PainWeek®

Updates on Complex Regional Pain Syndrome

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Disclosures

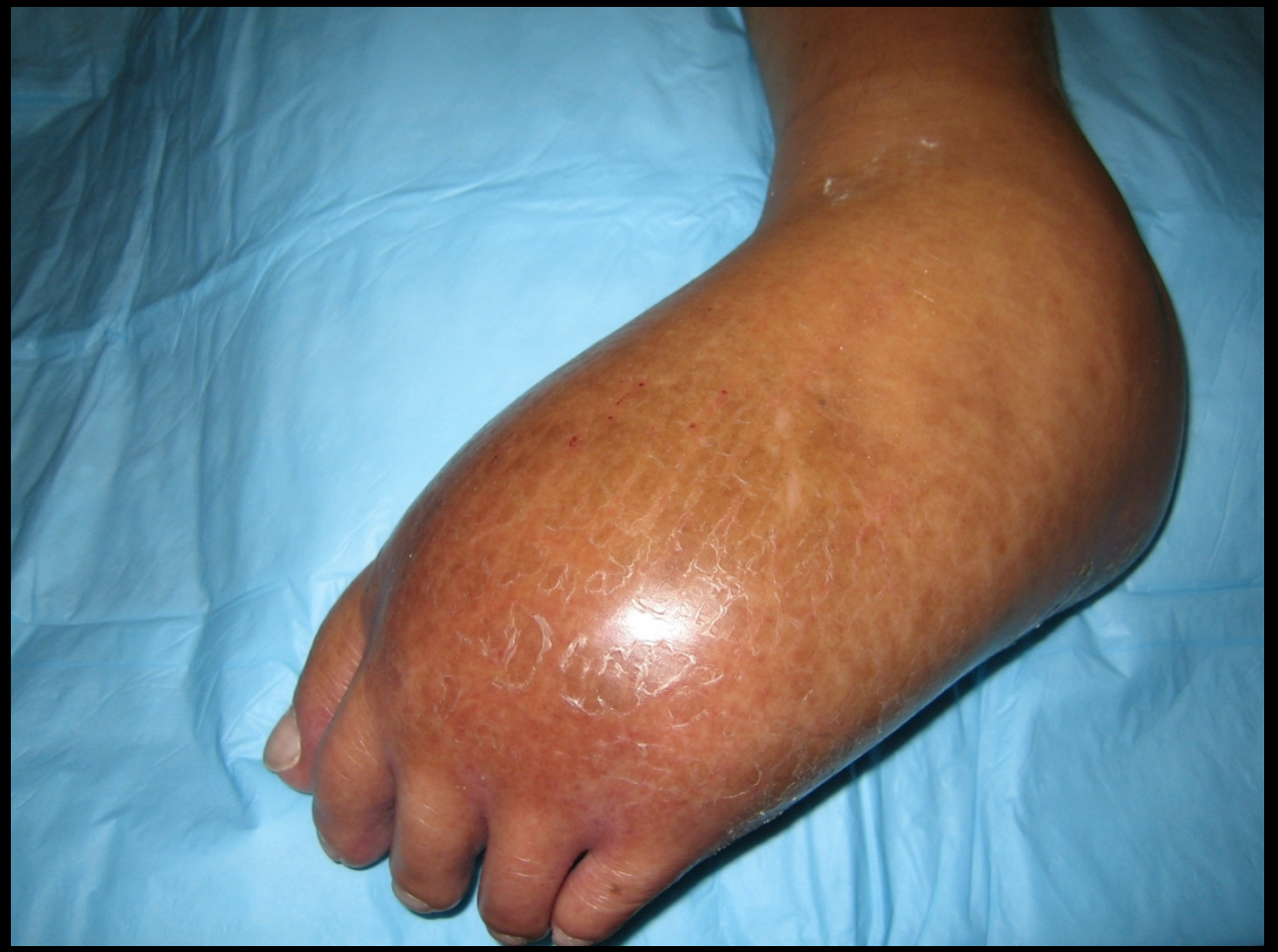
- Consultant/Advisory Board: GlaxoSmithKline Consumer Healthcare, Eli Lilly, Y-mAbs, Exicure

- This presentation may contain references to off-label or investigational use of drugs or products

Learning Objectives

- Identify the current diagnostic criteria for CRPS
- Recognize the hallmark of the diagnosis
- Review evidence on current treatments for CRPS

Complex Regional Pain Syndrome



What Is Complex Regional Pain Syndrome (CRPS)?

- Debilitating chronic pain syndrome characterized by
  - Pain and hypersensitivity
  - Vasomotor skin changes
  - Functional impairment
  - Various degrees of trophic change
- Generally follows musculoskeletal trauma
- Occurs more frequently in young adults and women
- Triggered by trauma (fractures), surgery, inflammation, stroke, crush injury, MI, neoplasms, immobilization, sprains
- Psychological stressors and poor coping skills can influence natural history and severity of CRPS
- At least 50,000 new cases of CRPS I occur annually in U.S.

Bruehl S. Complex Regional Pain Syndrome. BMJ. 2015;351:h2730; Uritis I, Shen AH, Jones MR, et al. Complex Regional Pain Syndrome, Current Concepts and Treatment Options. Current Pain and Headache Reports (2018) 22:10

Diagnostic Criteria for CRPS
Budapest Criteria

- Diagnosis of exclusion
- Continuing pain disproportionate to any inciting event
- Patients should report at least one symptom in 3 of the 4 categories and display one sign in 2 or more categories:
  - Sensory: report hyperesthesia = increased sensitivity to a sensory stimulation; evidence of hyperalgesia or allodynia
  - Vasomotor: temperature asymmetry or skin color changes
  - Sudomotor/edema: edema or sweating changes
  - Motor/trophic: decreased range of motion or weakness, tremor, dystonia or trophic changes (hair, nail, skin changes)
- Designed to retain diagnostic sensitivity of orginal criteria while doubling specificity (reduce false positives)
- Validity supported; official IASP diagnostic criteria in 2012

Stanton-Hicks M. CRPS: what's in a name? Taxonomy epidemiology, neurologic, immune and autoimmune considerations. Reg Anes Pain Med 2019;44:376-387

Clinical Features of CRPS

- Systems: autonomic, sensory, motor changes
- Symptoms: stinging, burning pain, aching, shooting, squeezing, throbbing sensations
- Type I: Lacks specific nerve lesion;
  Type II (Causalgia): reflects clear evidence of nerve injury, but symptoms extend beyond the course of the affected peripheral nerve distinguishing it from isolated mononeuropathy
- Stage I: early, acute with sensory/vasomotor, sudomotor changes
  Stage II: increased pain, vasomotor changes, substantial motor/trophic changes
  Stage III: diminished pain, sig. increased motor/trophic changes and continued vasomotor changes. No definite sequence occurs in all patients
  - More common: transition from warm, red CRPS to cold, bluish common as CRPS progresses from acute to chronic state
  - Warm and Cold CRPS: More likely to resolve within 12 months if initially diagnosed with warm CRPS.

Bruehl S. Complex Regional Pain Syndrome. *BMJ.* 2015;351:h2730; Stanton-Hicks M. CRPS: what's in a name? Taxonomy epidemiology, neurologic, immune and autoimmune considerations. *Reg Anes Pain Med* 2019;44:376-387

Clinical Features of CRPS

- Hyperesthesia: increased sensitivity to stimulation
  - Allodynia: pain associated with stimulus that normally provokes no pain
  - Hyperalgesia: exaggerated painful response to a painful stimulus
- Limb Disuse: Animal and human studies report disuse in development of CRPS. Early mobilization important after injury to prevent chronic CRPS.
- Natural Course: Many cases probably resolve with limited intervention. Smaller subset of persistent pts seen in tertiary care clinics.

Bruehl S. Complex Regional Pain Syndrome. *BMJ*. 2015;351:h2730

Clinical Features of CRPS (cont'd)

- Sympathetic Component
  - Presumptive evidence that SNS involved in initiation and maintenance
    - May be direct link between SNS and nociceptor, or indirect via inflammatory cytokines (TNF-alpha, IL-6) & macrophages that sensitize nociceptors
  - Sympathetic blockade can help distinguish presence
  - SMP = pain maintained by sympathetic efferent system or circulating catecholamines
    - SMP conditions = HZ, CRPS, Phantom pain, neuralgias
    - Sympatho-afferent coupling can trigger pain & play role in severity of syndrome
- Psychological Component
  - Depression common (24% - 49% of pts); higher risk of suicide
  - Anxiety, depression, anger may have greater pain impact due to sympatho-afferent coupling

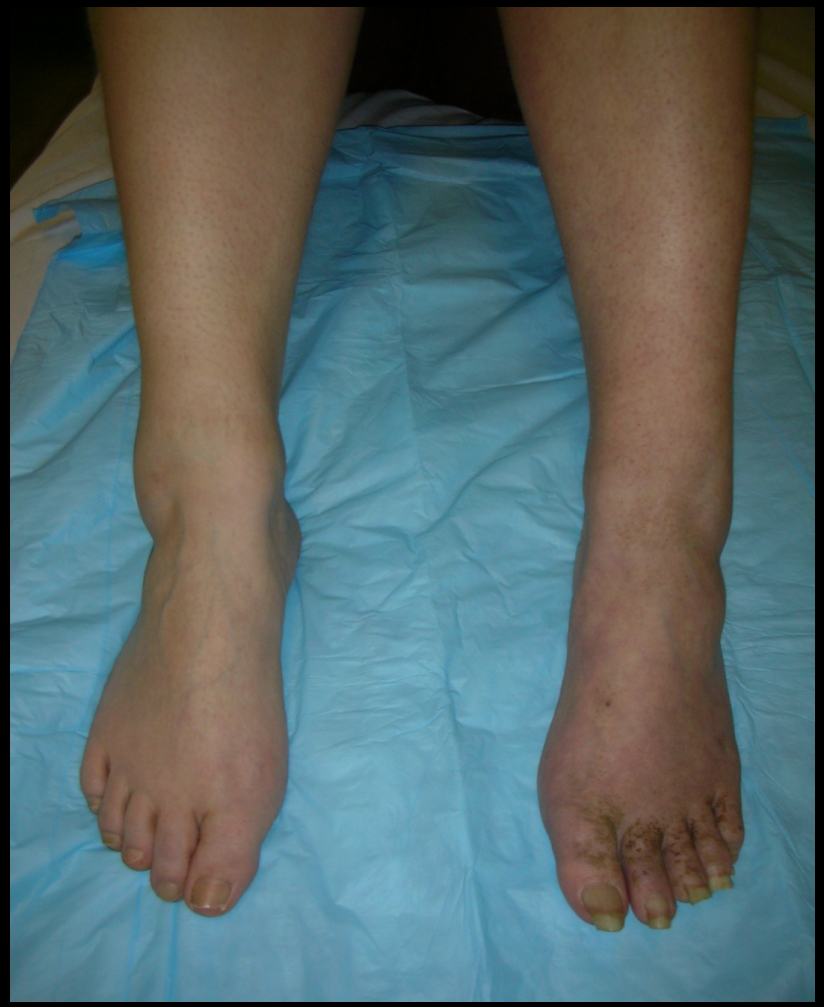
Van Rijn MA, et al. *J Neural Transm.* 2011;118:1301-1309.; Bruehl S. Complex Regional Pain Syndrome. *BMJ.* 2015;351:h2730; Gierthmuhlen J, Bincer A, Baro R. Mechanism based treatment in CRPS. *Nat Rev Neurol* 2014;10:518-28

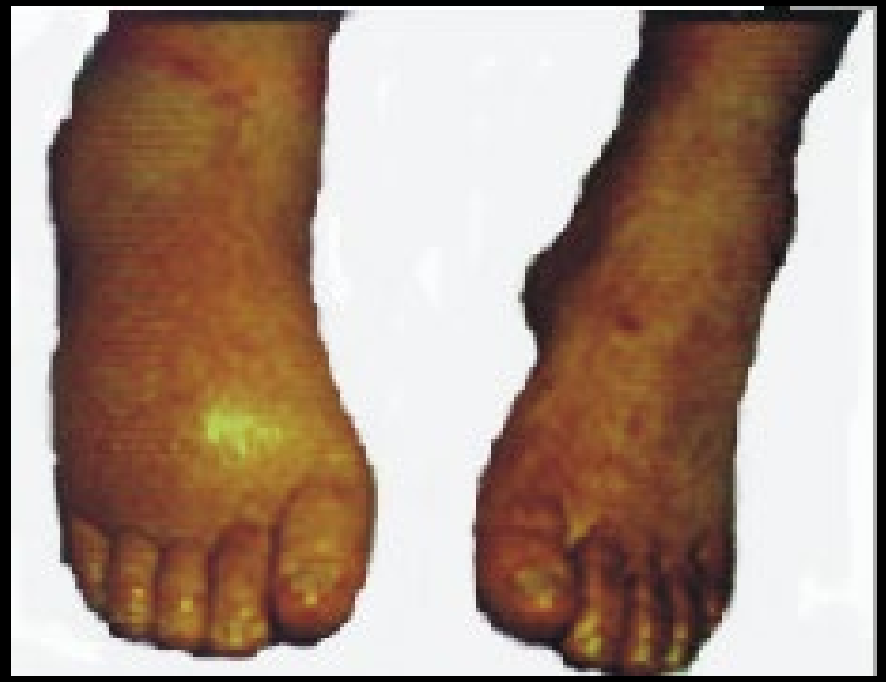
Clinical Features of CRPS (cont'd)

- Spread Patterns (not universal; 48% report spreading)
  - Contiguous Spread = enlargement of the affected area (common)
  - Independent spread = location distant and non-contiguous with the initial site (less common)
  - Mirror-image spread = symptoms opposite the area of initial presentation (uncommon)
    - But, mirror image spread is most common according to Van Rijn et al, then contiguous spread

Van Rijn MA, Marinus J, Putter H, et al. Spreading of complex regional pain syndrome: not a random process. *J Neural Transm.* 2011;118:1301-1309.; Bruel S. *BMJ.* 2015;351:h2730.;

CRPS Type I





Evaluation of CRPS

- Hallmark of diagnosis
  - Thorough clinical evaluation of symptoms and signs
- Laboratory testing
  - Vascular studies = R/O DVT
  - EMG/NCT = R/O peripheral neuropathy
  - MRI and x-ray = R/O soft tissue, disc, central canal stenosis, neuroforaminal stenosis, bone disease
  - Blood testing = R/O infection, cellulitis, rheumatologic diseases
    - No other diagnosis better explains the signs and symptoms. Testing may be needed to rule out other conditions

Evaluation of CRPS

- Other Testing – may support clinical diagnosis
  - Thermography, Three-phase bone scan, Sudomotor testing, Sympathetic blockade
    - Three phase bone scan to support a diagnosis is questionable since bone changes not part of diagnostic criteria
-
- Outcome studies fail to support value of lab tests

Bruehl S. Complex Regional Pain Syndrome. *BMJ.* 2015;351:h2730

Pathophysiology – Proposed Model

- Tissue injury elicits proinflammatory cytokines and neuropeptides (TNF-alpha, IL-1b, IL-2, substance P, CGRP), B cell activation
  - High levels of osteoprotegerin may determine progression to CRPS or if injury resolves normally (? Biomarker)
- Neural injury may trigger CRPS as well
- Genetic factors may include polymorphisms of Alpha 1a adrenoceptors and the HLA system
- Nerve trauma may cause reduced density of nociceptive fibers causing alteration of sweat glands/hair follicles
- Nociceptive fibers now express adrenergic receptors; SNS and catecholamines can trigger nociceptive firing (sympatho-afferent coupling)
- Decreased SNS outflow after initiating trauma causes vasodilatation

Bruehl S. *BMJ.* 2015;351:h2730.; Kramer HH, et al. *Pain.* 2014;155:889-895.

Pathophysiology

- Decreased SNS outflow causes upregulation of local adrenergic receptors leading to vasoconstriction in presence of catecholamines
- Regional blood flow reductions cause local hypoxia leading to trophic changes
- Ongoing nociceptive input produces central sensitization (spinal cord)
- Altered afferent input from affected extremity contributes to reduced somatosensory representation in the brain
  - Impaired tactile sensation (↑pain intensity & hyperalgesia)
- Result: CRPS reflects a disease of the CNS as well as SNS, and a disorder of immune and autoimmune systems
  - Evidence of changes in somatosensory systems' processing tactile, thermal, noxious stimuli

Birklein F, Schlereth T. Complex regional pain syndrome-significant progress in understanding pain. *Pain.* 2015;156:S94-103; Bruehl S. *BMJ.* 2015;351:h2730

Pathophysiology

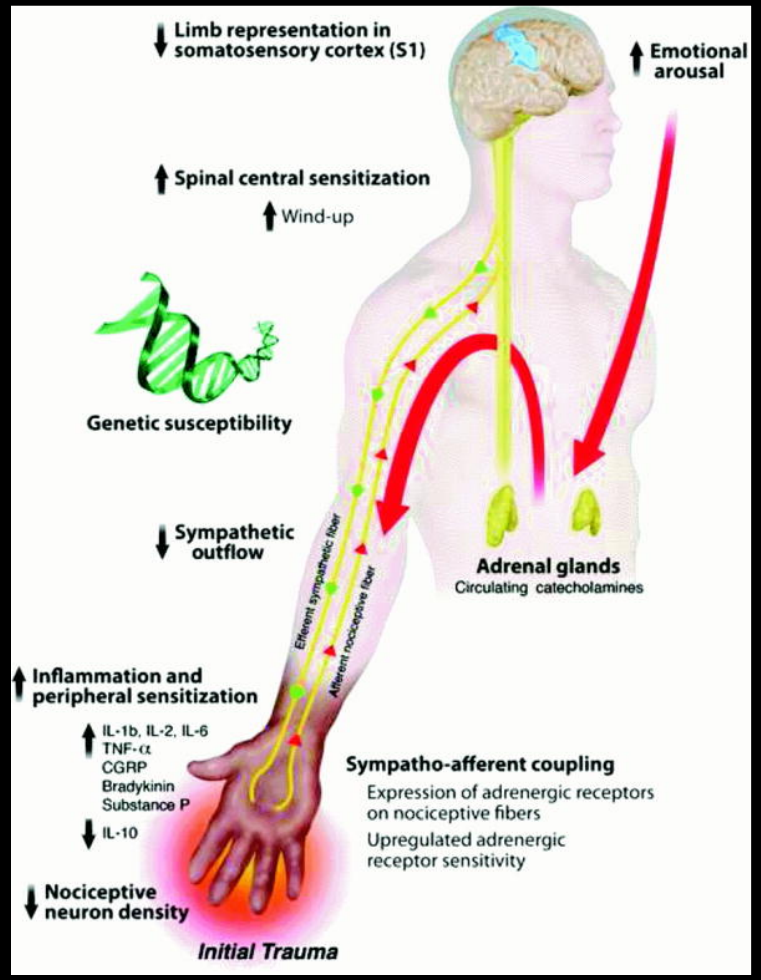


Fig. 1. Speculative model of interacting complex regional pain syndrome mechanisms. CGRP = calcitonin gene-related peptide; IL = interleukin; TNF = tumor necrosis factor.

Possible mechanisms involved in complex regional pain syndrome:

- Nerve injury
- Ischemic reperfusion injury or oxidative stress
- Central sensitization
- Peripheral sensitization
- Altered sympathetic nervous system function or sympatho-afferent coupling
- Inflammatory and immune related factors
- Brain changes
- Genetic factors
- Psychological factors and disuse

Bruel S. BMJ 2015;351:h2730.

Pathophysiology

- Brain Changes
  - Endogenous pain inhibitory pathways impaired (opioid mediated)
  - Reduced representation of affected limb in primary/secondary somatosensory cortices (sensory processing disrupted)
    - Why? Increase somatosensory representation of unaffected limb
  - Motor changes occur – disinhibition of primary motor cortex
    - Paresis, tremor, dystonia, myoclonus
  - Structural changes – reduced gray matter in insula and cingulate cortex (affective pain component), and hippocampus (memory)
  - Successful treatment can normalize altered somatosensory representation ⟶ reduction in pain and allodynia

Cappello ZJ, et al. *J Hand Surg Am.* 2012;37:288-296.; Bruel S. *BMJ*. 2015;351:h2730; Stanton-Hicks M. CRPS: what's in a name? Taxonomy epidemiology, neurologic, immune and autoimmune considerations. *Reg Anes Pain Med* 2019;44:376-387

Pathophysiology

- Autoimmunity
  - Speculation based on improvements seen in CRPS patients treated with intravenous immunoglobulin (IVIG) for unrelated medical conditions
  - Serum studies of CRPS patients show autoantibodies against autonomic structures (Beta 2 adrenergic; muscarinic type 2 receptors)
  - Animal model shows increased levels of Krt16 (biomarker for RA and psoriasis) suggesting autoimmune response in CRPS
  - CRPS may have autoimmune pathology in subset of pts
  - But, randomized controlled study of IVIG in patients with CRPS showed no significant response over placebo

Cappello ZJ, et al. *J Hand Surg Am.* 2012;37:288-296.; Kohr D, et al. *Pain.* 2011;152:2690-2700.; Goebel A, Bisla J, Carganillo R, et al. Low dose intravenous immunoglobulin treatment for long standing CRPS. *Ann intern Med* 2017;167:476-83

Onset

- Symptoms should occur within first few weeks of initiating event, based on mechanisms
- Data suggest development during 3 - 4 month window after initiating injury
  - Onset after this period unlikely and hard to explain mechanistically
- Studies suggest more severe pain early after initiating event & longer CRPS-like presentation, more likely to be CRPS versus delayed normal healing

Beerthuizen A, et al. *Pain.* 2012;153:1187-1192.; Bruehl S. *BMJ* 2015;351:h2730.

Treatment (cont'd)

- Multimodal Approach: early, aggressive
  - Goals: Normalize use of affected limb and prevent disuse
    - Incorporate mirror therapy and graded motor imagery
- Modalities:
  - Pharmacotherapy
    - TCAs, Anticonvulsants, Corticosteroids, Topical, Transdermal, Opioids, Tramadol, Bisphosphonates, Sympatholytic agents, Calcitonin, Ketamine
  - Sympathetic Nerve Blocks: Stellate Ganglion and Lumbar Sympathetic
  - Neuromodulation – Spinal Cord Stim and Dorsal Root Ganglion Stim
  - Intrathecal Baclofen for Dystonia
  - Behavioral Approaches
  - Surgical Sympathectomy

O'Connell NE, Wand BM, McAuley J, et al. Interventions for treating pain and disability in adults with CRPS.Cochrane Database Syst Rev. 2013;4:CD009416; Bruehl S. BMJ 2015;351:h2730

Treatment (cont'd)

- Physical and occupational therapy
  - Scrubbing, stress loading, desensitization, myofascial release, isometric strenthening
- Steroids
  - Pulse of oral steroids in acute stage may improve symptoms
    - 30-40 mg/day prednisolone x 2 weeks and taper
- Gabapentinoids
  - Gabapentin – mild analgesia, but larger effect on sensory deficits
- Antidepressants
  - Meta analyses support TCAs for non CRPS neuropathic pain
- Topical Lidocaine
  - No RCTs, but can help with hyperesthesia
- Opioids
  - Only to facilitate functional therapies and daily activities

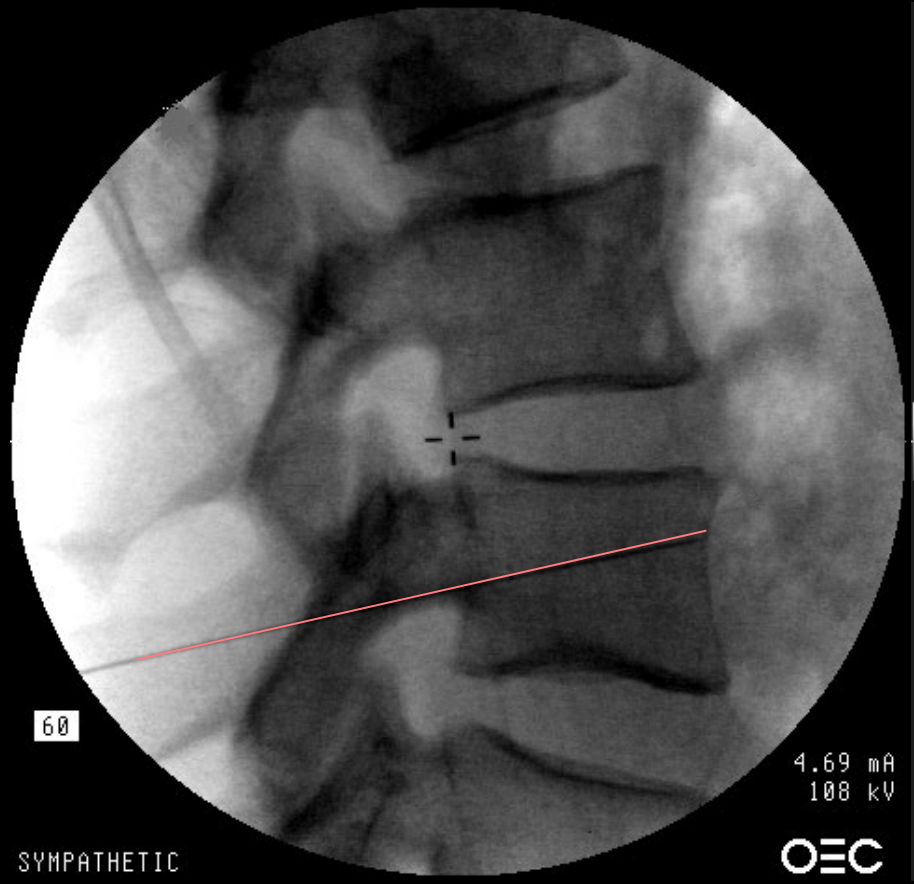
Bruehl S. *BMJ.* 2015;351:h2730.; Duong S, Bravo D, Todd KJ, et al. Treatment of CRPS: an updated systematic review and narrative synthesis. *Can J Anesth* (2018) 65:658-684

Treatment (cont'd)

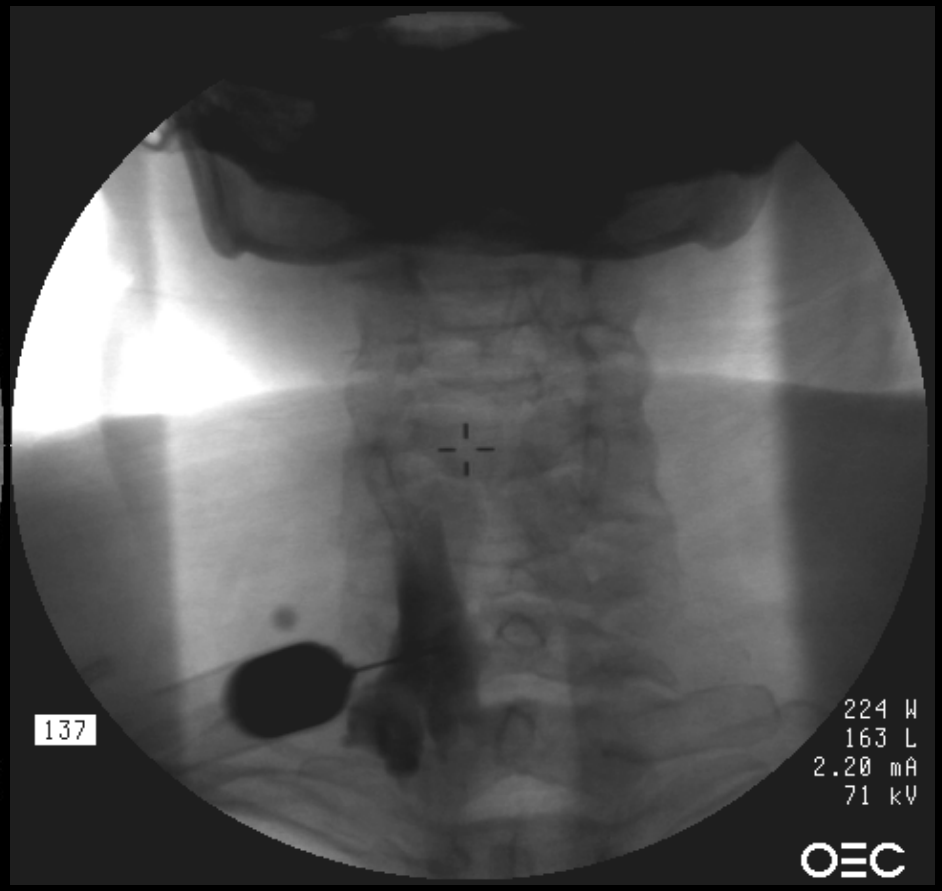
- Psychological Treatment
  - Pain focused CBT typically beneficial for chronic CRPS
- Sympathetic Blockade
  - Stellate ganglion blocks/lumbar sympathetic blocks may assist in functional therapies for those with sympathetically maintained pain
  - Not curative
- Spinal Cord Stimulation
  - Beneficial, but efficacy can diminish over time (3-5 years)
  - Evidence for positive effect on pain relief, quality of life, and satisfaction
- Dorsal Root Ganglion Stimulation
  - Promising new therapy with improved analgesia, function and mood compared to SCS
- Ketamine (NMDA antagonist, ↓ IL-6 & TNF-alpha; affects central sensitization (hyperalgesia, allodynia) and cytokine release (immunomodulator)
  - May have clinically meaningful pain relief for <3 months; Topical ketamine and subanesthetic infusions may be useful for refractory CRPS; weaker support for anesthetic doses (ketamine coma). Hepatic injury possible with repeat infusions so monitor liver enzymes before and during treatment

Connolly SB, Prager JP, Harden RNA.Systematic review of ketamine for CRPS. *Pain Med.* 2015;16:943-969; Visnjevac O, Costandi S, Patel BA, et al. A comprehensive outcome-specific review of the use of spinal cord stimulation for CRPS. *Pain Pract.* 2017;17(4):533-45; Bruehl S. *BMJ.* 2015;351:h2730.; Zhao J, Wang Y, Wang D. The Effect of Ketamine Infusion in the Treatment of CRPS: A Systematic Review and Meta-Analysis. *Curr Pain Headache Rep* (2018) 22:12; Deer TR, Levy RM, Kramer J et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017;158:669–681.

Sympathetic Blocks

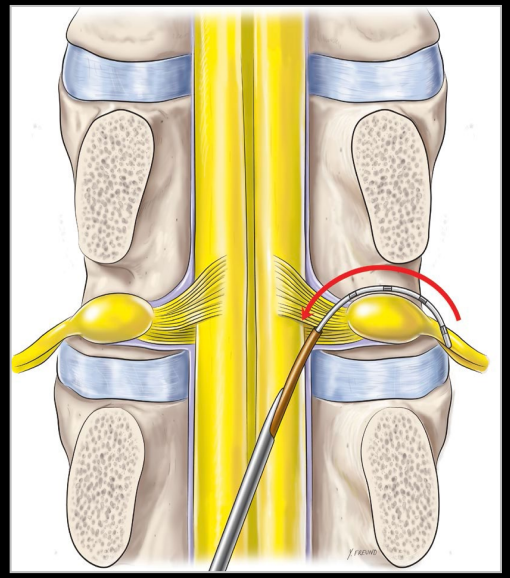


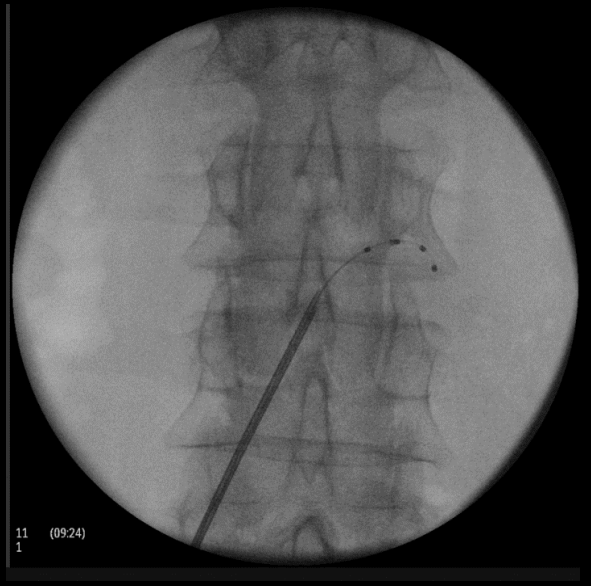
Lumbar Sympathetic



Stellate Ganglion

Neuromodulation
Dorsal Column and Dorsal Root Ganglion





Treatment

- **Bisphosphonates**
  - Agents show promise in small RCTs; inhibit osteoclastic bone resorption
  - Rationale: Impaired bone metabolism may occur in CRPS
  - Most benefit if dz duration <12 months
  - Neridronate study stopped
- **Calcitonin**
  - Agents show promise in small RCTs
  - Inhibits osteoclasts and has independent antinociceptive effect
  - Most benefit if dz duration >12 months
- **Antioxidants**
  - Topical Dimethyl Sulfoxide – warm CRPS
    - Significant relief topically for 17-52 weeks
  - Oral N-acetylcysteine – cold CRPS
- **Intrathecal therapies** (pain pumps)
  - Baclofen – benefit in reducing dystonia and pain

Wertli MM, et al. *Pain Med.* 2014;15:1575-1589; Ne OC, Bm W, Mcauley J, et al. Interventions for treating pain and disability in adults with CRPS – an overview of systematic reviews. *Cochrane Libr* 2013;1-68; Van Der Plas AA, Van Rijn MA, Marinus J, et al. Efficacy of intrathecal baclofen on different pain qualities in CRPS. *Anesth Analg* 2013;116(1):211-5

Emerging Therapies

- Mirror Box Therapy/Virtual Reality Body Swapping
  - First described for treatment of phantom limb pain
  - Moving unaffected limb in front of mirror causes cortical reorganization of the sensory homunculus
  - Included in functional therapy programs
  - Identify a virtual body and mimic movements of CRPS limb on a video
    - ⟹ Less body disturbance perception/ No pain change
- IV Immunoglobulin
  - Interferes with autoantibodies and down regulates proinflammatory cytokines
  - Small RCT found efficacy, but large RCTs show no benefit
- Lose dose naltrexone
  - RCT ongoing; may reduce glial inflammation

O'Connell NE, et al. *Cochrane Database Syst Rev*. 2013 Apr 30;4:CD009416.; Bruehl S. *BMJ*. 2015;351:h2730; Stanton-Hicks M. CRPS: what's in a name? Taxonomy epidemiology, neurologic, immune and autoimmune considerations. *Reg Anes Pain Med* 2019;44:376-387

Emerging Therapies (cont'd)

- Cannabinoids
  - Emerging support in peripheral and central neuropathic pain conditions

- Botulinum Toxin
  - Case reports and observations show improvement in dystonia, pain, allodynia after S/Q or IM injection

Mittal SO, et al. *Semin Neurol*. 2016;36:73-83.; Lynch ME, Ware MA. *J Neuroimmune Pharmacol.* 2015;10:293-301; Neumeister MW, Romaneli MR. CRPS. *Clin Plastic Surg* 47 (2020) 305-310

Emerging Therapies (cont'd)

- Scrambler Therapy
  - FDA cleared in 2014 for neuropathic and cancer pain
  - Used in Europe for chemotherapy-induced peripheral neuropathy (CIPN)
  - Studies on CRPS, Failed Back Surgery Syndrome, Postherpetic Neuralgia, CIPN
    - Many patients had dramatic relief without side effects
  - Mechanism – transmits 16 sequences of low frequency electrical stimulation; inhibits pain impulse transmission
  - 30-45 minute sessions
  - Relief for weeks to months

Majithia N, Smith TJ, et al. Scrambler therapy for the management of chronic pain. *Support Care Cancer*. 2016 Jun;24(6):2807-14.

Amputation

- Option of last resort
  - Unbearable, therapy resistant, dysfunctional limb
- Controversial
  - Risk stump pain, phantom limb pain, recurrent CRPS and stump pain in affected limb, occurrence in another limb
- Comparative study: Amputees with CRPS and non-amputees with CRPS
  - Amputees reported better pain scores, less disability, improved quality of life, and less depression

Midbari A, Suzan E, Adler T, et al. Amputation in patients with complex regional pain syndrome. Bone Joint J 2016;98-B:548-54; Bodde MI, Dijkstra PU, Schrier E, et al. Informed Decision-Making Regarding Amputation for CRPS Type I. J Bone Joint Surg Am 2014;96:930-4

Prevention

- Primary
  - Vitamin C (reduces inflammation via antioxidant effect)
    - Two meta analyses showed substantial reduction in prevalence of CRPS after limb fracture or surgery (wrist fractures mainly)
      - 500 mg/day for at least 45 days from injury
    - Large RCT = no benefit to patients with a displaced or nondisplaced fracture of the distal aspect of the radius
  - Minimize tourniquet duration & ischemic reperfusion injury
- Secondary (prevent relapse)
  - Postpone surgery until signs are minimal
  - Use regional anesthetic techniques (epidural/brachial plexus block)
  - Salmon calcitonin of 100 IU daily s.c. perioperatively for 4 weeks

Meena S, Sharma P, Gangary SK, et al. Role of vitamin C in prevention of CRPS after distal radius fractures: a meta-analysis. *Eur J Orthop Surg Traumatol*. 2015;25(4):637-41.; Shibuya N, Humphers JM, Agarwal MR, et al. Efficacy and safety of high dose vitamin C on CRPS in extremity trauma and surgery-systematic review and meta-analysis. *J Foot Ankle Surg* 2013;52:62-6; Ekrol I, Duckworth AD, Ralston SH, et al. The influence of vitamin C on the outcome of distal radial fractures: a double blind, randomized controlled trial. *J Bone Joint Surg Am* 2014;96:1451-1459.