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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

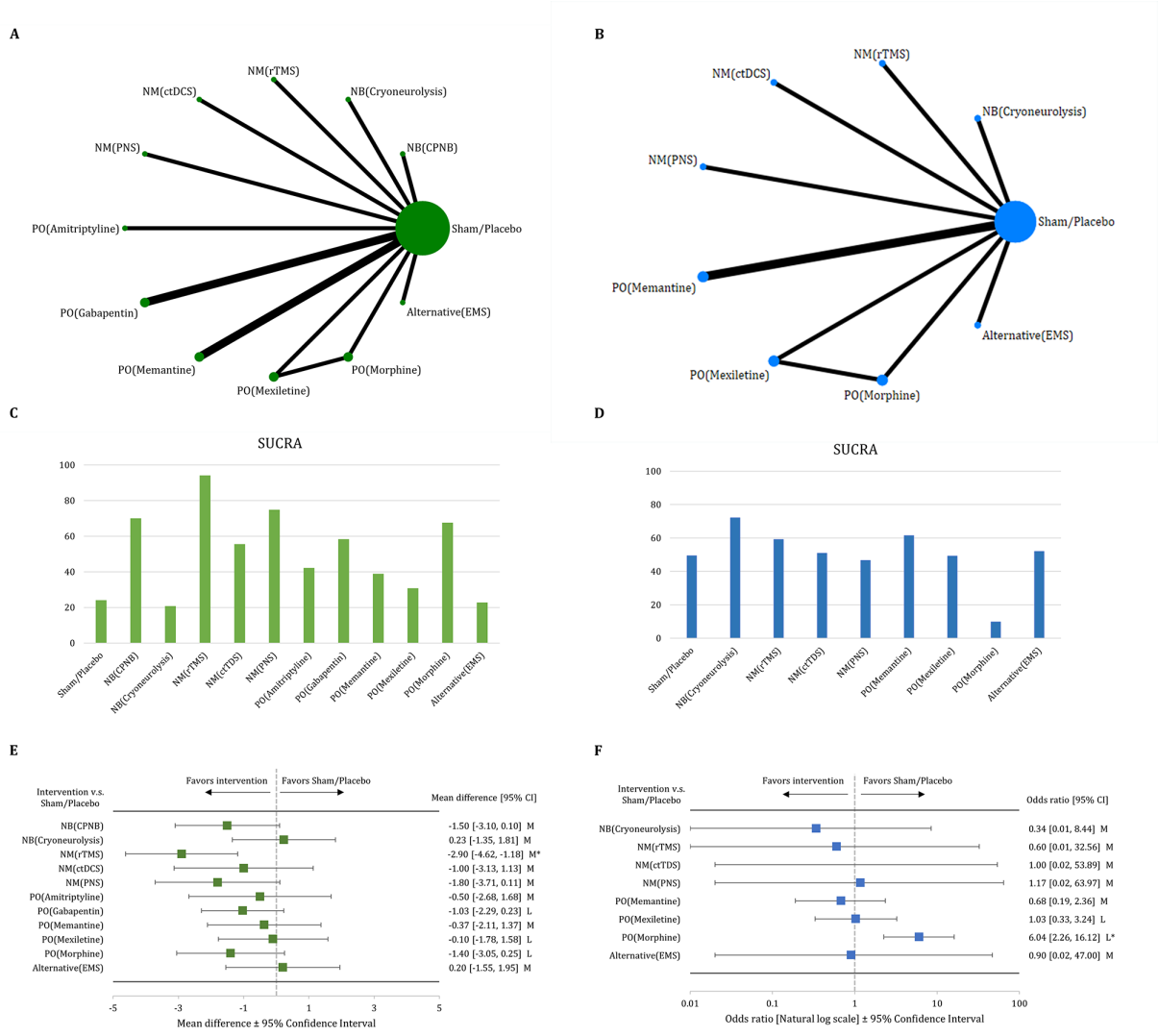

Figure 1 PRISMA flow diagram of studies identified and included in this network meta-analysis. CPNB, continuous perineural block; ctDCS, cerebellar transcranial direct current stimulation; EMS, electromagnetic shielding; NM (rTMS), neuromodulation with repetitive transcranial magnetic stimulation; PNS, 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.

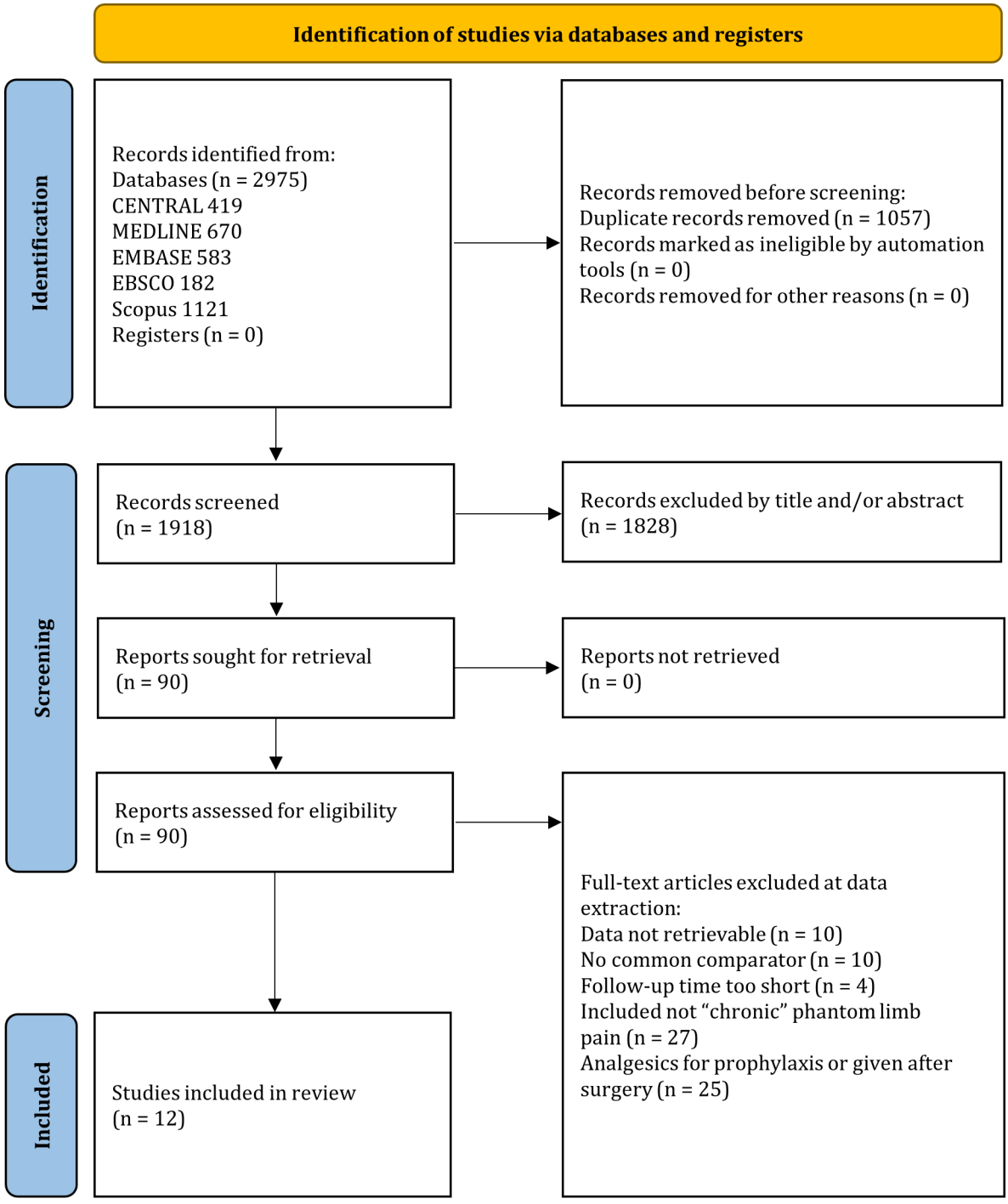

Figure 2 Network geometry of different interventions for comparisons of changes in pain intensity (A) and adverse event rate (B). SUCRA value as numeric presentation of the overall ranking for all interventions (C–D). The rank would be better with larger value. Forest plots of network estimates were 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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Appendix 1: PRISMA checklist

Section/Topic	Item #	Checklist Item [16]	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1, Title section**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives; **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.***Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**3, Abstract section**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**6-7, Introduction (3rd paragraph)**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6-7, Introduction (3rd paragraph); Appendix 2**
METHODS			

Protocol and registration	5	Indicate whether a review protocol exists: **PROSPERO register：CRD42022328360**	**8, Method (1st paragraph)**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**8, Method (2nd paragraph);**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**8, Method (1st paragraph);**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**8, Method (2nd paragraph); Appendix 2, 3**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**8, Method (2nd paragraph); Appendix 3**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**8, Method (1st and 2nd paragraph)**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**8, Method (1st paragraph) Appendix 2**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**8-9, Method (3rd paragraph); Figure 2**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**10, Method (7th paragraph**

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**11, Method (9th paragraph**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis.	**11, Method (9th paragraph)**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**11, Method (9th paragraph)**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**10, Method (7th paragraph)**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified.	**11, Method (9th paragraph)**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**12, Findings (1st paragraph); Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 2**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**12, Findings (1st paragraph); Figure 2**

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**12, Findings (1st paragraph); Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**13-14, Findings (4th paragraph); Appendix 6**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals.	**12-13, Findings (2nd-3rd paragraphs)**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. If additional summary measures were explored (such as treatment rankings), these should also be presented.	**12-13, Findings (2nd-3rd paragraphs) Figure 2**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**14, Findings (6th paragraph); Appendix 10**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**13-14, Findings (4th paragraph); Appendix 6**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**14-15, Findings (8th -9th paragraph); Appendix 12-13**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome;	**28, Discussion (1st paragraph)**

		consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**32**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**32-33**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**2**

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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Appendix 2: Protocol and search strategies

Protocol as published in PROSPERO CRD42023455949

2.1. Review eligibility criteria

eTable 2.1. PICOS, Inclusion and exclusion criteria

Patient	Participants with chronic phantom limb pain
Intervention	Interventions include neuromodulation methods such as repeated transcranial magnetic stimulation and transcranial direct current stimulation. Neural block techniques, such as perineural infusion, are also utilized. Oral administration options encompass drugs like morphine, mexiletine, amitriptyline, memantine, and gabapentin. Additionally, any other alternative, non-invasive, or invasive treatments can be considered.
Comparator	Placebo, normal saline injection, or sham procedure
Outcomes	Improvement of VAS/NRS scores, adverse event rate
Study design	Prospective randomized controlled trials
Inclusion criteria	1. Studies that were randomized controlled trials 2. Studies that compared various treatment modalities, including neuromodulation, neural blocks, oral medication, and alternative treatments. 3. Amputees who had experienced phantom limb pain for a duration exceeding 2 months. 4. Studies where the term “chronic phantom limb pain” was specifically mentioned.
Exclusion criteria	1. Studies employing observational designs, single-arm setups, or quasi-RCTs. 2. Studies lacking available arm-level data. 3. Studies involving patients with acute phantom limb pain or those slated for amputation surgery.

2.2. Search vocabulary

Database	#	Search syntax
CENTRAL	1	[mh "phantom limb"]
	2	(pseudomelia* OR (phantom NEAR/4 (limb* OR pain* OR sensation*))):ti,ab,kw
	3	#1 or #2
	4	#3 Limits in Trials
MEDLINE Ovid	1	exp "phantom limb"/
	2	(pseudomelia* OR (phantom adj4 (limb* OR pain* OR sensation*))).mp
	3	1 or 2
	4	3 and (randomized controlled trial.pt. or controlled clinical trial.pt. or randomi*ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. not (exp animals/ not humans.sh.))
Embase	1	"phantom limb"/exp
	2	(pseudomelia* OR (phantom NEAR/4 (limb* OR pain* OR sensation*))):ti,ab,kw,de
	3	(#1 OR #2) AND [embase]/lim
	4	#3 AND ("randomized controlled trial"/de or "controlled clinical trial"/de or "randomization"/de or "intermethod comparison"/de or "double blind procedure"/de or "human experiment"/de OR (random* or placebo or assigned or allocated or volunteer or volunteers or (open NEXT/1 label) or ((double or single or doubly or singly) NEXT/1 (blind or blinded or blindly)) or "parallel group?" or crossover or "cross over" or ((assign* or match or matched or allocation) NEAR/5 (alternate or group? or intervention? or patient? or subject? or participant?)) OR (controlled NEAR/7 (study or design or trial))):ti,ab OR (compare or compared or comparison or trial):ti OR ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)):ab) NOT (((random* NEXT/1 sampl* NEAR/7 ("cross section*" or questionnaire? or survey* or database?)):ti,ab not ("comparative study"/de or "controlled study"/de or "randomi?ed controlled":ti,ab or "randomly assigned":ti,ab)) OR ("Cross-sectional study"/de not ("randomized controlled trial"/de or "controlled clinical

		study"/de or "controlled study"/de or randomi?ed controlled:ti,ab or "control group?":ti,ab)) OR ((((case NEXT/1 control*) and random*) not randomi?ed controlled):ti,ab) OR ("Systematic review" not (trial or study)):ti OR (nonrandom* not random*):ti,ab OR "Random field*":ti,ab OR ("random cluster" NEAR/3 sampl*):ti,ab OR ((review:ab and review/it) not trial:ti) OR ("we searched":ab and (review:ti or review/it)) OR "update review":ab OR (databases NEAR/4 searched):ab OR ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset?):ti and "animal experiment"/de) OR ("animal experiment"/de not ("human experiment"/de or "human"/de)))
CINAHL	1	mh ("phantom limb")
	2	pseudomelia* OR (phantom N3 (limb* OR pain* OR sensation*))
	3	S1 or S2
	4	S3 and (MH ("randomized controlled trials" OR "double-blind studies" OR "single-blind studies" OR "random assignment" OR "pretest-posttest design" OR "cluster sample") OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR MH ("crossover design" OR "comparative studies") OR AB (cluster W3 RCT)) NOT ((MH ("animals+" OR "animal studies") OR TI (animal model*)) NOT MH (human))
Scopus	1	TITLE-ABS-KEY(pseudomelia* OR phantom W/3 (limb* OR pain* OR sensation*))
	2	(INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR

		"randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE (clinical trial OR trial OR rct* OR random* OR blind*))
	3	#1 AND #2

Appendix 3: Excluded studies and reasons

(3.1) Trials with non-retrievable data or not providing useable data: 10

1. Masters, T., A. Mishra, and H. Mishra, *Phantom limb and a new approach to understanding the WTA-WTP disparity.* Journal of Neuroscience, Psychology, and Economics, 2017. **10**(2-3): p. 111-120.
2. Bokkon, I., et al., *Phantom pain reduction by low-frequency and low-intensity electromagnetic fields.* Electromagnetic biology and medicine, 2011. **30**(3): p. 115-27.
3. Casale, R., et al., *Phantom limb pain relief by contralateral myofascial injection with local anaesthetic in a placebo-controlled study: preliminary results.* Journal of rehabilitation medicine, 2009. **41**(6): p. 418-22.
4. Moseley, G.L., Graded motor imagery for pathologic pain: a randomized controlled *trial.* Neurology, 2006. **67**(12): p. 2129-34.
5. Wilder-Smith, C.H., L.T. Hill, and S. Laurent, *Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo.* Anesthesiology, 2005. **103**(3): p. 619-28.
6. Schwenkreis, P., et al., *The NMDA antagonist memantine affects training induced motor cortex plasticity - A study using transcranial magnetic stimulation [ISRCTN65784760].* BMC Neuroscience, 2005. **6**.
7. Brodie, E.E., A. Whyte, and B. Waller, *Increased motor control of a phantom leg in humans results from the visual feedback of a virtual leg.* Neuroscience Letters, 2003. **341**(2): p. 167-169.
8. Ben Abraham, R., N. Marouani, and A.A. Weinbroum, *Dextromethorphan mitigates phantom pain in cancer amputees.* Annals of surgical oncology, 2003. **10**(3): p. 268-74.
9. Ben Abraham, R., et al., *Dextromethorphan for phantom pain attenuation in cancer amputees: a double-blind crossover trial involving three patients.* The Clinical journal of pain, 2002. **18**(5): p. 282-5.
10. Flor, H., et al., *Effect of sensory discrimination training on cortical reorganisation and phantom limb pain.* Lancet (London, England), 2001. **357**(9270): p. 1763-4.

Study	Reason for exclusion
Masters et al., 2017	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.
Bokkon et al., 2011	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.

Casale et al., 2009	Preliminary outcome, reporting results of a few participants.
Moseley et al., 2006	Mix population: Phantom limb and complex regional pain syndrome type 1 (CRPS1).
Wilder-Smith et al., 2005	Reporting only data of treatment responder. Data of non-responder lacking.
Schwenkreis et al., 2005	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.
Brodie et al., 2003	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.
Ben et al., 2003	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.
Ben et al., 2002	A double-blind crossover trial involving only 3 participants. Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.
Flor et al., 2001	Useable data (e.g., mean difference or odds ratio and 95% CI) not provided.

(3.2) Trials without a common comparator suitable for network meta-analysis: 10

1. Yanagisawa, T., et al., *Neurofeedback Training without Explicit Phantom Hand Movements and Hand-Like Visual Feedback to Modulate Pain: A Randomized Crossover Feasibility Trial.* The journal of pain, 2022. **23**(12): p. 2080-2091.
2. Gunduz, M.E., et al., *Effects of Combined and Alone Transcranial Motor Cortex Stimulation and Mirror Therapy in Phantom Limb Pain: A Randomized Factorial Trial.* Neurorehabilitation and neural repair, 2021. **35**(8): p. 704-716.
3. Yanagisawa, T., et al., *BCI training to move a virtual hand reduces phantom limb pain: A randomized crossover trial.* Neurology, 2020. **95**(4): p. e417-e426.
4. Limakatso, K., et al., *The effectiveness of graded motor imagery for reducing phantom limb pain in amputees: a randomised controlled trial.* Physiotherapy, 2020. **109**: p. 65-74.
5. Dumanian, G.A., et al., *Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial.* Annals of surgery, 2019. **270**(2): p. 238-246.
6. Aranda-Moreno, C., et al., *Stimulation of the semicircular canals or the utricles by clinical tests can modify the intensity of phantom limb pain.* Frontiers in Neurology, 2019. **10**(FEB).
7. Rostaminejad, A., et al., *Efficacy of eye movement desensitization and*

reprocessing on the phantom limb pain of patients with amputations within a 24-month follow-up. International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation, 2017. **40**(3): p. 209-214.

8. Brede, E., E.J. Metter, and L.A. Talbot, *Neuromuscular electrical stimulation for pain management in combat-related transtibial amputees during rehabilitation and prosthetic training.* Journal of Applied Biobehavioral Research, 2017. **22**(4).

9. Wu, H., et al., *A prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection versus Lidocaine/Depomedrol injection on residual and phantom limb pain: initial report.* The Clinical journal of pain, 2012. **28**(2): p. 108-12.

10. Brodie, E.E., A. Whyte, and C.A. Niven, *Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement.* European journal of pain (London, England), 2007. **11**(4): p. 428-36.

Study	Interventions
Yanagisawa et al., 2022	Contralateral vs. Ipsilateral neurofeedback training
Gunduz et al., 2021	Mirror therapy + Real tDCS therapy vs. Covered mirror therapy + Real tDCS therapy vs. Mirror therapy + Sham tDCS therapy vs. Covered mirror therapy + Sham tDCS therapy
Yanagisawa et al., 2020	Brain-computer interface (BCI) training: “Real training” vs. “Random training”
Limakatso et al., 2020	Graded motor imagery (GMI) vs. Routine physiotherapy
Dumanian et al., 2019	Target muscle reinnervation vs. Standard treatment for neuroma
Aranda-Moreno et al., 2019	Vestibular stimulation: Right/left caloric test vs. Right/ left centrifugation
Rostamineiad et al., 2017	Eye movement desensitization and reprocessing (EMDR) vs. Usual rehabilitation programs
Brede et al., 2017	NMES+MARP vs. MARP only MARP, military amputee rehabilitation program; NMES, neuromuscular electrotherapy stimulation.
Wu et al., 2012	Botulinum toxin type A injection vs. Lidocaine/Depomedrol injection
Brodie et al., 2007	Only viewed the movements of their intact limb

	vs. A mirror condition in which they additionally viewed the movements of a 'virtual' limb

(3.3) Trials with an inadequately short follow-up period (ranging from minutes to hours): 4

. Buch, N.S., et al., *The role of afferent input in postamputation pain: a randomized, double-blind, placebo-controlled crossover study.* Pain, 2019. **160**(7): p. 1622-1633.

2. Bolognini, N., et al., *Motor and parietal cortex stimulation for phantom limb pain and sensations.* Pain, 2013. **154**(8): p. 1274-1280.

3. Eichenberger, U., et al., *Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds.* Anesthesia and analgesia, 2008. **106**(4): p. 1265-contents.

4. Wu, C.L., et al., *Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial.* Anesthesiology, 2002. **96**(4): p. 841-8.

(3.4) Trials where the period of enduring phantom limb pain was either too brief, not explicitly mentioned in the inclusion criteria, or the term "chronic" was not cited in the full text: 27

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of the perioperative perineural infiltration of bupivacaine and clonidine at the site of injury following lower extremity amputation. Acute Pain, 2006. **8**(3): p. 117-123.
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Appendix 4: List of included studies

4.1. Study population, intervention, outcome

Author (Year)	Treatment type	Outcome measures	Total follow up time*
Ilfeld et al., 2023	Ultrasound-guided percutaneous cryoneurolysis	Change in NRS score / Adverse event	4† months
	Sham treatment		
Ilfeld et al., 2021	Continuous perineural neural block with ropivacaine	Change in NRS score	1, 2, 3, 4 †‡ weeks 6§, 12§ months
	Continuous perineural infusion of normal saline		
Bocci et al., 2019	Cerebellar transcranial direct current stimulation	Change in VAS score	0, 2, 4†‡ weeks
	Sham treatment		
Gilmore et al., 2019	Peripheral nerve stimulation	Change in NRS score / Adverse event	4†‡ weeks
	Placebo treatment		
	Sham treatment		
Hsiao et al., 2012	Electromagnetic shielding	Change in NRS score	6, 12† weeks
	Sham treatment		
Ahmed et al., 2011	Repetitive transcranial magnetic stimulation	Change in VAS score	0, 1, 2† months
	Sham treatment		

Wu et al., 2008	Oral mexiletine	Change in NRS score / Adverse event	8†‡ weeks
	Oral sustained-release morphine		
	Oral Placebo tablets		
Smith et al., 2005	Oral gabapentin	Change in NRS score	6†‡ weeks
	Oral Placebo tablets		
Robinson et al., 2004	Oral amitriptyline	Change in NRS score	6† weeks
	Oral benztropine mesylate (placebo)		
	Oral placebo tablets		
Maier et al., 2003	Oral memantine	Change in NRS score / Adverse event	4† weeks
	Oral placebo tablets		
Schwenkreis et al., 2003	Oral memantine	Change in NRS score	3† weeks
	Oral Placebo tablets		
Bone et al., 2002	Oral Gabapentin	Change in VAS score	6†‡ weeks
	Oral Placebo tablets		

*For crossover RCT, total follow-ups time stands for the follow-up periods in each session (either before or after crossover). † Timepoint of data extraction. ‡ Timepoint of crossover. § Long term follow-up.

Abbreviations: VAS, visual analogue scale; NRS, numerical rating scale.

4.2. Study enrollment criteria

Author (Year)	Inclusion	Exclusion
Ilfeld et al., 2023	1. Adult patients aged 18 years and above. 2. Patients who have undergone a traumatic or surgical lower limb amputation for at least 12 weeks. 3. The amputation must be distal to the hip, with the femoral head intact. 4. Patients experiencing at least moderate phantom limb pain, defined as a score of 3 or more on the Numeric Rating Scale, consistently for the preceding 2 months.	1. Allergy to amide local anesthetics. 2. Pregnancy. 3. Incarceration. 4. Inability to communicate with the investigators. 5. Morbid obesity (BMI > 40 kg/m2). 6. Any contraindication specific to cryoneurolysis such as a localized infection at the treatment site, cryoglobulinemia, cold urticaria, and Raynaud's syndrome.
Ilfeld et al., 2021	1. Patients aged 18 years and above. 2. Individuals who have had an upper or lower limb traumatic amputation occurring at least 12 weeks prior, and is distal to the midhumerus for the upper limb or the knee for the lower limb. 3. The amputation must include at least one metacarpal bone for the upper limb or one metatarsal bone for the lower limb. 4. Experience phantom limb pain of at least a 2 or higher on the Numeric Rating Scale.	1. Renal insufficiency. 2. Allergy to study medication. 3. Pregnancy. 4. Incarceration. 5. Inability to communicate with the investigators. 6. Morbid obesity (BMI > 40 kg/m2). 7. Comorbidity that resulted in moderate-to-severe functional limitations. 8. Contraindication to a continuous peripheral nerve block.
Bocci et al., 2019	1. Participants aged between 18 to 70 years. 2. Normal score (> 24) on the Mini-Mental State Examination. 3. Limb amputation at least 6 months before study enrollment. 4. Stable presence of PLP for at least 2 months.	None stated.

	5. No coexistence of major neurologic, neuropsychological, and psychiatric diseases. 6. Stable pharmacological therapy maintained for at least one month before being included in the study.	
Gilmore et al., 2019	1. Traumatic lower extremity amputees aged ≥18 years. 2. Moderate-to-severe RLP and/or PLP (rated ≥4 on a 0 – 10 pain scale). 3. A healed residual limb is required, with no accompanying comorbidities. 4. No constraints regarding time since amputation.	1. Changes in pain medications within the previous 4 weeks. 2. Beck Depression Inventory II (BDI-II) score >20. 3. Compromised immune system (e.g., HIV, undergoing chemotherapy, immunosuppressive medications). 4. Diabetes mellitus type I or II. 5. Presence of implanted electrical stimulation devices. 6. Anticoagulation therapy (excluding aspirin or warfarin with an international normalized ratio (INR) of ≤1.5), history of bleeding disorders, or valvular heart disease. 7. Pregnancy. 8. Confounding central nervous system (CNS) disorders. 9. Allergies to local anesthetic agents or skin-contact materials. 10. History of recurrent skin infections. 11. Previous botulinum toxin injections in the affected limb within the last 3 months or steroid injections in the affected limb within the last 6 weeks.
Hsiao et al., 2012	1. Upper or lower extremity amputation with healed stump that experienced episodes or intermittent PLP. 2. At least 3 episodes of PLP in the previous 6 weeks.	1. Stump complications (e.g., cellulitis or stump pain caused by a new bone spur in the past 12 months). 2. Use of Farabloc within the last 6 months.

	3. No use of Farabloc in the past 6 months.	3. Pregnancy.
Ahmed et al., 2011	1. Patients with unilateral amputation: 11 patients had upper limb amputations (10 of which were above the elbow), and 16 patients had below-knee amputations. 2. All patients experienced chronic phantom pain.	None stated.
Wu et al., 2008	1. Adults aged 18 years or older. 2. Presence of persistent post-amputation pain rated as greater than 3 on a 0–10 numerical rating scale, persisting for a duration of 6 months or more.	1. History of allergic reaction to any of the study drugs (e.g., morphine and mexiletine). 2. Cardiac conduction defects (such as second-degree or complete heart block) or myocardial infarction within the past 3 months. 3. Severe pulmonary disease. 4. Current history of conditions like alcohol or substance abuse, seizures, dementia, or encephalopathy. 5. Being pregnant or currently breastfeeding. 6. Chronic hepatic disease, hepatic or renal failure, or any hematologic disease associated with leukopenia or thrombocytopenia. 7. Presence of any terminal disease with a life expectancy of less than 6 months.
Smith et al., 2005	1. Lower-limb amputation conducted at least 6 months prior. 2. Average pain rating in the past month of at least 3 on a 0-10 numerical rating scale (NRS) for either the phantom or residual limb. 3. Agreement to adhere to medication schedules and protocols. 4. Ability to read and speak English.	1. Age under 18 years. 2. Concurrent use of other antiepileptic medication or cimetidine (Tagamet). 3. Consumption of more than two alcoholic drinks daily. 4. If female, either pregnant or breastfeeding. 5. High serum creatinine clearance or low estimated creatinine clearance from

		a screening serum creatinine; or a known history of kidney disease.
Robinson et al., 2004	1. Amputation conducted more than 6 months ago. 2. Pain present for at least 3 months, with an average pain rating in the last month of at least 2 on a 0-10 scale.	1. Age under 18 years or over 65 years. 2. History of cardiovascular disease or seizures. 3. Pregnancy. 4. Current use of any type of antidepressant medication or reported consumption of more than 2 alcoholic drinks daily.
Maier et al., 2003	1. Upper or lower limb amputation. 2. At least 12 months of PLP history with an average pain rating of at least 4 on an 11-point numeric scale.	1. Changes in PLP treatment within the 4 weeks leading up to the investigation. 2. Renal function impairment.. 3. History of seizures, severe depression, panic disorders, or other contraindications to memantine.
Schwenkreis et al., 2003	1. Chronic phantom pain following upper or lower limb amputation. 2. At least 12 months of consistent phantom limb pain.	1. Any modifications to phantom pain treatment within the 4 weeks before study commencement.
Bone et al., 2002	1. Phantom pain persisting for at least 6 months after surgical amputation. 2. Age range between 18 and 75 years. 3. Pain score of at least 40 mm on a 100-mm visual analog scale.	1. Coexisting epilepsy. 2. Known allergy to gabapentin. 3. Significant hepatic or renal insufficiency or severe hematologic disease. 4. History of illicit drug or alcohol abuse, or any serious psychiatric condition. 5. Patients suffering from other severe pain conditions that might affect assessment.

4.3. Baseline characteristics

Author (Year)	Level of evidence	Treatment type	Age(years)	N	Sex (Male %)	Baseline NRS/VAS	Amputation site (n, upper limb)	Amputation site (n, lower limb)	Amputation type (n, traumatic)	Amputation type (n, non-traumatic)
Ilfeld et al., 2023	I	Ultrasound-guided percutaneous cryoneurolysis	58±13	71	74.65	5 [4, 6]	0	71	N.A.	N.A.
		Sham treatment	58±13	73	60.27	5 [4, 7]	0	73	N.A.	N.A.
Ilfeld et al., 2021	I	Continuous perineural neural block with ropivacaine	49±14	71	70.42	5 [4, 7]	13	58	20	51
		Continuous perineural infusion of normal saline	50±14	73	59.9	5 [4, 7]	10	63	16	57
Bocci et al., 2019	I	Cerebellar transcranial direct current stimulation	40.21±9.74	14	42.86	5.4±2	14	0	11	0
		Sham treatment	40.21±9.74	14	42.86	5.3±1.8	14	0	11	0
Gilmore et al., 2019	I	Peripheral nerve stimulation	48.3±12.3	12	83.33	6.9±1.7	0	12	12	0
		Placebo treatment	45±13.2	14	28.57	6.8±1.7	0	14	14	0
Hsiao et al., 2012	I	Electromagnetic shielding	61.8±12.3	30	96.67	5.9±1.9	0	30	5	25
		Sham treatment	65.8±13.4	27	100	6.5±1.8	0	27	8	19
Ahmed et al., 2011	I	Repetitive transcranial magnetic stimulation	52.01±12.7	17	76.47	7.4±1.3	7	10	2	15
		Sham treatment	53.3±13.3	10	60	7.6±0.84	4	6	4	6
Wu et al., 2008	I	Oral mexiletine	63.4±16.4	60	78.33	6.657±0.381	12	48	26	34
		Oral sustained-release	63.4±16.4	60	78.33	6.657±0.381	12	48	26	34

		morphine								
		Oral Placebo tablets	63.4±16.4	60	78.33	6.657±0.381	12	48	26	34
Smith et al., 2005	I	Oral gabapentin	52.1±15.5	24	75	4.38±2.57	3	21	13	11
		Oral Placebo tablets	52.1±15.5	24	75	4.09±2.44	3	21	13	11
Robinson et al., 2004	I	Oral amitriptyline	44.4±9.4	20	85	3.6±2.4	2	18	16	4
		Oral benztropine mesylate (placebo)	45.3±13.3	19	90	3.1±2.6	2	18	14	5
Maier et al., 2003	I	Oral memantine	62 (28-76)	18	77.78	5.1±2.13	10	8	9	9
		Oral placebo tablets	61 (35-77)	18	83.33	5.2±2.02	10	8	15	3
Schwenkreis et al., 2003	I	Oral memantine	Unknown	8	87.5	6.8 (0.3-7.7)	8	0	8	0
		Oral Placebo tablets	Unknown	8	87.5	4.1 (1.7-6.3)	8	0	7	1
Bone et al., 2002	I	Oral Gabapentin	56.25±17.5	19	78.95	6.1±1.8 (n=14)	N.A.		N.A.	
		Oral Placebo tablets	56.25±17.5	19	78.95	6.7±1.9 (n=14)				

Data reported as: Mean ± Standard deviation, Median [First quartile1, third quartile], Median (Range), or **Mean (Range)**.

Abbreviations: VAS, visual analogue scale; NRS, numerical rating scale.

Appendix 5: Assessment of transitivity

Before conducting statistical analysis, we assessed the transitivity assumption. This involved verifying that the trials included in the NMA were broadly similar in terms of characteristics that could potentially influence the treatment effect. The baseline characteristics evaluated across these trials are detailed in Appendices 5.1-5.9, which include:

Appendix 5.1 Age (in years)
Appendix 5.2 Percentage of male participants (%)
Appendix 5.3 Baseline VAS/NRS score
Appendix 5.4 Duration since amputation (in years)
Appendix 5.5 Duration of phantom limb pain (in years)
Appendix 5.6 Sample size (n)
Appendix 5.7 Year of publication
Appendix 5.8 Follow-up period (in weeks)
Appendix 5.9 Amputation site / type percentage (%)

Summary of findings for baseline characteristics

Significant differences were observed in the baseline characteristics of age and VAS/NRS score. Notably, the neuromodulation group—which includes interventions like repetitive transcranial magnetic stimulation, cerebellar transcranial direct current stimulation, and peripheral neural stimulation—tended to have higher baseline pain intensity and a younger age profile compared to other groups (refer to Appendices 5.1 and 5.3).

This pattern was consistent when classifying interventions into five main categories: neuromodulation, neural block, oral medication, and alternative modalities (refer to the Summary Table below). The neuromodulation category consistently exhibited higher pain severity and a younger demographic than the other groups. However, the baseline characteristics of the other categories did not significantly differ from one another.

In addressing the intransitivity concerning age and pain severity, we used the GRADE approach to downgrade the quality of evidence for all outcomes related to the neuromodulation group. We also highlighted the observed intransitivity between direct and indirect evidence (see Appendix 11), which aids in preventing the overestimation of the effectiveness of neuromodulation in pain reduction.

Summary Table. Comparison of age and baseline pain score between different groups

Baseline Age (Mean, SD), ANOVA test: p=**6.72e-05**					
	Placebo	NM	NB	PO	Alternative
Placebo	N/A	**0.02162**	0.81655	0.13149	0.24435
NM	**0.02162**	N/A	0.1846	**0.00037**	**0.00222**
NB	0.81655	0.1846	N/A	**0.0338**	0.09781
PO	0.13149	**0.00037**	**0.0338**	N/A	0.88544
Alternative	0.24435	**0.00222**	0.09781	0.88544	N/A
Baseline VAS/NRS score, ANOVA test: p=**5.61e-03**					
	Placebo	NM	NB	PO	Alternative
Placebo	N/A	**0.01715**	0.45978	0.99934	0.99955
NM	**0.01715**	N/A	**0.00136**	**0.03465**	0.30072
NB	0.45978	**0.00136**	N/A	0.43472	0.8465
PO	0.99934	**0.03465**	0.43472	N/A	0.99998
Alternative	0.99955	0.30072	0.8465	0.99998	N/A

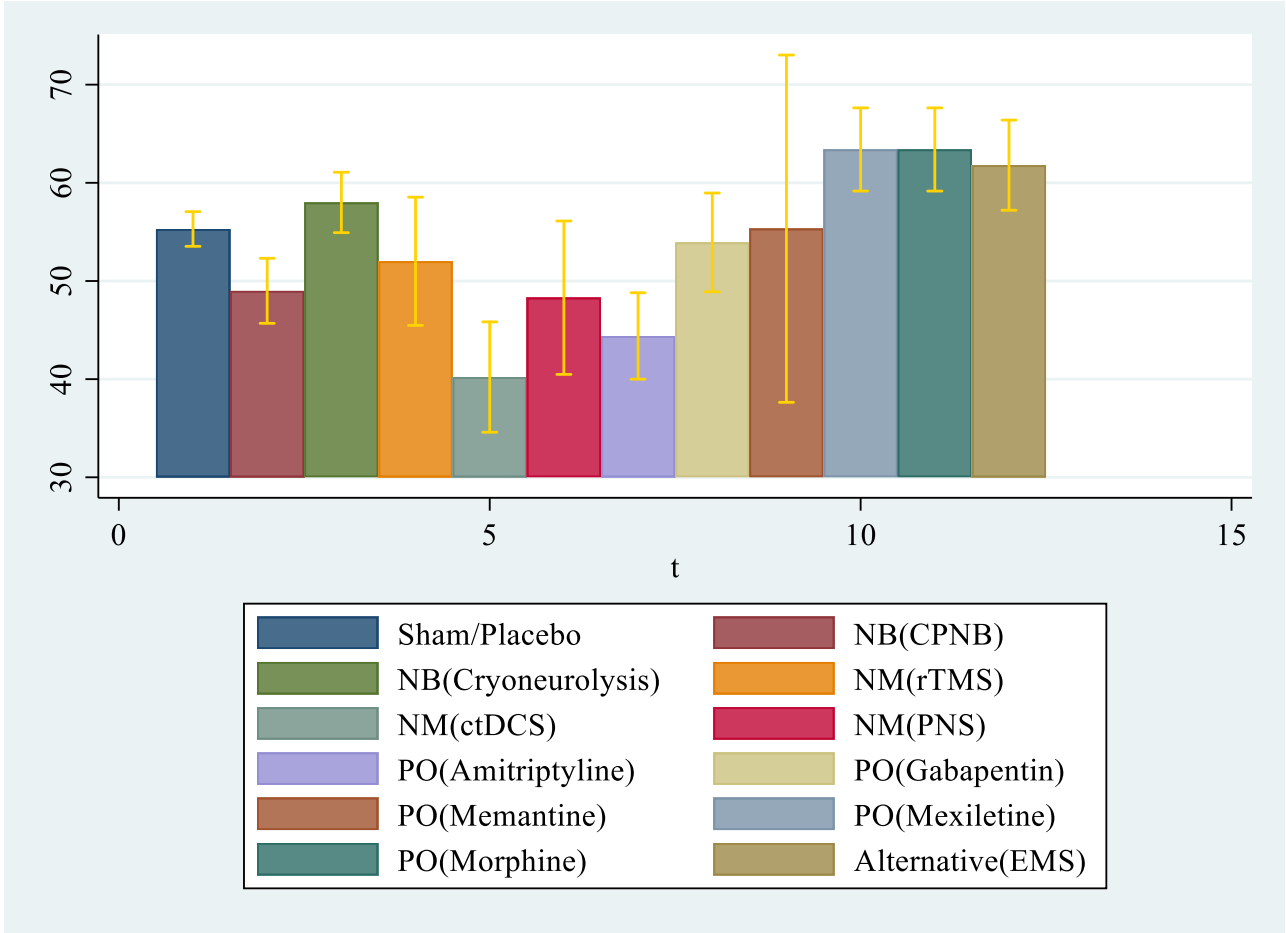
*Numbers in **Bold** indicate a significant difference (p<0.05).

*Abbreviations: NM, neuromodulation; NB, neural block; PO, oral medication.

Intervention Categories

1. Neural Block (NB):
   NB(CPNB): Continuous perineural neural block
   NB(cryoneurolysis): Neural block with cryoneurolysis
2. Neuromodulation (NM):
   NM(rTMS) - Neuromodulation with repetitive transcranial magnetic stimulation
   NM(ctDCS) - Neuromodulation with cerebellar transcranial direct current stimulation
   NM(PNS) - Neuromodulation with percutaneous peripheral neural stimulation
3. Oral Medication (PO):
   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
4. Alternative Modality (Alternative):
   Alternative(EMS) - Alternative treatment with electromagnetic shielding.

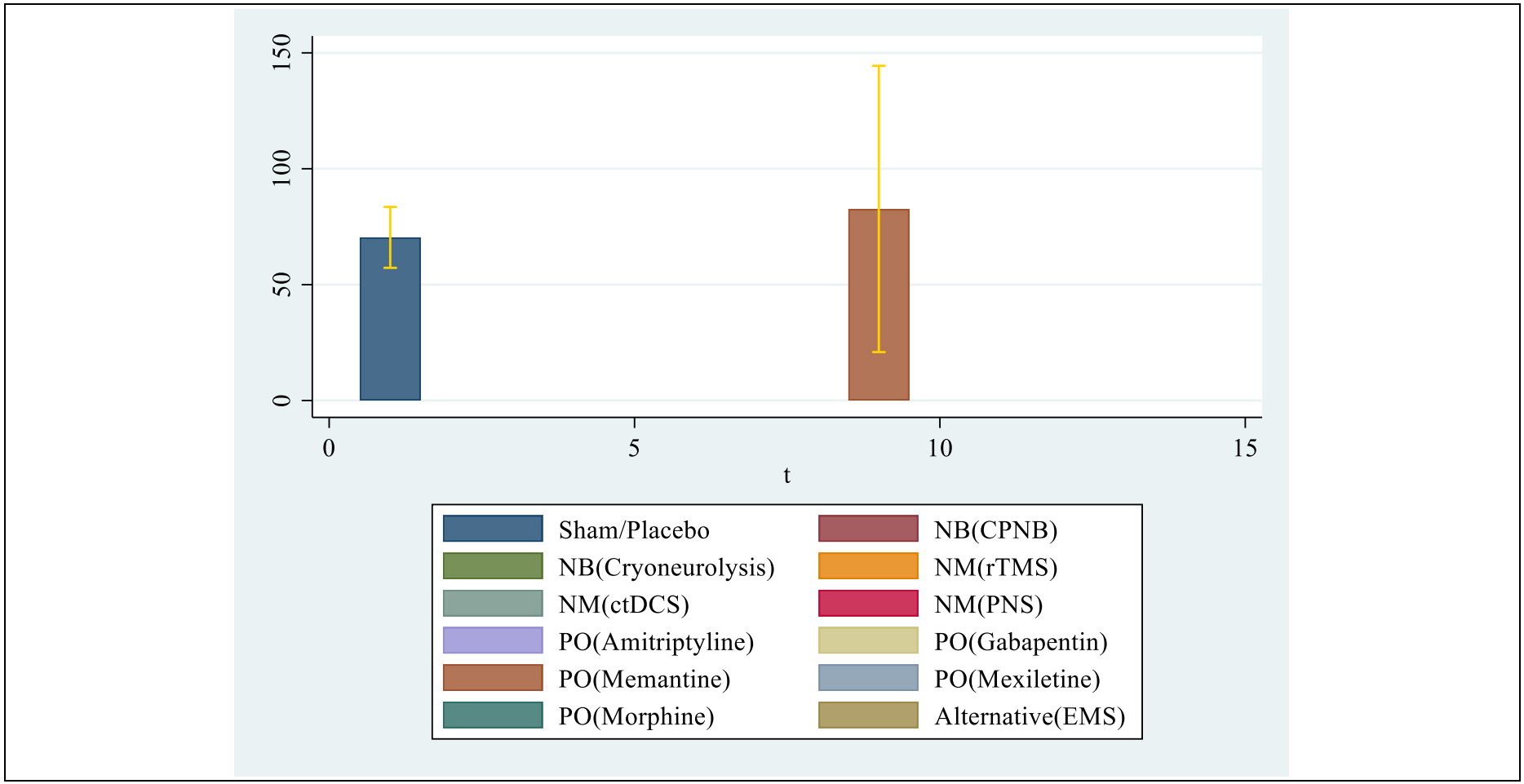
5.1. Age (in years)



Age (year)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	55.2949	49	58	52.01	40.21429	48.3
SD	16.8247	14	13	12.7	9.73636	12.3
P value	Reference	0.12037	0.98198	0.99967	**0.03481***	0.95028
Age (year)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	44.4	53.9337	55.33	63.4	63.4	61.8
SD	9.4	16.3452	35.58	16.4	16.4	12.3
P value	0.14038	1.00000	1.00000	**0.02019***	**0.02019***	0.62456

The *P*-value from the ANOVA test is 2.96e-10, indicating significance. *P*-values in bold and marked with an asterisk denote significance when compared with the reference, as determined by the Tukey post-hoc test. Data was not provided in Schwenkreis (2003).

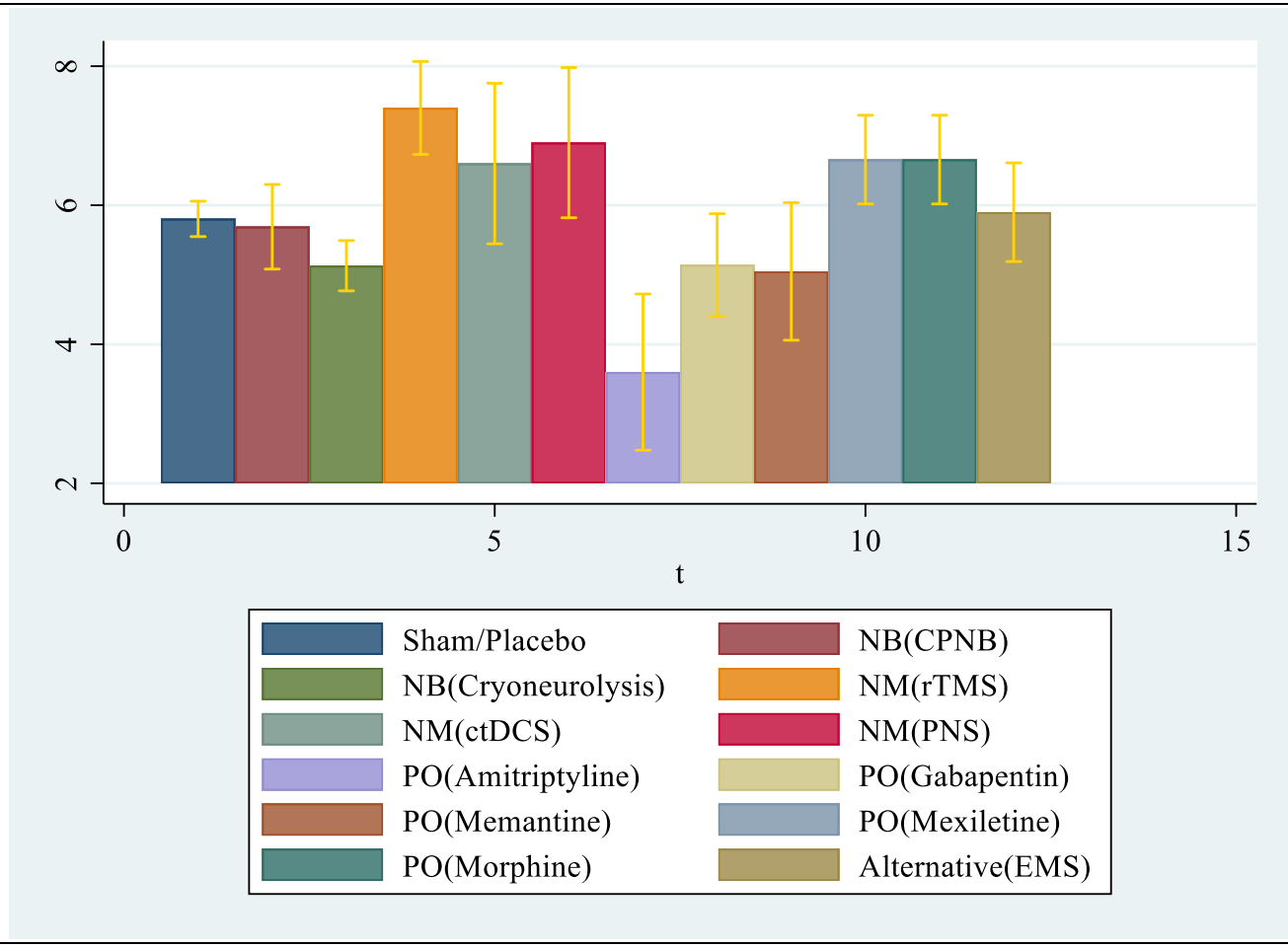
5.2. Male percentage (%)



Male (%)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	70.3925	-	-	-	-	-
SD	20.6844	-	-	-	-	-
P value	Reference	-	-	-	-	-
Male (%)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	-	-	82.64	-	-	-
SD	-	-	6.873078	-	-	-
P value	-	-	0.43609	-	-	-

The *P*-value from the ANOVA test is 0.436, indicating no statistical significance. Data was available in all included studies. However, the mean ± SD could not be computed for some arm-level data due to the availability of only one sample data point.

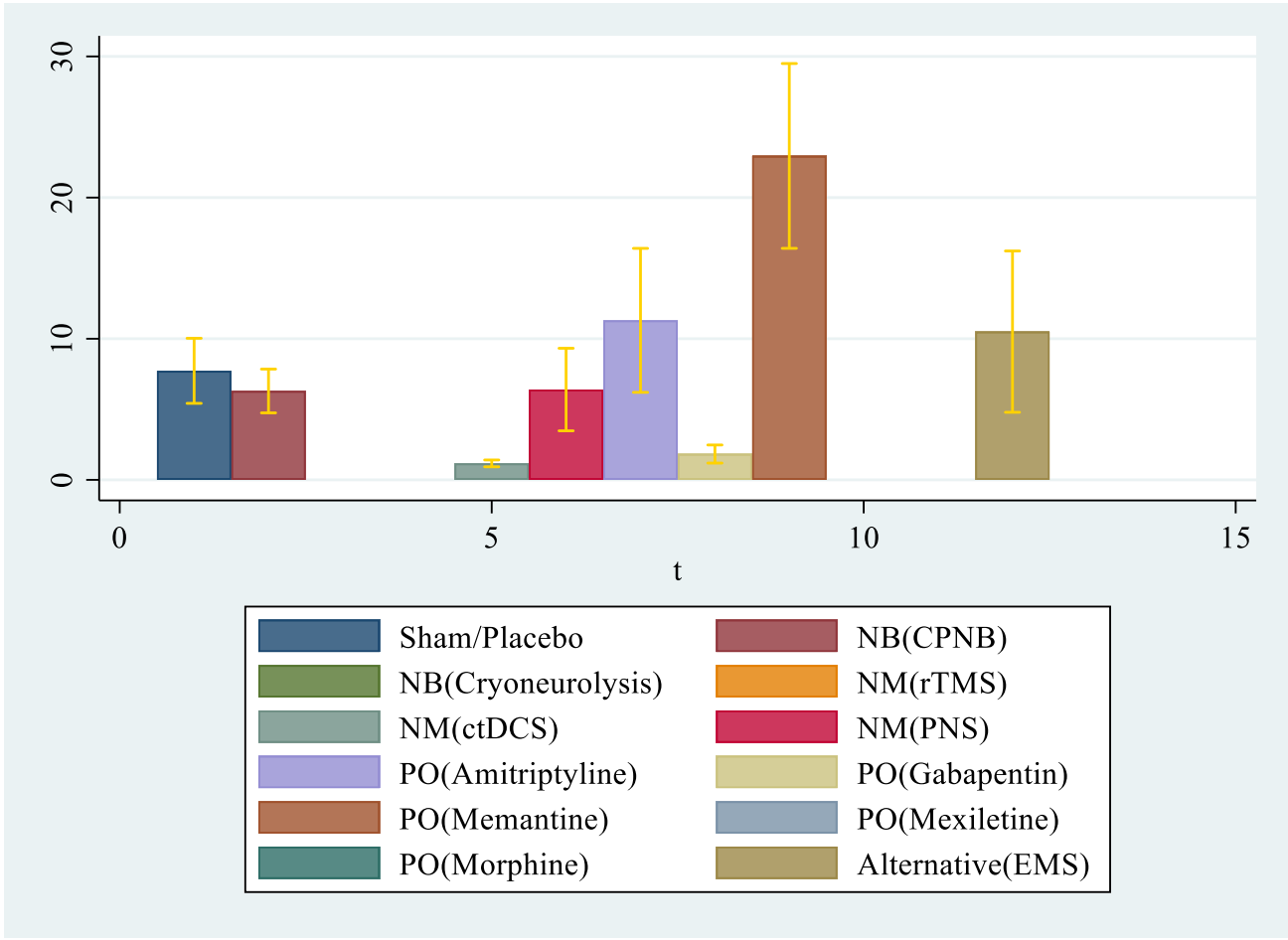
5.3. Baseline VAS/NRS score



Baseline pain	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	5.8036	5.69	5.13	7.4	6.6	6.9
SD	2.4544	2.57	1.53	1.3	2	1.7
P value	Reference	1.00000	0.53762	0.20435	0.98464	0.90999
Baseline pain	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	3.6	5.14	5.0477	6.657	6.657	5.9
SD	2.4	2.3984	2.4484	2.469	2.469	1.9
P value	**0.00266***	0.84008	0.91215	0.27250	0.27250	1.00000

The *P*-value from the ANOVA test is 4.92e-08, indicating significance. *P*-values in bold and marked with an asterisk denote significance when compared with the reference, as determined by the Tukey post-hoc test. Data was available in all included studies.

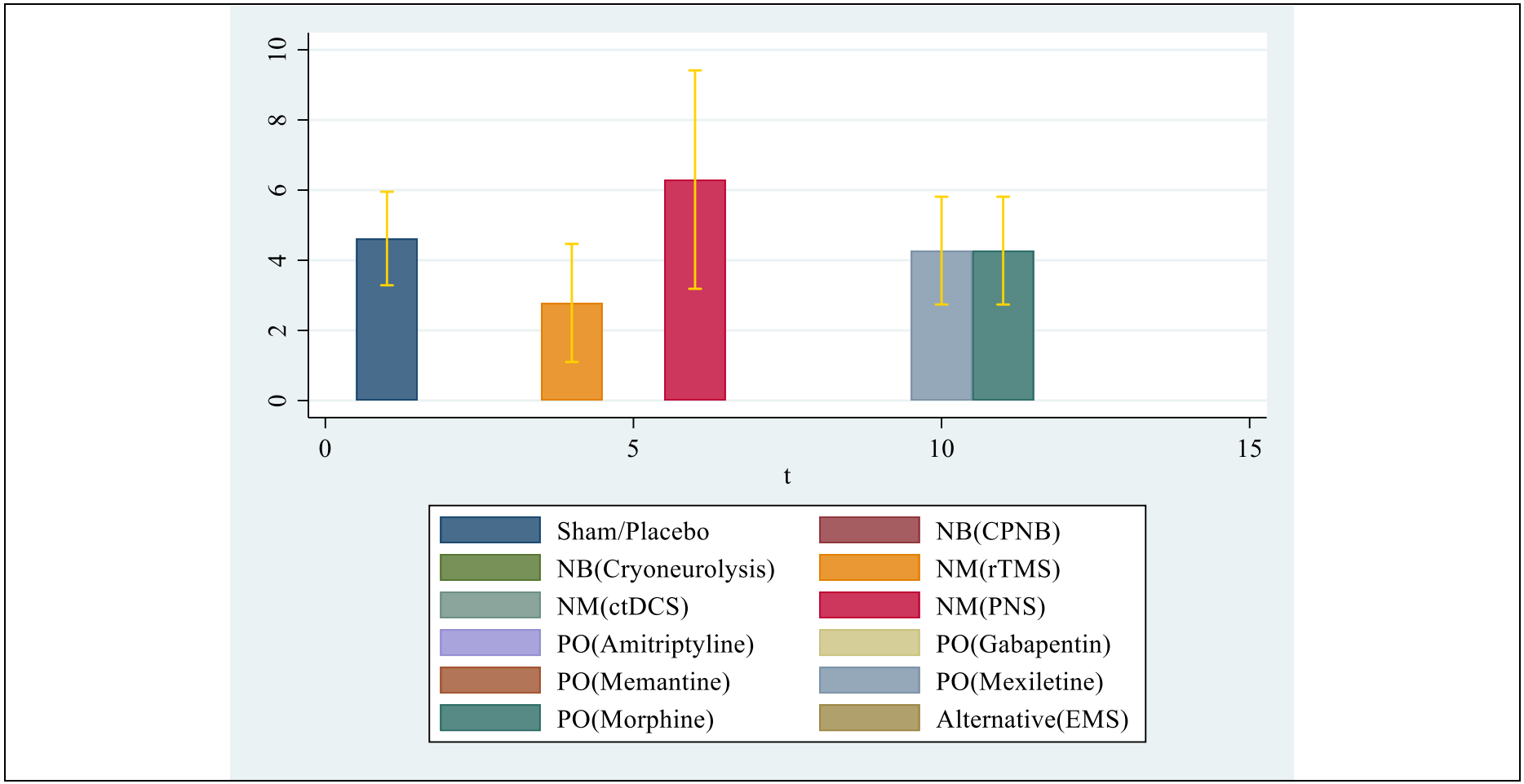
5.4. Duration since amputation (in years)



Duration after amputation (yrs)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	7.7271	6.298333	-	-	1.166667	6.4
SD	16.1935	6.5475	-	-	0.42113	4.6
P value	Reference	0.99495	-	-	0.65442	0.99998
Duration after amputation (yrs)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	11.3	1.83	22.9492	-	-	10.5
SD	10.9	1.33	16.2087	-	-	15.3
P value	0.95159	0.61333	**<0.00001***	-	-	0.96750

The *P*-value from the ANOVA test is 9.8e-07, indicating statistical significance. *P*-values in bold and marked with an asterisk signify significance when compared with the reference, as determined by the Tukey post-hoc test. Data was not provided in Smith (2005), Wu (2008), Ahmed (2011), and Ifeld (2023).

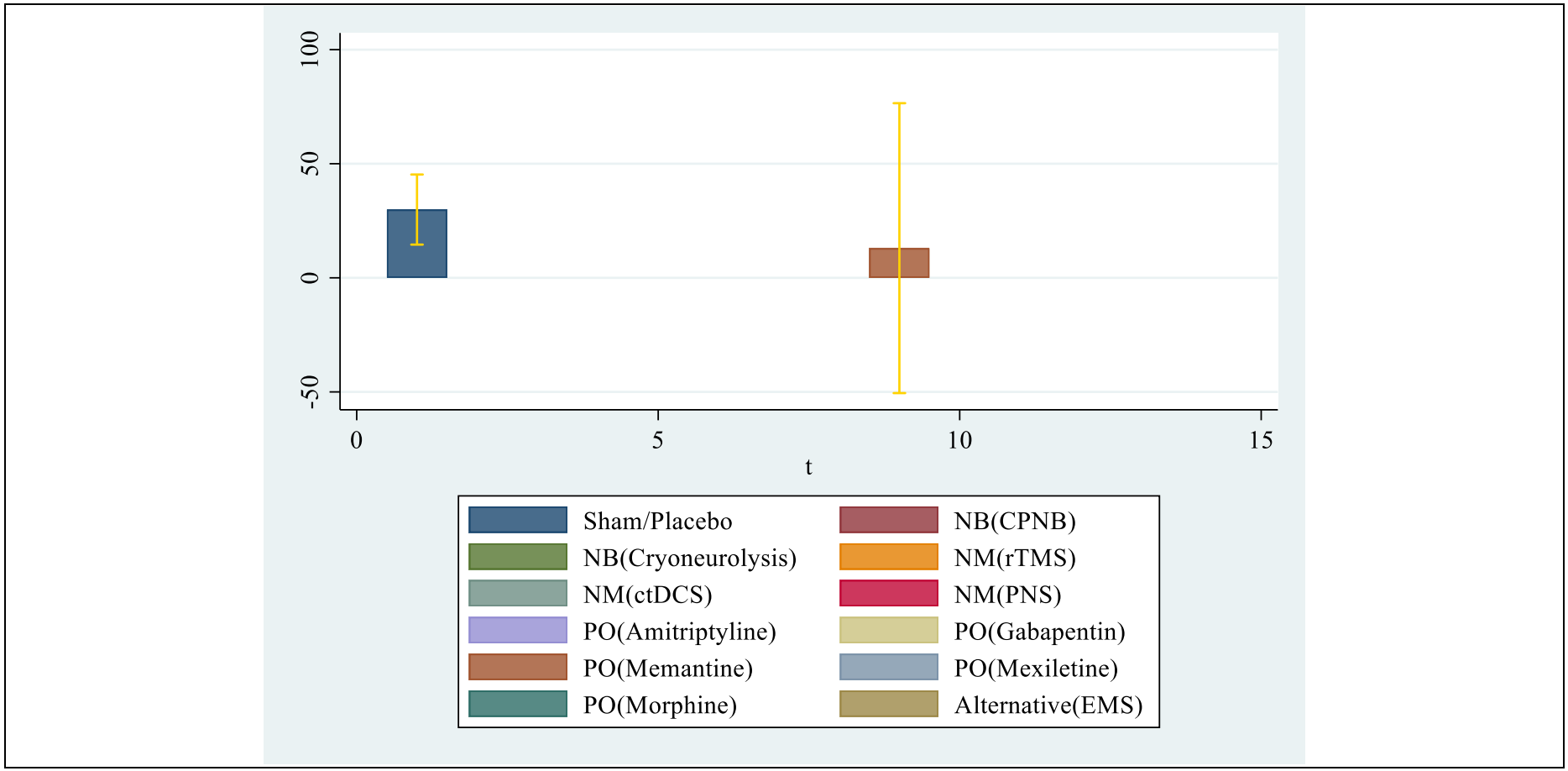
5.5. Duration of phantom limb pain (in years)



Duration of PLP (yrs)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	4.62	-	-	2.783333	-	6.3
SD	6.1442	-	-	3.275	-	4.9
P value	Reference	-	-	0.76011	-	0.88344
Duration of PLP (yrs)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	-	-	-	-	4.275	4.275
SD	-	-	-	-	5.95	5.95
P value	-	-	-	-	0.99676	0.99676

The *P*-value from the ANOVA test is 0.6, indicating no statistical significance. Data was not available in the following studies: Bone (2002), Maier (2003), Schwenkreis (2003), Robinson (2004), Smith (2005), Hsiao (2012), Bocci (2019), Ifeld (2021), and Ifeld (2023).

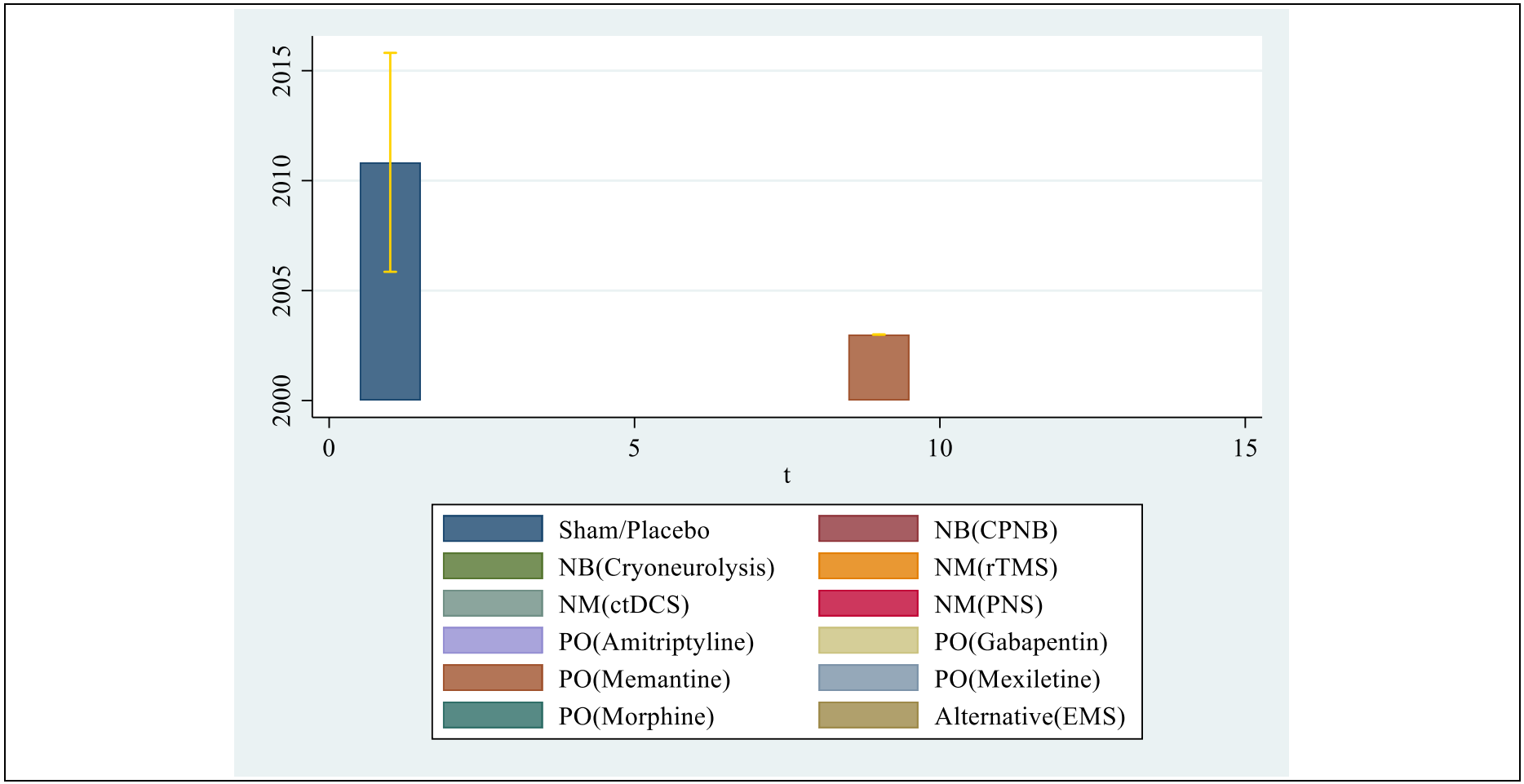
5.6. Sample size (n)



Sample size (n)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	29.91667	-	-	-	-	-
SD	24.16782	-	-	-	-	-
P value	Reference	-	-	-	-	-
Sample size (n)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	-	-	13	-	-	-
SD	-	-	7.071068	-	-	-
P value	-	-	0.35914	-	-	-

The *P*-value from the ANOVA test is 0.359, indicating no statistical significance. While data was available in all included studies, the mean ± SD could not be computed for some arm-level data because only one sample data point was available.

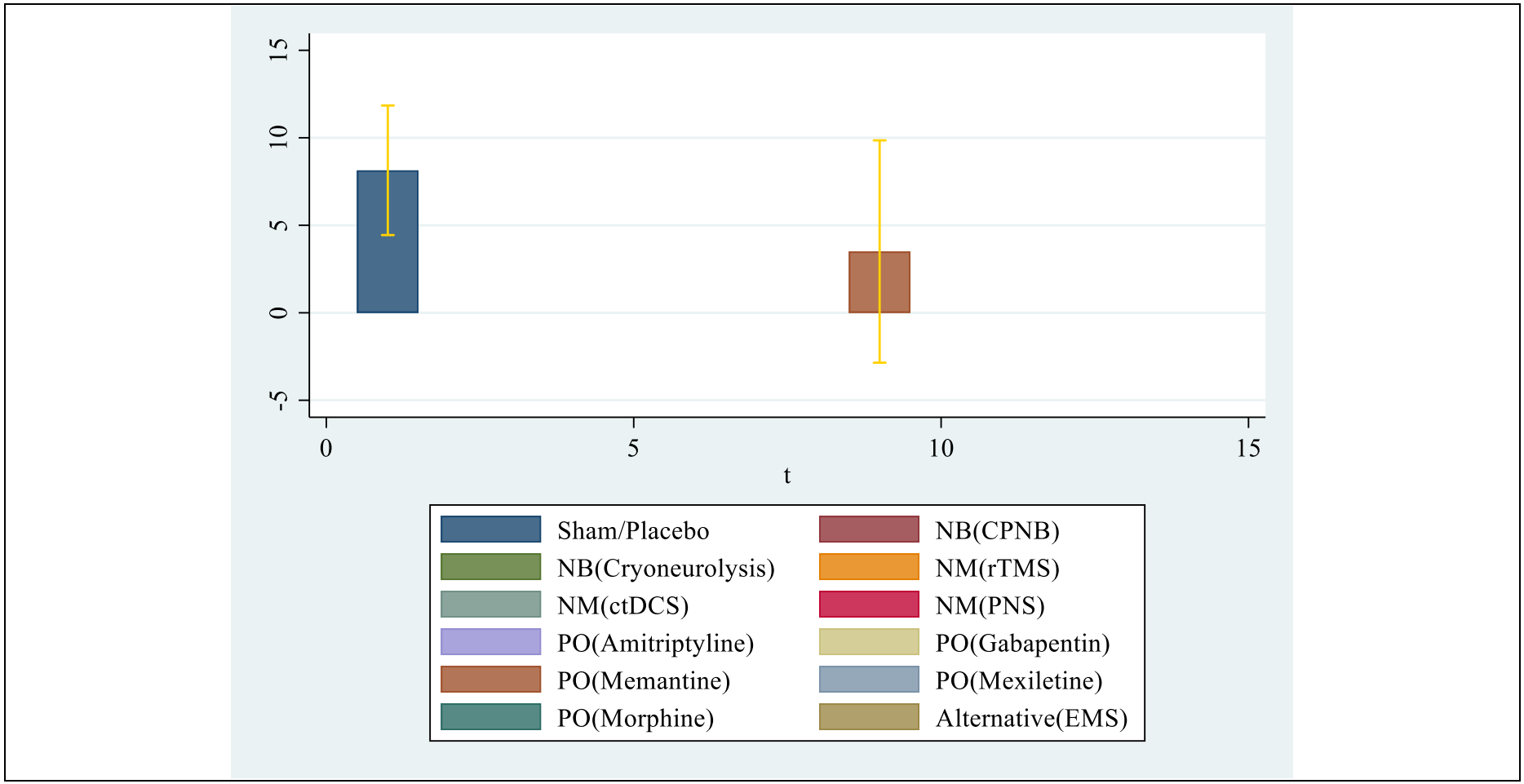
5.7. Publication year



Publication year	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	2010.833	-	-	-	-	-
SD	7.837362	-	-	-	-	-
P value	Reference	-	-	-	-	-
Publication year	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	-	-	2003	-	-	-
SD	-	-	0	-	-	-
P value	-	-	0.19674	-	-	-

The *P*-value from the ANOVA test is 0.197, indicating no statistical significance. While data was available in all included studies, the mean ± SD could not be computed for some arm-level data because only one sample data point was available.

5.8. Follow-up period (in weeks)



Follow-up period (wks)	Sham/Placebo	NB(CPNB)	NB(Cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Mean	8.142833	-	-	-	-	-
SD	5.825219	-	-	-	-	-
P value	Reference	-	-	-	-	-
Follow-up period (wks)	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Mean	-	-	3.5	-	-	-
SD	-	-	0.707107	-	-	-
P value	-	-	0.29745	-	-	-

The *P*-value from the ANOVA test is 0.297, indicating no statistical significance. Data was available in all included studies. However, for some arm-level data, the mean ± SD could not be computed due to the availability of only one sample data point.

5.9. Amputation site / type percentage (%)

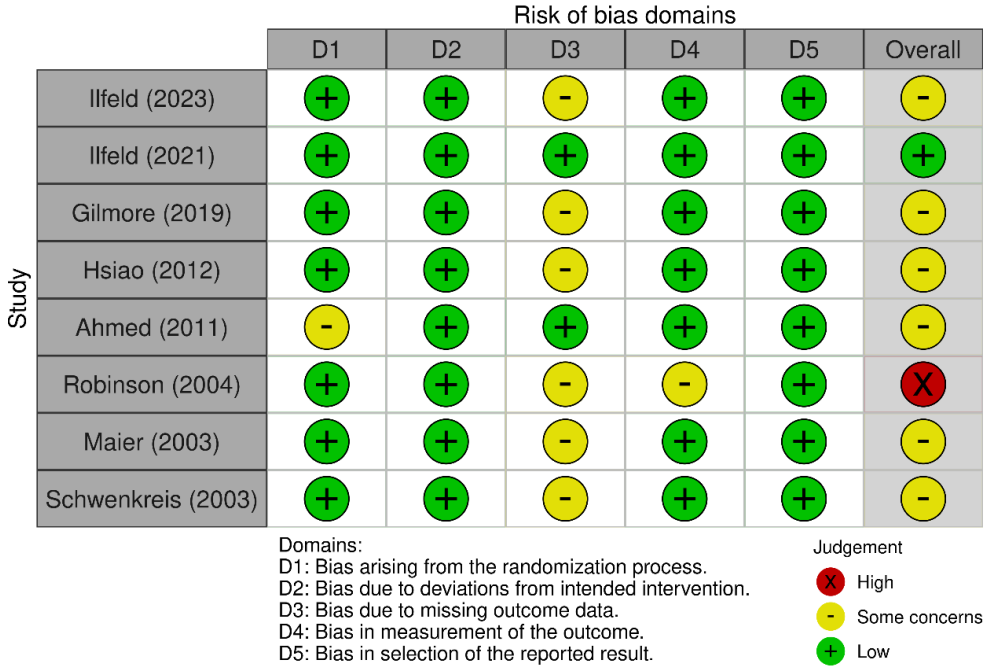
Author (Year)	Treatment type	N	Amputation site (n, upper limb)	Amputation site (n, lower limb)	Percentage of upper limb (%)	Amputation type (n, traumatic)	Amputation type (n, non-traumatic)	Percentage of traumatic type (%)
Ilfeld et al., 2023	Ultrasound-guided percutaneous cryoneurolysis	71	0	71	0	N.A.	N.A.	N.A.
	Sham treatment	73	0	73	0	N.A.	N.A.	N.A.
Ilfeld et al., 2021	Continuous perineural neural block with ropivacaine	71	13	58	18.31	20	51	28.17
	Continuous perineural infusion of normal saline	73	10	63	13.70	16	57	21.92
Bocci et al., 2019	Cerebellar transcranial direct current stimulation	14	14	0	100	11	0	100
	Sham treatment	14	14	0	100	11	0	100
Gilmore et al., 2019	Peripheral nerve stimulation	12	0	12	0	12	0	100
	Placebo treatment	14	0	14	0	14	0	100
Hsiao et al., 2012	Electromagnetic shielding	30	0	30	0	5	25	16.67
	Sham treatment	27	0	27	0	8	19	29.63
Ahmed et al., 2011	Repetitive transcranial magnetic stimulation	17	7	10	41.18	2	15	11.77
	Sham treatment	10	4	6	40	4	6	40
Wu et al., 2008	Oral mexiletine	60	12	48	20	26	34	43.33
	Oral sustained-release morphine	60	12	48	20	26	34	43.33
	Oral Placebo tablets	60	12	48	20	26	34	43.33
Smith et al., 2005	Oral gabapentin	24	3	21	12.5	13	11	56.52
	Oral Placebo tablets	24	3	21	12.5	13	11	56.52
Robinson et al., 2004	Oral amitriptyline	20	2	18	10	16	4	80

	Oral benztropine mesylate (placebo)	19	2	18	10.53	14	5	73.68
Maier et al., 2003	Oral memantine	18	10	8	55.56	9	9	50
	Oral placebo tablets	18	10	8	55.56	15	3	83.33
Schwenkreis et al., 2003	Oral memantine	8	8	0	100	8	0	100
	Oral Placebo tablets	8	8	0	100	7	1	87.5
Bone et al., 2002	Oral Gabapentin	19	N.A.			N.A.		
	Oral Placebo tablets	19						

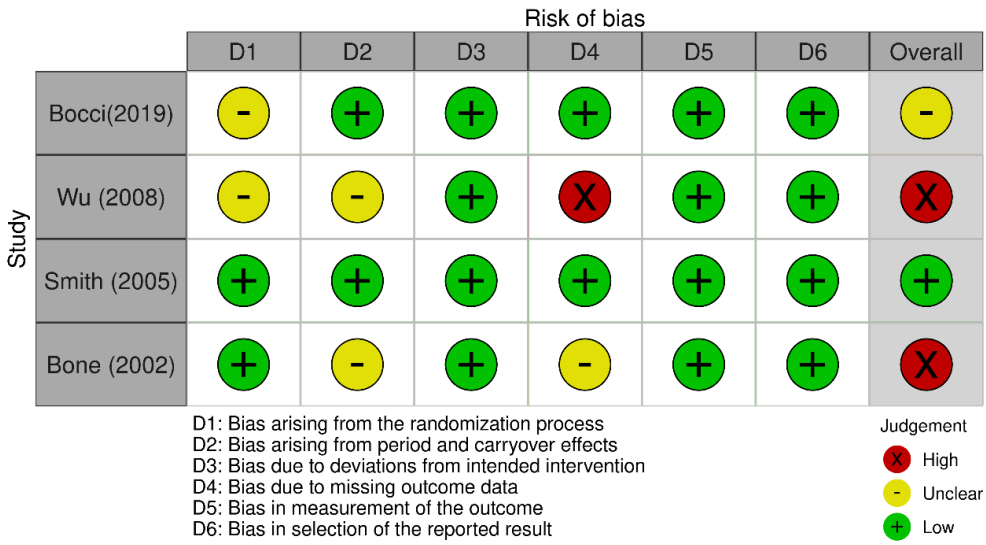
Appendix 6: Risk of bias

6.1. Risk of bias assessment for the individual domains (Traffic-light plot)

eFigure 6.1.1. Risk of bias assessment for the individual domains

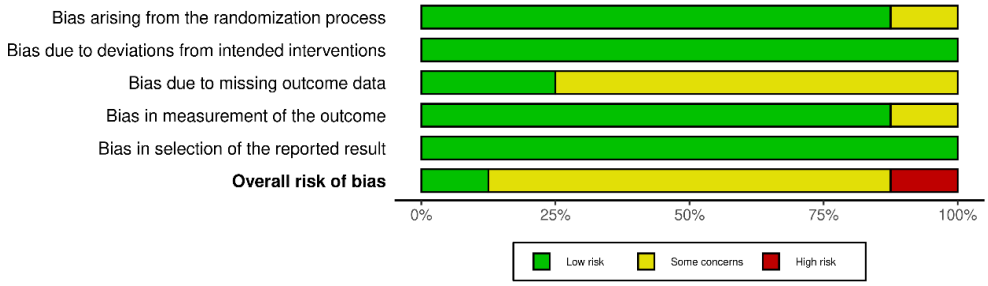


eFigure 6.1.2. Risk of bias assessment for the individual domains (cross-over trials)

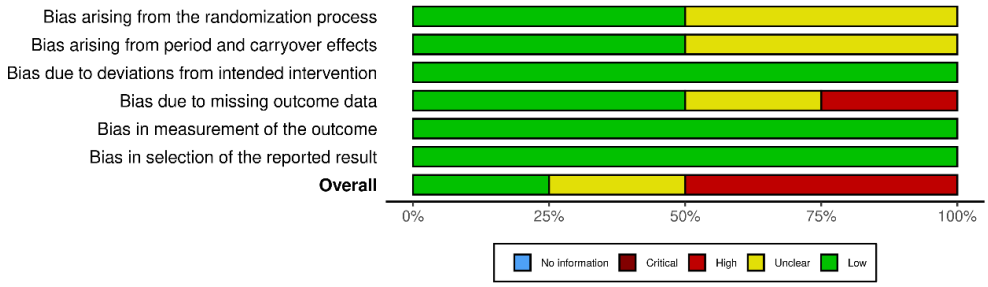


6.2. Risk of bias assessment for the individual studies (Summary plot)

eFigure 6.2.1. Risk of bias assessment for the individual trials



eFigure 6.2.2. Risk of bias assessment for the individual trials (cross-over trials)



6.3. Risk of bias notes for the individual studies

eTable 6.3. Risk of bias notes

Study ID	Notes for risk of bias assessment
Ilfeld et al., 2023	Domain 1. Randomization was stratified by institution in randomly chosen block sizes using computer-generated lists by the informatics group of the Department of Outcomes Research at the Cleveland Clinic (Cleveland, Ohio).
	Domain 3. Missing data were imputed using last observation carried forward for the primary outcome and using multiple imputation for secondary outcomes and sensitivity analysis on the primary outcome.
	Domain 4. Investigators, participants, and all clinical staff were masked to treatment group assignment (with the exception of the treating physician performing the cryoneurolysis). Treating physicians did not have subsequent contact with study participants, or data collection, management, and analysis.
Ilfeld et al., 2021	Domain 1. A multicenter, randomized, quadruple-masked, placebo-controlled clinical trial.
Bocci et al., 2019	Domain 1. No information about random element used in generating the allocation sequence.
	Domain S. The allocation ratio was 1:1.
	Domain 4. A crossover, double-blind, sham-controlled design.
Gilmore et al., 2019	Domain 1. Qualifying participants were randomized 1:1 in blocks of two to one of two groups, stratified by enrolling institution, using a masked allocation sequence generated by the study's data capture system. Two participants, both in group 1, were excluded from efficacy analyses due to changes in eligibility prior to implantation. No profound difference was noted in baseline characteristics. Only the distribution of participants with amputations above the knee versus below the knee was significantly different between groups.
	Domain 3. Two participants, both in group 1, were excluded from efficacy analyses due to changes in eligibility prior to implantation. 1 participants in experimental group and 1 in control group withdrew from study at 4 weeks.
	Domain 4. A multicenter, randomized, double- blind, placebo- controlled trial. Treating physicians were unmasked, while participants and outcomes assessors were masked to group assignment.
Hsiao et al., 2012	Domain 3. 7 participants in experimental group and 3 in control group lost to 12-week follow-up and effects were evaluated on an intent-to-treat

	basis.
	Domain 4. Randomized, double-blind, placebo-controlled trial.
Ahmed et al., 2011	Domain 1. Patients were randomly assigned to one of the two groups, depending on the day of the week on which they were recruited. One group (consisting of patients recruited on Saturday to Tuesday) received real rTMS and the other group (recruited on Wednesday to Thursday) received sham-rTMS.
	Domain 4. None of the patients had experienced rTMS previously, they were unaware of which stimulation was real and which was sham.
Wu et al., 2008	Domain 1. Some participants quitted after randomization.
	Domain S. No statement about allocation ratio, and the carry-over effect was seen as a potential confounding factor in this study.
	Domain 3. It is likely that missingness in the outcome depended on its true value.
Smith et al., 2005	Domain 1. A randomized double-blind cross-over trial.
	Domain S. The allocation ratio was equal. Participants were then randomly assigned to receive either gabapentin (n = 11) or placebo (n = 13) during the first phase of treatment. Also, there was a 5-week washout period.
Robinson et al., 2004	Domain 1. A double-blind, randomized, active placebo-controlled study design.
	Domain 3. It is possible that missingness in the outcome was influenced by its true value, but there is no reason to believe that it did.
	Domain 4. Two subjects did not complete posttreatment measures.
Maier et al., 2003	Domain 1. A randomized double-blinded, placebo-controlled trial
	Domain 3. It is possible that missingness in the outcome was influenced by its true value, but there is no reason to believe that it did.
Schwenkreis et al., 2003	Domain 3. It is possible that missingness in the outcome was influenced by its true value, but there is no reason to believe that it did.
Bone et al., 2002	Domain 1. A randomized, double-blind, placebo controlled, cross-over clinical trial.
	Domain S. The allocation ratio was approximately equal.
	Domain 3. It is possible that missingness in the outcome was influenced by its true value, but there is no reason to believe that it did.

Appendix 7. Results

7.1. Changes in pain intensity

Author (Year)	Treatment	No. of cases	Mean	Standard deviation
Ilfeld et al., 2023	Ultrasound-guided percutaneous cryoneurolysis	71	-1.33	2.35*
	Sham treatment	73	-1.56	2.70*
Ilfeld et al., 2021	Continuous perineural neural block with ropivacaine	71	-2.4	3.00
	Continuous perineural infusion of normal saline	73	-0.9	2.30
Bocci et al., 2019	Cerebellar transcranial direct current stimulation	14	-1.1	2.11*
	Sham treatment	14	-0.1	2.35*
Gilmore et al., 2019	Peripheral nerve stimulation	11	-3.3	1.90
	Placebo treatment	13	-1.5	1.40
Hsiao et al., 2012	Electromagnetic shielding	30	-2.2	2.10
	Sham treatment	27	-2.4	2.20
Ahmed et al., 2011	Repetitive transcranial magnetic stimulation	17	-2.9	1.92*
	Sham treatment	10	0	0.91*
Wu et al., 2008	Oral mexiletine	42	-1.5	2.11
	Oral sustained-release morphine	50	-2.8	1.95
	Oral Placebo tablets	43	-1.4	2.62
Smith et al., 2005	Oral gabapentin	24	-0.94	1.98
	Oral Placebo tablets	24	-0.49	2.20
Robinson et al., 2004	Oral amitriptyline	18	-0.5	2.56*

	Oral benztropine mesylate (placebo)	19	0	2.76*
Schwenkreis et al., 2003	Oral memantine	7	-2.83	3.09†
	Oral placebo tablets	8	-0.97	1.91†
Maier et al., 2003	Oral memantine	18	-1.91	2.37*
	Oral Placebo tablets	18	-2.21	2.10*
Bone et al., 2002	Oral Gabapentin	14	-3.2	2.10*
	Oral Placebo tablets	14	-1.6	0.70*

* A change-from-baseline standard deviation was imputed under Cochrane guidance, a correlation coefficient specified as 0.5 was utilized.

https://handbook-5-1.cochrane.org/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm

† Original data presented as Median (Range). Mean and standard deviation were imputed.

7.2. Adverse events

Possible adverse events of various modalities

- **Neuromodulation (NM)**: Discomfort over treatment site, headache, eye pain, toothache, muscle twitch, facial pain, and skin pain.
- **Neural block (NB)**: Rash, itching, soreness, weakness, bleeding, and infection.
- **Oral medication (PO)**: Headache, vertigo, dizziness, nausea, drowsiness, constipation, excitation, restlessness, cramping, and others.
- **Alternative modalities (Alternative)**: For electromagnetic shielding, allergy, rash, and itching.

Author (Year)	Treatment	No. of cases	No. of adverse events	Detail of adverse events
Ilfeld et al., 2023	Ultrasound-guided Percutaneous Cryoneurolysis	71	0	N.A.
	Sham treatment	73	1	Profound quadriceps femoris weakness and some insensate areas of skin on the medial thigh.
Ilfeld et al., 2021	Continuous perineural neural block with ropivacaine	71	N.A.*	8 catheter sites showed signs of possible localized infection out of 382 total catheters (2.1%); one serious adverse event among 382 catheters (0.3%): one patient reported increased phantom pain beginning 2 days after catheter insertion.
	Continuous perineural infusion of normal saline	73	N.A.*	
Bocci et al., 2019	Cerebellar transcranial direct current stimulation	14	0	N.A.
	Sham treatment	14	0	N.A.
Gilmore et al., 2019	Peripheral nerve stimulation	11	0	N.A.
	Placebo treatment	13	0	N.A.

Hsiao et al., 2012	Electromagnetic shielding	30	0	N.A.
	Sham treatment	27	0	N.A.
Ahmed et al., 2011	Repetitive transcranial magnetic stimulation	17	0	N.A.
	Sham treatment	10	0	N.A.
Wu et al., 2008	Oral mexiletine	42	7	Constipation (n=2), nausea (n=0), drowsiness (n=4), dizziness (n=2)
	Oral sustained-release morphine	50	27	Constipation (n=17), nausea (n=4), drowsiness (n=9), dizziness (n=2)
	Oral Placebo tablets	43	7	Constipation (n=2), nausea (n=1), drowsiness (n=3), dizziness (n=2)
Smith et al., 2005	Oral gabapentin	24	N.A.*	The term “Side effect” was mentioned in the original article. However, detailed data was lacking.
	Oral Placebo tablets	24	N.A.*	
Robinson et al., 2004	Oral amitriptyline	18	N.A.*	Dry mouth (n=13), drowsiness/tiredness/fatigue (n=9), blurred vision (n=1), constipation (n=4), dizziness (n=2), heartburn (n=0), poor sleep (n=2), palpitations (n=0), nausea/vomiting (n=2), better sleep (n=2), urinary retention (n=1), diarrhea (n=1), tinnitus (n=1), tremor (n=0), sweating (n=0), headache (n=0)
	Oral benztropine mesylate (placebo)	19	N.A.*	Dry mouth (n=13), drowsiness/tiredness/fatigue (n=9), blurred vision (n=5), constipation (n=3), dizziness (n=3), heartburn (n=3), poor sleep (n=2), palpitations (n=2), nausea/vomiting (n=0), better sleep (n=0),

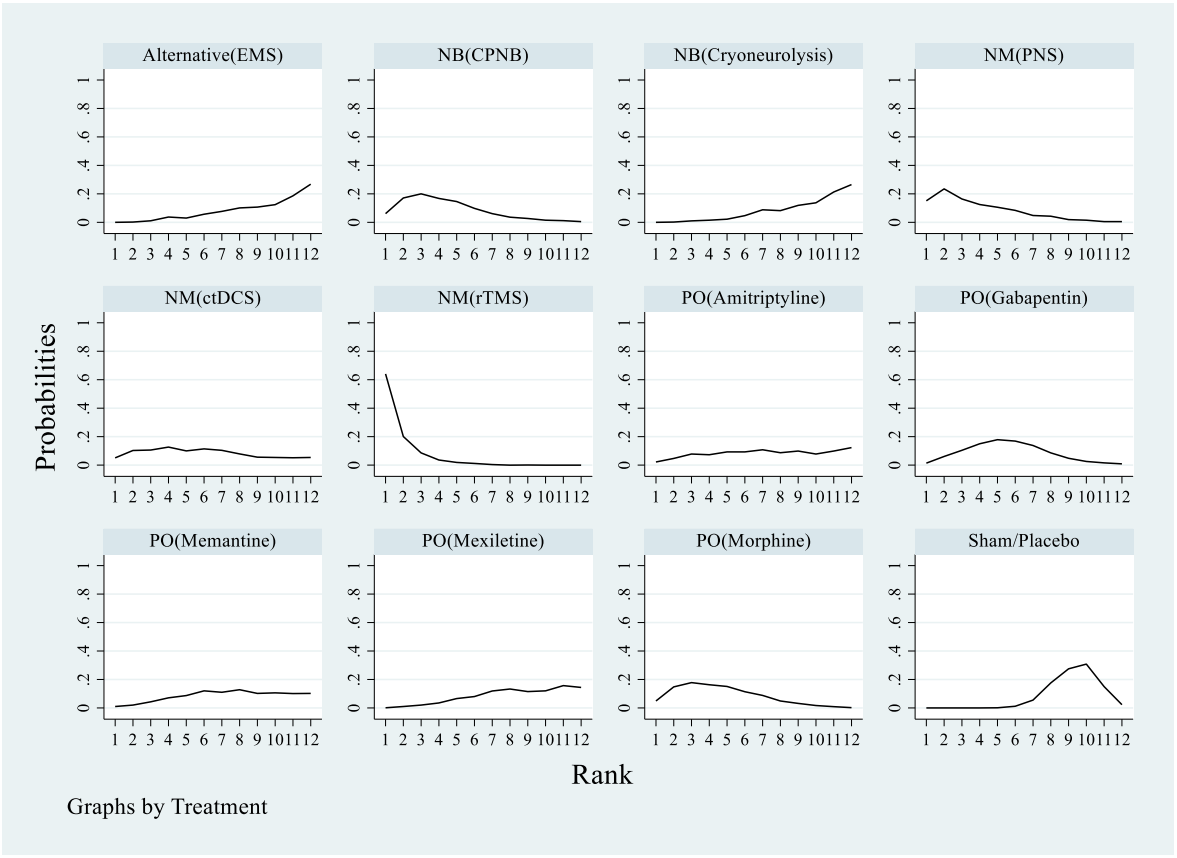
				urinary retention (n=1), diarrhea (n=1), tinnitus (n=1), tremor (n=1), sweating (n=1), headache (n=1)
Schwenkreis et al., 2003	Oral memantine	7	0	N.A.
	Oral placebo tablets	8	0	N.A.
Maier et al., 2003	Oral memantine	18	8	Number of patients with at least one event (e.g. vertigo, tiredness, headache, nausea, restlessness, excitation, cramping, and others)
	Oral Placebo tablets	18	10	
Bone et al., 2002	Oral Gabapentin	14	N.A.*	Somnolence (n=7), dizziness (n=2), headache (n=2), nausea (n=1)
	Oral Placebo tablets	14	N.A.*	Somnolence (n=2), dizziness (n=1), headache (n=1), nausea (n=1)

*Indicating “Total number” of patients reporting at least one episode of adverse event is unavailable in original studies.

Appendix 8. Relative ranking

8.1. Changes in pain intensity

eTable 8.1 Changes in pain intensity in relative ranking probability

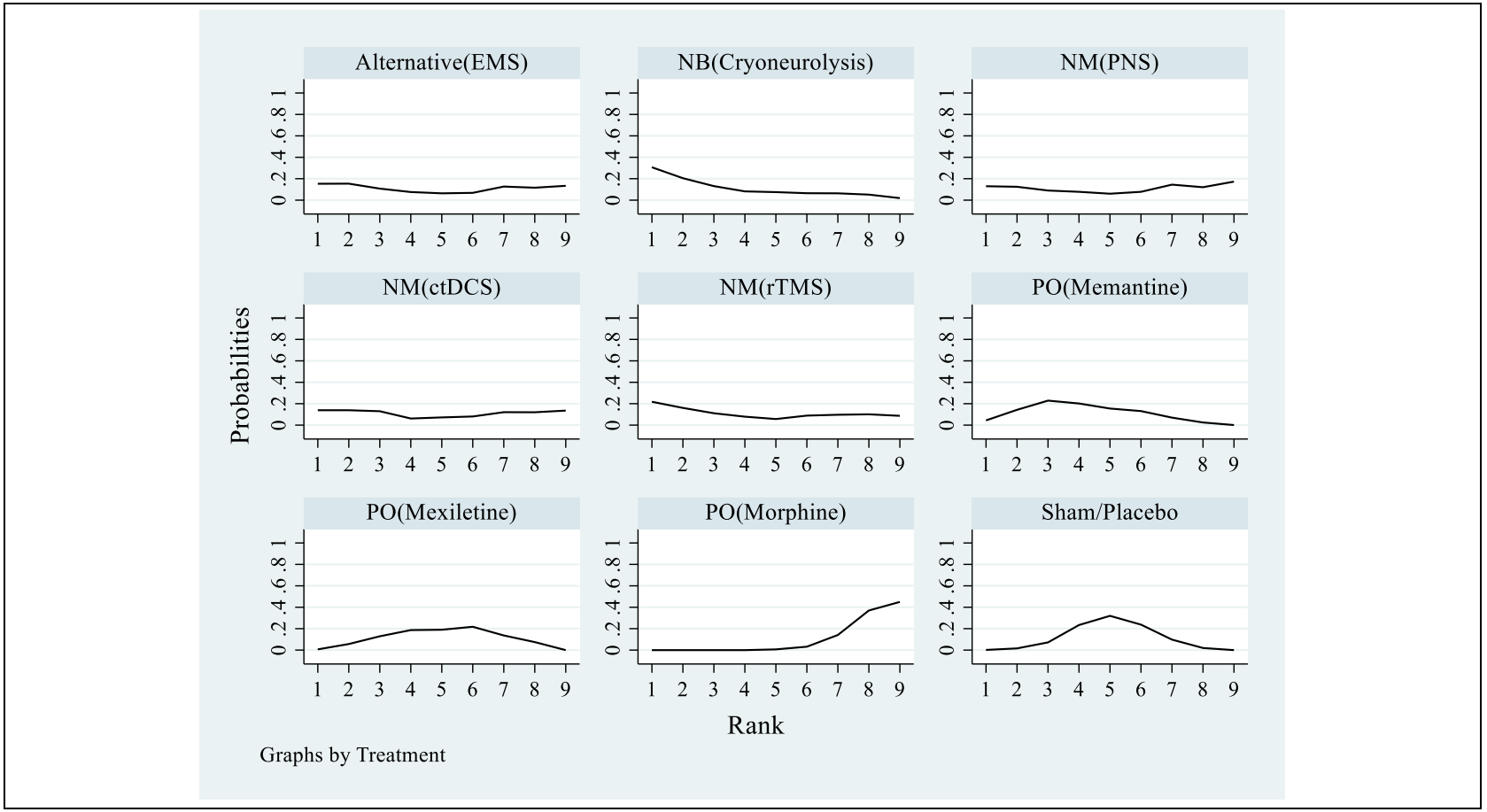


Ranking\ Treatment	Sham/Placebo	NB (CPNB)	NB (Cryoneurolysis)	NM (rTMS)	NM (ctDCS)	NM (PNS)	PO (Amitriptyline)	PO (Gabapentin)	PO (Memantine)	PO (Mexiletine)	PO (Morphine)	Alternative (EMS)
Best	0.0	6.1	0.0	64.1	5.1	15.1	2.2	1.4	1.0	0.1	4.9	0.0
2nd	0.0	17.1	0.2	20.1	10.3	23.5	4.7	6.1	2.0	1.0	14.8	0.2
3rd	0.0	20.0	1.0	8.6	10.6	16.4	7.8	10.4	4.3	2.0	17.8	1.1
4th	0.0	16.8	1.5	3.6	12.7	12.5	7.3	15.0	7.1	3.5	16.3	3.7
5th	0.1	14.6	2.2	1.9	10.0	10.6	9.3	17.9	8.7	6.6	15.4	3.0
6th	1.2	9.8	4.7	1.2	11.4	8.4	9.3	16.9	12.0	8.0	11.4	5.7
7th	5.5	6.1	8.8	0.4	10.4	4.8	10.8	13.8	11.0	11.9	8.8	7.7
8th	17.6	3.6	8.2	0.0	7.9	4.3	8.7	8.6	12.8	13.3	4.9	10.1
9th	27.5	2.7	11.9	0.1	5.6	1.9	9.9	4.8	10.2	11.5	3.2	10.7
10th	30.8	1.5	13.7	0.0	5.4	1.5	7.8	2.6	10.6	12.0	1.7	12.4
11th	15.0	1.2	21.3	0.0	5.2	0.5	9.9	1.6	10.1	15.7	0.9	18.6
Worst	2.3	0.5	26.5	0.0	5.4	0.5	12.3	0.9	10.2	14.4	0.2	26.8
Mean Rank	9.4	4.3	9.7	**1.6**	5.9	3.8	7.4	5.6	7.7	8.6	4.6	9.5
SUCRA	24.1	70.1	20.7	**94.1**	55.5	74.9	42.2	58.3	38.9	30.7	67.6	22.8

Abbreviations: NB(CPNB), Continuous perineural neural block; NB(cyroneurolysis), neural block with cryoneurolysis; NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural 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; Alternative(EMS), Alternative treatment with electromagnetic shielding.

8.2. Adverse events

eTable 8.2. Adverse events in relative ranking probability

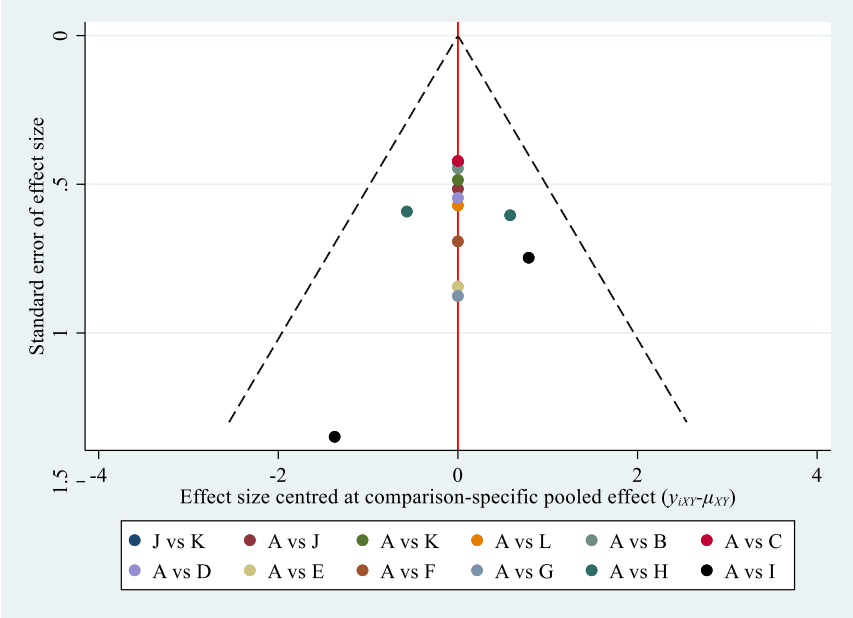


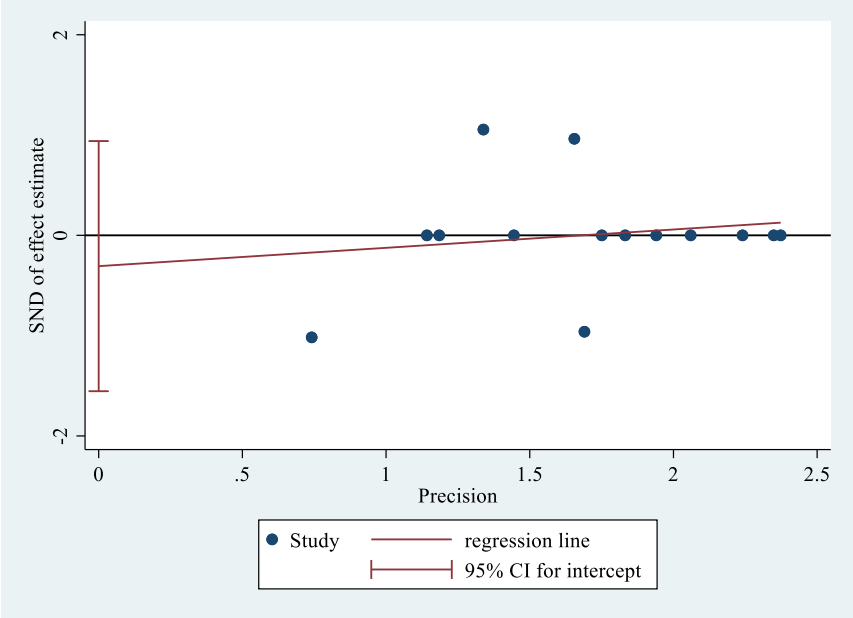
Ranking\ Treatment	Sham/Placebo	NB (Cryoneurolysis)	NM (rTMS)	NM (ctDCS)	NM (PNS)	PO (Memantine)	PO (Mexiletine)	PO (Morphine)	Alternative (EMS)
Best	0.2	30.7	21.8	13.9	13.0	4.4	0.7	0.0	15.3
2nd	1.6	20.5	16.1	13.9	12.5	14.3	5.7	0.0	15.4
3rd	7.2	13.1	11.1	13.0	9.0	22.9	12.9	0.0	10.8
4th	23.4	8.2	7.9	6.2	7.8	20.2	18.7	0.0	7.6
5th	32.0	7.5	5.7	7.2	6.0	15.5	19.0	0.7	6.4
6th	23.8	6.5	8.9	8.1	7.8	13.1	21.8	3.2	6.8
7th	9.8	6.4	9.7	12.1	14.5	7.0	13.7	14.1	12.7
8th	2.0	5.2	10.1	12.0	12.1	2.5	7.5	37.0	11.6
Worst	0.0	1.9	8.7	13.6	17.3	0.1	0.0	45.0	13.4
Mean Rank	5.1	**3.2**	4.3	4.9	5.3	4.1	5.1	8.2	4.8
SUCRA	49.3	**72.0**	59.0	50.9	46.6	61.4	49.1	9.7	52.0

Abbreviations: NB(cyroneurolysis), neural block with cryoneurolysis; NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural stimulation; PO(Memantine), oral administration of Memantine; PO(Mexiletine), oral administration of mexiletine; PO(Morphine), oral administration of morphine; Alternative(EMS), Alternative treatment with electromagnetic shielding.

Appendix 9. Publication bias

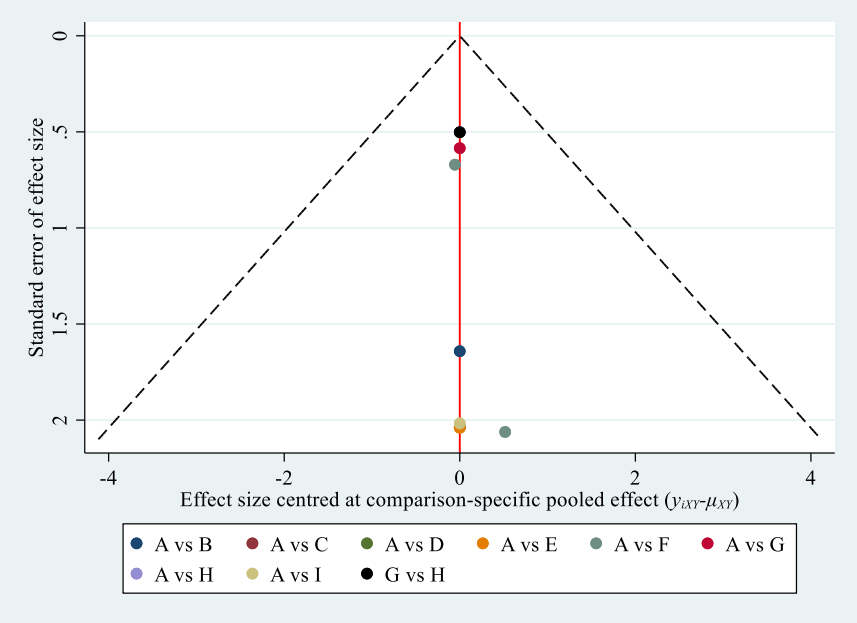
9.1. Changes in pain intensity

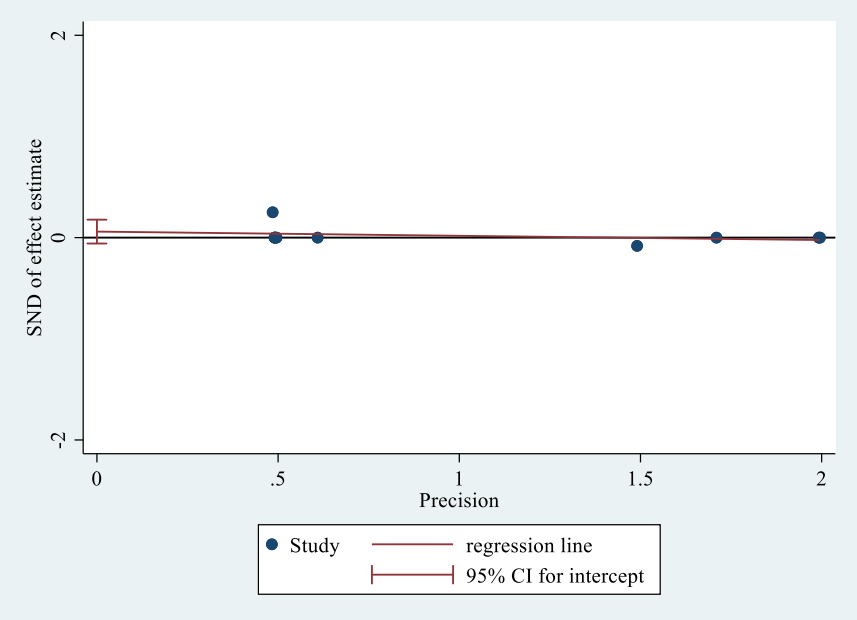




Egger's test for small-study effects:						
Std_Eff	Coef.	Std. Err.	T	*P*>t	[95% Conf.	Interval]
slope	.1827465	.3253001	0.56	0.585	-.5260215	.8915146
bias	-.3071203	.5723094	-0.54	0.601	-1.554075	.9398347
Test of H0: no small-study effects= *P* = 0.601						

9.2. Adverse events





Egger's test for small-study effects:						
Std_Eff	Coef.	Std. Err.	T	*P*>t	[95% Conf.	Interval]
slope	-.0416279	.0422257	-0.99	0.353	-.1390006	.0557448
bias	.0595802	.0511462	1.16	0.278	-.0583631	.1775235
Test of H0: no small-study effects= *P* = 0.278						

Appendix 10: Inconsistency

In this study, we assessed both local and global inconsistencies within our network analysis framework. For local inconsistency, we employed two methods: the loop-specific method, which focuses on discrepancies between direct and indirect evidence, and the node-splitting approach. This approach divides evidence related to a specific comparison into direct and indirect categories, enabling a thorough evaluation of their differences. Additionally, to address global inconsistency in the network, a design-by-treatment analysis was conducted.

10.1. Overview of global design inconsistency and local loop inconsistency

Outcome	**Fit design-by-treatment interaction model**	**Explore Loop inconsistency**
Changes in pain intensity	***P*=0.8228**	***P*=0.8228**
Adverse events	***P*=0.9591**	***P*=0.9591**

10.2. Changes in pain intensity

eTable 10.2.1. Side-splitting inconsistency between direct and indirect evidence

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	*P*>|z|
A B *	.	.	.	.	.	.	.
A C *	.	.	.	.	.	.	.
A D *	.	.	.	.	.	.	.
A E *	.	.	.	.	.	.	.
A F *	.	.	.	.	.	.	.
A G *	.	.	.	.	.	.	.
A H *	.	.	.	.	.	.	.
A I *	.	.	.	.	.	.	.
A J *	.	.	.	.	.	.	.
A K *	.	.	.	.	.	.	.
A L *	.	.	.	.	.	.	.
J K	.	.	.	.	.	.	.

*Symbols for abbreviation: A for Sham/Placebo; B for NB(CPNB); C for NB(Cryoneurolysis); D for NM(rTMS); E for NM(ctDCS); F for NM(PNS); G for PO(Amitriptyline); H for PO(Gabapentin); I for PO(Memantine); J for PO(Mexiletine); K for PO(Morphine); L for Alternative(EMS).

* Due to the absence of sufficient direct comparison data from neuromodulation, neural block, oral medication, and alternative modalities, along with the scarcity of closed loops in the network map, the results from the side-splitting approach were not estimable in this outcome.

eTable 10.2.2. Design inconsistency

Multivariate meta-analysis

Variance-covariance matrix = proportional .5*I(11)+.5*J(11,11,1)

Method = reml Number of dimensions = 11

Restricted log likelihood = -3.7920797 Number of observations = 12

	Coefficient	Std. err.	z	*P*>|z|	[95% conf.	interval]
_y_B _cons	-1.5	.81887	-1.83	0.067	-3.104956	.1049555
_y_C _cons	.2299999	.8055357	0.29	0.775	-1.348821	1.808821
_y_D _cons	-2.9	.8770884	-3.31	0.001	-4.619062	-1.180938
_y_E _cons	-1	1.087872	-0.92	0.358	-3.132189	1.132189
_y_F _cons	-1.8	.9748193	-1.85	0.065	-3.710611	.1106108
_y_G _cons	-.5	1.11261	-0.45	0.653	-2.680675	1.680675
_y_H _cons	-1.030209	.6437646	-1.60	0.110	-2.291964	.2315465
_y_I _cons	-.369534	.8890859	-0.42	0.678	-2.11211	1.373042
_y_J _cons	-.1	.858456	-0.12	0.907	-1.782543	1.582543
_y_K _cons	-1.4	.8408012	-1.67	0.096	-3.04794	.2479401
_y_L _cons	.2	.8930739	0.22	0.823	-1.550393	1.950393

*Symbols for abbreviation: A for Sham/Placebo; B for NB(CPNB); C for NB(Cryoneurolysis); D for NM(rTMS); E for NM(ctDCS); F for NM(PNS); G for PO(Amitriptyline); H for PO(Gabapentin); I for PO(Memantine); J for PO(Mexiletine); K for PO(Morphine); L for Alternative(EMS).

10.3. Adverse event rate

eTable 10.3.1. Side-splitting inconsistency between direct and indirect evidence

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	*P*>|z|
A B *	.	.	.	.	.	.	.
A C *	.	.	.	.	.	.	.
A D *	.	.	.	.	.	.	.
A E *	.	.	.	.	.	.	.
A F *	.	.	.	.	.	.	.
A G *	.	.	.	.	.	.	.
A H *	.	.	.	.	.	.	.
A I *	.	.	.	.	.	.	.
G H	.	.	.	.	.	.	.

*Symbols for abbreviation: A for Sham/Placebo; B for NB(Cryoneurolysis); C for NM(rTMS); D for NM(ctDCS); E for NM(PNS); F for PO(Memantine); G for PO(Mexiletine); H for PO(Morphine); I for Alternative(EMS).

* Due to the absence of sufficient direct comparison data from neuromodulation, neural block, oral medication, and alternative modalities, along with the scarcity of closed loops in the network map, the results from the side-splitting approach were not estimable in this outcome.

eTable 10.3.2. Design inconsistency

Multivariate meta-analysis

Variance-covariance matrix = proportional .5*I(8)+.5*J(8,8,1)

Method = reml Number of dimensions = 8

Restricted log likelihood = -1.7275568 Number of observations = 8

	Coefficient	Std. err.	z	*P*>|z|	[95% conf. interval]	
_y_B _cons	-1.084723	1.641477	-0.66	0.509	-4.301958	2.132512
_y_C _cons	-.5108256	2.037739	-0.25	0.802	-4.504721	3.48307
_y_D _cons	-9.39e-12	2.03419	-0.00	1.000	-3.98694	3.98694
_y_E _cons	.1603427	2.03986	0.08	0.937	-3.83771	4.158396
_y_F _cons	-.3915852	.6379059	-0.61	0.539	-1.641858	.8586873
_y_G _cons	.0281709	.584862	0.05	0.962	-1.118137	1.174479
_y_H _cons	1.797951	.5011489	3.59	0.000	.8157176	2.780185
_y_I _cons	-.1035407	2.017214	-0.05	0.959	-4.057207	3.850125

*Symbols for abbreviation: A for Sham/Placebo; B for NB(Cryoneurolysis); C for NM(rTMS); D for NM(ctDCS); E for NM(PNS); F for PO(Memantine); G for PO(Mexiletine); H for PO(Morphine); I for Alternative(EMS).

Appendix 11. Grading the evidence using GRADE

The Grade approach[25]

The GRADE approach was similarly applied in assessing the impact of treatment effect estimates, with an emphasis on the quality and transitivity of the data.

The GRADE approach categorized data into four levels: high, moderate, low, and very low. This stratification aimed to quantify the level of trust in a given treatment effect estimate. It evaluated both direct and indirect evidence by examining five core components: risk of bias, heterogeneity or inconsistency, indirectness, imprecision, and publication bias. 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. Any discrepancy between direct and indirect evidence would lead to a one-level downgrade in the network rating.

11.1. Summary of the direct evidence finding table

Population: Patients with chronic phantom limb pain

Outcome: Improvement of pain intensity, assessed with VAS/NRS score: -10 – 0 cm (worst)						
Comparison: Intervention vs. Comparator	Intervention Mean (SD)	Comparator Mean (SD)	Mean difference [95% Confidence Interval]	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
NB(CPNB) vs. Sham/Placebo	-2.4 (3)	-0.9 (2.3)	-1.5 (-2.37, -0.63)	144 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had no concern of risk of bias.
NB(cryoneurolysis) vs. Sham/Placebo	-1.33 (2.35)	-1.56 (2.70)	0.23 (-0.60, 1.06)	144 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.

NM(rTMS) vs. Sham/Placebo	-2.9 (1.92)	0 (0.91)	-2.90 (-3.97, -1.83)	27 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
NM(ctDCS) vs. Sham/Placebo	-1.1 (2.11)	-0.1 (2.35)	-1.00 (-2.65, 0.65)	28 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
NM(PNS) vs. Sham/Placebo	-3.3 (1.9)	-1.5 (1.4)	-1.80 (-3.16, -0.44)	24 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.

PO(Amitriptyline) vs. Sham/Placebo	-0.5 (2.56)	0 (2.76)	-0.50 (-2.22, 1.22)	37 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
PO(Gabapentin) vs. Sham/Placebo			-1.03 (-2.16, 0.10)	76 (2 studies)	⊕⊕◯◯ LOW*‡	No concern for 1 trial; High risk for another one. Downgraded for imprecision due to wide confidence interval. Moderate heterogeneity (I^2=45.9%)
PO(Memantine) vs. Sham/Placebo			-0.49 (-2.53, 1.55)	51 (2 studies)	⊕⊕⊕◯ MODERATE‡	Some concerns for 1 trial; High risk for another one. Downgraded for imprecision due to wide confidence interval. Moderate heterogeneity (I^2=49.0%)

PO(Mexiletine) vs. Sham/Placebo	-1.5 (2.11)	-1.4 (2.62)	-0.10 (-1.11, 0.91)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.
PO(Morphine) vs. Sham/Placebo	-2.8 (1.95)	-1.4 (2.62)	-1.40 (-2.35, -0.45)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.
Alternative(EMS) vs. Sham/Placebo	-2.2 (2.1)	-2.4 (2.2)	0.20 (-0.92, 1.32)	57 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.

PO(Morphine) vs. PO(Mexiletine)	-2.8 (1.95)	-1.5 (2.11)	-1.30 (-2.13, -0.47)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.
Outcome: Adverse event						
Comparison: Intervention vs. Comparator	Intervention (event/total)	Comparator (event/total)	Odds ratio [95% Confidence Interval]	Number of participants (studies)	Quality or certainty of the evidence (GRADE)	Comments
NB(cryoneurolysis) vs. Sham/Placebo	0/71	1/73	0.34 (0.01, 8.44)	144 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.

NM(rTMS) vs. Sham/Placebo	0/17	0/10	0.60 (0.01, 32.56)	27 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
NM(ctDCS) vs. Sham/Placebo	0/14	0/14	1.00 (0.02, 53.89)	28 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
NM(PNS) vs. Sham/Placebo	0/11	0/13	1.17 (0.02, 63.97)	24 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.

PO(Memantine) vs. Sham/Placebo	8/25	10/26	0.68 (0.19, 2.36)	51 (2 studies)	⊕⊕⊕◯ MODERATE*	Some concerns for 1 trial; High risk for another one. Downgraded for imprecision due to wide confidence interval. Moderate heterogeneity (I^2=49.0%)
PO(Mexiletine) vs. Sham/Placebo	7/42	7/43	1.03 (0.33, 3.24)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.
PO(Morphine) vs. Sham/Placebo	27/50	7/43	6.04 (2.26, 16.12)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.

Alternative(EMS) vs. Sham/Placebo	0/30	0/27	0.90 (0.02, 47.00)	57 (1 study)	⊕⊕⊕◯ MODERATE‡	Singular trial, heterogeneity not applicable. One trial had some concern of risk of bias.
PO(Morphine) vs. PO(Mexiletine)	27/50	7/42	5.87 (2.19, 15.70)	135 (1 study)	⊕⊕◯◯ LOW*‡	One trial with high risk of bias. Singular trial, heterogeneity not applicable.

Abbreviations: SD, standard deviation; VAS, visual analogue scale. GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

* Risk of bias. † Inconsistency. ‡Imprecision. §Only one study, inconsistency cannot be evaluated. ¶ Intransitivity.** Contributing direct evidence of moderate quality. †† Contributing evidence of low or very low quality.

11.2. Evidence profiles the network meta-analysis

Outcome: Improvement of pain intensity								
Comparison: Intervention vs. Comparator	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Quality or certainty of the evidence (GRADE)		
						Direct evidence	Indirect evidence	Network meta-analysis
NB(CPNB) vs. Sham/Placebo	No concern	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NB(cryoneurolysis) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NM(rTMS) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NM(ctDCS) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NM(PNS) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
PO(Amitriptyline) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
PO(Gabapentin)	No concern for 1	Moderate	Not detected	Wide	Not detected	⊕⊕◯◯	N.A.	⊕⊕◯◯

vs. Sham/Placebo	trial; High risk for another one	heterogeneity (I^2=45.9%)		confidence interval		LOW[*‡]		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 confidence interval	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
PO(Mexiletine) vs. Sham/Placebo	High risk of bias	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Morphine) vs. Sham/Placebo	High risk of bias	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. Sham/Placebo	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NB(cryoneurolysis) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE	⊕⊕⊕◯ MODERATE
NM(rTMS) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
NM(ctDCS) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
NM(PNS) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
PO(Amitriptyline) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
PO(Gabapentin)	-	-	-	-	-	N.A.	⊕⊕◯◯	⊕⊕◯◯

vs. NB(CPNB)							LOW*‡	LOW
PO(Memantine) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE‡	⊕⊕⊕◯ MODERATE
PO(Mexiletine) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
PO(Morphine) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
Alternative(EMS) vs. NB(CPNB)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE‡	⊕⊕⊕◯ MODERATE
NM(rTMS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(ctDCS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(PNS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Amitriptyline) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE‡	⊕⊕⊕◯ MODERATE
PO(Gabapentin) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
PO(Memantine) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE‡	⊕⊕⊕◯ MODERATE
PO(Mexiletine)	-	-	-	-	-	N.A.	⊕⊕◯◯	⊕⊕◯◯

vs. NB(cryoneurolysis)							LOW[*‡]	LOW
PO(Morphine) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
NM(ctDCS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
NM(PNS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
PO(Amitriptyline) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
PO(Gabapentin) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW[*‡¶]	⊕◯◯◯ VERY LOW
PO(Memantine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
PO(Mexiletine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW[*‡¶]	⊕◯◯◯ VERY LOW
PO(Morphine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW[*‡¶]	⊕◯◯◯ VERY LOW
Alternative(EMS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
NM(PNS)	-	-	-	-	-	N.A.	⊕⊕⊕◯	⊕⊕⊕◯

vs. NM(ctDCS)							MODERATE‡	MODERATE
PO(Amitriptyline) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Gabapentin) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Memantine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Mexiletine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Morphine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
Alternative(EMS) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Amitriptyline) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Gabapentin) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Memantine) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Mexiletine) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Morphine)	-	-	-	-	-	N.A.	⊕◯◯◯	⊕◯◯◯

vs. NM(PNS)							VERY LOW[*‡¶]	VERY LOW
Alternative(EMS) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[‡¶]	⊕⊕◯◯ LOW
PO(Gabapentin) vs. PO(Amitriptyline)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Memantine) vs. PO(Amitriptyline)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
PO(Mexiletine) vs. PO(Amitriptyline)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Morphine) vs. PO(Amitriptyline)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Amitriptyline)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
PO(Memantine) vs. PO(Gabapentin)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Mexiletine) vs. PO(Gabapentin)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Morphine) vs. PO(Gabapentin)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Gabapentin)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
PO(Mexiletine)	-	-	-	-	-	N.A.	⊕⊕◯◯	⊕⊕◯◯

vs. PO(Memantine)							LOW[*‡]	LOW
PO(Morphine) vs. PO(Memantine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Memantine)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE[‡]	⊕⊕⊕◯ MODERATE
PO(Morphine) vs. PO(Mexiletine)	High risk of bias	N.A.	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Mexiletine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Morphine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW[*‡]	⊕⊕◯◯ LOW
Outcome: Adverse event								
Comparison: Intervention vs. Comparator	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	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	⊕⊕⊕◯ MODERATE[‡]	N.A.	⊕⊕⊕◯ MODERATE
NM(rTMS)	Some concerns	N.A. [§]	Not detected	Singular trial	Not detected	⊕⊕⊕◯	N.A.	⊕⊕⊕◯

vs. Sham/Placebo						MODERATE‡		MODERATE
NM(ctDCS) vs. Sham/Placebo	Some concerns	N.A. §	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE‡	N.A.	⊕⊕⊕◯ MODERATE
NM(PNS) vs. Sham/Placebo	Some concerns	N.A. §	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE‡	N.A.	⊕⊕⊕◯ MODERATE
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	⊕⊕⊕◯ MODERATE*	N.A.	⊕⊕⊕◯ MODERATE
PO(Mexiletine) vs. Sham/Placebo	High risk of bias	N.A. §	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
PO(Morphine) vs. Sham/Placebo	High risk of bias	N.A. §	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
Alternative(EMS) vs. Sham/Placebo	Some concerns	N.A. §	Not detected	Singular trial	Not detected	⊕⊕⊕◯ MODERATE‡	N.A.	⊕⊕⊕◯ MODERATE
NM(rTMS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(ctDCS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(PNS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Memantine) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE*‡	⊕⊕⊕◯ MODERATE

PO(Mexiletine) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
PO(Morphine) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
Alternative(EMS) vs. NB(cryoneurolysis)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE*‡	⊕⊕⊕◯ MODERATE
NM(ctDCS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(PNS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Memantine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡¶	⊕⊕◯◯ LOW
PO(Mexiletine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Morphine) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
Alternative(EMS) vs. NM(rTMS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
NM(PNS) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE*‡	⊕⊕⊕◯ MODERATE
PO(Memantine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡¶	⊕⊕◯◯ LOW

PO(Mexiletine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Morphine) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
Alternative(EMS) vs. NM(ctDCS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Memantine) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡¶	⊕⊕◯◯ LOW
PO(Mexiletine) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
PO(Morphine) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕◯◯◯ VERY LOW*‡¶	⊕◯◯◯ VERY LOW
Alternative(EMS) vs. NM(PNS)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW‡¶	⊕⊕◯◯ LOW
PO(Mexiletine) vs. PO(Memantine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
PO(Morphine) vs. PO(Memantine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Memantine)	-	-	-	-	-	N.A.	⊕⊕⊕◯ MODERATE*‡	⊕⊕⊕◯ MODERATE
PO(Morphine) vs. PO(Mexiletine)	High risk of bias	N.A. §	Not detected	Singular trial	Not detected	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW

Alternative(EMS) vs. PO(Mexiletine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW
Alternative(EMS) vs. PO(Morphine)	-	-	-	-	-	N.A.	⊕⊕◯◯ LOW*‡	⊕⊕◯◯ LOW

* Risk of bias. † Inconsistency. ‡Imprecision. §Only one study, inconsistency cannot be evaluated. ¶ Intransitivity.

Abbreviations: N.A., not applicable.

Appendix 12: Meta-regression

SUCRA and mean ranks changes before and after model adjustment

Abbreviations:

1. Neural block (NB):

NB (CPNB), Continuous perineural neural block;

NB (cyroneurolysis), neural block with cryoneurolysis.

2. Neuromodulation (NM):

NM (rTMS), neuromodulation with repetitive transcranial magnetic stimulation;

NM (ctDCS), neuromodulation with cerebellar transcranial direct current stimulation;

NM (PNS), neuromodulation with percutaneous peripheral neural stimulation.

3. Oral medication (PO):

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.

4. Alternative modality (Alternative):

Alternative (EMS), Alternative treatment with electromagnetic shielding.

12.1. Changes in pain intensity (Age)

Cutoff value: Baseline Age = **55.0**

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	26.3	72.2	21.1	95.5	57.2	77.0
Baseline Age	29.9	65.6	32.2	87.5	54.4	66.6
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	43.3	60.2	22.9	31.4	69.8	23.0
Baseline Age	44.4	64.0	27.0	36.5	62.9	28.9

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	9.1	4.1	9.7	1.5	5.7	3.5
Baseline Age	8.7	4.8	8.5	2.4	6.0	4.7
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	7.2	5.4	9.5	8.5	4.3	9.5
Baseline Age	7.1	5.0	9.0	8.0	5.1	8.8

12.2. Changes in pain intensity (Baseline VAS/NRS score)

Cutoff value: Baseline VAS/NRS score = **5.8**

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	24.1	70.1	20.7	94.1	55.5	74.9
Baseline VAS/NRS score	29.4	67.8	28.5	89.0	55.8	71.0
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	42.2	58.3	38.9	30.7	67.6	22.8
Baseline VAS/NRS score	44.8	42.6	44.7	33.0	65.5	28.0

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	9.4	4.3	9.7	1.6	5.9	3.8
Baseline VAS/NRS score	8.8	4.5	8.9	2.2	5.9	4.2
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	7.4	5.6	7.7	8.6	4.6	9.5
Baseline VAS/NRS score	7.1	7.3	7.1	8.4	4.8	8.9

12.3. Changes in pain intensity (Duration since amputation)

Cutoff value: Duration since amputation (years) = **2.0**

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	24.8	65.8	-	-	54.1	72.2
Duration since amputation (yrs)	24.8	65.8	-	-	54.1	72.2
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	43.3	71.2	41.1	-	-	27.6
Duration since amputation (yrs)	43.3	71.2	41.1	-	-	27.6

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	6.3	3.4	-	-	4.2	2.9
Duration since amputation (yrs)	6.3	3.4	-	-	4.2	2.9
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	5.0	3.0	5.1	-	-	6.1
Duration since amputation (yrs)	5.0	3.0	5.1	-	-	6.1

12.4. Changes in pain intensity (Amputation site, upper/lower limb)

Cutoff value: Percentage of upper limb ≥ **50%**.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	28.9	67.3	26.8	89.2	55.5	71.3
Amputation site	28.9	67.3	26.8	89.2	55.5	71.3
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	44.2	43.5	44.2	35.3	65.3	28.7
Amputation site	44.2	43.5	44.2	35.3	65.3	28.7

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	8.8	4.6	9.1	2.2	5.9	4.2
Amputation site	8.8	4.6	9.1	2.2	5.9	4.2
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	7.1	7.2	7.1	8.1	4.8	8.8
Amputation site	7.1	7.2	7.1	8.1	4.8	8.8

12.5. Changes in pain intensity (Amputation type, traumatic/non-traumatic)

Cutoff value: Percentage of traumatic type ≥ **50%**.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	26.3	65.2	-	88.6	53.3	70.0
Amputation type	26.3	65.2	-	88.6	53.3	70.0
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	42.3	40.6	41.1	34.2	64.2	24.4
Amputation type	42.3	40.6	41.1	34.2	64.2	24.4

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	8.4	4.5	-	2.1	5.7	4.0
Amputation type	8.4	4.5	-	2.1	5.7	4.0
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	6.8	6.9	6.9	7.6	4.6	8.6
Amputation type	6.8	6.9	6.9	7.6	4.6	8.6

12.6. Adverse event (Age)

Cutoff value: Baseline Age = **55.0**.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	49.7	-	51.9	50.7	50.2	50.1
Baseline Age	49.8	-	69.1	58.2	48.7	47.9
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	48.7	49.2	49.6	49.9
Baseline Age	-	-	64.8	48.8	9.9	52.8

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	5.0	-	4.8	4.9	5.0	5.0
Baseline Age	5.0	-	3.5	4.3	5.1	5.2
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	5.1	5.1	5.0	5.0
Baseline Age	-	-	3.8	5.1	8.2	4.8

12.7. Adverse event (Baseline VAS/NRS score)

Cutoff value: Baseline VAS/NRS score = **5.8**.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	49.3	-	72.0	59.0	50.9	46.6
Baseline VAS/NRS score	49.3	-	72.0	59.0	50.9	46.6
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	61.4	49.1	9.7	52.0
Baseline VAS/NRS score	-	-	61.4	49.1	9.7	52.0

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	5.1	-	3.2	4.3	4.9	5.3
Baseline VAS/NRS score	5.1	-	3.2	4.3	4.9	5.3
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	4.1	5.1	8.2	4.8
Baseline VAS/NRS score	-	-	4.1	5.1	8.2	4.8

12.8. Adverse event (Duration since amputation)

Cutoff value: Duration since amputation (years) = **2.0**.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	44.8	-	-	-	47.9	44.9
Duration since amputation (yrs)	44.8	-	-	-	47.9	44.9
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	61.8	-	-	50.7
Duration since amputation (yrs)	-	-	61.8	-	-	50.7

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	3.2	-	-	-	3.1	3.2
Duration since amputation (yrs)	3.2	-	-	-	3.1	3.2
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	2.5	-	-	3.0
Duration since amputation (yrs)	-	-	2.5	-	-	3.0

12.9. Adverse event (Amputation site, upper/lower limb)

Cutoff value: Percentage of upper limb ≥ 50%.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	49.3	-	72.0	59.0	50.9	46.6
Amputation site	49.3	-	72.0	59.0	50.9	46.6
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	61.4	49.1	9.7	52.0
Amputation site	-	-	61.4	49.1	9.7	52.0

Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	5.1	-	3.2	4.3	4.9	5.3
Amputation site	5.1	-	3.2	4.3	4.9	5.3
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	4.1	5.1	8.2	4.8
Amputation site	-	-	4.1	5.1	8.2	4.8

12.10. Adverse event (Amputation type, traumatic/non-traumatic)

Cutoff value: Percentage of traumatic type ≥ 50%.

Covariate/ SUCRA	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	52.8	-	-	59.7	51.3	48.4
Amputation type	52.8	-	-	59.7	51.3	48.4
Covariate/ SUCRA	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	66.4	54.5	11.0	55.8
Amputation type	-	-	66.4	54.5	11.0	55.8

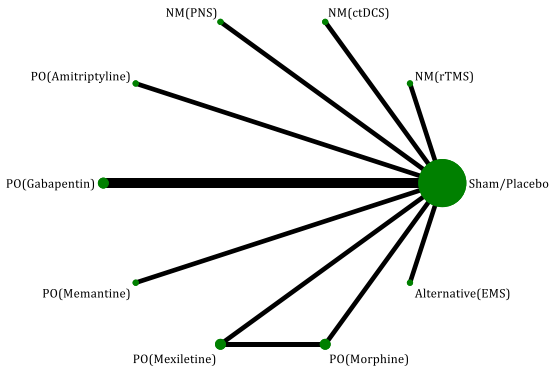
Covariate/ Mean rank	Sham/Placebo	NB(CPNB)	NB(cyroneurolysis)	NM(rTMS)	NM(ctDCS)	NM(PNS)
Unadjusted model	4.3	-	-	3.8	4.4	4.6
Amputation type	4.3	-	-	3.8	4.4	4.6
Covariate/ Mean rank	PO(Amitriptyline)	PO(Gabapentin)	PO(Memantine)	PO(Mexiletine)	PO(Morphine)	Alternative(EMS)
Unadjusted model	-	-	3.4	4.2	7.2	4.1
Amputation type	-	-	3.4	4.2	7.2	4.1

Appendix 13: Sensitivity analysis

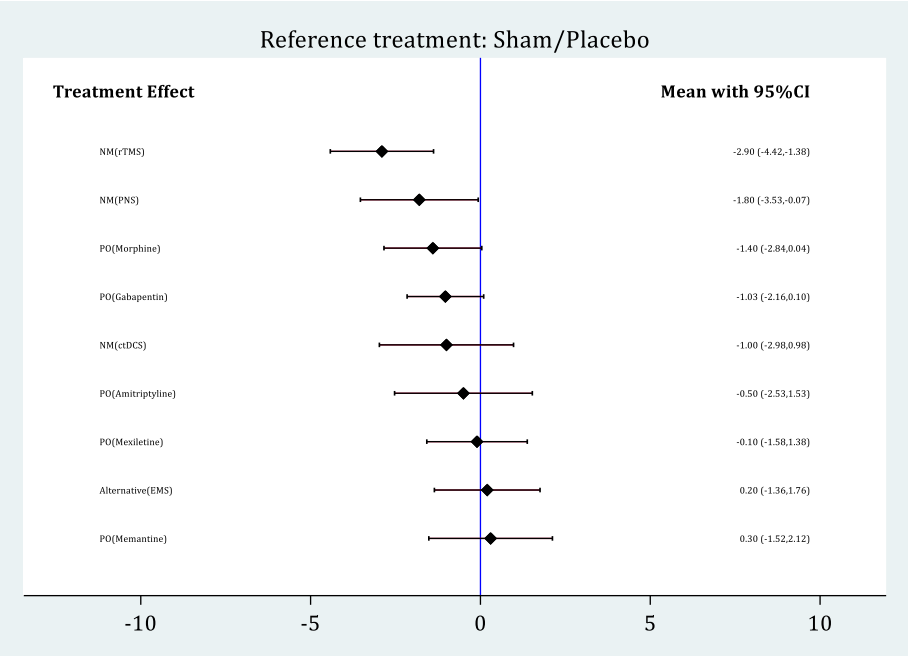
Three studies opted to use the median instead of the mean for their analyses: Ilfeld et al., 2023 (focusing on cryoneurolysis), Ilfeld et al., 2021 (concentrating on CPNB), and Schwenkreis et al., 2003 (studying memantine). To assess the impact of this methodological choice, we conducted sensitivity analyses by **excluding these three trials**.

13.1. Changes in pain intensity

eFigure 13.1.1. Network plot for changes in pain intensity

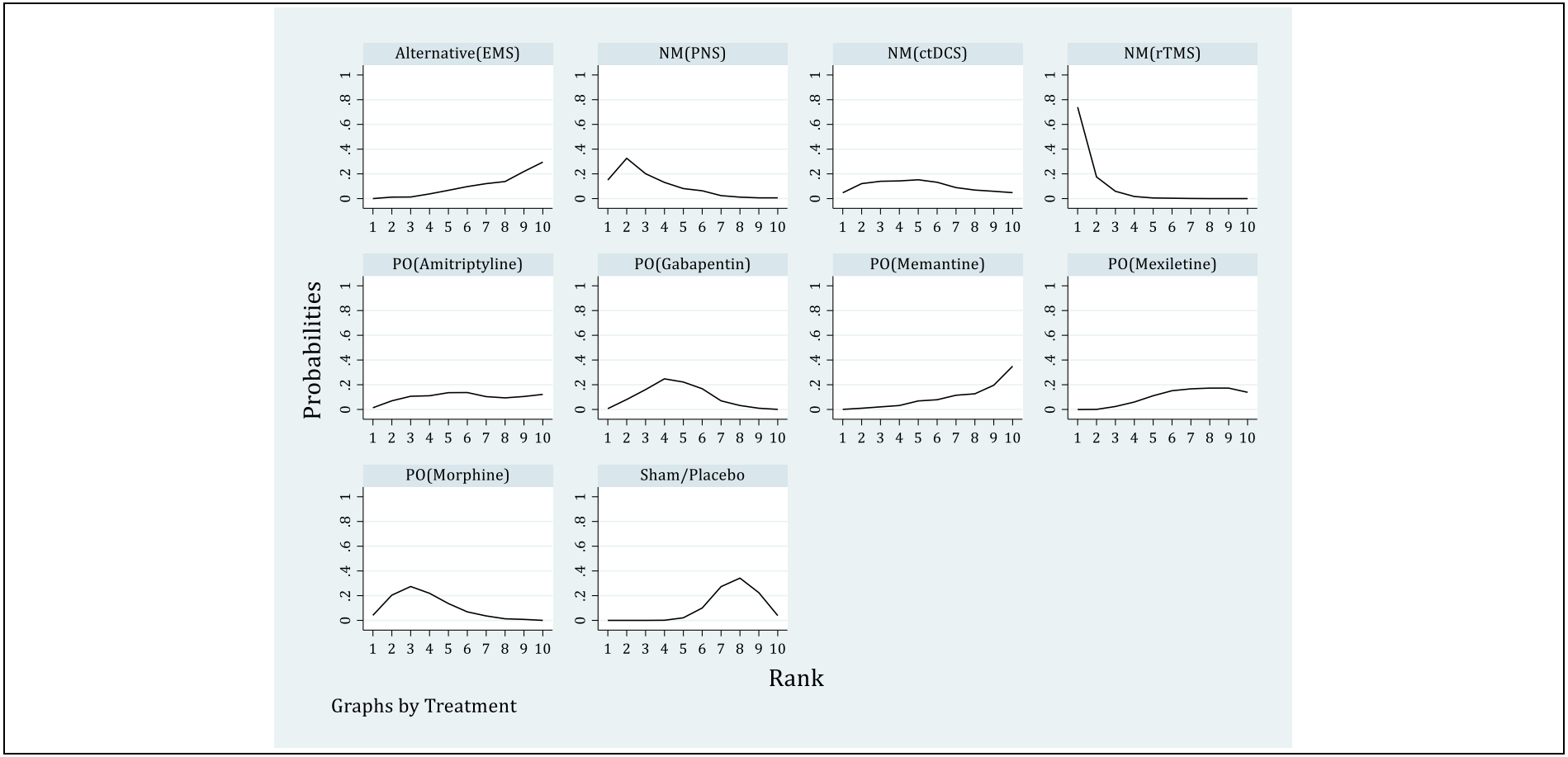


eFigure 13.1.2. Interval plot for changes in pain intensity



13.1.1. SUCRA value

eTable 13.1.1. Changes in pain intensity in relative ranking probability



Ranking\ Treatment	Sham/Placebo	NM (rTMS)	NM (ctDCS)	NM (PNS)	PO (Amitriptyline)	PO (Gabapentin)	PO (Memantine)	PO (Mexiletine)	PO (Morphine)	Alternative (EMS)
Best	0.0	74.0	4.7	15.0	1.4	0.7	0.1	0.0	4.1	0.0
2nd	0.0	17.5	12.1	32.6	7.0	8.1	1.0	0.1	20.4	1.2
3rd	0.0	5.9	14.0	20.1	10.7	16.1	2.1	2.4	27.4	1.3
4th	0.1	1.7	14.3	13.1	11.1	24.8	3.2	6.0	21.9	3.8
5th	2.1	0.5	15.2	8.1	13.6	22.2	6.9	11.1	13.6	6.7
6th	10.0	0.3	13.2	6.3	13.7	16.8	7.9	15.2	6.9	9.7
7th	27.3	0.1	8.9	2.4	10.4	7.0	11.5	16.7	3.6	12.1
8th	34.2	0.0	6.9	1.2	9.4	3.2	12.7	17.3	1.3	13.8
9th	22.4	0.0	5.9	0.6	10.5	1.0	19.6	17.3	0.8	21.9
Worst	3.9	0.0	4.8	0.6	12.2	0.1	35.0	13.9	0.0	29.5
Mean Rank	7.8	**1.4**	5.0	3.1	6.1	4.6	8.1	7.3	3.7	8.0
SUCRA	24.9	**95.7**	55.3	76.8	43.7	59.9	20.9	30.2	70.3	22.2

Abbreviations: NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural 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; Alternative(EMS), Alternative treatment with electromagnetic shielding.

13.1.2. League table

eTable 13.1.2. League table of the changes in pain intensity between different interventions.

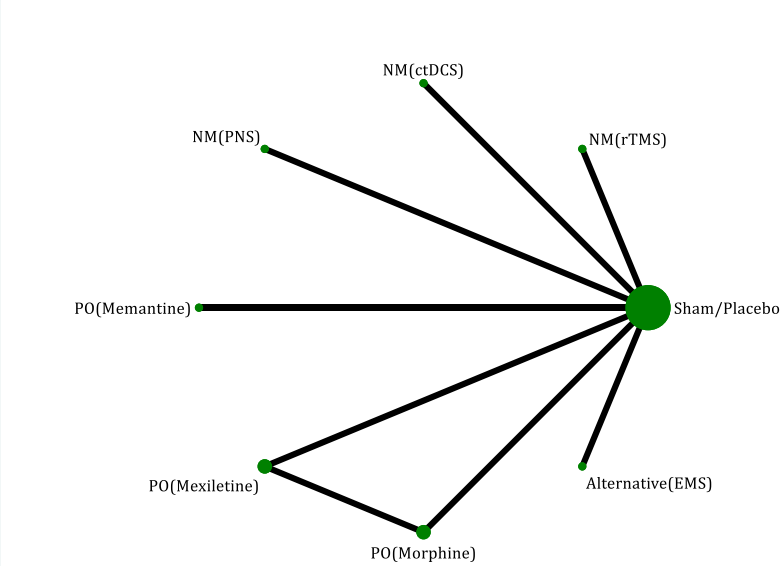
Pairwise Meta-analysis										
Network Meta-analysis	Sham/Placebo	**-2.90 (-3.97, -1.83)** **Singular trial**	-1.00 (-2.65, 0.65) **Singular trial**	**-1.80 (-3.16, -0.44)** **Singular trial**	-0.50 (-2.22, 1.22) **Singular trial**	-1.03 (-2.16, 0.10) **I^2 = 45.9% (2 trials)**	-0.30 (-1.13, 1.76) **Singular trial**	-0.10 (-1.11, 0.91) **Singular trial**	**-1.40 (-2.35, -0.45)** **Singular trial**	0.20 (-0.92, 1.32) **Singular trial**
	-2.90 (-4.42, -1.38)	NM(rTMS)	-	-	-	-	-	-	-	-
	-1.00 (2.98, 0.98)	1.90 (-0.59, 4.39)	NM(ctDCS)	-	-	-	-	-	-	-
	-1.80 (-3.53, -0.07)	1.10 (-1.21, 3.41)	-0.80 (-3.43, 1.83)	NM(PNS)	-	-	-	-	-	-
	-0.50 (-2.53, 1.53)	2.40 (-0.13, 4.93)	0.50 (-2.33, 3.33)	1.30 (-1.37, 3.97)	PO(Amitriptyline)	-	-	-	-	-
	-1.03 (-2.16, 0.10)	1.87 (-0.02, 3.76)	-0.03 (-2.31, 2.24)	0.77 (-1.30, 2.84)	-0.53 (-2.85, 1.79)	PO(Gabapentin)	-	-	-	-
	0.30 (-1.52, 2.12)	3.20 (-0.83, 5.57)	1.30 (-1.39, 3.99)	2.10 (-0.41, 4.61)	0.80 (-1.92, 3.52)	1.33 (-0.81, 3.47)	PO(Memantine)	-	-	-
	-0.10 (-1.58, 1.38)	2.80 (-0.68, 4.92)	0.90 (-1.57, 3.37)	1.70 (-0.58, 3.98)	0.40 (-2.11, 2.91)	0.93 (-0.93, 2.79)	-0.40 (-2.74, 1.94)	PO(Mexiletine)	**-1.30 (-2.13, -0.47)** **Singular trial**	-

	-1.40 (-2.84, 0.04)	1.50 (-0.59, 3.59)	-0.40 (-2.84, 2.04)	0.40 (-1.85, 2.65)	-0.90 (-3.39, 1.59)	-0.37 (-2.20, 1.46)	-1.70 (-4.02, 0.62)	-1.30 (-2.66, 0.06)	PO(Morphine)	-
	0.20 (-1.36, 1.76)	3.10 (-0.92, 5.28)	1.20 (-1.31, 3.71)	2.00 (-0.33, 4.33)	0.70 (-1.86, 3.26)	1.23 (-0.69, 3.15)	-0.10 (-2.49, 2.29)	0.30 (-1.85, 2.45)	1.60 (-0.52, 3.72)	Alternative(EMS)

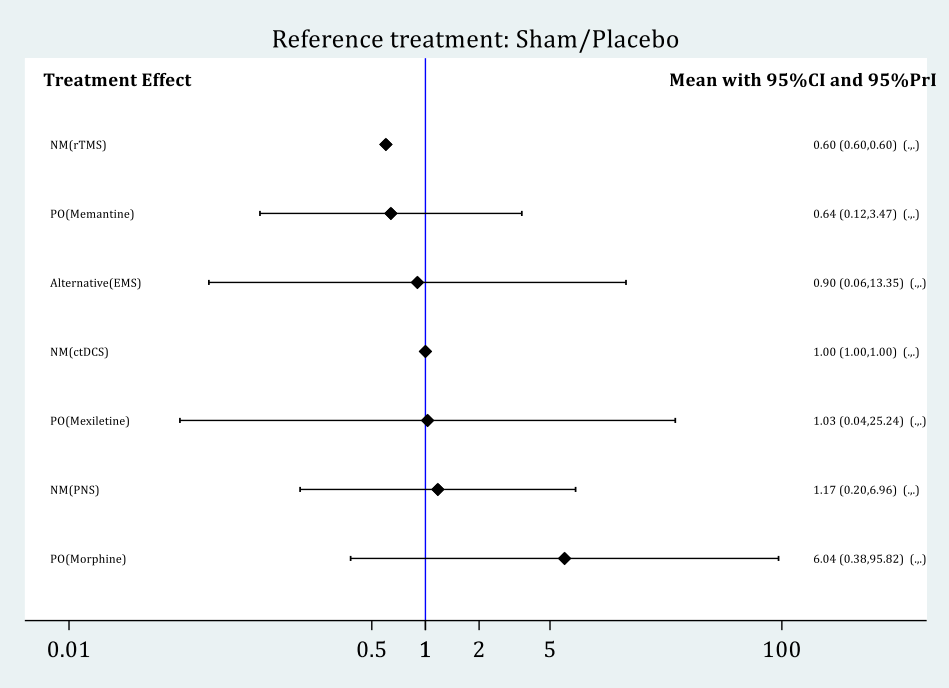
Effect estimate was expressed as MD with 95% CI for changes in pain intensity in random-effects model for network meta-analysis. The upper right triangle presents the effects of direct estimates, and the lower-left triangle presents the effects of network estimates. A negative MD value indicates a favorable outcome for the intervention in the lower diagonal. Number in **bold** represent statistically significant results. Abbreviations: NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural 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; Alternative(EMS), Alternative treatment with electromagnetic shielding.

13.2. Adverse event rate

eFigure 13.2.1. Network plot for adverse event rate

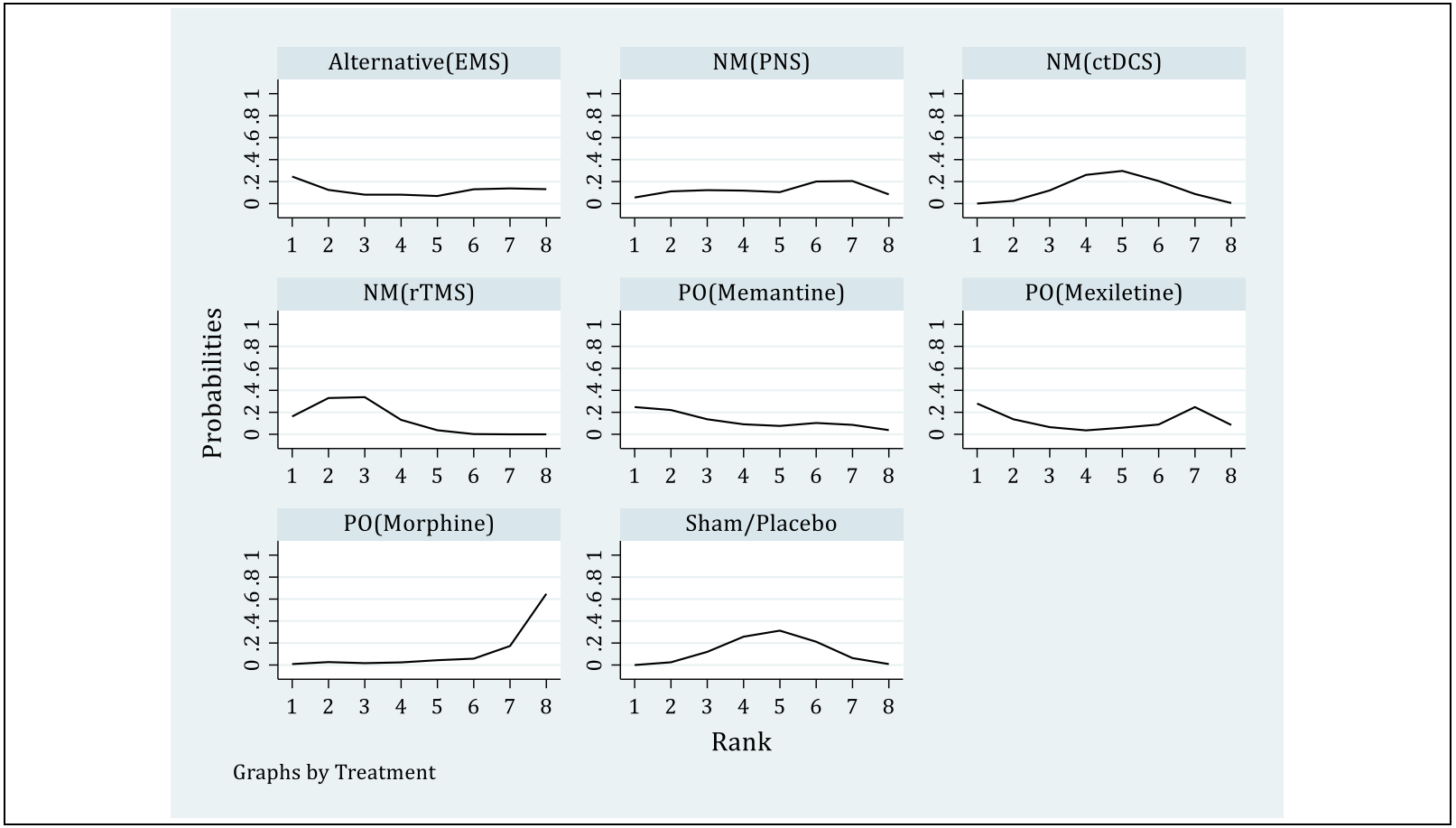


eFigure 13.2.2. Interval plot for adverse event rate



13.2.1. SUCRA value

eTable 13.2.1 Adverse events in relative ranking probability



Ranking\ Treatment	Sham/Placebo	NM (rTMS)	NM (ctDCS)	NM (PNS)	PO (Memantine)	PO (Mexiletine)	PO (Morphine)	Alternative (EMS)
Best	0.0	16.2	0.0	5.5	24.8	28.0	0.9	24.6
2nd	2.5	33.0	2.5	11.1	22.1	13.7	2.7	12.4
3rd	12.0	33.8	12.0	12.2	13.7	6.5	1.7	8.1
4th	25.8	13.1	26.1	11.8	9.1	3.6	2.4	8.1
5th	31.3	3.7	29.7	10.4	7.6	6.0	4.4	6.9
6th	21.2	0.2	20.5	20.1	10.3	8.9	5.8	13.0
7th	6.3	0.0	8.7	20.5	8.6	24.8	17.3	13.8
Worst	0.9	0.0	0.5	8.4	3.8	8.5	64.8	13.1
Mean Rank	4.8	2.6	4.8	4.9	3.4	4.1	7.2	4.2
SUCRA	45.8	**77.8**	45.5	43.6	66.2	55.1	11.8	54.3

Abbreviations: NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural stimulation; PO(Memantine), oral administration of Memantine; PO(Mexiletine), oral administration of mexiletine; PO(Morphine), oral administration of morphine; Alternative(EMS), Alternative treatment with electromagnetic shielding.

13.2.2. League table

eTable 13.2.2. League table presenting the adverse event rate across different interventions.

	Pairwise Meta-analysis							
Network Meta-analysis	Sham/Placebo	**0.60 (0.01, 32.56)** **Singular trial**	1.00 (0.02, 53.89) **Singular trial**	1.17 (0.02, 63.97) **Singular trial**	0.64 (0.17, 2.38) **Singular trial**	1.03 (0.33, 3.24) **Singular trial**	**6.04 (2.26, 16.12)** **Singular trial**	0.90 (0.02, 47.00) **Singular trial**
	0.60 (0.60, 0.60)	NM(rTMS)	-	-	-	-	-	-
	1.00 (1.00, 1.00)	1.67 (1.67, 1.67)	NM(ctDCS)	-	-	-	-	-
	1.17 (0.20, 6.96)	1.96 (0.33, 11.60)	1.17 (0.20, 6.96)	NM(PNS)	-	-	-	-
	0.64 (0.12, 3.47)	1.07 (0.20, 5.79)	0.64 (0.12, 3.47)	0.55 (0.05, 6.35)	PO(Memantine)	-	-	-
	1.03 (0.04, 25.24)	1.71 (0.07, 42.07)	1.03 (0.04, 25.24)	0.88 (0.02, 34.11)	1.61 (0.04, 60.00)	PO(Mexiletine)	**5.87 (2.19, 15.70)** **Singular trial**	-
	6.04 (0.38, 95.82)	10.06 (0.63, 159.69)	6.04 (0.38, 95.82)	5.14 (0.19, 137.75)	9.43 (0.37, 241.12)	5.87 (0.29, 118.62)	PO(Morphine)	-
	0.90 (0.06, 13.35)	1.50 (0.10, 22.24)	0.90 (0.06, 13.35)	0.77 (0.07, 8.24)	1.41 (0.06, 33.94)	0.88 (0.01, 57.51)	0.15 (0.00, 7.09)	Alternative(EMS)

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. Number in **bold** represent statistically significant results. Abbreviations: NM(rTMS), neuromodulation with repetitive transcranial magnetic stimulation; NM(ctDCS), neuromodulation with cerebellar transcranial direct current stimulation; NM(PNS), neuromodulation with percutaneous peripheral neural stimulation; PO(Memantine), oral administration of Memantine; PO(Mexiletine), oral administration of mexiletine; PO(Morphine), oral administration of morphine; Alternative(EMS), Alternative treatment with electromagnetic shielding.

PRISMA checklist

Section/Topic	Item #	Checklist Item [16]	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1, Title section**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives; **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.***Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**3, Abstract section**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**6-7, Introduction (3rd paragraph)**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6-7, Introduction (3rd paragraph); Appendix 2**
METHODS			

Protocol and registration	5	Indicate whether a review protocol exists: **PROSPERO register：CRD42022328360**	**8, Method (1st paragraph)**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**8, Method (2nd paragraph);**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**8, Method (1st paragraph);**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**8, Method (2nd paragraph); Appendix 2, 3**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**8, Method (2nd paragraph); Appendix 3**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**8, Method (1st and 2nd paragraph)**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**8, Method (1st paragraph) Appendix 2**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**8-9, Method (3rd paragraph); Figure 2**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**10, Method (7th paragraph**

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**11, Method (9th paragraph**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis.	**11, Method (9th paragraph)**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**11, Method (9th paragraph)**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**10, Method (7th paragraph)**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified.	**11, Method (9th paragraph)**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**12, Findings (1st paragraph); Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 2**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**12, Findings (1st paragraph); Figure 2**

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**12, Findings (1st paragraph); Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**13-14, Findings (4th paragraph); Appendix 6**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals.	**12-13, Findings (2nd-3rd paragraphs)**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. If additional summary measures were explored (such as treatment rankings), these should also be presented.	**12-13, Findings (2nd-3rd paragraphs) Figure 2**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**14, Findings (6th paragraph); Appendix 10**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**13-14, Findings (4th paragraph); Appendix 6**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**14-15, Findings (8th -9th paragraph); Appendix 12-13**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome;	**28, Discussion (1st paragraph)**

		consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**32**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**32-33**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**2**

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.