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## Search Strategy

**Identification**

Cochrane, Medline, CINAHL, Scopus, Clinicaltrials.gov, and Embase were searched

**Screening**

Titles and Abstracts of each study were reviewed. Bibliographies of major reviews or meta-analyses were searched for additional relevant articles

**Eligibility**

Excluded articles: Non-English, Commentaries, Case-Studies, Narratives, Book Chapters, Editorials, Non-systematic Reviews (scoping reviews), and conference abstracts.

Included Articles: English language articles, RCTs, observational studies and systematic reviews/meta-analysis. Relevant guidelines addressing the topic were also included.

**Included**

A total of 6 Articles and 5 Guidelines

Cochrane, clinicaltrials.gov, Medline, EMBASE, CINAHL and Scopus were searched using the keywords: Stroke AND Pain AND Central Nervous System. Titles and abstract of each article were reviewed for relevance. The same databases were searched to identify paediatric related evidence using the additional keywords: “(paediatric OR paediatrics OR youth OR child OR children OR young)”. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 6 articles and 5 guidelines were included and were separated into categories designed to answer specific questions.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 June. P.p. 35-36 | In patients with central post-stroke pain unresponsive to standard treatment, and where clinician and patient are aware of potential side effects, amitriptyline (titrated to a dose of 75 mg) may be considered. (B)  
If amitriptyline is ineffective, or contraindicated, lamotrigine or carbamazepine are alternatives although the high incidence of side effects should be recognized. (B) |
| Management of Stroke Rehabilitation Working Group. VA/DoD clinical practice guideline for the management of stroke rehabilitation. Washington (DC): Veterans Health Administration, Department of Defense; 2010. P.30 | Recommend balancing the benefits of pain control with possible adverse effects of medications on an individual’s ability to participate in and benefit from rehabilitation. [I]  
When practical, utilize a behavioral health provider to address psychological aspects of pain and to improve adherence to the pain treatment plan. [C]  
When appropriate, recommend use of non-pharmacologic modalities for pain control such as biofeedback, massage, imaging therapy, and physical therapy. [C]  
Recommend that the clinician tailor the pain treatment to the type of pain. [C]  
Neuropathic pain can respond to agents that reduce the activity of abnormally excitable peripheral or central neurons. (No level of recommendation)  
Opioids and other medications that can impair cognition should be used with caution. (No level of recommendation)  
Recommend use of lower doses of centrally acting analgesics, which may cause confusion and deterioration of cognitive performance and interfere with the rehabilitation process. [C] |
| Clinical Guidelines for Stroke Management 2010. Melbourne (Australia): National Stroke Foundation; 2010 Sep. p. 102 | 7.6.2 People with stroke found to have unresolved pain CPSP should receive a trial of: tricyclic antidepressants, e.g., amitriptyline first, followed by other tricyclic agents or venlafaxine. (B) anticonvulsants e.g. carbamazepine (C)  
Any patient whose CSPS is not controlled within the a few weeks should be referred to a specialist pain management team. (GPP) |
Recommend use of lower doses of centrally acting analgesics, which may cause confusion and deterioration of cognitive performance and interfere with the rehabilitation process. (No level of recommendation) |
### SUMMARY OF CPSP INTERVENTIONS AND ASSOCIATED STRENGTH OF EVIDENCE FROM SELECTED GUIDELINE DOCUMENTS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SIGN 118 2010</th>
<th>NSF 2010</th>
<th>VA/DoD 2010</th>
<th>AHA/ASA 2005</th>
<th>RCP 2012 <em>NEW</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants e.g. amitriptyline</td>
<td>B</td>
<td>B</td>
<td>Not included</td>
<td>Not included</td>
<td>Recommended (amitriptyline)</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors e.g. venlafaxine</td>
<td>Not included</td>
<td>C</td>
<td>Not included</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Anticonvulsants e.g. lamotrigine, carbamazepine, levetiracetam</td>
<td>B</td>
<td>C</td>
<td>Not included</td>
<td>Not included</td>
<td>Recommended (gabapentin, pregabalin)</td>
</tr>
<tr>
<td>Behavioral approach to manage psychosocial aspects of pain</td>
<td>Not included</td>
<td>Not included</td>
<td>C</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Non-pharmacological modalities e.g. biofeedback, massage, imaging therapy</td>
<td>Not included</td>
<td>Not included</td>
<td>C</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Treatment should be specific to pain type</td>
<td>Not included</td>
<td>Not included</td>
<td>C</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Use lower doses of centrally acting analgesics to avoid confusion and cognitive performance</td>
<td>Not included</td>
<td>Not included</td>
<td>C</td>
<td>No level of recommendation</td>
<td>Not included</td>
</tr>
<tr>
<td>Referral to specialist for unresolved pain issues</td>
<td>Not included</td>
<td>Not included</td>
<td>GPP</td>
<td>Not included</td>
<td>Not included</td>
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</table>

GPP - Good practice point
## 2.1 Evidence Table

### Pharmacological Treatment of CPSP

<table>
<thead>
<tr>
<th>Study/Type</th>
<th>Quality Rating</th>
<th>Sample Description</th>
<th>Method</th>
<th>Outcomes</th>
<th>Key Findings and Recommendations</th>
</tr>
</thead>
</table>
| Jungehulsing et al. 2013 Germany RCT | CA: ✔️ Blinding: Assessor ✔️ Patient ✔️ ITT: ✔️ | 42 subjects with a diagnosis of CPSP of duration ≥3 months from a stroke with a score of ≥4 on a numeric Likert scale for pain intensity (range 0-10). | Subjects were randomized to 1) a levetiracetam (LEV; maximum dose=3000 mg) group, or 2) a control (placebo) group. Trial duration per subject was 24 weeks which consisted of a 4-week baseline period, followed by two 8-week treatment periods each followed by a 2-week washout period. | **Primary Outcome:** Reduction in spontaneous and/or evoked pain by ≥2 points on the numeric Likert scale for pain intensity (range 0-10). | For the treatment group, mean LEV dose was 2130±830 mg/day during the first and 2782±524 mg/day during the second treatment period.  
Compared to controls, LEV did not show an improvement in spontaneous or evoked pain (p>0.05); further, no significant improvements were noted in MPQ, BDI, or SF-12 (p>0.05) for either group over time.  
Side-effects including tiredness, pain increase, dizziness, pruritus, nausea, and headache were common in the LEV group compared to controls (p<0.05) but only in the first treatment period. |
| Kim et al. 2011 South Korea RCT | CA: ✔️ Blinding: Assessor ✔️ Patient ✔️ ITT: ✔️ | 220 patients with a diagnosis of CPSP of duration of ≥3 months from a stroke that had occurred ≥4 months previously. Score of ≥40 mm on the Short Form McGill Pain Questionnaire Visual Analogue Scale (SF-MPS VAS) | Patients were randomized to receive either 150-600 mg of pregabalin (n=110) or placebo (n=109) over 13 weeks (2 week screening/washout, 4-week dose adjustment, 8 week maintenance 1-week taper phase). | **Primary Outcome:** Mean pain score on the Daily Pain Rating Scale over the last 7 days on study drug up to week 12 or early termination visit.  
**Secondary Outcome:** Daily Sleep Interference Scale (DSIS), Neuropathic Pain symptom Inventory (NPSI), Hospital Anxiety & Depression Scale (HADS), EQ-5d, Patient Global Impression of Change (PGIC) Clinical Impression of Change (CGIC)  
Outcomes were assessed at baseline and at week 12. | The mean pain score change between groups was -0.2, 95% CI -0.7 to 0.4, p=0.578, favoring the pregabalin group.  
Mean difference & 95% CI in means between the 2 groups at the end of treatment was:  
SF-MPS VAS: -1.0 (-7.0 to 5.00), p=0.741  
NPSI: -2.8 (-6.5 to 0.90), p=0.138  
HADS-A: -1.0 (-1.8 to -0.2), p=0.15  
HADS –D: 0.2 (-0.6 to 1.0), p=0.60  
EQ-5D (utility):0.0 (-0.1 to 0.1), p=0.566  
PGIC: -0.2 (-0.5 to 0.1), p=0.144  
CGIC: -0.3 (-0.6 to 0.0), p=0.049  
Drop outs: Pregabalin group n=17, Placebo group n=19 |
<table>
<thead>
<tr>
<th>Study/Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Vranken et al. 2011</td>
<td></td>
<td>48 patients (12 with stroke) suffering from severe neuropathic pain, visual analog scale score ≥6 caused by lesion or dysfunction in the central nervous system, with pain persisting ≥6 months.</td>
<td>Patients were randomized to receive escalating doses of either duloxetine (60 and 120mg/day) or matching placebo capsules for 8 weeks. In both groups, patients started with 1 capsule per day. If pain relief was insufficient, patients were titrated to a higher dose.</td>
<td>Primary outcome: Pain relief assessed using a 10-point VAS. &lt;br&gt; Secondary outcomes: Patient Disability Index (PDI), EQ-5D, SF-36 and the Patients Global Impressions of Change (PGIC). &lt;br&gt; For the primary outcome, assessments were conducted weekly. Secondary outcomes were assessed at baseline and at the end of treatment.</td>
<td>Adverse events: more frequent with pregabalin than with placebo and caused discontinuation in 9 (8.2%) of pregabalin patients versus 4 (3.7%) of placebo patients. Adverse events: Episodes of nausea/vomiting were significantly greater among patients in the treatment group (12 vs. 2, p=0.003). There were no other significant differences between groups (dizziness, confusion, headache, dry mouth, somnolence, constipation). Drop outs: treatment group n=3, control group n=1.</td>
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<tr>
<td>The Netherlands RCT</td>
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<td>40 patients with central pain (19 with stroke) suffering from severe neuropathic pain, visual analog scale score ≥6 caused by lesion or dysfunction in the central nervous system, with pain persisting ≥6 months.</td>
<td>Patients were randomized to receive a 4-week course of treatment with escalating doses of pregabalin (max 600 mg/day) or placebo.</td>
<td>Primary outcome: Pain relief, measured on a 10-point VAS and was based on an average of 3 measurements scored within the last 24 hours of treatment. Secondary outcomes: Pain Disability Index (PDI), EQ-5D and SF-36. For the primary outcome, assessments were conducted weekly.</td>
<td>Mean ± sd scores at baseline and end of treatment for treatment and control groups: &lt;br&gt; VAS pain: 7.1±0.8 to 5.0±2.0 vs. 7.2±0.8 to 6.1±1.7, p=0.05 (no difference in treatment effect was observed for patients with spinal cord injury vs. stroke). &lt;br&gt; PDI: 33±11.2 to 28±12.2 vs. 38±14.3 to 36±13.3, p=0.06. &lt;br&gt; EQ-5D VAS: 63±18 to 59±21 vs. 56±18 to 53±17, p=0.70 &lt;br&gt; SF-36 (pain):33±13 to 45±17 vs. 31±12 to 35±14, p=0.035. Drop outs: treatment group n=3, control group n=1.</td>
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<td>Serpell et al. 2002 UK RCT</td>
<td>CA: ☑️</td>
<td>307 patients with a wide range of neuropathic pain syndromes (9 with post stroke pain) based on clinical examination and history. In addition, all subjects were required to have at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia</td>
<td>Patients were randomized to receive either gabapentin (n=153) or placebo (n=152) initiated at 900 for 8-weeks following a run-in period. Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2,400 mg/day if required by the end of week 5.</td>
<td>Secondary outcomes were assessed at baseline and at the end of treatment.</td>
<td>Adverse events: incidence was similar between groups (36 vs.35, p=ns) Drop outs: treatment group n=4, control group n=3. Patients in the treatment group experienced a significantly greater reduction in pain over the study period (mean reduction of 21% vs. 14%, p=0.048). SF-MPQ: Greater improvement in the scores of patients in the treatment group (p&lt;0.05) PGIC: A greater % of patients in the treatment group reported their pain was improved (34% vs. 16%, p=0.03) CGIC: A greater % of investigators in the treatment group reported their patients’ pain was improved (38% vs. 18%, p=0.01) SF-36: Greater improvement in the scores of patients in the treatment group (p&lt;0.05) Adverse events: treatment n=117 incidents, placebo n=103 incidence. 57.5% (treatment) vs. 36.8% (control) were likely attributable to treatment Drop outs: treatment group n=41, control group n=32</td>
</tr>
<tr>
<td>Vestergaard et al. 2001 Denmark RCT</td>
<td>CA: ☑️</td>
<td>30 consecutive patients with CPSP from two centers with pain ≥4 (on a 0-10 scale), persisting for ≥3 months</td>
<td>Patients were entered into a double-blind, placebo-controlled cross-over study evaluating lamotrigine. There were two 8-week treatment periods separated by 2 weeks of wash-out. Dosage was initiated at 25 mg/d and increased every 2 weeks, to 50, 100 and ending at 200 mg/d.</td>
<td>Primary outcome: Median value of the mean daily pain score during the last week of treatment while treated with 200 mg/d lamotrigine. Secondary outcomes: Median pain scores while on lamotrigine 25 mg/d, 50 mg/d, and 100 mg/d; a global pain score; assessment of evoked pain; areas of spontaneous pain; and allodynia/dysesthesia</td>
<td>Median pain score decrease from 7 to 5 among patients receiving 200 mg/d lamotrigine compared with a pain score that was unchanged at 7 (p=0.01). There were no significant differences between groups at any other level of lamotrigine doses. Global pain rating (physical): The median score was lower among patients in the treatment group (p=0.02). Median pain evoked pain scores at end of treatment for patients in the treatment and placebo groups: Von Frey hairs: 4 vs. 5, p=0.13 Toothbrush: 4 vs. 5, p=0.23 Acetone drop: 1 vs. 2, p=0.01 Adverse events: treatment group n=17, placebo</td>
</tr>
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<td>group n=18. Drop outs: treatment first arm n=7, placebo first arm n=1</td>
</tr>
</tbody>
</table>

**Glossary**

- **RCT** = Randomized Controlled Trial
- **N/A** = Not Applicable
- **CA** = Concealed Allocation
- **ITT** = Intention to treat
- **VAS** = Visual Analogue Scale
- **CPSP** = Central Post Stroke Pain
- **OR** = Odds Ratio
- **IQR** = Interquartile Range
- **SMD** = Standardized Mean Difference
- **CI** = Confidence Interval
**Reference List**


