Complex Regional Pain Syndrome and Therapies for Treatment

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Historical Perspective

- Mitchell (1864) - First to use the term “causalgia” in description of Union soldiers after injuries in the Civil War.
- Leriche (1916) - Linked the sympathetic nervous system to causalgia (*un nerve du sympathique)*
- Evans (1946) - Introduced the term reflex sympathetic dystrophy (RSD)

RSD Synonyms and Similar Diagnoses

- Acute atrophy of the bone
- Algoneurodystrophy
- Causalgia
- Chronic traumatic edema
- Postinfarctional sclerodactyly
- Posttraumatic dystrophy
- Posttraumatic osteoporosis
- Posttraumatic spreading neuralgia
- Reflex neurovascular dystrophy
- Reflex sympathetic dystrophy
- Shoulder-hand syndrome
- Sudeck's atrophy
- Sympathalgia
- Traumatic angiospasm
- Traumatic vasospasm

IASP Consensus Meeting: Complex Regional Pain Syndrome

Complex Regional Pain Sydrome I (RSD)

- History of initiating injury or immobilization
- Continuing pain, allodynia, or hyperalgesia out of proportion to the initiating event
- Evidence ***at some time*** of edema, changes in skin blood flow or abnormal pseudomotor activity in the painful area
- No other cause of the pain exists

Complex Regional Pain Syndrome II (causalgia)

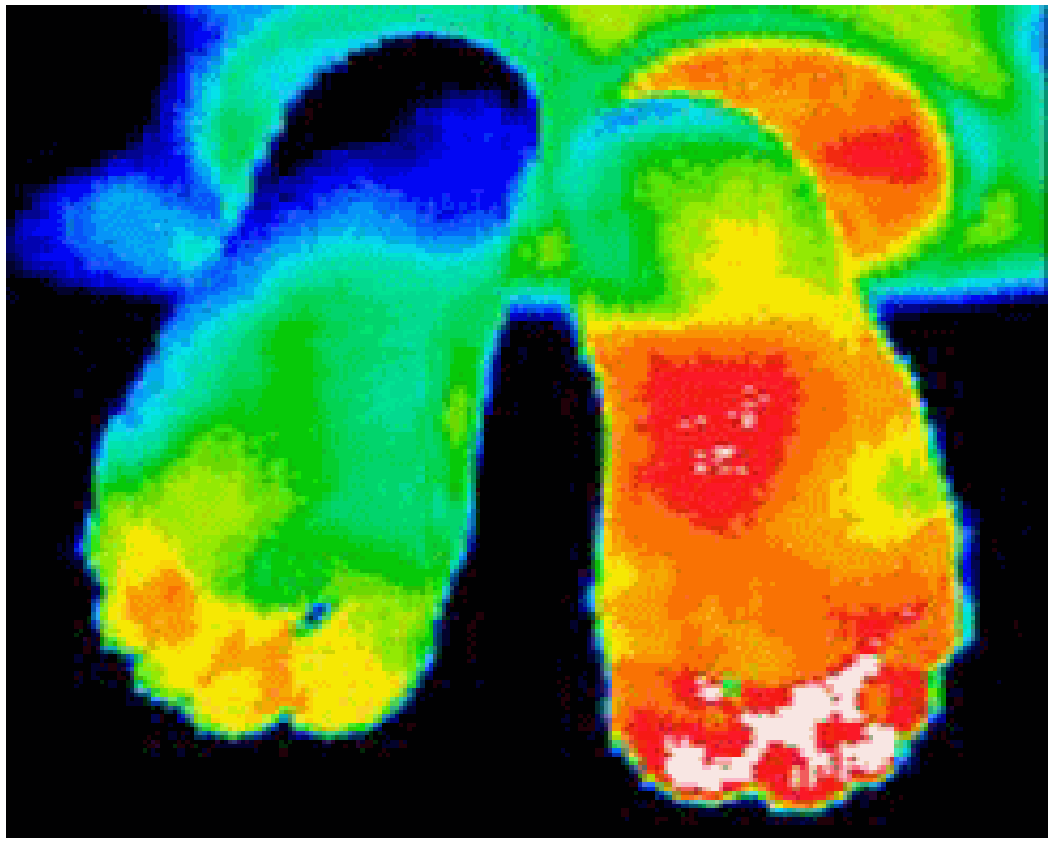
- Differs from CRPS I by the presence of a known nerve injury

New Diagnostic Criteria for CRPS

- R. Norman Harden, Stephen Bruehl, Michael Stanton-Hicks, Peter Wilson. Pain Medicine 2007, 4:326-331

New Clinical Diagnostic Criteria for CRPS

- Continuing pain disproportionate to the inciting event
- No other diagnosis better explaining the signs and symptoms



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New Clinical Diagnostic Criteria for CRPS

- Report 1 symptom in 3 of 4 categories
  - Sensory - hyperesthesia &/or allodynia
  - Vasomotor - temperature asymmetry &/or skin color changes
  - Sudomotor/Edema - edema &/or sweating changes
  - Motor/Trophic - decrease ROM, &/or motor dysfunction &/or trophic changes

New Clinical Diagnostic Criteria for CRPS

- Display 1 sign in 2 or more categories
  - Sensory – hyperesthesia; allodynia (mechanical, temperature); deep somatic pressure/joint movement
  - Vasomotor - temperature asymmetry (>1 ºC); skin color changes
  - Sudomotor/Edema – edema; sweating changes
  - Motor/Trophic - decrease ROM; motor weakness; tremor; dystonia; trophic changes

New Diagnostic Criteria (research)

Symptoms

- + sensory symptoms
- Vascular symptoms
- Edema, sweating abnormalities
- Motor, trophic changes

Signs

- + sensory signs
- Vascular signs
- Edema, sweating abnormalities
- Motor, trophic changes

4 symptoms & ≥2 signs

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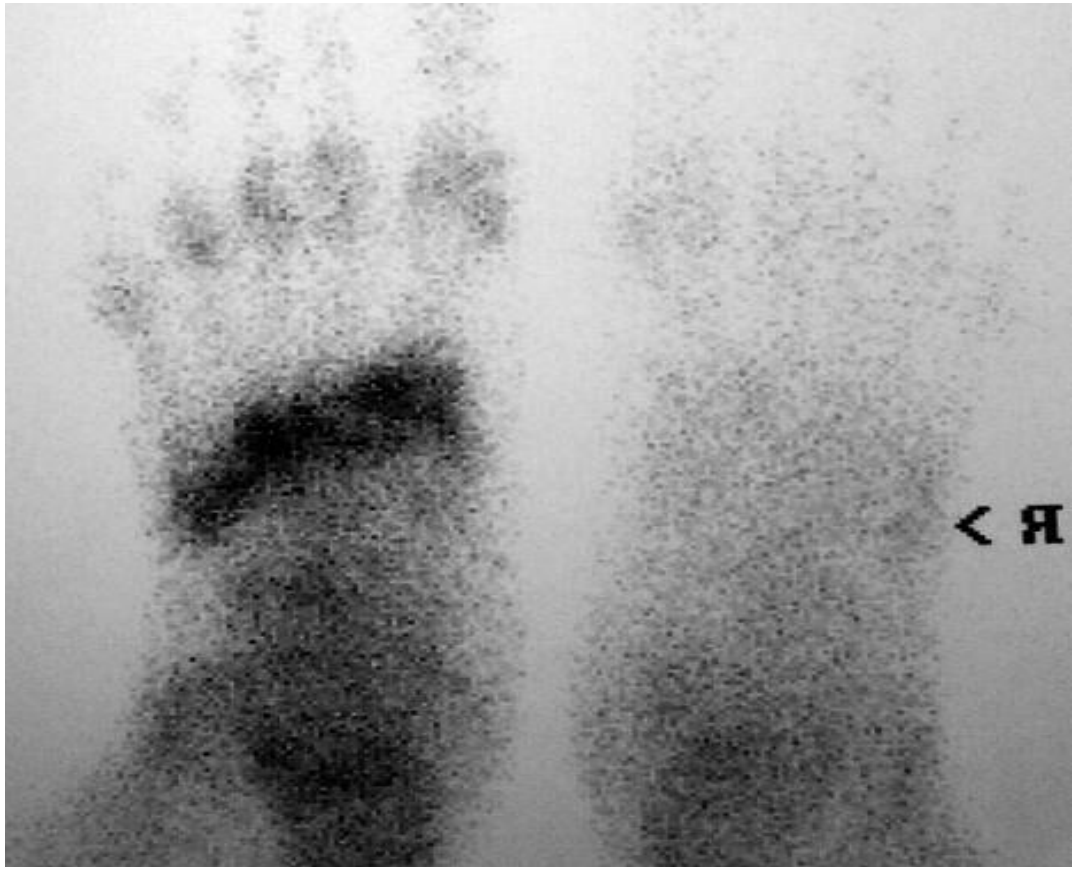
Differential Diagnosis

- CNS: post-stroke syndrome, tumor, transverse myelitis, syringomyelia, MS
- Neuropathy: DM, toxic, infectious, post-traumatic, entrapment, neuroma, CIDP
- Vascular: Raynauds, PVD, phlebothrombosis
- Psychological: somatoform disorder
- Radiculopathy
- Plexopathy

Diagnostic Tests: To Exclude Other Etiologies

- Labs: diabetic, vasculitic, rheumatologic markers
- EMG: nerve injury, compressive peripheral or nerve root lesion
- Vascular Studies: PVD
- Imaging: plain film, 3-phase bone scintigraphy
- Quantitative Sensory Testing

X-ray and Bone Scans



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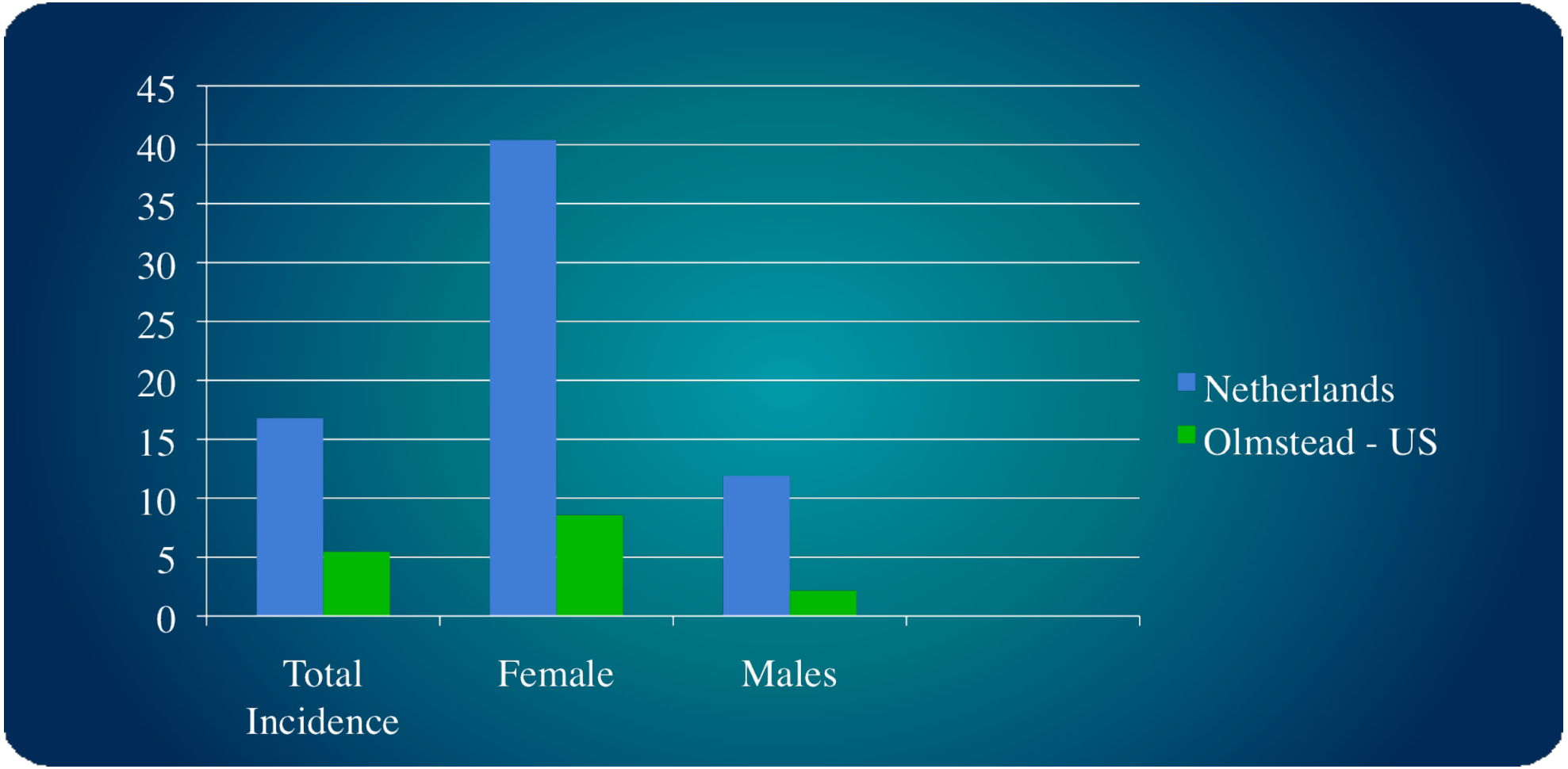
Incidence CRPS per 100,000



Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain*. May 2003;103(1-2):199-207.
M de Mos et al. Incidence of Complex Regional Pain Syndrome: A Population Based Study. J Pain, 2007; 129:12-20.

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Epidemiology

Inciting Event	Percent
None	10.8%
Fracture	44.1%
Sprain	17.6%
Elective Surgery	12.2%
Other	8.8%

Body Location	Percent of Cases
Upper Extremity	59.2
Lower Extremity	39.1

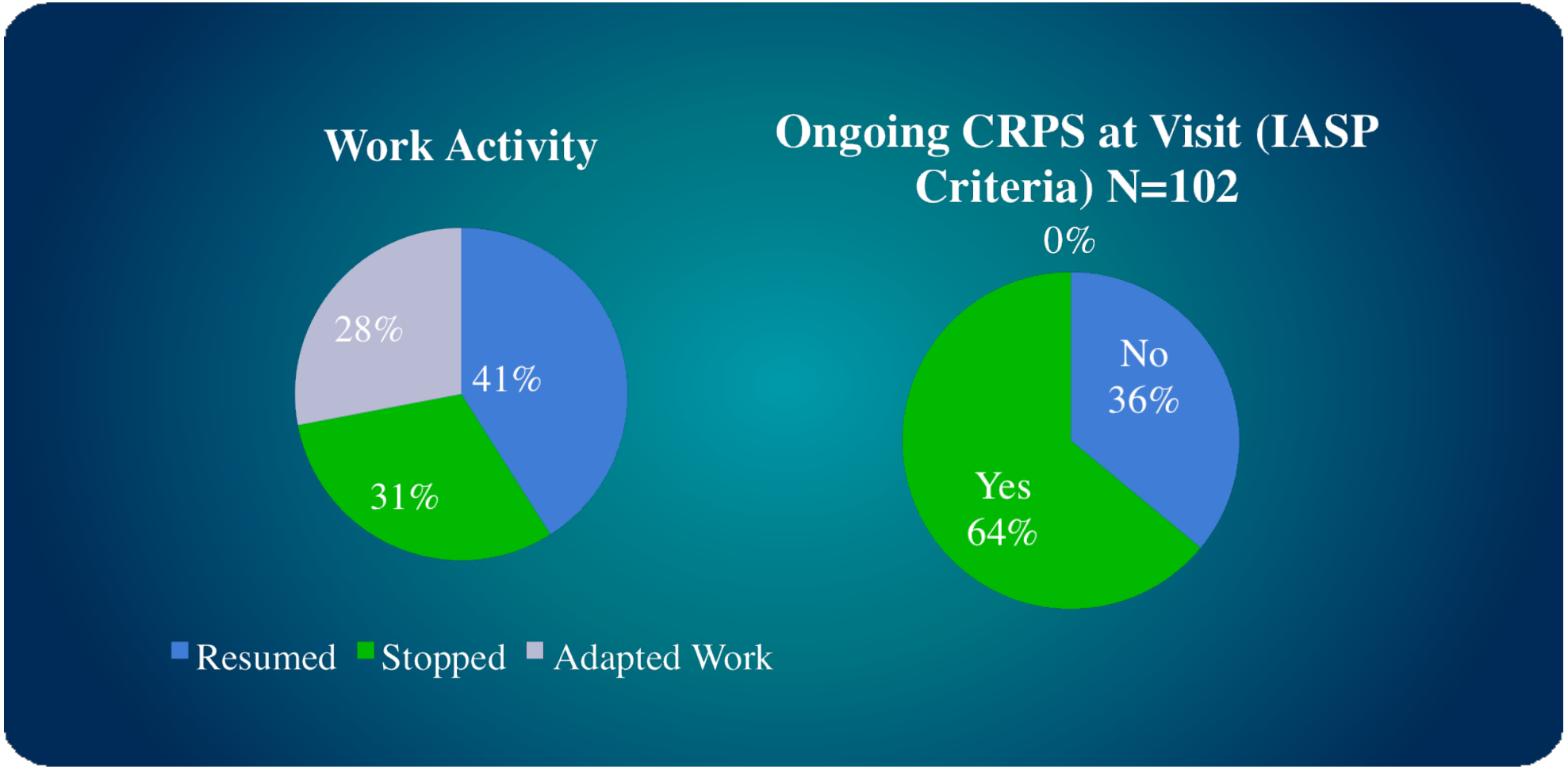
- Incidence CRPS I after fracture 1-2%
- Incidence CRPS II after peripheral nerve injury 2-5%
- No racial difference in incidence

Baron R, Binder A. Pappagallo M (ed). *complex regional pain syndromes, in The neurological basis of pain*. New York: McGraw-Hill; 2005:359-378.
Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet*. Oct 23 1993;342(8878):1012-6
M de Mos et al. Incidence of Complex Regional Pain Syndrome: A Population Based Study. J Pain, 2007; 129:12-20.

Symptoms/Signs

Symptom/Sign	% Symptoms Present	% Signs Present
Sensory		
Spontaneous Pain	81%	37%
Allodynia	9%	11%
Vasomotor		
Temperature asymmetry	56%	44%
Color asymmetry	51%	43%
Sudomotor		
Swelling/Edema	53%	55%
Sweating asymmetry	23%	29%
Motor/Trophic		
Decreased ROM	20%	51%
Paresis	7%	15%
Altered hair/nail growth	2-4%	4-5%

CRPS Outcomes



Mean 5.8 years from inciting injury

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Stages

- Classic 3 “stages”
  - Early – Acute: hyperalgesia, allodynia, vasomotor & sudomotor disturbance prominent edema
  - Middle – Distrophic: (3-6 months later) progressive pain/sensory dysfunction, with increased motor/trophic changes
  - Late – Atrophic: decreased pain/sensory disturbance, markedly increased motor/trophic disturbances

Pathophysiology

- Common Hypothesis: Hyperactive Sympathetic Outflow aka SMP
  - Supported by relief with sympathectomy
  - But, not all CRPS patients get relief
  - Some symptoms more consistent with hypoactive sympathetic activity or inflammatory activity

Pathophysiology

Multifactorial

1. Altered Cutaneous Innervation
2. Central sensitization
3. Peripheral sensitization
4. Altered SNS function
5. Circulating catecholamines
6. Inflammatory factors
7. Brain plasticity
8. Genetic factors
9. Psychologic factors

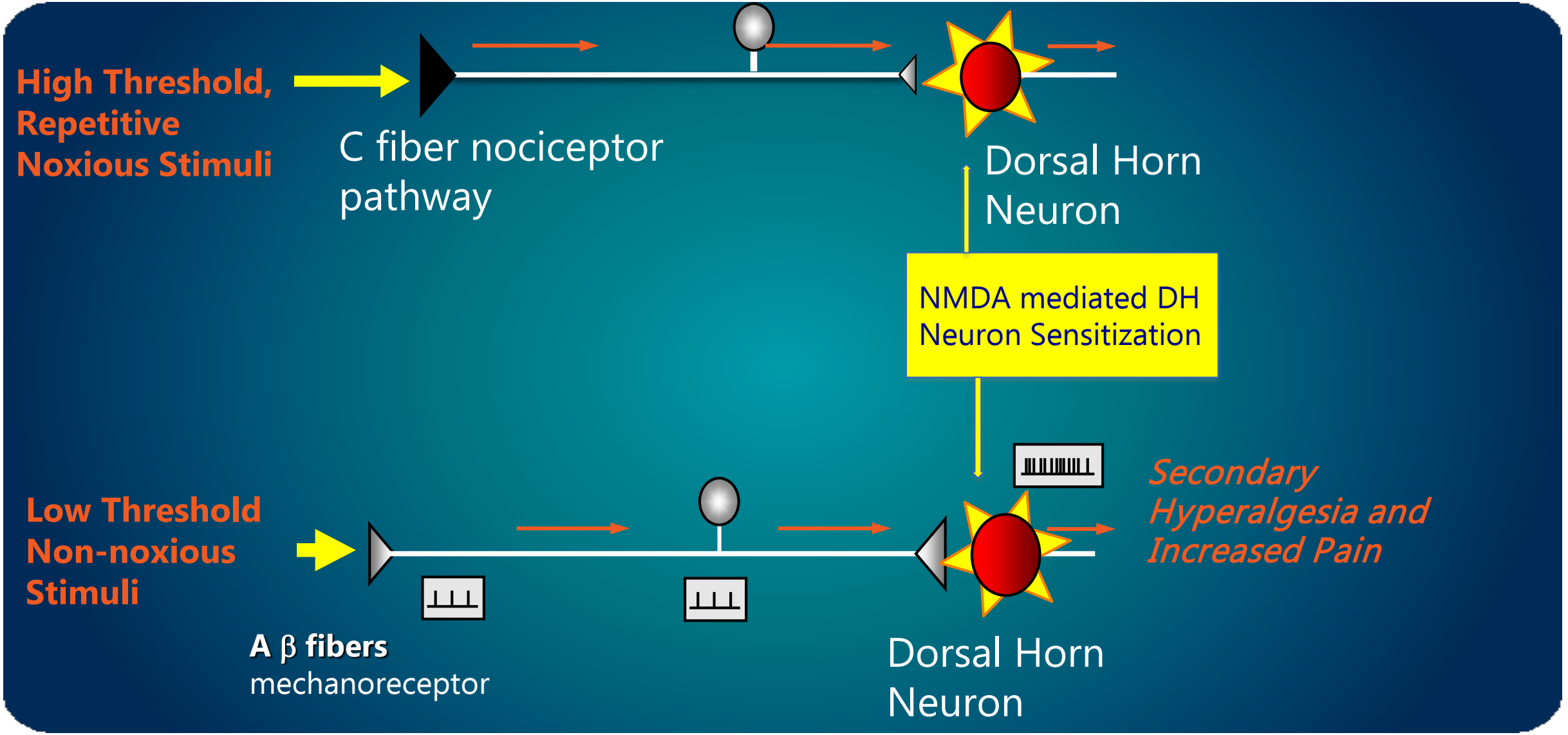
Cutaneous Innervation

- Decreased (29%) density epidermal neurites
- Decreased density C-fiber and A-delta fibers
- Altered innervation of hair follicles and sweat glands

Central Sensitization

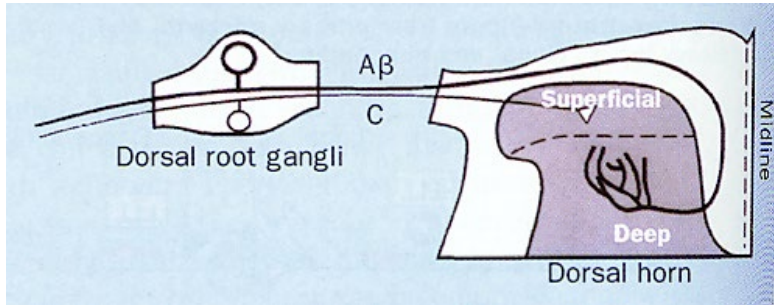
- Persistent noxious input to spinal cord nociceptive neurons
- Results in hyperalgesia and allodynia
- Dorsal Horn sprouting of A-fibers

Central Sensitization

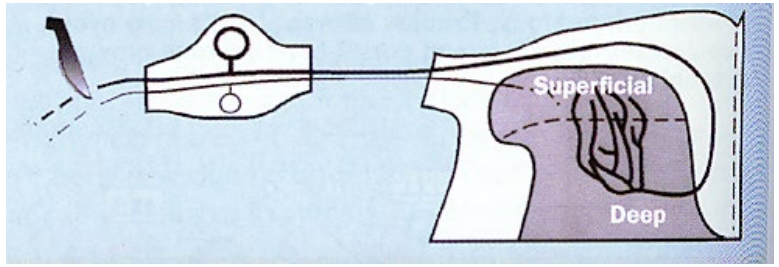


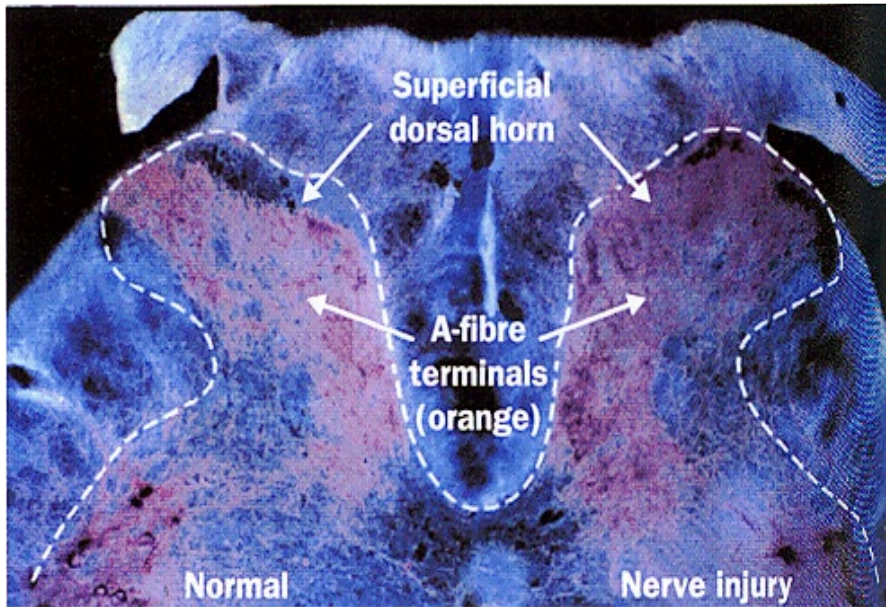
Nerve Injury → Dorsal Horn Sprouting

Normal terminations of primary afferents in the dorsal horn



After nerve injury, C-fiber terminals atrophy and A-fiber terminals sprout into the superficial dorsal horn





Adapted from Woolf CJ, Mannion RJ. *Lancet*. 1999;353:1959-1964.

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Peripheral Sensitization

- Primary afferent fibers release pronociceptive neuropeptides: substance P, bradykinnin and other inflammatory factors
- Sensitize nociceptors
- Increase background firing of nociceptors
- Lower threshold mechanical and thermal stimuli

Sympathetic Nervous System

- Animal Studies: adrenergic receptors expressed on nociceptors after nerve injury
- Sympatho-afferent coupling
- Cool challenge: different response in early/acute vs late/chronic CRPS

Circulating Catecholamines

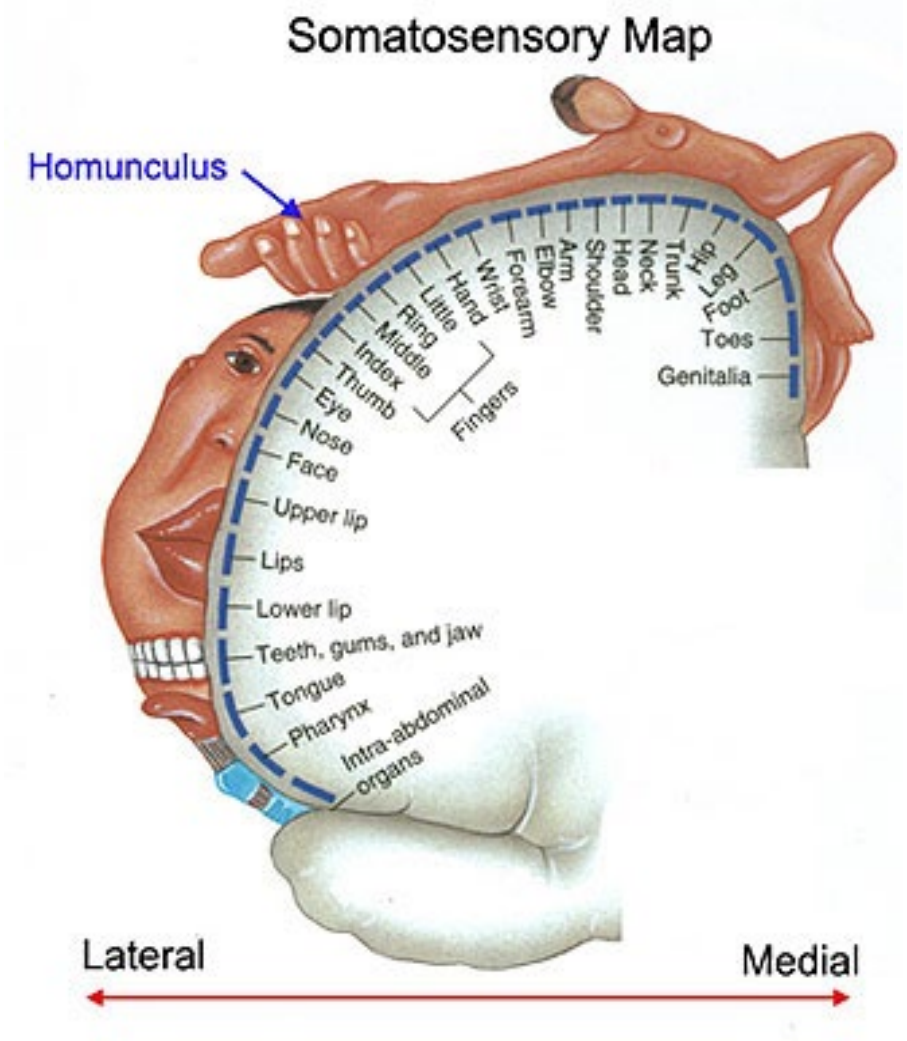
- Chronic CRPS: decreased local norepinephrine levels on affected side vs. unaffected side
- Despite this: Hypersensitivity to NE = exaggerated sweating, vasoconstriction and decreased temperature

Inflammatory Factors

- Classic Inflammation
  - Tissue trauma – immune cells release proinflammatory cytokines
  - Local edema
- Neurogenic Inflammation
  - Nerve injury – nociceptive fibers release proinflammatory cytokines and neuropeptide mediators
  - Plasma extravesation, vasodilation
  - Peripheral sensitization

Neural Plasticity

- Reorganization of somatotopic maps
- Degree of reorganization correlates with hyperalgesia and pain



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Genetic Factors

- Small studies: familial aggregation of CRPS cases
  - Earlier onset
  - Increased spontaneous CRPS cases

Psychological Factors

- No good evidence
- Small self report studies showed correlation between level of depression and subsequent pain intensity
- Small prospective studies of distal radius fx and TKA – conflicting results regarding pre-injury stress levels and development of CRPS

Pathophysiology Summary

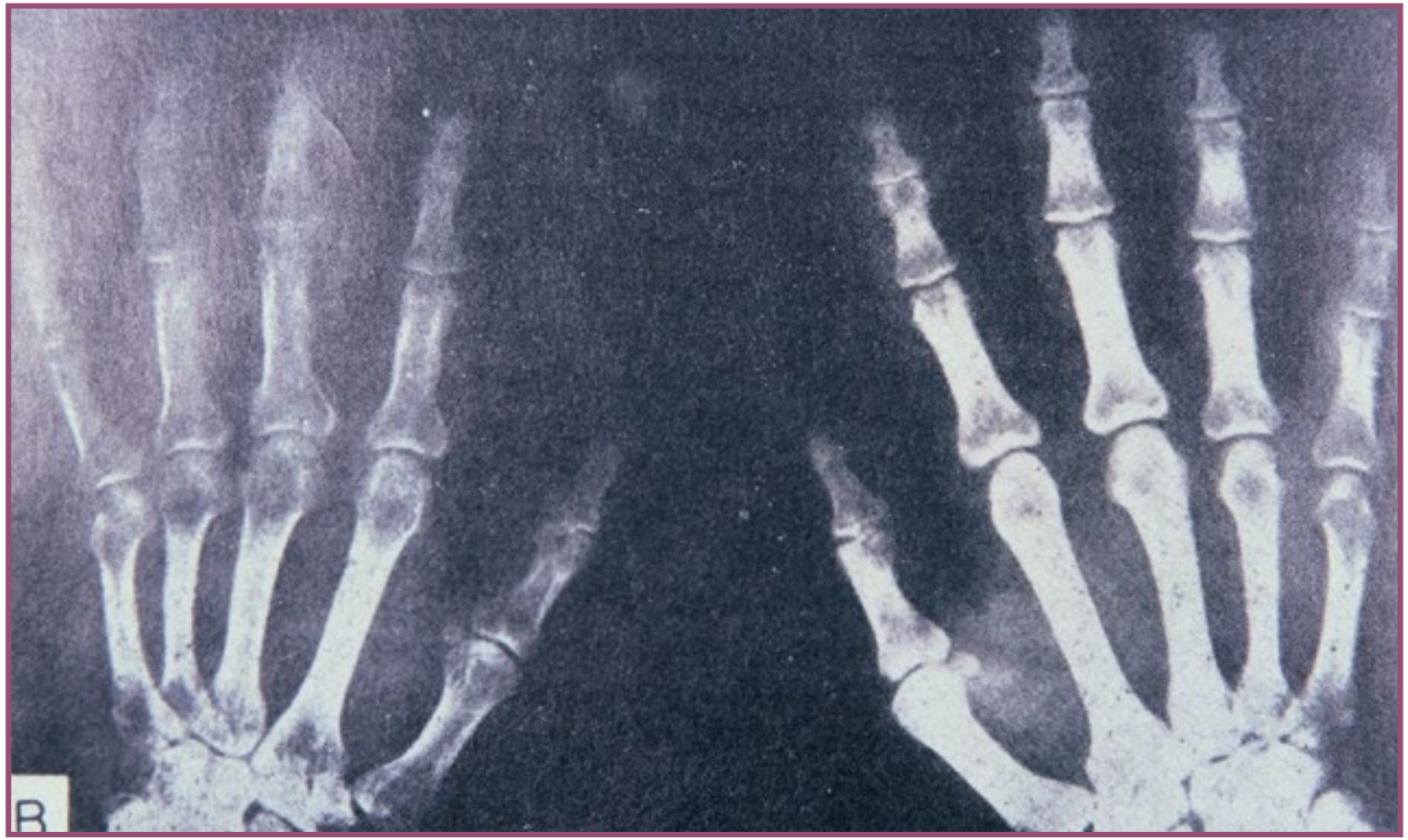
- CRPS has an extremely complex pathophysiology involving sensory, motor and autonomic abnormalities
- It is unknown as to how the autonomic abnormalities and inflammatory processes affect the pain and sensory/motor abnormalities
- It is unknown if and how the syndrome can be prevented

Complex Regional Pain Syndrome: Vasomotor Changes

Complex Regional Pain Syndrome: Osteoporosis

Affected

Unaffected



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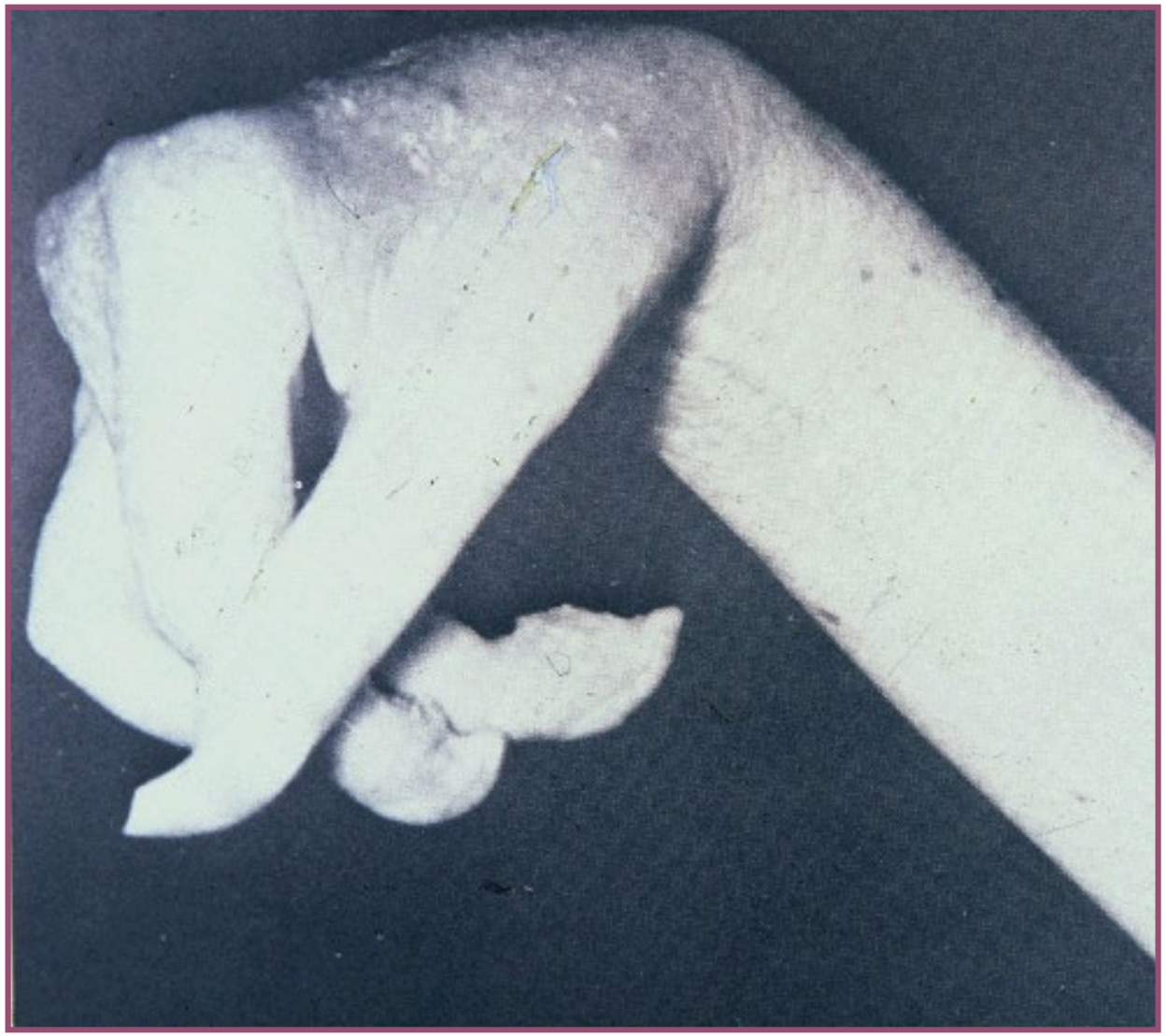
CRPS Atrophic/Dystrophic Changes



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Treatment of Complex Regional Pain Syndrome

- Physical Therapy
- Pharmacotherapy
- Sympathetic Blockade
  - IV Regional and Sympathetic ganglion blockade
  - Should be coordinated with physical therapy
- Psychological Counseling
- Spinal Cord Stimulation

Physical Therapy

- Graded Motor Imagery
- Sensorimotor Treatment
- Mirror Box

- TENS
- Stress Loading Exercise

A. Daly et al. *Does evidence support physiotherapy management of adult Complex Regional Rain Syndrome Type I? A systematic review*. Eur J Pain, 2009. 13:339-353

Pharmacotherapy for Complex Regional Pain Syndrome

- No single drug with clear efficacy
- No predictors of response to specific drugs
  - Opioids
  - Anti-Neuropathic & Anti-Inflammatory agents
  - Calcium modulation
  - IV Ketamine

Opioid Therapy

- Opioids can be effective in neuropathic pain
- Not systematically studied in CRPS
- Widely used despite lack of studies especially if other treatments fail

Anti-Neuropathic/Anti-Inflammatory Agents

- Steroids
  - pulsed dose early in CRPS
  - Small studies limited follow-up
- TCA's/SNRI's: No studies in CRPS
- Lidocaine Patch 5%
- Gabapentin
  - Two RCT - mildly beneficial
- Other AED's: No studies in CRPS
- Clonidine
  - One uncontrolled study of clonidine patch
  - No evidence for oral clonidine

Bisphosphonates

- Localized Bone Resorption
- Improved pain, mobility, edema
- 4 RCT of IV/PO
  - Systematic review VAS change 22 mm at 4wks 21 mm at 12 wks
  - Alendronate 40 mg/day oral x 8 weeks
  - Alendronate 7.5 mg/day x3 days IV
  - Clondronate 300 mg/day x10 days IV
  - Pamidronate 60 mg single infusion

Brunner et al. Eur J Pain, 2007. Biphosphonates for the therapy of complex regional pain syndrome I – Systematic review.

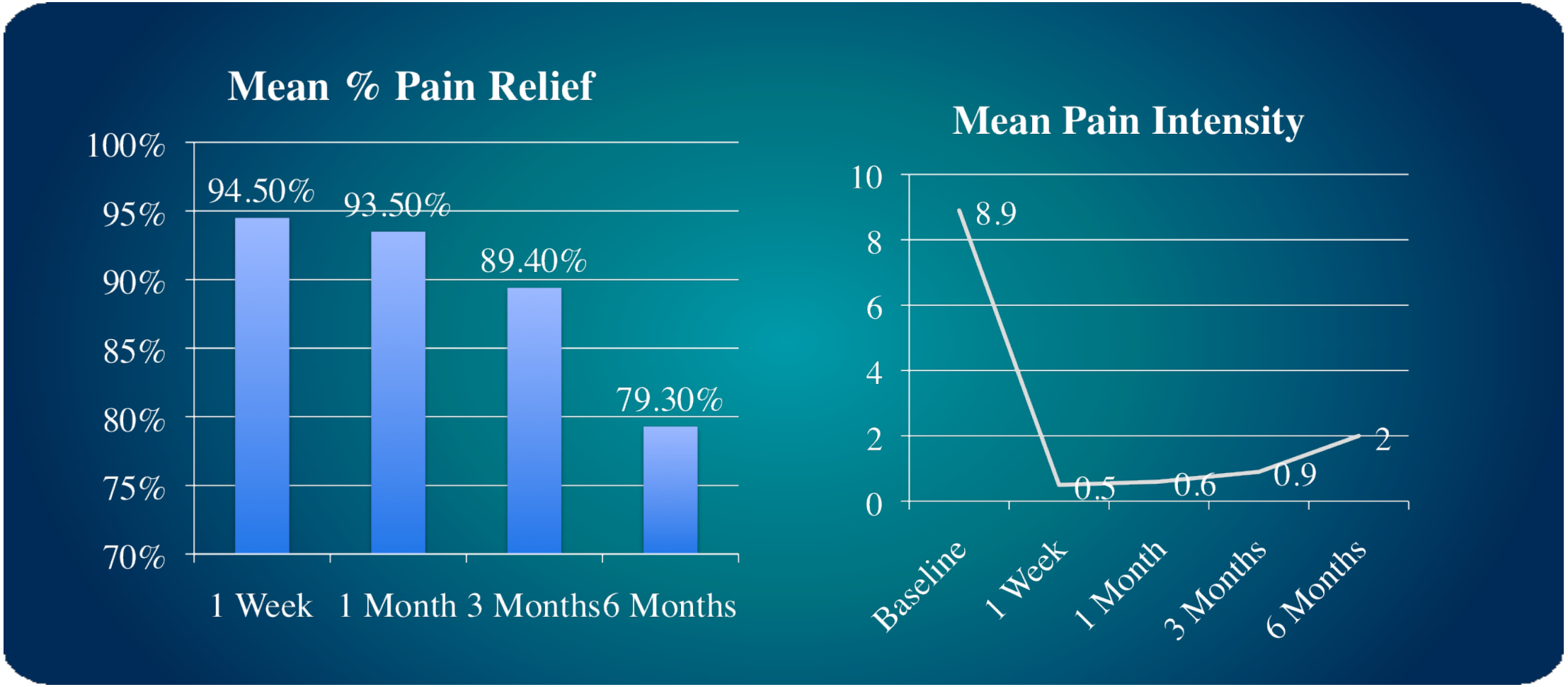
Ketamine Infusion

- Low-dose outpatient
  - 4hrs/day, 10days; Ketamine max infusion 0.35 mg/kg/hr NTE 100mg in 4 hrs; clonidine 0.1mg po, midazolam 2mg IV before and after infusion
  - 4 day infusion; stepwise to mean 0.32mg/kg/hr

- Ketamine Coma
  - 5 days intubated in ICU
  - Ketamine 3-7 mg/kg/hr & midazolam 0.15-0.4 mg/kg/hr

R. Schwartzman et al. *Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study.* Pain, 2009. 147:107-115.
Sigtermans et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type I. Pain, 2009. 145:304-311.
R-T Kiefer et al. Efficacy of ketamin in anesthetic dosage for the treatment of refractory complex regional pain syndrome: An open label phase II study. J Pain Medicne, 2008. 9:1173-1201.

Ketamine Coma



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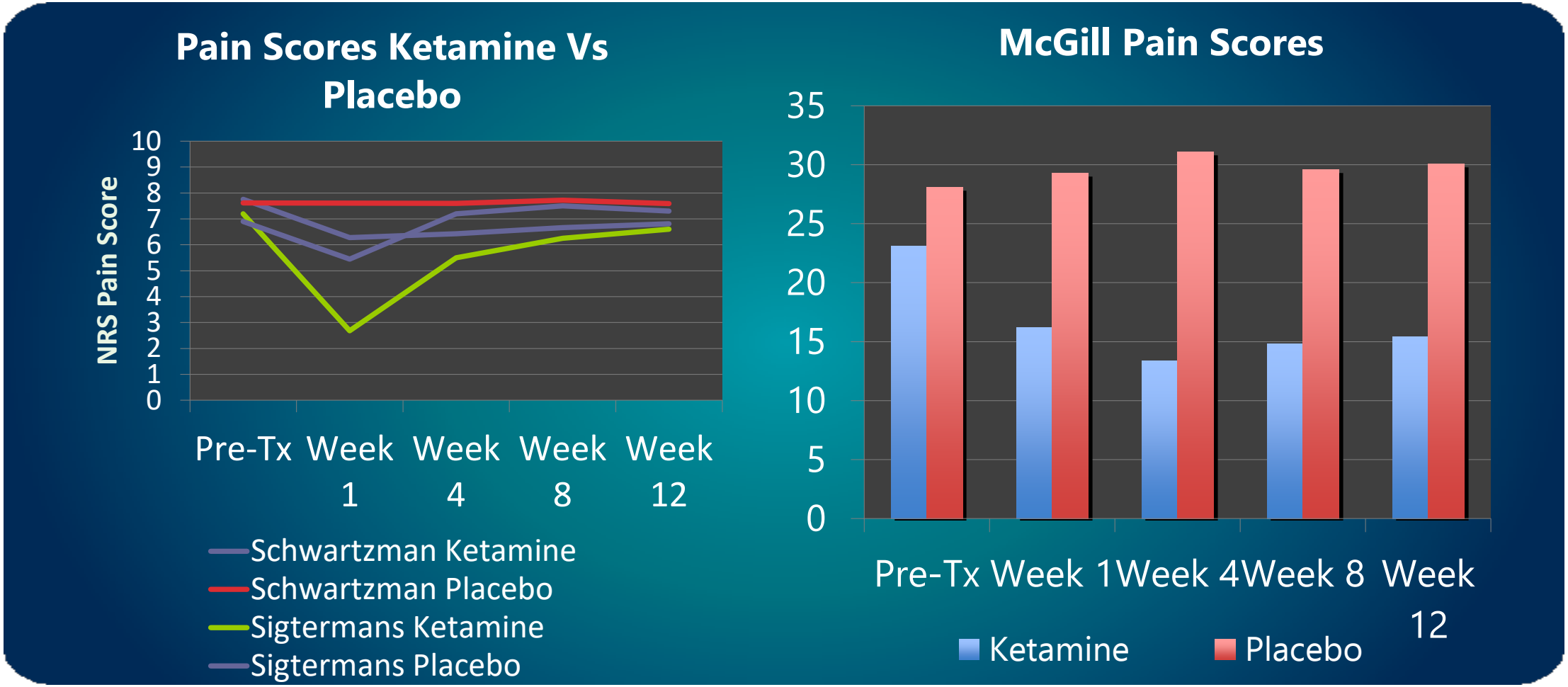
Low Dose Ketamine



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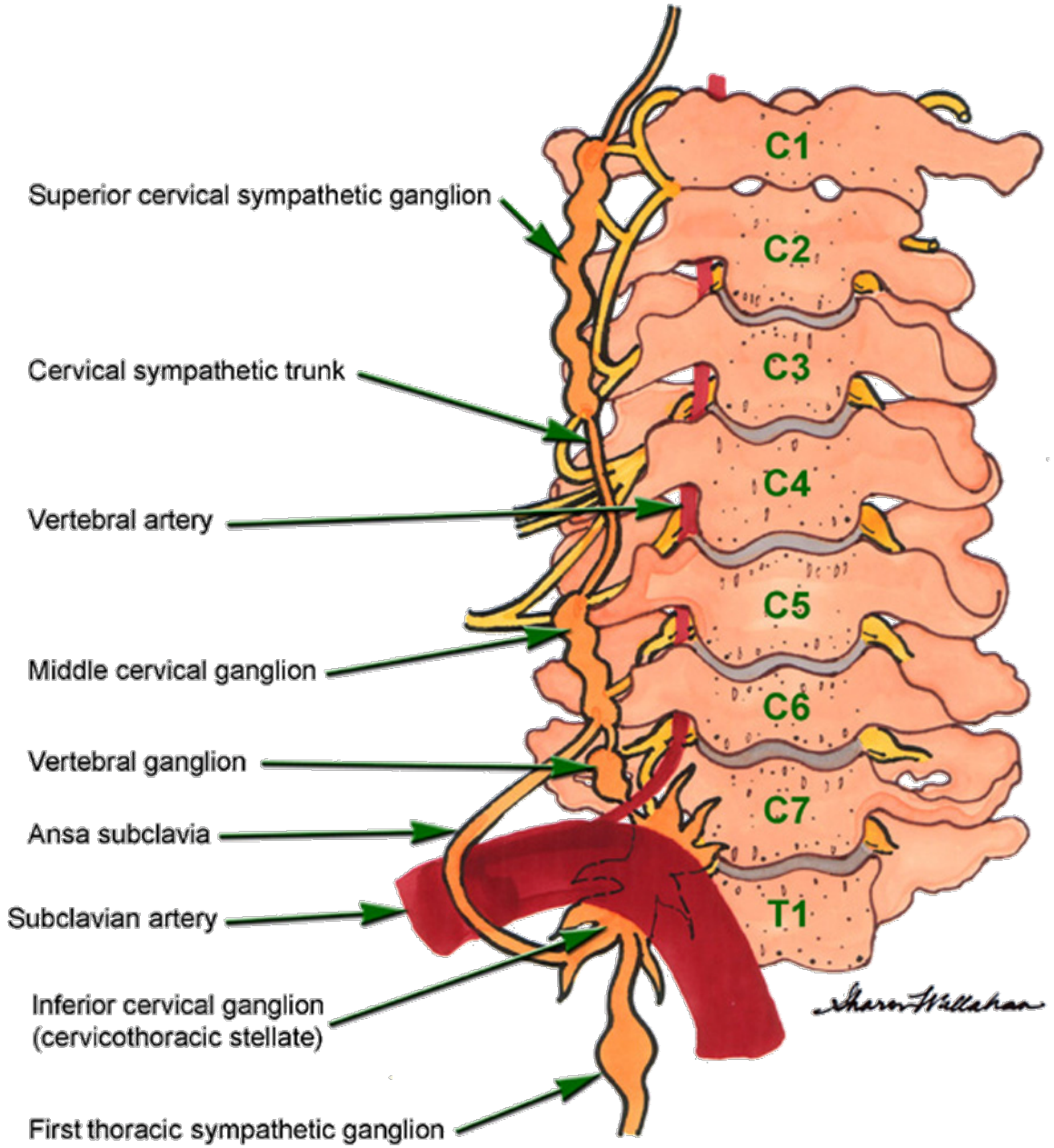
Complex Regional Pain Syndrome: Role of Sympathetic Blockade

- Dx sympathetically maintained pain, not to diagnose CRPS
- Short-term pain relief & facilitate physical therapy
- Predict response to oral sympatholytic medication - not supported by evidence
- Methods of sympathetic blockade
  - Local anesthetic sympathetic block
  - Phentolamine infusion
  - Intravenous regional blockade
  - Oral sympatholytics

Stellate Ganglion

- Inferior Cervical and First Thoracic Ganglia
- Located C7-T1
- Contributions from T2 & T3 gray communicating rami



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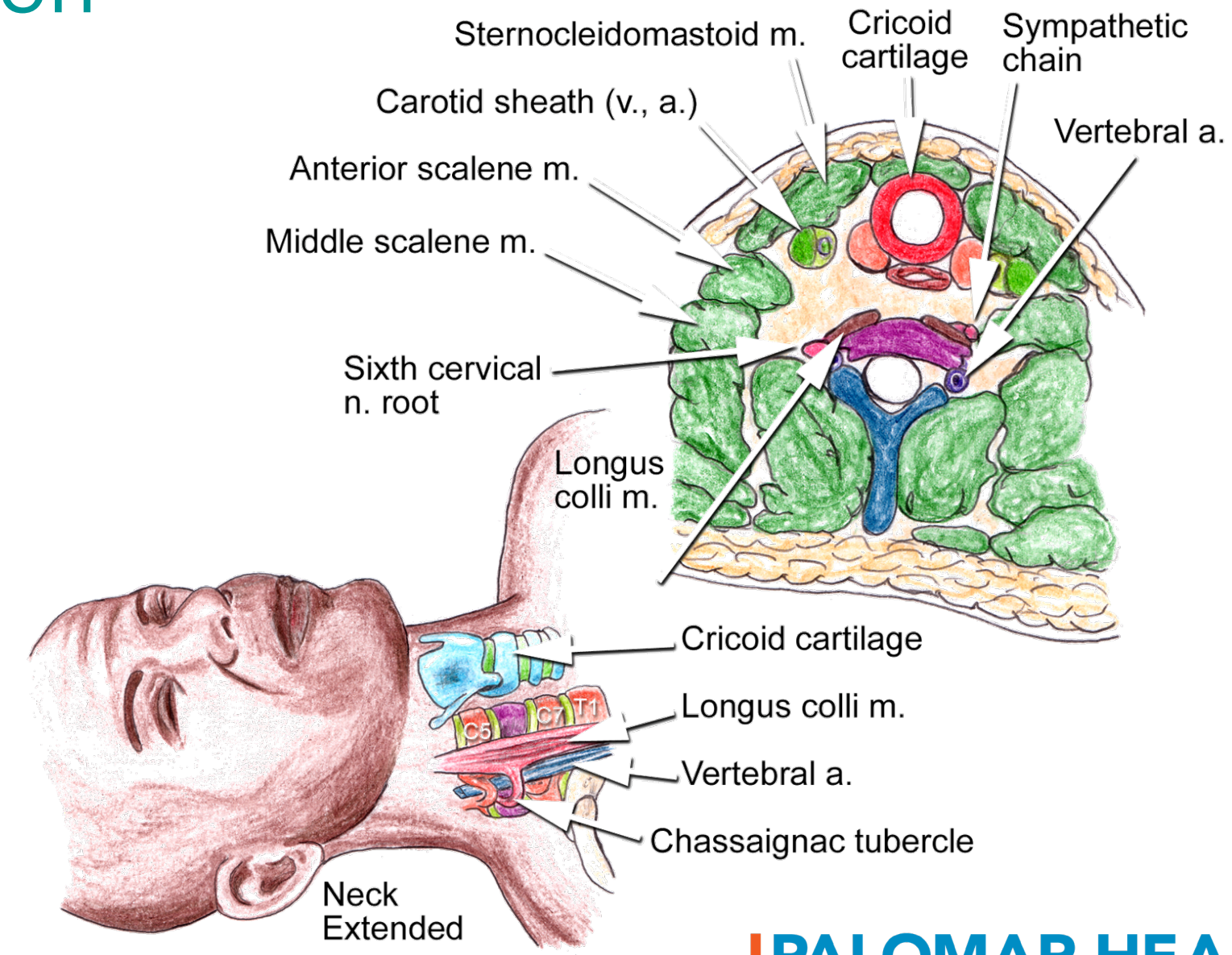
Stellate Ganglion



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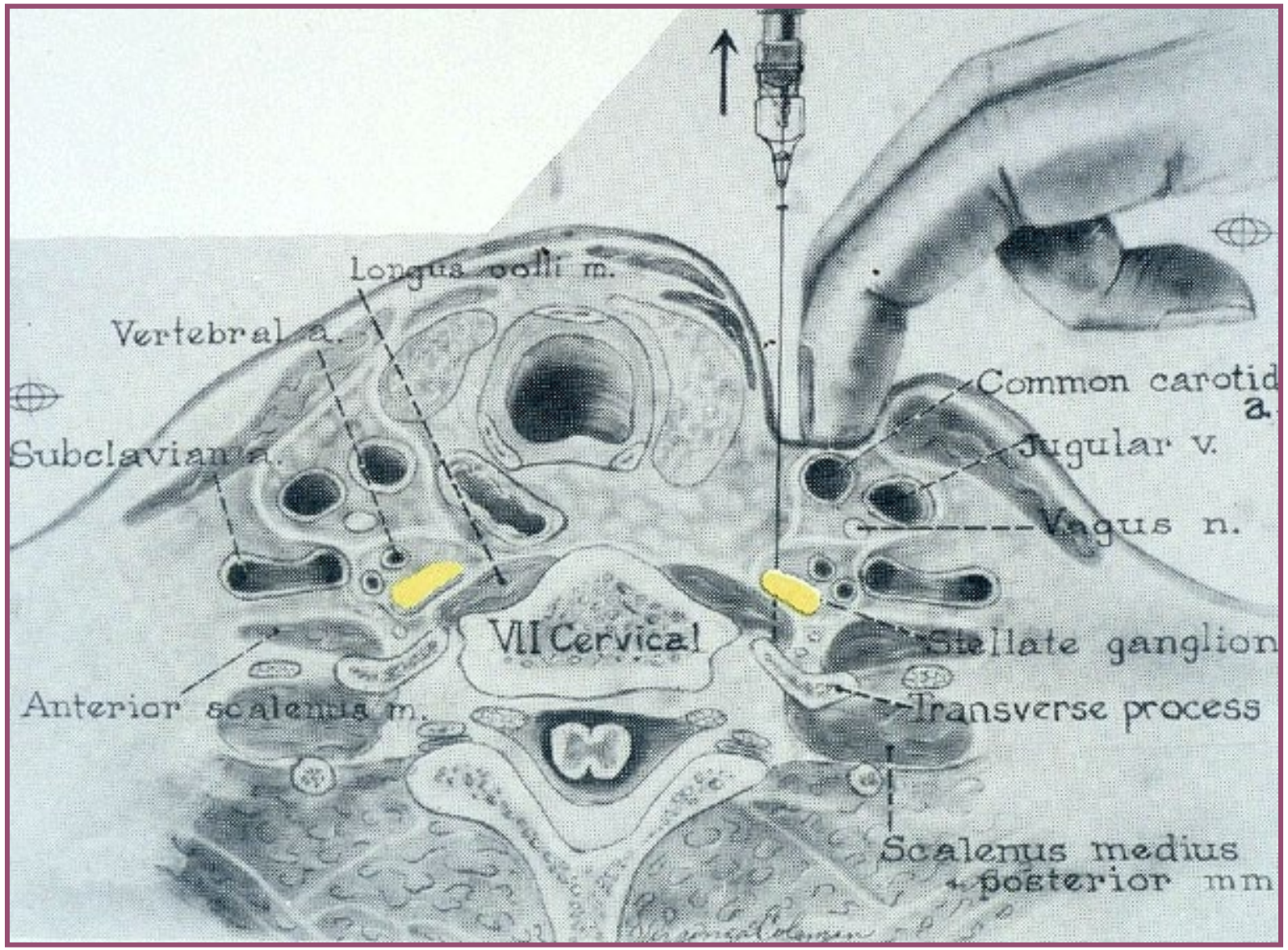
Stellate Ganglion Block



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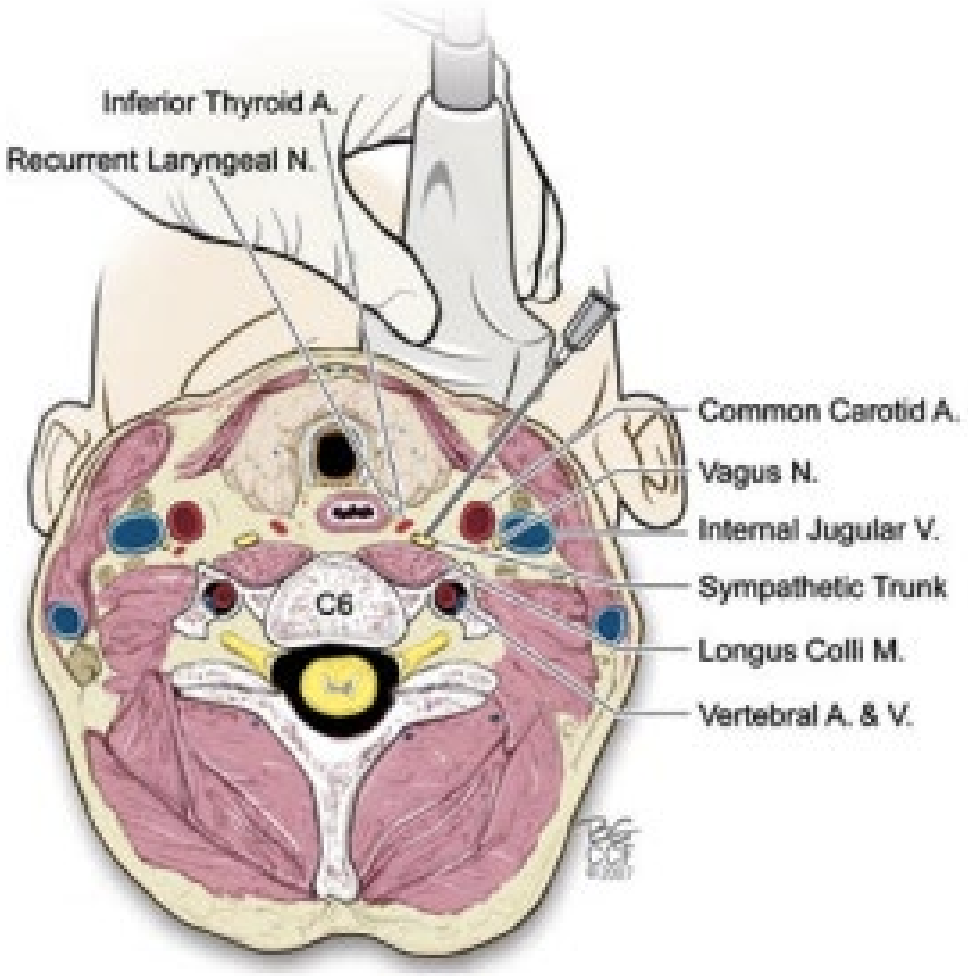

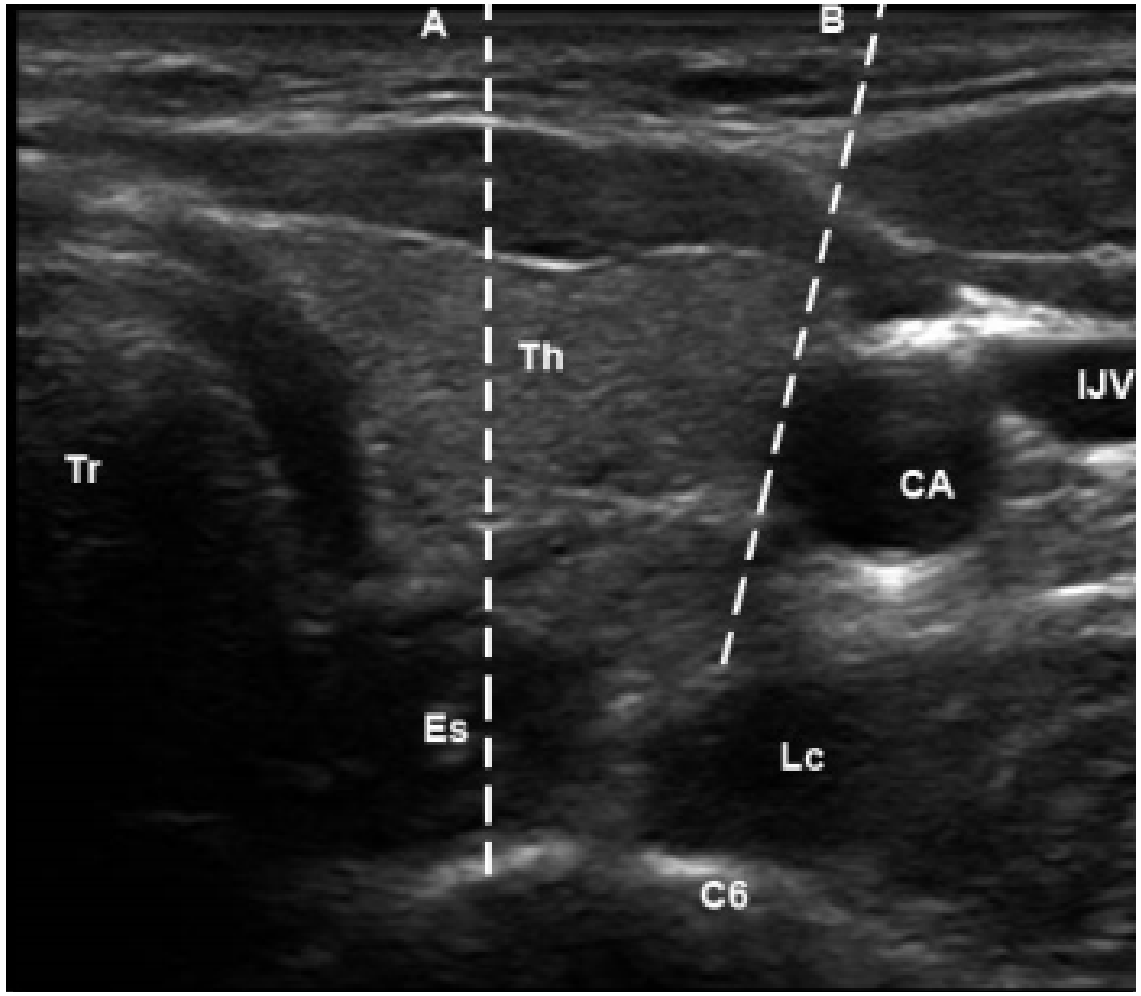

Fig. 3. *Ultrasound imaging of the left stellate ganglion. A: the needle path with the anterior paratracheal approach. B: the needle path with ultrasound guidance. Tr: trachea, Es: esophagus, Th: thyroid, Lc: longus coli muscle, CA: carotid artery, IJV: internal jugular vein. Reprinted with permission from the Cleveland Clinic Foundation.*

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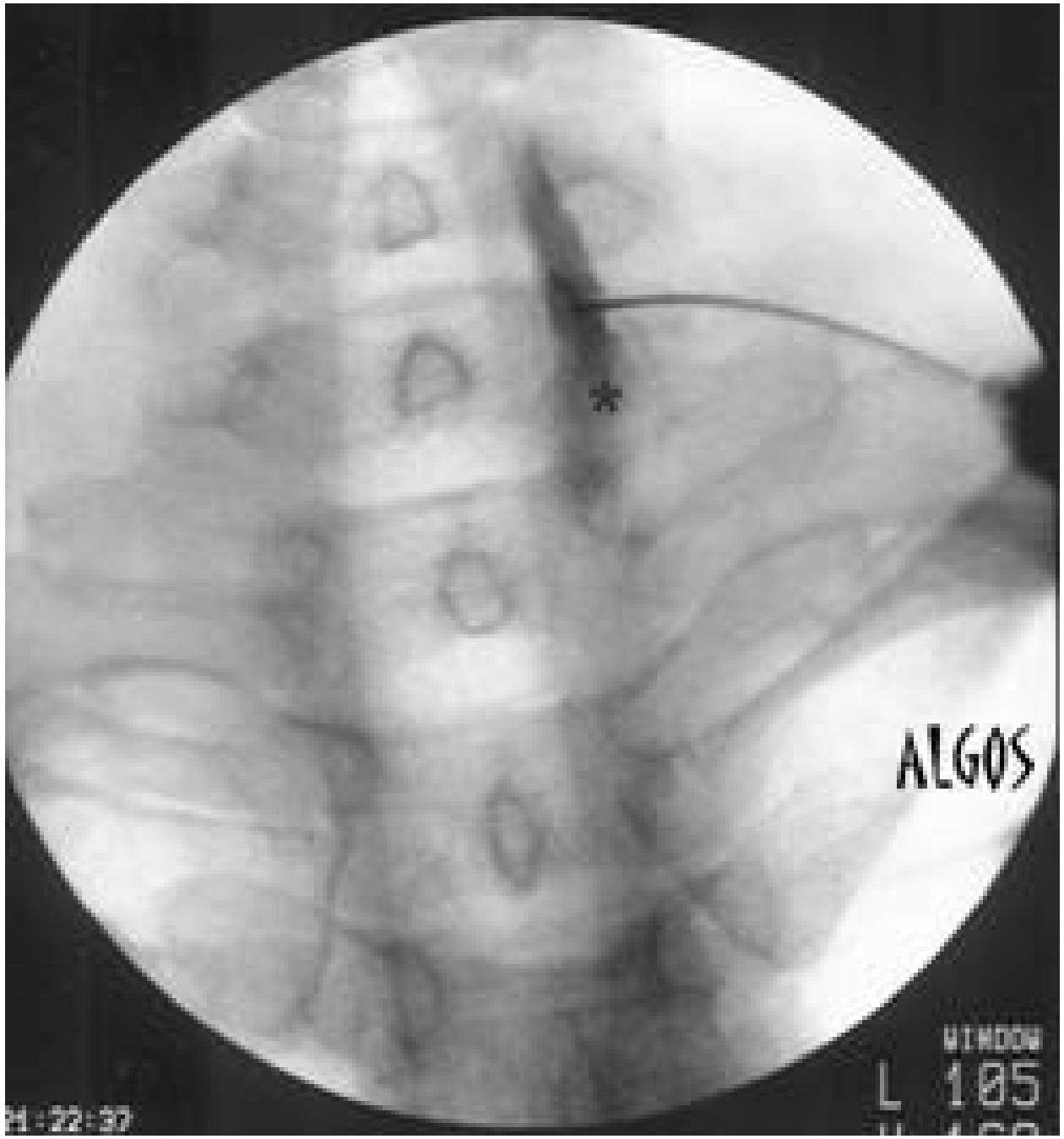

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Stellate Contraindications/Complications

Contraindications

- Coagulopathy
- Pneumothorax/ Pneumonectomy
- Recent MI

Complications-Severe

- Pneumothorax
- Intraspinal Injection
- Intravascular Injection – seizure

Complications-Common/Expected

- Horner's
- RLN block – hoarseness
- Phrenic block - SOB

Brachial Plexus Block

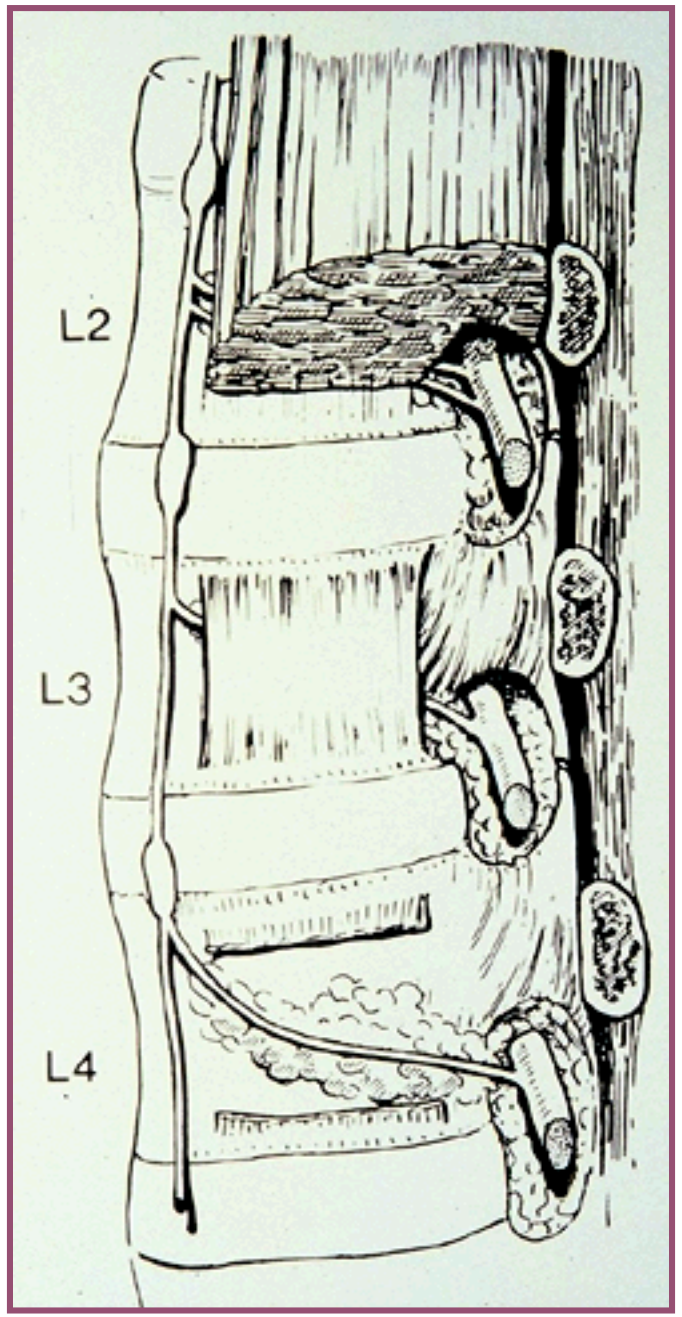
Case reports and case series

- Infraclavicular
- Axial

Randomized non-controlled study

- Continuous stellate vs continuous infraclavicular
  - 33 pts randomized
  - 1 week of 0.125% bupiv
  - IC>Stellate at 12 hrs
  - No difference between tx grps at 1 week and 4 weeks (both better than baseline)

Toshniwal et al. Pain Medicine 2012



Lumbar

Sympathetic

Chain

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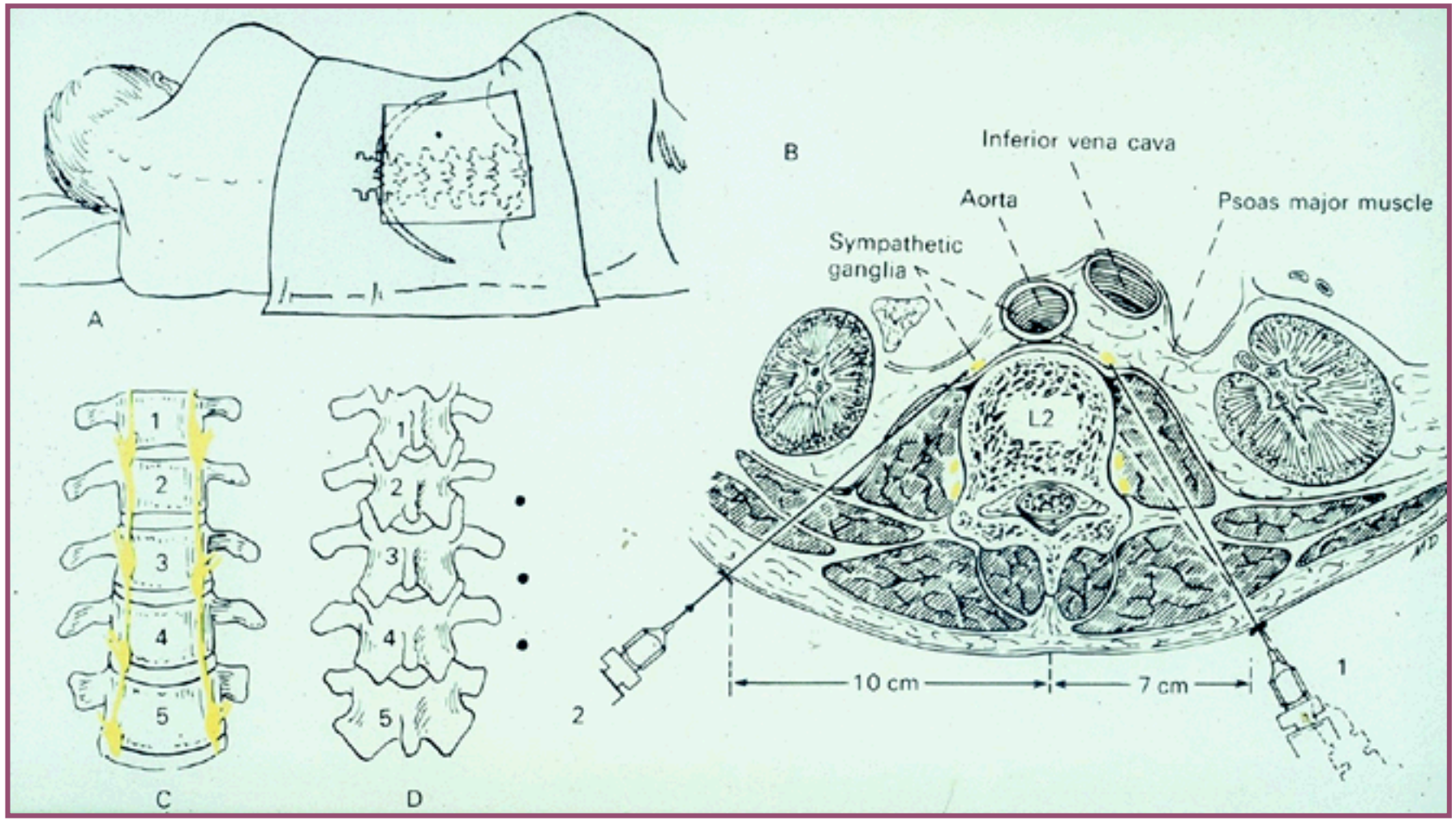
Lumbar Sympathetic Block



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Dorsal Column Nerve Stimulation

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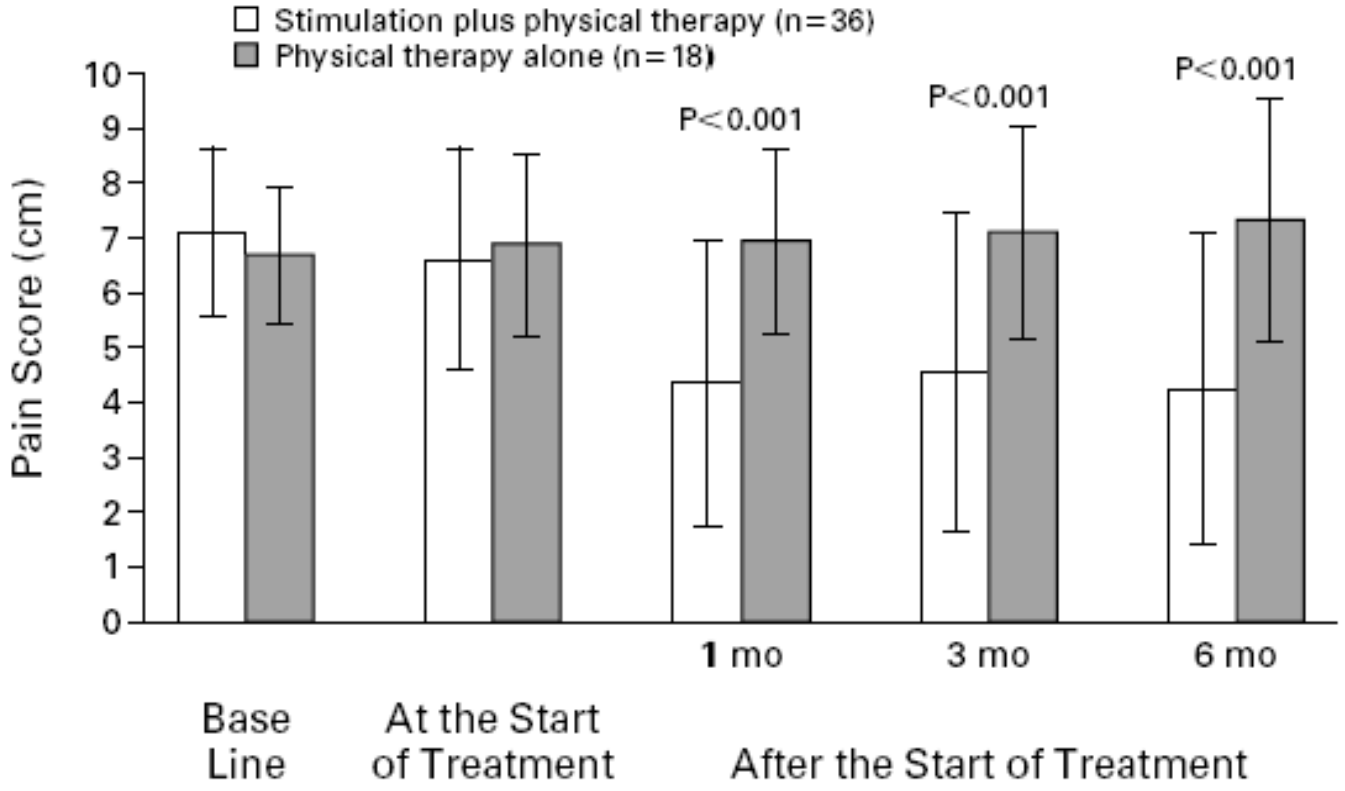
SCS and CRPS Studies

- 1 RCT: Kemler
  - Significant reduction in pain up to year 2
  - No improvement in function
- 25 Case Series
  - 67% of implanted patients achieved 50% pain relief
  - Mean VAS reduction 4.7
  - 33% experienced complications; leads, generator

RS Taylor et al. *Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost effectiveness literature and assessment of prognostic factors.* Eur J Pain, 2006. 10:91-101.

Spinal Cord Stimulation for CRPS



- N=54 patients with CRPS
- SCS + PT vs PT alone.[1]
- SCS was more effective at reducing pain than PT alone.[1]
- The efficacy of SCS was lost at year 3 (*P*=0.29)) of followup.[2]

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Spinal Cord Stimulation for CRPS

- Multiple trials have demonstrated the efficacy of SCS in the treatment of CRPS pain
    - Kemler, 2000; Kumar, 1998; Barolat, 1989
- Pain relief is independent of the vasodilatory effect of SCS
    - Kemler, 2000