

Recommendations for the Management of Central Post-stroke Pain

The Multidisciplinary Panel on Neuropathic Pain


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Many types of pain can occur following a stroke. The term *central pain* is used for pain caused by stroke-related damage to the central nervous system. A neuropathic pain syndrome, central post-stroke pain (CPSP) is characterized by constant and intermittent pain following stroke. This article discusses CPSP, including its pathophysiology, prevalence and symptoms; diagnosis; management; and treatments.

Pathophysiology, Prevalence and Symptoms

Several types of pain can occur following a stroke. Pain caused by stroke-related damage to the central nervous system is termed 'central pain'.¹ Pain may also arise from rigidity and reduced mobility, or from pre-existing conditions, such as osteoarthritis, which should be differentiated from central pain in diagnosis. Central post-stroke pain (CPSP) is a neuropathic pain syndrome that is characterized by constant or intermittent pain following stroke. CPSP was initially termed 'thalamic syndrome' as the lesions caused by the stroke were thought to be located in the thalamus. However, most CPSP cases arise from extrathalamic lesions.² Nociceptive pain (eg, frozen shoulder) may coexist in patients with CPSP.

The incidence of CPSP in stroke patients has been reported at 8%; the pain is moderate to severe in 5% of all stroke patients.³ In a



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survey of elderly subjects, at least 11% of the completed stroke subjects had what seemed to be CPSP.⁴ The onset of pain occurs within 1 month in over half of all CPSP patients; however, in some CPSP patients, the pain can take more than 6 months to develop.³ It is not clear whether age influences the risk of developing CPSP; evidence both for and against an influence of age exists.^{3,5} The following symptoms are typical⁶:

- Burning or freezing pain sensation
- Difficulties distinguishing sharp from blunt and warm from cool in the affected area
- Allodynia (pain sensation from a normally non-painful stimulus)

Altered temperature sensibility appears to be almost ubiquitous in CPSP,² while only about half of patients with CPSP experience allodynia.⁷ Allodynia may be tactile-, cold- or movement-evoked, and in some cases allodynia type is correlated with thalamic lesion site (eg, patients with cold allodynia tend to have more dorsally placed thalamic lesions than those without, and those with movement allodynia have more anteriorly placed lesions).⁷

Pain may be unilateral or may only affect small areas. Pain intensity may also vary within the affected area. Furthermore, symptoms can be exacerbated by stress and reduced by relaxation.

Diagnosis

As the onset of CPSP can occur several months after the stroke, primary care physicians involved in post-stroke care and responsible for follow-up must be alert to the development of this pain. The following should be assessed in all stroke patients reporting pain to differentiate CPSP from nociceptive pain⁶:

- Test the sensation to sharp and blunt objects in the affected area.
- Test the sensation to warmth (eg, touch with a finger) and coolness (eg, a metal instrument) in the affected area.
- If a patient is unable to differentiate between sensations in either or both of the above tests and the affected area corresponds to the site of the cerebrovascular lesion, CPSP is a probable diagnosis.

Management

Nociceptive pain, such as frozen shoulder, should be treated with analgesic agents (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and opioids), intracapsular injection and physiotherapy. Physiotherapy should be commenced as soon as possible after a stroke. Conventional analgesics tend not to be effective in treating CPSP.⁶ The key steps in CPSP management are as follows:

1. Differentiate nociceptive pain from CPSP, and treat nociceptive pain appropriately.
2. Record the patient's baseline or pre-treatment pain intensity to allow comparison with post-treatment pain. The visual analogue scale (VAS), where patients rate their pain on a scale from 0 mm (no pain) to 100 mm (excruciating pain), is one of the simplest means of assessing pain.
3. Counsel patients in relaxation techniques, as stress can exacerbate pain.
4. Commence treatment of CPSP with a tricyclic antidepressant (TCA), such as amitriptyline, as first-line therapy. Early treatment improves outcomes for CPSP patients. The alpha-2-delta (A2D) ligands gabapentin and pregabalin may also be effective in CPSP and may be used

as either first- or second-line therapy. Lamotrigine can be considered as an alternative first-line or a second-line therapy. If pain relief is unsatisfactory with first-line agents, mexiletine may be used as an adjunct therapy.

5. Referral to a multidisciplinary pain centre should be considered if a patient remains refractory to pharmacological treatment.

Pain Treatments

Relatively few clinical trials have investigated the treatment of CPSP. However, TCAs and anticonvulsants are the usual first-line treatment for this condition. Pharmacological management should be supplemented with physical and psychological interventions.

The pharmacological treatments in these recommendations are based on published clinical evidence and current clinical practice. However, some agents may not be indicated for use in neuropathic pain syndromes. Clinicians should consult the local prescribing information for these treatments.

Patients should be referred to a multidisciplinary pain centre for treatment if pain continues despite pharmacological therapy. Pain from CPSP tends to be persistent and, thus, can be more difficult to treat.

1. The TCA amitriptyline more effectively controls pain in CPSP patients than the anticonvulsant carbamazepine and is better tolerated.⁸ Therefore, TCAs such as amitriptyline or nortriptyline should be considered as first-line therapy. To minimize side effects, patients should commence at a low dose and titrate to a higher maintenance dose. Particularly in elderly patients, amitriptyline should be commenced at 25 mg daily and titrated to 75 mg daily, or the maximum tolerated dose. If frail or very elderly

patients are sedated by the TCAs, a lower starting dose of amitriptyline, for example, 10 mg daily, should be considered.

Pregabalin, an A2D ligand, has demonstrated efficacy in a variety of peripheral neuropathic pain syndromes. It has also been shown to significantly reduce pain and improve health status in patients with central pain, including CPSP.⁹

2. Gabapentin, another A2D ligand, is approved for the treatment of neuropathic pain and may be effective in treating CPSP.¹⁰

3. Gabapentin should be commenced at 300 mg at bedtime and increased by 300 mg every 3 days up to a dose of 1,800 mg daily after 1 week (given in three divided doses). If higher daily doses are required for maintenance, the maximum recommended dose is 3,600 mg daily (a lower dose is recommended in patients with renal impairment). For elderly patients or patients susceptible to side effects, it is recommended to increase gabapentin dosage by 300 mg every week or to commence with a lower dose (eg, 100 mg).

4. Lamotrigine may be used as a second-line agent or an alternative first-line treatment to TCAs.¹¹ Lamotrigine should be titrated from 25 mg daily to a maximum dose of 200 mg daily, or the maximum tolerated dose.

5. Mexiletine, an antiarrhythmic agent, may be used as an adjunct to TCAs when patients do not respond to TCAs alone.⁶

6. Intravenous (IV) lignocaine may provide pain relief in some patients with CPSP.^{12,13} It may be used as a temporary 'rescue' agent in severe cases refractory to oral medications.

7. Central pain appears to be poorly responsive, but not totally unresponsive, to opioids.²

8. Intrathecal baclofen may be effective in some patients with CPSP,^{14,15} but as the evidence is limited, it should only be considered after the failure of other pharmacological therapies.

9. Surgical interventions can be considered for patients unresponsive to pharmacological therapy; however, these treatments may be associated with morbidity and mortality. Motor cortex stimulation (MCS), spinal cord stimulation and stereotactic mesencephalic tractotomy are surgical treatments that may be beneficial for CPSP patients.^{16,17}

Figure 1 shows the treatment algorithm recommended by the Multidisciplinary Panel on Neuropathic Pain to help guide the choice of pharmacological therapy for CPSP.

Evidence-based Management of Central Post-stroke Pain

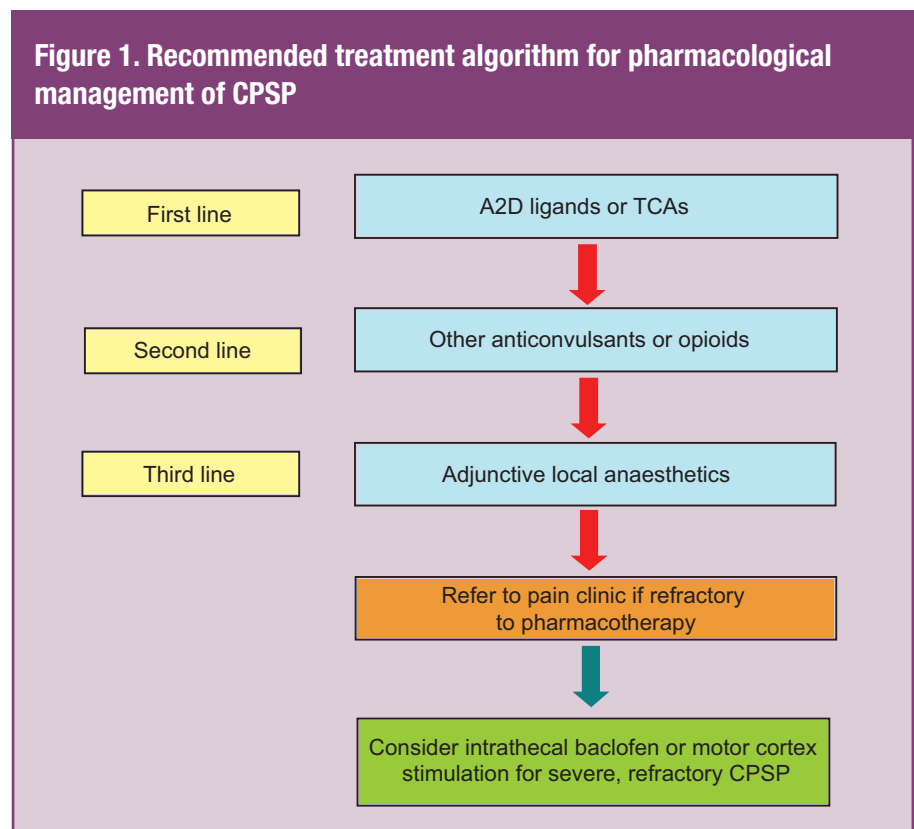
These recommendations have been based on the published evidence for currently available CPSP treatments and are reviewed below. However, it must be noted that few randomized, controlled trials have been performed to assess the effectiveness of CPSP treatments.

Pharmacological Management

Antidepressants

1. The TCA amitriptyline remains one of the first choices in treating CPSP. A randomized, controlled, cross-over study in 15 patients with CPSP—but no signs of depression—investigated the effectiveness of amitriptyline (maximum dose, 75 mg per day for

Figure 1. Recommended treatment algorithm for pharmacological management of CPSP



4 weeks), carbamazepine (maximum dose, 800 mg per day for 4 weeks) and placebo.⁸ Amitriptyline significantly reduced pain compared with placebo and was generally well tolerated. Carbamazepine offered some pain relief but was not significantly better than placebo. Carbamazepine was also associated with more adverse events. In addition, a study to test the prophylactic efficacy of amitriptyline in the development of CPSP in 39 patients with thalamic stroke found amitriptyline (10 to 75 mg/day) reduced, although it did not completely prevent, the development of CPSP.¹⁸

Other antidepressants that may be used in CPSP include nortriptyline and desipramine.⁶ However, there is little evidence for their effectiveness in this condition. TCAs are associated with adverse events, such as sedation, anticholinergic effects and postural hypotension, to which elderly stroke patients may be more susceptible.

Anticonvulsants

Anticonvulsants are often used as first-line agents in the treatment of neuropathic pain conditions, particularly if antidepressants are contraindicated or ineffective. Carbamazepine and phenytoin were two of the earliest anticonvulsant drugs investigated in controlled clinical trials for treating neuropathic pain syndromes.¹⁹ Carbamazepine is less effective than amitriptyline in the treatment of CPSP,⁸ but it is beneficial in other neuropathic pain conditions.²⁰ Little evidence exists for phenytoin in the treatment of CPSP. Lamotrigine and the A2D ligands gabapentin and pregabalin have demonstrated some benefit in CPSP.

Pregabalin. In randomized clinical trials, pregabalin has been shown to be effective in various types of chronic neuropathic pain, including post-herpetic neuralgia, diabetic peripheral

neuropathy and neuropathic pain following spinal cord injury.^{21,22} A recently published, 4-week, randomized, double-blind, placebo-controlled trial involving 40 patients with severe central neuropathic pain (including 12 patients with CPSP) investigated the effects of pregabalin (150–600 mg/day) on pain relief, health status and quality of life.⁹ After 4 weeks, pregabalin produced clinically significant reductions in pain and improvements in health status and was well tolerated. The authors concluded that pregabalin may be proposed as a first-line pharmacological treatment of central neuropathic pain.⁹

Gabapentin. Gabapentin is approved for treating neuropathic pain syndromes and is effective in the treatment of painful diabetic neuropathy²³ and post-herpetic neuralgia.^{24,25} However, no randomized controlled trials with gabapentin have been performed to date in CPSP patients. A recently published case study does suggest, however, that gabapentin may be beneficial in CPSP.¹⁰ This case describes a male patient with CPSP who had failed to respond to a number of oral analgesic agents. However, after 2 weeks of gabapentin treatment, the patient had substantially less pain and also improved functioning. Controlled clinical studies are required to investigate further the effectiveness of gabapentin in CPSP.

A double-blind, placebo-controlled trial demonstrated that gabapentin reduced pain and improved quality of life measures in patients with a variety of neuropathic pain syndromes. However, only 3% of patients in this trial had post-stroke pain.²⁶

Lamotrigine. Lamotrigine may be an alternative treatment for CPSP. In a placebo-controlled, cross-over trial, 30 patients were randomized to lam-

otrigine (maximum dose, 200 mg per day) or placebo.¹¹ The treatment period was 8 weeks. Lamotrigine reduced the median pain score and improved some other outcome measures. The treatment was generally well tolerated with few transient side effects.

Systemic use of Local Anaesthetic Agents

Intravenous lignocaine (5 mg/kg IV) was compared with placebo in a randomized controlled trial of 16 patients (six with CPSP and 10 with spinal cord injury-related pain).¹² Brush-induced allodynia and mechanical hyperalgesia were improved with lignocaine; however, pain from thermal allodynia and hyperalgesia were not statistically improved with IV lignocaine compared with placebo.¹² In a small study of four patients with CPSP, IV lignocaine was also shown to provide some pain relief.¹³ One disadvantage is that the effect of IV lignocaine is often brief, and a positive response does not necessarily indicate a favourable response to oral mexiletine.

An antiarrhythmic agent, mexiletine is an orally available local anaesthetic sodium channel blocker structurally similar to lignocaine. Mexiletine (10 mg/kg/day) was administered to nine patients with CPSP in a preliminary 4-week open-label study.²⁷ Pain improved in eight patients. However, the high doses required for response often give rise to tolerability issues that limit use.¹⁵ Patients should stop any antihypertensive therapy for 2 days before commencing mexiletine (400 mg orally, followed by 200 mg every 6 hours) but should continue with any antidepressant agents, such as TCAs.⁶ Blood pressure must be monitored when treating patients with mexiletine. There may be a role for mexiletine in selected patients with CPSP as add-on therapy to TCAs.^{6,15}

A 2005 review examined all randomized studies comparing lignocaine and mexiletine with placebo or active agents in patients with neuropathic pain of any aetiology.²⁸ It found that the local anaesthetics were superior to placebo in decreasing the intensity of neuropathic pain. No differences in efficacy or adverse event rates were found between lignocaine and mexiletine and amitriptyline, gabapentin or morphine.²⁸

Intrathecal Baclofen

Intrathecal baclofen has been reported to relieve pain and allodynia in a small number of patients with central pain due to brain or spinal lesions.^{14,15} The data are largely limited to case reports and anecdotal evidence; however, intrathecal baclofen may be considered in CPSP patients who fail to respond to other recommended pharmacological therapies.

Opioids

Although no large trials have been conducted, the use of opioids for CPSP has been investigated in a few studies. Intravenous naloxone had no benefit compared with vehicle in 20 CPSP patients.²⁹ Oral levorphanol was investigated for the treatment of central pain in 81 patients; little benefit was observed in the patients with CPSP.³⁰ A randomized controlled trial comparing IV morphine with placebo was performed in 15 patients with either CPSP (six patients) or spinal cord injury-related pain (nine patients).³¹ Although some pain relief occurred with IV morphine, the authors concluded that only a minority of patients would benefit from long-term treatment, particularly in light of the prevalent side effects. On balance, the available data suggest that forms of central neuropathic pain are poorly responsive, but not totally unresponsive, to opioids.²

Non-pharmacological Management

Physical Stimulation and Surgery

Patients remaining refractory to pharmacological treatment may benefit from surgical intervention. Stereotactic mesencephalic tractotomy has been used for a number of years to treat CPSP. Although a study has shown this intervention to provide long-term relief (67% of 24 patients), the mortality rate was 7.4%.¹⁷

A newer procedure, motor cortex stimulation (MCS), was investigated in 23 patients with central neuropathic pain.¹⁶ Twenty patients were followed-up after at least 1 year; 60% of patients had good to excellent pain relief, while 25% did not obtain any benefit. Using data from 159 cases of central pain secondary to ischaemic or haemorrhagic stroke, the MCS success rate was calculated as 52% (83/159).³² More recently, a task force of the European Federation of Neurological Societies (EFNS) concluded that there is level C evidence that MCS is useful in 50–60% of patients with CPSP, with a small risk of medical complications.³³ Thus, MCS should be considered as an alternative treatment of confirmed efficacy for patients with severe, refractory CPSP.³⁴

A recently published case report describes a patient with severe CPSP of the right leg benefiting from a combination of multidisciplinary therapies and acupuncture.³⁵ Further investigation into the efficacy of this treatment modality is warranted.

Psychological Treatment

Early cognitive behavioural therapy (CBT) and other psychological treatment approaches may be beneficial in many types of chronic pain, including CPSP. CBT can help to modify negative thoughts related to pain and teach coping strategies for residual pain. This can help patients to increase their activity level and functioning,

which in turn can help improve mood, sleep and quality of life. Psychological interventions should be used as part of the multidisciplinary approach to pain management, in concert with pharmacotherapy or surgical treatment.

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A complete list of references can be obtained upon request to the editor.

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