Pain Management for Primary Care

Series: Thirteen
Neuropathic Pain

Module 13–1
Central Neuropathic Pain

Module 13–1

Central Neuropathic Pain

By the end of the module, you will be able to:

- Describe a general overview of pain taxonomy.
- Identify classic central neuropathic pain syndromes.
- Explain basic mechanisms of neuropathic pathophysiology.
- Demonstrate competence in evidence-based treatments for central neuropathic pain syndromes.

We will review:

Topic One: Pain Taxonomy and Definitions

Topic Two: Central Neuropathic Pain Pathophysiology

Topic Three: Specific Neuropathic Pain Syndromes

Topic Four: Treatment of Central Neuropathic Pain

Topic Five: Phantom Limb Pain

Lead Authoring Subject Matter Experts

Department of Defense
LTC Jeffrey M. Tiede, USA

Topic One

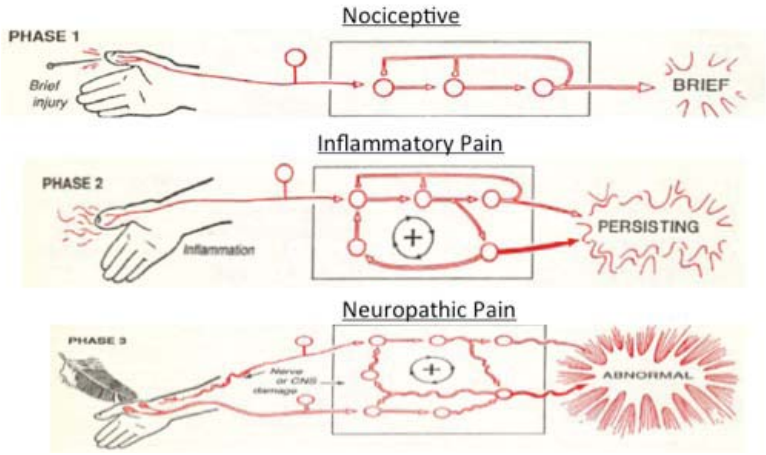
Pain Taxonomy and Definitions

Lord Horatio Nelson

The Battle of Santa Cruz de Tenerife was an assault by the British on the Spanish city of Santa Cruz de Tenerife. Launched by Rear-Admiral Horatio Nelson on 22 July 1797. The assault was defeated, and he withdrew under a truce with the loss of several hundred British casualties. Nelson himself had been wounded in the arm, which was subsequently partially amputated: a stigma that he carried to his grave as a constant reminder of his failure.

He developed Phantom Pain in the amputated arm. He believed his arm (although gone) had a soul. To him, this was direct evidence that man must have a soul as well. Would he have suffered the same pain if the British would have captured the city? It is well known that psychological distress in the setting of an injury will predispose to chronicity. The question arises if he would have had phantom pain if the British had won the battle.

Nociceptive, inflammatory and neuropathic pain have different etiologies, features, and treatments.



Notes

Scientists and providers will often categorize different diseases in order to provide a framework for understanding and treatment. Mechanistically, three types of pain exist: Nociceptive, inflammatory and neuropathic. Nociceptive and inflammatory pain function as a warning to prevent further injury. Neuropathic pain has no identifiable teleological purpose.

Nociceptive pain is the brief sensation in response to a noxious stimulus such as a pin prick.

Inflammatory pain is the sensation and hypersensitivity seen after an injury such as a hammer to the thumb and the 3-5 days of pain after the accident.

Neuropathic pain is the pain caused by a lesion or disease of the somatosensory nervous system.

Neuropathic pain is pain that arises in an injured or diseased nervous system. It can be peripheral, central, or both.

Peripheral Neuropathic Pain	Central Neuropathic Pain	Both
Radiculopathy	Stroke	Phantom Limb Pain
Medication related neuropathy (chemotherapy)	Multiple Sclerosis	Complex Regional Pain Syndrome (CRPS)
Entrapment neuropathy (carpal tunnel)	Parkinson's	
Compressive neuropathy (tumor)	Trauma	
Diabetic/Alcoholic/ Heavy Metal neuropathy	Transverse Myelopathy	
Vitamin deficiencies (B_{12})	Syringomyelia	
Infectious (PHN, HIV) neuropathies		
Autoimmune		
Hereditary (CMT)		

Notes

Classification of neuropathic pain is typically based on location of lesion or disease.

A better characterization is a mechanistic approach with peripheral neuropathic pain primarily caused by ectopic discharges and nociceptor sensitization. Central neuropathic pain is predominantly a disease of disinhibition and windup. This is why Complex Regional Pain Syndrome (CRPS) and phantom limb pain are mechanistically both a peripheral and central pathology (Phantom Limb Pain and CRPS falls within both columns).

Look for the distinct clinical signs of Neuropathic pain.

- Hyperalgesia - Increased sensitivity to pain, especially to repetitive stimulus.
- Allodynia - Pain due to a stimulus that does not normally provoke pain.
- Paresthesia - An abnormal sensation, whether spontaneous or evoked.
- Dysesthesia - An unpleasant abnormal sensation, whether spontaneous or evoked.
- Hyperesthesia - Increased sensitivity to stimulation, excluding the special senses.
- Anesthesia dolorosa - Pain in an area or region which is anesthetic (numb).
- Perform a complete neurological exam in every pain patient.

Notes

Neuropathic pain is characterized by spontaneous or evoked pain typically described as shooting, lancinating, burning or searing.

Gait disturbance, usually characterized by a spastic, scissoring quality.

Sensory deficits, usually related to dorsal column function (reduced joint position and vibratory sense) and loss of pain sensation, can be elicited in the lower extremities and may contribute to the gait impairment.

Weakness in the lower extremities with upper motor neuron characteristics: increased reflexes, increased tone, and present Babinski signs.

Bladder dysfunction, urgency, frequency, and/or retention.

Lhermitte's sign. An electric shock-like sensation in the neck, radiating down the spine or into the arms, produced by forward flexion of the neck.

Depending on the location of the myelopathic lesion, various physical exam manifestations can arise. Any of the aforementioned physical exam findings should alert the provider to a central mechanism. Localized findings such as lower motor disease and dermatomal numbness will present at level of lesion. For example hand numbness is seen in cervical myelopathy.

Knowledge Check

What are the general types of pain?

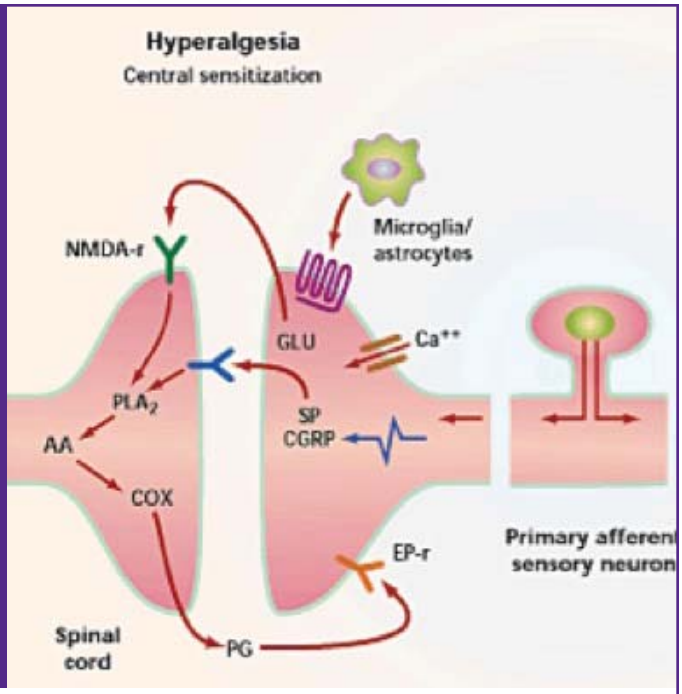
a. Inflammatory
b. Neuropathic
c. Sensory
d. Nociceptive
e. A, B, & D
f. All of the Above

Knowledge Check – Answer

What are the general types of pain?

a. Inflammatory
b. Neuropathic
c. Sensory
d. Nociceptive
e. A, B & D
f. All of the Above

Topic Two
Central Neuropathic Pain Pathophysiology



This image shows the synapse between the sensory neuron (on the right) and the neuron in the spinal cord

Chronic pain causes excitation (sensitization) between these neurons.

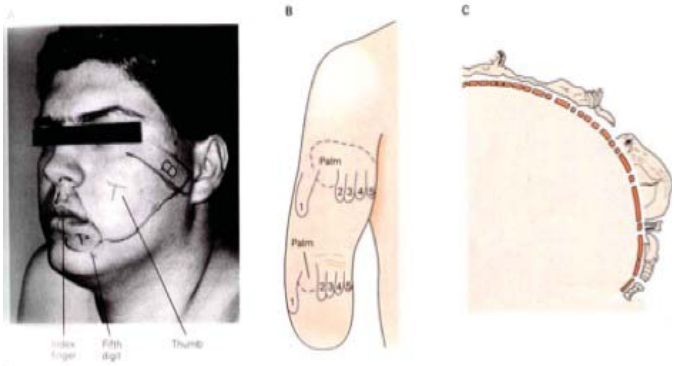
Facilitator may detail:
Central sensitization (Windup) is the progressive increase in the frequency and magnitude of firing of dorsal horn neurons produced by repetitive activation of C fibers.

Ensitization involves Glutamate metabolism and Gilal activation and inflammation
Windup of wide dynamic range (WDR) neurons at the spinal level will increase the transmission of signals to the supraspinal levels responsible for perception. These signals may be generated by noxious (hyperpathia) or non-noxious (allodynia) stimuli.

The complicated cellular mechanisms for this increased sensitivity involves the metabolism of glutamate. The NMDA receptor has been implicated in neuropathic pathophysiology and serves as a target for analgesics (Ketamine).

Microglial cells comprise less than 20% of spinal glial cells under normal conditions but proliferate rapidly at the dorsal root after injury. On activation, these cells stimulate the release of cytokines and other pro-inflammatory substances.

Neuropathic pain causes significant changes in the spinal cord and brain.



The image shows that brushing an amputee's face provokes phantom limb pain.

This is because the proximity of the face and the extremities in the somatosensoty cortex.

Notes

Disinhibition

Spinal Level: GABAergic dorsal horn interneurons will inhibit nociceptive signals to attenuate pain. This inhibitory control will diminish in pathologic states.

Supraspinal – Descending inhibitory pathways are seen in the periaqueductal gray, locus coeruleus, anterior cingulate gyrus, amygdala and hypothalamus.

Under normal circumstances, the brain is constantly bombarded with sensory signals; it deals with these sensory barrages by applying a substantial amount of inhibition. An important component of neuropathic pain is the lifting of this inhibition do to a damage of these pathways.

Supraspinal reorganization

The brains of patients with chronic neuropathic pain are different from those without pain, with variations in metabolism, connectivity and cellular viability in areas such as the primary somatosensory cortex and cingulate cortex.

Upper extremity amputees with phantom limb pain: Because of the close proximity of the somatotropic representations, the area of the brain responsible for sensation of the lips transgresses into the hand sensation area of the somatosensory cortex; this phenomenon does not occur in amputees without phantom limp pain. Here we see a patient with the sensation of someone touching his thumb with a

Knowledge Check

What is the main excitatory neurotransmitter implicated in central sensitization and windup?

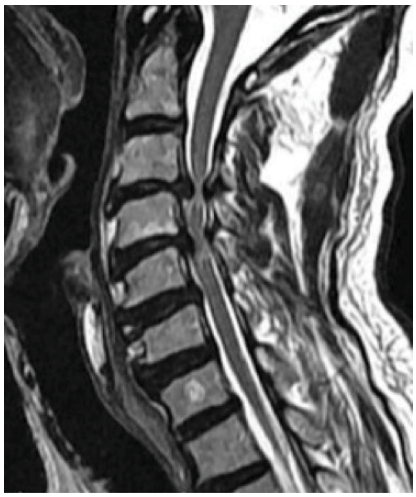
Knowledge Check – Answer

Glutamate

Glutamate is the main excitatory neuroamine implicated in central sensitization. It is an agonist of the NMDA receptor and NMDA receptor antagonists (ketamine, dextromethorphan, etc.) can be powerful analgesics.

Topic Three

Specific Neuropathic Pain Syndromes



Cervical stenosis can present with myelopathy and neuropathic pain.

Degenerative cervical spine pathology can lead to central stenosis with cord compression.

Common cause of myelopathy in older adults

Often associated with localized radiculopathy

Notes

Cervical spondylosis refers to a progressive degenerative process affecting the cervical vertebral bodies and intervertebral discs. This process can lead to narrowing (stenosis) of the central spinal canal, compressing the cervical spinal cord and producing a syndrome of spinal cord dysfunction known as cervical spondylotic myelopathy. Myelopathy occurs in 5 to 10 percent of patients with symptomatic cervical spondylosis.

Cervical spondylotic myelopathy is the most common cause of myelopathy in adults over 55 years, causing progressive disability and impairing the quality of life.

Flexion and extension of the neck may exacerbate compression; the canal diameter is reduced by 2 to 3 mm in flexion, while extension can cause inward buckling of the ligamentum flavum.

The neurologic syndrome of cervical spondylotic myelopathy is sometimes referred to as a radiculomyelopathy because the spondylotic process can simultaneously damage spinal nerve roots as well as the cord itself.

Neuropathic Central Pain is common among patients with Spinal Cord Injury (SCI)

- Overall, 30-50% develop central pain within weeks to months after injury.
- Pain can be at or below the level of injury and is accompanied with segmental allodynia and hyperalgesia.
- This pains is due to changes in the spinal cord and brain as well as Syringomyelia or nerve root entrapment secondary to SCI.

Notes

Pain is a frequent phenomena after spinal cord injury (SCI) and is very difficult to treat. It may involve various aspects of the brain. These patients may experience central pain beginning within weeks or months after injury. It is typically felt at or below the level of SCI in areas where patients have lost some or all of their sensation.

There also may be segmental pain around the border where patients have normal sensation and loss of feeling secondary to the SCI. Segmental pain may be associated with allodynia and hyperalgesia in the painful region. If a patient also has nerve root entrapment and/or syringomyelia (a hollow fluid-filled cavity, or syrinx) in the spinal cord, which commonly expands, more neurological damage may also develop. Some research have demonstrated the development of central sensitization of dorsal horn neurons after spinal cord hemisection. This would provide a logical mechanism for the development of mechanical and thermal allodynia after SCI.10

Recent research takes this hypothesis further. Dendritic spine remodeling occurs on second-order wide dynamic range neurons and accompanies neuropathic pain after SCI, showing the possibility that a synaptic model of long-term memory storage could explain the persistent nature of neuropathic pain, as SCI-induced synaptic potentiation engages a putative spinal memory mechanism.11

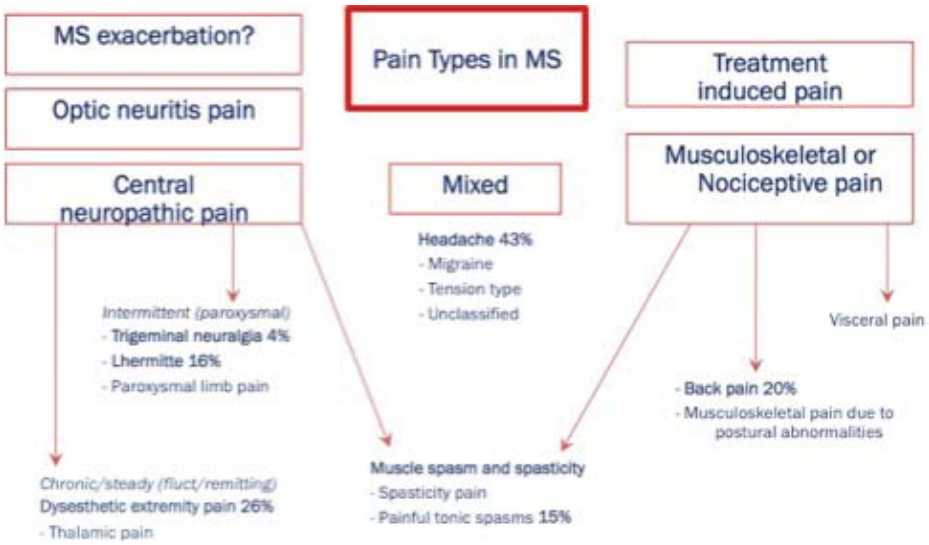
However, other research demonstrates that chronic pain after SCI appears to be associated with nociceptive primary afferent neurons, which display persistent hyperexcitability and spontaneous activity in their peripheral branches and somata in dorsal root ganglia (DRG) after SCI, suggesting that SCI-induced alterations of primary nociceptors contribute to central sensitization and chronic pain after SCI.12

Gwak et al indicate the SCI-induced release of glutamate, proinflammatory cytokines, adenosine triphosphate (ATP), reactive oxygen species, and neurotrophic factors trigger activation of postsynaptic neuron and glial cells via their own receptors and channels that contribute to neuronal-neuronal- and neuronal-glial interaction as well as microglia-astrocytic interactions. Post SCI, dysfunctional glia, a condition they call "gliopathy," is a key contributor to underlying cellular mechanisms contributing to neuropathic pain.1

Finnerup indicates that chronic pain is present in about 70% of patients with SCI and chronic CNP in 30% to 50%.14 She concluded that: 1) evoked types of pain are more common in SCI patients with central pain; 2) lesions in central gray matter are larger in SCI patients with central pain; and 3) spinothalamic tract lesions are equally common in SCI patients with and without central pain.

Pain is common among patients with Multiple Sclerosis (MS) for many reasons.

- Pain is more common in elderly women with progressive MS (50%-80%)



Notes

Multiple sclerosis is and example of a mixed neuropathic and nociceptive pain.

- Pathophysiology: damage to myelinated nerve fibers in CNS
  - Ectopic impulses at demyelinated lesions → paroxysmal pain
  - Trigeminal Neuralgia, painful Lhermitte
  - Interruption of inhibitory impulses removes the modulation of afferent A-δ and C-fiber pain pathways → constant pain
  - Dysesthetic extremity pain due to lesions in spinothalamic pathways

Truini abstract includes:

"Emerging evidence suggests that pain might be more effectively classified and treated according to symptoms and underlying mechanisms. The new mechanism-based classification we propose here distinguishes nine types of MS-related pain:"

- trigeminal neuralgia and Lhermitte's phenomenon (paroxysmal neuropathic pain due to ectopic impulse generation along primary afferents)
- ongoing extremity pain (deafferentation pain secondary to lesion in the spino-thalamocorticalpathways)
- painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motorpathways but mediated by muscle nociceptors)
- pain associated with optic neuritis (nerve trunk pain originating from nervi nervorum)
- musculoskeletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders),
- migraine (nociceptive pain favored by predisposing factors or secondary to midbrain lesions)
- treatment-induced pains

continued on next page

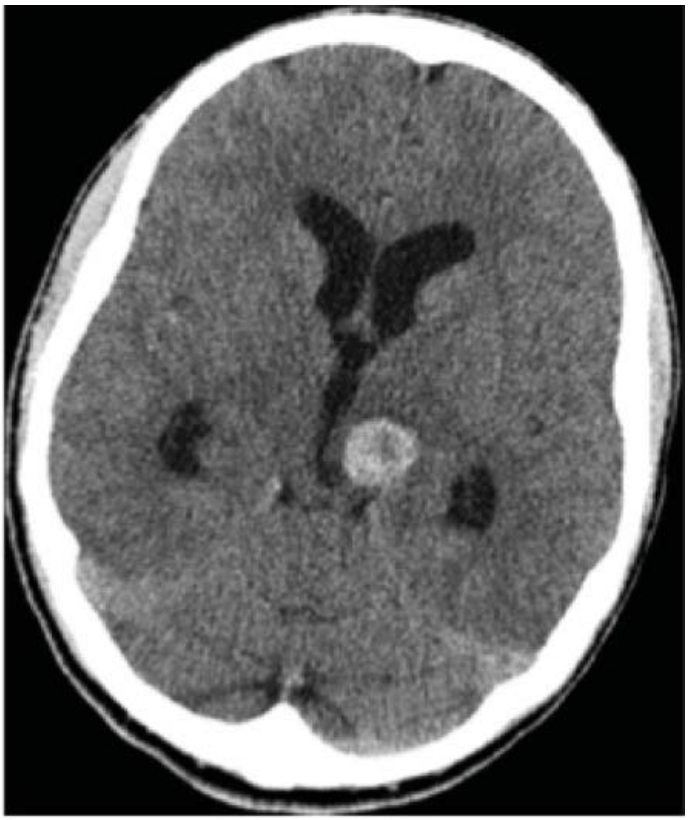
Notes - Continued

Identification of various types of MS-related pain will allow appropriate targeted pharmacological treatment and improve clinical practice.

- Moerke et al - Headache in MS
- N=98 MS patients (55.4%) reported headaches in the previous 4 weeks
- We subsequently grouped headache patients according to the IHS criteria and detected
- 16 (16.3%) MS patients suffering from migraine (migraine with aura: 2 [2%]; migraine without aura: 14 [14.3%])
- 23 (23.5%) sufferingfrom TTH
- none with a cluster headache.
- (60.2%) MS patients remained unclassified.

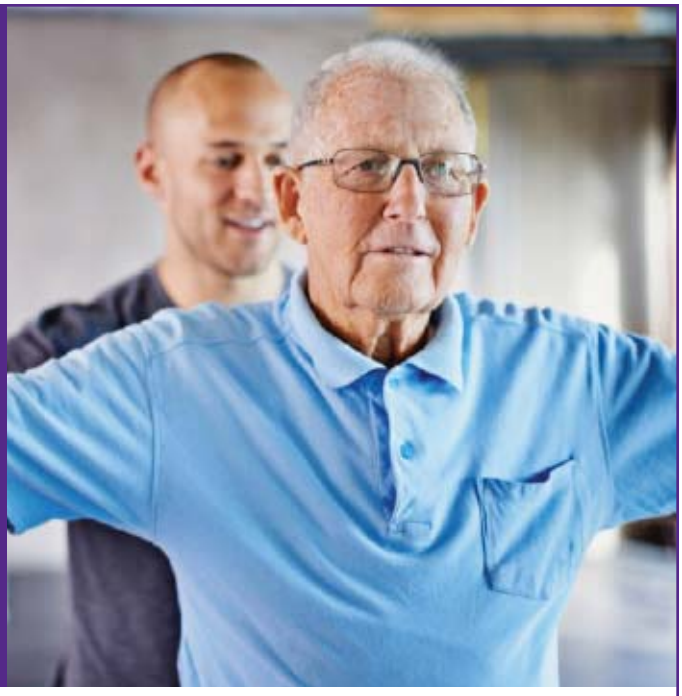
When comparing MS patients with and without headaches significant differences in age, gender, MS course, physical functioning, pain and social functioning occurred. MS patients with headaches were significantly younger of age (p=0.001), female (p=0.001) and reported more often of a clinically isolated syndrome (CIS) and relapsing/remitting MS (RRMS) instead ofsecondary chronic progressive MS (SCP). EDSS was significantly lower in MS patients suffering from headaches compared to the MS patients without headaches (p=0.001). In conclusion headache in MS patients is a relevant symptom, especially in early stages of the MS disease. Especially unclassified headache seems to represent an important symptom in MS course and requires increased attention.

Thalamic pain (Dejerine Roussy syndrome) can appear after stroke and is hard to treat.



- This is an example of thalamic pain.
- 40 y/o male with unremarkable medical history.
- Acute onset of severe HA associated feeling of cold water over half on body and anxiety.
- CT shows thalamic hemorrhage, MRI shows hemangioma (above).
- Surgical evacuation of hemangioma with good recovery leave patient with a persistent feeling of Right side of body being submerged in ice water. Usually pain is associated with some form of altered temperature sensation.

Topic Four
Treatment for Central Neuropathic Pain



The foundational treatment of central neuropathic pain is physical rehabilitation. Medical treatment with adjuvants can help.

Antidepressants (including TCA's, SSNRI's)

- Amitriptyline/ Nortriptyline
- Duloxetine/ Venlafaxine/ Milnacipran

Antiepileptics

- Gabapentin
- Pregabalin
- Carbamazepine/ Oxcarbazepine
- Lamotrigine/ Levetiracetam/ Zonisamide

Other

- Baclofen
- Tizanidine
- Ketamine
- Ziconotide

Notes

Refer to doses in module 4-2

Look for side effects, especially among the elderly.

- Anticholinergic side effects are dose dependent (amitriptyline > nortriptyline)
- Beware of postural hypotension and prolonged QT interval or conduction blocks when using amitriptyline and nortriptyline.
- Increases Appetite (amitriptyline and pregabalin)
- Dizziness and somnolence is a very common complaint (amitriptyline, carbamazepine, duloxetine, gabapentin, pregabalin, tramadol)
- Nausea is common with carbamazepine, duloxetine, and tramadol
- Look for sexual dysfunction - with all antidepressants, gabapentin, and pregabalin. Especially in younger patients.

Notes

Anticholinergic effects - These include dry mouth, postural hypotension, arrhythmias, cognitive impairment, constipation, and urinary retention. For elderly patients, those with prostate hyperplasia, and those for whom constipation or dry mouth is already a problem, consider using lower doses and monitoring closely. In elderly start all drugs at lower doses and with slower dose titration. Avoid drugs having anticholinergic effects in patients who have cognitive impairment. Do not give TCA's to elderly. 2.2 relative risk of hip fracture in elderly with TCA's.

Dizziness - Consider using lower doses and monitoring closely in elderly patients and those who already have a problem with dizziness. Warn patients about dizziness and falls. As duloxetine has no anticholinergic effects, it may be useful in treating elderly patients. It is also well known that Tricyclic antidepressants will result in weight gain.

Anticholinergic - These are dose dependent and strongest with amitriptyline, significantly weaker with nortriptyline and non-existent or minimal with tramadol, venlafaxine, duloxetine, carbamazepine, gabapentin, and lamotrigine.

Appetite - Commonly (≥1/100) increased with amitriptyline and pregabalin, whereas it is commonly decreased with duloxetine.

Dizziness - Very common (≥1/10) with carbamazepine, duloxetine, gabapentin, pregabalin, and tramadol and common (1/10) with amitriptyline.

Somnolence - Very common (≥1/10) with carbamazepine, duloxetine, gabapentin, and pregabalin and common with amitriptyline.

Nausea - Very common (≥1/10) with carbamazepine, duloxetine, and tramadol.

Cardiovascular effects - Postural hypotension and prolonged QT interval or conduction blocks are common (≥1/100) with antidepressants, more likely with amitriptyline and nortriptyline.

Sexual dysfunction - Common (≥1/100) with all antidepressants, gabapentin, and pregabalin. Anorgasmia is not uncommon in younger men.

Serious adverse events are rare.

- Lamotrigine can cause skin reactions, however serious allergic reactions are rare.
- Carbamazepine can cause Leucopenia and hypersensitivity syndrome, with fever, rash, lymphadenopathy and hepatosplenomegaly.
- Rarely Carbamazepine and Oxcarbazepine can cause Hyponatremia.
- Rarely Carbamazepine and Oxcarbazepine can cause Stevens-Johnson syndrome in susceptible individuals.

Notes

Pregnant women—Tricyclic antidepressants and antiepileptics are not recommended.

Breastfeeding women—Carbamazepine and gabapentin (maximum 2100 mg/day) can be taken. Tricyclic antidepressants should be avoided. There is little information for newer antiepileptics or duloxetine.

Knowledge Check

Ziconotide is an antiepileptic used for treatment of pain? (True or False)

Knowledge Check – Answer

False

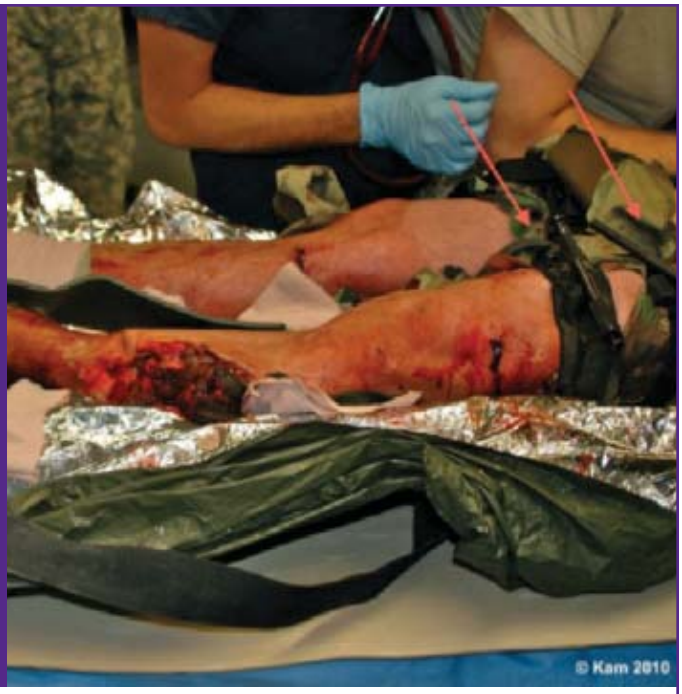
It is an N-type calcium channel blocker delivered intrathecally.

Notes

Ziconotide (Prialt™) was derived from a sea snail conotoxin. Despite case series with significant reduction in pain, side effects such as psychosis have been associated with its rapid titration. Use has been limited by this and the need for intrathecal delivery.

What are the first line treatments for neuropathic pain?

Topic Five
Phantom Limb Pain



Medics and Corpsman are taught to secure tourniquets during care under fire and then re-secure them after fire superiority is established during tactical field care. Such TTP's have resulted in a dramatic reduction in battle-related mortality. Many of the service members who would have died in previous conflicts are now faced with amputations.

Here, during Role One Care prior to surgical stabilization you see two deliberate tourniquets (both a SOF-T, special operations forces- tourniquet and a CAT, combat application tourniquet) placed proximal to the trauma on the Left Leg. You will also notice a Ready-Heat thermal blanket used to combat another preventable cause of combat mortality, hypothermia.

Up to 80% of veteran amputees report phantom limb pain.

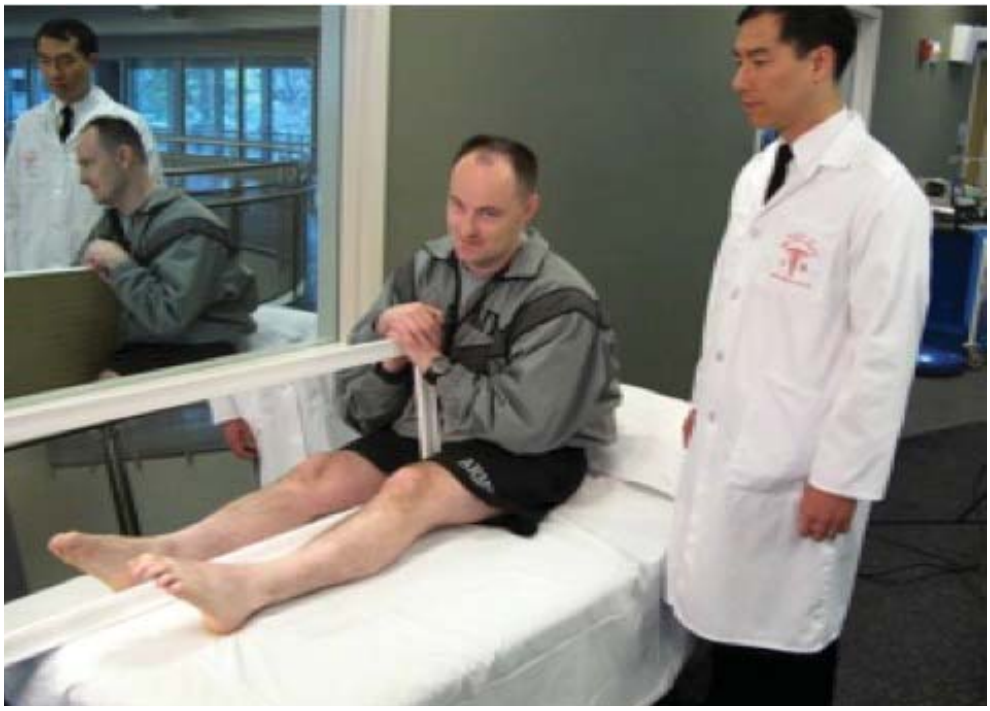
Notes

In a survey of 11,000 U.S. war veteran amputees, 80% reported having significant phantom pain (Stein and Warfield 1982).

Of the 200,000 patients who undergo surgical amputations in the United States each year, 70% experience phantom limb pain after the procedure, and 50% still experience phantom pain 5 years after surgery (Bloomquist 2001).

From traumatic amputation to surgical amputation, a great majority of amputees have phantom pain. The intensity of the pain and disability associated with this are dependent on biopsychosocial factors. It is well known that amputation after a long battle with illness (peripheral vascular disease) is more likely to produce severe pain than an acute injury. The hyper-vigilance associated with PTSD may also contribute to disability. This picture shows a group of WWII Soldiers participating in balance exercises.

Mirror therapy has been extremely successful in treating phantom limb and neuropathic pain in amputees and paraplegic patients.



Notes

Visual feedback is important for cortical remodeling. Mirror therapy as championed by Ramachandran uses a mirror placed next to the patient's residual limb. Thereby, the mirror image creates an illusion of an intact limb. The patients reported that they felt their amputated limb return. It is well known that integration of the visual cortex enhances the therapeutic neuroplasticity.

These treatments including graded motor imagery as well as mirror therapy require extensive expertise from a multi-disciplinary team.

Mirror feedback therapy. In this approach, the patients are told to use the mirror in a way that the image of the mirrored healthy limb seems to appear in the place of the missing extremity. It is based on the influence of sensory and motor training effects on the pain experience with cortical organization.

Again pain does not equal nociception. The pain is not in the spinal cord (or peripheral nerves); it is in the brain. The cortical processing of pain is disrupted in chronic neuropathic pain conditions such as pain after spinal cord injury. Using the visual cortex to augment the change in cortical reorganization is one way to combat these recalcitrant pain conditions.

In this study in 5 patients watch a film of an actor walking on a treadmill was projected onto the screen. A mirror placed over the top half of the screen meant that the patient could see the reflection of their own upper body. The patient would move their upper body in time with the lower body in the film so that it appeared to the patient as if they were watching themselves walk. A 5.3 point drop in VAS is greater than the effect seen with neuropathic medications, opioids and neuromodulation.

Combining physical, integrative and behavioral treatments is the best approach

- Proper fitting and prosthesis function must be optimized.
- Acupuncture, biofeedback, and/or TENS may be helpful in the setting of a multidisciplinary approach.
- Sleep hygiene and cognitive behavioral therapy is helpful with sleep and mood difficulties.
- Long-term adjuvants such as antidepressants and anticonvulsants might be of use.
- Neurosurgical procedures may be considered (Excision of stump neuroma), some as last resort (Deep brain or Motor cortex stimulation).
- Long-term use of muscle relaxants, sedatives (Benzos), NSAIDS, and opioids should be avoided.

Notes

Although phantom limb pain is not considered to be a psychiatric disorder, persistent severe pain can have psychological sequelae.

Psychologic interventions can lessen pain intensity and help the patient cope better with pain. A randomized clinical trial has showed that mental imagery, which involves limb laterality recognition, imagined movements, and mirror movements, reduced pain and disability in patients with phantom limb pain. There is growing evidence for the effectiveness of mind-body therapies for phantom limb pain even though it is empirical; in addition to mirror visual therapy, various approaches include targeting of cortical reorganization, autonomic nervous system deregulation, stress management, and coping ability.

Summary

Recall that all pain is real and that chronic pain has an enormous impact on individuals, families, and society.

Look for the sensory, emotion and cognitive components of the painful experience and encourage meaningful valued activities for the patient.

Remember that pain is influenced and determined by expectations, context and mood and requires a holistic and team based approach.

References

Baron, E. M., & Young, W. F. (2007). Cervical spondylotic myelopathy: a brief review of its pathophysiology, clinical course, and diagnosis. Neurosurgery, 60(1), S1-35.

Bouhassira, D., Lantéri-Minet, M., Attal, N., Laurent, B., & Touboul, C. (2008). Prevalence of chronic pain with neuropathic characteristics in the general population. Pain, 136(3), 380-387.

Bloomquist, T. (2001). Amputation and phantom limb pain: a pain-prevention model. AANA journal, 69(3), 211-217.

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: mechanisms and their clinical implications. Bmj, 348.

Dietrich, C., Walter-Walsh, K., Preißler, S., Hofmann, G. O., Witte, O. W., Miltner, W. H., & Weiss, T. (2012). Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. Neuroscience letters, 507(2), 97-100.

Finnerup, N. B., & Jensen, T. S. (2007). Clinical use of pregabalin in the management of central neuropathic pain. Neuropsychiatric disease and treatment, 3(6), 885.

Kalso, E., Aldington, D. J., & Moore, R. A. (2013). Drugs for neuropathic pain. BMJ, 347.

Mao, J., Price, D. D., Hayes, R. L., Lu, J., & Mayer, D. J. (1992). Differential roles of NMDA and non-NMDA receptor activation in induction and maintenance of thermal hyperalgesia in rats with painful peripheral mononeuropathy. Brain research, 598(1), 271-278.

Mika, J., Zychowska, M., Popiolek-Barczyk, K., Rojewska, E., & Przewlocka, B. (2013). Importance of glial activation in neuropathic pain. European journal of pharmacology, 716(1), 106-119

Moseley, G. L. (2006). Graded motor imagery for pathologic pain A randomized controlled trial. Neurology, 67(12), 2129-2134.

Moura, V. L., Faurot, K. R., Gaylord, S. A., Mann, J. D., Sill, M., Lynch, C., & Lee, M. Y. (2012). Mind-body interventions for treatment of phantom limb pain in persons with amputation. American Journal of Physical Medicine & Rehabilitation, 91(8), 701-714.

Merskey, H., & Bogduk, N. (1994). Part III: Pain terms, a current list with definitions and notes on usage. Classification of chronic pain, 209-214.

Ramachandran, V. S., & Altschuler, E. L. (2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain, awp135.

Stein, J. M., & Warfield, C. A. (1982). Phantom limb pain. Hospital practice (Office ed.), 17(2), 166.

Truini, A., Barbanti, P., Pozzilli, C., & Cruccu, G. (2013). A mechanism-based classification of pain in multiple sclerosis. Journal of

Notes

JPEP

Joint Pain Education Program