One of the most troublesome sequelae of stroke is pain, occurring in 19–74% of patients. A portion of this post-stroke pain is caused by the brain lesion itself; this is called ‘central post-stroke pain’ (CPSP). Although the prevalence of CPSP among stroke patients is low (1–8%), the persistent, often treatment-refractory, painful sensations can be a major problem, decreasing the affected patient’s quality of life. As the aging population continues to increase, CPSP will become an even more important problem in the future. Although the pathogenesis of CPSP is not yet known, it has been suggested that underlying causes include hyperexcitation in the damaged sensory pathways, damage to the central inhibitory pathways, or a combination of the two. Adrenergic antidepressants are currently the first-line drugs for CPSP, but their effect is frequently incomplete. Antiepileptics, such as lamotrigine, can be used as an adjunctive therapy, while GABAergic drugs, such as gabapentin or pregabalin, have recently emerged as a potentially useful therapy. Nonpharmacological treatments, such as motor cortex stimulation or deep brain stimulation, also appear to be useful in a certain group of patients. Additional studies are urgently needed to improve our understanding of the pathophysiology of CPSP and support the development of better treatment modalities.

Keywords: cerebrovascular disease • pain • post-stroke pain • sensation • spinothalamic sense

Central pain refers to pain due to CNS lesions, such as those in the brain or spinal cord. Pain occurring in the limbs after a contralateral thalamic stroke was first described by Greiff in 1883 [9]. In 1891, Edinger advanced the concept of central pain by describing a patient suffering from pain secondary to a stroke involving the internal capsule [10]. In 1906, Dejerine and Roussy described painful symptoms on the contralateral limbs in patients with infarcts occurring in the lateral posterior part of the thalamus. In this paper, they described delayed onset (weeks to months after initial strokes) painful symptoms in the presence of decreased perception of pain, touch and temperature, and are especially prevalent in patients with severe stroke (Barthel index ≤10) occurring in 52 and 55%, respectively [8]. Aside from the pain due to peripheral problems, another important cause of pain in stroke patients is that due to the brain lesion itself. The causal mechanism of this ‘central pain’ remains unknown and its treatment is frequently unsatisfactory. This review will primarily focus on this so-called ‘central post-stroke pain’ (CPSP).
occasional hyperperception. They also mentioned that the painful symptoms were refractory, despite the administration of analgesics [11]. In 1938, Riddoch described the characteristics of central pain in more detail, and defined central pain as “spontaneous pain and painful over-reaction to objective stimulation resulting from lesions confined to the substance of the CNS, including dysesthesia of disagreeable kind” [12].

Although these early authors did not define the thalamus as the only location causally related to central pain, central pain after stroke has often been described as ‘thalamic syndrome’ or ‘thalamic pain’. At present, it is widely recognized that strokes occurring anywhere in the sensory tract can produce similar central pain [13–16]. For this reason, the term CPSP is now generally used [17,18]. However, this terminology may not be perfect, because many patients describe the symptoms as sensations of, for example, burning, cold or squeezing, rather than as pain per se. Moreover, the cut-off point for defining ‘pain’ can be unclear when a patient complains of vague, often fluctuating sensory symptoms. Generally, pain specialists prefer the term pain, while stroke neurologists, who often see milder cases, are uncomfortable using this terminology. In this sense, terms such as ‘central post-stroke paraesthesia’ or ‘painful paresthesia’ might be more appropriate [19–21]. However, in this review, the widely used term CPSP will be used.

Epidemiology of CPSP

Although various diseases occurring in the brain, such as tumors, infections, multiple sclerosis or traumatic injury, can produce central pain, cerebrovascular disease is by far the most important causative lesion, accounting for more than 90% of central pain cases [12,14]. Among patients with stroke, CPSP is a relatively uncommon occurrence, with a reported incidence of 1–8% [22,23]. However, the delayed occurrence of symptoms, the lack of objective diagnostic criteria and the fluctuation of symptom severity make it difficult to unequivocally assess the prevalence of CPSP [24]. It seems probable that more than the reported proportion of patients suffer from painful or uncomfortable sensory symptoms after a stroke. Currently, it is assumed that more than 30,000 patients suffer from CPSP in the USA [25]. With an ever-increasing elderly population, it is expected that CPSP will become an even more important problem in the future. Furthermore, CPSP is frequently persistent, refractory to treatment and can adversely impact an affected patient’s quality of life [26]. Therefore, additional study is urgently required in the field of CPSP.

Clinical features

Central post-stroke pain may start at stroke onset, but more often its onset is delayed. In some cases, the delay may last up to several years. However, the vast majority of patients develop CPSP within 6 months after stroke onset [16,23,27]. The symptoms almost always develop within the area of initial sensory impairment [28], usually where the deficits were severe [20]. The symptoms most often occur in the stroke-affected half of the body, but may be restricted to distal body parts, such as the hand and foot, or less commonly to proximal body parts, such as the thigh or shoulder. In addition, prominent involvement of the anterior chest region may mimic pain due to myocardial ischemia [29]. Spinothalamic abnormalities, particularly those that are temperature sensory, are frequently associated with CPSP [4,16,28]. Increased sensory perception is occasionally observed, especially with regard to cold stimuli. However, patients with medial lemniscal sensory deficits [20,30] or without objective sensory deficits may also develop severe CPSP [14]. Dysesthesia is frequent [13,18] and allodynia induced by tactile, cold stimuli or movement is observed in 35–51% of patients with CPSP [27,31]. CPSP has been variably described by its sufferers as burning, aching, squeezing, prickling, cold and lacerating sensations [13,22], and such symptoms are frequently aggravated by a cold environment, psychological stress, heat, fatigue or body movement [28]. Symptoms are persistent in approximately 85% of patients, but the intensity frequently varies depending on the presence of aggravating factors, such as cold weather. Occasionally, symptoms may occur intermittently [32].

CPSP following stroke of different brain regions

Thalamic stroke

The thalamus is the brain region most closely related to CPSP [27,33]. This is understandable when we consider that the ventral posterior lateral (VPL) nucleus is the important sensory relay station, and that hemisensory symptoms are most characteristic in thalamic stroke [34]. Out of 100 patients with thalamic intracerebral hemorrhage (ICH), 9% developed CPSP [35], while 25% of patients with thalamic infarction involving the ventral posterior lateral had CPSP [36].

In thalamic stroke, CPSP is often accompanied by choreoathetotic limb movements; indeed, these were among the components of the classical thalamic syndrome described by Dejerine and Roussy [9,11]. However, while CPSP is mostly associated with spinothalamic sensory deficits, the choreoathetotic movements are related to persistent proprioceptive and cerebellar deficits in patients who have successfully recovered from their motor dysfunction [37]. Therefore, it was suggested that persistent failure in positional and cerebellar inputs, along with unbalanced motor integrity, results in pathological problems in the motor integrative system and consequent involuntary movements [37], whereas CPSP is more closely associated with pure spinothalamic sensory system derangement. Consistent with this, the thalamic lesions producing involuntary movements are generally larger (more often ICH than infarction) than those producing CPSP, thus involving motor, cerebellar and sensory systems together [37]. According to Bowsher, the nature of allodynia may still differ according to the lesion location in the sensory nucleus: cold allodynia is typically related to the dorsal part, while movement allodynia is more often associated with the rostral–dorsal area [34].

Lenticulocapsular stroke

Hemiparesis is the most important neurologic symptom of lenticulocapsular stroke, and post-stroke shoulder pain frequently occurs in patients with severe hemiparesis. However, lenticulocapsular strokes can occasionally produce predominant sensory dysfunction [38], leading to CPSP [21,27,33]. In some patients, CPSP and nociceptive shoulder pain coexist. We studied 20 patients who developed CPSP or paresthesia due to lenticulocapsular ICH
and found that CPSP occurred at an average of 2.9 months after onset [21]. The sensations were described as ‘numb’ in 19 patients, ‘cold’ in ten patients, ‘burning’ in nine patients and ‘aching’ in four patients. The lesions associated with CPSP were generally located posterolaterally, involved the most dorsal part of the posterior limb of the internal capsule and probably caused damage to the ascending thalamocortical sensory tracts. Interestingly, the CPSP in these patients tended to be more severe in the leg than in the arm or face, and some patients suffered from long-standing uncomfortable paresthesia localized to the lower leg.

Cortical stroke
Although less common than in thalamic strokes, strokes occurring in the parietal, insular or opercular areas can produce CPSP [15,23,33,39]. We studied 24 patients who had experienced strokes involving the cerebral cortex and showed prominent sensory symptoms without definitive motor dysfunction [39]. According to the sensory manifestations, patients could be divided into the dominant impairment of primitive sensation (DIPS), dominant impairment of cortical sensation (DICIS), and paresthesia-only groups. DIPS was related to lesions involving the parietal operculum and the insular cortex (SII), whereas DICIS was related to the lesions affecting the postcentral gyrus (SI). CPSP, defined as either a score of 5 or more on the visual numeric scale or symptoms requiring pain-relieving medications, developed only in the DIPS group of patients. These results agreed with the presence of dichotomized (SI and SII) sensory systems in the human cerebral cortex and confirmed that involvement of the insular and opercular areas (SII) is related to primitive sensory impairment and development of CPSP [15].

Pontine stroke
In the pons, ischemic lesions usually affect the ventral part, damaging the descending corticospinal tract, which results in motor dysfunction. Joint pain, especially on the shoulder, sometimes occurs in patients with severe hemiparesis. However, a dorsally located stroke involving ascending sensory fibers can produce significant sensory dysfunction and CPSP [40]. When the lesion is extensive (i.e., ICH), choreoathetotic or tremor-like involuntary movements may be added due to concomitant proprioceptive and cerebellar dysfunction similar to that seen in patients with thalamic stroke [34].

Medullary stroke
Sensory deficit is one of the most important clinical features in patients with lateral medullary infarction (LMI), where it is observed in more than 90% of patients [41]. Consistent with this, sensory symptoms are the most frequent sequelae of LMI, followed by dizziness and dysphagia [21]. MacGowan et al. reported that CPSP occurred in 25% of LMI patients, however, strict criteria were not provided in this study [42]. In medial medullary infarction (MMI), another subtype of medullary stroke, sensory deficit is the second most important symptom, followed by motor dysfunction [43]. Uncomfortable long-lasting sensory sequelae are also fairly common in these patients [21,43].

We studied 55 patients with medullary infarction (41 with LMI and 14 with MMI) who were followed up for at least 6 months [24]. The nature and intensity of sensory symptoms were assessed with the modified McGill–Melzack Pain Questionnaire and the VAS, respectively. We observed differences in the results between LMI and MMI patients. In LMI patients, the severity of residual sensory symptoms was significantly related to the initial severity of the objective sensory deficits. Sensory symptoms were described as cold (38%), numb (29%) and burning (27%) in the body/limbs of LMI patients, whereas MMI patients reported sensations of numb (60%), squeezing (30%) and cold (10%), but never burning in their body/limbs. LMI patients more often cited a cold environment as an aggravating factor for their sensory symptoms than did MMI patients. The subjective sensory symptoms were frequently of delayed onset (up to 6 months) in LMI patients, whereas they usually started immediately after stroke onset in MMI patients.

Pathogenesis of CPSP
The pathogenesis of CPSP is not yet known, but previous reports have suggested mechanisms including hyperexcitation in the damaged sensory pathways, damage to the central inhibitory pathways or a combination of the two [17,24,44]. It is highly likely that various neurotransmitters are involved in this process. The thalamus was believed to be responsible for the generation of this neuronal change. Casey proposed that hyperactivation of some critical neurons in the thalamus is essential for the generation of CPSP [45]. According to this model, the thalamic interneuron (TI) and brainstem reticular formation (BRF) normally inhibit the activity of the thalamic relay neuron (TRN), while the spinal cord activates the TI and BRF. Thus, a spinal cord lesion can excessively activate TRN through disinhibition of the TI and BRF. Thalamic lesions may directly damage the TI or the thalamic reticular nucleus, which normally inhibits TRN, thus increasing the activity of the TRN.

Supporting this theory, some reports have found increased electrical activity in the contralateral, intralaminar thalamic nuclei [46], while increased blood flow in the thalamus was identified by single photon emission computed tomography [47] in patients with CPSP. However, another study using PET found decreased glucose metabolism in the thalamus of patients with CPSP [48]. These inconsistent results may be attributed to technical difficulties in localizing fine structures in the thalamus. More importantly, evidence has suggested that structures related to CPSP are far beyond the thalamus, including various areas of the cerebral cortex. Indeed, CPSP may be aggravated by another stroke occurring on the opposite side [49], or alleviated by ipsilateral [50] or contralateral [51] parietal strokes, suggesting that CPSP may be functionally modified by other cerebral structures, including those in the opposite hemisphere.

One potential cortical structure candidate that may be related to pain generation is the anterior cingulate cortex (ACC). In normal subjects, increased regional cerebral blood flow in the area of the ACC was observed in response to pain stimulation [52–58], which correlated with the subjects’ feeling of unpleasantness [55,57]. However, in a study using PET, after application of cold or electrical stimuli to the painful limbs of patients with LMI, Peyron
et al. found increased blood flow in the contralateral thalamus and parietal area, but decreased blood flow in the cingulate gyrus [59]. In a subsequent study, the same investigators studied a patient with infarcts occurring in the parietal and ACC areas, and found that noxious stimuli triggered activation of the insular cortex with a failure of activation in the ACC [60]. Therefore, they speculated that the combination of increased SII activity and decreased (or a failure to increase) ACC activity in response to innocuous stimuli might be the brain response pattern specifically associated with allodynia.

These results illustrate that activation (or at least certain change) of the insular cortex may be related to the generation of CPSP. Indeed, perception of unpleasantness in skin and muscle was shown to be associated with bilateral insular activation [61]. Another study showed that parietal opercular lesion was related to a decreased ability to identify noxious stimuli as painful, while motivational and affective responses to noxious stimuli were associated with insular lesions [62]. However, what actually happens in the insular cortex of CPSP patients is not yet known. Using PET, Craig et al. found that contralateral brain activity correlated with graded cooling stimuli only in the dorsal margin of the middle/posterior insula in humans [63]. This corresponds to the thermo-receptive- and nociceptive-specific lamina I spinothalamocortical pathway in monkeys, and can be considered an enterointerceptive area within the limbic sensory cortex. Based on these observations, Craig proposed that CPSP results from central lesions affecting the pathways mediating cold sensation that unmask (or disinhibit) cold-induced activation of the polymodal C-fiber nociceptive pathway, which is responsible for the sensation of burning cold pain [64]. This so-called ‘thermosensory disinhibition hypothesis’ seems to be consistent with the very common occurrence of impaired thermal sensation and frequent complaint of burning sensation in CPSP patients, as well as the anatomical locations of lesions coinciding with the ascending lamina I spinothalamiocortical pathway to the dorsal posterior insula [64].

However, although the majority of patients with CPSP have impairment of spinothalamic sensory function, patients with lemniscal sensory disturbances also develop long-standing painful sensory symptoms [20]. This observation recalls an old, but still plausible theory that painful sensory symptoms may be due to disinhibition from a lesion affecting the medial lemniscal pathway [65]. The inter-relatedness of the two (spinothalamic and lemniscal) main sensory systems may be mediated by the spino reticulothalamic system [66]. In this context, medullary stroke is of particular interest in studying CPSP as the two main sensory pathways are anatomically separated in the medulla, with the spinothalamic sensory pathway located laterally and the lemniscal pathway more medially. These pathways are separately affected by LMI and MMI, respectively. By comparing the sensory sequelae due to LMI and MMI, we may obtain some insight into the pathogenesis of CPSP. As described earlier, we found that CPSP due to LMI and MMI differs. Compared with MMI, CPSP due to LMI often had a delayed onset, was more often described as burning or cold and was aggravated more often by a cold environment. These observations suggest that CPSP can occur due to both spinothalamic and medial lemniscal tract injuries, but via different pathogenic mechanisms.

The frequent description of burning or cold (temperature sensations) in LMI but not MMI patients implies that the spinothalamic, but not the lemniscal tract, injury is involved with CPSP in the former patients. We may speculate that CPSP following spinothalamic tract injury is related to uninhibited firing of certain central neurons through excessive feedback following partial damage to the spinothalamic pathways. The observation that cold and heat provoking factors more often in LMI patients than in MMI patients also appears to be consistent with this hypothesis. In our results, the severity of the initial spinothalamic sensory deficit predicted CPSP in LMI patients, suggesting that the degree of the initial spinothalamic tract injury may be a marker for the strength of the feedback inputs. Although we do not yet know how and where the hypersensitive phenomenon develops, one possible mediator for the hypersensitivity could be the spinoreticulothalamic system. Tasker and colleagues previously provided evidence that the spinothalamic and adjacent spinoreticulothalamic tracts are inter-related, such that deafferentation of the former renders the normally nonexcitable reticulothalamic system responsive to stimulation, thus provoking painful sensations [66–67]. Therefore, development of CPSP following a spinothalamic tract injury may depend, at least in part, on the presence of a relatively intact reticulothalamic system [68]. Indeed, MacGowan et al. reported that LMI lesions that extended medially to involve the reticular formation rarely produced CPSP [42]. Regarding the CPSP of MMI, evidence suggests that the lemniscal tract has certain components that inhibit the spinothalamic sensory functions [69–71], possibly through the reticulothalamic system [66]. It may, therefore, be speculated that lemniscal tract injury in MMI disinhibits the spinothalamic system via the reticulothalamic system, ultimately producing hypersensitivity of the spinothalamic sensations. The delayed onset of CPSP in LMI patients may reflect the time required for the partial recovery of the injured spinothalamic fibers (e.g., through sprouting and receptor hypersensitivity), a process not required in MMI patients.

**Treatment of CPSP**

Once developed, it is difficult to completely abolish CPSP. Medications generally help, but are frequently unsatisfactory. Before treating CPSP, the following should be considered. First, a physician should use appropriate examinations and diagnostic tests to confirm that the patient’s symptom is CPSP, rather than nociceptive pain caused by joint contracture, spasticity or peripheral nerve diseases. This is important because the treatment strategy should be different for CPSP versus pain due to other causes. Second, it is important to educate the patient regarding the nature of CPSP. Patients should be informed that pain relief may not occur until a maximal dose of drugs is gradually achieved over a certain period of time. They should also be informed that treatment may be only partly effective, and that the goal of treatment is to reduce the pain burden rather than completely abolishing the symptoms. This approach can help patients learn not to depend on other ineffective or unnecessary therapies. Third, patients with CPSP frequently suffer from comitant depression, anxiety or sleep disturbances. Medication or behavioral therapy aimed at improving these problems may have to be initiated concomitantly to maximize the
that fluvoxamine was partly effective in patients with CPSP controlled crossover study to placebo carbamazepine was not found to be superior to placebo in a double-blind, placebo-controlled, crossover study. However, it is often only partially effective in patients with severe symptoms, or effective only when a large dose (up to 100 mg/day) is administered. Unfortunately, the treatment side effects, such as dry mouth, urinary retention, somnolence and confusion, are frequently intolerable in elderly subjects. In a study investigating the effectiveness of amitriptyline for the prophylactic treatment of CPSP in 39 patients with thalamic stroke, CPSP occurred in 21 and 17% of patients receiving placebo and amitriptyline, respectively; this difference was not statistically significant. Although their efficacy has not been properly investigated in patients with CPSP, antidepressants with adrenergic activities similar to that of amitriptyline, such as nortriptyline, desipramine, imipramine, desexin or venlafaxine, are often used for patients in whom amitriptyline is not effective or not tolerated. Generally, serotonin-uptake inhibitors are less effective for CPSP than adrenergic drugs. For instance, citalopram was found to be ineffective in patients with CPSP, while an open-labeled study showed that fluvoxamine was partly effective in patients with CPSP.

Antidepressants
Amitriptyline was the first drug proven to be effective for patients with CPSP in a double blind, placebo-controlled, crossover study. Based on this result, amitriptyline has been considered as a first-line drug in the management of CPSP. However, it is now increasingly prescribed for CPSP patients. A closely related drug, pregabalin, was also found to be effective in the treatment of various neuropathic pains, including central pain due to a spinal cord lesion. Large clinical trials examining the efficacy of pregabalin in the treatment of CPSP are currently underway.

Opioids
In a double blind, placebo-controlled, crossover study, intravenous infusion of morphine was partially efficacious in treating central pain (reducing only brush-induced allodynia). Oral levorphanol was generally effective in patients with central pain when a high dose was used (8.9 mg/day), the effect was not prominent in patients with CPSP. Naloxone was not found to be effective in patients with CPSP.

Other miscellaneous drugs
Intrathecal baclofen was found to reduce central pain from various causes, including stroke, without inducing significant side effects. However, oral baclofen administration up to 60 mg/day was not effective for central pain. In a double blind, placebo-controlled, crossover study, intravenous lidocaine infusion (5 mg/kg over 30 min) effectively reduced pain scores in 16 patients with central pain due to either stroke or spinal cord injury. Ketamine,

With the postulation that CPSP is caused by unbalanced glutamate/GABA neurotransmission in the CNS, with relative hypofunction of the GABAergic inhibitory system, GABAergic drugs have been considered a potentially useful option for the treatment of CPSP. Valproic acid and clonazepam have been used in this context, but their efficacy has not been conclusively proven in controlled studies. These anticonvulsants may at least be effective in relieving paroxysmal, shooting pains. Zonisamide was reported to be effective in two patients with CPSP due to thalamic stroke, while topiramate, another GABAergic anticonvulsant, was found to be ineffective in diminishing central pain. Recently, gabapentin, a structural analogue of GABA, received special attention as it not only increases GABA levels in the CNS but also acts on voltage-sensitive calcium channels, which modulate the release of other neurotransmitters. Gabapentin was found to be effective in relieving neuropathic pain due to peripheral nerve disease, as well as central pain caused by spinal cord lesions. For this reason, gabapentin is now increasingly prescribed for CPSP patients. A closely related drug, pregabalin, was also found to be effective in the treatment of various neuropathic pains, including central pain due to a spinal cord lesion. A large clinical trial examining the efficacy of pregabalin in the treatment of CPSP is currently underway.

Anticonvulsants & GABAergic drugs
Various anticonvulsants have been tested in patients with CPSP under the assumption that CPSP is related to neuronal hyperexcitability in the sensory system. In a double-blind, controlled study, carbamazepine was not found to be superior to placebo. However, some tendency for improvement was observed, and carbamazepine is currently used as an adjunctive therapy when the efficacy of antidepressants is found to be insufficient. Phenytoin has been shown to be efficacious in some case series, but no double blind trial has been reported to date. On the other hand, lamotrigine, a novel antiepileptic drug that presynaptically inhibits sodium channels and suppresses glutamate release, was reported to be moderately effective in CPSP in both case series and in a double-blind, placebo-controlled crossover study.

Table 1. Treatment of central post-stroke pain.

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment modality</th>
</tr>
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<tbody>
<tr>
<td>Proven by controlled study</td>
<td>Amitriptyline, lamotrigine</td>
</tr>
<tr>
<td>Proven in other pain syndromes but not in central post-stroke pain</td>
<td>Gabapentin, pregabalin</td>
</tr>
<tr>
<td>Not proven in controlled study but potentially useful</td>
<td>Carbamazepine, valproic acid, phenytoin, clonazepam, zonisamide, Nortriptyline, desipramine, imipramine, dexamethasone, venlafaxine, fluvoxamine, levoephophanol, mexiletine, Motor cortex stimulation, deep brain stimulation</td>
</tr>
</tbody>
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a noncompetitive NMDA blocker, also reduced pain scores in patients with central pain due to spinal cord injury [98]. However, the oral NMDA channel blocker, dextromethorphan, was less effective in CPSP patients [99]. Ziconotide, a novel 25 amino acid peptide derived from the venom of the genus Conus (poisonous snails) [100], has been shown to be effective in chronic malignant or nonmalignant pain, including neuropathic pain [101–104]. The agent is thought to exert its antinociceptive properties by binding to, and directly blocking, voltage-sensitive calcium channels without interfacing with opioid receptors [100]. Although long-term experience with ziconotide is limited, tolerance problems and dependence, as found with opioids, do not occur [105]. Unfortunately, this agent is only effective via intrathecal delivery and the invasive administration method is a limitation in the management of long-standing problems of CPSP. Although oral calcium channel blockers have not been adequately studied for CPSP, these agents do not appear to be effective. However, they may produce cutaneous vasodilatation and a feeling of warmth in areas of CPSP, which could be of practical help in patients who experience distressing feelings of coldness in their affected limbs [84]. Finally, the anti-arrhythmic mexiletine occasionally produces pain-relieving effects when co-treated with antidepressants [84].

**Nonpharmacological treatment**

**Surgical operation**

Various surgical procedures have been reported to reduce central pain; these include rhizotomy [106], sympathectomy [17], dorsal root entry zone lesions [107], cordotomy [106], thalamotomy [2], post-central gyrectomy [17,108], frontal lobotomy and cingulotomy [17,109]. However, these methods have been attempted primarily in patients with cord lesions and only occasionally in those with CPSP. Moreover, the benefits were frequently unpredictable, short-term and associated with significant morbidity and mortality. With the development of effective drugs and less-invasive stimulation technologies, these outdated procedures are no longer recommended in patients with CPSP. Hypophysectomy, first described in 1953 [110], was also accompanied by significant complications, such as panhypopituitarism, diabetes insipidus and meningitis. To reduce the morbidity, radiosurgical hypophysectomy using a 200–250 Gy maximum irradiation was introduced [111]. According to a recent review of 24 patients with thalamic pain who underwent pituitary radiosurgery, significant pain reduction was achieved in 17 patients (71%) [112]. However, pain recurred within 6 months in the majority of cases, and at the time of the last follow-up, durable pain control was achieved in only five patients (21%), while ten patients (42%) had treatment-associated side effects, such as hormonal deficiency. Thus, this therapy is not recommended at this time, except for in an experimental setting.

**Stimulation therapy**

**Transcutaneous electrical nerve stimulation**

Transcutaneous electrical nerve stimulation, or acupuncture, has been reported to benefit some patients with CPSP [113] and has the advantage of producing few side effects. However, the improvement is not observed in many patients and the effect is usually temporary.

**Dorsal column stimulation**

Stimulation of the posterior columns of the spinal cord has shown some effectiveness in reducing central pain due to spinal cord lesions [114]. However, future studies are required to examine the efficacy of this strategy in CPSP patients.

**Deep brain stimulation**

Deep brain stimulation (DBS) with electrodes implanted within the periventricular gray, the specific sensory thalamic nuclei or the internal capsule, was found to be effective in selected patients with medically intractable pain. According to a series of 15 post-stroke patients with neuropathic pain who were treated by DBS, the treatment was most effective in reducing burning hyperesthesia, with average pain relief of the order of 40–50% [115]. The potential mechanisms for the pain-relieving effect include an inhibitory effect on the sensory thalamus [116], release of endogenous opioids [117] by periventricular gray stimulation and alteration of certain vasomotor systems after DBS [115]. However, the treatment response of DBS for CPSP is quite variable among patients, and is generally less satisfactory than with peripheral origin pain [118,119]. Possible reasons for therapeutic failure include central reorganization and neuroplastic changes of the pain-transmitting pathways and pain modulation centers following brain and spinal cord lesions [118,119]. Further studies are required to improve the efficacy and to find candidate patients who would gain the most benefit from this procedure.

**Motor cortex stimulation**

In 1991, Tsubokawa et al. first demonstrated the efficacy of electrical stimulation of the motor cortex in patients with CPSP [120]. The theoretical basis for this strategy was the inhibition of nociceptive ascending pathways by motor cortex stimulation (MCS) observed in experimental animals. Despite the lack of solid scientific background and still-evolving technologies, many neurosurgeons have reported beneficial effects of MCS in patients with pain. According to a recent review of 159 cases treated by MCS, the success rates at the time of last follow-up ranged from 0 to 67% (average 52%) [121]. Another review demonstrated that approximately 60% of patients with central pain showed improvement (greater than 50% pain relief) with this procedure [122]. Although uncommon, there are some complications associated with this procedure; these include stimulation-induced seizures, subdural hematoma and infection [110,122]. Loss of efficacy at long-term follow-up was observed in some patients, perhaps due to neural plasticity and reorganization of the deafferentated cortical area. According to Katayama et al., who compared the efficacy of spinal cord stimulation, DBS of the thalamic nucleus ventralis caudalis and MCS in 45 patients with post-stroke pain, satisfactory pain control was obtained more frequently as the stimulation site was moved to higher levels (7% by spinal cord stimulation, 25% by DBS and 48% by MCS) [123]. They hypothesized that abnormal processing of nociceptive information may develop and spread to higher levels, which explains why satisfactory pain control was obtained more frequently as the stimulation site was moved to higher levels.
Unfortunately, controlled studies proving the efficacy of MCS have been rare. Although Velasco et al. performed a randomized, blinded on-and-off stimulation test, and confirmed the efficacy of MCS in 11 patients with neuropathic pain, only one patient with CPSP was included in the study subjects. Recent reviews have shown that MCS is less efficacious in CPSP than in peripheral neuropathic pain. In response to this, investigators are trying to find candidate patients who would gain the most benefit from this procedure. According to one study, satisfactory pain control is achieved more frequently in patients with mild or no motor weakness than in those with severe weakness, suggesting that relatively intact motor fibers predict satisfactory therapeutic results. In agreement with this finding, Goto et al. applied diffusion tensor MRI in patients with central pain who were scheduled to undergo MCS and found that patients with higher delineation ratios in their corticospinal tracts and thalamocortical sensory tracts enjoyed good functional outcomes after MCS therapy. This fiber tracking method may, therefore, be used for predicting the MCS therapy response for CPSP patients. Recently, repetitive transcranial magnetic stimulation (rTMS) of the motor cortex was shown to be effective in patients with central pain. Since rTMS seems to be a good predictor of MCS efficacy, MCS may be recommended in patients who have good results following rTMS.

Although MCS is certainly a promising method for the treatment of CPSP, given the presence of a small but significant level of surgical morbidity and the lack of large clinical trial results, it is currently recommended as a last-resort method for medically intractable patients in the setting of a well-established, functional neurosurgery center.

**Vestibular caloric stimulation**

Recently, Ramachandran et al. reported dramatic improvement of CPSP following vestibular caloric stimulation. The theoretical basis for this therapy was that since the posterior insula receives both vestibular and pain signals, vestibular stimulation would activate the posterior insula, in turn inhibiting pain generation in the anterior cingulate. These fascinating and potentially important observations, however, await confirmation through a larger study. In addition, strategies for perpetuating the observed improvements should be developed for practical use.

**Expert commentary**

Although CPSP has long been recognized in the medical literature, it has received relatively little attention to date. However, in the face of consistent increases in the aging population, we must pay more attention to this issue. Thanks to the development of tools, such as functional MRI and molecular brain imaging, the pathogenesis of CPSP will be more vigorously investigated in the near future. As described herein, the treatment of CPSP is still unsatisfactory and only a few well-designed and controlled drug studies have been performed to date.

Certainly, there are reasons for this relative paucity of therapeutic investigations. First, although CPSP is an important problem, the prevalence of CPSP among stroke patients is low, meaning that each physician typically sees only a small number of these patients. Moreover, because CPSP may have a delayed onset, patients who are referred to smaller clinics in the chronic stage are often not adequately assessed or referred back to their initial neurologist. Therefore, it is difficult to assess or recruit a large number of CPSP patients. Second, drug companies generally have more interest in common pain disorders, such as root or peripheral nerve diseases, rather than relatively rare disorders, such as CPSP. Moreover, for financial reasons, such companies rarely show enthusiasm for further trials with potentially useful, but old and cheap drugs. Without interest and financial support from pharmaceutical companies, it is often difficult to carry out a large-scale clinical trial. Finally, the symptoms of CPSP are diverse and the pathogenesis may not be identical in each patient. Therefore, some drugs may be effective only in certain cases (i.e., a given drug may be effective in relieving burning but not cold sensations). Again, difficulty in recruiting a large number of well-assessed patients has so far prevented us from examining this issue correctly. Certainly, future studies should be carried out to elucidate the pathogenic mechanism of CPSP, and to develop better treatment modalities based on an improved understanding of the pathophysiology of this disorder.

Currently, for the management of CPSP, I start with amitryptiline and increase the dosage until it is tolerated. If the pain relief is not satisfactory, I add anticonvulsants, firstly lamotrigine, but often also carbamazepine, valproic acid or clonazepam. As a last resort, I use either gabapentin or pregabalin. I think it is important to increase the dosage of a drug until the maximum dosage is tolerated before switching to or adding another drug. We must consider side effects and costs at the same time. Nonpharmacological treatments, such as MCS, should be reserved for patients who are refractory to any medical treatment. Until more data are obtained on these methods, nonpharmacological therapies should be used only in experimental settings, under rigorous control from experts.

**Five-year view**

Some clinical trials are now ongoing, including a study on the use of pregabalin on patients with CPSP. The results from these studies will be available within the next few years. Existing, potentially useful drugs will be assessed with better-designed methods, while other newer drugs will appear on the market. Technical developments leading to improved nonpharmacological therapy, such as MCS, rTMS or DBS, will allow us to choose this method for patients who are likely to benefit most.

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Key issues

- Pain is one of the most troublesome sequelae of stroke, occurring in 19–74% of patients.
- The prevalence of central post-stroke pain (CPSP) among stroke patients is low (1–8%); however, its significance will increase in the future with an increase in the elderly population.
- The persistent, often treatment-refractory CPSP significantly decreases the affected patient’s quality of life.
- CPSP may start at stroke onset, but more often its onset is delayed. It is variably described by its sufferers as, for example, burning, aching, squeezing, pricking, cold or lacerating sensations, and is frequently aggravated by a cold environment, psychological stress, heat, fatigue or body movement.
- CPSP is usually, although not always, associated with spinothalamic abnormalities, particularly temperature-sensory ones.
- Suggested mechanisms of CPSP include hyperexcitation in the damaged sensory pathways, damage to the central inhibitory pathways or a combination of the two.
- Amitriptyline was the first drug proven to be effective for patients with CPSP in a double-blind, placebo-controlled, crossover study.
- Antiepileptics, such as lamotrigine, are moderately effective. GABAergic drugs, such as gabapentin or pregabalin, are promising, and their efficacy is currently under investigation. Nonpharmacologic therapies, such as motor cortex stimulation or deep brain stimulation or a combination of the two.

References

Papers of special note have been highlighted as:
• of interest
** of considerable interest

** Old, but still excellent, paper describing clinical features of central pain in detail.
** The first, and perhaps currently the only study that determines the incidence of central post-stroke pain (CPSP; in a prospective fashion) and describes the syndrome in an unselected group of stroke patients with respect to cerebrovascular lesion, somatosensory dysfunction and psychosocial outcome.
** Authors elucidated the differences in sensory sequelae between patients having damaged spinothalamic system and those with lemnisical sensory pathway lesions.
** The first, and perhaps currently the only study that determines the incidence of central post-stroke pain (CPSP; in a prospective fashion) and describes the syndrome in an unselected group of stroke patients with respect to cerebrovascular lesion, somatosensory dysfunction and psychosocial outcome.
- Nicely reviews the clinical characteristics of CPSP.
- The authors studied blood flow changes using PET in various cortical areas in a patient with lateral medullary infarction and allodynia.
- Addresses the ‘thermosensory disinhibition hypothesis’ of CPSP.
65 Head H, Holmes G. Sensory disturbances from cerebral lesions. Brain 34, 102–254 (1911).
66 Tasker RR, de Carvalho G, Dostrovsky JO. The history of central pain syndrome, with observations concerning pathophysiology.


• Small, but important study demonstrating that amitriptyline is effective in reducing CPSP.


• Nicely performed study showing the effectiveness of lamotrigine in CPSP.


Post-stroke pain

Review


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