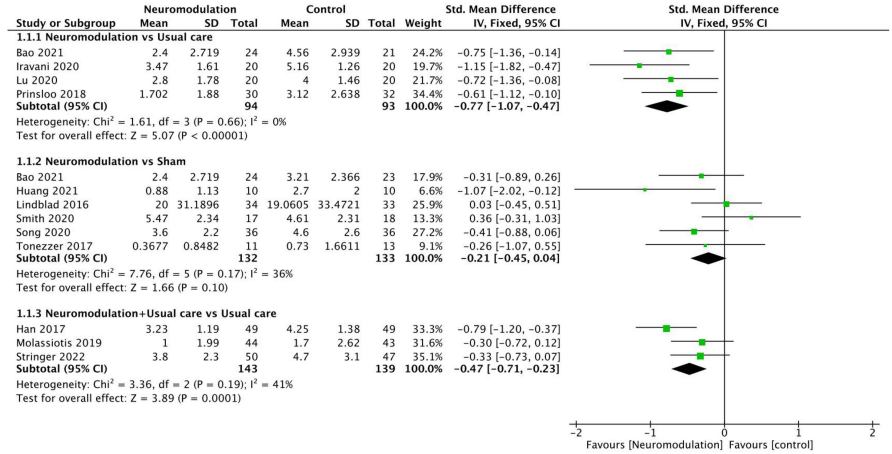

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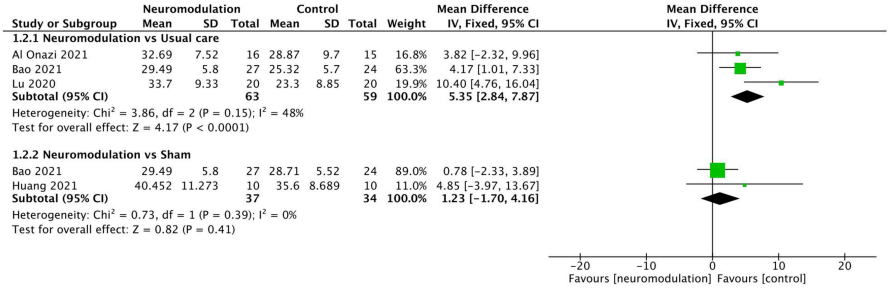

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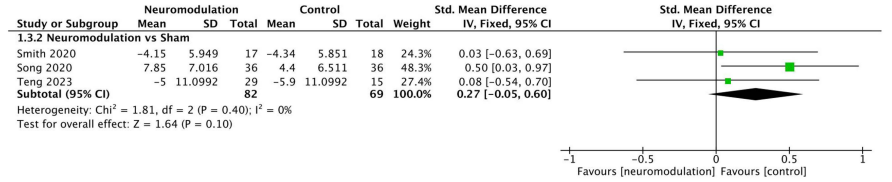

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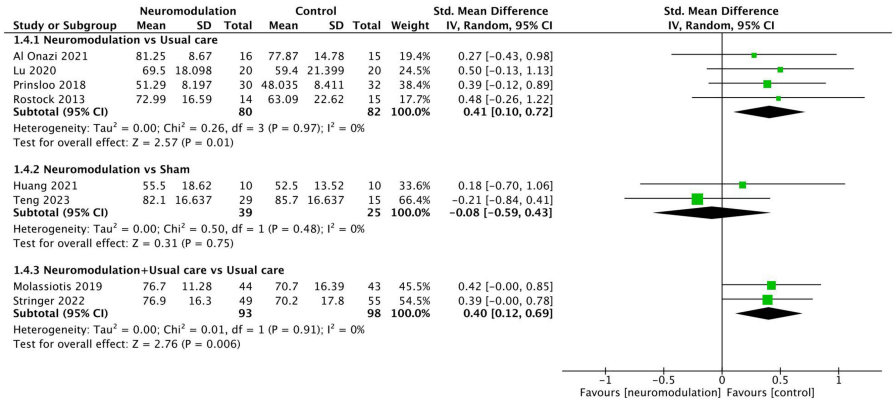

Figure 3 Forest plot of the immediate effects of neuromodulation interventions. (**A**) Effects of neuromodulation interventions on pain intensity. (**B**) Effects of neuromodulation interventions on FACT-Ntx. (**C**) Effects of neuromodulation interventions on EORTC QLQ-CIPN20. (**D**) Effects of neuromodulation interventions on QoL.

EORTC QLQ-CIPN20

Five RCTs reported between-group differences on the EORTC QLQ-CIPN20 scale. The outcomes were analyzed through a combination of descriptive and meta-analysis (details in Figure 3C).

One RCT[49] showed no statistical difference between neuromodulation interventions and usual care in improving QLQ-CIPN20 neurotoxicity indicators (MD=−0.34, 95% CI −1.05~ 0.37, *P*=0.35); 1RCT[35] compared neuromodulation interventions combined with usual care to usual care, and the results showed that neuromodulation interventions combined with usual care were more effective than usual care, but not statistically significant overall (MD=−0.35, 95% CI −0.74~ 0.03, *P*=0.07).

Three studies[25,36,44] comparing the difference in QLQ-CIPN20 neurotoxicity indicators between neuromodulation interventions and sham stimulation, combined results showed no statistical significance between the two groups (moderate evidence; fixed-effect model; N = 151; SMD = 0.27, 95% CI −0.05~ 0.6, *P* = 0.10; I^2= 0%).

Quality of Life

Seven studies with outcomes reporting between-group differences in quality of life (details in Figure 3D).

Four studies[38,41,48,49] compared neuromodulation interventions with usual care and showed a significant difference in the improvement of quality of life with neuromodulation interventions compared with usual care (moderate evidence; fixed-effect model; N = 162; SMD = 0.44, 95% CI 0.09~ 0.79, *P* = .01; I^2= 0%).

Two studies[40,44] compared neuromodulation interventions with the sham group and showed that there was no statistically significant difference in the improvement of quality of life with neuromodulation interventions compared with usual care (very low evidence; fixed-effect model; N = 64; SMD = −0.08, 95% CI −0.59~ 0.43, *P* = 0.75; I^2 = 0%).

Two studies[26,35] comparing neuromodulation interventions combined with usual care to usual care showed a significant difference in improvement in quality of life with neuromodulation interventions combined with usual care compared to usual care (moderate evidence; fixed-effect model; N = 191; SMD = 0.40, 95% CI 0.12~ 0.69, *P* = 0.006; I^2 =0%).

Short-Term Effect

We did a meta-analysis to evaluate the short-term effect of FACT-Ntx, EORTC QLQ-CIPN20 and QoL according to the different interventions and the reporting of outcome measures in the literature. The results of the GRADE evaluation are shown in Supplementary Material, Figure S2.

FACT-Ntx

Six studies with outcomes reporting between-group differences in FACT-Ntx scales. None of the three inter-group comparisons found that the intervention group was superior to the control group in improving the FACT-Ntx neurotoxicity index (details in the Figure 4A).

The results of the meta-analysis of the two RCTs[38,49] combined showed no statistically significant results for the neuromodulation interventions compared to the usual care group (very low evidence; fixed-effect model; N = 71; SMD = 0.05, 95% CI −0.42~ 0.51, *P*=0.84; I^2=0%).

Two RCTs[44,46] combined showed no statistically significant results for the neuromodulation interventions compared to the sham group (very low evidence; fixed-effect model; N = 95; SMD = 0.02, 95% CI −0.39~ 0.44, *P* = 0.92; I^2=0%).

Two RCTs[26,46] combined showed no statistically significant results for the neuromodulation interventions combined with usual care compared to usual care (moderate evidence; fixed-effect model; N = 138; SMD = 0.30, 95% CI −0.04~ 0.63, *P*=0.08; I^2=0%).

EORTC QLQ-CIPN20

Two studies[25,44] compared neuromodulation interventions with the sham group and showed that there was no statistically significant difference in the improvement of quality of life with neuromodulation interventions compared with usual care (very low evidence; fixed-effect model; N = 79; SMD = 0.10, 95% CI −0.36~ 0.55, *P* = 0.68; I^2=0%). (Details in Figure 4B)

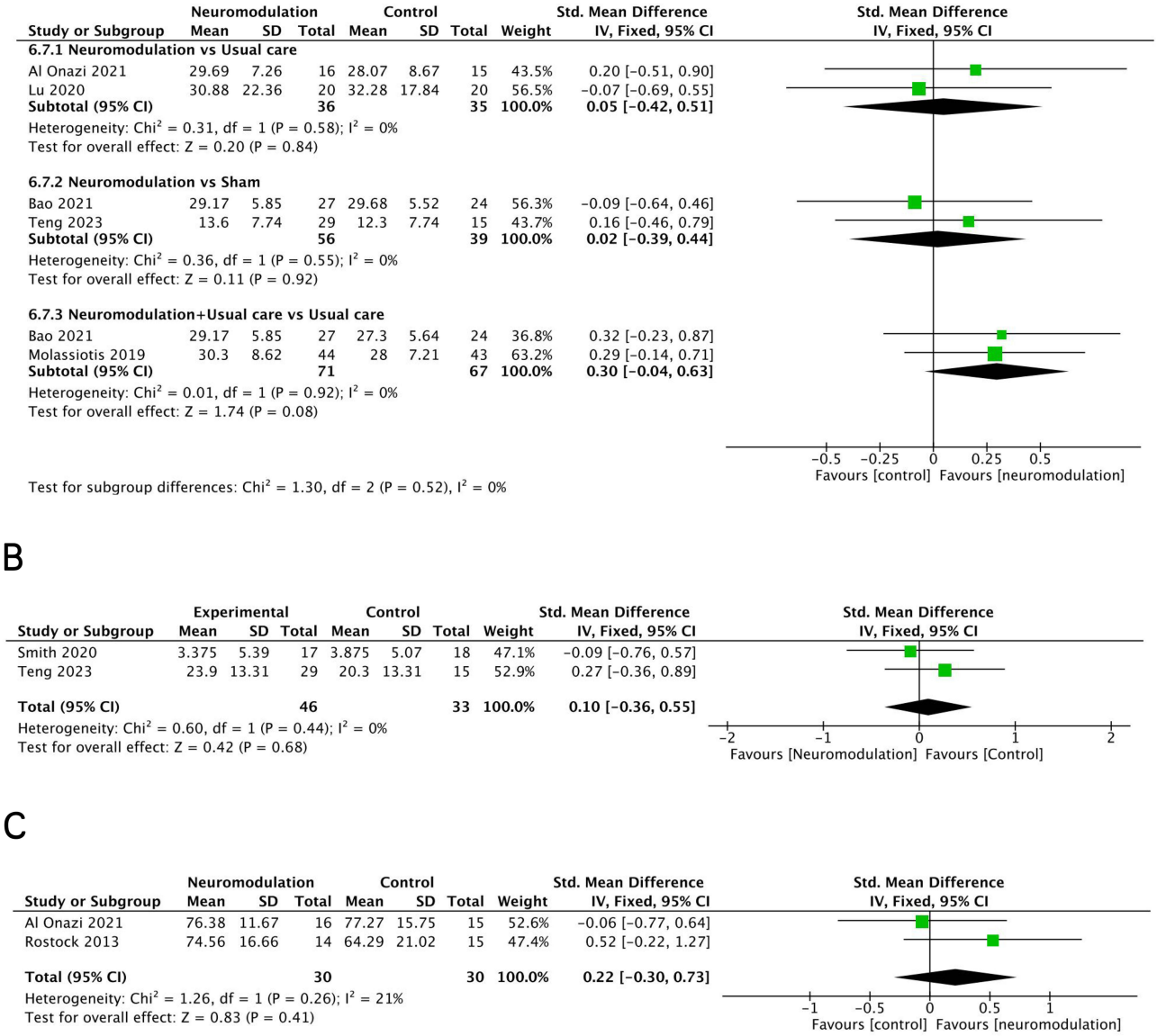

Figure 4 Forest plot of the short-term effects of neuromodulation interventions. (**A**) Effects of neuromodulation interventions on FACT-Ntx. (**B**) Effects of neuromodulation interventions on EORTC QLQ-CIPN20. (**C**) Effects of neuromodulation interventions on QoL.

Quality of Life

Two studies[41,49] compared neuromodulation interventions with the usual care group and showed that there was no statistically significant difference in the improvement of quality of life in the two groups (very low evidence; fixed-effect model; N = 60; SMD = 0.22, 95% CI −0.30~ 0.73, $P = 0.41$; $I^2 = 0\%$). (details in the Figure 4C)

Long-Term Effect

Only 1 study[45] with some concerns about the risk of bias followed the long-term effects of neuromodulation therapy on the degree of pain relief compared to sham stimulation and showed no statistically significant differences between the two groups ($P = 0.885 > 0.05$).

Adverse Events

A total of 10 studies[26,35,36,38,40,42,44,46,48,49] reported adverse events, of which 5 studies[26,40,46,48,49] reported that patients did not experience adverse effects related to neuromodulation interventions. The rest of the studies had no serious adverse events, and these minor adverse symptoms resolved independently and did not require interventions.

The adverse effects associated with acupuncture were pain, bruising, bleeding, and claustrophobia with a blindfold;[35,38,42,46] the possible adverse events related to electrical stimulation were diarrhoea, lymphedema, extremity oedema, and flu-like symptoms;[36] and the adverse events associated with the laser interventions were tingling and hot/cold changes in temperature.[44] Notably, Iravani[43] reported that the usual care of CIPN (gabapentin) causes somnolence and dizziness.

Publication Bias

Funnel plots were plotted for the immediate effect of improvement in pain intensity as an outcome indicator, and Egger tests were performed to analyze for publication bias. The results showed that the funnel plots were symmetrical, and Egger tests P=0.538>0.05, indicating that there was no publication bias in the 13 pieces of literature included in this outcome indicator (details in the Supplementary Material, Figure S3).

Discussion

Main Findings

Our review's conclusions complement those of previous systematic studies and advance their findings. The moderate evidence suggests that a treatment regimen of neuromodulation interventions with/without usual care lasting between 2 and 3 weeks is more efficacious than usual care alone in improving quality of life over the immediate-term period of 3 weeks. Furthermore, moderate evidence suggests that a treatment regimen of neuromodulation interventions lasting between 2 and 3 weeks is more efficacious than usual care in alleviating pain intensity over the immediate-term period of 3 weeks. There is moderate evidence of a significant difference in the short-term efficacy of neuromodulation interventions compared with usual care in FACT-Ntx.

The present results suggest that neuromodulation interventions could potentially be effective for treating pain, relieving symptoms, and improving QOL in individuals with CIPN. Both immediate-term improvements in QOL 0.4 points (95% CI 0.12~0.69) of neuromodulation interventions with the usual care group and 0.41 points (95% CI 0.10~0.72) of the neuromodulation intervention group exceed the minimum clinically important difference (MCID) of 0.1 points for EORTC QLQ-C30 or 0.3 points for FACT-G[52,53] when compared to usual care. In addition, the immediate-term decrease in FACT-Ntx of 5.35 points (95% CI 2.84~ 7.87) achieves the MCID of 1.38 points[54] in neuromodulation intervention groups when compared to usual care. However, the pain intensity of −0.77 points (95% CI −1.07~ −0.47) did not exceed the MCID of 2 points.[55,56] It is worth noting that the results regarding QLQ-CIPN20, pain intensity or FACT-Ntx did not favor neuromodulation interventions over sham interventions in the immediate-, short- or long-term; thus, it is likely that further replications of this research might provide remarkably different outcomes.

This study does not restrict tumor type or chemotherapeutic regimen; this study only produces generalized results without specific analysis of the individual cases. However, since this study only intakes a small number of individual outcome indicators in the original literature, the results should be interpreted cautiously.

The interventions we included were categorized into central neuromodulation techniques (eg, EEG neurofeedback) and peripheral neuromodulation techniques (including TENS, scrambler therapy, acupuncture, photobiomodulation, etc.)[18] In our inclusion of EEG neurofeedback, biofeedback training is done by monitoring the EEG activity of CIPN patients and providing feedback.[48] This therapy may reduce a patient's perception of discomfort by tuning sensory areas of the CIPN patient's brain, enhancing the brain's ability to filter signals such as pain or affecting pain-related neural pathways.[57–59] The mechanisms of peripheral neuromodulation techniques for the treatment of CIPN mainly include improving limb microcirculation,[60,61] reducing oxidative stress and inflammatory reactions,[62–64] inhibiting the release of pain signals through gate-control theory,[65–67] and regulating the release of neurotransmitters.[68,69]

There was no statistically significant improvement in various indicators between the neuromodulation intervention group and the sham group. The possible mechanisms may be due to the specificity of neuromodulation interventions;[44]

thus, it is difficult to achieve absolute non-stimulation of placebo control. The sham group included in this study had minor stimulation,[25,40,43,46] which enhanced the placebo effect. Secondly, the neuromodulation intervention treatment process involves a high level of doctor–patient interaction, which can produce certain neurobiological effects.[70,71] Thirdly, patient expectations are another primary source of the placebo effect for analgesia.[72–75] A secondary analysis[76] of one study concluded that it may be due to higher expectations of baseline outcomes among subjects in the sham acupuncture group.

Nerve conduction studies (NCS) is a generalized CIPN assessment method, and it has been shown that the sensitivity of the NCS to different types of drug-induced CIPN may vary.[77,78] Chemotherapy drug toxicity is prone to affect Aδ fibres and C fibres, while NCS is more sensitive to detecting lesions in Aα large nerve fibres.[79] The individual evidence suggests that neuromodulation interventions improve MCV of the common peroneal nerve, MCV of the tibial nerve and its wave amplitude, SCV of the ulnar nerve, SCV of the peroneal nerve, and wave amplitude in immediate effects. However, other studies contradict these results. Because of the clinical heterogeneity and the small number of included studies, the above results cannot present evidence-based support for clinical use.

Comparison of Similar Studies

There are currently 2 systematic reviews[18,27] of neuromodulation interventions and 4 studies[80–83] of acupuncture for CIPN similar to ours. There are similarities in the results, suggesting that such therapies reduce neuropathic pain[27,83,84] and improve patient quality of life.[81,83] It can also be combined with usual care to improve outcomes.[82] However, unlike other studies: we found that neuromodulation interventions significantly improved CIPN symptoms (FACT-Ntx and EORTC QLQ-CIPN20) compared with usual care, but there was no significant difference in efficacy compared with sham stimulation across all outcomes.

At the same time, our study conducted a meta-analysis and evidence pooling of all randomized controlled trials of neuromodulation interventions, expanding the sample size of evidence and complementing the overall evidence on neuromodulation interventions. A categorical assessment of the effects of neuromodulation interventions over time refines the evidence support for clinical practice.

Strengths and Limitations

The review's strengths include the study of a wide variety of neuromodulation interventions. The moderate quality data were sufficient to conclude that neuromodulation interventions, whether with or without usual care, are beneficial to usual care on immediate-term self-reported symptoms (pain, FACT-Ntx) and quality of life. Other strengths of this research include the adoption of rigorous procedures involving synthesizing and summarizing the quality of the evidence by the GRADE system.

This study is especially crucial since it provides a thorough assessment and identification of critical knowledge gaps in this field, which will help guide clinical practices and future research. These studies must be appropriately powered, have low bias risks, and have long-term follow-up. To increase transparency and minimize bias, future RCTs should adhere to the Consolidated Standards of Reporting Trials guideline when designing studies and presenting research results.

One limitation of this study is the possibility of language bias because only English publications were included. Studies with small sample sizes, which are more vulnerable to bias, were also included. Due to the characteristics of interventions, it is difficult to blind the intervenor and patients, and 6 studies did not blind the intervenor or subjects, thus potentially creating the bias due to deviations from the intended interventions. Few studies could be pooled due to the significant degree of heterogeneity between trials, such as types of cancer, cycles of chemotherapy drugs, stimulus intensity of interventions, and course of treatment. Moreover, harms associated with treatment were often not reported or inconsistently reported.

Implications for Future Research

Our study will provide the following implications for future research: first, there is a need for larger, high-quality pilot studies of the long-term effects of neuromodulation interventions. Second, future trials should concentrate on providing a thorough description (eg, stimulation intensity, frequency, waveform, lead position and coil orientation) of the

intervention itself, as well as a report of standardized outcomes, to make future meta-analysis easier to do. We also recommend analyzing different mechanisms or modalities of neuromodulation, such as those based on the peripheral and central nervous systems. Third, our findings suggest that expectations and placebo effects may play a larger role in the non-specific effects of sham stimulation, and thus patients' outcome expectations could be assessed in future studies using specialized multiscale or assessment methods.[85] Mechanistic studies of placebo effects and expectations could also be undertaken. Fourth, for trials comparing neuromodulation interventions with usual care, efforts should be strengthened to address issues such as treatment nonadherence, crossover, and blinding difficulties.

Conclusions

There is moderate-quality evidence that neuromodulation interventions are an immediately superior therapeutic strategy to usual care in relieving immediate pain, reducing CIPN symptoms and improving quality of life. However, no positive results were obtained for its comparative sham stimulation. Also, given the limited sample size, it is suggested that more extensive clinical trials of neuromodulation interventions for the treatment of CIPN could be conducted subsequently. Because of the severe impact of CIPN on the quality of survival of cancer patients and the paucity of current first-line therapies, evidence-based support for alternative therapies is, therefore, urgently needed.

Data Sharing Statement

The data used to support the findings of this study are available from the first author upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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