Central Pain

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Introduction

- **IASP definitions**

- Neuropathic pain

  Pain caused by a lesion or disease of the somatosensory nervous system

- Central pain (Central neuropathic pain)

  Pain caused by a lesion or disease of the central somatosensory nervous system

https://www.iasp-pain.org/terminology

- Conditions associated with central pain:
  - Stroke
  - Multiple sclerosis (MS)
  - Spinal cord injury (SCI)
  - Brain trauma
  - Brain tumors
  - Epilepsy
  - Parkinson's disease

Etiology of central pain states

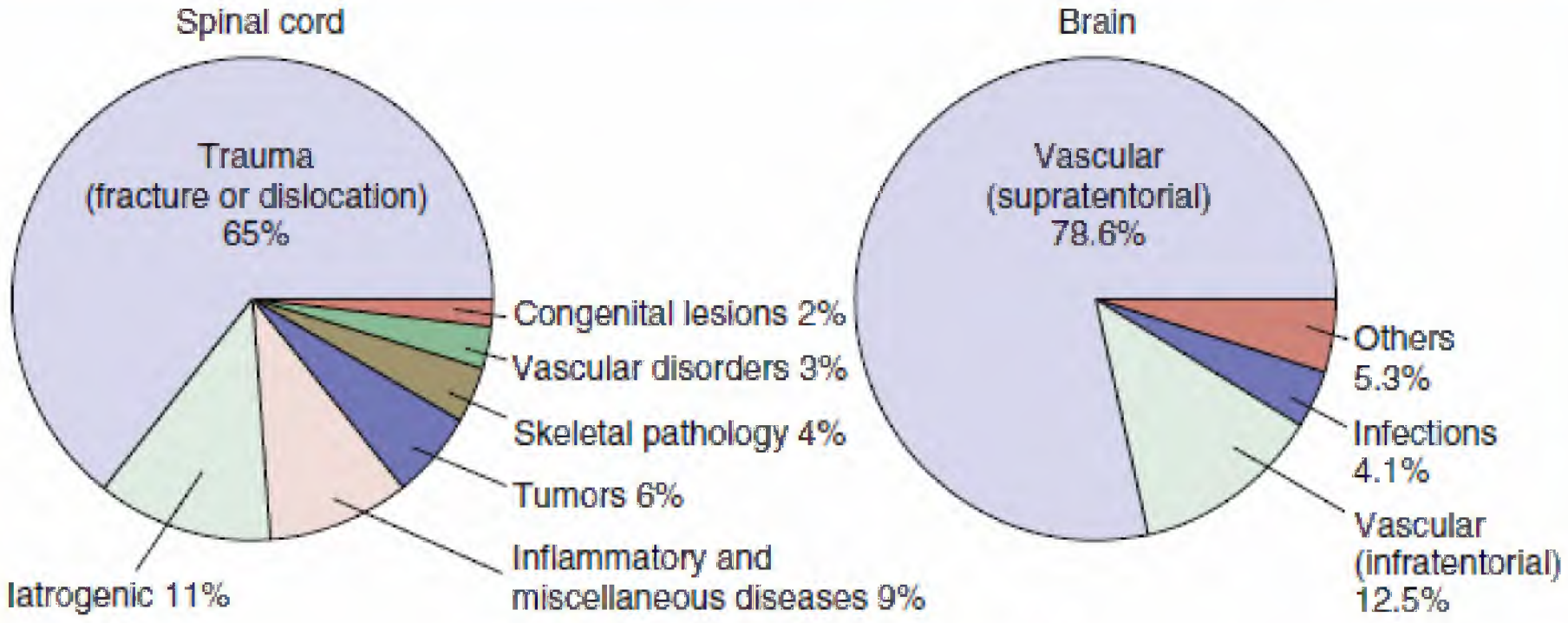
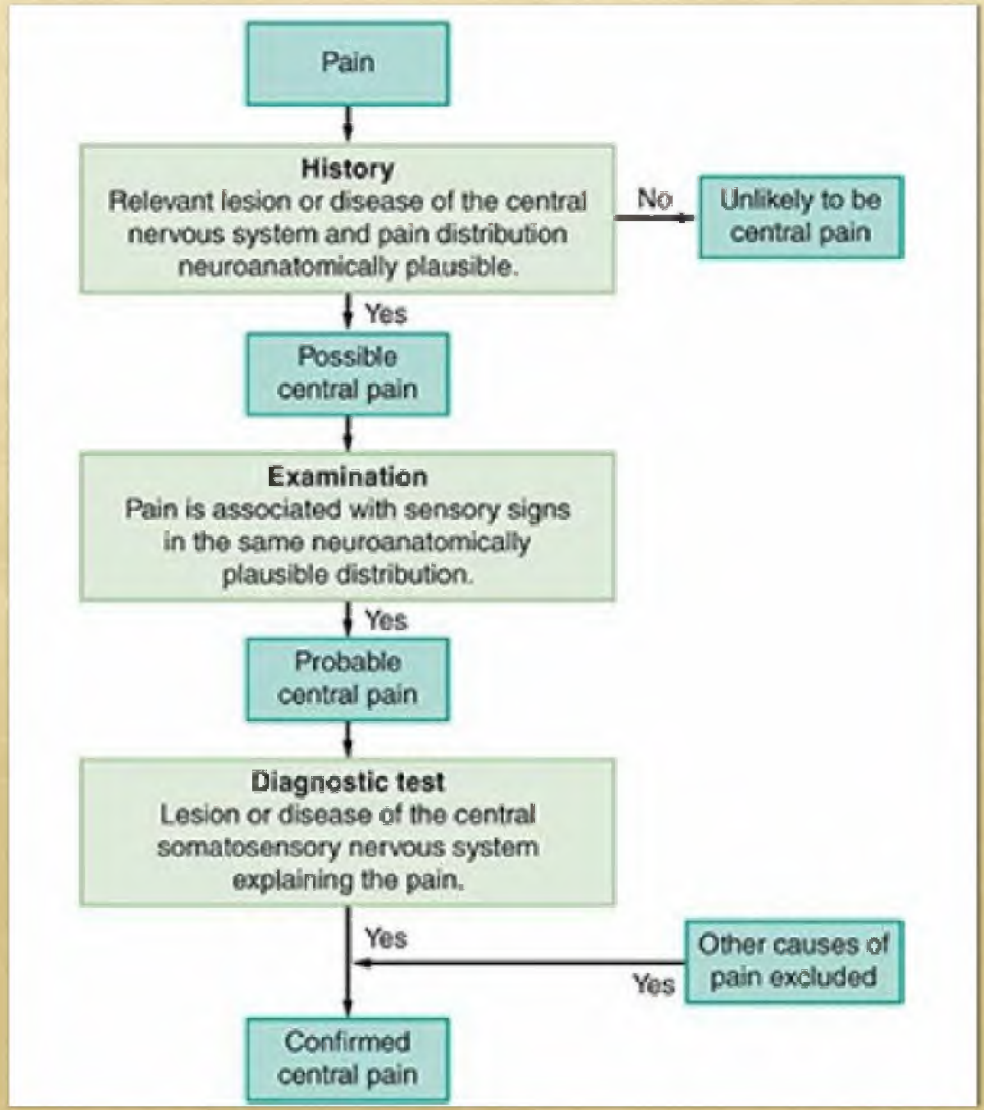


FIG. 30.1 Etiology of central pain states.

- Central pain often becomes chronic and may be disabling with a negative impact on quality of life, mood, sleep, and functioning.

- Treatment of central pain remains challenging.

Grading system for central pain



History

- Central pain is suspected when the history suggests that the pain is related to a central nervous system (CNS) disorder and not to other causes such as spasms, fractures, inflammation, etc.

- Different pain questionnaires have been developed as screening tools to identify the presence of neuropathic pain.
  - Neuropathic Pain Questionnaire (NPQ)
  - Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
  - Douleur Neuropathique en 4 Questions (DN4) questionnaire
  - PainDETECT questionnaire
  - IDPain questionnaire
  - Spinal Cord Injury Pain Instrument (SCIPI) developed for patients with SCI

- These screening tools may be useful in epidemiologic research, but they cannot be used alone for identifying central pain in the individual patient.

◈ Possible neuropathic pain:

1. History of a relevant CNS disorder and pain development at or after the onset of the CNS disorder
2. The pain distribution should be neuroanatomically plausible

◈ Following stroke, SCI, and other acute onset CNS disorders, the pain typically develops within months after the onset, but the onset of central pain may be delayed up to about 1 year after the incident.

Examination

- **Probable central pain**
- Clinical sensory examination and confirmation of sensory abnormalities in the same neuroanatomical location
- Demonstration of sensory loss to one or more sensory modalities such as touch, pinprick, cold, and warmth compatible with the CNS lesion is essential.
- Sensory abnormalities are often present on clinical examination.
- More thorough examination using quantitative sensory testing

Diagnostic test

- **Definite central pain**

- Computed tomography (CT)
- Magnetic resonance imaging (MRI) scan
- Heat- or laser-evoked potentials for spinothalamic tract (STT) pathways
- Trigeminal reflex recordings: Secondary trigeminal neuralgia in MS

- “Definite central pain” means that a CNS lesion can explain the pain but does not determine the cause of the pain.

- The exclusion of other causes of pain is critical when diagnosing central pain.
- The exclusion of other types of pain is challenging.

- Many patients experience more than one type of pain, and sometimes, different pain types occur in the same body location.

- Differential diagnoses should be considered:
  - Musculoskeletal pain (overuse, myofascial shoulder pain, stress fractures, spasticity, dystonia, etc.)
  - Visceral pain
  - Peripheral neuropathic pain

Clinical Characteristics

- Central pain is characterized by spontaneous and/or evoked pain in an area with partial or complete sensory loss to one or more modalities.
- Decreased sensation to thermal or painful stimuli is present in most.
- Decreased sensation to other modalities is less common.
- The location of pain and sensory abnormalities is within an area compatible with the CNS lesion.
- Pain intensity for brainstem and suprathalamic lesions are moderate in intensity, while pain in thalamic lesions can be severe.

- Spontaneous pain may be ongoing, intermittent, or paroxysmal.

- Most common pain descriptors

Hot/burning	Cold
Shooting	Sharp
Pricking	Squeezing
Pins and needles	Aching

- Spontaneous pain may be generated by central sensitization mechanisms by which decreased thresholds and temporal summation cause ongoing pain from stimuli common in daily life (e.g., movement, breathing, ambient temperature).

- Evoked pain may be present as **allodynia** and **hyperalgesia**.
- Cold allodynia and touch-evoked allodynia

- Aftersensations: pain continuing after the stimulation has ceased

  → The distinction between spontaneous and evoked pain may be difficult.

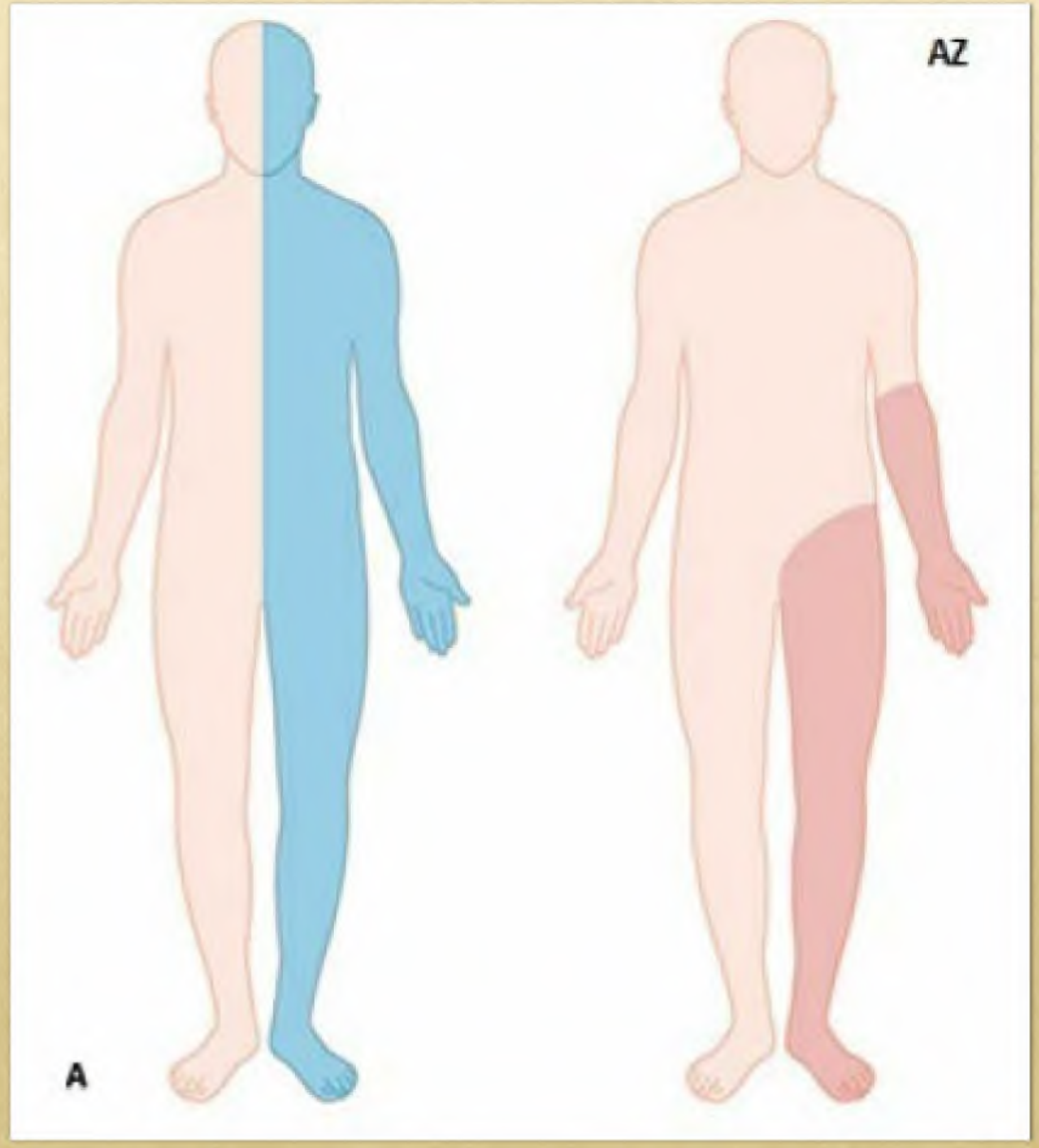
- Hyperpathia: an abnormal—often explosive—painful reaction to a stimulus in an area with increased sensory threshold when the stimulus exceeds the threshold.

- Nonpainful abnormal sensations are also common.
  - Paresthesia
  - Dysesthesia

Distribution of sensory abnormalities (blue) and central pain (red) in a patient with central poststroke pain

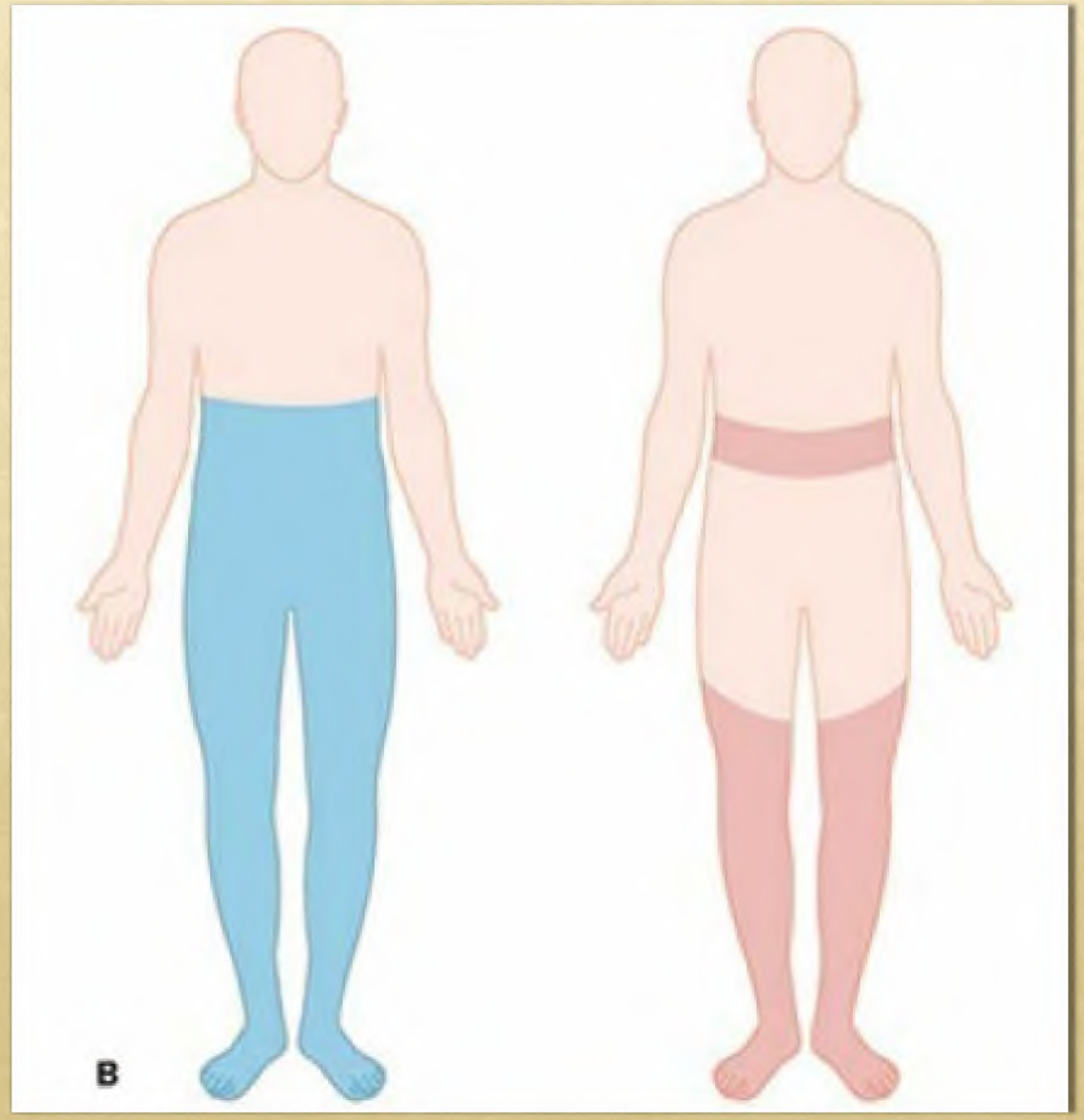
A 64-year-old woman with a stroke affecting the left side of the body.

MRI showed an infarct in the **right** internal capsule extending into part of the thalamus.



Distribution of sensory abnormalities (blue) and central pain (red) in a patient with central pain in spinal cord injury.

A 55-year-old man with a spinal cord injury (SCI) after a motorbike accident → complete SCI, neurologic level Th5.



Clinical Assessment

- In the assessment of central pain, it is relevant to evaluate the:
  - Intensity
  - Impact
  - Quality
  - Temporal aspects of pain
  - Physical functioning
  - Emotional functioning
  - Quality of life
  - Previous treatments

- Different scales have been developed to assess the multidimensional aspects of pain.

- Multidimensional Pain Inventory (MPI)
- Adapted for use in SCI (MPI-SCI).

- Neuropathic Pain Symptom Inventory (NPSI)
- Neuropathic Pain Questionnaire (NPQ)
- PainDETECT Questionnaire

- Other scales may be used to assess mood, sleep, resilience, pain catastrophizing, disability, and satisfaction with life.

TABLE 28.1 Clinical Assessment of Central Pain

Domain	Pain History and Clinical Assessment
Pain intensity	Numeric rating scale, visual analog scale
Pain quality	Pain questionnaires or interview
Pain location	Body map
Temporal aspects	Onset of pain, pain duration, pain frequency
Somatosensory function—sensory gain or loss	Thermal rollers Acetone droplet Pinprick Stroking the skin with brush Tuning fork
Psychological domains Pain impact Anxiety/depression Pain catastrophizing Participation	Questionnaires or interview

- **Mapping of sensory abnormalities and pain** is a crucial part of the diagnosis of central pain to ensure that the distribution is compatible with a CNS lesion.

- Laboratory tests can be used to confirm the diagnosis of a CNS lesion and specific abnormalities of the pain pathways.
  - CT scan
  - MRI
  - Heat- and laser-evoked potentials for assessing the function of the spinothalamic tract

Specific Central Pain Conditions

CENTRAL POSTSTROKE PAIN (CPSP)

- After a cerebrovascular lesion including ischemic and hemorrhagic lesions of the brainstem, thalamus, operculum-insula, and cerebral cortex.

- 3% to 8% of stroke patients

- Particularly common in patients with
  - Lateral medullary infarctions (prevalence may be as high as 25%)
  - Thalamus infarctions (prevalence of 18%)

CENTRAL POSTSTROKE PAIN (CPSP)

- CPSP is experienced contralateral to the side of the stroke.
- It may affect small areas such as the hand or the whole hemibody, which is common in thalamic infarctions.
- In patients with lateral medullary infarctions, the pain distribution may be crossed, involving one side of the body contralateral to the lesion and the other side of the face ipsilateral to the lesion, and periorbital pain is commonly described.

CENTRAL PAIN IN MULTIPLE SCLEROSIS

- Central pain is present in about 25% of patients with MS.
- The distribution of central pain is compatible with spinal or brain lesions of the somatosensory nervous system.
- Burning, tingling, pricking, and squeezing pain, sometimes associated with evoked pain
- In addition to this central pain type that is similar to central pain in other conditions, patients with MS may experience two specific types of central pain conditions
  - Secondary trigeminal neuralgia
  - Lhermitte's phenomenon

CENTRAL PAIN IN MS

- Trigeminal neuralgia
- In MRI scan: a lesion in the ipsilateral side of the pons along the course of trigeminal afferents
- The recordings of trigeminal reflexes and trigeminal-evoked responses should show increased latency.

- It is often unilateral but may be bilateral.
- Atypical forms of trigeminal neuralgia

CENTRAL PAIN IN MS

- Lhermitte's phenomenon
- A transient and short lasting electric shock-like sensation typically provoked by neck movement that is felt spreading down in the back.
- It is more common in younger patients and in patients with a progressive or progressive-relapsing course.
- Assumed to be caused by ectopic discharges due to demyelination in the dorsal column.

CENTRAL PAIN IN SPINAL CORD INJURY (SCI)

- Traumatic causes are traffic accidents and falls
- Nontraumatic causes include syringomyelia, tumors, ischemia, hemorrhage, arteriovenous malformations, transverse myelitis, and infections.

- Chronic pain is one of the most disabling consequences of an SCI—present in 70% to 80% of patients.
- Neuropathic pain is present in about 50% of patients.

- The onset of central pain may be immediately after the SCI or it may be delayed up to 1 year.
- A delayed onset and facial pain should alert the physician to the possibility of development of syringomyelia.

TABLE 30.1 Taxonomy of Spinal Cord Injury Pain

Broad Type (Tier One)	Broad System (Tier Two)	Specific Structures and Pathology (Tier Three)
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma, or inflammation Mechanical instability Muscle spasm Secondary overuse syndromes
	Visceral	Renal calculus, bowel dysfunction, and sphincter dysfunction Dysreflexic headache
Neuropathic	Above level	Compressive mononeuropathies Complex regional pain syndromes
	At level	Nerve root compression (including cauda equina) Syringomyelia Spinal cord trauma/ischemia Dual level cord and root trauma
	Below level	Spinal cord trauma/ischemia

Taxonomy of Spinal Cord Injury Pain Spinal Cord Injury Pain: Assessment, Mechanisms, Management, Yezierski, Burchiel, Taxonomy and Epidemiology of Spinal Cord Injury Pain, Siddal, Yezierski, Loeser. 2002 IASP Press. This table has been reproduced with permission of the International Association for the Study of Pain® (IASP). The table may not be reproduced for any other purpose without permission.

CENTRAL PAIN IN SCI

- Neuropathic pain following SCI is divided into:
  - At-level pain
  - Below-level pain

CENTRAL PAIN IN SCI

- At-level pain
- Early onset
- Located within the dermatome of the neurologic level of injury and three dermatomes below the neurologic level.
- May be caused by the SCI or a lesion of the nerve roots.
- It is often not possible to determine whether it is a peripheral neuropathic pain or a central pain.

CENTRAL PAIN IN SCI

- Below-level pain

- Develops months to years after the spinal injury

- Felt more than three dermatomes below the neurologic level

- It is a central pain caused by the spinal cord lesion.

- In patients with syringomyelia, the pain distribution is often segmental.

CENTRAL PAIN IN SCI

- Lesions above the **6th** thoracic level (splanchnic outflow) are often associated with **autonomic dysreflexia**.
- The dysreflexia is characterized by sudden dramatic increases in blood pressure, high or low heart rate, and headache after sensory input, such as a full bladder.
- This point becomes especially important in SCI patients having surgery below the level of their lesion, including minor operations of the urinary (i.e., cystoscopy) or gastrointestinal (i.e., colonoscopy) systems where the viscera will be stimulated.
- Even though patients may lack sensation in the area to which they are having surgery, intense stimulation can precipitate major hemodynamic instability.
- Complications may include seizures and cerebral hemorrhage.

OTHER CENTRAL PAIN CONDITIONS

- **Brain trauma**
- The diagnosis of central pain in brain trauma is often difficult and only few studies exist.
- The pain distribution is often unilateral, corresponding to the side with most severe sensory abnormalities and related to decreased thermal sensitivity.
- **Brain tumors** affecting the thalamus and the parietal cortex
- **Central pain following surgery** such as dorsal root entry zone lesions, thalamic destructions, and mesencephalic and medullary tractotomies are only infrequently reported because these procedures are rarely done today.

OTHER CENTRAL PAIN CONDITIONS

- **Parkinson's disease**

- Low back pain, pain in lower extremities, and musculoskeletal pain are the most common types.

- **Central pain:** rare and poorly localized diffuse pain
- Accompanied by autonomic symptoms, visceral pain
- Improvement with levodopa administration.

- This type of pain, however, does not entirely fulfill the criteria for central pain.

- However, there is increasing evidence that the basal ganglia and the dopaminergic system play an important role in the gating of nociceptive information and pain modulation, and it is possible that some pain types in Parkinson's disease are related to altered sensory processing of nociceptive inputs.

- **Epileptic seizures** may rarely be reported as pain.

Mechanisms

Mechanisms

- Sensitization of the CNS plays a major role in central pain and involves neuronal hyperexcitability resulting in:
  - Increased response to synaptic inputs
  - Decreased threshold
  - Expansion of receptive fields
  - Access of low-threshold Aβ mechanoreceptors to pain pathways

- The clinical consequences are allodynia, hyperalgesia, and aftersensations.

Mechanisms

- Damaged pain pathways or deafferented rostral neurons

  → spontaneous ongoing or intermittent pain.

- Decreased thresholds in nociceptor excitation and temporal summation of stimulus-evoked pain

  → Spontaneous pain

Mechanisms

- The functional changes underlying central sensitization involve a range of anatomical, neurochemical, excitotoxic, and inflammatory mechanisms.
- Changes in ion channels (sodium, calcium, potassium, acid-sensing)
- Phosphorylation of glutamate receptors
- Altered opioid receptor binding

Mechanisms

- Changes in the functions of microglia and astrocytes

  → release of inflammatory mediators → chronic pain following CNS injury

- Loss of inhibition:
  - Altered balance of descending inhibitory and facilitatory pathways
  - Loss of interneurons containing glycine or γ-aminobutyric acid (GABA)
  - Decreased GABAergic inhibitory function through downregulation of the potassium chloride exporter

Mechanisms

- Lesions of the STT and STT–thalamocortical pathways play an important but not well-understood role in the mechanisms of central pain.

- STT lesions are also frequent in pain-free subjects.
- Approximately 50% of patients with a lesion of the STT after SCI develop central pain.

- The question is why STT lesions cause pain in some but not all individuals.

Mechanisms

- It is suggested that central pain is caused by sensitization of partially preserved residual STT neurons in some patients.
- It is likely that the role of lesioned versus preserved ascending pathways in central pain depends on the pain phenotype.
- Patients with evoked pain are more likely to have preserved large- and small-fiber function than patients with spontaneous pain only.

Mechanisms

- The thalamus is implicated in central pain of spinal, brainstem, and brain origin.
  - Ventral caudal nucleus
  - Medial nucleus
  - Intralaminar nucleus
  - Ventral posterior nucleus

- Various disinhibition hypotheses
  - Imbalance between dorsal column compared to the STT pathways
  - Imbalance between spinothalamic and spinoreticulothalamic pathways

Mechanisms

- Loss of descending inhibitory pathways has been shown to be involved in central pain in SCI.
- Injury to the periaqueductal gray (PAG) matter plays an important role in dysfunction of descending pain modulation.
- Changes in spinal cord excitability are important for central pain following SCI.
- Central pain in SCI has been associated with changes in spontaneous EEG

Mechanisms

- Reorganization of the primary somatosensory cortex following SCI

- Changes in anterior cingulate and prefrontal cortices following SCI

Treatment of Central Pain

- Treating central pain remains a great challenge, and a broad approach is essential.

- Patients may be elderly, and they may have concurrent medical problems and impairments such as paralysis, spasticity, gastrointestinal and autonomic dysfunctions, intellectual impairment, as well as depression, fatigue, sleep disturbances, or psychosocial problems.

- They may be treated with multiple drugs with unwanted CNS-related side effects.

- The treatment of central pain is often **symptomatic**.
- In some cases, the underlying cause of neuropathic pain can be treated, for example, with the use of corticosteroids for the treatment of spinal cord compression.
- It is also important to be aware of factors that may exacerbate central pain (e.g., stress, depression, and urinary tract infections).
- Realistic expectations for the treatment outcome should be discussed with the patient.
- Often only partial pain relief

- Treatment of neuropathic pain is often a “trial-and-error” process.
- **Disease-based approach classification** of neuropathic pain
- **Mechanism-based classification** will improve the treatment of the individual patient.
- **Phenotype-based classification** has been advocated.
- The presence of specific clusters of pain descriptors or sensory profiles may reflect specific underlying pain mechanisms, and thus efficacy to specific drugs.

PHARMACOLOGIC TREATMENT

- Because there is no evidence for a disease-based pharmacologic treatment of central neuropathic pain, general treatment guidelines for neuropathic pain are also recommended for central pain—with the exception of topical treatments.
- **Topical treatments have no place.**
- Overall, randomized, double-blind, placebo-controlled studies in central pain support the general treatment recommendations for neuropathic pain.
- Responders experience only partial pain reduction at tolerable doses.

- Recommendations of Neuropathic Pain Special Interest group (NeuPSIG) of the International Association for the Study of Pain (IASP) are used.

- As for neuropathic pain in general, there is a relatively **large placebo response** in clinical trials of central pain—sometimes making it difficult to show superiority of different treatments.

- Numbers needed to treat (NNTs) are used to describe effect sizes.
- The NNT is the number of patients needed to treat with a certain drug to obtain one patient with a defined degree of pain reduction (usually 50%).
- It is calculated as the reciprocal of the absolute risk reduction.

Randomized Double-Blind Placebo-Controlled Trials of At Least 3 Weeks Duration in Central Pain

Central Pain Condition	Authors and Publication Year	Patients Randomized	Active Drug and Max. Daily Dose	Study Outcome
Antidepressants				
CPSP	Leijon and Boivie 1989[176]	15	Amitriptyline 75 mg	Ami > pla
SCI	Cardenas et al. 2002[177,a]	84	Amitriptyline 125 mg	Ami = pla
SCI	Rintala et al. 2007[178]	38	Amitriptyline 150 mg	Ami > pla
MS	Österberg and Boivie 2005[179]	23	Amitriptyline 75 mg	Ami > pla
SCI/CPSP	Vranken et al. 2011[180]	48	Duloxetine 120 mg	Dul = pla

Central Pain Condition	Authors and Publication Year	Patients Randomized	Active Drug and Max. Daily Dose	Study Outcome
Pregabalin/gabapentin				
MS	Kim et al. 2011[253]	220	Pregabalin 600 mg	Pre = pla
SCI	Siddall et al. 2006[181]	137	Pregabalin 600 mg	Pre > pla
SCI	Cardenas et al. 2013[182]	220	Pregabalin 600 mg	Pre > pla
SCI/CPSP	Vranken et al. 2008[254]	40	Pregabalin 600 mg	Pre > pla
SCI	Levendoglu et al. 2004[255]	20	Gabapentin 3,600 mg	Gab > pla
SCI	Rintala et al. 2007[178]	38	Gabapentin 3,600 mg	Gab = pla

Central Pain Condition	Authors and Publication Year	Patients Randomized	Active Drug and Max. Daily Dose	Study Outcome
Other Anticonvulsants				
CPSP	Vestergaard et al. 2001[183]	30	Lamotrigine 200 mg	Lam > pla
SCI	Finnerup et al. 2002[184]	30	Lamotrigine 400 mg	Lam = pla
MS	Breuer et al. 2007[256]	17	Lamotrigine 400 mg	Lam = pla
CPSP	Leijon and Boivie 1989[176]	15	Carbamazepine 800 mg	Car = pla
MS	Österberg and Boivie, 2005[179]	23	Carbamazepine 600 mg	Car = pla
SCI	Drewes et al. 1994[257]	20	Valproate 2,400 mg	Val = pla
SCI	Finnerup et al. 2009[258]	36	Levetiracetam 3,000 mg	Lev = pla
CPSP	Jungehulsing et al. 2012[259]	42	Levetiracetam 3,000 mg	Lev = pla
CPSP	Falah et al. 2012[260]	30	Levetiracetam 3,000 mg	Lev = pla

Central Pain Condition	Authors and Publication Year	Patients Randomized	Active Drug and Max. Daily Dose	Study Outcome
Opioids				
SCI	Norrbrink and Lundeberg 2009[261]	36	Tramadol 400 mg	Tra > pla
Cannabinoids				
MS	Svendsen et al. 2004[262]	24	Dronabinol 10 mg	Can > pla
MS	Rog et al. 2005[263,a]	66	Sativex spray	Can > pla
MS	Langford et al. 2013[264]	339	Sativex spray	Can = pla
SCI	Clinicaltrials.gov (NCT01606202)	111	Sativex spray	Can = pla
Other				
SCI	Chiou-Tan et al. 1996[265]	11	Mexiletine 450 mg	Mex = pla
SCI	Han et al. 2016[266]	40	Botulinum toxin type A	BTX-A > pla
SCI	Andresen et al. 2016[267]	73	Palmitoylethanolamide 600 mg	PEA = pla

First-line Pharmacologic Treatments

- Tricyclic antidepressants (TCAs)
- Serotonin-noradrenaline reuptake inhibitors (SNRIs)
- Gabapentinoids

- **TCAs and SNRIs** inhibit the presynaptic reuptake of serotonin and noradrenaline.

- In addition, TCAs act on
  - Voltage-gated sodium channels
  - Opioid receptors
  - N-methyl-D-aspartate (NMDA) receptors

- The site of action is through descending aminergic pathways at spinal or supraspinal sites, but a peripheral site of action via sympathetic fiber sprouting in the dorsal root ganglia may also be involved.

- The combined NNT for TCAs in neuropathic pain was 3.6 (95% CI, 3.0 to 4.4) with a moderate quality of evidence
- The combined NNT for SNRIs was 6.4 (5.2 to 8.4) with a high quality of evidence.

- The effect of antidepressants is independent of the antidepressant effect.

- Amitriptyline is the TCA most often studied in neuropathic pain, but there is no clinical evidence to suggest superior efficacy of one TCA over the other.
- Imipramine and the TCAs with secondary amine structure (nortriptyline and desipramine) are often better tolerated.

Central Pain Condition	Authors and Publication Year	Patients Randomized	Active Drug and Max. Daily Dose	Study Outcome
Antidepressants				
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- **Gabapentin and pregabalin** are ligands of the α2δ subunit of voltage-gated calcium channels → attenuation of calcium influx into cells and → reduced release of neurotransmitters.

- Other actions such as an effect on glia cells and expression of proinflammatory cytokines may also be involved.

- Interestingly, the expression of the α2δ calcium channel subunit can be increased in some neuropathic pain conditions.

- Act at peripheral, spinal, and supraspinal levels.

- The combined NNT for gabapentin in neuropathic pain was 6.3 (95% CI, 5.0 to 8.3), and the NNT for pregabalin was 7.7 (95% CI, 6.5 to 9.4) with a high quality of evidence.

- Pregabalin showed an effect on anxiety scores on the Hospital Anxiety and Depression Scale (HADS) in one study and on depression scores in another study.

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Second- and Third-Line Pharmacologic Treatments

- Tramadol
- Strong opioids

- **Tramadol** is a weak agonist of μ-opioid receptors and a SNRI.
- The combined NNT for tramadol in neuropathic pain was 4.7 (95% CI, 3.6 to 6.7) with a moderate quality of evidence.
- Particularly useful in the treatment of episodic exacerbations of pain.

- The combined NNT for strong opioids, including morphine and oxycodone, in neuropathic pain was 4.3 (95% CI, 3.4 to 5.8) with a moderate quality of evidence.

- Due to potential safety concerns with risk of abuse, cognitive impairment, and endocrine and immunologic changes, the final strength of recommendation was weak, and opioids were recommended as third-line drugs.

Other Drugs, Combination Therapy, and Intrathecal Drug Administration

- The recommendations for other antiepileptics for neuropathic pain are inconclusive due to conflicting and overall negative results.

- **Sodium channel blockers**
  - Lamotrigine
  - Carbamazepine
  - Oxcarbazepine

- **Cannabinoids**

- For neuropathic pain in general, there was an overall weak recommendation against the use of cannabinoids.

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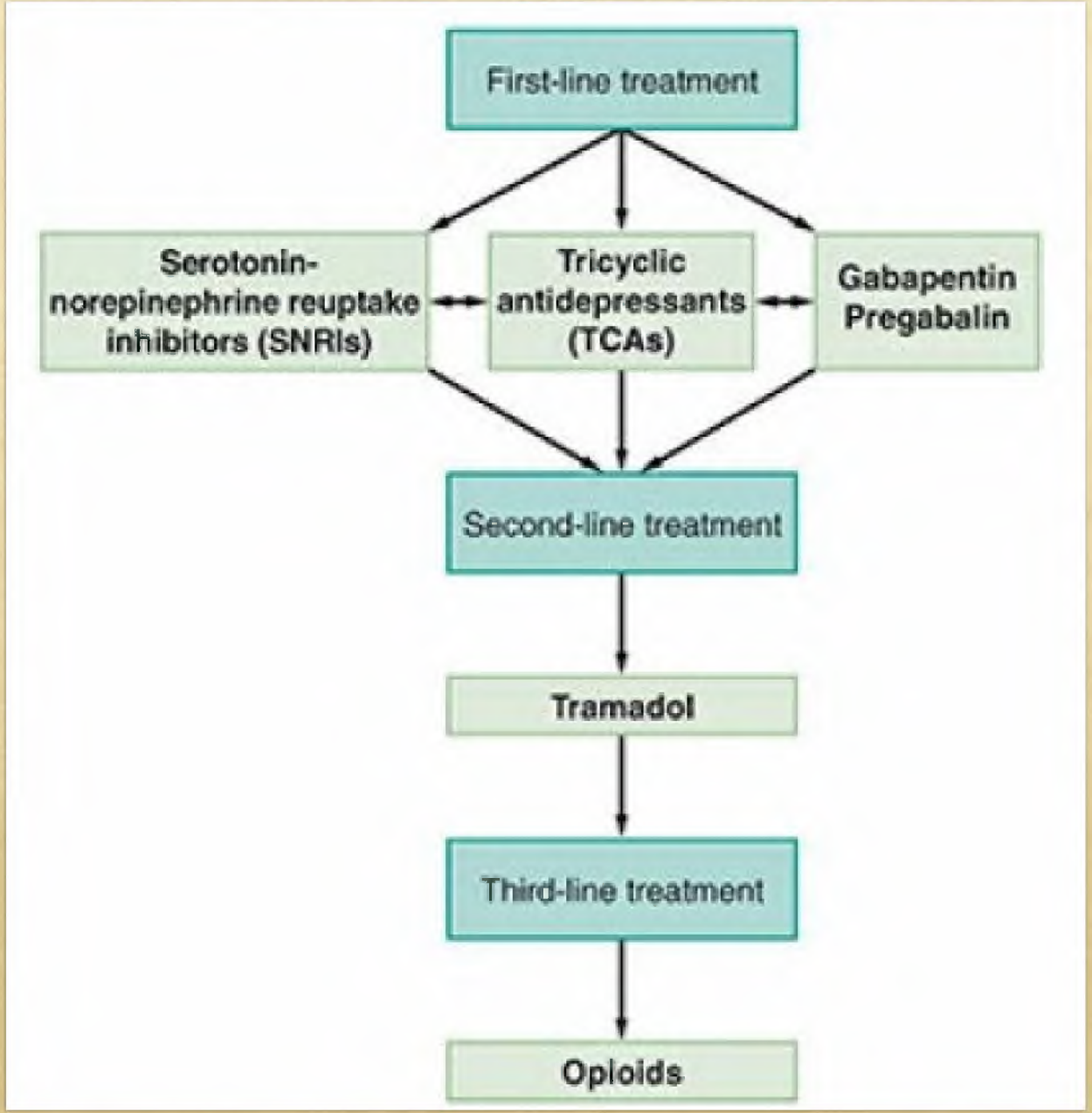
- When treatment with a single drug is only partly effective, combination with another drug of a complementary mechanism of action may be tried.


First-line treatment
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
Tricyclic antidepressants (TCAs)
Gabapentin Pregabalin
Second-line treatment
Tramadol
Third-line treatment
Opioids

Intrathecal drug administration

- Little evidence from randomized controlled trials.
- In one study, the combination of clonidine and morphine, but not each one alone, provided effect on central pain.
- The effect size correlated with the concentration of morphine in the cervical CSF, and it was suggested that if there is a pathology restricting the flow of CSF, the drugs need to be administered above the level of injury.

- **Ziconotide**

- Can be combined with intrathecal morphine or baclofen.

- There is limited experience with central pain.

- The treatment is often associated with severe side effects.

Other treatments:

- Psychological and physiotherapy treatment
- Neurosurgical management
  - Drug delivery via an intraventricular catheter
  - Neuroablation
    - Thalamotomy
    - Mesencephalotomy
  - Neuromodulation
    - Motor Cortex Stimulation
    - Deep Brain Stimulation
    - Spinal Cord Stimulation

Thanks for your attention