CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Rehabilitation, Recovery and Community Participation Following Stroke

Part Two: Delivery of Stroke Rehabilitation to Optimize Functional Recovery Evidence Tables

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Central Post-Stroke Pain

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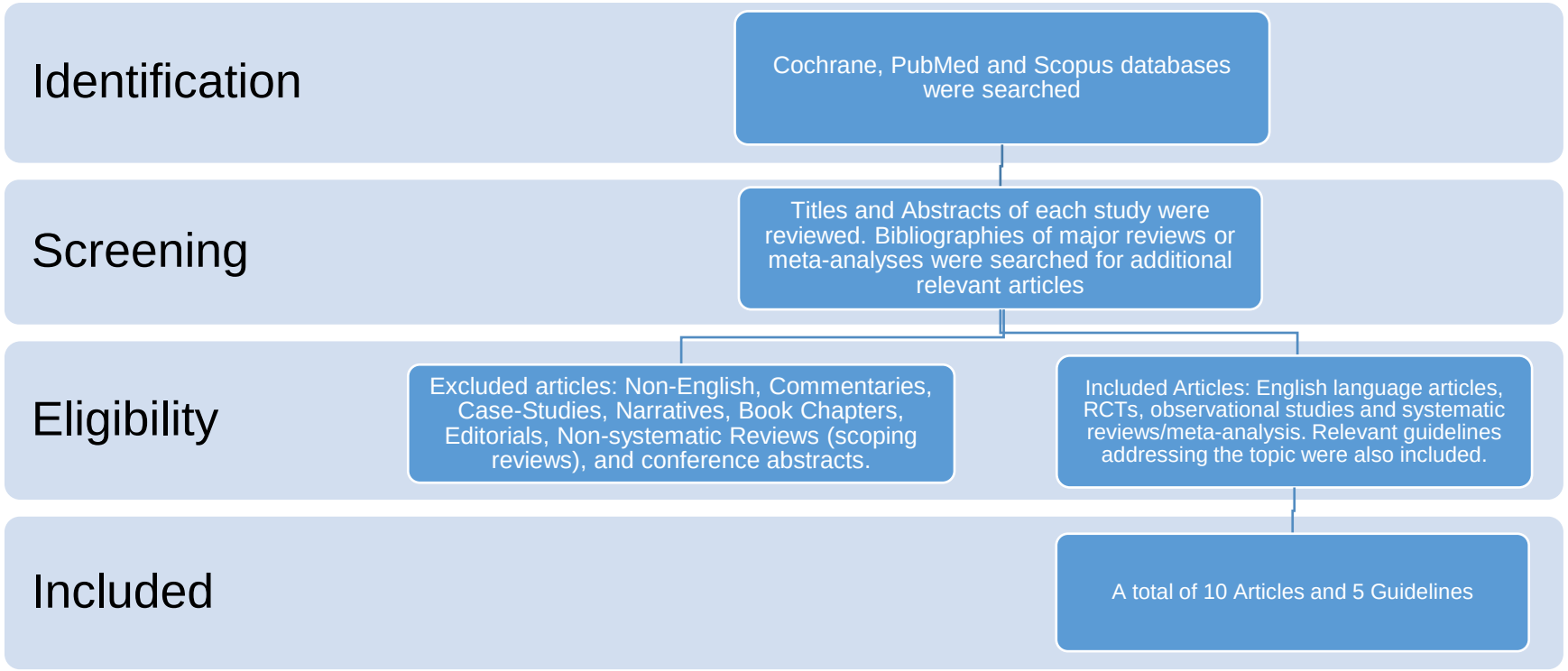
Search Strategy



Cochrane, PubMed and Scopus databases were searched using terms such as Stroke AND pain 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 10 articles and5 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. **Available at:** www.strokeguideline.org. **(selected)**	**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.
Zhang T, Zhao J, Li X, Bai Y, Wang B, Qu Y et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of stroke rehabilitation.** ***Stroke and Vascular Neurology* 2020:Sep;5(3):250-259.** **(selected)**	1. Individualised choice of CPSP treatment should be tailored according to patients' needs, treatment response and adverse reactions; multidisciplinary pain management combined with medication may also be effective (Class I recommendation, Level C evidence). 2. Amitriptyline and lamotrigine are reasonably considered as first-line treatments, while pregabalin, gabapentin, carbamazepine or phenytoin are considered as second-line treatment (Class IIa recommendation, Level B evidence).
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC et al; 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.	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

Guideline	Recommendations
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**	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
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
Mahesh et al. 2023 **India** **RCT**	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☑	82 participants, diagnosed with CPSP following ischemic or hemorrhagic stroke. Mean age was 56 years, 57.3% were men. Median duration of symptom onset was 60 days.	Patients were randomized 1:1 to receive 30 mg duloxetine or placebo daily for 4 weeks. Dose was doubled if there was no response to treatment at 2 weeks.	**Primary outcome:** Pain intensity assessed using the Numeric Rating Scale (NRS) at 4 weeks **Secondary outcomes:** Short-form McGill Pain Questionnaire-2 (SFMPQ-2) score and Pain Disability Index (PDI)	There was significantly greater reduction in the mean pain intensity score at 4 weeks in the duloxetine group (6.51 to 3.02 vs. 6.37 to 4.40, p=0.02). There were significantly greater decreases in mean SFMPQ-2 and PDI scores in the duloxetine group from baseline at 4 weeks (19.5 to 8.85 vs. 20.3 to 13.3, p=0.032 and 42.95 to 24.18 vs. 42.05 to 30.05, p=005, respectively). Adverse events (dizziness, somnolence, and nausea) were reported more frequently in the duloxetine group. One patient in the duloxetine group dropped out vs. 3 in the control group.
Bo et al. 2022 **China** **Systematic review & network meta-analysis**	Using the Cochrane RoB 2.0 tool, 7 RCTs had a low risk of bias, and 6 RCTs were classified with some concerns (missing outcome data and randomization process),	13 RCTs, including 529 participants, of which 9 included patients with post-stroke pain only. In the remaining trials patients with other conditions were also included (spinal cord injury or other central nervous lesions).	Trials examined pharmacotherapies including amitriptyline, carbamazepine, etanercept, ketamine, lamotrigine, levetiracetam, lidocaine, morphine, naloxone, pamidronate, prednisolone, and pregabalin. 7 trials assessed oral pharmacotherapies, 4 assessed intravenous pharmacotherapies, one assessed a peri-spinal injection, and one assessed a self-powered disposable patch. Control groups included	**Primary Outcome:** Pain intensity reduction measured by either VAS, NRS, or Likert scale following treatment.	*Pharmacotherapies vs placebo:* In order of effectiveness, the treatments with the highest P scores were: pamidronate (SMD -2.43, 95% CI -3.54 to -1.31, P=0.93), prednisone (SMD -2.38, 95% CI -3.09 to -1.67, P=0.92), levetiracetam (SMD -2.11, 95% CI -2.97 to -1.26, P=0.87), lamotrigine (SMD -1.39, 95% CI -2.21 to -0.58, P=0.73), etanercept (SMD -0.92, 95% CI -1.8 to -0.03, P=0.59), and pregabalin (SMD -0.46, 95% CI -0.71 to -0.22, P=0.49). *Pharmacotherapies vs each other:* Pamidronate was associated with the greatest reduction in pain intensity scores compared with carbamazepine (SMD -2.27, 95% CI -3.57 to -0.97), etanercept (SMD -1.51, 95% CI -2.93 to -0.09), ketamine (SMD -2.11, 95% CI -3.43 to -0.78), lidocaine (SMD -1.78, 95% CI -3.1 to -0.46), morphine (SMD -1.78, 95% CI -3.12 to -0.45), naloxone (SMD -2.4, 95% CI -3.68 to -1.13), and

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			placebo (n=10), other pharmacotherapies (n=2) and no treatment (n=1). 9 trials were conducted over a short period of time (≤1 month), 3 were of medium duration (8 and 12 weeks) and one, of long term (52 weeks).		pregabalin (SMD -1.96, 95% CI -3.1 to -0.82). Prednisone was significantly better than amitriptyline, carbamazepine, etanercept, ketamine, lidocaine, morphine, and naloxone. Levetiracetam was significantly better than amitriptyline, carbamazepine, ketamine, lidocaine, morphine, and naloxone.
Kim et al. 2019 **South Korea** **Prospective study**	NA	37 patients recruited from a single rehabilitation hospital with CPSP following first-ever stroke with Numeric Rating Scale (NRS) score of ≥4. Mean age was 59 years, 43% were men. Mean time since stroke onset was 3.1 years.	In addition to concurrent medications (antiepileptic drugs, antidepressants, muscle relaxants, benzodiazepines, nonsteroidal anti-inflammatories, antipsychotics and opioids), patients received 30 mg duloxetine or placebo daily for 3 weeks. The dose was doubled if there was no response to treatment after one week.	**Primary outcomes:** Pain severity (assessed using NRS) and the Short-form MC Gill Pain Questionnaire scores-2 (SFMPQ-2)	There was a significant reduction in mean (±SD) NRS scores from baseline to end of treatment at 3 weeks (5.9 ± 1.4 to 3.1 ± 1.7) and SFMPQ-2 (10.0 ± 4.4 to 4.8 ± 4.2). There was a ≥30% reduction in NRS pain scores in 70.2% of patients.
Kalita et al. 2017 **India** **RCT (crossover)**	CA: ☒ Blinding: Assessor ☒ Patient ☒ ITT: ☑	30 participants with CPSP (pain severity ≥50 mm on VAS). Mean age was 54 years, 87% were men. Median duration of pain was 165 days (3-2190), while the median duration of CPSP from the stroke onset was 70 days (0–820 days).	Participants were randomized to receive pregabalin or lamotrigine. The dose of lamotrigine escalated from an initial dose of 25 mg twice daily for 2 weeks to 50 mg twice daily for the next 2 weeks and thereafter 100 mg twice daily for 8 weeks. In the pregabalin group, the starting dose was 75 mg twice daily for 2 weeks followed by 150 mg twice daily for the next 2 weeks and then 300 mg twice daily for 8 weeks. The patients were crossed	**Primary Outcome:** ≥50% pain reduction in VAS scores. **Secondary Outcome:** Severity of different allodynia and improvement in Hospital Anxiety and Depression (HAD) Scale. Outcomes were assessed at baseline and 3 months after the start of intervention.	*Results based on the combined response of initial randomization and that of the crossover groups:* At 3 months, there was significant reduction in both pregabalin ($p < 0.0001$) and lamotrigine ($p<0.0001$) groups in mean VAS scores from baseline, with no significant differences between the groups with 19 (63.3%) patients in the pregabalin group and 16 (53.3%) in the lamotrigine group showing >50% improvement on VAS score ($p= 0.60$). The severity of cold allodynia, mechanical static allodynia, and HAD score improved significantly at 3 months in both the groups compared to the baseline. However, mechanical dynamic allodynia did not significantly improve.

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			over to the other study drug in the same manner after a washout period of at least 4 weeks if their pain on VAS score was ≥50 mm. The patients with possible remissions were not crossed over.		*Adverse events* 13 patients had side effects, 3 in the lamotrigine and 10 in the pregabalin group. In the lamotrigine group, all 3 patients had skin rash requiring drug withdrawal. In the pregabalin group, the major side effects were sedation (n=6), dizziness (n=4), pedal edema, tremor, blurred vision, and irritability (n=1 for all); however, no patient required drug withdrawal. .
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=3,000 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 2,130±830 mg/day during the first and 2,782±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 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. Mean	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	Mean pain scores at baseline for patients in the intervention and control groups were 6.5 and 6.3, respectively. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		duration of pain was >2 years.		(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.	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). 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, VAS score ≥6 caused by lesion or dysfunction in the central nervous system, with pain persisting ≥6 months. (Table 1 with patient demographics is missing).	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 (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	CA: ☑	40 patients with central pain (19 with stroke)	Patients were randomized 1:1 to receive a 4-week	**Primary outcome:** Pain relief, measured on a	Patients in the pregabalin group experienced a significantly greater reduction in mean pain scores

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
The Netherlands **RCT**	Blinding: Assessor ☑ Patient ☑ ITT: ☑	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.	course of treatment with escalating doses of pregabalin (max 600 mg/day) or placebo.	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.	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 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, except for 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. Neuropathic Pain Study Group 2002 **UK** **RCT**	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☒	305 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. Median age was 57 years, 46% were men.	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). There was significantly more improvement in SF-MPQ scores of patients in the treatment group (p<0.05). A significantly greater % of patients in the treatment group reported their pain was improved based on PGIC scores (34% vs. 16%, p=0.03), as well as pain reduction reported by the investigators (38% vs. 18%, p=0.01) There was significantly greater improvement in SF-36 scores of patients in the treatment group (p<0.05).

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					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
Attal et al. 2002 **France** **RCT**	CA: ☑ Blinding: Assessor ☑ Patient ☑ ITT: ☒	15 patients with poststroke (n=6) or spinal cord injury (n=9) related pain, which had persisted for >6 months. Mean age was 53.4 years (range: 32 to 73 years), 40% were men.	After an initial open titration phase aiming to determine the maximal tolerated dosage of IV morphine, patients received a mean dose of 16 mg for a 20 - minute period; infusion of saline solution was conducted on a separate session after 2 weeks During the second phase, within one week after the second infusion, all patients began to take sustained release oral morphine (starting from 20 mg/d during four weeks up to the maximum tolerated dosage).	**Primary outcomes:** First phase: ongoing pain intensity (VAS); evoked pain (intensity of allodynia [VAS]); intensity of mechanical pain (VAS); intensity of thermal pain (VAS) Second phase: mean pain intensity (VAS) **Secondary outcome:** Global assessment of pain relief (complete, a lot, moderate, slight, none, or worse pain)	First phase: There was a significant reduction in spontaneous pain in both the morphine and placebo conditions after the injection, lasting up to 120 minutes, with no significant difference between groups. Three patients were totally relieved by morphine at the end of injection (vs one after the placebo) and 2 patients experienced continuous relief over 60 minutes. In 4 patients, the pain was unchanged or worse after the placebo, and in one patient, pain was aggravated after the morphine injection. Morphine significantly reduced dynamic mechanical allodynia in 9 patients (reduction of 50% of pain intensity) compared with placebo, with no significant difference on ongoing pain intensity between morphine and placebo. Second phase: 3 patients out of 15 still took oral morphine after one year follow-up, reporting a 50–70% reduction of mean pain intensity.
Vestergaard et al. 2001 **Denmark** **RCT (crossover)**	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. The median duration of CPSP was 2 years.	Patients were randomized to receive lamotrigine or placebo. 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:** 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	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 significantly lower among patients in the treatment group phase (moderate vs. strong pain, p=0.02).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				pain; areas of spontaneous pain; and allodynia/dysesthesia	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 There were 17 adverse events reported during active treatment group, 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	ITT: Intention to treat
N/A: Not Assessed	NRS: Numerical Rating Scale
OR: Odds Ratio	RCT: Randomized Controlled Trial
VAS: Visual Analogue Scale	

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