A review of central neuropathic pain states

Nanna B. Finnerup

Danish Pain Research Center, Aarhus University Hospital, and the Spinal Cord Unit, Viborg Hospital, Denmark

Correspondence to Dr Nanna B. Finnerup, MD, Danish Pain Research Center, Aarhus University Hospital, Norrebrogade 44, Building 1A, 8000 Aarhus C, Denmark
Tel: +45 89493456; e-mail: finnerup@ki.au.dk


Purpose of review
Central neuropathic pain is an important and disabling but often neglected problem following central nervous system lesions. The present review highlights recent advances in the understanding of the underlying mechanisms and in the diagnosis and treatment of central pain.

Recent findings
Within the past year, the field of central pain has moved toward a more integrative understanding of central pain. The involvement of nonneuronal cells and interaction between multiple areas of the central nervous system has been recognized as important in the underlying mechanisms. The interest for conditions other than spinal cord injury, multiple sclerosis, and stroke has increased, and continued discussions on clear clinical diagnostic criteria are needed. The treatment of central pain is still a great challenge, but recent evidence points to tricyclic antidepressants, gabapentin and pregabalin, and selective serotonin–noradrenaline reuptake inhibitors as first-line drugs in central pain. An increased understanding of the psychosocial aspects of central pain also has implications for the treatment.

Summary
Increased insight into the mechanisms of central pain will hopefully lead to increased efforts to study mechanism-based treatment of central pain.

Keywords
central pain, multiple sclerosis, Parkinson’s disease, poststroke pain, spinal cord injury, traumatic brain injury

Introduction
Central pain is a heterogeneous group of chronic neuropathic pain conditions arising from injury or disease of the central nervous system (CNS), such as spinal cord injury (SCI), syringomyelia, multiple sclerosis (MS), stroke (infarction or hemorrhage), traumatic brain injury, Parkinson’s disease, tumors, and epilepsy [1]. Central pain is often chronic, disabling, and resistant to treatment and may have a major impact on the mood and quality of life in these patients. Available pharmacological agents often only reduce pain to some degree [2], and their use may be limited by unwanted side effects, poor tolerance to CNS-active drugs, or drug interactions.

Central pain conditions
Central pain is defined as ‘pain initiated or caused by a primary lesion or dysfunction of the CNS’ by the International Association for the Study of Pain (IASP) [3]. Recently, a more concise definition has been introduced suggesting that central pain is ‘pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system’ [4**]. Following this new proposal, the prerequisites for the diagnosis of definite central neuropathic pain are: the pain is in a neuroanatomically plausible pain distribution, a history of a relevant lesion or disease affecting the central somatosensory system, negative or positive sensory signs confined to the somatotopic representation of the body within the CNS, and a diagnostic test confirming a lesion or disease explaining the presence of neuropathic pain [4**]. The identification of central pain is important and may in addition involve several tests to exclude peripheral neuropathic or nociceptive pain. When evaluating central pain, methods validated in central pain conditions are preferably used [5*]. Various screening tools have been developed to differentiate between neuropathic and nonneuropathic pain [6], but none of these is validated in central pain conditions. The neuropathic pain scale (NPS) was developed to assess distinct pain qualities associated with neuropathic pain and is sensitive to measuring outcomes of therapeutic interventions [7]. This is the only tool that has currently been validated in a central pain condition. The NPS was found to be a valid and reliable tool in the assessment of central pain associated with MS [8*].

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Central pain occurs in approximately 8% of patients with stroke, 25% of patients with MS, and 40–50% of patients with SCI [1] and is relatively well described in these conditions. Less is known about the prevalence and characteristics of central pain in other CNS diseases, and the lack of clear diagnostic criteria for central pain makes the diagnosis difficult.

In Parkinson’s disease, chronic pain may arise because of musculoskeletal disorders, radiculo-neuritic syndromes, or dystonia [9*]. In addition to these types of pain, pain may be present with no obvious underlying mechanism and is thought to be a direct consequence of the disease, namely a central pain. This type of pain is characterized by painful sensations described as stabbing, aching, and burning, predominantly in the more affected side and ‘off’ condition [9*,10]. As sensory changes and lesions affecting the central somatosensory system are not obvious in Parkinson’s disease and thus do not seem to fulfill the new criteria for central pain [4**], recent studies have shown changes in heat pain thresholds that support a central underlying course of the pain. In a neurophysiologic study [9*], patients with Parkinson’s disease and pain with no other reason had normal warm sensory thresholds but lower heat pain and laser pinprick thresholds and higher amplitudes of laser-evoked potentials in the ‘off’ condition than patients with no pain with the differences attenuating by 3,4-dihydroxy-L-phenylalanine (L-dopa) in the ‘on’ condition. These changes suggest enhanced responsiveness to painful stimuli and a relationship between the hypersensitivity to painful stimuli and the dopaminergic activity. The mechanisms underlying this type of pain in Parkinson’s disease are unknown, but recent experimental, clinical neurophysiologic, pharmacological, and brain imaging studies indicate that the basal ganglia and dopaminergic system are involved in the gating of nociceptive information to higher areas in central pain modulation, and in the development of neuropathic pain [11,12*]. Involvement of striatal dopamine D2 receptors in the noradrenergic pain inhibitory circuitry is one of the mechanisms by which the basal ganglia may be involved in nociceptive integration and thus offers a possible explanation for pain associated with Parkinson’s disease [12*] and may explain the efficacy of levodopa on pain thresholds in this pain condition [10,13] as well as neuropathic pain in painful diabetic neuropathy [11].

In patients with brain trauma, lesions of the somatosensory pathways are often obvious and the diagnosis of central pain may thus be more straightforward. A systematic study [14**] of patients with brain trauma showed that chronic pain in traumatic brain injury resembles that of other central pain patients. Pain was chronic with an onset time of 0.5–30 months after injury. The pain was often unilateral, corresponding to the body side exhibiting a more severe motor and sensory dysfunction, and dispersed across several body regions. The mean pain intensity score on a visual analog scale VAS (0–10) at the day of testing was mild to moderate (2.8 ± 2), yet many patients reported that the pain had an impact on their ability to concentrate on work. Pain descriptors included pricking, cold, freezing, numb and wretched, pressing and burning and all described allodynia to cold, touch, physical effort, or movement. A decrease in thermal sensitivity was demonstrated supporting a lesion of the somatosensory pathways and the presence of central pain.

Mechanisms of central pain

Through experimental models of central pain, in particular SCI models, we have gained more knowledge of central pain mechanisms. Gain in neuronal excitability, loss of inhibition, and increased facilitation are thought to contribute to a central sensitization and disinhibition of pain pathways [1,15]. Recently, there has been an increased focus on the interaction between inflammation and neuropathic pain. Activated microglia was found to maintain neuronal hyperexcitability in the spinal cord through an extracellular signal-regulated kinase (ERK)-regulated prostaglandin E(2) signaling mechanism [16**]. Furthermore, a SCI was found to trigger remote changes with upregulation of the microglia activator cysteine–cysteine chemokine ligand 21 (CCL21) and induction of microglia activation in the thalamus, changes that were associated with pain behavior [17**]. Another study [18**] also found the chemokine CCL 2 (monocyte-chemoattractant protein-1) to be a possible candidate of integrating inflammation and central neuropathic pain after SCI.

In addition to animal studies pointing towards a role of brain mechanisms in pain following spinal lesions, human brain imaging studies emphasize supraspinal pain mechanisms. In an electroencephalogram (EEG) study, a cerebral slowing of the EEG towards the θ frequency range in individuals with SCI compared with controls, which was more pronounced and generalized in patients with neuropathic pain, suggests that alterations in brain electric activity may underlie the development of neuropathic pain [19*].

Decreased temperature sensation is a common feature in central pain patients and has been suggested to be a necessary but not sufficient condition for central pain. However, studies have failed to find any differences in thermal thresholds between patients with and without central pain [20]. Correlations between thermal thresholds and central pain have not been described, and patients with complete abolition of pain and temperature sensation may never develop central pain. On the contrary, evoked pain and gain in spinothalamic
tract function are more common in patients with central pain than without this pain, and it must be questioned whether loss of spinothalamic function is a predictor and necessary condition for central pain.

In central poststroke pain, various disinhibition theories have been proposed and various thalamic nuclei have been suggested to be implicated in thalamic pain. A recent small MRI study [21] of four patients with thalamic lesions (three with CPSP) aimed to examine which nuclei may be implicated in central pain. The study [21] suggested that lesions of the human thalamic ventral caudal nucleus not involving posterior part of the ventral medial nucleus (VMpo) were sufficient to impair cold sensitivity and produce CPSP.

Thus, despite the increasing number of experimental and clinical studies examining the mechanisms underlying central pain, we still need to know more about the spinal and cerebral processing of central pain and the molecular, cellular, and anatomical mechanisms underlying this pain condition. With the advent of neuroimaging, we may in the future be able to better understand the integrative mechanisms of pain processing and modulation [22,23].

Treatment of central pain

Treating central pain is a great challenge. The commonly used drugs have limited response rates, and responders typically experience only partial pain reduction at tolerable doses. New trials focusing exclusively on central pain have emerged in the last years and provide some evidence to make rational treatment recommendations. Antidepressants and the α,δ-calcium antagonists gabapentin and pregabalin have a well established beneficial effect in various neuropathic pain conditions [2]. Very recently, a randomized, triple crossover trial [24] comparing amitriptyline 150 mg, gabapentin 3600 mg, and the active placebo diphenhydramine in SCI patients with neuropathic pain was published. Of the 38 participants randomized, only 22 completed all three treatment arms. Amitriptyline relieved pain more than both diphenhydramine and gabapentin, whereas gabapentin was not more effective than diphenhydramine, although a type II error cannot be excluded. Amitriptyline was most effective in participants with many depressive symptoms at baseline, although amitriptyline treatment was not associated with mood improvement. Certain side effects (dry mouth, constipation, nausea, difficulty emptying the bladder, drowsiness, and fatigue) were more common during amitriptyline treatment than during the other two treatments. The high amitriptyline dose used in this study (150 mg/day) also raises concerns about long-term cardiac side effects. However, this study does suggest that tricyclic antidepressants (TCAs) should be considered a treatment option in this neuropathic pain population also.

Despite the lack of a pain-relieving effect of gabapentin in this study, gabapentin and pregabalin have been shown to relieve peripheral neuropathic pain and SCI pain [2]. A recent study [25] has also shown that pregabalin relieves central poststroke pain. In this study, pregabalin significantly relieved pain in patients with spinal or brain injury. Side effects were mild to moderate with no difference in frequency of adverse reactions in the two study groups.

Except for one study [10] evaluating duloxetine in primary pain in Parkinson’s disease, no randomized controlled trials have evaluated the efficacy of selective serotonin–noradrenaline reuptake inhibitors (SNRIs) in central pain. Whereas this class of drugs has shown a moderate effect on pain in painful polyneuropathy (reviewed in [2]), SNRIs may be a safer choice than TCAs in patients with cardiac disease and are therefore considered a possible drug of choice in central pain.

The anticonvulsant drug lamotrigine was recently studied in central pain in MS [26]. In this crossover study, in which 12 of 15 patients completed at least the first period, lamotrigine did not relieve central pain. Lamotrigine also has questionable or limited efficacy in peripheral neuropathic pain [27,28] and its role in the treatment of neuropathic pain is limited [2,29].

On the basis of recent studies [2,29] on central pain, TCAs and gabapentin and pregabalin are considered first-line drugs in central pain. These drug classes have a well documented efficacy demonstrated in peripheral and central neuropathic pain; the effect is clinically relevant and the side effect profile is acceptable, although the long-term efficacy, safety, and tolerability are not well documented and high doses of TCAs may be a matter of concern. Given the established efficacy of SNRIs in peripheral neuropathic pain, this drug class may be considered when TCAs are not tolerated. Opioids are a possibility if other treatment fails or as relief of intermittent pain when a chronic treatment is not indicated [2,29]. Lamotrigine may be considered in CPSP and cannabinoids in pain in MS [29]. As the efficacy of a given drug is unpredictable, treatment is often a trial-and-error process. Newer treatment options such as transcranial magnetic stimulation or motor cortex stimulation are suggested to be effective in central pain [30,31], but studies on long-term efficacy are needed. Treatment often needs to be a multidisciplinary approach to relieve the suffering of the patients, with focus not only on reducing pain intensity but also on depression and anxiety, coping strategies, patterns of adaption, catastrophizing, and social support [32,33].

Conclusion

Central pain is a challenging condition. Diagnosis of central pain is the first important step and continued
discussions on the boundaries of the central pain definition and development of a validated clinical diagnostic tool are important. Although we have made progress in the understanding of the mechanisms of central pain, we are still far from a full understanding of the anatomical basis and the cellular, molecular, and neurochemical mechanisms. In addition to developing new and better pharmacological treatments, we need a further understanding of the interaction with psychosocial factors.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 689).


The study suggests a new definition and a grading system of definite, probable, and possible neuropathic pain.


The review summarizes the reliability and validity of various pain outcome measures and provides recommendations for specific measures for use in clinical SCI trials.


The first study to demonstrate the efficacy of amitriptyline in SCI pain.


The first study to evaluate a neuropathic pain questionnaire in a central pain condition.


The study provides evidence for involvement of striatal dopamine D2 receptors in the noradrenergic pain inhibitory circuitry.


The study highlights the characteristics of central pain in traumatic brain injury, a previously neglected problem.


The study provides an insight into the mechanisms of signaling between microglia and neurons and highlights the role of microglial activation in central pain.


The observation of remote microglial activation has consequences for our understanding of supraspinal mechanisms in SCI pain. It also supports the role of microglial activation in evoked pain.


The study suggests that chemokines are potential candidates for integrating inflammation and central neuropathic pain after SCI.


The study suggests changes in brain activity following SCI with reduced electroencephalogram (EEG) spectral reactivity in those patients with neuropathic pain. This emphasizes the role of the brain in the generation or maintenance of central pain following a SCI.


The first study to demonstrate the efficacy of amitriptyline in SCI pain.


The study supports the efficacy of pregabalin in central pain conditions.


A comprehensive review provides evidence-based treatment recommendation for neuropathic pain.


