Management of Central Poststroke Pain
Systematic Review of Randomized Controlled Trials

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Background and Purpose—Central poststroke pain is a chronic neuropathic disorder that follows a stroke. Current research on its management is limited, and no review has evaluated all therapies for central poststroke pain.

Methods—We conducted a systematic review of randomized controlled trials to evaluate therapies for central poststroke pain. We identified eligible trials, in any language, by systematic searches of AMED, CENTRAL, CINAHL, DARE, EMBASE, HealthSTAR, MEDLINE, and PsychINFO. Eligible trials (1) enrolled ≥10 patients with central poststroke pain; (2) randomly assigned them to an active therapy or a control arm; and (3) collected outcome data ≥14 days after treatment. Pairs of reviewers, independently and in duplicate, screened titles and abstracts of identified citations, reviewed full texts of potentially eligible trials, and extracted information from eligible studies. We used a modified Cochrane tool to evaluate risk of bias of eligible studies, and collected patient-important outcomes according to recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. We conducted, when possible, random effects meta-analyses, and evaluated our certainty in treatment effects using the Grading of Recommendations Assessment, Development, and Evaluation System.

Results—Eight eligible English language randomized controlled trials (459 patients) tested anticonvulsants, an antidepressant, an opioid antagonist, repetitive transcranial magnetic stimulation, and acupuncture. Results suggested that all therapies had little to no effect on pain and other patient-important outcomes. Our certainty in the treatment estimates ranged from very low to low.

Conclusions—Our findings are inconsistent with major clinical practice guidelines; the available evidence suggests no beneficial effects of any therapies that researchers have evaluated in randomized controlled trials. (Stroke. 2015;46: 2853-2860. DOI: 10.1161/STROKEAHA.115.010259.)

Key Words: evidence-based medicine ■ pain management ■ review ■ stroke ■ therapeutics

Central poststroke pain (CPSP) is a chronic (≥3 months) neuropathic disorder that can occur after a lesion or disease affecting the central somatosensory system.1 The pain may be spontaneous, occurring either constantly or intermittently, or evoked in response to external stimuli.1 It may develop immediately after a stroke, or years later.2–5 To date, the largest prospective study, which enrolled 15 754 participants with ischemic stroke from 35 countries, found that 2.7% of patients developed CPSP at 1 year after stroke.6 Because CPSP case definition is complex,1 however, its reported prevalence is variable, and dependent on the site of lesion: 1 study, for instance, found that 25% of patients with brain stem infarcts developed CPSP within 6 months.1 Individuals with CPSP commonly experience sensory abnormalities, including increased tactile and thermal sensitivities, which impair their quality of life.2–5 The underlying mechanisms of CPSP are poorly understood,1 contributing to challenges in its management.

There are several pharmacological and nonpharmacological therapies available for patients with CPSP; few systematic
reviews have, however, summarized their effectiveness and safety.\textsuperscript{10–12} The available reviews suffer from important limitations, including the following: (1) limited strategies to identify relevant studies, including using few search terms, omitting major literature databases, and excluding non-English language studies, (2) limited safeguards against misleading results, including failure to conduct study selection, risk of bias assessment, and data extraction in duplicate, or (3) focusing on specific types of therapies, that is, either pharmacological or nonpharmacological. As well, none of the reviews evaluated treatment effects on patient-important outcomes beyond pain and adverse events, quantitatively synthesized results using meta-analytic techniques, or used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate certainty in the evidence.\textsuperscript{14}

We conducted a systematic review that addresses the limitations of previous reviews to inform evidence-based management of CPSP.

### Methods

#### Standardized Reporting

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of randomized controlled trials.\textsuperscript{15}

#### Protocol Registration

We registered our protocol with PROSPERO (registration number: CRD42014007189).

#### Literature Search

We searched for relevant studies, in any language, by tailored searches of AMED, CENTRAL, CINAHL, DARE, EMBASE, HealthSTAR, MEDLINE, and PsychINFO, from the inception of each database through December, 2013. An experienced academic librarian developed the search strategy for each electronic database (search strategy for MEDLINE are available in the online-only Data Supplement).

#### Eligibility Criteria

Eligible trials (1) enrolled \( \geq 10 \) patients with CPSP, (2) randomly assigned them to a therapeutic intervention (pharmacological or nonpharmacological) or a control arm, and (3) collected outcome data \( \geq 14 \) days after treatment. If a study enrolled a mixed clinical population, we followed a systematic approach (Figure I in the online-only Data Supplement) to determine its eligibility. Ultimately, we included such studies if they met the above criteria, and if (1) the authors provided the results separately for the participants with CPSP; or failing that, (2) at least 80% of a study’s sample comprised participants with CPSP.

We excluded trials that enrolled \(< 10 \) patients with CPSP because of the limited information that we would gain from such studies, and we excluded trials with \(< 2\)-week follow-up as patients with chronic pain will have little interest in short-acting treatment effects.\textsuperscript{16}

#### Study Selection

Teams of reviewers worked independently and in duplicate to determine eligibility status of all identified citations, first by screening the titles and abstracts, then by reviewing the full texts of all potential eligible articles. Reviewers resolved any disagreements by discussion, or with the help of an adjudicator. We recruited reviewers proficient in the relevant languages to review the full texts of all non-English studies. At this stage, we measured chance-independent agreement (\( \kappa \)), which has several advantages over traditional approaches (e.g., \( \kappa \)), including less vulnerability to unequal distributions of results—and interpreted results using established criteria.\textsuperscript{17} We used an online systematic review software application (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net/) to facilitate screening.

#### Data Extraction

Reviewers used a pilot-tested, standardized form to extract information from each eligible study, including participant demographics, treatment details, study methodology, and outcome data as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). Specifically, we collected outcome data, when available, across the following IMMPACT-recommended patient-important domains: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of global improvement and satisfaction with treatment, (5) symptoms and adverse events, (6) participant disposition, (7) role functioning, (8) interpersonal functioning, and (9) sleep and fatigue.\textsuperscript{18,19} Reviewers resolved any disagreements by discussion, or with the help of an adjudicator.

#### Risk of Bias Assessment

Reviewers assessed risk of bias for each eligible study using a modified Cochrane risk of bias instrument that includes response options of definitely or probably yes—assigned a low risk of bias—or definitely or probably no—assigned a high risk of bias—an approach that we have previously validated.\textsuperscript{20} Specifically, we evaluated random sequence generation, allocation concealment, blinding of participants and study personnel, and incomplete outcome data.

#### Meta-Analyses

When possible, we conducted meta-analyses using random-effects models that are conservative in that they consider both within- and between-study variability. We used the means and associated SDs of the scores from the longest follow-up time point in each study for our pooled analyses. If a study only reported a median score and a corresponding interquartile range, we assumed the mean score to be equal to the median, and calculated the SD to be equal to the interquartile range divided by 1.35.\textsuperscript{21} If investigators used \( > 1 \) instrument within a trial to measure the same construct, we chose a single measure as guided by the following prioritization, in descending order of importance: (1) most commonly used instrument, (2) instrument with the strongest evidence of validity, or (3) instrument with the most precise estimation of effect. In our analyses, we treated data from crossover trials as if they were from parallel trials.\textsuperscript{22}

#### Facilitating Interpretation of Results

For studies that provided binary outcome measures, we calculated relative risks and the associated 95% confidence intervals (CIs) to form relative effectiveness of treatments. For any pooled comparisons that suggested a statistically significant treatment effect, we planned to generate associated measures of absolute effect, that is, risk differences and numbers needed to treat.

When pooling continuous outcomes in which studies used the same instrument, we planned to calculate the weighted mean difference, which maintains the original unit of measurement and represents the average difference between groups. For trials that used different continuous outcome measures that addressed the same construct, we converted all instruments to the most commonly used outcome measure among studies, then pooled results using the weighted mean difference.\textsuperscript{22} For any pooled comparisons that suggested a statistically significant treatment effect, we planned to calculate the proportion of participants who benefited, that is, demonstrated improvement greater than or equal to the minimally important difference in each trial, then aggregate the results across all studies, and generate measures of relative and absolute treatment effects. For studies that reported effects of therapies on reducing pain, we also planned to use thresholds of \( \geq 20\% \), \( \geq 30\% \), and \( \geq 50\% \) improvement from baseline to optimize interpretation of treatment effects.\textsuperscript{19}
Assessment of Heterogeneity and Subgroup Analyses

For each pooled analysis, we examined heterogeneity using both the \( \chi^2 \) test and the \( I^2 \) statistic, which represents the percentage of variability that is because of true differences between studies (heterogeneity) rather than sampling error (chance).

We generated six a priori hypotheses to explain variability between studies: (1) interventions will show larger effects in trials that excluded participants in receipt of disability benefits or involved in litigation versus trials that included such participants; (2) interventions will show smaller effects among trials with longer follow-up times versus trials with shorter follow-up times; (3) interventions will show smaller effects among trials enrolling participants with psychiatric comorbidities versus trials that do not; (4) interventions will show smaller effects among trials enrolling participants with longer duration of CPSP before therapy versus trials that enroll participants with shorter duration of CPSP; (5) interventions will show larger effects in trials testing them at higher doses versus trials testing them at lower doses; and (6) interventions will show larger effects in trials with greater risk of bias versus trials with lower risk of bias. We planned to conduct this last subgroup analysis on a risk of bias component-by-component basis, only if there was considerable variability within the risk of bias component. We planned to conduct tests of interaction to establish if the effect size from the subgroups differed significantly from each other. We did not conduct subgroup analyses if there were <3 studies in a given subgroup.

Certainty in Treatment Estimates

We used the GRADE approach to categorize certainty in effect estimates for all reported outcomes as high, moderate, low, or very low. Using this approach, randomized controlled trials begin as high certainty but can be rated down because of (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. For any pooled comparisons that suggested a statistically significant treatment effect, we planned to use recent approaches to address missing participant data for binary and continuous outcomes. When plausible worst-case scenarios reversed treatment effects, we planned to rate down for risk of bias. We presented our results in GRADE evidence profiles.

Analytic Software

We conducted meta-analyses using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We rated our certainty in effect estimates and created GRADE evidence profiles using GRADEproGDT (http://www.guidelinedevelopment.org/).

Results

We identified 5015 unique records, of which we retrieved 324 in full text (Figure 1). After reviewing the full texts, we deemed 8 English language studies that enrolled 459 patients with CPSP eligible for our review (Table 1). There was almost perfect agreement (\( \kappa =0.82 \)) between reviewers at the full-text review stage. All trials evaluated treatment effects on pain, and none reported effects on physical functioning, role functioning, or interpersonal functioning (Figure 2). The longest follow-up among eligible studies ranged from 2 to 12 weeks. No study reported the number of participants that were receiving disability benefits or were involved in litigation during the study period. One study reported no difference in the number of participants (in the pregabalin and placebo groups) who presented with psychiatric comorbidities, specifically depression and insomnia. Figure 3 portrays the risk of bias assessment.

Figure 1. Study flow chart.

Effects of Pharmacotherapy on Patient-Important Outcomes

Anticonvulsants

Very low certainty evidence from 4 trials (Table 2), which enrolled a total of 307 participants, showed that, when compared with placebo, anticonvulsants did not significantly reduce pain intensity (weighted mean difference on an 11-step scale, \(-0.75; 95\% \text{ CI}, -1.71 \text{ to } 0.21; \, I^2=69\% \); Figure 4A), or increase adverse events (relative risk, 1.61; 95% CI, 0.90–2.88; \( I^2=80\% \); Figure 4B). Because of the small number of studies in each meta-analysis, and in line with our a priori criteria, we did not conduct our prespecified subgroup analyses to explain inconsistency in results.

Low certainty evidence from 3 studies evaluated the effects of anticonvulsants on emotional functioning, most commonly in context of managing depression. None reported a significant effect; variability in the presentation of the data precluded statistical pooling. Low certainty evidence from 1 study found that pregabalin (versus placebo) did not affect patient-reported global improvement, but did improve sleep (difference between least square means, \(-4.2; 95\% \text{ CI}, -8.4 \text{ to } 0.0; \, P=0.049 \)); Table 2).

Tricyclic Antidepressants

Low certainty evidence (Table I in the online-only Data Supplement) from 1 trial of 15 participants reported that, when compared with placebo, amitriptyline significantly reduced pain intensity during the last (fourth) week of treatment, although our reanalysis of the data did not find a significant effect. The authors also reported that amitriptyline did not affect depressive symptoms, and was associated with significantly more adverse events than placebo (relative risk, 2.00; 95% CI, 1.15–3.49).

Opioid Antagonists

Low certainty evidence (Table II in the online-only Data Supplement) from 1 trial of 20 participants reported that naloxone had no effect on pain when compared with placebo.
Table 1. Characteristics of Eligible Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country of Study</th>
<th>Study Design</th>
<th>Treatments</th>
<th>Frequency and Duration of Treatment</th>
<th>No. of Total CPSP Randomized</th>
<th>Age of CPSP Participants</th>
<th>Sex of CPSP Participants</th>
<th>Duration of CPSP</th>
<th>Participant Disposition/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leijon et al</td>
<td>Sweden</td>
<td>Crossover</td>
<td>Amitriptyline (75 mg, final dose)</td>
<td>4 wk (7-d washout)</td>
<td>15</td>
<td>Mean, 66 yr; Range, 53–74</td>
<td>Female, 3; Male, 12</td>
<td>Mean, 54 mo; Range, 11–154</td>
<td>One participant discontinued intervention because of interaction with existing medication</td>
</tr>
<tr>
<td>Bainton et al</td>
<td>United Kingdom</td>
<td>Crossover</td>
<td>Naloxone (8 mg)</td>
<td>One-time treatment (2- to 3-wk washout)</td>
<td>20</td>
<td>Mean, 61.1 yr; Range, 45–74</td>
<td>Female, 13; Male, 7</td>
<td>Mean, 7.5 yr; Range, 1–20</td>
<td>Three participants withdrew because of adverse events</td>
</tr>
<tr>
<td>Jiang et al</td>
<td>China</td>
<td>Parallel</td>
<td>Electroacupuncture</td>
<td>60</td>
<td>NR</td>
<td>Electroacupuncture: Female, 10; Male, 20 Carbamazepine</td>
<td>Female, 9</td>
<td>Electroacupuncture: Mean, 3.6 mo; Control: Mean, 3.8 mo</td>
<td></td>
</tr>
<tr>
<td>Vestergaard et al</td>
<td>Denmark</td>
<td>Crossover</td>
<td>Lamotrigine (200 mg, final dose)</td>
<td>8 wk (2-wk washout)</td>
<td>30</td>
<td>Median, 59 yr; Range, 37–77</td>
<td>Female, 12; Male, 18</td>
<td>Median, 2 yr; Range, 0.3–12</td>
<td>Three participants withdrew because of adverse events One participant did not complete the first treatment period, but continued the study in the second treatment period Four participants withdrew because of lack of efficacy Three participants withdrew because of protocol violations</td>
</tr>
<tr>
<td>Kim et al</td>
<td>Asia Pacific region</td>
<td>Parallel</td>
<td>Pregabalin (600 mg/d, final maximum dose)</td>
<td>12 wk (4-wk dose adjustment, 8-wk maintenance)</td>
<td>220</td>
<td>Pregabalin: Mean, 59.4 yr; SD, 9.8; Placebo: Mean, 57.1; SD, 10.2</td>
<td>Pregabalin: Female, 43; Male, 67; Placebo: Female, 39; Male, 70</td>
<td>Pregabalin: Mean, 2.2 yr; Range, 0.1–17.7; Placebo: Mean, 2.5; Range, 0.2–14.1</td>
<td>One participant did not receive intervention Nine participants withdrew because of reasons related to the study drug Twenty-seven participants withdrew because of reasons not related to the study drug</td>
</tr>
<tr>
<td>Jungehulsing et al</td>
<td>Germany</td>
<td>Crossover</td>
<td>Levetiracetam (3000 mg/d, maximum dose)</td>
<td>8 wk (2-wk washout)</td>
<td>42</td>
<td>Median, 61.5 yr; Range, 40–76</td>
<td>Female, 16; Male, 26</td>
<td>Median, 4 yr; Range, 0.4–11</td>
<td>Three participants withdrew because of protocol violations Three participants withdrew consent Three participants withdrew because of adverse events</td>
</tr>
<tr>
<td>Hosomi et al</td>
<td>Japan</td>
<td>Crossover</td>
<td>Repetitive transcranial magnetic stimulation (5 Hz)</td>
<td>Once daily, 10 d (at least 17-d washout)</td>
<td>NR (see notes)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Seventy participants randomized (unclear how many with CPSP) Two participants did not receive intervention (unclear how many with CPSP) Four participants did not provide data (unclear how many with CPSP) Three participants discontinued intervention (unclear how many with CPSP) Sody-four participants included in authors’ intention-to-treat analysis set; 52 with CPSP</td>
</tr>
<tr>
<td>Cho et al</td>
<td>Republic of Korea</td>
<td>Parallel</td>
<td>Acupuncture (0.05 mL)</td>
<td>Twice weekly, 3 wk</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>One participant withdrew because of adverse event Three participants discharged/left hospital before follow-up</td>
</tr>
</tbody>
</table>

CPSP indicates central poststroke pain; and NR, not reported.
Effects of Nonpharmacotherapy on Patient-Important Outcomes

Repetitive Transcranial Magnetic Stimulation

Low certainty evidence (Table III in the online-only Data Supplement) from 1 trial (n=52) of repetitive transcranial magnetic stimulation versus sham stimulation found no significant differences in adverse events, depressive symptoms, or patient-reported global improvement.

Acupuncture

Low certainty evidence (Table IV in the online-only Data Supplement) from 1 study (n=20) reported a significant effect of acupuncture over saline acupuncture for pain reduction (median 100-point Visual Analogue Scale score decrease: 36.50 versus 11.50; \( P=0.009 \)). Very low certainty evidence (Table V in the online-only Data Supplement) from another study (n=60) found no significant effect of electroacupuncture versus carbamazepine on a composite measure of joint pain, dysfunction, and tenderness.

Discussion

Our systematic review found low or very low certainty evidence suggesting that anticonvulsants, tricyclic antidepressants, opioid antagonists, and electroacupuncture have no effect on reducing pain associated with CPSP. Low certainty evidence suggests that acupuncture may reduce pain, anticonvulsants may improve sleep, repetitive transcranial magnetic stimulation has no effect on depressive symptoms or patient-reported global improvement, and tricyclic antidepressants do not improve depressive symptoms and produce significantly more side effects.

Strengths and Limitations

Our review has several strengths. First, we reviewed all nonpharmacological and pharmacological therapies for managing patients with CPSP. Second, we explored a wider range of literature databases than previous reviews, and searched for eligible studies in all languages. Third, teams of reviewers, who worked independently and in duplicate, made all subjective decisions, including study selection, risk of bias assessment, and data extraction. Fourth, we followed a systematic approach, which included working with expert clinicians and contacting study authors, to assess the eligibility of studies that enrolled mixed clinical populations. Fifth, we collected all patient-important outcomes across IMMPACT-recommended core outcome domains. Finally, we used the GRADE approach to evaluate our certainty in the evidence, and presented our findings with GRADE evidence profiles. Our findings, however, are limited by shortcomings of the primary studies that were eligible for our review. This led to our ratings of low or very low certainty for all treatment effects.

Implications

Our findings are inconsistent with clinical practice guidelines by 3 major professional groups—the International Association...
for the Study of Pain Neuropathic Pain Special Interest Group, the European Federation of Neurological Societies, and the Canadian Pain Society—all of whom recommend tricyclic antidepressants as first-line therapy for managing patients with CPSP.45–47 These recommendations are because of 1 trial of 15 participants that concluded that amitriptyline significantly reduced pain intensity versus placebo after 4 weeks of treatment.37

Follow-up scores on the 10-step scale for pain,
however, were very similar for amitriptyline (mean, 4.2; SD, 1.6) and placebo (mean, 5.3; SD, 2.0), and our reanalysis of the data found no significant effect (P=0.11).

The European Federation of Neurological Societies and Canadian Pain Society also recommend anticonvulsants as first-line pharmacological treatment for CPSP.45,46 Our review found no evidence that they reduce pain. The European Federation of Neurological Societies, however, formulated its recommendations on the success of anticonvulsants in patients with other chronic neuropathic pain conditions. This assumes that treatment responses are consistent across chronic neuropathic pain conditions. A recent systematic review provides some support for this assumption,48 and we are further validating this hypothesis in an ongoing network meta-analysis of all therapies for all chronic neuropathic pain conditions.49

In the face of only low, or in most cases very low, certainty evidence, with initial evidence providing minimal or no support for benefit, management of CPSP remains extremely challenging. Investigators should mount large, multicenter, randomized trials using standardized instruments with known, satisfactory measurement properties to assess patient-important outcomes, including function. Such trials should include longer observation, and should implement strategies to reduce risk of bias, including generating the randomization sequence, concealing treatment allocation, and implementing strategies to minimize loss to follow-up. Given results thus far, such trials should evaluate both existing and innovative therapeutic options.

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