# Poststroke Pain

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## Abstract

Pain is common but often underrecognized after stroke. Poststroke pain (PSP) hinders recovery, impairs quality of life, and is associated with the psychological state of patients with stroke. The most common subtypes of PSP include central PSP, complex regional pain syndrome, shoulder pain, spasticity-related pain, and headache. The pathophysiologies of these PSP subtypes are not yet clearly understood, and PSP is refractory to conventional treatment in many patients. However, recent studies have proposed potential pathophysiologies of PSP subtypes, which may help prioritize therapies that target specific mechanisms.

**Keywords**

- poststroke pain
- central poststroke pain
- complex regional pain syndrome
- shoulder pain
- spasticity-related pain
- headache

Pain after stroke is common, reported in 10 to 45.8% of cases.[1,2] It can decrease quality of life and hinder recovery in stroke patients.[1,3–6] However, owing to impairments in cognition or communication following stroke, PSP is frequently overlooked. If physicians do not actively inquire about the presence of pain, it is frequently undisclosed by patients. PSP is not always responsive to conventional treatments; therefore, treatment of PSP may be challenging in clinical practice. Prognosis of PSP is improved when pain is treated early and aggressively,[7] highlighting the importance of early recognition.

The most common subtypes of PSP are central poststroke pain (CPSP), complex regional pain syndrome (CRPS), shoulder pain, spasticity-related pain, and headache (►**Table 1**).[7,8] Many patients concurrently experience more than one PSP subtype. The pathophysiologies of these subtypes are not yet clearly elucidated. However, recent studies have proposed potential mechanisms for these subtypes, and based on these, various treatment methods are being actively applied to patients with PSP. Here, we review the common subtypes of PSP, with a focus on their pathophysiology and treatment.

## Central Poststroke Pain

CPSP is defined as central neuropathic pain that occurs after stroke.[9] The nature of this pain can range from aching, dull, and throbbing to sharp, stabbing, shooting, and burning.[10] The prevalence of CPSP in patients with stroke is between 1 and 12%,[10–12] and most commonly develops within 1 to 6 months after stroke.[11,13–15] CPSP can manifest either spontaneously or by induction. Induced pain results from an increased sensitivity to stimulation (hyperesthesia), which includes pain induced by nonpainful stimulation (allodynia) and increased sensitivity to painful stimulation (hyperalgesia).[16] Spontaneous pain is continuous or paroxysmal, and occurs independent of stimulation. CPSP commonly presents in the distal parts of the body, such as the hand and foot, and is less commonly experienced in proximal regions such as the shoulder and thigh.[14] Furthermore, the development of CPSP has been associated with sensory impairment.[17–19] In previous studies, the prevalence of CPSP was found to be 8% in patients with stroke.[20,21] CPSP can occur following a lesion involving the thalamus (ventral posterolateral and ventral posteromedial nuclei) and/or the

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**Table 1** The pathophysiology and treatment of poststroke pain

| | Pathophysiology | Treatment |
|---|---|---|
| Central poststroke pain | Neuronal excitability → central sensitization, hyperexcitability of the spinothalamic tract | Oral medication, deep brain stimulation, rTMS |
| Complex regional pain syndrome | Hyperactivity of sympathetic nervous system, persistent noxious input → central sensitization, overactivation of inflammatory response | Oral medication (including oral prednisolone), sympathetic blockade, spinal cord stimulation, active or passive mobilization, massage, contrast baths, TENS |
| Shoulder pain | Immobilization, weakness, spasticity | Oral medication, corticosteroid injection, passive ROM exercise, NMES, rTMS |
| Spasticity-related pain | Abnormal distribution of mechanical loading → additional mechanical stress | Oral antispasticity medication, neurolysis with alcohol or phenol, botulinum toxin injection, stretching exercise, NMES, rTMS, serial casting, brace, surgery |
| Headache | Altered biomechanics, poor posture, stimulation of trigeminovascular afferents, dural stretch by mass effect | Oral medication, botulinum toxin injection, occipital nerve block, TPI, PRF stimulation, cognitive behavioral therapy, biofeedback, exercise |

Abbreviations: NMES, neuromuscular electrical stimulation; PRF, pulsed radiofrequency; ROM, range of motion; rTMS, repetitive transcranial magnetic stimulation; TENS, transcutaneous electrical nerve stimulation; TPI, trigger point injection.

spinothalamic tract (STT), which are structures responsible for the transmission of pain in the central nervous system (CNS).[22,23] In particular, partial damage of the STT reportedly leads to a higher risk for the development of CPSP.[22] In 2012, using diffusion tensor tractography, Hong et al demonstrated that the prevalence of CPSP in patients with partial injury of the STT was higher than that of patients with complete injury of the STT.[22]

### Pathophysiology of Central Poststroke Pain

While the pathophysiology of the occurrence of CPSP has not yet been clearly elucidated, some possible mechanisms have been suggested. First, CNS lesions often induce neurochemical, excitotoxic, and inflammatory changes, which can increase neuronal excitability.[24] This excitability may cause central sensitization, which in turn leads to chronic pain. Second, hyperexcitability and ongoing activity in the STT after STT injury could be responsible for CPSP.[25] Third, central pain could be caused by a lesion in the lateral thalamus that interrupts inhibitory pathways, which results in disinhibition of the medial thalamus.[26] Finally, thalamic changes after CNS lesions, including deafferentation, loss of inhibitory gamma amino butyric acid (GABA)-containing neurons in the thalamus, and microglial activation, are also proposed to underlie CPSP.[27–30]

### Treatment for Central Poststroke Pain

The management of CPSP is often refractory and dosages may be limited due to side-effects. Various oral medications and nonpharmacological treatments are used to manage CPSP. Oral medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and antiepileptics (such as gabapentin, pregabalin, and lamotrigine), have been reported to effectively control CPSP.[31–33] Although opioids are not considered first-line agents, they have a role in effectively controlling CPSP.[34] Intravenous lidocaine and propofol have been shown to alleviate CPSP during infusion, but studies on intravenous agents are limited to case reports.[35,36] Nonpharmacological treatment options for CPSP include deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS). The success rate of DBS for managing CPSP has been reported to be around 50% in previous studies.[37,38] rTMS is a safe, noninvasive, and effective therapeutic intervention that uses an electromagnetic coil applied to the scalp to produce a magnetic field.[39,40] This induces changes in cortical excitability at the stimulation site and transsynaptically at distant areas.[39,40] The application of high-frequency unilateral rTMS to the motor cortex in patients with chronic pain may have long-term analgesic effects. Indeed, in 2015, Kobayashi et al applied high-frequency (5 Hz) rTMS to 18 patients with CPSP once a week for 12 weeks. Approximately 60% of the patients experienced pain reduction at 12 weeks after initiating rTMS.[41] However, the study involved a limited number of individuals and lacked a control group, making it difficult to draw any definite conclusions regarding the long-term pain reduction effects of rTMS.

## Complex Regional Pain Syndrome

CRPS is a chronic severe pain condition usually affecting the limbs (hand, arm, foot, or leg), and is accompanied by increased sensitivity to tactile stimulation, vasomotor changes including edema and changes in skin temperature and color, limited range of motion, and osteopenia.[42] Its cause is not clearly understood, but it is believed to be a result of damage to both the peripheral and CNS.[42] CRPS is classified into two types: Type I, where there is no evidence of nerve damage in the affected limb, and Type II, where a distinct nerve lesion is present. CRPS following stroke is categorized as Type I CRPS.[43] Because there is little consensus on diagnostic criteria for CRPS, the reported incidence of CRPS after stroke is highly variable and ranges from 2 to 49%.[44,45] Recently, the Budapest criteria were developed to aid in the standardization of the diagnosis of CRPS (►**Table 2**).[46] Three-phase bone scan and digital infrared thermal imaging can be used as supportive

**Table 2** The Budapest clinical diagnostic criteria for complex regional pain syndrome

| |
|---|
| 1. Continuing pain, which is disproportionate to any inciting event |
| 2. Must report at least one symptom in all four of the following categories: |
| *Sensory*: reports of hyperaesthesia and/or allodynia |
| *Vasomotor*: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry |
| *Sudomotor/edema*: reports of edema and/or sweating changes and/or sweating asymmetry |
| *Motor/trophic*: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) |
| 3. Must display at least one sign at time of evaluation in two or more of the following categories: |
| *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) |
| *Vasomotor*: evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry |
| *Sudomotor/edema*: evidence of edema and/or sweating changes and/or sweating asymmetry |
| *Motor/trophic*: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) |
| 4. There is no other diagnosis that better explains the signs and symptoms |

diagnostic tools for CRPS.[47,48] Wüppenhorst et al reported that the sensitivity and specificity of three-phase bone scan for diagnosing CRPS were 31 to 50% and 83 to 100%, respectively.[49] Thus far, no studies on the sensitivity and specificity in digital infrared thermal imaging have been conducted.

### Pathophysiology of Complex Regional Pain Syndrome

Several mechanisms have been suggested to contribute to CRPS, some of which may coexist. Local hyperactivity of the sympathetic nervous system has been proposed to be one of the causes of CRPS.[50] This has been supported by several previous studies reporting that local anesthetic blockade of the sympathetic chain effectively controlled CRPS symptoms.[51–53] Furthermore, persistent noxious input resulting from nerve damage increases the excitability of nociceptive neurons in the spinal cord, referred to as central sensitization.[54] Central sensitization results in hyperesthesia, allodynia, and hyperalgesia. Overactivation of inflammatory responses or relative hypoxia of the affected limb may also contribute to the development of CRPS.[55–57]

### Treatment of Complex Regional Pain Syndrome

While there is no gold standard for the treatment of CRPS, outcomes are better when CRPS is treated earlier.[58] Several oral medications, such as steroids, antiepileptics, opioids, nonsteroidal anti-inflammatory drugs and antidepressants, are currently used to reduce pain and to improve the functional status of patients with CRPS, although there is a lack of convincing evidence for the efficacy of these medications.[59] The commonly used medications for alleviating pain from CRPS are anti-inflammatory agents, analgesics, antidepressants, oral muscle relaxants, anticonvulsants, and topical agents.[60–62] On the basis of theoretical evidence that inflammation is responsible for the pathogenesis and propagation of CRPS, oral prednisolone therapy has also been studied.[61,63] Atalay et al[63] investigated the effect of oral prednisolone for CPRS of the upper extremity. They retrospectively reviewed the medical records of 45 patients with CRPS who were treated with 30 mg prednisolone and tapered the dose by 5 mg every 3 days until discontinuation after 3 weeks. After the treatment, patients' CRPS symptoms, such as pain, sweating, stiffness, cold intolerance, and cyanosis, were significantly reduced. Additionally, several previous studies have found that repeated sympathetic blockade with local anesthetics can attenuate CRPS symptoms.[51–53] In refractory cases of CRPS, spinal cord stimulation was found to have potential to relieve such symptoms.[64] In addition to the aforementioned medications and procedures, combined treatment with active or passive mobilization, massage, contrast baths, and transcutaneous electrical nerve stimulation have been used as adjunctive therapies to help manage CRPS, although data regarding efficacy are limited.[65]

## Shoulder Pain

Shoulder pain is one of the most common nociceptive pain syndromes after stroke, occurring in approximately 75% of patients with stroke.[66] Pain usually begins within 3 weeks of the stroke.[67] In particular, shoulder pain frequently occurs in those with severe motor deficits or spasticity in the affected upper extremity.[68,69] Although the majority of cases of shoulder pain after stroke resolve by 6 months, approximately 20% of patients complain of persistent and debilitating shoulder pain.[70] Shoulder pain is known to lead to poor functional recovery. In 2012, Pong et al[71] conducted a prospective study to evaluate the correlation between shoulder pain and stroke recovery in 67 acute stroke patients with hemiplegic shoulder. At follow-up evaluation in the chronic stage, shoulder pain was significantly correlated with worse recovery of shoulder function.

### Pathophysiology of Shoulder Pain

The development of shoulder pain is known to be multifactorial, and several factors such as glenohumeral subluxation, impingement, rotator cuff tears, glenohumeral capsulitis, and weakness and spasticity are thought to be involved.[5,70] The shoulder joint is loosely constrained by a thin joint capsule attached along the outside ring of the glenoid cavity and the anatomical neck of the humerus.[72] Stability of the shoulder joint depends on the surrounding muscles and ligaments. Therefore, weakness in these surrounding muscles following stroke can cause instability or immobilization of the glenohumeral joint.[73] This instability can lead to impingement and rotator cuff tears. Also, immobilization after stroke is a risk factor of glenohumeral capsulitis. Flaccid

upper-extremity muscle tone can also cause glenohumeral subluxation, and the spasticity alters the equilibrium between the shoulder abductor/adductor and internal/external rotator muscles.[7,74] Glenohumeral subluxation and imbalance between the shoulder muscles lead to shoulder instability and limitation of shoulder joint motion, which can also lead to shoulder pain.[7,74]

### Treatment of Shoulder Pain

The management of poststroke shoulder pain should begin first with its prevention. Patients who have severe weakness in their upper extremity prior to the development of spasticity tend to develop shoulder laxity.[75] Early stabilization of the patient's shoulder joint using passive range of motion exercises on the affected side may help prevent shoulder pain.[75] Slings are also used in patients with glenohumeral subluxation and severe motor weakness of shoulder elevators to both prevent and manage shoulder pain after stroke.[76] However, immobilization is a major risk factor for adhesive capsulitis or shoulder joint contracture, so long-term use of slings is not recommended.[77] External support using a sling can be discontinued when the muscle tone around the glenohumeral joint is sufficient to prevent subluxation.[78] Functional electrical stimulation that targets the supraspinatus and posterior deltoid muscles has been found to prevent glenohumeral subluxation by maintaining isometric strength of the shoulder girdle.[79] Linn et al recruited 40 patients with significant motor deficit of the upper limb after stroke, and randomly allocated 20 patients to the treatment group and 20 to the control group.[79] The patients in the treatment group received functional electrical stimulation four times a day over 4 weeks (30–60 minutes/stimulation). The supraspinatus and posterior deltoid muscles were stimulated by two electrodes. The treatment group showed lesser subluxation on the radiographs and reduced pain during the treatment period. Range-of-motion exercises should also be used in patients who wear shoulder slings.[75] Additionally, in patients using a wheelchair, the wheelchair lap tray can help maintain proper positioning of the shoulder and prevent glenohumeral subluxation.[7]

Several pharmacological and nonpharmacological interventions can be applied to manage poststroke shoulder pain.[80] Nonsteroidal anti-inflammatory drugs, other oral analgesics,[7,74,80] and antispasmodic medications have been shown to reduce spasticity.[7,74,80] For the management of persistent pain that is unresponsive to oral medications, intra-articular or subacromial bursa corticosteroid injections may also be effective, likely related to anti-inflammatory mechanisms.[5] In 2017, Chang recruited 30 patients with poststroke shoulder pain and administered intra-articular or subacromial bursa corticosteroid injections into the shoulder joint under the guidance of ultrasonography.[5] After the injections, the patients' shoulder pain was significantly relieved, passive range of shoulder motion was significantly increased, and the effects were sustained for at least 2 months. Treated patients also reported decreased rates of depression and anxiety. Although sample size was small, this study suggested that corticosteroid injections can be a beneficial treatment option for shoulder pain after stroke. Additionally, several previous studies have reported that injection of botulinum toxin into surrounding muscles, such as the pectoralis major and subscapularis, can alleviate poststroke shoulder pain, likely related to both antispasmodic and antinociceptive effects.[81–83]

Nonpharmacological treatments including passive range-of-motion exercises can be performed easily and help control shoulder muscle tone.[75] Transcutaneous neuromuscular electrical stimulation has also been proposed to control shoulder pain according to the gate-control theory of pain; this works by activating myelinated sensory fibers and disrupting the pain signals of unmyelinated C-fibers.[84] rTMS might also be a possible adjuvant treatment option for shoulder pain.[70] In 2018, Choi and Chang performed high-frequency (10 Hz) rTMS over the primary motor cortex of the affected hemisphere in 12 patients with chronic shoulder pain after stroke.[70] They reported that 20 to 30% of initial shoulder pain was reduced after 10 sessions of rTMS. Surgical procedures, such as release of shoulder capsule or ligament and repair of rotator cuff tears, can be considered when conservative treatments have failed and motion limitation of the shoulder joint is severe to the point of functional impairment.[85]

## Spasticity-Related Pain

About 65% of all patients with stroke develop spasticity.[86] Spasticity is characterized by a velocity-dependent increase in muscle tone during passive stretching, which results from hyperexcitability of the stretch reflex following upper motor neuron injury.[86] Spasticity not only impairs functional outcome of patients with stroke, but is also associated with spasticity-related pain.[87] In 2010, Wissel et al reported a strong association between spasticity after stroke and pain.[88] In that study, while 72% of patients with spasticity experienced pain, only 1.5% of nonspastic patients experienced pain. Therefore, appropriate management of spasticity is important for PSP management.

### Pathophysiology of Spasticity-Related Pain

Spasticity-related pain is usually nociceptive, related to excess loading on muscles and ligaments resulting from spasticity.[6] Persistent spasticity leads to changes in the rheologic properties of the involved muscles, which can lead to fibrosis and atrophy.[89] In addition, in the lower leg, spasticity usually occurs in the ankle plantar flexor and inverter; accordingly, the mechanical loading on the foot during standing or walking is abnormally distributed.[90,91] Loading imbalance can cause additional mechanical stress to the foot, which may cause pain in the joints or soft tissues.[90,91]

### Treatment of Spasticity-Related Pain

Oral antispasticity medications are first line in managing spasticity-related pain after stroke.[92] These medications are broadly classified as GABA agonists that affect ion flux and include baclofen, dantrolene sodium, and benzodiazepines, as well as agents affecting α2 adrenal receptors, such as tizanidine and clonidine.[92] When treating spasticity with

oral medications, clinicians should be aware of the potential development of side effects, including fatigue, dry mouth, seizure, and liver dysfunction. Peripheral nerve blocks with ethyl alcohol or phenol and intramuscular botulinum toxin injections have been demonstrated to help manage spasticity in stroke.[90,91,93] Case reports of neurolysis of the medial and lateral motor branches of the tibial nerve to the gastrocnemius muscle with 20% ethyl alcohol in stroke patients with refractory metatarsalgia and pain have been reported to improve spasticity in the ankle and foot, as well as reduce the abnormal distribution of loading on the foot.[90,91] Stretching exercises, neuromuscular electrical stimulation, rTMS, serial casting, antispastic brace use, and surgery have also been used to control spasticity after stroke, although data regarding efficacy of these therapies remain limited.[86]

## Persistent Poststroke Headache

Headache is common around the time of stroke onset. The reported frequency of headache at the acute stage of stroke ranges from 30 to 50%.[94–97] However, persistent headache for months or years after stroke is underrecognized in clinical practice, despite being relatively common.[98] Its prevalence has been reported to be approximately 10% of total stroke patients.[99,100] The severity of persistent poststroke headache is described as moderate to severe, and may be worse than the headaches experienced in the acute phase.[98] The most common types of persistent poststroke headache are probable tension type (50%), followed by probable migraine type (31%).[98] Persistent headache after stroke has been associated with depression and anxiety in patients with stroke.[99]

### Pathophysiology of Persistent Poststroke Headache

Several mechanisms have been suggested to underlie persistent poststroke headache.[101–104] Altered biomechanics of the musculoskeletal system and poor posture following stroke stimulate pericranial myofascial structures, which can trigger sensitization of spinal and supraspinal central neurons resulting in chronic tension-type headaches.[103,104] Alternatively, mechanical or chemical stimulation of the trigeminovascular afferents, which innervate extra- and intracranial vessels, may contribute to headache.[101,102] Another possible underlying mechanism of persistent poststroke headache is dural stretch due to mass effect from infarction or hemorrhage, and ischemia to brainstem nuclei or the pain-sensitive dura.[101,102]

### Treatment of Persistent Poststroke Headache

The treatment of persistent poststroke headache is challenging. Treatment strategies are chosen according to presumed headache type, and are similar to those in patients with headache unrelated to stroke.[105] The oral medications used to treat migraine-type persistent poststroke headache include nonsteroidal anti-inflammatory drugs and antiemetic agents.[106] Ergot derivatives and 5-hydroxytryptamine receptor agonists are usually avoided due to their vasoconstrictive effects. For tension-type headaches, ibuprofen, nonsteroidal anti-inflammatory drugs, and other oral analgesics can be used.[106] Botulinum toxin injection, occipital nerve block, and trigger point injections are also available for these two types of headache.[106,107] Recently, Kwak and Chang reported that pulsed radiofrequency stimulation to the greater occipital nerve can effectively manage refractory chronic migraine pain, although these were not specifically stroke-related headaches.[107] Cognitive behavioral therapy, biofeedback, and exercise are also known to be beneficial nonpharmacological options for managing persistent poststroke headache.[105,107] In 2015, Harris et al conducted a systematic review of cognitive behavioral therapy for the treatment of chronic headache in adults, and reviewed 10 randomized controlled trials.[108] They concluded that cognitive behavioral therapy can be an effective treatment option for reducing the intensity, frequency, and duration of headache. Furthermore, in 2007, Ciancarelli et al reported that biofeedback reduced oxidative stress and migraine symptoms in 20 patients with chronic migraine.[109] The researchers suggested that the decrement of oxidative stress results in muscular relaxation, which would be associated with controlled migraine symptoms. Exercise has also been proposed to increase β-endorphin and endocannabinoid in plasma, which can modulate patients' pain perception.[110]

## Conclusion

Various pathophysiologies have been proposed to contribute to the development of PSP subtypes, and treatment modalities often target these proposed mechanisms. Nonetheless, PSP is often refractory to initial therapies, and randomized, controlled data regarding efficacy of treatment options is needed. Regardless of specific intervention, careful evaluation and early, aggressive treatment of PSP can enhance both functional recovery and quality of life in patients who are recovering from stroke.

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