



# Recommendations for the Management of Poststroke Pain

The Multidisciplinary Panel on Neuropathic Pain\*

## I. 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”.<sup>1</sup> Pain may also arise from rigidity and reduced mobility, or from pre-existing conditions, such as osteoarthritis, that 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, CPSP may also arise from extrathalamic lesions. Nociceptive pain (e.g., 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.<sup>2</sup> 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

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6 months to develop.<sup>2</sup> Patients with CPSP tend to be younger stroke patients. The following symptoms are typical:<sup>3</sup>

- 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).

Pain may be unilateral, or it 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.

## II. Diagnosis

As the onset of CPSP can occur several months after the stroke, primary-care physicians involved in poststroke 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 pain:<sup>3</sup>

**“Allodynia (pain sensation from a normally non-painful stimulus) is a typical symptom of CPSP”**

- Test the sensation to sharp and blunt objects in the affected area;
- Test the sensation to warmth (e.g., touch with a finger) and coolness (e.g., a metal instrument) in the affected area;
- If a patient is unable to differenti-

ate between sensations in either or both of the above tests, CPSP is a probable diagnosis.

## III. Management

Nociceptive pain, such as frozen shoulder, should be treated with analgesic agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] and opioids), intracapsular injection and physiotherapy. Physiotherapy should be commenced as soon as possible after a stroke. Conventional analgesics, including opioids, tend not to be effective in treating CPSP.<sup>3</sup>

The key steps in CPSP management are:

1. Differentiate nociceptive pain from CPSP, and treat nociceptive pain appropriately;
2. Record the patient’s baseline, or pretreatment, pain intensity to

allow comparison with posttreatment pain. The visual analogue scale (VAS), by which 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. Lamotrigine can be considered as an alternative first-line therapy. Gabapentin may also be effective in CPSP. 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 after 2 to 3 months' treatment.

**“TCAs and anticonvulsants are the usual first-line treatment for CPSP”**

#### IV. 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 for 2 to 3 months despite pharmacological therapy. Pain from CPSP tends to be persistent and, thus, can be more difficult to treat.

The TCA amitriptyline controls pain in CPSP patients more effectively than the anticonvulsant carbamazepine, and is better tolerated.<sup>4</sup> 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. 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 old patients are sedated by TCAs, a lower starting dose of amitriptyline, for example 10 mg daily, should be considered.

Lamotrigine may be an alternative first-line treatment to TCAs.<sup>5</sup> Lamotrigine should be titrated from 25 mg daily to a maximum dose of 200 mg daily, or the maximum tolerated dose.

Gabapentin, an anticonvulsant, is approved for the treatment of neuropathic pain, and may be effective in treating CPSP.<sup>6</sup> 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 3 divided doses). If higher daily doses are required for main-

tenance, 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 (e.g., 100 mg).

Mexiletine is an antiarrhythmic agent and may be used as an adjunct to TCAs, when patients do not respond to TCAs alone.<sup>3</sup>

**“Surgical interventions can be considered for patients unresponsive to pharmacological therapy”**

Intravenous lignocaine may provide pain relief in some patients with CPSP.<sup>7,8</sup>

Surgical interventions can be considered for patients unresponsive to pharmacological therapy; however, these treatments may be associated with morbidity and mortality. Pre-central cortex stimulation, spinal cord stimulation and stereotactic mesencephalic tractotomy are surgical treatments that may be beneficial for CPSP patients.<sup>9,10</sup>

#### V. Evidence-based Management of CPSP

These recommendations are based on published evidence for currently available CPSP treatments, which are reviewed below. However, some agents may not be approved for use

Relaxation techniques are one of the key steps in CPSP management.



in neuropathic pain syndromes. Full prescribing information should be consulted before initiating drug therapy. It must also be noted that few randomized, controlled trials have been performed to assess the effectiveness of treatments for CPSP.

### Pharmacological Management

#### *Antidepressants*

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 4 weeks), carbamazepine (maximum dose 800 mg per day for 4 weeks) and placebo.<sup>4</sup> 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.

Other antidepressants that may be used in CPSP include nortriptyline and desipramine.<sup>3</sup> 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.

**“TCAs are associated with adverse events 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.<sup>11</sup> Carbamazepine is less effective than amitriptyline in the treatment of CPSP;<sup>4</sup> however, it is beneficial in other neuropathic pain conditions.<sup>12</sup> Little evidence exists for phenytoin in the treatment of CPSP. Lamotrigine and gabapentin, two newer anticonvulsant agents, have demonstrated some benefit in CPSP.

**Lamotrigine:** Lamotrigine may be an alternative to amitriptyline in the first-line treatment of CPSP. In a placebo-controlled, cross-over trial, 30 patients were randomized to lamotrigine (maximum dose, 200 mg per day) or placebo.<sup>5</sup> 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.

**Gabapentin:** Gabapentin is approved for treating neuropathic pain syndromes, and is effective in the treatment of painful diabetic neuropathy<sup>13</sup> and postherpetic neuralgia.<sup>14,15</sup> 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.<sup>6</sup> 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 further investigate 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 poststroke pain.<sup>16</sup> The clinical experience of the Multidisciplinary Panel on Neuropathic Pain members indicates that around one-third to one-half of CPSP patients respond to gabapentin.

#### *Mexiletine*

The antiarrhythmic agent mexiletine was administered to nine patients with CPSP in a preliminary, open-label study.<sup>17</sup> At a dose of 10 mg/kg/day for 4 weeks, pain improved in eight patients. In general, mexiletine

was well tolerated with two patients experiencing transient nausea and dizziness. Patients are recommended to stop any anti-hypertensive therapy for 2 days before starting mexiletine (400 mg orally, followed by 200 mg every 6 hours), but should continue with any antidepressant agents, such as TCAs.<sup>3</sup> Blood pressure should be monitored when treating patients with mexiletine.

#### *Systemic Agents*

### “Precentral cortex stimulation could be an option for patients with severe, refractory CPSP”

Intravenous administration of naloxone, morphine and lignocaine has been investigated in CPSP. Naloxone had no benefit compared with vehicle in 20 CPSP patients.<sup>18</sup> A randomized, controlled trial comparing morphine with placebo was performed in 15 patients with CPSP (6 patients) or spinal cord injury-related pain (9 patients).<sup>19</sup> Although some pain relief occurred with intravenous morphine, the authors concluded that only a minority of patients would benefit from long-term treatment. Nevertheless, some patients may benefit from opioids when other pharmacological therapy fails.

Intravenous lignocaine may be of greater benefit. In a randomized, controlled trial of 16 patients (6 with CPSP and 10 with spinal cord injury-related pain), intravenous lignocaine (5 mg/kg) was compared with placebo.<sup>7</sup> Brush-induced allodynia and mechanical hyperalgesia were improved with lignocaine; however,

pain from thermal allodynia and hyperalgesia was not statistically improved with intravenous lignocaine compared with placebo. In a small study of four patients with CPSP, intravenous lignocaine was also shown to provide some pain relief.<sup>8</sup>

#### *Nonpharmacological 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 received relief from pain), the mortality rate was 7.4%.<sup>12</sup>

A newer procedure, precentral cortex stimulation, was investigated in 23 patients with central neuropathic pain.<sup>11</sup> Twenty patients were followed up after at least 1 year; 60% had good to excellent pain relief, while 25% did not obtain any benefit. This procedure could be an option for patients with severe, refractory CPSP.

#### *Psychological Treatment*

Early cognitive behavioural therapy may be beneficial in many types of chronic pain, including CPSP. As CPSP can be exacerbated by stress, patients should receive counselling on stress reduction and relaxation techniques in addition to pharmacotherapy or surgical treatment.

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