CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Rehabilitation and Recovery following Stroke

Evidence Tables

Rehabilitation to Improve Central Post-Stroke Pain

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Rehabilitation and Recovery following Stroke Writing Group

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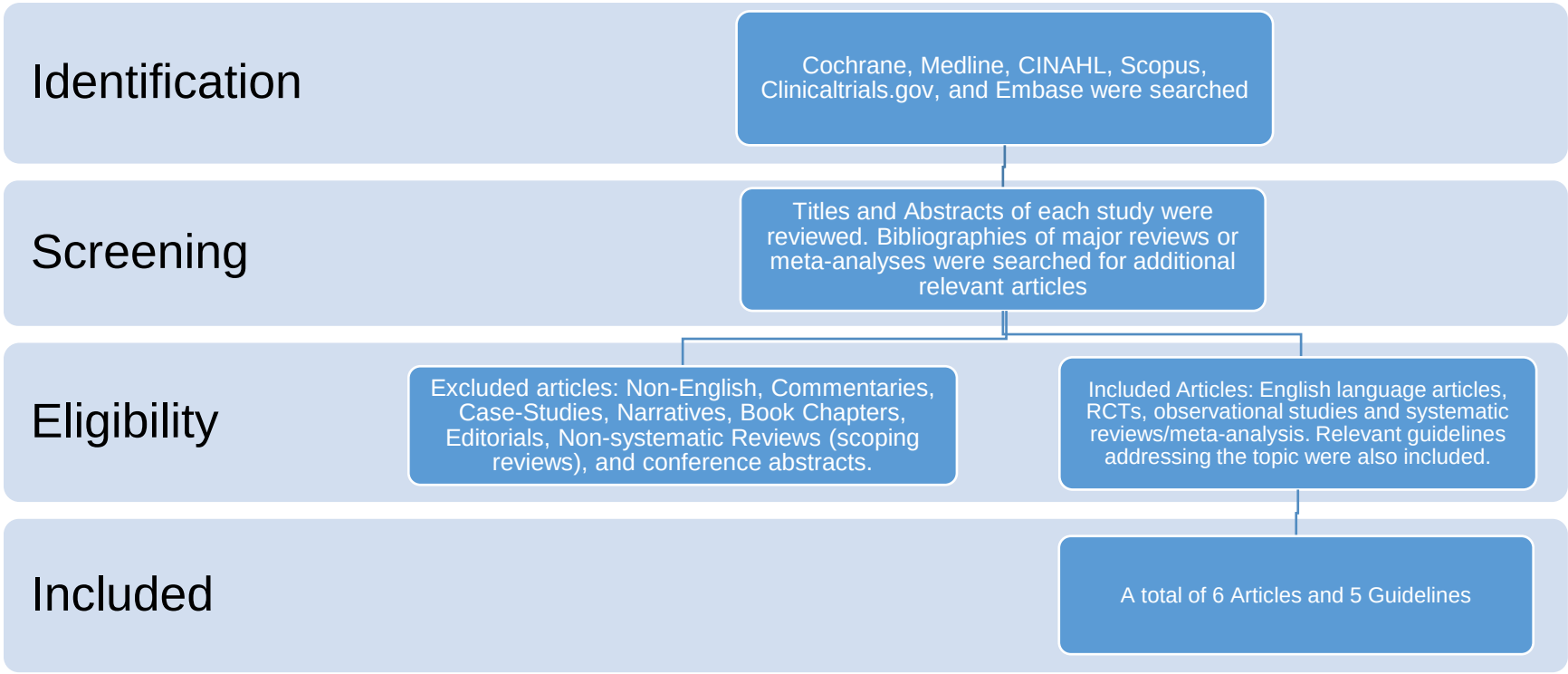
Search Strategy



Cochrane, clinicaltrials.gov, Medline, EMBASE, CINAHL and Scopus were searched using the keywords: Stroke AND Pain AND Central Nervous System OR “central post stroke pain”. Titles and abstract of each article were reviewed for relevance. 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
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. **Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;47:e98–e169**	The diagnosis of central poststroke pain should be based on established diagnostic criteria after other causes of pain have been excluded. Class I; LOE C The choice of pharmacological agent for the treatment of central poststroke pain should be individualized to the patient's needs and response to therapy and any side effects. Class I; LOE C Amitriptyline and lamotrigine are reasonable first-line pharmacological treatments. Class IIa; LOE B Interprofessional pain management is probably useful in conjunction with pharmacotherapy. Class IIa; LOE C Standardized measures may be useful to monitor response to treatment. Class IIb; LOE C Pregabalin, gabapentin, carbamazepine, or phenytoin may be considered as second-line treatments. Class IIb; LOE B TENS has not been established as an effective treatment. Class III; LOE B Motor cortex stimulation might be reasonable for the treatment of intractable central poststroke pain that is not responsive to other treatments in carefully selected patients. Class IIb; LOE B Deep brain stimulation has not been established as an effective treatment. Class III; LOE B
National Clinical guidelines for stroke" 5th Edition 2016; Intercollegiate Stroke Working Party. Royal College of Physicians	**4.12.1.1 Recommendations** A People with central post-stroke pain should be initially treated with amitriptyline, gabapentin or pregabalin: – amitriptyline starting at 10 mg per day, with gradual titration as tolerated, but no higher than 75 mg per day (higher doses could be considered in consultation with a specialist pain service); – gabapentin starting at 300 mg twice daily with titration as tolerated to a maximum of 3.6 g per day; – pregabalin starting at 150 mg per day (in two divided doses; a lower starting dose may be appropriate for some people), with titration as tolerated but no higher than 600 mg per day in two divided doses. B People with central post-stroke pain who do not achieve satisfactory pain reduction with initial pharmacological treatment at the maximum tolerated dose should be considered for treatment with another drug of or in combination with the original drug: – if initial treatment was with amitriptyline switch to or combine with pregabalin; – if initial treatment was with gabapentin switch to pregabalin; – if initial treatment was with pregabalin switch to or combine with amitriptyline. C People with central post-stroke pain should be regularly reviewed including physical and psychological wellbeing, adverse effects, the impact on lifestyle, sleep, activities and participation, and the continued need for pharmacological treatment. If there is sufficient improvement, treatment should be continued and gradual reductions in the dose over time should be considered if improvement is sustained.
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. Edinburgh	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)

Guideline	Recommendations
(Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 June. P.p. 35-36	
Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T. **European federation of neurological societies. EFNS guidelines on the pharmacological treatment of neuropathic pain. 2010.** ***Eur J Neurol* 2010. Sep;17(9):1113-e88.**	Lamotrigine, TCA have a Level B rating for efficacy for CPSP.
Dworkin RH, O'connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK. **Pharmacologic management of neuropathic pain: evidence-based recommendations.** ***Pain.* 2007 Dec 5;132(3):237-51.**	Efficacy has been shown for TCAs and calcium channel α_2 -δ ligands in central poststroke

Evidence Table

Pharmacological Treatment of Central Post Stroke Pain (CPSP)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Jungehulsing et al. 2013 **Germany** **Crossover RCT**	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☑	42 patients ≥18 years, with a diagnosis of CPSP, indicated by a score of ≥4 on an 11-point Likert scale for pain intensity (0-10), of duration ≥3 months. Mean age 61.5 years, 62% were men. Median baseline pain score was 7. Median duration of pain was 4 years.	Patients 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, where patients recorded their pain intensity 4x daily, 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 the control condition, patients in the LEV group did not show an improvement in spontaneous or evoked pain (p>0.05). There were no significant improvements 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. 33 patients completed the study.
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). Mean age was 58 years, 68.5% were men.	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:** Pain, assessed using the Daily Pain Rating Scale, using the mean of scores from the last 7 days on study drug. **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) and Short-Form McGill Pain Questionnaire (SF-MPQ) Outcomes were assessed at baseline and at week 12.	Mean pain scores at baseline for patients in the intervention and control groups were 6.5 and 6.3, respectively. Mean duration of pain was >2 years, in both groups. Mean final pain scores for patients in the intervention and control groups were 4.9 and 5.0, respectively. The mean change in daily pain scores between groups was not significant (-0.2, 95% CI -0.7 to 0.4, p=0.578). At 12 weeks, there were no significant differences between groups for most of the secondary outcomes (SF-MPQ, NPSI, HAD-D, EQ-5D or PGIC). Treatment with pregabalin was associated with improvement in 2 secondary outcome measures, HADS-A (difference in means -1.0, 95% CI -1.8 to -0.2, p=0.015), and CGIC: (difference in means -0.3, 95% CI -0.6 to 0.0, p=0.049).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Dropouts: Pregabalin group n=17, Placebo group n=19 Adverse events were more frequent with pregabalin, causing discontinuation in 9 (8.2%) of 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 VAS pain scores decreased from 7.1 to 5.0 in the duloxetine group and from 7.2 to 6.1 in the placebo group. The difference between groups was borderline significant, p=0.05. Mean PDI scores improved from 33 to 28 for patients in the duloxetine group compared with a change of 38 to 36 for patients in the placebo group (p=0.06). There were no significant differences between groups in mean change of EQ-5D VAS or utility scores over the treatment period. There was significantly greater improvement in SF-36 (pain) scores for patients in the duloxetine group (33 to 45 vs.31 to 35, p=0.035). 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. Dropouts: 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. Mean age was 54.5 years, 48% were men.	Patients were randomized 1:1 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, 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.	Patients in the pregabalin group experienced a significantly greater reduction in mean pain scores from baseline (from 7.6 to 5.1 vs. 7.4 to 7.3; mean difference 2.18, 95% CI 0.57–3.80; p = 0.01) There was no significant difference between groups in improvement in mean PDI scores from baseline to post treatment (39.9 to 35.7 vs. 41.7 to 43.3, p=0.111). Patients in the placebo group experienced a deterioration of EQ-5D scores (utility and VAS), while patients in the pregabalin group experienced

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					improvement. The differences in scores between groups were significant. There were no significant differences between groups for any of the domains of the SF-36, with the exception of pain, whereby patients in the pregabalin group experienced greater improvement (30.7 to 46.3 vs. 26.2 to 27.8, p=0.009). Adverse events: incidence was similar between groups (36 vs.35) Dropouts: 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:** Change 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 Dropouts: 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. Median age was 59 years, 60% were men.	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.	**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 score decreased from 7 to 5 among patients receiving 200 mg/d lamotrigine compared with a pain score that was unchanged at 7 during the placebo phase (p=0.01). There were no significant differences between groups at any other level of lamotrigine doses. The median Global Pain Rating (physical) score was

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			Dosage was initiated at 25 mg/d and increased every 2 weeks, to 50, 100 and ending at 200 mg/d.	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	significantly lower among patients in the treatment group phase (moderate vs. strong pain, p=0.02). Median pain evoked pain scores at end of treatment for patients in the treatment and placebo phases: 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 during active treatment group was 17, compared with 18 during the placebo phase. Dropouts: treatment first arm n=7, placebo first arm n=1

Abbreviations

CA = Concealed Allocation	CI = Confidence Interval
CPSP = Central Post Stroke Pain	IQR = Interquartile Range
ITT = Intention to treat	N/A = Not Assessed
OR = Odds Ratio	RCT= Randomized Controlled Trial
VAS = Visual Analogue Scale	

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. *Euro J Neurol.* 2013;20:331-337.

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Vranken JH, Hollmann MW, van der Vegt MH, et al. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. *Pain* 2011;152:267-73.

Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008;136:150-57.

Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain* 2002;99:557-66.

Vestergaard K, Andersen G, Gottrup H, et al. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology* 2001;56:184-90.