CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Stroke Rehabilitation Evidence Tables

Rehabilitation to Improve Central Pain

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on Behalf of the Canadian Stroke Best Practice Recommendations
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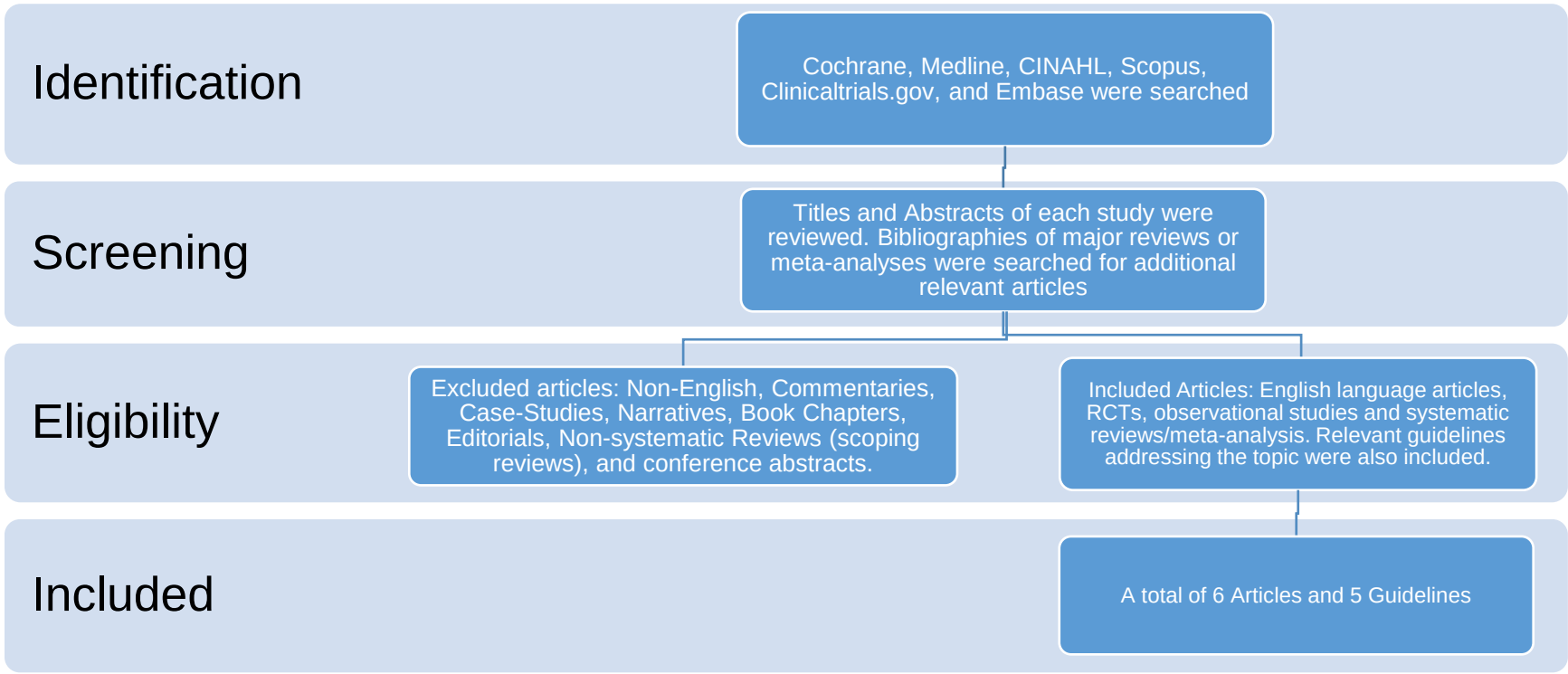
Search Strategy



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.

Published Guidelines

Guideline	Recommendations
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)
Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, Katz RC, Lamberty K, Reker D. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke, 2005;36:e117	Control pain that interferes with therapy. (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. (No level of recommendation)

Guideline	Recommendations
Intercollegiate Stroke Working Party. *National clinical guideline for stroke,* 4th edition. London: Royal College of Physicians, 2012.	**Neuropathic pain (central post-stroke pain) (6.19.3.1)** A Every patient whose pain has been diagnosed by someone with appropriate expertise in neuropathic pain should be given oral amitriptyline, gabapentin or pregabalin as firstline treatment.

SUMMARY OF CPSP INTERVENTIONS AND ASSOCIATED STRENGTH OF EVIDENCE FROM SELECTED GUIDELINE DOCUMENTS

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

GPP - Good practice point

2.1 Evidence Table

Pharmacological Treatment of CPSP

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
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). **Secondary Outcome:** McGill Pain Questionnaire (MPQ), revised Beck Depression Inventory (BDI), Short Form-12 Health Survey (SF-12). Outcomes were assessed at baseline, and visits 4 and 7.	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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.
Vranken et al. 2011 The Netherlands RCT	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☑	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.	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.	**Primary outcome:** Pain relief assessed using a 10-point VAS. **Secondary outcomes:** Patient Disability Index (PDI), EQ-5D, SF-36 and the Patients Global Impressions of Change (PGIC). For the primary outcome, assessments were conducted weekly. Secondary outcomes were assessed at baseline and at the end of treatment.	Mean ± sd scores at baseline and end of treatment for treatment and control groups: 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). PDI: 33±11.2 to 28±12.2 vs. 38±14.3 to 36±13.3, p=0.06. EQ-5D VAS: 63±18 to 59±21 vs. 56±18 to 53±17, p=0.70 SF-36 (pain):33±13 to 45±17 vs. 31±12 to 35±14, p=0.035. 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.
Vranken et al. 2008 The Netherlands RCT	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☑	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.	Patients were randomized to receive a 4-week course of treatment with escalating doses of pregabalin (max 600 mg/day) or placebo.	**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.	Mean ± sd scores at baseline and end of treatment for treatment and control groups: VAS: 7.6±0.8 to 5.1±2.9 vs. 7.4±1.0 to 7.3±2.0, p=0.01 PDI: 39.9±13.2 to 35.7±14.9 vs. 41.7±14.8 to 43.3±14.7, p=0.111 EQ-5D VAS: 60.4±17.0 to 65.7±17.0 vs. 50.1±19.7 to 37.8±18.5, p<0.001 SF-36 (pain): 30.7±16.1 to 46.3±20.2 vs. 26.2±15.4 to 27.8±19.4, p=0.009

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Secondary outcomes were assessed at baseline and at the end of treatment.	Adverse events: incidence was similar between groups (36 vs.35, p=ns) Drop outs: treatment group n=4, control group n=3.
Serpell et al. 2002 UK RCT	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☒	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	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.	**Primary outcome:** Changed in average daily pain diary score (baseline versus final week) using a 0-10 point Likert scale. **Secondary outcomes:** Short-Form McGill Pain Questionnaire (SF-MPQ), Clinical Global Impression of Change (CGIC), Patient Global Impression of Change (PGIC), SF-36. Outcomes were assessed at baseline and weekly thereafter.	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<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<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
Vestergaard et al. 2001 Denmark RCT	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☑	30 consecutive patients with CPSP from two centers with pain ≥4 (on a 0-10 scale), persisting for ≥3 months	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.	**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	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					group n=18. Drop outs: treatment first arm n=7, placebo first arm n=1

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

Jungehulsing GJ, Israel H, Safar N, et al. Levetiracetam in patients with central neuropathic post-stroke pain--a randomized, double-blind, placebo-controlled trial. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* 2013;20:331-337.

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