# Pain Management for Primary Care


## Series: Thirteen
Neuropathic Pain

## Module 13–2
Peripheral Neuropathic Pain

# Module 13–2

## Peripheral Neuropathic Pain

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

- Identify peripheral neuropathic pain syndromes.
- Explain basic mechanisms of neuropathic pathophysiology.
- Demonstrate competence in evidence-based treatments for peripheral neuropathic pain syndromes.

### We will review:

Topic One: Pain Taxonomy and Definitions

Topic Two: Peripheral Neuropathic Pain Pathophysiology

Topic Three: Peripheral Neuropathic Pain Syndromes

Topic Four: Common Peripheral Neuropathies Diagnosis

Topic Five: Treatments for Peripheral Neuropathy


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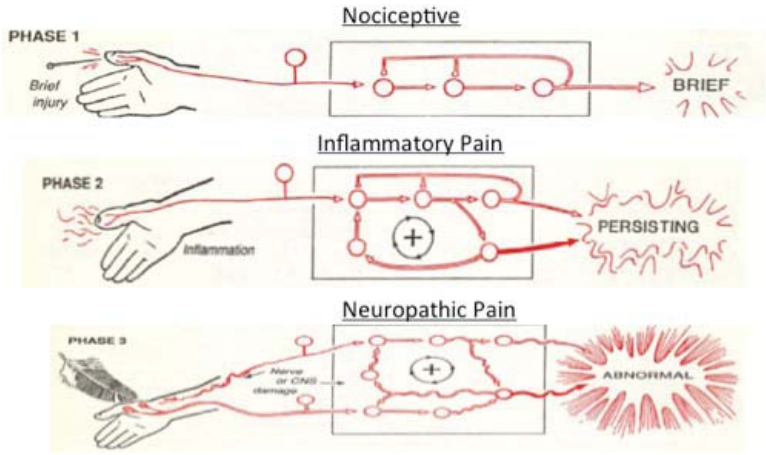
# Topic One

## Pain Taxonomy and Definitions

"Perhaps few persons who are not physicians can realize the influence which long-continued and unendurable pain may have on both body and mind. Under such torments the temper changes, the most amiable grow irritable, the bravest soldier becomes a coward and the strongest man is scarcely less nervous than the most hysterical girl. Perhaps nothing can better illustrate the extent to which these statements may be true than the cases of burning pain, Causalgia, the most terrible of all tortures which a nerve wound may inflict."

– Silas Weir Mitchell

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).

Peripheral Sensitization – the nociceptor becomes more efficient

Central Sensitization/Wind Up – the spinal cord and brain become more efficient

Anatomic Reorganization – non-painful stimuli become painful

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.
- Glutamate metabolism
- Glial 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.

## 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.

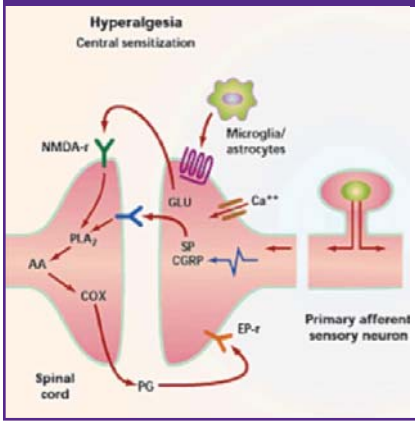
Weakness in the lower extremities with upper motor neuron characteristics: increased reflexes, increased tone, and present Babinski signs.

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.

# Topic Two
## Peripheral Neuropathic Pain Pathophysiology




### Neuropathic pain causes significant changes in the spinal cord.

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.

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 brushing of the cheek.

## 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

## Peripheral Neuropathic Pain Syndromes

### Acute peripheral neuropathies are diagnostic emergencies.

- Population prevalence is 2.4% rising to 8.0% with age.
- Neuropathy due to diabetes mellitus and alcohol misuse are the most prevalent.
- A quarter of peripheral neuropathies are idiopathic.
- Neurophysiological tests distinguish axonal from demyelinating neuropathies.
- Axonal neuropathies have multiple causes.
- Demyelinating neuropathies are commonly inflammatory and treatable.

Notes

In industrialized countries the most common cause is diabetic mellitus and alcohol. Infectious causes including leprosy is still prevalent in Africa, India and SE Asia.

- Up to one-quarter of patients with polyneuropathy at referral centers despite extensive investigations
- Seen mostly in elderly
- Proposed but unproven causes include impaired glucose tolerance, hypertension, dyslipidemia, and increased oxidative stress

Although population-based data are lacking, no specific cause is identified in up to one-quarter of patients with polyneuropathy at referral centers despite extensive investigations. A variety of terms have been employed to describe this disorder, including chronic idiopathic axonal polyneuropathy (CIAP) and idiopathic neuropathy. Most such cases present in those ≥50 years old and progress slowly over months to years. The symptoms are typically sensory, involving paresthesia, numbness or pain. Electrodiagnostic studies show a primarily axonal polyneuropathy.

# Acute Peripheral Neuropathies

| Cause | Predominantly motor | Mixed | Predominantly sensory |
|---|---|---|---|
| Guillain-Barré syndrome | + | + | — |
| Vasculitis | — | + | — |
| Diabetes mellitus | — | + | + |
| Drugs | — | + | + |
| Porphyria | + | — | — |
| Diphtheria | — | + | — |
| Paraneoplastic neuropathy | — | + | + |
| Acute idiopathic sensory neuropathy | — | — | + |
| Critical illness | + | + | — |

Notes

Acute neuropathies are medical emergencies with acute inflammatory Demyelinating polyradiculoneuropathy (Guillan-Barre Syndrome) being the prototypical disease.

This condition is typically preceded by a viral disease by one to two weeks and presents with rapid progression of sensory or motor deficits. It is caused by an autoimmune response directed against the Schwann cells or myelin. Treatment with IVIG/ ± steroids.

Drug causes of ACUTE peripheral neuropathy include nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

Acute multiple mononeuropathy is also an neurological emergency with vasculitis being the most common cause.

## There are many reasons for chronic peripheral neuropathy.

### Axonal (80%)

- Diabetes
- Toxin (ETOH)
- Hypothyroidism
- Uremia
- B12 Deficiency
- Multiple other causes

### Demyelinating (20%)

- Charcot-Marie-Tooth
- CIDP
- Paraproteinemia

Notes

A peripheral nerve can react to injury in a limited number of ways; therefore, multiple conditions present in similar fashions.

Chronic peripheral neuropathies can affect motor, sensory, autonomic or a combination of nerves. This, along with electrodiagnostic studies, will help determine etiology.

Broadly, CHRONIC peripheral neuropathies can be divided into axonal or demyelinating etiologies. Axonal neuropathies are by far the most common with diabetes and ETOH dominating the prevalence.

In demyelinating neuropathy the distal motor latency is prolonged and nerve conduction velocity slowed to less than 80% of normal. In axonal neuropathy the action potential is reduced, but the distal motor

latency and nerve conduction velocity are unaffected.

## Initial work up includes:

- Full blood count, erythrocyte sedimentation rate, vitamin B-12, folate
- Fasting blood glucose concentration, renal function, liver function, thyroid stimulating hormone
- Urine - Glucose, protein
- Electroneuromyography (ENMG) and nerve conduction velocity (NCV) studies can help if the above workup is equivocal and you are referring to a neurologist.

Notes

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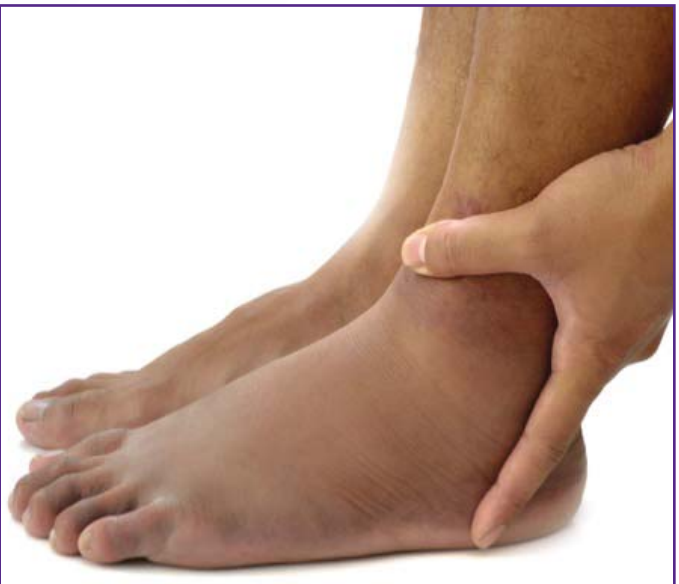
# Topic Four
## Common Peripheral Neuropathies



### Example:

- 55 year old patient
- 2 years of toe numbness, paresthesia and pain
- Stocking numbness of toes with absent ankle jerks
- No medical history or family history or medications
- Multiple consultations & lab testing without etiologic diagnosis

# Ethanol Neuropathy

- Among the most common neuropathies worldwide
- Numbness, paresthesia, pain in stocking distribution
- Sensory >>> Motor
- Loss of ankle reflexes
- Ethanol toxicity and nutritional deficiency
- Vitamin B1 Deficiency (thiamine)

Notes

Alcohol abusers have a high incidence of peripheral nerve disorders, including symmetric polyneuropathy, autonomic neuropathy, and compression mononeuropathies. As an example, peripheral neuropathy was detected in 32 percent and autonomic neuropathy in 24 percent of 107 consecutively examined alcohol abusers in one report. The majority of patients in this series were middle class working men, and evidence of malnutrition was present in only a small minority. The prevalence of autonomic and peripheral neuropathy each correlated best with lifetime alcohol consumption more than with nutritional deficiency

## Example:

- 23 y/o patient with no past medical or family history and no medications.
- Severe pain in back and flank followed by weakness over hours to inability to walk.
- Severe weakness legs, milder weakness arms
- Areflexia
- Numbness of feet
- Diarrheal illness 2 weeks ago

# Guillain-Barre Syndrome

- Rapid, severe, typically ascending paralysis
- Post infectious in 60%
- Paresthesia, pain, numbness
- Autonomic nerves
- Reflexes lost

Peter-Brian Andersson, Approach to Peripheral Neuropathy, ppt

Notes

Acute peripheral neuropathy is rare but important because the most common cause is Guillain-Barre syndrome, which can be fatal.

Common early symptoms are distal paresthesia and proximal or distal weakness occurring one to two weeks after a respiratory or GI infection.

Once a patient loses the ability to walk and develops facial and bulbar weakness the diagnosis becomes obvious.

The rapid progression of sensory or motor deficit requires emergency Investigation. Patients usually have to be admitted to the hospital because of the danger of respiratory failure.

## Example:

- 55 year old obese woman
- Family history positive for diabetes
- 4-5 years of nocturia and 1-2 years of polyuria
- Dry skin over the feet
- Stocking numbness in all modalities to the ankles
- Absent ankle reflexes

# Diabetic Polyneuropathy

- Multiple forms of neuropathy in diabetes
- Sensory >>> motor polyneuropathy
- Autonomic involvement common
- Glucose control!
- Foot care

Peter-Brian Andersson, Approach to Peripheral Neuropathy, ppt

Notes

Optimal glucose control is considered the cornerstone for the treatment of diabetes and its complications. Intensive glucose control has been shown to prevent the development of peripheral neuropathy.

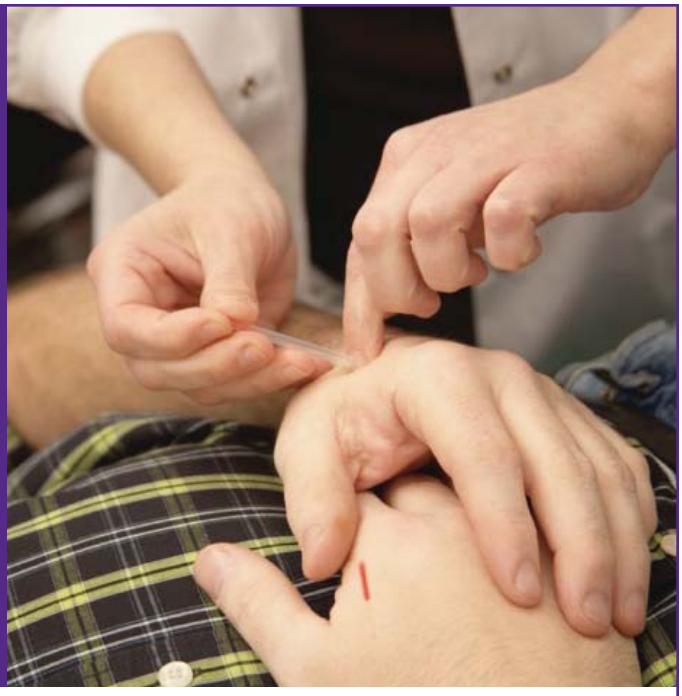
However, whether near-normal glycemic control can ameliorate established symptomatic diabetic neuropathy, and painful neuropathy in particular, is not as clear.

For patients with diabetic neuropathy, foot care is important to prevent ulceration, infection, and amputation.

Only a small fraction of patients with diabetic polyneuropathy have painful symptoms. In addition, the pain associated with diabetic polyneuropathy is often self-limited; evidence from a small prospective study suggests that

Resolution occurs  over 12 months in approximately one-half of patients.

# Topic Five
## Treatments for Peripheral Neuropathies



## Peripheral Neuropathy – Treatment

AAN – Guidelines for treatment of painful diabetic peripheral neuropathy

**Table 1** Summary of recommendations

| | Recommended drug and dose | Not recommended |
|---|---|---|
| **Level A** | Pregabalin, 300-600 mg/d | |
| **Level B** | Gabapentin, 900-3,600 mg/d | Oxcarbazepine |
| | Sodium valproate, 500-1,200 mg/d | Lamotrigine |
| | Venlafaxine, 75-225 mg/d | Lacosamide |
| | Duloxetine, 60-120 mg/d | Clonidine |
| | Amitriptyline, 25-100 mg/d | Pentoxifylline |
| | Dextromethorphan, 400 mg/d | Mexiletine |
| | Morphine sulphate, titrated to 120 mg/d | Magnetic field treatment |
| | Tramadol, 210 mg/d | Low-intensity laser therapy |
| | Oxycodone, mean 37 mg/d, max 120 mg/d | Reiki therapy |
| | Capsaicin, 0.075% QID | |
| | Isosorbide dinitrate spray | |
| | Electrical stimulation, percutaneous nerve stimulation ×3-4 weeks | |

## Notes

- Suggestion of using one of the antidepressants or anticonvulsants as initial therapy. The available evidence suggests that these agents have similar modest benefit. Patients who fail to improve with a reasonable trial of one of these agents can be switched to monotherapy with another agent.
- For patients who do not improve on one drug, we suggest combination therapy employing two drugs from different medication classes as the next step in the treatment paradigm.
- For patients who are unable to tolerate any of these drugs, alternative treatments include capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray.
- The use of opioids for chronic nonmalignant pain is controversial. We suggest not using opioids for the treatment of painful diabetic neuropathy because of the lack of evidence regarding long-term effectiveness, and because of the potential for opioid tolerance, addiction, and overdose. However, other experts believe that opioids have a role in the management of painful diabetic neuropathy despite these concerns.
    - Bril V et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.
    - What is included in the treatment recommendations with evidence, identify preference
    - Reference 2014 AAN guidelines

## Specific Diseases

Diabetic Peripheral Neuropathy: Alpha-lipoic acid (ALA), a potent antioxidant, has been associated with benefit for symptomatic diabetic neuropathy in several prospective, placebo-controlled studies.

- oral dose of ALA 600 mg once daily
- Post-herpetic Neuralgia: 8% Capsaicin patch
- Applied to painful area after local anesthetic pretreatment.
- Empiric benefits seen with amputee stump pain at SAAMC.

In the Sydney 2 trial, 181 patients with diabetes and symptomatic distal symmetric polyneuropathy. A clinically meaningful response, defined as ≥50 percent reduction in neuropathic symptoms, was observed in 50 to 62 percent of patients treated with ALA versus 26 percent with placebo, a difference that was statistically significant.

High-concentration capsaicin must be administered by a healthcare professional and patients are monitored for up to two hours after treatment. To manage local pain from capsaicin application, the skin is pretreated with a local anesthetic such as topical lidocaine.

A 2013 systematic review identified four randomized controlled trials that evaluated 1272 subjects with PHN treated with one application of either high-concentration capsaicin patch or standard concentration capsaicin. The only common endpoint reported by all four trials, a ≥30 percent pain intensity reduction at eight weeks compared with baseline, was significantly greater for high-concentration capsaicin patch

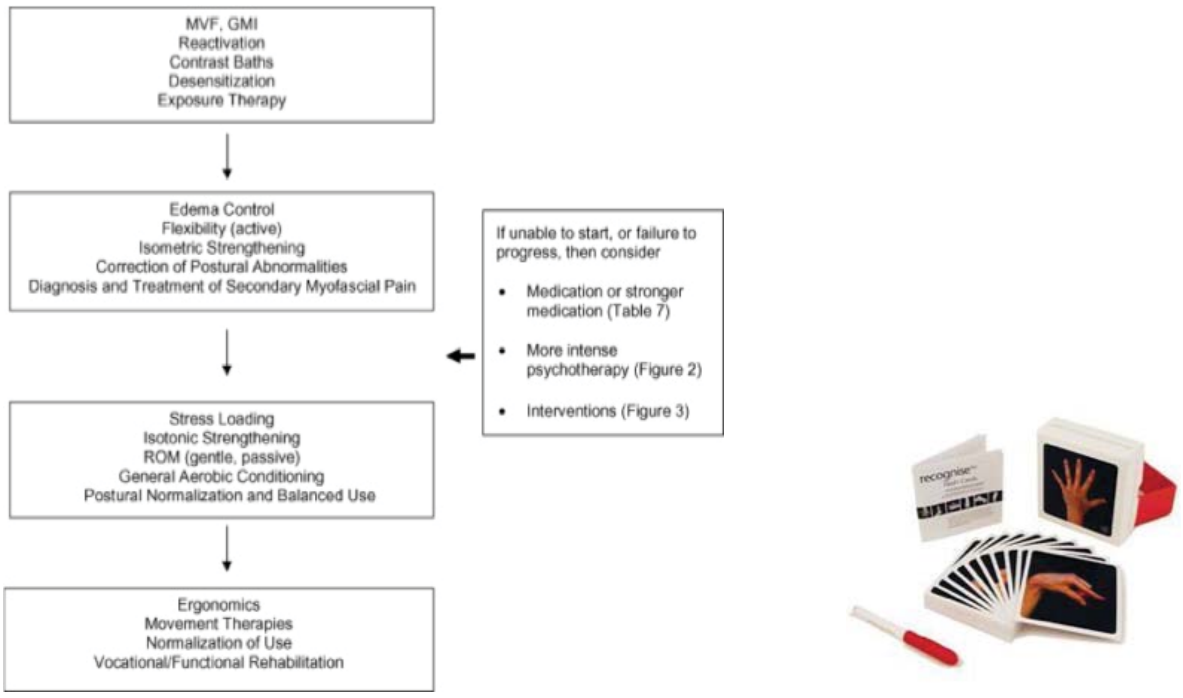
## Complex Regional Pain Syndrome (CRPS) is a painful debilitating condition with:

1. Continuing disproportionate pain,
2. Must report at least one symptom in three of the four following categories:
    - Sensory: Reports of hyperesthesia and/or allodynia
    - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
    - Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
    - Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
    - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
    - Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
    - Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
    - Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Notes

CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings.

## Mirror therapy and graded motor imagery has been successful in treating CRPS pain.




### Notes

MVF-mirror visual feedback, GMI – graded motor imagery

The principle of functional restoration is based on a gradual and steady progression from activation of pre-sensorimotor cortices to very gentle active movements to weight bearing such as carrying light bags with the upper extremity or putting partial weight on the lower extremity in gait trainings. Gradual desensitization to increasing sensory stimulus goes along with increased function.

Another basic principle of these functional restoration guidelines is that if patients do not progress through the steps in a reasonable time, then other interventions will progressively be added to give the patient greater comfort to proceed to the next level.

The interventions/pharmacotherapy and psychotherapy should not be used in isolation.

REVIEW: Neuropathic pain is associated with reorganization of the somatosensory and motor cortices.

- Non-invasive exercises in neuroplasticity such as graded motor imagery (GMI) and tactile discrimination.
- GMI randomized controlled trial in CRPS - the number needed to treat for a 50% reduction in neuropathic pain score was ~2.
- Tactile discrimination training with pen lid vs. cork for 10 days resulted in improvement in pain and disability.

As part of the anatomic reorganization, the primary sensory cortex corresponding to an affected limb will loose efficiency and volume of synaptic connections. This is manifest by decreased tactile acuity (two point discrimination). In order to harness the brain's plasticity many providers have developed non-traditional treatment protocols which have subsequently shown benefit.

Graded Motor Imagery is one such program. It consists of 3 stages. The first stage involves hourly sessions of left/right limb judgments. The second stage used imagined movements and the third stage involves mirror therapy. Such treatment protocols (which include conscious exercises by the patient) have shown improvements in pain, tactile acuity and reversal of cortical reorganization.

## Combining physical, integrative and behavioral treatments is the best approach.

- Acupuncture, biofeedback, TENS may be helpful in the setting of a multi-disciplinary approach.
- Sleep hygiene and cognitive behavioral therapy is helpful with sleep and mood difficulties.
- Long-term adjuvants such as anti-depressants and anticonvulsants might be of use.
- Long-term use of muscle relaxants, sedatives (Benzos), NSAIDS, and opioids should be avoided.

Notes

As with most treatments, drug therapy works best when prescribed in conjunction with functional restoration and treatment of other comorbid conditions. Rational polypharmacy is often necessary and is pursued on a mechanistic approach.

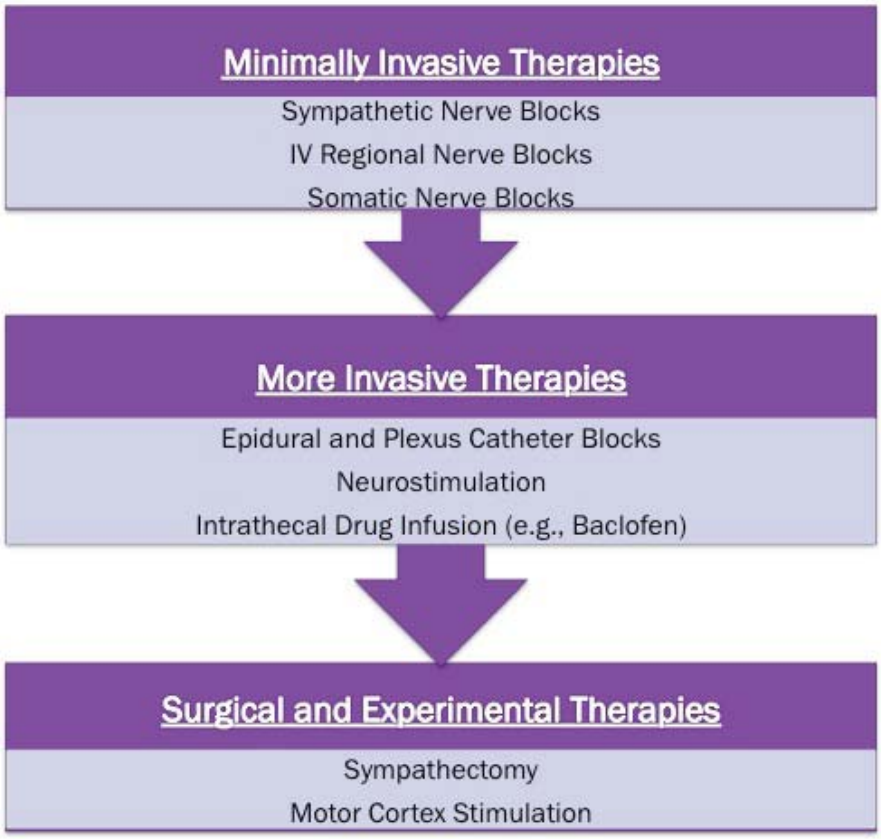
Most anticonvulsant literature is extrapolated from other neuropathic conditions such as DPN and PHN.

The indication for opioids, especially long term opioids, is questionable with one small RCT with extended release morphine being no better than placebo.

In a small trial, anesthetic doses of ketamine (a NMDA receptor antagonist) did show benefit up to 6 months after infusion.

The vigorous bone remodeling seen in CPRS can be painful and bisphosphonates and Calcitonin can improve this. Bisphosphonates are shown in RCT to improve pain.

Image guided procedures may be considered for refractory cases.




Notes

There is poor evidence for the efficacy of the classic Stellate Ganglion Block and Lumbar Sympathetic Block. If the block provides good analgesia in a patient, then a short series of blocks in conjunction with active reanimation physiotherapy is advocated.

Neurostimulation mechanisms are indicated in patients who cannot progress through rehabilitation. These techniques in isolation will only provide modest benefits without improvement in function.

Sympathetic ablation techniques have been advocated for many years, mainly by surgeons. In general, neurodestructive techniques to treat chronic pain syndromes due to deafferentation syndromes or post-sympathectomy neuralgia have fallen from favor. The same holds true for neurolytic blocks utilizing alcohol or phenol.

## Knowledge Check

Given the severity of pain in CRPS, opioids are considered always indicated. (true or false)

## Knowledge Check – Answer

False

The indication for opioids, especially long term opioids, is  questionable with one small RCT with extended release morphine being no better than placebo. BLUF: no matter how severe the pain, long-term opioid use may be associated with declining function, aberrant use, and hyperalgesia.

# 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.

# Resources

American Academy of Neurology Guidelines for the treatment of painful diabetic peripheral neuropathy - dosage recommendations
https://www.aan.com/Guidelines/home/GetGuidelineContent/480

Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines, 4th edition
http://rsds.org/wp-content/uploads/2014/12/CRPS-guidlines-4th-ed-2013-PM.pdf

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