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Beyond traditional therapies: a network meta-analysis on the treatment efficacy for chronic phantom limb pain

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ABSTRACT

Background Phantom limb pain (PLP) frequently affects individuals with limb amputations. When PLP evolves into its chronic phase, known as chronic PLP, traditional therapies often fall short in providing sufficient relief. The optimal intervention for chronic PLP remains unclear.

Objective The objectives of this network meta-analysis (NMA) were to examine the efficacy of different treatments on pain intensity for patients with chronic PLP.

Evidence review We searched Medline, EMBASE, Cochrane CENTRAL, Scopus, and CINAHL EBSCO, focusing on randomized controlled trials (RCTs) that evaluated interventions such as neuromodulation, neural block, pharmacological methods, and alternative treatments. An NMA was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The primary outcome was pain score improvement, and the secondary outcomes were adverse events.

Findings The NMA, incorporating 12 RCTs, indicated that neuromodulation, specifically repetitive transcranial magnetic stimulation, provided the most substantial pain improvement when compared with placebo/sham groups (mean difference=−2.9 points, 95% CI=−4.62 to −1.18; quality of evidence (QoE): moderate). Pharmacological intervention using morphine was associated with a significant increase in adverse event rate (OR=6.04, 95% CI=2.26 to 16.12; QoE: low).

Conclusions The NMA suggests that neuromodulation using repetitive transcranial magnetic stimulation may be associated with significantly larger pain improvement for chronic PLP. However, the paucity of studies, varying patient characteristics across each trial, and absence of long-term results underscore the necessity for more comprehensive, large-scale RCTs.

PROSPERO registration number CRD42023455949.

INTRODUCTION

Phantom limb pain (PLP) is a common consequence of limb amputations, occurring in 60%–70% of cases.[1] Of these individuals, 10%–15% experience severe pain episodes, while 50%–85% may develop chronic PLP.[2 3] Among those with chronic PLP, up to 25% endure significant pain-related disability.[4] As PLP advances to a chronic stage, treatment becomes more challenging due to persistent functional and structural alterations in pain pathways.[5] Despite ongoing research, a definitive treatment for chronic PLP remains elusive, with fewer than 10% of patients achieving sustained relief from conventional treatments such as medications or epidural injections.[6]

A wide range of treatments for chronic PLP exists,[1–4 6–13] yet no standard treatment for chronic PLP has been established, making the most effective option remains challenging. These treatments encompass neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS),[11] cerebellar transcranial direct current stimulation (ctDCS),[12] and peripheral nerve stimulation (PNS),[13] established nerve-blocking methods such as continuous perineural block (CPNB)[2] and cryoneurolysis,[3] pharmaceutical options such as oral amitriptyline,[9] gabapentin,[4] memantine,[1] mexiletine,[10] and morphine,[10] and other techniques, notably electromagnetic shielding (EMS).[6] The absence of in-depth knowledge about the mechanisms of PLP presents challenges in establishing consistent clinical guidelines.[14] Currently, only expert consensus guides the treatment of general PLP, emphasizing the importance of non-pharmacological treatments.

Previous research, encompassing multiple systemic review and pairwise meta-analyses[15–20] or a network meta-analysis (NMA),[21] has evaluated treatments for PLP. However, these studies primarily focused on perioperative treatment and the general PLP,[15–21] rather than honing in on the specificities of the "chronic" PLP subgroup. Addressing chronic PLP requires a more tailored therapeutic approach compared with standard PLP treatments.[22] Moreover, although several randomized controlled trials (RCTs) have been established to gage the effectiveness of treatments for chronic PLP, a holistic multiarm comparative analysis has proven either intricate or clinically impractical. Consequently, this NMA aims to compare the clinical outcomes of different chronic PLP treatments, based on a systematic review and a detailed examination of recent RCT results.

METHODS

Search strategy

The NMA protocol was prospectively registered on PROSPERO (Registration number: CRD42023455949). We followed the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses 2020 extension guidelines for reporting the results of NMA in healthcare interventions. Our comprehensive database searches encompassed Medline, EMBASE, Cochrane CENTRAL, Scopus, and CINAHL EBSCO, spanning from inception to July 10, 2023, without language restrictions. In addition, we screened and incorporated references from relevant studies that met our inclusion criteria. Detailed search strategies are available in online supplemental appendix 2.

Inclusion and exclusion criteria

We incorporated all relevant RCTs assessing different treatment approaches for chronic PLP in individuals who have been experiencing pain for at least 2 months or more, or where the term "chronic PLP" was specifically mentioned. We excluded non-randomized trials, quasi-experimental designs, trials focused on preventive or immediate postoperative PLP treatments, single-arm trials, trials without predefined outcome measures, trials without accessible arm-level data, and trials with a duration of only a few minutes to hours.

Data extraction and management

Two authors (S-MC and J-CW) independently screened titles and abstracts of all entries that met our search criteria. Full texts were retrieved for selected trials to assess their eligibility for inclusion. Data extraction from the included RCTs was conducted using a predesigned data sheet, which captured the following information: authors' names, publication year, journal of publication, study design, inclusion and exclusion criteria, intervention and control protocols, patient characteristics, outcome measures, and risk of bias. Any disagreements or conflicts between the authors were resolved through discussion or by seeking the judgment of the third author (C-AS).

Type of intervention

We considered interventions addressing chronic PLP and categorized them as follows: (1) neuromodulation, which comprises rTMS, ctDCS, and PNS; (2) nerve block, including CPNB and cryoneurolysis; (3) pharmacological treatments, such as oral amitriptyline, gabapentin, memantine, mexiletine, and morphine; and (4) alternative approaches, exemplified by EMS.

Type of outcome measurement

The primary outcome assessed was the change in pain intensity before and after treatment, which was measured using either the Numerical Rating Scale (NRS) or Visual Analog Scale (VAS). The secondary outcome focused on determining the total rate of adverse events for each individual intervention. Data were obtained from RCTs at the end of follow-up periods. For cross-over RCTs, data were extracted at the time point just before the cross-over occurred. However, in some trials that only presented pooled results for each intervention arm before and after cross-over, these pooled data were extracted.

Addressing missing parameters

In addressing missing parameters for this NMA, intention-to-treat analysis results were used. If mean values were missing for numerical variables, they were replaced with medians. SDs were derived from CIs when available, or else, IQRs were divided by 1.35 to estimate SDs. We also calculated the average values and SDs of the changes in pain scores when only baseline and follow-up measurements were available.[23]

Quality assessment

The Cochrane Collaboration's RoB2 tool, comprising five domains and an overall risk assessment, was employed to assess bias risk.[24] Two authors (SMC, JCW) independently reviewed and scored all included RCTs, categorizing them as "high risk," "some concerns," or "low risk" using RoB2. For cross-over RCTs, we applied the RoB2 framework for cross-over trials, which includes an additional domain, "Domain S: Bias arising from period and carryover effects." In cases of disagreement, a third author (C-AS) provided input.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for NMA was used to evaluate evidence certainty across five domains: study limitation, inconsistency/heterogeneity, indirectness, imprecision, and publication bias, assigning confidence ratings as high, moderate, low, or very low.[25 26]

Publication bias

For assessing publication bias, the presence of small-study effects was evaluated for each outcome using the comparison-adjusted funnel plot and Egger's test.

Data synthesis and statistical analysis

Data synthesis and statistical analysis were conducted by using STATA V. 15.0 (StataCorp). A frequentist approach was employed for contrast-based model meta-analysis, integrating random-effects NMA to facilitate comparisons among multiple interventions, incorporating both direct and indirect evidence to enhance the robustness of estimates. The effect measures were reported as the mean difference (MD) with a 95% CI for changes in pain intensity, and as ORs with a 95% CI for adverse events. The ranking of interventions was determined using the surface under the cumulative ranking curve area (SUCRA).[27] Inconsistency was assessed through various models, encompassing global inconsistency through design-by-treatment interaction models and local inconsistency through loop inconsistency models and node-splitting models.[28 29] To validate the transitivity assumption, we scrutinized effect modifier distributions such as age, male percentage, and baseline VAS/NRS score. Heterogeneity was evaluated using I^2 in pairwise meta-analysis, the tau value for between-study heterogeneity, and a comprehensive examination of study characteristics. We performed a meta-regression analysis to identify potential effect modifiers, drawing on thresholds established in previous studies concerning chronic pain and PLP.[30 31] This process entailed categorizing data according to several criteria: baseline pain score (either above or below 5.8 points),[30] patient age (either above or below 55 years),[31] and duration postamputation (either more than or less than 2 years),[31] and the predominant amputation site and type (accounting for more than 50%). Additionally, we conducted a sensitivity analysis by excluding trials that relied on imputed data, opting instead for those using the mean and SD to assess pain severity.

FINDINGS

A total of 2975 studies were identified through database searches (figure 1). After removing duplicates and screening the titles and abstracts (online supplemental appendix 3), 12 studies[1–4 6–13] were selected for inclusion in the analysis (table 1 and online supplemental appendix 4). Out of these, seven trials[1 3 6 8 9 11] are RCTs, while the remaining five trials[2 4 10 12 13] are cross-over

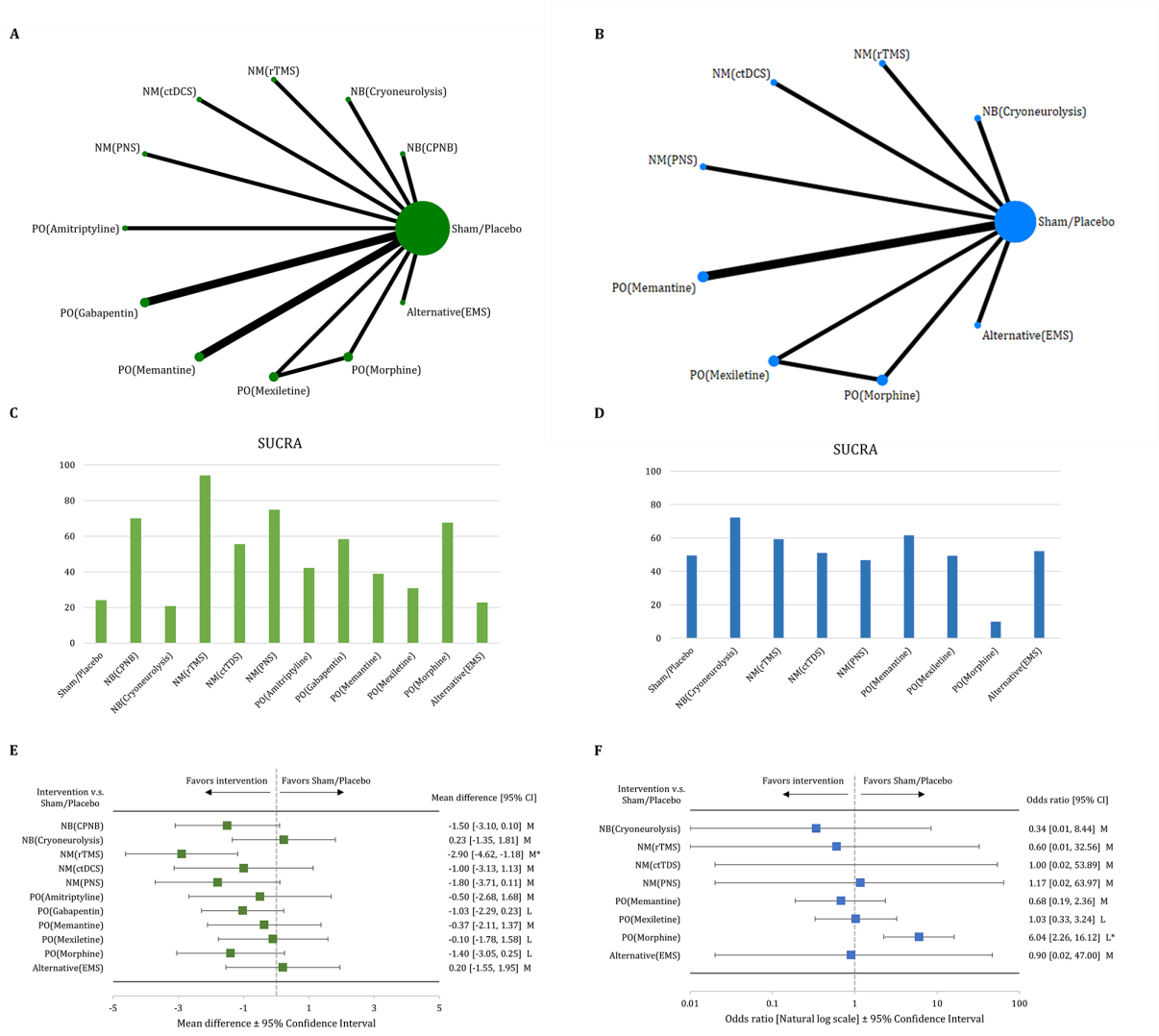

Figure 1 PRISMA flow diagram of studies identified and included in this network meta-analysis. CPNB, continuous perineural block; ctDCS, cerebellar transcranial direct current stimulation; EMS, electromagnetic shielding; NM (rTMS), neuromodulation with repetitive transcranial magnetic stimulation; PNS, peripheral nerve stimulation; PO (Amitriptyline), oral administration of amitriptyline; PO (Gabapentin), oral administration of gabapentin; PO (Memantine), oral administration of memantine; PO (Mexiletine), oral administration of mexiletine; PO (Morphine), oral administration of morphine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SUCRA, surface under the cumulative ranking curve area.

RCTs. The assessment of transitivity is presented in online supplemental appendix 5. Regarding these trials, the risk of bias was evaluated as follows: two trials[2 4] showed no concern, seven trials[1 3 6 9 11–13] had some concerns, and three trials[7 8 10] (online supplemental appendix 6). Among these trials, nine trials[1–3 7–10 12] included patients with PLP lasting longer than 2 months, while the others four trials[4 6 11 13] included patients with "chronic PLP" without stated chronic PLP duration. Information on adverse events was retrievable in eight trials.[1 3 6 8 10–13] The duration since amputation was reported in eight trials.[1 2 6–9 12 13] Data on amputation site and type were reported in 11 trials[1–4 6–11 13] and 10 trials,[1 2 4 6–11 13] respectively. In these studies, a variety of treatment modalities were used, including: neural block techniques (CPNB and cryoneurolysis) in two trials; neuromodulation therapies (rTMS, ctDCS, and PNS) in three trials; oral medications (amitriptyline, gabapentin, memantine, mexiletine, and morphine) in six trials; and alternative methods (EMS) in one trial. The NMA results, including the MD with 95% CIs and rank probabilities, are illustrated in figure 2. A qualitative summary and network meta-analyses, presented in a league table format, can be found in table 2A,B. Detailed results and relative ranking are listed in online supplemental appendix 7.

Changes in pain intensity

Twelve trials,[1–4 6–13] encompassing 783 participants, were included for analysis of changes in pain intensity. Compared with the sham/placebo group, the summary MD of changes in pain intensity were as follows: −2.90 points (95% CI: −4.62 to −1.18) for rTMS; −1.00 points (95% CI: −3.13 to 1.13) for ctDCS; −1.80 points (95% CI: −3.71 to 0.11) for PNS; −1.50 for CPNB (95% CI: −3.10 to −0.10); 0.23 for cryoneurolysis (95% CI: −1.35 to 1.81); −0.50 for oral amitriptyline (95% CI: −2.68 to 1.68); −1.03 for oral gabapentin (95% CI: −2.29 to 0.23); −0.37 for oral memantine (95% CI: −2.11, 1.37); −0.10 for the oral mexiletine method (95% CI: −1.78 to 1.58); −1.40 for oral morphine (95% CI: −3.05 to −0.25); and 0.20 for the alternative EMS (95% CI: −1.55 to 1.95). A negative MD

Table 1 Demographic data for the included trials

Author (year)	Study type	Level of evidence	Patients (n)	Treatment type	Baseline VAS/ NRS score*	Duration since amputation (years)	Phantom limb pain duration (years)	Outcome measures	Total follow-up time*
Ilfeld *et al*[3] 2023	RCT	Therapeutic Level I	71	Ultrasound-guided percutaneous cryoneurolysis	5 (4, 6)	N.A.	N.A.	Change in NRS score/adverse event	4† months
			73	Sham treatment	5 (4, 7)	N.A.			
Ilfeld *et al*[2] 2021	RCT (cross-over)	Therapeutic Level I	71	Continuous perineural neural block with ropivacaine	5 (4, 7)	4.33 (1.583, 8.667)	6.298±6.55	Change in NRS score	1, 2, 3, 4 †‡ weeks 6§, 12§ months
			73	Continuous perineural infusion of normal saline	5 (4, 7)	3.416 (1.33, 7.416)	5.418±6		
Bocci *et al*[12] 2019	RCT (cross-over)	Therapeutic Level I	14	Cerebellar transcranial direct current stimulation	5.4±2	1.167±0.421	1.167±0.42	Change in VAS score/adverse event	0, 2, 4†‡ weeks
			14	Sham treatment	5.3±1.8	1.167±0.421	1.167±0.42		
Gilmore *et al*[13] 2019	RCT (cross-over)	Therapeutic Level I	12	Peripheral nerve stimulation	6.9±1.7	6.4±4.6	6.4±4.6	Change in NRS score/adverse event	4†‡ weeks
			14	Placebo treatment	6.8±1.7	7.5±8.1	7.5±8.1		
Hsiao *et al*[6] 2012	RCT	Therapeutic Level I	30	Electromagnetic shielding	5.9±1.9	10.5±15.3	10.5±15.3	Change in NRS score/adverse event	6, 12† weeks
			27	Sham treatment	6.5±1.8	15.6±19.5	15.6±19.5		
Ahmed *et al*[11] 2011	RCT	Therapeutic Level I	17	Repetitive transcranial magnetic stimulation	7.4±1.3	N.A.	N.A.	Change in VAS score/adverse event	0, 1, 2† months
			10	Sham treatment	7.6±0.84	N.A.			
Wu *et al*[10] 2008	RCT (cross-over)	Therapeutic Level I	42	Oral mexiletine	6.657±0.381	N.A.	N.A.	Change in NRS score/adverse event	8†‡ weeks
			50	Oral sustained-release morphine	6.657±0.381	N.A.			
			43	Oral placebo tablets	6.657±0.381	N.A.			
Smith *et al*[4] 2005	RCT (cross-over)	Therapeutic Level I	24	Oral gabapentin	4.38±2.57	N.A.	N.A.	Change in NRS score	6†‡ weeks
			24	Oral placebo tablets	4.09±2.44	N.A.			
Robinson *et al*[9] 2004	RCT	Therapeutic Level I	20	Oral amitriptyline	3.6±2.4	11.3±10.9	11.3±10.9	Change in NRS score	6† weeks
			19	Oral benztropine mesylate (placebo)	3.1±2.6	10.6±9.1	10.6±9.1		
Maier *et al*[1] 2003	RCT	Therapeutic Level I	18	Oral memantine	5.1±2.13	17.5 (2–43)	21.71±19.62	Change in NRS score/adverse event	4† weeks
			18	Oral placebo tablets	5.2±2.02	24.5 (2–49)	25.17±20.43		
Schwenkreis *et al*[8] 2003	RCT	Therapeutic Level I	7	Oral memantine	6.8 (0.3–7.7)	**23.5 (1–49)**	23.5±15.06	Change in NRS score/adverse event	3† weeks
			8	Oral placebo tablets	4.1 (1.7–6.3)	**6 (2–57)**	6±39.36		
Bone *et al*[7] 2002	RCT (cross-over)	Therapeutic Level I	14	Oral gabapentin	6.1±1.8	1.5 (0.5–4.25)	1.83±1.33	Change in VAS score	6†‡ weeks
			14	Oral placebo tablets	6.7±1.9	1.5 (0.5–4.25)	1.83±1.33		

For cross-over RCT, total follow-ups time stands for the follow-up periods in each session (either before or after cross-over).
*Data is reported as follows: mean ± standard deviation (SD), median [first quartile, third quartile], median (range), or mean (range). Numbers in bold denote the mean (range).
†Time point of data extraction.
‡Time at which crossover occurs.
§Long-term follow-up period.
N.A., not applicable; NRS, Numerical Rating Scale; RCT, randomized controlled trial; VAS, Visual Analog Scale.

indicates better pain improvement. The rTMS (SUCRA=94.1%) ranked best for changes in pain intensity, followed by PNS (SUCRA=74.9%) and the CPNB group (SUCRA=70.1%).

Adverse event rate

Eight trials,[1 3 6 8 10–13] with a total of 466 participants, were included for the analysis of adverse event rate. In comparison with the sham/placebo group, the summary ORs for adverse event rate were: 0.34 (95% CI: 0.01 to 8.44) for cryoneurolysis; 0.60 (95% CI: 0.01 to 32.56) for rTMS; 1.00 (95% CI: 0.02 to 53.89) for ctDCS; 1.17 (95% CI: 0.02 to 63.97) for PNS; 0.68 (95% CI: 0.19 to 2.36) for oral memantine; 1.03 (95% CI: 0.33 to 3.24) for oral mexiletine; 6.04 (95% CI: 2.26 to 16.12) for oral morphine; and 0.90 (95% CI: 0.02 to 47.00) for EMS. An OR less than 1 indicates fewer adverse events. The cryoneurolysis (SUCRA=72.0%) ranked best for adverse event rate, followed by oral memantine (SUCRA=61.4%) and rTMS (SUCRA=59.0%). Reported adverse events for various modalities are detailed in online supplemental appendix 7.2.

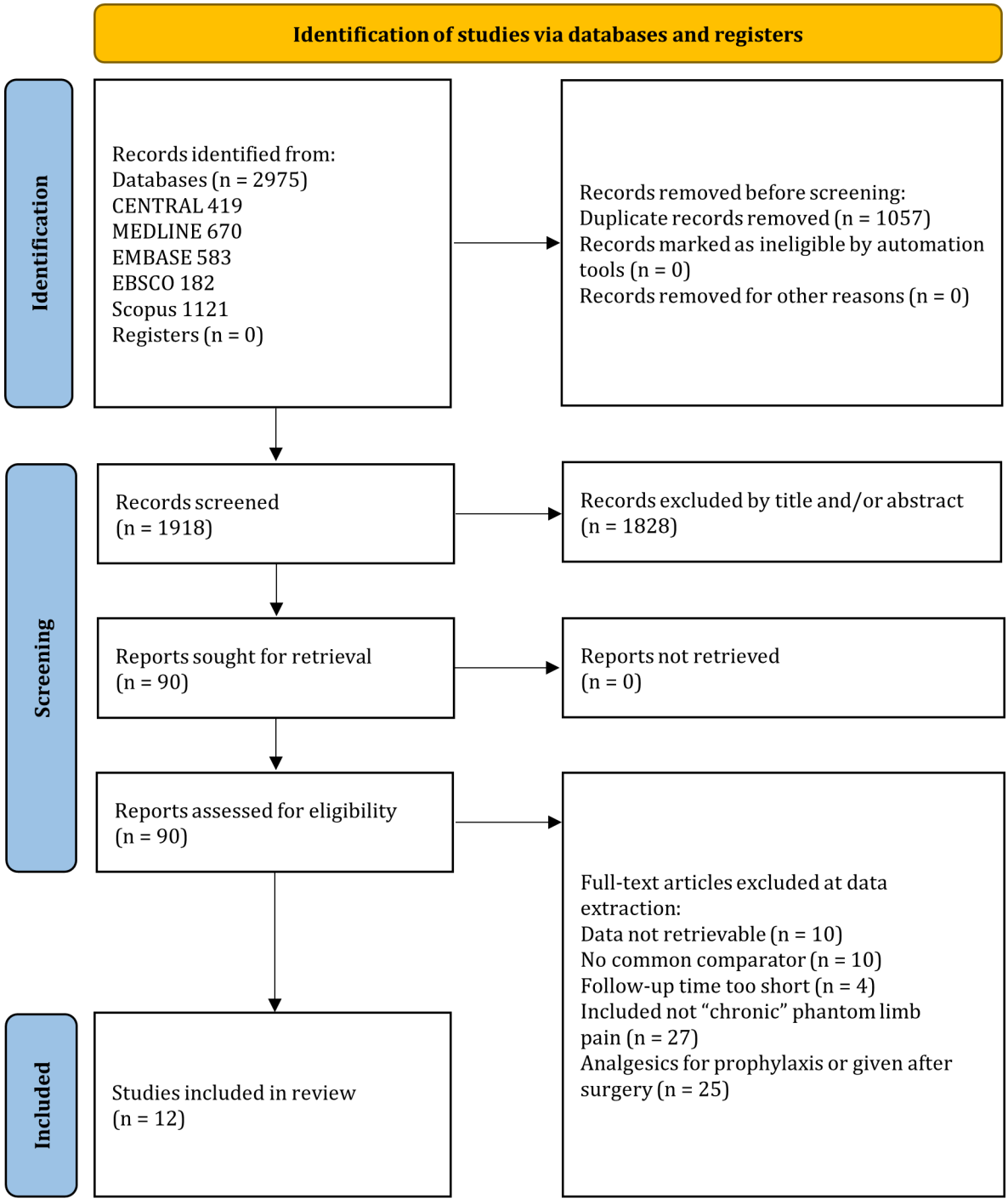

Figure 2 Network geometry of different interventions for comparisons of changes in pain intensity (A) and adverse event rate (B). SUCRA value as numeric presentation of the overall ranking for all interventions (C–D). The rank would be better with larger value. Forest plots of network estimates were displayed (E–F). Number marked with asterisk indicate significance compared with sham/placebo group. L, low confidence rating; M, moderate confidence rating; SUCRA, surface under the cumulative ranking curve area.

Quality of evidence

The evidence and summary profile, including GRADE results, is presented in table 3 of online supplemental appendix 11. Most comparisons demonstrated a low to moderate level of confidence regarding changes in pain intensity and the rate of adverse events. Nonetheless, certain comparisons were assigned a very low rating, especially in cases of intransitivity and a high risk of bias.

Inconsistency

No global inconsistencies (design-by-treatment interaction model) or local inconsistencies (loop approach) were found in changes in pain intensity or adverse event rates (online supplemental appendix 10). The lack of direct comparison data between interventions and the limited closed loops in the network map rendered the results from the side-splitting approach unestimable.

Table 2 (A) League table of the changes in pain intensity between different interventions and (B) league table presenting the adverse event rate across different interventions

Pairwise meta-analysis												
Network meta-analysis	Sham/placebo	**−1.50 (−2.37, −0.63)** Singular trial	0.23 (−0.60, 1.06) Singular trial	**−2.90 (−3.97, −1.83)** Singular trial	−1.00 (−2.65, 0.65) Singular trial	**−1.80 (−3.16, −0.44)** Singular trial	−0.50 (−2.22, 1.22) Singular trial	−1.03 (−2.16, 0.10) I^2=45.9% (2 trials)	−0.49 (−2.53, 1.55) I^2=49.0% (2 trials)	−0.10 (−1.11, 0.91) Singular trial	**−1.40 (−2.35,−0.45)** Singular trial	0.20 (−0.92, 1.32) Singular trial
	−1.50 (−3.10, 0.10) ⊕⊕⊕◯	NB(CPNB)	–	–	–	–	–	–	–	–	–	–
	0.23 (−1.35, 1.81) ⊕⊕⊕◯	1.73 (−0.52, 3.98) ⊕⊕⊕◯	NB(cryoneurolysis)	–	–	–	–	–	–	–	–	–
	−2.90 (−4.62, −1.18) ⊕⊕⊕◯	−1.40 (−3.75, 0.95) ⊕⊕◯◯	**−3.13 (−5.46, −0.80)** ⊕⊕◯◯	NM(rTMS)	–	–	–	–	–	–	–	–
	−1.00 (−3.13, 1.13) ⊕⊕⊕◯	0.50 (−2.17, 3.17) ⊕⊕◯◯	−1.23 (−3.88, 1.42) ⊕⊕◯◯	1.90 (−0.84, 4.64) ⊕⊕⊕◯	NM(ctDCS)	–	–	–	–	–	–	–
	−1.80 (−3.71, 0.11) ⊕⊕⊕◯	−0.30 (−2.80, 2.20) ⊕⊕◯◯	−2.03 (−4.51, 0.45) ⊕⊕◯◯	1.10 (−1.47, 3.67) ⊕⊕⊕◯	−0.80 (−3.66, 2.06) ⊕⊕⊕◯	NM(PNS)	–	–	–	–	–	–
	−0.50 (−2.68, 1.68) ⊕⊕⊕◯	1.00 (−171, 3.71) ⊕⊕⊕◯	−0.73 (−3.42, 1.96) ⊕⊕⊕◯	2.40 (−0.38, 5.18) ⊕⊕◯◯	0.50 (−2.55, 3.55) ⊕⊕◯◯	1.30 (−1.60, 4.20) ⊕⊕◯◯	PO(amitriptyline)	–	–	–	–	–
	−1.03 (−2.29, 0.23) ⊕⊕◯◯	0.47 (−1.57, 2.51) ⊕⊕◯◯	−1.26 (−3.28, 0.76) ⊕⊕◯◯	1.87 (−0.26, 4.00) ⊕◯◯◯	−0.03 (−2.51, 2.45) ⊕◯◯◯	0.77 (−1.52, 3.06) ⊕◯◯◯	−0.53 (−3.05, 1.99) ⊕⊕◯◯	PO(gabapentin)	–	–	–	–
	−0.37 (−2.11, 1.37) ⊕⊕⊕◯	1.13 (−1.24, 3.50) ⊕⊕⊕◯	−0.60 (−2.95, 1.75) ⊕⊕⊕◯	**2.53 (0.08, 4.98)** ⊕⊕◯◯	0.63 (−2.12, 3.38) ⊕⊕◯◯	1.43 (−1.16, 4.02) ⊕⊕◯◯	0.13 (−2.66, 2.92) ⊕⊕⊕◯	0.66 (−1.49, 2.82) ⊕⊕◯◯	PO(memantine)	–	–	–
	−0.10 (−1.78, 1.58) ⊕⊕◯◯	1.40 (−0.93, 3.73) ⊕⊕◯◯	−0.33 (−2.64, 1.98) ⊕⊕◯◯	**2.80 (0.39, 5.21)** ⊕◯◯◯	0.90 (−1.82, 3.62) ⊕◯◯◯	1.70 (−0.85, 4.25) ⊕◯◯◯	0.40 (−2.35, 3.15) ⊕⊕◯◯	0.93 (−1.17, 3.03) ⊕⊕◯◯	0.27 (−2.15, 2.69) ⊕⊕◯◯	PO(Mexiletine)	**1.30 (0.47, 2.13)** Singular trial	–
	−1.40 (−3.05, 0.25) ⊕⊕◯◯	0.10 (−2.20, 2.40) ⊕⊕◯◯	−1.63 (−3.91, 0.65) ⊕⊕◯◯	1.50 (−0.88, 3.88) ⊕◯◯◯	−0.40 (−3.09, 2.29) ⊕◯◯◯	0.40 (−2.12, 2.92) ⊕◯◯◯	−0.90 (−3.63, 1.83) ⊕⊕◯◯	−0.37 (−2.45, 1.71) ⊕⊕◯◯	−1.03 (−3.43, 1.37) ⊕⊕◯◯	−1.30 (−2.88, 0.28) ⊕⊕◯◯	PO(Morphine)	–
	0.20 (−1.55, 1.95) ⊕⊕⊕◯	1.70 (−0.67, 4.07) ⊕⊕⊕◯	−0.03 (−2.39, 2.33) ⊕⊕⊕◯	**3.10 (0.65, 5.55)** ⊕⊕◯◯	1.20 (−1.56, 3.96) ⊕⊕◯◯	2.00 (−0.59, 4.59) ⊕⊕◯◯	0.70 (−2.10, 3.50) ⊕⊕⊕◯	1.23 (−0.93, 3.39) ⊕⊕◯◯	0.57 (−1.90, 3.04) ⊕⊕⊕◯	0.30 (−2.13, 2.73) ⊕⊕◯◯	1.60 (−0.80, 4.00) ⊕⊕◯◯	Alternative(EMS)
Pairwise meta-analysis												

Continued

Table 2 Continued

Pairwise meta-analysis									
Network Meta-analysis	Sham/placebo	0.34 (0.01, 8.44) Singular trial	0.60 (0.01, 32.56) Singular trial	1.00 (0.02, 53.89) Singular trial	1.17 (0.02, 63.97) Singular trial	0.68 (0.19, 2.36) I^2=0.0% (2 trials)	1.03 (0.33, 3.24) Singular trial	6.04 (2.26, 16.12) Singular trial	0.90 (0.02, 47.00) Singular trial
	0.34 (0.01, 8.44) ⊕⊕⊕◯	NB(cryoneurolysis)	–	–	–	–	–	–	–
	0.60 (0.01, 32.56) ⊕⊕⊕◯	1.78 (0.01, 299.59) ⊕⊕◯◯	NM(rTMS)	–	–	–	–	–	–
	1.00 (0.02, 53.89) ⊕⊕⊕◯	2.96 (0.02, 496.63) ⊕⊕◯◯	1.67 (0.01, 470.66) ⊕⊕◯◯	NM(ctDCS)	–	–	–	–	–
	1.17 (0.02, 63.97) ⊕⊕⊕◯	3.47 (0.02, 588.06) ⊕⊕◯◯	1.96 (0.01, 556.87) ⊕⊕◯◯	1.17 (0.00, 332.48) ⊕⊕⊕◯	NM(PNS)	–	–	–	–
	0.68 (0.19, 2.36) ⊕⊕⊕◯	2.00 (0.06, 63.10) ⊕⊕⊕◯	1.13 (0.02, 74.01) ⊕⊕◯◯	0.68 (0.01, 44.11) ⊕⊕◯◯	0.58 (0.01, 37.98) ⊕⊕◯◯	PO(memantine)	–	–	–
	1.03 (0.33, 3.24) ⊕⊕◯◯	3.04 (0.10, 92.60) ⊕⊕◯◯	1.71 (0.03, 109.30) ⊕◯◯◯	1.03 (0.02, 65.15) ⊕◯◯◯	0.88 (0.01, 56.09) ⊕◯◯◯	1.52 (0.28, 8.30) ⊕⊕◯◯	PO(mexiletine)	5.87 (2.19, 15.70) Singular trial	–
	6.04 (2.26, 16.12) ⊕⊕◯◯	17.86 (0.62, 516.21) ⊕⊕◯◯	10.06 (0.16, 615.04) ⊕◯◯◯	6.04 (0.10, 366.54) ⊕◯◯◯	5.14 (0.08, 315.62) ⊕◯◯◯	8.93 (1.82, 43.79) ⊕⊕◯◯	5.87 (2.19, 15.70) ⊕⊕◯◯	PO(morphine)	–
	0.90 (0.02, 47.00) ⊕⊕⊕◯	2.67 (0.02, 436.35) ⊕⊕⊕◯	1.50 (0.01, 414.52) ⊕⊕◯◯	0.90 (0.00, 247.49) ⊕⊕◯◯	0.77 0.00, 212.50) ⊕⊕◯◯	1.33 (0.02, 84.33) ⊕⊕⊕◯	0.88 (0.01, 53.77) ⊕⊕◯◯	0.15 (0.00, 8.78) ⊕⊕◯◯	Alternative(EMS)

Effect estimate was expressed as MD with 95% CI for changes in pain intensity in random-effects model for network meta-analysis. The upper right triangle presents the effects of direct estimates, and the lower-left triangle presents the effects of network estimates. A negative MD value indicates a favorable outcome for the intervention in the lower diagonal. Number in bold represents statistically significant results.
Effect estimate was expressed as OR with 95% CI for changes in pain intensity in random-effects model for network meta-analysis. The upper right triangle presents the effects of direct estimates, and the lower-left triangle presents the effects of network estimates. An OR value less than 1 indicates a reduced risk of incidence and a favorable outcome for the intervention in the lower diagonal.
*Symbols representing the quality (certainty) of evidence are as follows: ⊕⊕⊕⊕ for high, ⊕⊕⊕◯ for moderate, ⊕⊕◯◯ for low, and ⊕◯◯◯ for very low.[25, 26] Numbers highlighted in bold represent significant results.
Alternative (EMS), alternative treatment with electromagnetic shielding; MD, mean difference; NB (cyroneurolysis), neural block with cryoneurolysis; NM (ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM (PNS), neuromodulation with percutaneous peripheral neural stimulation; NM (rTMS), neuromodulation with repetitive transcranial magnetic stimulation; PO (memantine), oral administration of memantine; PO (mexiletine), oral administration of mexiletine; PO (morphine), oral administration of morphine.

Table 3 Evidence profiles for chronic phantom limb pain treatment in the network meta-analysis

Outcome: improvement of pain intensity										
Comparison: intervention vs comparator	Limitations (risk of bias)	Inconsistency/ heterogeneity	Indirectness	Imprecision	Publication bias	Number of participants (studies)	Mean difference (95% CI) (NMA)	Quality or certainty of the evidence (GRADE)		
								Direct evidence	Indirect evidence	Network meta-analysis
NB(CPNB) vs sham/ placebo	No serious limitations (low RoB)	N.A.*	Not detected	Singular trial	Not detected	144 (1 study)	−1.5 (−3.10 to 0.10)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
NB(cryoneurolysis) vs sham/placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	144 (1 study)	0.23 (−1.35 to 1.81)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
NM(rTMS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	27 (1 study)	−2.90 (−4.62 to −1.18)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
NM(ctDCS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	28 (1 study)	−1.00 (−3.13 to 1.13)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
NM(PNS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	24 (1 study)	−1.80 (−3.71 to 0.11)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
PO(amitriptyline) vs sham/placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	37 (1 study)	−0.50 (−2.68 to 1.68)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
PO(gabapentin) vs sham/ placebo	No concern for 1 trial; High risk for another one	Moderate heterogeneity (I^2=45.9%)	Not detected	Wide CI	Not detected	76 (2 studies)	−1.03 (−2.29 to 0.23)	⊕⊕◯◯ LOW†‡	N.A.	⊕⊕◯◯ LOW
PO(memantine)vs sham/ placebo	Some concerns for 1 trial; High risk for another one	Moderate heterogeneity (I^2=49.0%)	Not detected	Wide CI	Not detected	51 (2 studies)	−0.37 (−2.11 to 1.37)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
PO(mexiletine) vs sham/ placebo	High	N.A.*	Not detected	Singular trial	Not detected	135 (1 study)	−0.10 (−1.78 to 1.58)	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW
PO(morphine) vs sham/ placebo	High	N.A.*	Not detected	Singular trial	Not detected	135 (1 study)	−1.40 (−3.05 to 0.25)	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW
Alternative(EMS) vs sham/placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	57 (1 study)	0.20 (−1.55 to 1.95)	⊕⊕⊕◯MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
Outcome: adverse event rate										
Comparison:intervention vs comparator	Limitations (Risk of bias)	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Number of participants (studies)	Odds Ratio (95% CI) (NMA)	Quality or certainty of the evidence (GRADE)		
								Direct evidence	Indirect evidence	Network meta-analysis
NB(cryoneurolysis) vs sham/placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	144 (1 study)	0.34 (0.01 to 8.44)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯MODERATE
NM(rTMS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	27 (1 study)	0.60 (0.01 to 32.56)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯MODERATE
NM(ctDCS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	28 (1 study)	1.00 (0.02 to 53.89)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE
NM(PNS) vs sham/ placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	24 (1 study)	1.17 (0.02 to 63.97)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE

Continued

Table 3 Continued

Outcome: improvement of pain intensity									
PO(memantine) vs sham/placebo	Some concerns for 1 trial; High risk for another one	Low heterogeneity (I^2=0.0%)	Not detected	Not detected	Not detected	51 (2 studies)	0.68 (0.19 to 2.36)	⊕⊕⊕◯ MODERATE‡	N.A.	⊕⊕⊕◯ MODERATE
PO(Mexiletine) vs sham/placebo	High	N.A.*	Not detected	Singular trial	Not detected	135 (1 study)	1.03 (0.33 to 3.24)	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW
PO(morphine) vs sham/placebo	High	N.A.*	Not detected	Singular trial	Not detected	135 (1 study)	6.04 (2.26 to 16.12)	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW†‡	⊕⊕◯◯ LOW
Alternative(EMS) vs sham/placebo	Some concerns	N.A.*	Not detected	Singular trial	Not detected	57 (1 study)	0.90 (0.02 to 47.00)	⊕⊕⊕◯ MODERATE†	N.A.	⊕⊕⊕◯ MODERATE

The GRADE approach:[25,26] criteria for downgrading direct evidence include: (1) over one -third of the studies showing a high risk of bias, (2) substantial heterogeneity (I^2>50%), (3) imprecision, denoted by a wide confidence interval or singular trial, and (4) publication bias ascertained by Egger's test with a *p* value below <0.05. Indirect evidence was graded using the primary first order loop. When choosing between two direct comparisons, the lower confidence rating was selected. The rank of indirect evidence was reduced by a level if transitivity was absent. In cases where either direct or indirect evidence was missing, the quality rating for the network meta-analysis would hinge on the singular estimate. If both types of evidence were present, the higher rating would be chosen as the network rating.

*Only one study, inconsistency cannot be evaluated.

†Imprecision.

‡Risk of bias.

§Inconsistency.[25,26]

¶Intransitivity.[25,26]

Alternative(EMS), alternative treatment with electromagnetic shielding; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NB(cyroneurolysis), neural block with cryoneurolysis; NMA, network meta-analysis; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation withpercutaneous peripheral neural stimulation; NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; PO(memantin), oral administration of memantine; PO(mexiletine), oral administration of mexiletine; PO(morphine), oral administration of morphine.

Publication bias

In general, the funnel plots displayed a notable degree of symmetry, and Egger's regression plots did not reveal any significant signs of asymmetry (online supplemental appendix 9).

Meta-regression

The meta-regression, which included variables such as the mean initial pain score (above or below 5.8 points), patient age (older or younger than 55 years), time since amputation (more than or less than 2 years), and the predominant amputation site and type (accounting for more than 50%), did not demonstrate statistically significant moderating effects on outcomes related to changes in pain intensity and adverse events (online supplemental appendix 12).

Sensitivity analysis

A sensitivity analysis, excluding three trials[2 3 8] using imputed pain data (online supplemental appendix 13), showed that rTMS significantly reduced pain compared with placebo or sham (MD=−2.9, 95% CI=−4.42 to −1.38). This method also had fewer adverse events (OR=0.6, 95% CI=0.6 to 0.6) and was top-ranked for pain intensity reduction (SUCRA=95.7%) and low adverse event rates (SUCRA=77.8%).

DISCUSSION

This is the first NMA to compare different treatment modalities in terms of efficacy for chronic PLP. Our findings suggest that neuromodulation using rTMS results in a significantly larger pain improvement for chronic PLP than neuromodulation using PNS or nerve blocks with CPNB. Pharmacological treatment with morphine was linked to a significant rise in adverse event rates. The qualitative findings of the NMA are concisely summarized in table 4. The meta-regression analysis, which took into account the baseline pain score, patient age, time since amputation, and amputation site and type, did not influence the results for any of the outcomes. The confidence rating for comparisons varied from very low to moderate, particularly when considering the NMA evidence for changes in pain intensity and adverse event rate.

Chronic PLP stems from complex interactions within the peripheral, spinal, and brain systems.[32] A notable cause is the sensorimotor cortex's misalignment postamputation, leading to heightened neuronal activity.[4 8] The extent of cortical reorganization correlates directly with phantom pain severity.[3] Additionally, central nervous system adaptations, especially brain reorganization, play a pivotal role in perpetuating the pain.[33] Chronic pain, in turn, induces observable brain changes, including gray matter reduction, associated with emotional and cognitive disturbances[34] Peripheral elements, such as neuroma development and irregular nerve activity, compound the issue.[35] As PLP progresses to chronic neuropathic pain, its intricacies deepen, severely diminishing the patient's quality of life and rendering treatments like N-methyl D-aspartate (NMDA) antagonists less effective.[3 13] There's a marked disparity between clinical perceptions of PLP prevalence and reality, with current conventional treatments often falling short.[6] Comprehensive therapeutic strategies, from pharmaceuticals to innovative techniques, are vital. Notably, methods such as percutaneous PNS, rTMS, and CPNB have shown promise in providing extended relief.[2 11 13] Addressing PLP effectively requires a personalized and multifaceted approach, informed by a deep understanding of its roots.[36]

In recent literature, neuromodulation modalities have been put forth as potential therapeutic approaches for chronic pain due to their ability to alter maladaptive neuroplasticity and enhance descending inhibitory pathways.[16 18 37] A recent NMA suggests that both mirror therapy with phantom exercise and various neuromodulation techniques may be particularly effective in alleviating general PLP. Our NMA further indicated that with the exception of the ctDCS method targeting the cerebellum via cutaneously placed electrodes on the scalp,[12] all other neuromodulation interventions presented promising outcomes for chronic PLP alleviation, with none reporting significant adverse events. Particularly noteworthy was rTMS, which uses brief, high-intensity magnetic fields to excite neurons.[11] It ranked as the top modality in our NMA and showed an improvement of 2.9 points (95% CI: 1.18 to 4.62) which surpassed the minimal clinically important difference (MCID) threshold set at 1.7 points for chronic PLP[36] and 2.0 points for other chronic pains.[38] This superior efficacy of rTMS aligns with the theory posited in literature that it potentially restores the motor cortex's defective areas, possibly through mechanisms involving an increase in serum beta-endorphin levels.[11] PNS, which employs flexible open-coil leads placed away from the target nerve using ultrasound guidance,[13 39] ranked second. PNS is believed to activate large-diameter fibers effectively, thereby reversing aberrant plasticity and achieving a substantial supraspinal effect.[13] Overall, these findings reiterate the conclusions from previous pairwise meta-analyses and clinical studies emphasizing the superiority of neuromodulation modalities in managing chronic pain.[16 18]

The administration of peripheral nerve blockade is predominantly used for perioperative management of PLP, frequently targeting the brachial plexus, femoral nerve, and sciatic nerve.[3] Traditional nerve blocks, however, often fall short of delivering

Table 4 Summary findings based on relative rankings from this network meta-analysis

	Sham/placebo	NB (CPNB)	NB (cyroneurolysis)	NM (rTMS)	NM (ctDCS)	NM (PNS)
Pain intensity improvement	Intermediate (10th)	More (3rd) (more favored)	Fewest (12th) (least favored)	Most (1st) (most favored)	Intermediate (6th)	More (2nd) (more favored)
Adverse event incidence	Intermediate (6th)	Require further trials	Lowest (1st) (most favored)	Lower (3rd) (more favored)	Intermediate (5th)	Intermediate (8th)
	PO (Amitriptyline)	PO (Gabapentin)	PO (Memantine)	PO (Mexiletine)	PO (Morphine)	Alternative (EMS)
Pain intensity improvement	Intermediate (7th)	Intermediate (5th)	Intermediate (8th)	Intermediate (9th)	Intermediate (4th)	Intermediate (11th)
Adverse event incidence	Require further trials	Require further trials	Lower (2nd) (more favored)	Intermediate (7th)	Highest (9th) (least favored)	Intermediate (4th)

Alternative (EMS), Alternative treatment with electromagnetic shielding; NB (CPNB), Continuous perineural neural block; NB (cyroneurolysis), neural block with cryoneurolysis; NM (ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM (PNS), neuromodulation with percutaneous peripheral neural stimulation; NM (rTMS), neuromodulation with repetitive transcranial magnetic stimulation; PO (Amitriptyline), oral administration of amitriptyline; PO (Gabapentin), oral administration of gabapentin; PO (Memantine), oral administration of memantine; PO (Mexiletine), oral administration of mexiletine; PO (Morphine), oral administration of morphine.

sustained pain relief for chronic PLP sufferers.[2 3] In light of this, continuous perineural infusion and nerve block via cryoneurolysis have been trialed, although with varying outcomes.[2 3] Our NMA revealed that nerve block augmented by continuous perineural infusion was notably superior to the control, ranking the third place concerning reductions in pain intensity among all treatments (SUCRA=74.9%). However, the pooled MD in our NMA for pain alleviation by continuous perineural infusion was 1.8 points, falling just above the MCID threshold of 1.7 points set for chronic PLP and under 2.0 for other chronic pains.[36 38] Previous study using continuous perineural ropivacaine infusion for 6 days reported that PLP ameliorated shortly post a single ropivacaine injection, maintaining this effect for up to 4 weeks.[2] Contrastingly, nerve block using cryoneurolysis, which involves the reversible ablation of peripheral nerves by chilling them with nitrous oxide to approximately −70°C,[3] did not exhibit significant pain improvement in our analysis. Earlier studies had similarly reported lackluster outcomes, theorizing that earlier positive results might be attributed to placebo effects, selection biases, or the natural pain resolution process.[3] The cryoneurolysis procedure had the lowest ranking for adverse events; however, a previous study emphasized a severe adverse event in a participant who suffered significant weakness in the quadriceps femoris following a transtibial amputation.[3] It is worth noting that despite the mixed results for cryoneurolysis, some uncontrolled case series have shown its analgesic benefit for PLP patients.[40–42]

Pharmacological interventions have been used historically to treat phantom pain following amputation. These interventions encompass a range of drugs: beta-blockers, calcitonins, anticonvulsants, antidepressants, selective serotonin-reuptake inhibitors, anesthetics, opioids, tramadol, analgesics, NMDA receptor antagonists, non-steroidal anti-inflammatory drugs, and muscle relaxants.[15] Despite this variety, for patients suffering from chronic PLP, identifying the optimal pharmacological approach has proven elusive. Most studies have concentrated on opioid analgesics, tricyclic antidepressants, anticonvulsants, NMDAR antagonists, and sodium channel blockers.[1 4 7–10] However, our NMA found that none of the following pharmacological treatments: amitriptyline (a tricyclic antidepressant), gabapentin (an anticonvulsant), memantine (an NMDAR antagonist), mexiletine (a sodium channel blocker), or morphine (an opioid analgesic) outperformed the control in terms of pain reduction. Past studies also corroborated these findings, revealing limited efficacy of certain drugs like amitriptyline, memantine, and mexiletine in reducing chronic PLP.[1 5 9 10] Furthermore, while some reports suggest morphine's effectiveness in alleviating chronic PLPs, our NMA contradicts these findings. Our NMA also revealed that morphine, despite its potential benefits for chronic PLP,[10 43] carries notable side effects such as nausea, vomiting, dizziness, and drowsiness.[10 15] Moreover, the rate of adverse events with morphine was significantly higher compared with placebo (OR=6.04; (95% CI 2.26 to 16.12)) and other pharmacological interventions such as memantine (OR=8.93; (95% CI 1.82 to 43.79)) and mexiletine (OR=5.87; (95% CI 2.19 to 15.70)) (table 2; online supplemental appendix 7.2).

The EMS system, designed to shield against electromagnetic fields, was believed to work by protecting sensitive nerve endings from environmental electromagnetic disturbances, such as those during thunderstorms.[44 45] So far, two RCTs have produced mixed results; one found EMS to be effective,[44] while the other found it no better than a placebo.[6] In our NMA, EMS performed poorly, ranking below even sham/placebo treatments. This suggests that countering the effects of electromagnetic fields may not play a crucial role in alleviating chronic PLP.

Limitations

Our research faces several constraints, most notably the lack of long-term outcome data from the studies reviewed. Of these, only eight trials[2–4 6 7 9–11] assessed the effects of interventions beyond 1 month, and just one study[2] explored outcomes beyond 6 months. Further RCTs are needed to determine if the immediate benefits persist over time. Additionally, certain interventions, such as neuromodulations (rTMS, ctDCS, and PNS), nerve blocks (CPNB and cryoneurolysis), pharmacological treatments (amitriptyline, mexiletine, and morphine), and the EMS, have each been assessed in just one trial. An analytical approach is thus required for their findings. Confidence in the study outcomes was generally moderate to low, particularly for those with ambiguous evidence. Concerning adverse events, confidence levels were even lower, signaling the need for extra caution. Notably, there was a significant difference in baseline age and pain intensity between the neuromodulation group and others. To prevent overstating the effectiveness of neuromodulations in pain improvement, we downgraded the evidence quality in all related outcomes and acknowledged this inconsistency in our GRADE assessment. Moreover, including cross-over data from the end of the trials tends to underestimate the variance of the treatment effects within these trials, especially when combined with non-cross-over, parallel-group trials. A significant issue highlighted is the absence of standardized methodologies for treating chronic PLP, which might yield inconsistent results. Yet, no inconsistencies between global or local strategies were identified. Finally, the power of our outcome conclusions might be limited due to the inclusion of a comparatively small number of studies.

Conclusion

The NMA suggests that neuromodulation using rTMS may be associated with significantly larger pain improvement for chronic PLP. However, the paucity of studies, varying patient characteristics across each trial, and absence of long-term results underscore the necessity for more comprehensive, large-scale RCTs.

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