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Review Article

Management of Central Poststroke Pain: Systematic Review and Meta-analysis

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ABSTRACT

Central poststroke pain (CPSP) is a neuropathic pain condition prevalent in 8 to 35% of stroke patients. This systematic review and meta-analysis aimed to provide insight into the effectiveness of available pharmacological, physical, psychological, and neuromodulation interventions in reducing pain in CPSP patients (PROSPERO Registration: CRD42022371835). Secondary outcomes included mood, sleep, global impression of change, and physical responses. Data extraction included participant demographics, stroke etiology, pain characteristics, pain reduction scores, and secondary outcome metrics. Forty-two original studies were included, with a total of 1,451 participants. No studies providing psychological therapy to CPSP patients were identified. Twelve studies met requirements for a random-effects meta-analyses that found pharmacological therapy to have a small effect on mean pain score (SMD = −.36, 96.0% confidence interval [−.68, −.03]), physical interventions did not show a significant effect (SMD = −.55 [−1.28, .18]), and neuromodulation treatments had a moderate effect (SMD = −.64 [−1.08, −.19]). Fourteen studies were included in proportional meta-analysis with pharmacological studies having a moderate effect (58.3% mean pain reduction [−36.51, −80.15]) and neuromodulation studies a small effect (31.1% mean pain reduction [−43.45, −18.76]). Sixteen studies were included in the narrative review, the findings from which largely supported meta-analysis results. Duloxetine, amitriptyline, and repetitive transcranial magnetic stimulation had the most robust evidence for their effectiveness in alleviating CPSP-induced pain. Further multicenter placebo-controlled research is needed to ascertain the effectiveness of physical therapies, such as acupuncture and virtual reality, and invasive and noninvasive neuromodulation treatments.

Perspective: This article presents a top-down and bottom-up overview of evidence for the effectiveness of different pharmacological, physical, and neuromodulation treatments of CPSP. This review could provide clinicians with a comprehensive understanding of the effectiveness and tolerability of different treatment types.

Central poststroke pain (CPSP) is a neuropathic pain condition evident in 8 to 35% of stroke patients.[1,2] The International Association for the Study of Pain describes CPSP as a disorder that "is caused by a cerebrovascular lesion, infarct, or hemorrhage of the brain or brainstem. The pain may be spontaneous or evoked, as an increased response to a painful stimulus (hyperalgesia) or a painful response to a normally nonpainful stimulus (allodynia)."[3] This definition captures pain symptoms but not sensory signs associated with CPSP, while the International Classification of Diseases Version 11 continues to use the legacy name of Dejerine-Roussy syndrome with a focus on pain symptoms arising from thalamic lesions.[4] Dejerine-Roussy syndrome was redefined to CPSP as more variations of the disorder were identified, and no clear lesion etiology could be established.[5,6]

CPSP patients may experience symptom onset immediately after stroke, but most patients begin showing symptoms after 1 month to 3 months.[1,2] Some sources have reported onset as late as 10 years after a patient's initial stroke.[7] Evoked or spontaneous short-term and long-term pain varies in intensity, but most patients experience medium- to high-intensity pain of 64 to 70 on the visual analog scale (VAS).[8-13] CPSP is described as long-term and potentially life-long, but there is a

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lack of longitudinal research to define the length of this disorder.[10]

To complicate the CPSP definition further, there are sensory signs that can differ between CPSP patients.[14] Cold hypoesthesia and allodynia appear to be the most common sensory signs in CPSP patients, followed by mechanical allodynia, hyperalgesia, dysesthesia, and hyperesthesia.[10,12,14-18] As CPSP patients may have muted sensory responses to some stimuli and exaggerated responses to others, there is an added difficulty in finding the right treatment to address sensory abnormalities specific to each patient.

Alongside complicated sensory signs, CPSP patients are also at a higher risk of developing physical and psychological comorbidities than stroke patients without CPSP.[14] These include headaches, shoulder pain, depression, insomnia, drug dependency, and suicide.[1,19] Therefore, when deciding on a treatment strategy, it is important to consider how different treatment options affect a patient's quality of life and any comorbidities that they may have.

Both International Association for the Study of Pain and International Classification of Diseases Version 11 provide only broad treatment overviews stating that antiepileptic and antidepressant medication, as well as some nonpharmacological approaches, are used for treatment.[20] A guide on CPSP pharmacological treatment[21] has been published, but pharmacological prescriptions still vary greatly in practice.[12,22] CPSP patients have stated that treatment often provides short-lived pain alleviation and comes with multiple unpleasant side effects,[21] arising from a lack of treatment guidelines and few literature reviews comparing the evidence for effectiveness and tolerability of available treatments.[1,7,23-25]

Antidepressants, opioids, and anticonvulsants were the most commonly used medication treatments for CPSP pain relief.[26] Alongside pharmacological interventions, patients with CPSP have also been treated with neuromodulation therapy,[27,28] physical therapy, such as acupuncture and mirror therapy,[29-31] and psychological therapy.[12,28,32] However, the effectiveness of different treatments has been debated with no defined golden-standard treatment pathways.[26,33] Literature reviews and guidelines of CPSP treatments are small in scale, outdated, or focus on a single treatment modality.[22,23,25,27,31-36] The current research hoped to provide a comprehensive top-down understanding of different CPSP treatment pathways for clinicians and researchers trying to define a benchmark approach. Here, we aimed to evaluate the evidence for the effectiveness and harm of pharmacological, physical, psychological, and neuromodulation interventions on CPSP pain relief. Our secondary aim was to evaluate the secondary effect of CPSP pain relief interventions on quality-of-life assessments.

Methods

Protocol Registration

This review paper followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses[37] flowchart and checklist. The protocol of this review was registered with PROSPERO prior to literature review (CRD42022371835).[38] An amendment was submitted to PROSPERO to extend the completion date. There were not deviations from the protocol.

Data Sources and Searches

A systematic search of electronic databases was undertaken for interventional studies on pain reduction in CPSP patients. With the search included studies inception to the day the search was undertaken (December 2022 and a follow-up search in August 2023). Databases were searched in full, and select journals were additionally hand-searched to ensure that no relevant papers are missed (Table 1).

The search terms used in the study were formulated using patient, intervention, comparison, and outcome framework.[39] The search strategy was developed to capture research studies on 4 different intervention types: pharmacological, physical, psychological, and neuromodulation. Different wordings for treatment methods within a treatment type were combined using the "OR" operator. The sample and phenomenon of interest keywords related to different names of CPSP were combined using "AND" operator with design and evaluation terms relating to each treatment type. An example search would include "Central Post*Stroke Pain"AND"Pharmacological"OR"-Anticonvulsant." Full search terms are provided in Supplementary Table 1.

Table 1
Databases Searched in Full, and Additionally Hand-Searched Journals

databases	*journals*
CINAHL	*Disability and Rehabilitation*
Cochrane	*Patient Education and Counselling*
Frontiers	*International Journal of Stroke*
Google Scholar	*Journal of Neurology*
PsycINFO	*Journal of Pain*
PubMed	*Journal of Pain and Symptom Management*
Sage	*Journal of Stroke and Cerebrovascular Diseases*
	Neurosurgery and Psychiatry
Springer	*Journal of Stroke*
Taylor and Francis	*Journal of Pain Research*
Web of Science	

Study Selection

The inclusion criteria were 1) randomized trials and nonrandomized studies, 2) longitudinal and cross-sectional studies, 3) within- and between-subjects design studies, 4) studies with samples that were either only CPSP-diagnosed participants, or 5) studies where CPSP group-specific data could be extracted from the wider sample. The exclusion criteria for the type of studies were 1) qualitative studies, 2) case studies, 3) reviews, 4) book chapters or articles, 5) animal studies, 6) dissertations, 7) abstract-only articles, 8) papers in non-English language, and 9) gray literature. For gray literature pieces that could fit the inclusion criteria, the authors were emailed for details of publications. Studies that included multiple chronic pain or poststroke pain conditions were excluded if data relating specifically to CPSP participants were not extractable. Studies were excluded if dosage was not disclosed, virtual reality (VR) environments were not defined, or neuromodulation parameters were not stated.

All identified studies were collated using Rayyan[40] systematic review management tool. Titles and abstracts for all studies (n = 5,565) were blindly and independently screened by 2 reviewers (A.T. and B.S.P.) to see if they met at least 1 inclusion criterion and were excluded if they met any exclusion criterion. The remaining studies were subjected to a full-text review. Studies that used "thalamic pain" or "post stroke pain" were reviewed with the third reviewer (A.M.), who has years of clinical experience with CPSP patients, to confirm whether the condition was CPSP or a different neuropathic pain condition. If the study did not contain enough detail on the participants' symptoms to make an informed decision on whether the participants had CPSP or another poststroke pain condition, the study was excluded from this review. The only identified psychological studies were case studies and were not retained following abstract screening. Interrater reliability was calculated using Cohen's Kappa score.

Data Extraction

Once final papers for inclusion were agreed on, a data extraction tool was created by reviewers using Microsoft (US) Excel.[41] Data extraction included mean pain score change, percentage pain score change, standard deviations (SDs), confidence intervals (CIs), demographic information, quality-of-life improvements, and reported side effects. Where studies reported multiple outcome timepoints, the pain

relief results were extracted from the timepoint related to the primary outcome. There was an attempt to collect quality-of-life improvements from multiple timepoints, but due to limited reporting, only the mean change in quality-of-life scores was included. Details of all variables extracted from articles are presented in Supplementary Table 2, which is the data extraction form used by the authors.

For studies that did not report SD, mean pain change, or mean percentage change, the authors were emailed for information. Out of 15 studies, 6 had listed expired contact information and 7 contacted authors did not respond. Where only an SD score was missing, it was imputed using other available metrics and statistical calculations outlined in Cochrane Handbook for Systematic Reviews of Interventions.[39] Where a mean was not reported but all VAS, numeric rating scale (NRS), or percentage scores were provided, the mean and SD were calculated by reviewers (A.T. and S.L.) following a systematic review methodology paper.[42] Studies that had multiple treatment methods or groups with sufficiently different approaches, such as repetitive Transcranial Magnetic Stimulation (rTMS) studies with different target locations or different medications covered in 1 study, were divided for meta-analysis using calculations from Cochrane Handbook.[43] The approach of splitting the sample size of the main group into multiple groups with smaller sample sizes was adopted for this. Other approaches were considered, such as combining treatment groups into one, but in the interest of covering as many treatment methodologies as possible, these approaches were not adopted.

Quality and Risk Assessment

All studies were quality- and risk-of-bias assessed by 2 reviewers blindly and independently (A.T. and S.L.). Cross-sectional studies that were not randomized studies were assessed using the Newcastle-Ottawa Scale.[44] Randomized control trials and crossover studies were assessed using a revised Cochrane risk-of-bias tool 2[45,46] and a risk-of-bias tool 2 for crossover trials, respectively.[47] The respective tools ensured that the quality and risk assessment were appropriate for the study methods.

All studies were additionally scored using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework[43] by 2 independent reviewers (A.T. and S.L.). Randomized controlled trials started with high confidence, while all other studies started with low confidence. Studies were considered against patient, intervention, comparison, and outcome criteria on imprecision, indirectness, inconsistency, publication bias, and risk of bias (Table 2). For each criteria, the study could be downgraded up to 2 times. There were also 3 positive criteria that could increase the rating of the study: 1) whether different dosage was tested, 2) whether an effect size was calculated and reported, and 3) whether the study considered confounders.

Table 2
GRADE Framework Negative Criteria

grade domain	*journals*
Population	How certain is participants' CPSP diagnosis?
Population	Was recruitment of participants explained well?
Intervention	Does the intervention sequence follow best practice?
Intervention	Was the blinding procedure adequate?
Comparison	Was demographic data between participants not significantly different?
Comparison	Was there placebo control?
Outcomes	Were side effects reported?
Outcomes	Would further evidence change our confidence in the estimate of effect?
Imprecision	Was the sample sufficiently large enough for statistical power?
Imprecision	Were statistical assumptions checked before analysis?
Indirectness	Were pain measures thoroughly explained?
Inconsistency	Is the reporting of results consistent?
Publication Bias	Was there Conflict of Interest or Industry sponsorship?
Risk of Bias	Is the estimated risk of bias high?

Meta-analysis

Data extraction revealed most studies included in meta-analysis reported VAS scores, while others reported NRS scores. In total, 11 studies reported mean pain score difference and SD metrics for both intervention and comparator groups. All 11 of these studies used pain measurements on a 11-point scale, and the primary outcome timepoints were immediately after treatment. In total, 10 studies that did not report mean pain score change and SD, or metrics that would enable SD extrapolation were excluded from a random-effects model meta-analysis.

As this is a field where there is a lack of rigorous comparative studies and summative CPSP treatment reviews, a proportional meta-analysis was conducted on studies that could not be included in the random-effects model. Majority of studies that were eligible for a proportional meta-analysis reported percentage pain change after treatment. Studies that reported only the number of people who achieved "satisfactory" pain control without exact percentage mean change or change for each participant were excluded. In total, 6 studies were excluded due to only reporting the number of people who achieved "satisfactory" or "good" pain. A meta-analysis of these 6 studies was not possible due to each study having different and arbitrary percentage pain thresholds for classifying the degree of pain relief. Additionally, 2 studies were excluded due to having a different mechanism of action that would not be comparable to other included studies. All included studies measured pain on a 11-point scale. The inclusion and exclusion decisions were based on a proportional meta-analysis guide[48] and existing proportional model meta-analysis studies.[49-51] Unlike a random-effects meta-analysis, proportional meta-analysis does not allow for any causal inference, but can summarize the effect of an intervention on a specific condition by calculating the effect rates as proportions and 95% CIs.[48] The proportional analysis used the DerSimonian-Laird model that operates with an assumption that the analyzed studies were different but had a related intervention effect.[48] Heterogeneity for each random-effects and proportional meta-analyses was determined using Cochran's Q-statistic, and Higgin's and Thompson's I^2.

All random-effects meta-analyses were run using R Project using meta library,[17,52] while the proportional meta-analyses were run using OpenMeta software.[53] Meta-analysis was performed on each treatment group: physical, pharmacological, and neuromodulating. These studies were pooled by treatment group to provide a top-down overview of differences between each group for clinicians considering alternative treatment methods or combination treatment. This was then refined to subgroups of specific treatments, where statistically possible, to provide a more detailed view to clinicians and researchers of each treatment type's evidence of effectiveness. Subgroup analyses were performed when there were 2 or more studies on a specific treatment type. Funnel plot and Egger's test were performed on all meta-analyses to identify publication bias.

Effect sizes for all meta-analyses were interpreted using Standardised Mean Difference (SMD) and 95% CIs. Findings from studies high in risk of bias or having scored low on quality assessment were considered, but these findings should be interpreted cautiously. Random-effects or proportional meta-analyses were not possible for quality-of-life assessments due to the highly varied and heterogeneous assessment methods. Therefore, quality-of-life assessment changes and side effects are presented as narrative summary.

Results

Results of the Search

The systematic database and journal search found 14,233 articles. Once duplicates were deleted, 5,565 unique studies were identified.

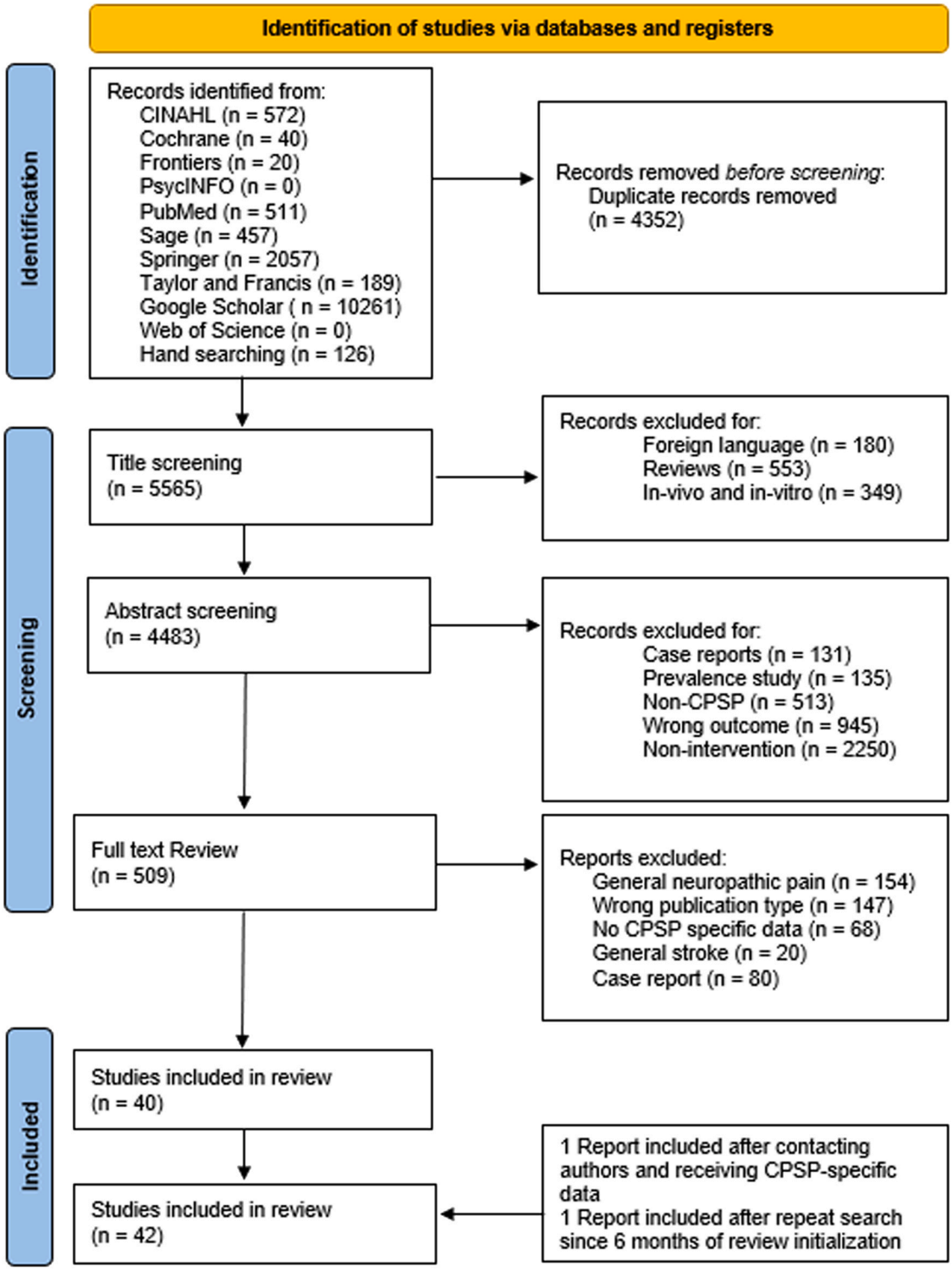

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of literature review.

After a review of the study titles, 4,483 journal articles had their abstracts screened, and 509 of those were selected for full-text review. There were 21 studies that were included, and 22 studies that resulted in conflicting reviewer opinions. The main conflict was ambiguity around CPSP patient diagnosis. After deliberation and consultation with a third reviewer (A.M.), it was decided to include 19 of those studies. The search was rerun after 6 months, which resulted in 1 additional study being identified for inclusion. There were 7 studies that did not have CPSP-specific data but met all other inclusion criteria. The authors of these studies were emailed to ask for data but only 1 study provided it, while other studies were excluded.[54-58] Finally, 42 journal articles were identified that met inclusion and exclusion criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the review process is detailed in Fig 1. The interrater reliability for both reviewers was found to be Kappa = .645 (P = .04).

Out of the 42 studies, 12 were randomized control trials, 8 were randomized crossover studies, 5 were retrospective, and 18 were cross-sectional interventions. There were 14 pharmacological intervention

Table 3
Study Characteristics

Study ID	Control T: Type N: Number of participants A: age in years mean (SD/range) G: Gender, N; Male (Female) C: CPSP duration months (SD/range)	Experimental CPSP Group N: Number of participants A: age in years mean (SD/range) G: Gender, N; Male (Female) C: CPSP duration months (SD/range)	Methodology T: Type C: Control B: Blinding	Intervention T: Type S: Specific Treatment C: Control/Sham type	Treatment Specificity S: Strength A: Administration D: Duration	Reported outcome measures A: Pain B: Psychological C: Physical
Bae, 2014[7]	**T:** CPSP **N:** 7 **A:** 52.3 (2.8) **G:** 3 (4) **C:** 14.5 (3.2)	**N:** 7 **A:** 51.1 (3.1 **G:** 4 (3) **C:** 14.7 (2.7)	**T:** Randomised trial **C:** Sham trial **B:** Single	**T:** Neuromodulation **S:** tDCS[A] **C:** Current only applied for 30 seconds	**S:** 2mA **A:** M1[B] **D:** 3 times per week for 3 weeks	**A:** VAS[1] **B:** NR **C:** Skin temperature, QST[2]
Cho, 2013[25]	**T:** CPSP **N:** 8 **A:** NR (36 - 88) **G:** NR **C:** NR	**N:** 8 **A** : NR (36 - 88) **G:** NR **C:** NR	**T:** Randomised trial **C:** Placebo-control **B:** Single	**T:** Physical **S:** Bee venom acupuncture **C:** Saline injection in to 1 acupoint	**S:** 0.05ml diluted bee venom **A:** acupoints of affected side **D:** Once	**A:** VAS **B:** NR **C:** NR
De Oliveira, 2014[32]	**T:** CPSP **N:** 10 **A:** 57.8 (11.86) **G:** 5 (5) **C:** 50.1 (28.04)	**N:** 11 **A:** 55 (9.67) **G:** 5 (6) **C:** 64.18 (49.27)	**T:** Randomised trial **C:** Sham-control **B:** Double	**T:** Neuromodulation **S:** rTMS[C] **C:** Identical sham coil emitting sound	**S:** 1250 pulses at 10 Hz, 50% MT[D] **A:** Premotor cortex **D:** RI	**A:** VAS, NPS[4] **B:** HAM-A[5], HAM-D[6] **C:** NR
Kim, 2011[66]	**T:** CPSP **N:** 109 **A:** 57.1 (10.2) **G:** 70 (39) **C:** 30 (2.4-169.2)	**N:** 110 **A:** 59.4 (9.8) **G:** 67 (43) **C:** 26.4 (1.2-212.4)	**T:** Randomised trial **C:** Placebo control **B:** Double	**T:** Pharmacological **S:** Pregabalin **C:** Placebo pill	**S:** Mean 356.8 mg (125 – 539.70) **A:** Daily pill **D:** 4 weeks	**A:** VAS[1] **B:** HADS[7] **C:** NR
Mahesh, 2022[83]	**T:** CPSP **N:** 41 **A:** 52.66 (8.48) **G:** 26 (15) **C:** 1.97 (0.07-35.51	**N:** 41 **A:** 58.90 (10.33) **G:** 21 (20) **C:** 1.97 (0.23-47.34)	**T:** Randomised trial **C:** Placebo control **B:** Double	**T:** Pharmacological **S:** Duloxetine **C:** Placebo pill	**S:** 30mg to 60mg (based on NRS[8] pain intensity at 2 weeks) **A:** Daily pill **D:** 4 weeks	**A:** NRS[8], SF-MPQ[9], PDI[10] **B:** PGIC[11] **C:** NR
McGeoch, 2008[86]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 9 **A:** 60.22 (15.72) **G:** 3 (6) **C:** NR (30-180)	**T:** Cross sectional **C:** Within-subject sham-control **B:** Single	**T:** Neurostimulation **S:** Vestibular stimulation **C:** Body temperature irrigation or ice pack application to the pinna	**S:** Cold water **A:** Injection in to air canal **D:** 1 session	**A:** NRS[8] **B:** NR **C:** NR
O'Neill, 2018[94]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 23 **A:** NR **G:** 7 (2) **C:** NR	**T:** Randomised trial **C:** Crossover **B:** Double	**T:** Neuromodulation **S:** tDCS[A] **C:** Current only applied for 5 seconds	**S:** 1.4mA **A:** M1[B] **D:** Daily for 5 days	**A:** NRS[8] **B:** HADS[7] **C:** NR
Ojala, 2021[97]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 17 **A:** 58.80 (7.10) **G:** 8 (9) **C:** 67.2 (38.4)	**T:** Randomised trial **C:** Crossover **B:** Double	**T:** Neuromodulation **S:** rTMS[C] **C:** non-conductive plastic cover	**S:** 5050 pulses at 10Hz, 90% of MT[D] **A:** M1[B] and S2[E] as separate sessions **D:** 2 weeks per crossover session	**A:** NRS[8] **B:** BDI[12], PASS-20[13], EQ-5D-3L[14] **C:** DASH[15]
Onouchi, 2014[98]	**T:** Spinal Cord Injury **N:** 38 **A:** 63.6 (12.7) **G:** 35 (3) **C:** NA	**N:** 60 **A:** 61.70 (8.50) **G:** 42 (18) **C:** NR	**T:** Open-label **C:** Comparison **B:** None	**T:** Pharmacological **S:** Pregabalin **C:** Another pain group	**S:** 300mg to 600mg **A:** Daily pill **D:** 52 weeks	**A:** BPI[16], VAS[1], SF-MPQ[9] **B:** NR **C:** NR
Xiao-nong, 2012[131]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 11 **A:** NR **G:** 4 (2) **C:** NR	**T:** Clinical Efficacy Trial **C:** Crossover **B:** None	**T:** Physical **S:** Acupuncture **C:** Western Medicine	**S:** Puncture of acupoints 8-12 mm to 20-40mm in depth, 0.4g to 1.2g of carbamazepine **A:** NR **D:** 15 minutes	**A:** VAS[1] **B:** NR **C:** NR
Zhao, 2021[137]	**T:** CPSP **N:** 19 **A:** 48.95 (11.51) **G:** RI **C:** 6.47 (12.57)	**N:** 19 **A:** 50.16 (11.34) **G:** RI **C:** 6.00 (3.07)	**T:** Randomised trial **C:** Sham-control **B:** Double	**T:** Neuromodulation **S:** rTMS[C] **C:** Identical coil with sound but no stimulation	**S:** 1500 pulses at 10HZ, 80% of MT[D] **A:** M1[B] **D:** 6 days per week for 3 weeks	**A:** NRS[8], SF-MPQ-CN[17] **B:** HAM-A[5], HAM-D[6] **C:** NR
Boccard, 2013[18]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 23 **A:** 58.8 (9.10) **G:** 14 (2) **C:** NR	**T:** Cross sectional **C:** None **B:** None	**T:** Neuromodulation **S:** DBS[F] **C:** None	**S:** 5 to 50Hz, pulse width 200 to 450ms, amplitude 0.5 to 5V **A:** PVG[G], VPL[H], VPM[I] **D:** 3 months	**A:** VAS[1], MPQ[18] **B:** EQ-5D[14] **C:** SF-36[19]

(*continued on next page*)

Table 3 (*continued*)

Guo, 2022[42]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 21 **A:** 58.52 (7.27) **G:** NR **C:** 34.38 (28.39)	**T:** Retrospective **C:** None **B:** None	**T:** Neuromodulation **S:** MCS[K] **C:** None	**S:** 30-50 HZ, pulse width 210–300 μs at 3.5 – 7.0 V **A:** M1[B] **D:** 5-7 days	**A:** VAS[1], NPSI[20] **B:** PSQI[21] **C:** NR
Kim, 2019[67]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 37 **A:** 48.90 (12.10) **G:** 16 (21) **C:** 37.2 (49.2)	**T:** Cross sectional **C:** None **B:** None	**T:** Pharmacological **S:** Duloxetine **C:** None	**S:** 30mg-60mg once daily **A:** Daily pill **D:** 3 weeks	**A:** NRS[8], SF-MPQ[17] **B:** NR **C:** NR
Lefaucheur, 2004[74]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 12 **A:** RI **G:** RI **C:** NR	**T:** Randomised trial **C:** Within-subjects sham-control **B:** Single	**T:** Neuromodulation **S:** rTMS[C] **C:** Magstim placebo coil	**S:** 20 pulses of 5 seconds at 10HZ, 80% MT[D] **A:** M1[B] **D:** NR	**A:** VAS[1] **B:** NR **C:** NR
Lin, 2018[82]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 7 **A:** 53.57 (7.16) **G:** 5 (2) **C:** 44.4 (6-132)	**T:** Cross sectional **C:** None **B:** None	**T:** Neuromodulation **S:** rTMS[C] **C:** None	**S:** 1000 pulses at 10HZ daily, 90% MT[D] **A:** M1[B] **D:** 10 days	**A:** VAS[1] **B:** HAM-A[5], HAM-D[6] **C:** Laser Evoked Potentials
Matsumura, 2012[85]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 20 **A:** 63.60 (8.10) **G:** 12 (8) **C:** 38.15 (6 –190)	**T:** Within-subjects **C:** Placebo control **B:** NR	**T:** Neuromodulation **S:** rTMS[C] **C:** Coils elevated at an angle of 45° from the skull	**S:** 500 pulses at 5 Hz, 100% MT[D] **A:** M1[B] **D:** 1 day	**A:** VAS[1] **B:** PGIC[11] **C:** NR
Mohamed, 2010[91]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 30 **A:** 64.80 (7.40) **G:** 21 (9) **C:** 44.80 (6 – 156)	**T:** Retrospective **C:** None **B:** None	**T:** Neuromodulation **S:** SCS[L] **C:** None	**S:** RI **A:** Spinal level C4 to C7 for upper limb pain or T9 to T12 for lower limb **D:** 2-7 days trial, then permanent	**A:** VAS[1] **B:** NR **C:** NR
Ohn, 2012[96]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 22 **A:** 54.90 (9.00) **G:** 13 (9) **C:** 21.90 (17.20)	**T:** Cross sectional **C:** None **B:** None	**T:** Neuromodulation **S:** rTMS[C] **C:** None	**S:** 1000 pulses at 10HZ, 90% MT[D] **A:** M1[B] **D:** 5 times per day for 5 days	**A:** VAS[1] **B:** HAM-D[6] **C:** NR
Owen, 2006[100]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 15 **A:** 58.60 (37 - 74) **G:** 12 (3) **C:** 62.4 (NR)	**T:** Cross sectional **C:** None **B:** None	**T:** Neuromodulation **S:** DBS[F] **C:** None	**S:** NR **A:** VPL[H], PVG[G] **D:** 1 week	**A:** VAS[1], MPQ[17] **B:** NR **C:** NR
Quesada, 2019[104]	**T:** SGE **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 19 **A:** RI **G:** RI **C:** RI	**T:** Randomised Trial **C:** Sham-control Crossover **B:** Double	**T:** Neuromodulation **S:** rTMS[C] **C:** Sham train side of coil	**S:** 1600 pulses at 20 Hz, 80% MT[D] **A:** M1[B] **D:** 27 minute session	**A:** VAS[1], NPSI **B:** EQ-5D[20] **C:** NR
Shimodozono, 2009[113]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 28 **A:** 62.20 (9.70) **G:** 13 (15) **C:** NR (1-108)	**T:** Cross sectional **C:** None **B:** None	**T:** Pharmacological **S:** Fluvoxamine **C:** None	**S:** 25mg to 125mg **A:** Daily pill **D:** Daily for 2 to 4 weeks	**A:** VAS[1] **B:** SDS[22] **C:** NR
Tanei, 2019[118]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 18 **A:** 63.90 (8.80) **G:** 10 (8) **C:** 54 (43.20)	**T:** Retrospective **C:** None **B:** None	**T:** Neuromodulation **S:** SCS[L] **C:** None	**S:** 30Hz with pulse width 240 μs **A:** Midline ipsilateral to area of pain **D:** 12 months	**A:** VAS[1] **B:** NR **C:** NR
Zhang, 2018[9136]	**T:** No Control **N:** NA **A:** NA **G:** NA **C:** NA	**N:** 16 **A:** 59.9 (7.80) **G:** 8 (8) **C:** NR	**T:** Cross sectional **C:** None **B:** None	**T:** Neuromodulation **S:** MCS[K] **C:** None	**S:** 30-50 HZ, pulse width 210–300 μs at 3.5 – 7.0 V **A:** M1[B] **D:** 5-7 days	**A:** VAS[1], NPSI[20] **B:** NR **C:** NR

A, transcranial direct current stimulation; B, primary motor cortex; C, repetitive transcranial magnetic stimulation; D, motor threshold; E, secondary somatosensory cortex; F, deep-brain stimulation; G, periventricular gray; H, ventral posterolateral nucleus (thalamus); I, ventral posteromedial nucleus; J, peripheral nerve block; K, motor cortex stimulation; L, spinal cord stimulation.

1, visual analog scale; 2, Quantitative Sensory Testing; 3, Brief Pain Inventory (0–10); 4, Neuropathic Pain Scale; 5, Hamilton Rating Scale—Anxiety; 6, Hamilton Rating Scale—Depression; 7, Hospital Anxiety and Depression Scale; 8, numeric rating scale (0–100); 9, Short Form McGill Pain Questionnaire; 10, Pain Disability Index; 11, Patient Global Impression of Change; 12, Beck Depression Inventory; 13, Pain Anxiety Symptoms Scale; 14, European Quality of Life 5 Dimensions 3 Level Version; 15, Disabilities of the Arm, Shoulder, and Hand; 16, Brief Pain Inventory (0–10); 17, SF-MPQ Mandarin Chinese version; 18, McGill Pain Questionnaire; 19, Short Form 36-Item Survey Instrument; 20, Neuropathic Pain Symptom Inventory; 21, Pittsburgh Sleep Quality Index; 22, Self-rating Depression Scale; SE, same group as experimental; NA, not applicable; RI, reporting indiscernible—not possible to extract the exact numerical value; NR, not reported.

NOTE. Random-effects meta-analysis in gray and proportional meta-analysis in light blue.

Table 4
Study Risk of Bias and Certainty of Evidence

Study ID	Risk of Bias Tool	Risk of Bias Score	GRADE Score
Bae, 2014	ROB 2: Control Trials	SOME CONCERNS	MODERATE
Bainton, 1992	ROB 2: Crossover	SOME CONCERNS	MODERATE
Cho, 2013	ROB 2: Control Trials	HIGH	LOW
De Oliveira, 2014	ROB 2: Control Trials	HIGH	MODERATE
Kim, 2011	ROB 2: Control Trials	LOW	HIGH
Mahesh, 2022	ROB 2: Control Trials	SOME CONCERNS	HIGH
McGeoch, 2008	ROB 2: Control Trials	HIGH	VERY LOW
O'Neill, 2018	ROB 2: Crossover	LOW	HIGH
Ojala, 2021	ROB 2: Crossover	SOME CONCERNS	HIGH
Onouchi, 2014	Newcastle-Ottawa	SOME CONCERNS	LOW
Xiao-nong, 2012	ROB 2: Crossover	HIGH	VERY LOW
Zhao, 2021	ROB 2: Control Trials	LOW	MODERATE
Boccard, 2012	Newcastle-Ottawa	LOW	LOW
Choi, 2021	Newcastle-Ottawa	SOME CONCERNS	LOW
Gou, 2022	Newcastle-Ottawa	SOME CONCERNS	VERY LOW
Kim, 2019	Newcastle-Ottawa	HIGH	VERY LOW
Lefaucheur, 2004	ROB 2: Control Trials	HIGH	MODERATE
Lin, 2018	Newcastle-Ottawa	HIGH	VERY LOW
Matsumura, 2012	ROB 2: Control Trials	SOME CONCERNS	HIGH
Mohamed, 2010	Newcastle-Ottawa	SOME CONCERNS	LOW
Ohn, 2012	Newcastle-Ottawa	SOME CONCERNS	VERY LOW
Owen, 2006	Newcastle-Ottawa	SOME CONCERNS	VERY LOW
Quesada, 2019	ROB 2: Crossover	LOW	HIGH
Shimodozono, 2009	Newcastle-Ottawa	SOME CONCERNS	VERY LOW
Tanei, 2019	Newcastle-Ottawa	SOME CONCERNS	VERY LOW
Zhang, 2018	Newcastle-Ottawa	SOME CONCERNS	VERY LOW

NOTE. Random-effects meta-analysis in gray and proportional meta-analysis in white.

studies, 5 physical intervention studies, and 25 neuromodulation studies, but no psychological interventions were found. The characteristics of studies that were included in either random-effects or proportional meta-analyses are reported in Table 3. Full study characteristics are provided in Supplementary Table 3.

Risk of Bias and Certainty of Evidence

Risk of bias and certainty of evidence for individual studies included in either random-effects or proportional meta-analyses are presented in Table 4. The mean risk-of-bias rating for studies included in random-

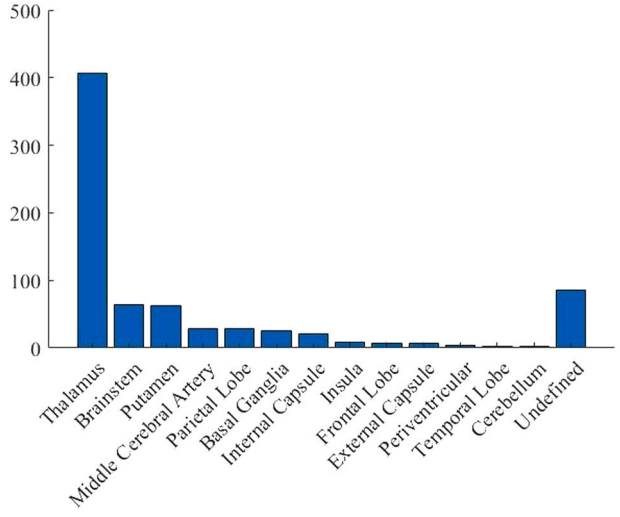

Figure 2. Distribution of CPSP participant stroke locations, *y* axis is the number of participants, and *x* axis is the stroke location.

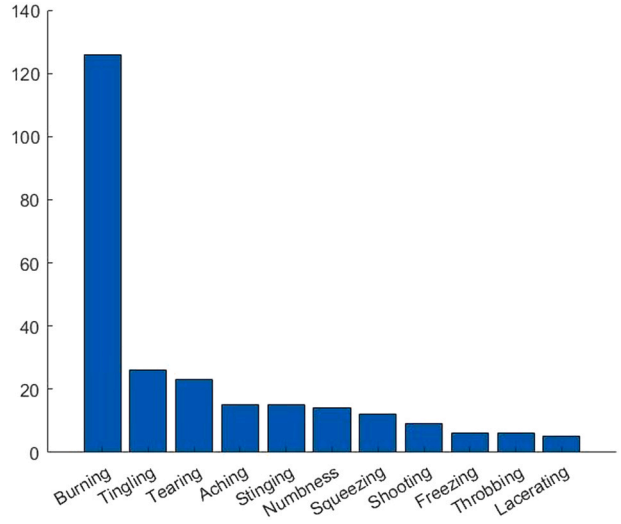

Figure 3. Distribution of CPSP participant qualities of pain, *y* axis is the number of participants, and *x* axis is the pain quality.

effects meta-analysis was "Some Concerns," the mean risk rating for proportional meta-analysis studies was "Some Concerns," and the mean risk rating for studies that were not included in meta-analyses was "Some Concern." GRADE framework identified that random-effects meta-analysis that included studies' mean rating was "moderate" certainty of evidence, proportional meta-analysis studies' mean rating was "low," and studies not included in meta-analyses had a mean rating of "low."

Demographics of Included CPSP Participants

There were a total of 1,191 CPSP participants included across 42 studies. The mean number of participants across all studies was 28.4, with the minimum number of CPSP participants in a study being 5 and a maximum of 219. The mean reported age of CPSP participants was 58.4 with a range of 23 to 82 years old. Out of the studies that reported CPSP participant gender, 58.8% (n = 597) were male and 41.2% (n = 419) were female. As only a small sample of studies reported participant race, this was omitted from data summary.

Stroke Etiology

Out of the reported stroke etiologies, 46.2% (n = 233) were ischemic and 53.8% (n = 271) were hemorrhagic. Most of the strokes were thalamic, making up 52.1% (n = 406) out of 780 reported cases. Extra-thalamic strokes made up 36.8% (n = 287), cortical strokes 8.9% (n = 69), and multimodal strokes 2.3% (n = 18) of reported cases. More specific distribution of stroke locations is illustrated in Fig 2, but the most commonly reported lesions were in the thalamus, brainstem, and putamen. Some studies did not specify the location of a stroke other than "Extra-Thalamic" or "Cortex," and thus were labeled as "Undefined" (n = 86).

Specification of Pain

The mean duration of pain symptoms was 32.4 months with a range of 1 to 190 months across included studies. The mean pretreatment VAS score across studies was 69.0. Pain was located on the left side of the body in 52.1% of participants (n = 152), right side of the body in 47.3% of participants (n = 138), and in alternate sides in .7% (n = 2). Upper limb was the most common localization of pain with 30.9% (n = 175) of participants, hemibody pain was the second most common with 30.4% (n = 172), lower limb pain was reported by 23.0% (n = 130), face-localized pain by 12.4% (n = 70), and trunk by 3.4% (n = 19) of participants. Regarding abnormal pain sensations, 43.5% (n = 245) of participants reported allodynia, 28.2% (n = 159) reported hyperalgesia, 11.2% (n = 63) reported spontaneous pain, 10.5% (n = 59) reported continuous pain, and 6.5% (n = 37) of participants reported hypoesthesia. The most common quality of pain reported was burning, which was reported by 49.0% (n = 126) of participants, the second most common quality was tingling in 10.12% (n = 26), and the third most common was tearing in 9.0% (n = 23) of participants. Full breakdown of reported qualities of pain is presented in Fig 3.

Pharmacological Interventions

Random-Effects Meta-analysis

A meta-analysis of 2 pregabalin studies (n = 279) did not show a significant effect on pain reduction (SMD −.31, 95% CI −.78 to .15, I^2 = 72.5%; Fig 4). This meta-analysis interpretation is limited by having only 2 studies included and having considerable heterogeneity. Additionally, the risk of bias for these studies was "Some Concerns" and certainty of evidence was only moderate.

Proportional Meta-analysis

The analysis was conducted on 2 antidepressant studies of Duloxetine and Fluvoxamine[59,60] (n = 65). The results showed a reduction of mean pain score by 61.9% (CI −35.05 to −88.72, I^2 = 95.89%; Fig 5). There was considerable and significant heterogeneity among the studies that is reflected in the large variation in effect size seen from the CI.

Narrative Summary

There were 2 antidepressant studies that were not included in either meta-analysis due to not reporting SD metrics. Lampl et al[61] performed a randomized placebo-controlled double-blind trial of 39 participants treated with up to 75 mg of amitriptyline as prophylaxis to CPSP. After 3 weeks, 1 less participant developed CPSP in Amitriptyline group than the placebo group and the mean VAS score was 2.0 smaller in the intervention group. These findings were not significant. Leijon and Boivie[58] performed a randomized placebo-controlled crossover study of 15 participants treated with 75 mg of amitriptyline (antidepressant) and 800 mg of carbamazepine (anticonvulsant) on mean pain score. After 4 weeks, only amitriptyline had a sustained significant reduction of pain with 10 patients reporting reduced pain with a mean 5-point reduction from the initial mean 47-point score.

There were 5 more anticonvulsant studies that could not be included in meta-analyses. Jungehulsing et al[62] conducted a randomized placebo

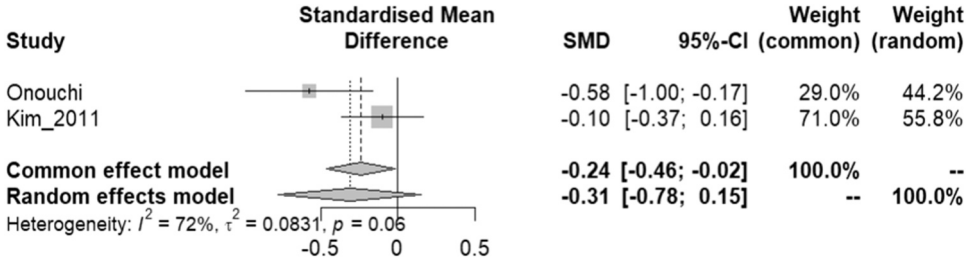

Figure 4. Meta-analysis results and forest plot from pregabalin studies.

crossover double-blind trial of 42 participants for levetiracetam as CPSP treatment, but this was not found to be effective. Contrary to the random-effects meta-analysis, Rahajeng et al[63] showed pregabalin effectiveness in 26 participants who had more than 26% mean pain reduction, which was a significant effect ($P < .05$). A similar effect was also seen in Kalita et al[64] as pain alleviation of over 50% was achieved by 19 participants with pregabalin ($P < .0001$) and 16 with lamotrigine ($P < .0001$). These studies would indicate that out of 66 participants across both Pregabalin studies, over 50% pain reduction was achieved in 37.9% (n = 25) of participants. Petramfar et al[65] performed a retrospective review of 17 participants taking lamotrigine for CPSP. After 24 weeks, there was a significant mean pain score decrease by 24.1 points ($P = .001$) from the initial mean score of 68.2. The Vestergaard et al[18] RCT also further supported lamotrigine effectiveness as the median pain score after treatment was reduced by 10 compared with the placebo group's increase by 10. This was a significant reduction in pain scores ($P = .02$), but the decision to report median rather than mean score was not described or justified.

There was 1 anesthetic study[66] that investigated the effectiveness of morphine, thiamylal, and ketamine as compared with motor cortex stimulation (MCS) and placebo saline. This was a cross-sectional, within-subjects design with 39 participants. The effectiveness of each treatment was measured by the number of patients with reduced pain: 8 for morphine, 22 for thiamylal, 11 for ketamine, and 13 for MCS. The percentage or mean reduction of pain was not reported. Additionally, a crossover double-blind Naloxone study[67] showed a 9.4 VAS mean score decrease after .8 mg of naloxone treatment and a 14 mean VAS score decrease after 8 mg of naloxone treatment, but neither of these were significant when compared with control groups. Similarly, Lidocaine delivered as peripheral nerve block (PNB)[68] showed a 43.6% mean NRS score reduction, but this study did not report significant or include a comparison control group.

Secondary Outcomes and Side Effects

Mahesh et al[2] duloxetine study found a significantly increased Patient Global Impression of Change score when compared with the placebo group. The reported side-effect symptoms included nausea, agitation, somnolence, dizziness, and recurring vomiting. Studies of amitriptyline and carbamazepine[58,61] did not have a significant effect on depression scores. Across both studies, 64.8% (n = 35) out of 54 total participants reported mild reactions that included tiredness, dry mouth, vertigo, and gait disturbances. Further, 3.7% (n = 2) reported undisclosed moderate side effects. Fluvoxamine was found to have a significant effect on the Self-rating Depression Scale with a 7.7-point decrease ($P < .01$) from the initial 44.3. Out of 28 participants, 10.5% (n = 3) withdrew due to side effects, but the side effects of the remaining participants were not tracked.[60] Across all antidepressant studies, 36.8% (n = 74) out of 201 participants reported side effects.

Levetiracetam was not found to have a significant effect on McGill Pain Questionnaire or Beck Depression Inventory.[62] There were 34 counts of mild adverse events reported in levetiracetam intervention group: 11 reported tiredness, 8 reported pain increase, 7 reported dizziness, 4 reported pruritus, and 4 reported headaches. There were 7 people who reported withdrawals from levetiracetam with symptoms of fatigue and pain increase.

Pregabalin was found to significantly improve allodynia, Hamilton Anxiety Rating Scale, and sleep.[1,9] However, across 2 studies of pregabalin,[1,9] side effects were reported in 56.4% (n = 213) out of 378 participants. These included somnolence, tremor, sedation, dizziness, pedal edema, peripheral edema, blurred vision, weight gain, and irritability. Out of all side effects, 10 were moderate and 8 were severe. Withdrawal was not observed or recorded in any of these studies. Across 2 lamotrigine studies that reported other improvements, it was found that Hospital Anxiety and Depression Scale (HADS) score, allodynia, sleep, and mood significantly improved.[1,18] From all 3 lamotrigine studies,[1,18,69] mild side effects were reported in 36.4% (n = 28), and moderate-to-severe side effects were reported in 7.8% (n = 6) out of 77 participants. These side effects included skin rash, somnolence, dizziness, fatigue, nausea, severe headaches, and severe pain. Overall, anticonvulsant studies found 54.3% (n = 247) out of 455 participants experienced side effects.

From the study of anesthetics,[66] no secondary improvements were reported. Out of all treatments, ketamine was the only drug to induce side effects. About 5.1% (n = 2) out of 39 people experienced transient abnormal sensations. From a study of opioid antagonist Naloxone,[67] no secondary outcomes were reported. There were 3 participants (15%) out of 20 who reported adverse reactions: 1 with increased pain and 2 with substantial rise in pulse due to sweating, tremor, salivation, and pain.

A PNB study[68] reported that patients who responded to PNB showed a significantly reduced impact of pain on ability to work, relations with other people, and nonsignificant improvements of mood ($P = .10$) and sleep ($P = .06$). No participants reported adverse effects other than some transient weakness and numbness that lasted up to 3 hours.

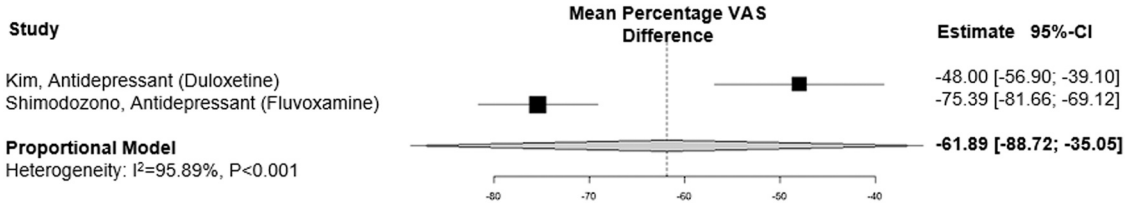

Figure 5. Proportional meta-analysis results and forest plot from antidepressant studies.

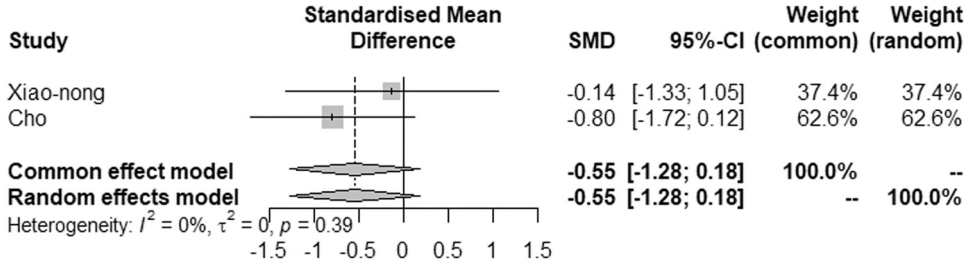

Figure 6. Random-effects meta-analysis results and forest plot from acupuncture studies.

Physical Interventions

Random-Effects Meta-analysis

An analysis of 2 acupuncture studies[29,70] did not show a significant effect on pain reduction as the CI contains 0 (SMD −.55, 95% CI −1.28 to .18, I^2 = 0%; Fig 6). Funnel plot showed symmetrical spread within 95% CI, but heterogeneity could not be reliably tested with 2 studies. Overall risk-of-bias score was "High" and certainty of evidence was low to very low, which severely limits the interpretation of this analysis.

Narrative Summary

No physical intervention studies were included in the proportional meta-analysis. Simmonds and Shahrbanian[71] cross-sectional sham-controlled within-subjects study exposed 12 participants to "hot world," "snow world," neutral stimuli, or no stimuli. "Hot world" included scenes of volcanoes, "snow world" included snowy mountains, and neutral stimuli consisted of alternating white pillars on a black background. "Hot" stimuli significantly decreased participant mean VAS score by 17 points on a 101-point scale (P = .01), "Cold" stimuli significantly decreased it by 17 points (P = .01), neutral stimuli showed a 3.8-point increase (P = .87), and no VR showed a 3-point increase. Pain scores were collected only twice—before and after intervention—on the same day. Other improvements included significant increased threshold to cold and heat stimuli. No side effects were reported.

Secondary Outcomes and Side Effects

Neither of the 2 acupuncture studies reported any secondary improvements.[29,70] Across both studies, only 1 person (3.7%) out of 27 experienced side effects from acupuncture who left the study due to itching. VR[15] was found to significantly increase threshold to cold and heat stimuli. No side effects were reported.

Neuromodulation Interventions

Random-Effects Meta-analysis

Out of the 6 neuromodulation studies included in this analysis (n = 99),[72-77] 1 rTMS study[76] was split as per Cochrane guidelines into 2 groups—1 for primary motor cortex and 1 for secondary sensory cortex. One other study used rTMS of primary motor cortex,[77] 1 used rTMS of premotor cortex and prefrontal cortex,[73] 2 used transcranial direct current stimulation (tDCS),[72,75] and 1 used vestibular caloric stimulation.[74] Neuromodulation was found to have a medium effect on mean pain scores across these studies (SMD −.71, 95% CI −1.05 to −.37, I^2 = 0%; Fig 7). Funnel plot of studies showed symmetrical spread within 95% confidence, and Egger's test of heterogeneity was not significant (P = .57). As this meta-analysis had low heterogeneity and moderate certainty of evidence, it would indicate that there is a consistent therapeutic effect of neuromodulation on CPSP.

A subgroup analysis of all rTMS studies (n = 76)[73,76,77] found a moderate effect on mean pain reduction (SMD −.64, 95% CI −1.1 to −.19, I^2 = 3.4%). Funnel plot showed symmetrical spread, and Egger's test was not significant (P = .38). When only M1-targeting rTMS studies were included (n = 55),[76,77] the effect size was large (SMD −.89, 95% CI −1.45 to −.33, I^2 = 0%). Subgroup analysis of tDCS studies did not find an effect on pain[72,75] (SMD −.64, 95% CI −1.35 to .01, I^2 = 0%). While both M1 rTMS and tDCS were shown to have low heterogeneity, both meta-analyses only included 2 studies, which greatly reduces the validity of heterogeneity tests.

Proportional Meta-analysis

An analysis of 11 neuromodulation studies (n = 238) included 5 rTMS,[78-82] 2 spinal cord stimulation (SCS),[83,84] 2 surgically implanted electrode MCS,[85,86] and 2 deep-brain stimulation (DBS)[8,87] studies. The mean percentage reduction of mean pain scores across studies was 31.1% (CI −43.45 to −18.76, I^2 = 97.02%, Fig 8). There was considerable and significant heterogeneity among these studies.

A subgroup analysis of 5 rTMS studies[78-82] found a reduction of mean pain score by 16.7% with significant heterogeneity (CI −23.63 to −9.70, I^2 = 69.27%). Subgroup analysis of 2 M1 DBS studies[8,87] found a reduction of mean pain score by 46.3% with low heterogeneity (CI −55.18 to −37.40, I^2 = 46.22%). Subgroup analysis of 2 MCS[85,86] studies found a reduction of mean pain score by 41.6% with low heterogeneity (CI −57.16 to −26.12, I^2 = 59.79%). Subgroup analysis of 2 SCS[83,84] studies found a reduction of mean pain score by 42.4% with significant heterogeneity (CI −72.02 to −12.79, I^2 = 94.17%).

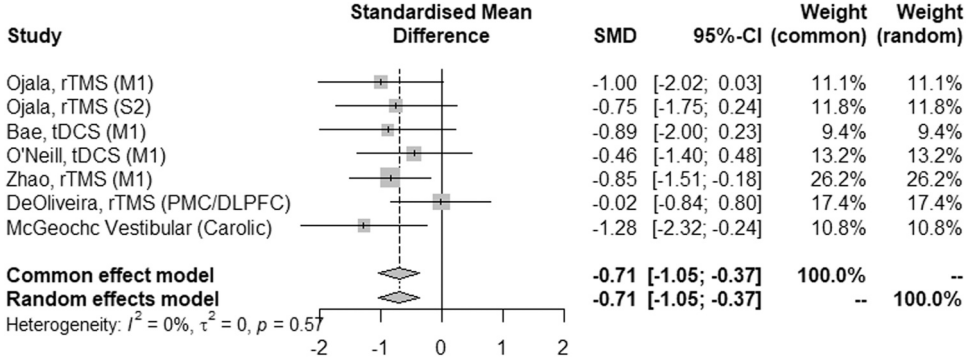

Figure 7. Random-effects meta-analysis results and forest plot from neuromodulation studies.

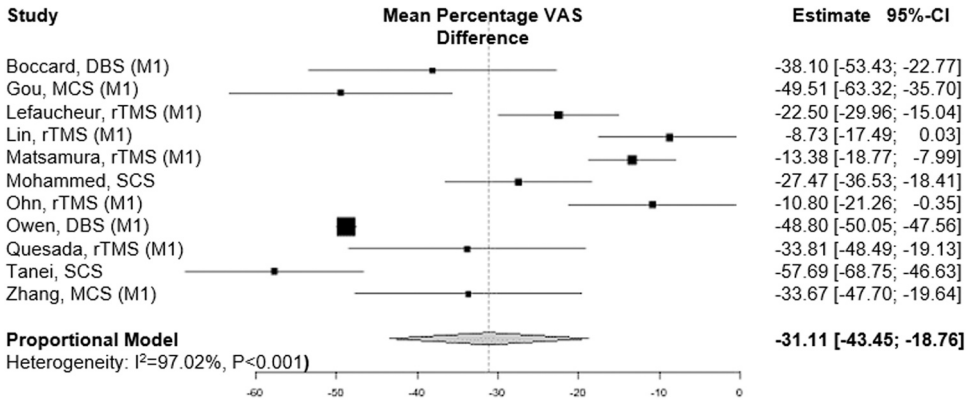

Figure 8. Proportional meta-analysis results and forest plot from neuromodulation studies.

Narrative Summary

There were 4 rTMS studies that were not included in either meta-analysis. Khedr et al[88] reported that 50% of all patients achieved satisfactory (over 40%) VAS reduction in a placebo-controlled trial of rTMS as compared with the control group where no one achieved satisfactory pain control. Kobayashi et al[89] further supported rTMS of M1 effectiveness as 13 participants out of 18 showed VAS percentage reduction of over 40%, whereas the sham group did not show any significant reduction in the mean VAS score. McLean et al[90] found that after 6 weeks of M1 rTMS stimulation, CPSP participants reported a 53-point mean pain score decrease. However, they did not report whether this was a significant decrease. The final rTMS study[91] found that rTMS over M1 resulted in mean VAS score reduction of 7 points or 10% on a 11-point scale ($P = .02$). However, after 4 weeks, the total score reduction was only 4 points from baseline and was no longer significant ($P = .17$).

Three cortex stimulation studies, not included in meta-analyses, appear to support the findings of MCS effectiveness. In Tsubokawa et al[92] cross-sectional study of only the active treatment group, 9 out of 11 participants achieved good pain reduction of over 50%. However, tolerance to treatment developed within 7 months and good pain control reduced to only 38% of participants after 2 years. Yamamoto et al[66] study utilized cross-sectional within-subjects design of MCS versus ketamine, thiamylal, and morphine treatments. Out of 39 participants treated with MCS, 13 were reported to have reduced pain by over 40%, which was statistically significant ($P < .05$). The final MCS study[93] investigated the effect of chronic MCS in a cross-sectional study without sham or control. Out of 31 participants, 23 participants saw pain being reduced by over 40%. After implantation, 15 out of 23 participants maintained pain reduction of over 40%. Significance metric was not reported for these reductions. Overall, from 81 participants across MCS studies, 42% (n = 34) achieved satisfactory pain control.

Yamamoto et al[94] performed a cross-sectional within-subjects comparative study of SCS effectiveness versus morphine, thiopental, and ketamine. Of the 22 participants, SCS reduced the VAS score of 15 participants by over 30%, and 6 of those received pain alleviation of over 60%. Significance was not reported for SCS pain alleviation, but it significantly added to pain alleviation for ketamine treatment as add-on therapy. No side effects or other improvements were reported.

Secondary Outcomes and Side Effects

Out of all rTMS studies, Neuropathic Pain Inventory, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale scores showed no significant improvement.[73,76,79,81,82] Two rTMS studies[80,91] reported Patient Global Impression of Change improvement in 17 out of 34 participants across these studies. From 12 rTMS studies, 7 reported side effects and across those studies, 16% (n = 32) out of 200 reported mild adverse side effects that included increased pain, slight scalp discomfort, headache, dizziness, tiredness, paresthesia, and facial muscle twitching. The most common side effects were transient increased pain (n = 6), scalp discomfort (n = 5), and headaches (n = 4). There was 1 moderate adverse event—collapse.

One study on tDCS[72] reported that there were no significant differences in cold sensation, warm sensation, cold pain, or heat pain thresholds. No side effects were reported.

Vestibular stimulation study[74] did not report any secondary outcome improvements or side effects. Two SCS studies[83,84] did not report any secondary outcomes but did report an interaction of age and stroke location—younger participants and participants with nonthalamic stroke were more likely to respond to treatment. No side effects were reported for either study.

From the included studies, the responder rate for MCS was 52.7% out of 74 participants and 60.9% out of 46 participants for DBS. From all 5 MCS studies,[66,85,86,92,93] only 1 study reported secondary outcomes.[30] They found that MCS significantly improved Pittsburgh Sleep Quality Index score from mean 16.4 score to mean 14.0 score. Side effects were reported in 3 MCS studies,[66,92,93] and mild adverse events were seen in 3.7% (n = 3) out of 81 participants: 1 participant had a postoperative infection; 2 participants reported increased pain. There were 3 patients (3.7%) with generalized seizures when high-frequency pulses went above muscle contraction threshold.

Discussion

This systematic review and meta-analysis set out to review and assess the evidence of 4 different intervention types: pharmacological, physical, psychological, and neuromodulation. While this review cannot provide a clear statement on what treatment should be the standard approach, this review's results do provide an overview of the current evidence of different treatment types and the potential for future research. An overwhelming majority of participants reported in this review had thalamic lesions and, therefore, further research is needed to understand the effectiveness of available treatments on different lesion origin CPSP conditions.

Pharmacological treatment of CPSP was found to have a small effect on pain overall, with the effect being treatment-dependent. Pregabalin's effect had limited support as meta-analysis placebo-controlled studies showed no significant effect and only narrative summary studies had some participants that reported pain relief. While the wider pain literature seems to support the use of pregabalin in pain relief, further large-scale RCT research is needed to determine whether it can be reliably used for CPSP.[21,95] Carbamazepine and levetiracetam effectiveness was not supported by any of the included studies, which is in contrast to a recent systematic review[33] that found levetiracetam as one of the most effective treatments. The disparity in results may be explained by different review methodologies, as this meta-analysis included only CPSP patient scores.

While no lamotrigine studies were included in meta-analyses, narrative summary appears to indicate a significant number of participants

reporting pain relief. Generalizability of this effect is limited as only 1 study utilized a control group. This is contrary to lamotrigine's effectiveness evaluation in a practical guide on CPSP pharmacological treatment,[21] some support in the wider pain management literature,[96] and another CPSP systematic review that included case reports in their results.[26] Both pregabalin and lamotrigine were shown to significantly improve mood and sleep across multiple studies, although lamotrigine appears to be better tolerated by CPSP patients with less incidence of and milder side effects.

From antidepressants, duloxetine appears to have the most concise evidence for effectiveness, followed by amitriptyline and fluvoxamine. Additionally, duloxetine and fluvoxamine, but not amitriptyline, showed improvements in mood. These findings are contradictory to the practical guides on CPSP, as amitriptyline is suggested as the preferred treatment method.[21,22] As the guide is over 8 years old, it did not include recent Duloxetine studies that are included in this review. The wider pain literature appears to support the use of both duloxetine and amitriptyline in pain management, with duloxetine potentially having more support than amitriptyline.[34,97-100] From side-effect incidence, antidepressants appear to be tolerated slightly worse than anticonvulsants by CPSP patients.

Support for opioid or local anesthetic medication to alleviate pain is minimal, with morphine, thiamylal, and ketamine but not naloxone or lidocaine showing some nonsignificant reduction in pain for some patients. While only few side effects were reported, opioids are notorious for complications, side effects, and potential for addiction.[101-105] The findings of this review reflect the statement in a practical guide on CPSP pharmacological treatment,[21] that opioids are not an effective treatment for CPSP even though they are one of the most common medication types prescribed for CPSP.[26]

There were only 2 physical intervention types identified in this review: acupuncture and VR. From the 2 acupuncture studies,[29,70] significant pain relief was only seen in Xiao-nong et al.[70] This pain relief could have been modulated by the expectancy by their East Asian sample[106-108] as opposed to Cho et al[29] blinded sample. With further research, acupuncture may potentially be a worthwhile low side-effect risk add-on therapy to reduce subjective pain perception.

While Simmonds et al[71] would indicate VR effectiveness in alleviating cold and heat allodynia in CPSP participants, further RCT testing is required to understand the reliability of these findings. There is additional support from the wider poststroke rehabilitation and chronic pain management literature of VR as an efficient and cost-effective therapy.[109-113]

No studies investigating any psychological therapies on CPSP were identified in literature searches. While it is possible that some therapy keywords may have been missed in the literature search, other CPSP reviews were not able to identify any psychological therapy studies either[21,32] other than 2 case studies.[114,115] This may indicate a gap in literature that should be explored as psychotherapy has been found to provide alleviation for anxiety and depressive symptoms in other neuropathic pain groups.[47,116,117]

Out of all noninvasive neuromodulation treatment types, M1-targeting rTMS appears to have the most robust evidence for CPSP patient pain alleviation but not mood improvement. Stimulation of the secondary motor and dorsolateral prefrontal cortices does not appear to provide significant pain relief. The successful use of rTMS to alleviate pain is additionally seen in other pain conditions.[118-121] Systematic reviews provide conflicting evidence of whether participants can correctly guess whether a rTMS procedure is sham or real.[122,123] Placebo controls varied between studies, and while nonconductive coils and coil angling techniques are not likely to induce a convincing sham sensation, some studies utilized sensation-mimicking coils that may elicit a placebo response.[28,124-126] Additionally, not all patients respond to rTMS due to the heterogeneous chronic pain pathophysiology,[119] this is reinforced by the large CI of rTMS studies that suggests great variety in effectiveness between studies. Nonetheless, the variety of placebo controls and stroke pathophysiology variations among participants included in this review provide additional robustness of evidence for the effectiveness of rTMS for CPSP pain management, although rTMS may not be tolerated by all patients due to the possible transient side effects.

The effect of tDCS on CPSP alleviation was more ambivalent and for rTMS. Researcher[72] rather than self-administered[75] tDCS appears to have a significant effect on pain. Since the data collection of this review, an additional researcher-administered RCT study has been published to show that tDCS was not significantly better in reducing pain than a sham tDCS.[127] Conversely, a recent review of noninvasive neuromodulation for CPSP found tDCS as more effective in VAS reduction than rTMS[128]; however, their review included a smaller number of rTMS and tDCS studies than the present review. Further research is needed to understand whether tDCS pain alleviation can be reliably replicated by other researchers.

Both the proportional meta-analysis and narrative review appear to provide consistent support for the use of SCS as noninvasive neuromodulation therapy for CPSP, but the lack of control groups in the included studies limits SCS effect generalizability and reliability. These findings support the conclusions of a review of neurostimulation for CPSP[27] that SCS could be a beneficial neuromodulation therapy, particularly for CPSP patients who may not tolerate the sensation of other neuromodulation therapies.

MCS was found to have more supporting research than DBS. Proportional meta-analysis and narrative summary supported the effectiveness of MCS on pain relief and showed a potential effect on sleep quality improvement. The effect is limited to the responder groups as the included MCS and DBS studies did not report nonresponder pain scores and did not utilize control groups; the wider MCS and DBS literature does support a beneficial effect on pain even in placebo-controlled studies.[129-133] The 2 main limitations of MCS and DBS are that they are both invasive procedures that require surgery and that it is difficult to predict whether someone will respond to treatment. Utilizing rTMS prior to MCS may be a good way to explore a patient's responsiveness to neuromodulation and could potentially indicate MCS effectiveness.[134]

Limitations

While all care was taken to ensure that the search strategy was as broadly encompassing as possible, search strategies for pharmacological treatments could have been more granular. This might have resulted in more pharmacological studies being identified, but the current study has already included more pharmacological studies than some other CPSP pharmacological treatment reviews.[23,30]

There was some disagreement between reviewers on studies to include, which resulted in a significant Kappa score. However, the Kappa score of .645 is deemed as moderate agreement and enough to place confidence in the study's findings.[135] All disagreements were also resolved with a third reviewer who has clinical knowledge of CPSP.

Studies included in this review varied in treatment duration, participant numbers, and pain assessment scales. While both VAS and NRS scales utilize a 11-point scale from 0 to 10 and have significant concordance,[136] VAS provides visual guidance to the feelings evoked by pain that may make it easier for people to provide a more accurate measurement. Statistical power of meta-analyses was also limited in estimating the overall effect of therapies due to subgroup analyses having fewer than 5 studies included.

Conclusions

There is a distinct lack of large-sample multicenter randomized controlled trials and longitudinal studies investigating the effectiveness and potential side effects of each treatment modality. With the biggest gap in literature being on psychotherapy's effectiveness for CPSP as

stand-alone or add-on therapy. Due to the varied response rate and mechanisms of effect between treatments, CPSP treatments should not focus on 1 “gold-standard” treatment but instead should aim to optimize concomitant treatments for pain and mood symptom relief.

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Supplementary Data

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