MAYO CLINIC

Central Neuropathic Pain Syndromes

James C. Watson, MD, and Paola Sandroni, MD, PhD

From the Department of Neurology (J.C.W., P.S.) and Department of Anesthesiology, Division of Pain Medicine (J.C.W.), Mayo Clinic, Rochester, MN.

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*.™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Credit Statement: Successful completion of this CME activity enables the participant to earn up to 1 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC points.

Learning Objectives: On completion of this article, you should be able to (1) recognize clinical features that differentiate central neuropathic pain from other pain types seen as sequelae of chronic neurologic impairment; (2) define the typical temporal profile of the onset of central neuropathic pain syndromes; and (3) differentiate the roles of various pharmacological, surgical, and neuromodulatory techniques in the treatment of specific central pain syndromes.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

Drs Watson and Sandroni discuss off-label use of various medications as well as spinal cord stimulation, deep brain stimulation for central pain treatment, rTMS, and motor cortex stimulation.

In their editorial and administrative roles, William L. Lanier, Jr, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry. The authors report no competing interests.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 3/1/2016

Expiration Date: 2/28/2018 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html.

Questions? Contact dletcsupport@mayo.edu.

Abstract

Chronic pain is common in patients with neurologic complications of a central nervous system insult such as stroke. The pain is most commonly musculoskeletal or related to obligatory overuse of neurologically unaffected limbs. However, neuropathic pain can result directly from the central nervous system injury. Impaired sensory discrimination can make it challenging to differentiate central neuropathic pain from other pain types or spasticity. Central neuropathic pain may also begin months to years after the injury, further obscuring recognition of its association with a past neurologic injury. This review focuses on unique clinical features that help distinguish central neuropathic pain. The most common clinical central pain syndromes—central poststroke pain, multiple sclerosis–related pain, and spinal cord injury–related pain—are reviewed in detail. Recent progress in understanding of the pathogenesis of central neuropathic pain is reviewed, and pharmacological, surgical, and neuromodulatory treatments of this notoriously difficult to treat pain syndrome are discussed.

 ■ Mayo Clin Proc. 2016;91(3):372-385

The International Association for the Study of Pain defines neuropathic pain as pain originating from a lesion or disease of the somatosensory nervous system.[1] Clinicians most commonly encounter neuropathic pain stemming from impairment within peripheral nervous system pathways (eg, painful peripheral neuropathy, radiculopathy, complex regional pain syndrome, postherpetic neuralgia). Less commonly, neuropathic pain can develop from disease affecting the brain, brainstem, or spinal cord. This disorder is termed *central*

neuropathic pain. Central neuropathic pain can result from any type of injury to the central nervous system (CNS) including vascular (ischemic or hemorrhagic), infectious (abscess, encephalitis, myelitis), demyelinating, traumatic (brain or spinal cord), or neoplastic disorders. It can also result from syrinx formation in the spinal cord or brainstem. However, central neuropathic pain is most commonly a sequela of stroke (central poststroke pain [CPSP]), multiple sclerosis (MS), or spinal cord injury (SCI).

There are unique challenges in distinguishing central neuropathic pain from musculoskeletal or peripheral neuropathic pain in patients who are neurologically impaired. Additionally, central neuropathic pain often occurs months or years after the original CNS insult and at a time when a patient's medical care may have transitioned back to their primary care physician and away from specialty care. Finally, central pain is very challenging to treat and may not respond to pharmacological agents routinely used for peripheral neuropathic pain. As such, it is important for primary care physicians, as well as specialists, to be familiar with the distinguishing features of central neuropathic pain and its unique treatment options.

DISTINCTION BETWEEN CENTRAL NEUROPATHIC PAIN AND CENTRAL SENSITIZATION

Central neuropathic pain syndromes should not be confused with central sensitization, which is a sequela of chronic pain. Central sensitization refers to a situation in which chronic nociceptive afferent input from a peripheral pain generator causes reversible ("plastic") changes of central nociceptive pathways (up-regulation or "wind-up") such that nonpainful peripheral stimuli are interpreted as painful (allodynia) and painful peripheral stimuli (eg, pinprick) are interpreted as overly painful (hyperalgesia). In contradistinction, central neuropathic pain refers only to pain that results directly from the CNS injury. Central sensitization from chronic peripheral neuropathic pain generators should not be labeled as central pain syndrome.

PAIN IN NEUROLOGICALLY IMPAIRED PATIENTS

Pain is common in patients who are neurologically impaired, but it is usually not central neuropathic pain. For example, after a stroke, 11% to 55% of patients will experience chronic pain, but it is frequently musculoskeletal nociceptive pain as a consequence of impaired mobility putting a greater burden on nonimpaired limbs.[2] Musculoskeletal shoulder pain in patients with arm paresis is particularly common (30%-40% of patients) following stroke.[3,4] Patients with gait disorders from CNS insults often experience knee, hip, and low back pain from altered mechanics, and patients who are wheelchair bound are at risk for low back pain and upper limb overuse syndromes (up to 75% of patients with SCI).[5] In MS populations with chronic pain, nociceptive pain from low back and musculoskeletal joint pain is common (20%-40% of patients)[6-8] and at least as common as central neuropathic pain.[9] In patients with SCI, musculoskeletal pain is the most common type of pain (50%-70% of those with pain),[9,10] but it is also less severe or limiting than the less prevalent central neuropathic pain.[9] Of course, patients can have multiple pain generators. In SCI cohorts, it has been well recognized that most patients with central neuropathic pain also have superimposed nonneuropathic pain contributors (musculoskeletal or visceral).[9,11] Comorbid noncentral pain types have also been found to be common in CPSP and MS pain cohorts.[8,12,13]

In neurologically intact patients, distinguishing these musculoskeletal pain types from a neuropathic pain etiology may seem straightforward. However, in patients with impaired discriminatory sensation, pain descriptors are frequently vague and localization and pain triggers are poorly defined.[9,14] Further, clinical examination in the office may be challenging in patients who are wheelchair bound or have severe mobility limitations. Ancillary testing and imaging may be necessary if the diagnosis remains in question.

Spasticity (increased tone- and velocity-dependent resistance to movement in the neurologically affected limb) is also a common consequence of CNS lesions and often leads to symptoms of tightness, stiffness, or discomfort in the neurologically affected limb. Central neuropathic pain will have obligatory accompanying sensory deficits that may help distinguish it from spasticity, but when spasticity occurs in a limb with central motor and sensory deficits, the distinction can be difficult. All patients with possible central pain should have the tone of the neurologically affected

limb assessed to assure that poorly controlled spasticity is not a major contributor to the limb pain. Spasticity is tested by rapid passive movement of the affected limb. For the upper limb, the examiner takes the patient's hand and rapidly supinates an initially pronated hand or rapidly flexes and extends the patient's elbow. Substantial resistance to the movement indicates spasticity. In testing the lower limb, the patient is supine and the examiner rapidly lifts a relaxed knee off the bed. When there is no spasticity, the knee will flex easily and the heel will drag up the bed. Resistance to knee flexion causing the foot to come off the bed indicates lower limb spasticity.

CENTRAL NEUROPATHIC PAIN CHARACTERISTICS

Pain Descriptors and Differentiation

Common neuropathic pain descriptors include burning, uncomfortable cold, prickling, tingling, pins-and-needles, stabbing, shooting, lancinating, tight, swollen, and squeezing sensations that are distressing. Chronic itching in the region of a neurologic deficit can also be a neuropathic pain equivalent. Importantly, although these descriptors suggest a neuropathic pain etiology, they are not specific for neuropathic pain and are frequently used in some common musculoskeletal pain syndromes as well. For example, burning is a common descriptor for both neuropathic pain and trochanteric bursitis. In a study of patients with SCI who are at high risk for both musculoskeletal pain complications from limited mobility and central neuropathic pain, pain descriptors were insufficient to differentiate central neuropathic from musculoskeletal nociceptive pain.[15] As such, the presence of one of these descriptors does not prove a neuropathic pain etiology, and the absence of one of these descriptors does not fully exclude it.

Several neuropathic pain scales have been developed to screen populations for the presence of neuropathic pain of any type or etiology (the Neuropathic Pain Questionnaire[16] and the Leeds Assessment of Neuropathic Symptoms and Signs[17]) and for categorizing subtypes of neuropathic pain (the Neuropathic Pain Symptom Inventory[18] and the Neuropathic Pain Scale[19]), but even these scales are limited in sensitivity and specificity, generally in the range of 70% to 85%. Although less common, the presence of allodynia or hyperalgesia is very specific for neuropathic pain. Neuropathic pain descriptors do not distinguish central from peripheral nerve pain generators. For example, neuropathic pain developing in the arm and hand of a patient with hemiparesis from a stroke could represent central neuropathic pain or alternatively result from a compressive mononeuropathy. History and examination should differentiate these disorders, but clinical descriptors of the pain will not.

Central neuropathic pain can be continuous, occur suddenly and without warning (paroxysmal), be evoked by mechanical touch or temperature stimuli, or can manifest as some combination of these factors (most common), irrespective of where the lesion occurs in the CNS or the cause of the CNS dysfunction. Similarly, pain can be deep, superficial, or both.[14] Central neuropathic pain is usually moderate to severe in intensity and functionally limiting.[12,13,20-23] As in other chronic pain types, adverse effects on mood and sleep (87% and 50%, respectively, in patients with CPSP) are common in all central pain syndromes.[9,13,22-25]

Temporal Onset

The onset of central neuropathic pain is highly variable. In patients with stroke, central pain may occur at stroke onset, but there is usually a delay of weeks to months and sometimes years (Table 1).[14,20,26] Central poststroke pain has been reported 3 or more years after the original stroke,[14,27] although given the risk of recurrent strokes in patients with prior cerebrovascular disease that could be unrecognized in a patient with severe residual deficits from their original infarction, it is possible that some of these rare, very late-onset CPSP cases are related to unrecognized new infarctions.[2] The prevalence of silent ischemic strokes is estimated at 6% to 28%, with a higher prevalence with increasing age.[28]

Pain can be a presenting feature of MS (either alone, as in cases of trigeminal neuralgia [TN], or in combination with other neurologic deficits) in 5.5 % to 10% of all patients with MS.[29-32] When pain is part of the presenting constellation of MS symptoms, chronic and central pain are more likely in the future.[30]

The longest average latency to the development of central pain occurs in patients with SCI. In almost half of patients with SCI who have development of radiating neuropathic pain at

Mayo Clin Proc. ■ March 2016;91(3):372-385 ■ http://dx.doi.org/10.1016/j.mayocp.2016.01.017
www.mayoclinicproceedings.org

TABLE 1. Temporal Onset of Central Poststroke Pain[a,b]

Stroke type	At time of stroke (%)	Within 1 mo (%)	At 1-3 mo (%)	At 4-6 mo (%)	At 6-12 mo (%)	At >1 y (%)
All types[20]	NR	62	19[c]		19	NR
Thalamic strokes[26]	18	38	15	12	6	11
Lateral medullary infarctions[14]	14	29	43	7	7	NR

[a]NR = not reported.
[b]Central poststroke pain may occur several years after the implicated stroke. This feature is consistent with the long delay in the onset of multiple sclerosis–related and post–spinal cord injury central pain syndromes.
[c]Nineteen percent presented between 1 and 6 months and the study did not break down these time epochs.

the level of the injury ("at-level pain"), it develops within 3 months but can present up to 5 years after SCI, and the mean time to the development of at-level neuropathic pain is 1.2 years.[9] Central neuropathic pain below the level of the SCI ("below-level pain") can be seen within 3 months of the injury, but more than half of patients who experience below-level pain have onset more than 2 years after the injury.[9]

Obligate Sensory Deficits

Although intuitive, for pain to be classified as a central pain syndrome, it must occur in the body region clinically affected by the CNS insult. Importantly, the pain need not involve the entirety of the neurologically affected region; it can involve just a portion of it. Nonaffected limbs are prone to overuse pain syndromes that can be musculoskeletal or peripheral neuropathic. Again, these are not central pain syndromes. Central neuropathic pain stems from impairment within somatosensory pathways. Spinothalamic tract dysfunction (pinprick and temperature) appears to be a near-obligate requirement pathophysiologically for the development of central neuropathic pain. Patients with a possible central pain syndrome should be examined to determine whether there is impaired pinprick and/or temperature sensation (indicating spinothalamic tract dysfunction) in the neurologically affected painful limb. If pinprick and temperature sensations are normal, it is unlikely that the limb pain is due to a central pain syndrome, and alternative etiologies should be considered.

SPECIFIC CENTRAL PAIN SYNDROMES

Central Poststroke Pain

Each year, almost 795,000 strokes occur in the US population,[28] with an incidence rate of 3.73 per 1000 person-years.[33] Stroke is one of the top 5 causes of death in the United States[34] and is responsible for 1 in 20 deaths.[28] Stroke is also one of the leading causes of disability in the United States.[35] Because the prevalence of stroke far exceeds that of MS, SCI, or other CNS insults, CPSP is the most common form of central neuropathic pain.[36,37] Considering all stroke locations and types, the overall incidence of CPSP is 2% to 8%.[20,38] A Danish population-based study that screened all patients with stroke (of any type or location) in a single calendar year found that despite 40% having evidence of chronic pain 4 years after their stroke, only 7.3% had CPSP.[12] Of all patients with strokes that include somatosensory deficits, 18% have development of CPSP.[20]

By absolute numbers, most cases of CPSP are seen following ischemic stroke simply because approximately 80% of all strokes are ischemic.[39] The risk of CPSP is similar for ischemic or hemorrhagic stroke. Stroke location is more important to the risk for CPSP than stroke etiology, with thalamic and lateral medullary strokes having the highest incidence of CPSP.[21,37,40] The thalamic pain syndrome, as described by Dejerine and Roussy,[41] is the classic example of a type of CPSP. However, most cases of CPSP are from nonthalamic strokes.[14,20,42]

Thalamic infarctions represent 25% to 33% of all cases of CPSP.[20,42] One meta-analysis found the frequency of CPSP development after thalamic infarction to be 11% overall but higher (almost 25%) when the ventral posterior nuclei were affected.[26] Thalamic CPSP does not appear to develop with infarctions of the median and centromedian thalamic nuclei.[14]

Lateral medullary strokes (Wallenberg syndrome) also have a high incidence of CPSP (25% at 6 months).[21] These strokes affect

TABLE 2. Pain Types Following Spinal Cord Injury

Nociceptive pain
Musculoskeletal pain—joint pain, axial spine pain, overuse syndromes, muscle spasms
Visceral pain—eg, complications of neurogenic bowel and bladder
Other nociceptive pain—eg, headache or skin ulcer
Neuropathic pain
At-level neuropathic pain—neuropathic pain within the dermatomes at the level of the SCI; pain from nerve root or dorsal horn injury from the SCI
Below-level neuropathic pain—a central pain type
Other neuropathic pain—neuropathic pain unrelated to the SCI, eg, from compressive mononeuropathies or painful diabetic neuropathy
Other or unknown pain type—eg, fibromyalgia, interstitial cystitis

spinothalamic and trigeminothalamic pathways, causing abnormal pain and temperature sensation in the ipsilateral aspect of the face and contralateral portion of the body, as well as hoarseness, dysphagia, ipsilateral Horner syndrome, and vestibular symptoms. Central pain syndromes in patients with lateral medullary infarction therefore affect the ipsilateral aspect of the face and/or the contralateral portion of the body.[43]

Some studies have suggested that CPSP is more likely in younger patients who experience stroke[21,26,37] (median age of 58-67 years compared with greater than 65 years in three-quarters of the general stroke population). Others have not found younger age to be a risk factor.[2,20] In one of the largest studies of thalamic CPSP, right-sided infarctions were more commonly associated with CPSP than left-sided infarctions, a finding believed to be consistent with evidence that the right hemisphere is important in pain mediation and body image representation.[26] Stroke laterality has not been found to be a risk factor in other stroke subtypes.[2,20,21]

SCI Pain

Spinal cord injury is characteristically a disease of young adults, with a median age at the time of injury of 28.7 years. However, data accumulated since 2000 suggest an increase to 38 years, consistent with the right shift in the age of the US population.[44] This young age at onset as well as the male predominance (~78%) of SCI is consistent with the demographic characteristics of their common traumatic etiologies (motor vehicle accidents [47%], falls, acts of violence [most recently ~14%], and recreational and sports injuries).[44] The incidence of SCI is estimated at 40 cases per million US population (~11,000 new cases each year), with an estimated prevalence of approximately 253,000 US survivors of SCI in June 2006.[44] Many SCI studies would include patients with vascular etiologies (spinal cord infarction), whereas these patients would typically be excluded from CPSP studies.

The International Spinal Cord Injury Pain Classification recognized that patients with a CNS lesion and marked functional impairment can have multiple types of pain.[45,46] Classifying pain by its type is practical when approaching pain in patients with SCI (Table 2). By definition, below-level neuropathic pain represents central pain. At-level pain can stem from root and/or dorsal horn SCI and as such represents peripheral (root) and/or central (dorsal horn) neuropathic pain.

The question as to the prevalence of central neuropathic pain following SCI has been complicated by the absence of categorization by type in the earliest literature and a latency in the appearance of some post-SCI pain types (particularly neuropathic pain below the level of injury) after the SCI.[9] Estimates of post-SCI pain (of any type) range from 13%[6] to 94%,[47] but a prevalence of about 65% to 80% is suggested by most studies.[7,9,10,22,48-50] In a recent study that adequately distinguished pain types, 31% of patients with SCI had at-level and 31% had below-level neuropathic pain 12 months after the injury.[51] At-level pain was more prevalent in the early months after SCI than below-level pain and was also more likely to resolve with time than below-level pain.[51] Given a median of more than 2 years for the development of below-level pain in some series,[9] the results of this 1-year study may underrepresent the number of patients who would eventually have below-level pain. However, 2 other studies that distinguished below-level pain from other pain types also found a prevalence of below-level pain in approximately one-third of patients with SCI.[9,52]

In studies that stratify pain subtype, it is clear that musculoskeletal pain predominates (occurring in 50%-70% of those reporting chronic pain)[9,10] but is also the least severe and functionally limiting.[9] Although reported in a smaller proportion of patients following SCI (34%-47%),[7,9,10] neuropathic pain (at any level) is consistently rated as severe and functionally limiting. In a longitudinal study, 59 of

Mayo Clin Proc. ■ March 2016;91(3):372-385 ■ http://dx.doi.org/10.1016/j.mayocp.2016.01.017
www.mayoclinicproceedings.org

73 patients (81%) reported pain at 5 years following SCI; 59% reported musculoskeletal pain, 41% at-level (segmental) neuropathic pain, 34% below-level neuropathic pain, and 5% visceral pain.[9] Most patients have multiple concomitant pain types or sites.[7,9-11,22]

Pain is rated third behind decreased ambulation/mobility and decreased sexual function as the most difficult SCI complication.[9] In one series, about half of those with at least a component of their pain being neuropathic reported that this pain was their most significant post-SCI problem.[7] In another study, 38% of patients with SCI were willing to trade recovery from paralysis or sexual dysfunction for pain relief.[53]

Unfortunately, the trend of SCI-related pain is toward worsening with time, stabilizing at best, and infrequently improving or resolving.[7,9,54] One study found that 6% of patients had resolution of pain, 7% reported decreasing pain intensity and frequency with time, and almost one-half reported increasing intensity (and one-third reported increasing frequency) of pain with time.[22] Neuropathic pain is more likely than nociceptive pain to worsen with time.[51,55]

MS-Related Pain

Multiple sclerosis affects an estimated 400,000 individuals in the United States and over 2.3 million worldwide.[56] It is an autoimmune disorder in which demyelinating plaques cause dysfunction of areas of the brain and spinal cord. There are several forms of MS, with most patients (~85%) having a relapsing-remitting form in which they experience subacute development of neurologic impairment (eg, motor, sensory, visual, gait, or coordination) from a CNS lesion that subsequently improves and is followed by periods without neurologic deterioration. There are progressive forms of MS in which neurologic dysfunction accumulates without distinct attacks. This dysfunction can occur after a period in which the disease was relapsing and remitting (secondary progressive MS) or from the onset of disease (primary progressive MS). Regardless of type, patients with MS usually have accumulating levels of disability as the disease progresses. Accompanying this progression is a high prevalence of chronic pain ranging from 29%[29] to 80%,[8,57] with the most complete systematic review noting a point prevalence of pain (of any type) of 50% with approximately 75% of patients reporting pain within the month preceding evaluation.[23] Like SCI-related pain, there are several pain types commonly seen in MS.

Musculoskeletal and axial spine pain as a consequence of immobility, pain from decubitus ulcers, and spasticity are common causes of pain in MS. Treatments for MS can also be painful. Interferon beta causes flulike symptoms, myalgias, and headache, and MS treatments can also cause injection site pain and reactions.[58]

Pain occurs as part of the original MS symptom complex in 5.5% to 23% of patients, and when it does, patients are more likely to have development of central or chronic pain.[23,29-32] In 14% of patients with MS-related TN, it was the presenting symptom of MS.[59] Central pain is rarely the presenting symptom in MS (1%-2% of patients).[30,31]

The Lhermitte sign is classically associated with MS. It refers to a paroxysmal electrical sensation shooting down the spine and sometimes into the limbs that is triggered by neck flexion. In 7% to 41% of patients with MS, Lhermitte sign develops at some point in their disease.[60-62] It is usually associated with an acute or subacute demyelinating plaque in the cervical spine and resolves over several weeks.[63] Magnetic resonance imaging (MRI) and electrophysiologic data have documented that Lhermitte sign is associated with the posterior column (touch, proprioception) and not nociceptive spinothalamic tract dysfunction.[23,61,64] This feature distinguishes Lhermitte sign from central neuropathic pain, in which spinothalamic tract sensory loss is invariable.

Patients with an active MS relapse may experience painful tonic spasms (6%-19% of patients), which are a sudden, paroxysmal short-lived painful posturing of a limb or facial distortion frequently triggered by an innocuous stimulus (eg, light touch, movement, emotions).[60,63,65] Frequently, patients report a sense of sensory loss with this phenomenon. Like the Lhermitte sign, painful tonic spasms are self-limited and usually resolve over several weeks to months.

In patients with MS related to a demyelinating plaque affecting the trigeminal nerve root entry zone or trigeminal nuclei within the pons, TN has a prevalence of 1% to

6%,[31,60,62,66] which is 20 times the prevalence of TN in patients without MS.[23] Although TN can result from demyelinating disease, it can also occur in MS unrelated to pontine demyelination. Similar to non-MS TN cases, vascular compression of the proximal trigeminal nerve may cause TN in patients with MS as a comorbid, but non-MS–related, condition. It is most common when TN presents unilaterally in patients older than 50 years.[65] Distinct from sporadic forms of TN, TN caused by MS more commonly presents at an earlier age, may be bilateral (in 14%-18% of patients), and is less likely to affect ophthalmic V_1 sensory distribution.[59,63,65,67,68] Subacute bilateral TN should be presumed to be MS until proven otherwise.

Central neuropathic pain has a lifetime prevalence of 12% to 28% in patients with MS, often occurring more than 1 year after the development of neurologic symptoms in the region of pain.[23,65] Given the multifocality of demyelinating lesions within the CNS, it is not surprising that central neuropathic pain can occur in more than one location.[23,30] Pain occurs in the neurologically affected body region and specifically in areas with evidence of spinothalamic tract sensory loss.[58,64] Central pain is more common in progressive forms of MS than in the relapsing- remitting form, in patients who are older, in those who have had longer duration of disease, and in patients with higher levels of disability.[23,58,62,65]

PATHOPHYSIOLOGY

It has been recognized for some time that dysfunction of spinal-thalamic-cortical pathways (clinically evident as impaired pain [pinprick] and temperature sensation) appears to be critical in the development of central neuropathic pain.[9,21,26,30,69-72] However, not all patients with spinothalamic tract sensory loss experience central pain, and there must be a required cofactor to drive its development.[20] Increasing evidence suggests this cofactor to be denervation hypersensitivity of surviving spinothalamic tract axons. Abnormal thermal sensation (cold especially) appears to be more critical in the development of CPSP than impairment of spinothalamic tract pain (pinprick) pathways.[20] This concept has evolved with recent work that has determined that patients who experience below-level SCI-related central pain have evidence of a "discomplete" lesion of the spinothalamic tract with sparing of thermosensitive, mechanical-insensitive nociceptive afferents within an otherwise dysfunctioning spinothalamic tract.[73] Patients with SCI who do not have below-level neuropathic pain have complete loss of spinothalamic tract function, without any recordable activity from these thermosensitive afferents.[73] In the setting of central pain, there is some trigger of neuronal hyperexcitability in these preserved spinothalamic tract neurons either directly or via disinhibition.[74] One theory is that in the setting of an SCI damaging the spinothalamic tract, there is microglial activation that directly activates the surviving spinothalamic tract neurons.[75] Additionally, SCI disrupts descending inhibitory pathways. The sum result is chronic activation (a spinal pain generator) of these surviving spinothalamic tract nociceptive neurons in the region of the cord injury.[73] The ability of spinal anesthesia to transiently reduce below-level pain confirms a pain generator at the cord level.[76] Additionally, an important prospective study of patients with SCI who were followed up at regular intervals from the time of injury to 6 months postinjury found that those who experienced below-level central pain had demonstrable clinical signs of sensory hyperexcitability (eg, foot allodynia) and higher thermal thresholds soon after the injury than those who did not.[74] This finding suggests that even if there is an incomplete lesion sparing thermosensitive afferents in the spinothalamic tracts, they are not functioning normally. This study also highlighted the importance of triggered neuronal hyperexcitability (via direct activation or disinhibition) to the development of central pain.

Disinhibition is also important in the development of CPSP. It is thought that lesions of the lateral thalamus disinhibit the medial thalamus. This process may be related to disruption of GABAergic neurons in the ventral posterolateral thalamic nuclei. Subsequent sensory input via surviving or recovering sensory neurons ascends to cortical centers in an "unlearned fashion" resulting in painful sensation.[14] Further supporting the importance of neuronal hyperexcitability in central pain, microelectrode recordings have documented abnormal spontaneous burst activity in deafferented thalamic regions in CPSP, in the intact thalamus following SCI,

Mayo Clin Proc. ■ March 2016;91(3):372-385 ■ http://dx.doi.org/10.1016/j.mayocp.2016.01.017
www.mayoclinicproceedings.org

and in patients with phantom limb pain.[69,77,78] In CPSP, this abnormal thalamic burst firing may be the central pain generator, whereas when seen with SCI, it represents central sensitization from chronic nociceptive afferent signaling from distal microglial activation or disinhibition of surviving ascending nociceptive axons at the level of the cord injury. Notably, the integrity (or lack thereof) of the lemniscal (large fiber, posterior column) sensory pathway (carrying the modalities of light touch, vibration, and proprioception) does not appear to be fundamentally important to the development of CPSP.[21,69,79]

Implications from pharmacological treatment trials have led to hypotheses regarding which neurotransmitter systems and/or channels are important in central neuropathic pain. The efficacy of intravenous lidocaine (for SCI pain and CPSP) suggests that sodium channels are important in mediating central pain states.[80] Increased sodium channel expression has been noted with MS demyelinating lesions.[81] Intravenous infusion of ketamine, an *N*-methyl-D-aspartate antagonist, significantly reduces continuous and evoked pain in patients with SCI-related central pain, suggesting the importance of activation of central *N*-methyl-D-aspartate receptors in this syndrome (which has also been shown to be important in central sensitization of peripheral neuropathic pain).[82]

TREATMENT

The treatment of central neuropathic pain is very challenging. As a rule, pain resolution is unlikely. However, patient reports of a clinically meaningful improvement in their pain correlate with improvement of 2 points (on a 0-10 numerical pain rating scale) or 30% from baseline pain levels.[83] Because individual agents are limited in their degree of benefit, multimodal pharmacotherapy using different medications with distinct mechanisms of action is frequently required (eg, pregabalin and a tricyclic antidepressant). Combination therapy has been consistently reported to be more efficacious than monotherapy.[84,85]

Further complicating central neuropathic pain treatment recommendations is the limited number of high-quality, randomized controlled trials of treatment options. Given limited data and evidence of overlap in the pathophysiology of the different central pain syndromes, it is appropriate to extrapolate data from the rare controlled trial of one central pain state to guide treatment of another central pain disorder.

This extrapolation still leaves major gaps in the treatment algorithms for central neuropathic pain, and the approach to a central pain state is often taken from one of the many published neuropathic pain treatment algorithms, even though these algorithms were established primarily from data on the treatment of peripheral neuropathic pain disorders (most commonly painful diabetic neuropathy and postherpetic neuralgia).[86-90] Although rational as a starting point within the context of limited data for these rare central pain disorders, clinicians should recognize that there is evidence that not all types of neuropathic pain are alike and they do not respond equally well to treatments. For example, although gabapentin and tricyclic antidepressants are considered first-line treatments in painful diabetic neuropathy or postherpetic neuralgia,[86-90] they were ineffective in well-designed trials of painful chemotherapy-induced peripheral neuropathy.[91,92] Similarly, the paroxysmal pain of TN responds dramatically to treatment with carbamazepine or oxcarbazepine,[93] but studies of these agents for painful diabetic neuropathy have reported a much less significant effect.[94]

Pharmacotherapy

All pharmacological treatments have potential adverse effects. Patients with central pain disorders have associated physical, cognitive, and/or language complications from the original CNS insult and may be less tolerant of medications that cause dizziness, ataxia, confusion, or sedation. In addition, patients with CNS disorders often require multiple medications to treat the underlying disorder and other nonpain complications. As such, drug interactions and polypharmacy can further complicate central neuropathic pain drug choices.

Randomized controlled trial data support the use of the following agents for the treatment of central neuropathic pain (Table 3). Gabapentin (at least 1800 mg/d) was effective for SCI-related central pain in one study[95] but not in another (with dosages up to 3600 mg/d).[96] Two trials[97,98] have reported that pregabalin (mean dosage, 410-460 mg/d) was effective for SCI central pain. Pregabalin was no better than

TABLE 3. Summary of Evidence for Pharmacological Treatments for Central Pain Types

Drug	CPSP	SCI central pain	MS central pain
Gabapentin	?	Mixed data	?
Pregabalin	Mixed data	++	?
Lamotrigine	+	+	?
Amitriptyline	+	Mixed data	?
Duloxetine	?	?	+
Cannabinoids	?	?	++

CPSP = central poststroke pain; MS = multiple sclerosis; RCT = randomized controlled trial; SCI = spinal cord injury; ? = no RCTs; + = positive RCT; ++ = multiple positive RCTs; Mixed data = both positive and negative RCTs of pharmacological agent for same condition.

placebo for CPSP in one trial,[99] but a study including a mixed cohort of patients with SCI central pain and CPSP did find a benefit of pregabalin over placebo with no difference in the response between patients with SCI and CPSP.[100] Lamotrigine (mean dosages, 200-400 mg/d) was effective for CPSP[101] and for incomplete SCI—related at-level and below-level central pain.[102] Amitriptyline (goal at least 75 mg/d) was effective for CPSP.[42] Results of studies of amitriptyline for SCI are mixed, with no response at moderate dosages of 50 mg/d[103] and a significant response in patients with comorbid depression receiving higher dosages (up to 150 mg/d).[96] Duloxetine (60 mg/d) was effective for MS-related neuropathic pain.[104] Cannabinoids have been found to be effective for MS-related central pain[105,106] and for treatment of MS spasticity and pain related to muscle stiffness.[107-110] The data for carbamazepine for central pain states is mixed. A study that reported positive results was poorly powered, and although supportive of probable efficacy, the strength of its conclusions was limited.[111] Of course, carbamazepine is the criterion standard first-line treatment for TN (regardless of etiology).[93] Table 4 provides practical dosing information for these agents.

Surgical Treatment

Given the refractory nature of central neuropathic pain states, multiple surgical interventions attempting to interrupt aberrant ascending nociceptive signaling or stimulation procedures attempting to modulate this signaling (neuromodulation) have been proposed to treat refractory central neuropathic pain. Surgical creation of destructive lesions ("lesioning") is most commonly applied to the spinal cord and includes commissurotomy (ie, midline myelotomy transecting the crossing fibers in the spinal cord), dorsal root entry zone lesioning, cordotomy (selective lesioning of the lateral spinothalamic tract pain pathways in the anterolateral cord contralateral to the side of pain), and cordectomy (transaction of the spinal cord).[36,112] If effective, destructive lesions seem to be most effective for paroxysmal shooting pain and allodynia.[36,113] Unfortunately, pain frequently returns (generally over years), and given the associated surgical risks, destructive procedures are now used less frequently.[112,114] Destructive brain lesions have been described for CPSP but the results have been disappointing, and these lesions are used even less frequently than spinal cord destructive lesions.[36]

Neuromodulation has had an expanding role in the management of refractory neuropathic pain types of central or peripheral origin. For central neuropathic pain, neuromodulation includes spinal cord stimulation whereby a wire with stimulating electrodes is placed within the epidural space parallel to the posterior sensory columns of the spinal cord, motor cortex stimulation (MCS) whereby a stimulating electrode array is placed in the epidural space overlying the primary motor cortex, and deep brain stimulation (DBS) of supratentorial nuclei that can modulate central pain signaling. The neuromodulation signal needs to interrupt ascending nociceptive signaling or activate descending inhibitory pathways above the central pain causative lesion. As such, spinal cord stimulation cannot be used for CPSP and is most effective for thoracic cord lesions where stimulation can be applied to the high thoracic or cervical cord. Incomplete spinal cord injuries are more amenable to spinal cord stimulation because wallerian degeneration of ascending sensory pathways from a complete cord lesion may make effective cord stimulation unlikely. Patients with traumatic SCI often require urgent surgical fixation, and subsequently, surgical hardware and altered anatomy may limit the possibility of spinal cord stimulator placement in some patients. New-generation spinal cord stimulators are now MRI compatible, so the need for future MRIs (eg, in patients with MS or central pain from a CNS malignant neoplasm)

Mayo Clin Proc. ■ March 2016;91(3):372-385 ■ http://dx.doi.org/10.1016/j.mayocp.2016.01.017
www.mayoclinicproceedings.org

TABLE 4. Practical Dosing Recommendations for Medications With Randomized Controlled Trial Data Supporting Their Usage in Central Pain Syndromes

Agent	Usual starting dosage	Dosing	Effective dosage in central pain RCTs	Maximum dosage	Precautions	Common and notable adverse effects
Gabapentin	300 mg at bedtime(100-mg increments available for slower titration)	Increase by 300-mg increments every 4-7 d initially to 3 times daily, then to goal of 1800 mg/d	At least 1800 mg/d	Increase as necessary to 3600 mg/d (split 3 times daily)	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped	Sedation, dizziness, confusion, edema, tremor
Pregabalin	75 mg twice daily (25-mg and 50-mg dosing available for slower titration)	Increase by 75 mg after 4-7 d to goal of 300 mg/d	Mean dosage of 410-460 mg/d	Increase as necessary to 600 mg/d	Renal insufficiency (dosage adjust); risk of seizure if abruptly stopped; psychiatric disease or addiction history (euphoria risk)	Sedation, dizziness, confusion, edema, tremor, euphoria
Lamotrigine	25 mg/d for 2 wk	Increase to 25 mg twice daily for 2 wk, then increase weekly by 25 mg twice daily to goal of at least 100 mg twice daily	Mean dosage of 200-400 mg/d	400 mg/d	Dose adjust with liver disease or renal impairment; patients taking medications such as valproic acid that inhibit hepatic P450 system require slower titration regimen; risk of seizure if abruptly stopped	Rash (Stevens-Johnson syndrome); abdominal pain, diarrhea; headache; dizziness. Slow titration to minimize the risk of toxicities
Carbamazepine	200 mg once daily	Increase by 200 mg every 4-7 d to twice daily, then thrice daily, and as necessary 4 times daily (extended-release formulations allow twice-daily dosing of same total daily dosage)	500-760 mg/d	1200 mg/d	Test for inherited allelic variant *HLA-B*1502* in patients of Asian descent and if present do not use carbamazepine; risk of seizure if abruptly stopped	Stevens-Johnson syndrome; hematologic suppression (monitor CBC); hepatic dysfunction (monitor LFTs); hyponatremia; nausea; dizziness; drowsiness
Amitriptyline	10-25 mg at bedtime	Increase every 4-7 d to goal of 100 mg at bedtime	At least 75 mg/d	150 mg/d	Risk of emerging suicidality (children/young adults—see boxed warning); risk of serotonin syndrome; use with caution if patient has cardiac disease or dysrhythmia history	Sedation, dry mouth, orthostatism, confusion, weight gain, urinary retention, constipation, blurred vision
Duloxetine	20-30 mg once daily	Increase weekly by same dosage to goal of 60 mg/d	60 mg/d	120 mg/d (split BID)	Risk of emerging suicidality (children/young adults—see boxed warning); risk of serotonin syndrome; increased bleeding risk (use cautiously with anticoagulants); withdrawal syndromes with abrupt discontinuation; use with caution in patients with hepatic failure	Sedation, fatigue, nausea, hyperhidrosis, dizziness
Cannabinoids	Dosing and relative proportion of tetrahydrocannabinol and cannabidiol (the 2 most common medical cannabinoids) were highly variable in RCTs. Form of administration varied in RCTs. No recommendations possible				Federally illegal for medicinal usage (Schedule I drug), but increasing number of states have legalized medicinal cannabinoids	Palpitations, hypotension, dry mouth, dizziness, depression, inattention, hallucinations, paranoia, addiction

BID = twice a day; CBC = complete blood cell count; LFT = liver function test; RCT = randomized controlled trial.

is no longer a contraindication to neuromodulation. Unfortunately, the efficacy of spinal cord stimulation for central pain states seems to wane with time.[36,114-116]

There has been increasing interest in MCS and DBS (using the same technology utilized for treatment of Parkinson disease and movement disorders) for central pain, although these procedures have not been approved for this indiction.[117] Unlike surgically created destructive lesions, neuromodulation techniques can be tried before permanent implantation and are adjustable and reversible. Functional imaging has suggested that epidural MCS activates structures involved in the appraisal of pain as opposed to modulation of pain intensity. The extent of pain alleviation also correlates with the increase of blood flow in the cingulate gyrus, suggesting that stimulation also works by reducing the emotional affective pain component (suffering).[118] Meta-analyses of DBS are limited by variability in surgical techniques and central targets and older studies using more limited technology. Traditionally, the periaqueductal and periventricular gray matter have been targeted with DBS, resulting in the release of endogenous opioids.[118] The ventral caudal thalamus and the nucleus accumbens have promise as targets in the treatment of central pain via activation of inhibitory pathways.[118,119] Deep brain stimulation appears to be more effective for nociceptive and peripheral neuropathic pain than for central neuropathic pain.[117,120-122] The efficacy of DBS may also vary depending on central pain type. For CPSP, DBS may be effective in 50% to 70% of patients, although an important proportion of patients (up to one-third) do not experience sustained benefit with the permanent implant.[122,123] Deep brain stimulation is generally believed to be less efficacious for spinal cord–mediated central pain (16%-57% of patients have significant improvement) than for CPSP.[120,123] Motor cortex stimulation is better suited for face- and arm-predominant central pain disorders (given the more superficial representation of the face and arm portions of the homunculus), and up to two-thirds of patients with CPSP have significant improvement with MCS.[117] Motor cortex stimulation has particular promise in the treatment of atypical facial pain.[117,124,125]

Although imperfect, in patients who do respond, neuromodulation may substantially improve pain control and quality of life in those with otherwise refractory central neuropathic pain. The efficacy of neuromodulation for any indication relies heavily on proper patient selection as well as appropriate choice of stimulation targets. Referral of patients with refractory central neuropathic pain to a multidisciplinary team including specialists in pain medicine, neurology, psychiatry, and neurosurgery is appropriate.

CONCLUSION

Chronic pain syndromes are common in patients with functional impairment from CNS disorders. Most of these disorders are related to musculoskeletal and overuse syndromes. Central neuropathic pain syndromes may be difficult to recognize given the delay (weeks to years) in onset and impaired sensory discriminatory abilities from the CNS insult. Central pain should be suspected when pain is limited to the region of neurologic deficit and when associated with spinothalamic tract sensory loss. Treatment of central pain syndromes is challenging but may benefit from advanced neuromodulation techniques, and patients with refractory central pain may benefit from referral to a multidisciplinary pain management team.

Abbreviations and Acronyms: **CNS** = central nervous system; **CPSP** = central poststroke pain; **DBS** = deep brain stimulation; **MCS** = motor cortex stimulation; **MRI** = magnetic resonance imaging; **MS** = multiple sclerosis; **SCI** = spinal cord injury; **TN** = trigeminal neuralgia

Correspondence: Address to James C. Watson, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Watson.james@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Pain Medicine will be available for purchase from our website www.mayoclinicproceedings.org.

The Symposium on Pain Medicine will continue in an upcoming issue.

REFERENCES

1. International Association for the Study of Pain. IASP taxonomy. International Association for the Study of Pain website. http://www.iasp-pain.org/Taxonomy#Neuropathicpain. Updated October 6, 2014. Accessed August 3, 2015.
2. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol.* 2009;8(9):857-868.
3. Gamble GE, Barberan E, Laasch HU, Bowsher D, Tyrrell PJ, Jones AK. Poststroke shoulder pain: a prospective study of the association and risk factors in 152 patients from a

consecutive cohort of 205 patients presenting with stroke. *Eur J Pain*. 2002;6(6):467-474.
4. Lindgren I, Jönsson AC, Norrving B, Lindgren A. Shoulder pain after stroke: a prospective population-based study. *Stroke*. 2007;38(2):343-348.
5. Cardenas DD, Felix ER. Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment. *PM R*. 2009;1(12):1077-1090.
6. Berić A, Dimitrijević MR, Lindblom U. Central dysesthesia syndrome in spinal cord injury patients. *Pain*. 1988;34(2):109-116.
7. Levi R, Hultling C, Nash MS, Seiger A. The Stockholm spinal cord injury study: 1. Medical problems in a regional SCI population. *Paraplegia*. 1995;33(6):308-315.
8. Svendsen KB, Jensen TS, Overvad K, Hansen HJ, Koch-Henriksen N, Bach FW. Pain in patients with multiple sclerosis: a population-based study. *Arch Neurol*. 2003;60(8):1089-1094.
9. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*. 2003;103(3):249-257.
10. Rintala DH, Loubser PG, Castro J, Hart KA, Fuhrer MJ. Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and relationship with impairment, disability, handicap, and subjective well-being. *Arch Phys Med Rehabil*. 1998;79(6):604-614.
11. Cardenas DD, Turner JA, Warms CA, Marshall HM. Classification of chronic pain associated with spinal cord injuries. *Arch Phys Med Rehabil*. 2002;83(12):1708-1714.
12. Klit H, Finnerup NB, Andersen G, Jensen TS. Central post-stroke pain: a population-based study. *Pain*. 2011;152(4):818-824.
13. Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. *Mult Scler*. 2006;12(5):629-638.
14. Kumar G, Soni CR. Central post-stroke pain: current evidence. *J Neurol Sci*. 2009;284(1-2):10-17.
15. Putzke JD, Richards JS, Hicken BL, Ness TJ, Kezar L, DeVivo M. Pain classification following spinal cord injury: the utility of verbal descriptors. *Spinal Cord*. 2002;40(3):118-127.
16. Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain*. 2003;19(5):306-314.
17. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*. 2001;92(1-2):147-157.
18. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain*. 2004;108(3):248-257.
19. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology*. 1997;48(2):332-338.
20. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central post-stroke pain. *Pain*. 1995;61(2):187-193.
21. MacGowan DJ, Janal MN, Clark WC, et al. Central poststroke pain and Wallenberg's lateral medullary infarction: frequency, character, and determinants in 63 patients. *Neurology*. 1997;49(1):120-125.
22. Störmer S, Gerner HJ, Grüninger W, et al. Chronic pain/dysaesthesiae in spinal cord injury patients: results of a multicentre study. *Spinal Cord*. 1997;35(7):446-455.
23. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: a systematic review and proposed classification. *Pain*. 2008;137(1):96-111.
24. Widar M, Ek AC, Ahlström G. Coping with long-term pain after a stroke. *J Pain Symptom Manage*. 2004;27(3):215-225.
25. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. *J Neurol Neurosurg Psychiatry*. 2006;77(5):590-595.
26. Nasreddine ZS, Saver JL. Pain after thalamic stroke: right diencephalic predominance and clinical features in 180 patients. *Neurology*. 1997;48(5):1196-1199.
27. Leijon G, Boivie J, Johansson I. Central post-stroke pain—neurological symptoms and pain characteristics. *Pain*. 1989;36(1):13-25.
28. Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-e322.
29. Clifford DB, Trotter JL. Pain in multiple sclerosis. *Arch Neurol*. 1984;41(12):1270-1272.
30. Österberg A, Boivie J, Thuomas K-Å. Central pain in multiple sclerosis—prevalence and clinical characteristics. *Eur J Pain*. 2005;9(5):531-542.
31. Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology*. 1988;38(12):1830-1834.
32. Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. *Mult Scler*. 2005;11(3):322-327.
33. Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. 2014;312(3):259-268.
34. Centers for Disease Control and Prevention. FastStats: Leading Causes of Death. Centers for Disease Control and Prevention website. Updated September 30, 2015. http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed September 5, 2015.
35. Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009;58(16):421-426.
36. Tasker RR. Central pain states. In: Warfield CA, Bajwa ZH, eds. *Principles and Practice of Pain Medicine*. 2nd ed. New York, NY: McGraw-Hill; 2004:394-404.
37. Bowsher D. Central pain: clinical and physiological characteristics. *J Neurol Neurosurg Psychiatry*. 1996;61(1):62-69.
38. Bowsher D. Sensory consequences of stroke. *Lancet*. 1993;341(8838):156.
39. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? *Neurology*. 2007;68(5):326-337.
40. Bowsher D, Leijon G, Thuomas KA. Central poststroke pain: correlation of MRI with clinical pain characteristics and sensory abnormalities. *Neurology*. 1998;51(5):1352-1358.
41. Dejerine J, Roussy G. La syndrome thalamique. *Rev Neurol (Paris)*. 1906;14:521-532.
42. Leijon G, Boivie J. Central post-stroke pain—a controlled trial of amitriptyline and carbamazepine. *Pain*. 1989;36(1):27-36.
43. Fitzek S, Baumgärtner U, Fitzek C, et al. Mechanisms and predictors of chronic facial pain in lateral medullary infarction. *Ann Neurol*. 2001;49(4):493-500.
44. National Spinal Cord Injury Statistical Center. Spinal cord injury (SCI) facts and figures at a glance. University of Alabama at Birmingham website. https://www.nscisc.uab.edu/PublicDocuments/reports/pdf/Facts%202011%20Feb%20Final.pdf. Published 2015. Accessed September 30, 2015.
45. Bryce TN, Biering-Sørensen F, Finnerup NB, et al. International Spinal Cord Injury Pain Classification, part I: Background and description. *Spinal Cord*. 2012;50(6):413-417.
46. Finnerup NB. Pain in patients with spinal cord injury. *Pain*. 2013;154(suppl 1):S71-S76.
47. Davis L, Martin J. Studies upon spinal cord injuries, II: The nature and treatment of pain. *J Neurosurg*. 1947;4(6):483-491.
48. Siddall PJ, Taylor DA, McClelland JM, Rutkowski SB, Cousins MJ. Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. *Pain*. 1999;81(1-2):187-197.

49. Fenollosa P, Pallares J, Cervera J, et al. Chronic pain in the spinal cord injured: statistical approach and pharmacological treatment. *Paraplegia*. 1993;31(11):722-729.
50. Ravenscroft A, Ahmed YS, Burnside IG. Chronic pain after SCI: a patient survey. *Spinal Cord*. 2000;38(10):611-614.
51. Finnerup NB, Norrbrink C, Trok K, et al. Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study. *J Pain*. 2014;15(1):40-48.
52. Werhagen L, Budh CN, Hultling C, Molander C. Neuropathic pain after traumatic spinal cord injury—relations to gender, spinal level, completeness, and age at the time of injury. *Spinal Cord*. 2004;42(12):665-673.
53. Nepomuceno C, Fine PR, Richards JS, et al. Pain in patients with spinal cord injury. *Arch Phys Med Rehabil*. 1979;60(12):605-609.
54. Rose M, Robinson JE, Ells P, Cole JD. Pain following spinal cord injury: results of a postal survey [letter]. *Pain*. 1988;34(1):101-102.
55. New PW, Lim TC, Hill ST, Brown DJ. A survey of pain during rehabilitation after acute spinal cord injury. *Spinal Cord*. 1997;35(10):658-663.
56. National Multiple Sclerosis Society. Estimating the prevalence of MS. National Multiple Sclerosis Society website. http://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed September 15, 2015.
57. Kassirer MR, Osterberg DH. Pain in chronic multiple sclerosis. *J Pain Symptom Manage*. 1987;2(2):95-97.
58. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. *J Neurol*. 2013;260(2):351-367.
59. Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology*. 1995;45(7):1294-1296.
60. Solaro C, Brichetto G, Amato MP, et al; PalMS Study Group. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology*. 2004;63(5):919-921.
61. Al-Araji AH, Oger J. Reappraisal of Lhermitte's sign in multiple sclerosis. *Mult Scler*. 2005;11(4):398-402.
62. Martinelli Boneschi F, Colombo B, Annovazzi P, et al. Lifetime and actual prevalence of pain and headache in multiple sclerosis. *Mult Scler*. 2008;14(4):514-521.
63. Nick ST, Roberts C, Billiodeaux S, et al. Multiple sclerosis and pain. *Neurol Res*. 2012;34(9):829-841.
64. Truini A, Galeotti F, La Cesa S, et al. Mechanisms of pain in multiple sclerosis: a combined clinical and neurophysiological study. *Pain*. 2012;153(10):2048-2054.
65. Nurmikko TJ, Gupta S, MacIver K. Multiple sclerosis-related central pain disorders. *Curr Pain Headache Rep*. 2010;14(3):189-195.
66. Putzki N, Pfriem A, Limmroth V, et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. *Eur J Neurol*. 2009;16(2):262-267.
67. Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. *Acta Neurol Scand*. 1982;65(3):182-189.
68. Brisman R. Trigeminal neuralgia and multiple sclerosis. *Arch Neurol*. 1987;44(4):379-381.
69. Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. *Pain*. 1995;61(2):177-186.
70. Jensen TS, Lenz FA. Central post-stroke pain: a challenge for the scientist and the clinician. *Pain*. 1995;61(2):161-164.
71. Greenspan JD, Ohara S, Sarlani E, Lenz FA. Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. *Pain*. 2004;109(3):357-366.
72. Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. *Brain*. 2003;126(pt 1):57-70.
73. Wasner G, Lee BB, Engel S, McLachlan E. Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. *Brain*. 2008;131(pt 9):2387-2400.
74. Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. *Brain*. 2012;135(pt 2):418-430.
75. Wasner G. Central pain syndromes. *Curr Pain Headache Rep*. 2010;14(6):489-496.
76. Loubser PG, Donovan WH. Diagnostic spinal anaesthesia in chronic spinal cord injury pain. *Paraplegia*. 1991;29(1):25-36.
77. Lenz FA, Seike M, Richardson RT, et al. Thermal and pain sensations evoked by microstimulation in the area of the human ventrocaudal nucleus. *J Neurophysiol*. 1993;70(1):200-212.
78. Lenz FA, Kwan HC, Martin R, Tasker R, Richardson RT, Dostrovsky JO. Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. *J Neurophysiol*. 1994;72(4):1570-1587.
79. Boivie J, Leijon G, Johansson I. Central post-stroke pain—a study of the mechanisms through analyses of the sensory abnormalities. *Pain*. 1989;37(2):173-185.
80. Attal N, Gaudé V, Brasseur L, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology*. 2000;54(3):564-574.
81. Max MB, Hagen NA. Do changes in brain sodium channels cause central pain [editorial]? *Neurology*. 2000;54(3):544-545.
82. Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery*. 1995;37(6):1080-1087.
83. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158.
84. Holbech JV, Bach FW, Finnerup NB, Brøsen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. *Pain*. 2015;156(5):958-966.
85. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;7:CD008943.
86. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173.
87. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19(6):328-335.
88. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3, suppl):S3-S14.
89. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-1123.
90. Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. *Mayo Clin Proc*. 2015;90(7):940-951.
91. Pachman DR, Watson JC, Lustberg MB, et al. Management options for established chemotherapy-induced peripheral neuropathy. *Support Care Cancer*. 2014;22(8):2281-2295.
92. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacol Ther*. 2011;90(3):377-387.
93. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ Clin Evid*. 2009;3:1207.
94. Rull JA, Quibrera R, González-Millán H, Lozano Castañeda O. Symptomatic treatment of peripheral diabetic neuropathy

with carbamazepine (Tegretol): double blind crossover trial. *Diabetologia*. 1969;5(4):215-218.
95. Levendoglu F, Ogün CO, Ozerbil O, Ogün TC, Ugurlu H. Gabapentin is a first line drug for treatment of neuropathic pain in spinal cord injury. *Spine (Phila Pa 1976)*. 2004;29(7):743-751.
96. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil*. 2007;88(12):1547-1560.
97. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology*. 2006;67(10):1792-1800.
98. Cardenas DD, Nieshoff EC, Suda K, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology*. 2013;80(6):533-539.
99. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central poststroke pain. *Pain*. 2011;152(5):1018-1023.
100. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain*. 2008;136(1-2):150-157.
101. Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology*. 2001;56(2):184-190.
102. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*. 2002;96(3):375-383.
103. Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. *Pain*. 2002;96(3):365-373.
104. Vollmer TL, Robinson MJ, Risser RC, Malcolm SK. A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. *Pain Pract*. 2014;14(8):732-744.
105. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329(7460):253-260.
106. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65(6):812-819.
107. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse*. 1987;7(1):39-50.
108. Wissel J, Haydn T, Müller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol*. 2006;253(10):1337-1341.
109. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012;83(11):1125-1132.
110. Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol*. 2007;14(3):290-296.
111. Espir MLE, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (Tegretol). *J Neurol Neurosurg Psychiatry*. 1970;33(4):528-531.
112. Kanpolat Y. The surgical treatment of chronic pain: destructive therapies in the spinal cord. *Neurosurg Clin N Am*. 2004;15(3):307-317.
113. Sindou M, Mertens P, Wael M. Microsurgical DREZotomy for pain due to spinal cord and/or cauda equina injuries: long-term results in a series of 44 patients. *Pain*. 2001;92(1-2):159-171.
114. Siddall PJ. Pain following spinal cord injury. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2005:1043-1055.
115. Tasker RR, DeCarvalho GTC, Dolan EJ. Intractable pain of spinal cord origin: clinical features and implications for surgery. *J Neurosurg*. 1992;77(3):373-378.
116. Cioni B, Meglio M, Plentimalli L, Visocchi M. Spinal cord stimulation in the treatment of paraplegic pain. *J Neurosurg*. 1995;82(1):35-39.
117. Levy R, Deer TR, Henderson J. Intracranial neurostimulation for pain control: a review. *Pain Physician*. 2010;13(2):157-165.
118. Sukul VV, Slavin KV. Deep brain and motor cortex stimulation. *Curr Pain Headache Rep*. 2014;18(7):427.
119. Mallory GW, Abulseoud O, Hwang SC, et al. The nucleus accumbens as a potential target for central poststroke pain. *Mayo Clin Proc*. 2012;87(10):1025-1031.
120. Nardone R, Höller Y, Leis S, et al. Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: a review. *J Spinal Cord Med*. 2014;37(1):19-31.
121. Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. *Neurosurgery*. 1997;40(4):736-746.
122. Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: a meta-analysis. *J Clin Neurosci*. 2005;12(5):515-519.
123. Boccard SG, Pereira EA, Moir L, Aziz TZ, Green AL. Long-term outcomes of deep brain stimulation for neuropathic pain. *Neurosurgery*. 2013;72(2):221-230.
124. Rasche D, Ruppolt M, Stippich C, Unterberg A, Tronnier VM. Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. *Pain*. 2006;121(1-2):43-52.
125. Brown JA, Pilitsis JG. Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observations of enhanced sensory and motor function during stimulation. *Neurosurgery*. 2005;56(2):290-297.