Post Stroke Pain Syndromes: Part 2

Complex Regional Pain Syndrome and Central Post Stroke Pain

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Complex Regional Pain Syndrome in Stroke

Complex Regional Pain Syndrome

- Classic description: "…continuous, intense pain out of proportion to the severity of the injury, which gets worse rather than better."
- Complex Regional Pain Syndrome (CRPS) 1
  - Previously called "Reflex Sympathetic Dystrophy"
  - Occurs after an illness or injury that didn't directly damage nerves
  - Encompass 90% of CRPS
- CRPS II
  - Previously called "Causalgia"
  - Follows distinct nerve injury

Chae J. Top Stroke Rehabil. 2010; 17: 151

Symptoms and signs of CRPS

General

- “Burning” pain
- Increased skin sensitivity
- Changes in skin temperature: warmer or cooler compared to the opposite limb
- Changes in skin color: blotchy, purple, pale or red
- Changes in skin texture: shiny and thin and at times excessively sweaty
- Changes in nail and hair growth patterns
- Swelling and stiffness in affected joints

Stroke specific

- Shoulder pain
- Hand pain
- MCP tenderness on palpation
- Pain with passive wrist, MCP, and PIP extension
- Upper limb dystonia
- Associated with:
- -Severe motor impairment
- -Sensory impairments
- -Subluxation
- -Flaccidity

Chae J. Top Stroke Rehabil. 2010; 17: 151

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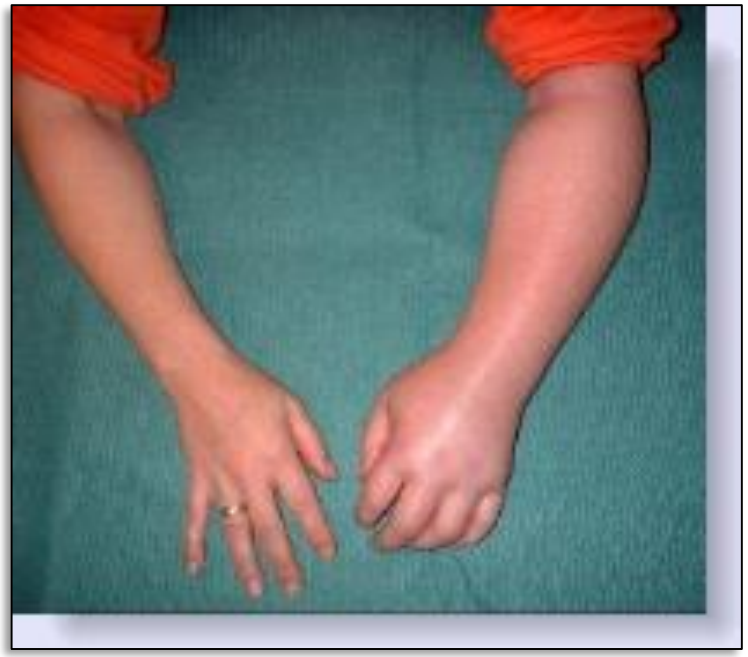
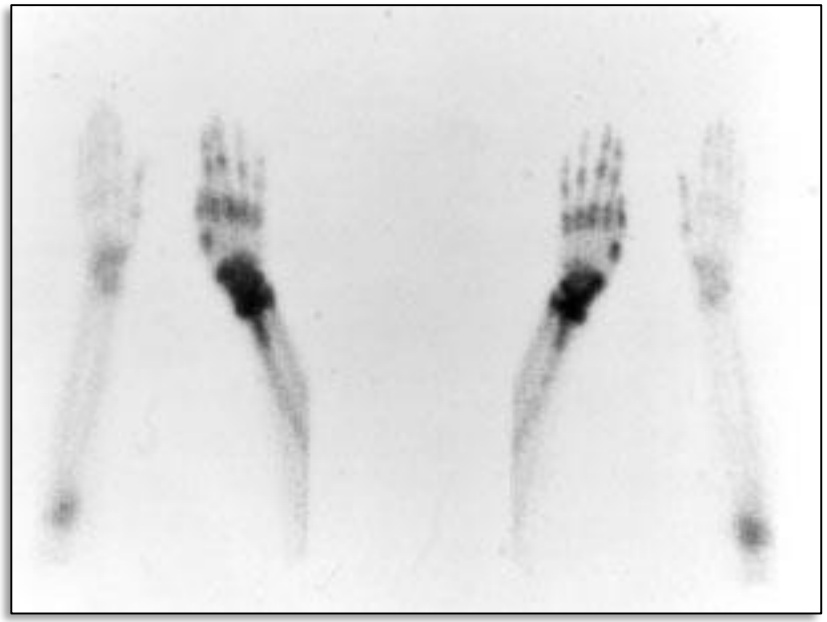
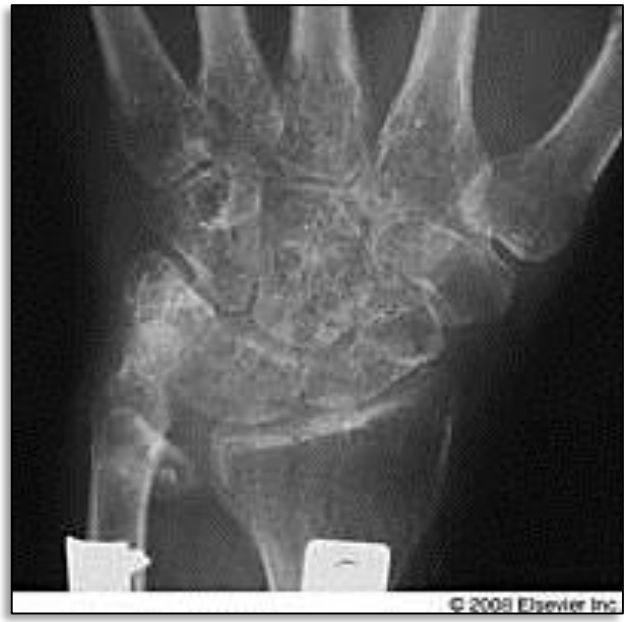
Symptoms and Signs of CRPS







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CRPS Criteria
Budapest Consensus Group (2007)

	Factor 1: Sensory	Factor 2: Vasomotor	Factor 3: Sudomotor/ Edema	Factor 4: Motor/Trophic
Symptoms	•Hyperesthesia •Allodynia	•Temperature asymmetry •Skin color changes •Skin color asymmetry	•Edema •Sweating changes •Sweating asymmetry	•Decreased ROM •Motor dysfunction (weakness, tremor, dystonia) •Trophic changes (hair, nail, skin)
Signs	•Hyperalgesia (to pinprick) •Allodynia (to light touch, deep pressure or joint ROM)	•Temperature asymmetry •Skin color changes •Skin color asymmetry	•Edema •Sweating changes •Sweating asymmetry	•Decreased ROM •Motor dysfunction (weakness, tremor, dystonia) •Trophic changes (hair, nail, skin)

Harden RN, Bruehl S, Stanton-Hicks M, et al. Pain Med. 2007; 8: 326-331

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CRPS treatment

Physiotherapeutic

- Contrast baths
- Desensitization
- Gentle ROM and strengthening exercises
- Edema control
- Stress loading (scrubbing)
- Ergonomics
- Movement therapy and normalization of use
- Functional restoration

Psychotherapeutic

- Patient and family education
- Psychological evaluation
- Psychological pain management intervention

Pharmacology

- Oral Pharmacology
- Minimally invasive injections
- Invasive (pumps)

Comprehensive Pain Center

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Oral pharmacology

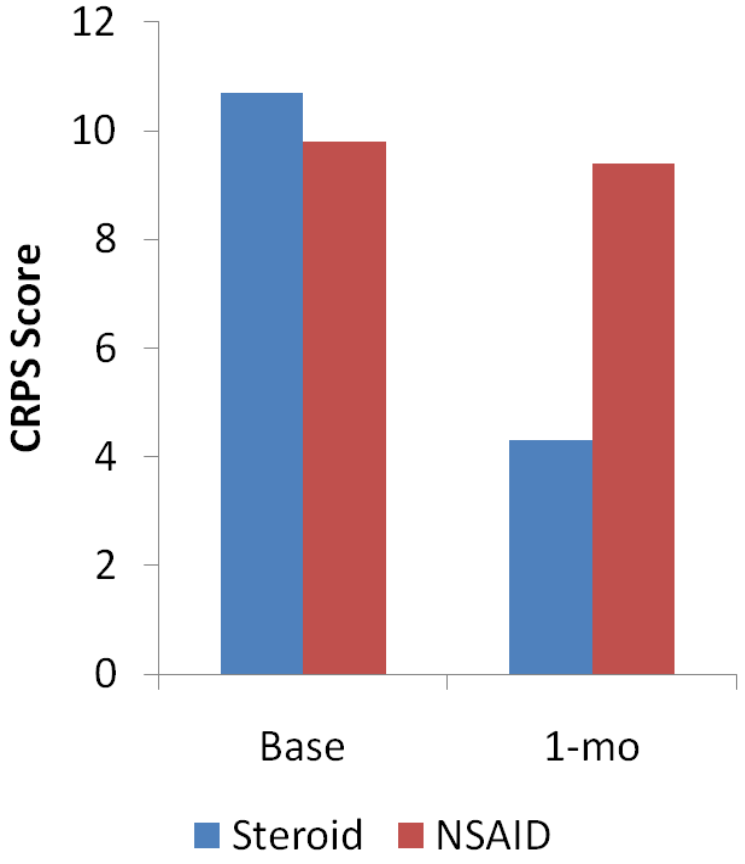
- Acetaminophen
- NSAID’s
- Opiods
- Oral Steroids
- Anticonvulsants
- Calcitonin/Bisphosphanates
- Calcium channel blockers

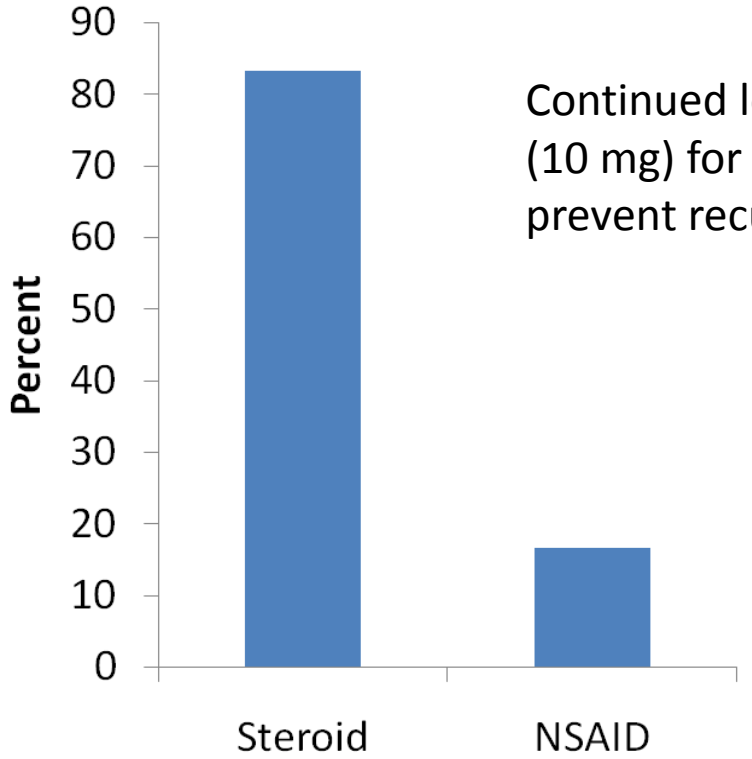
Oral Steroids in CRPS

- n=60
- CRPS score >7 (0-20)
- Prednisolone: 40 mg/d x 14 days, 10mg/wk taper
- Piroxicam: 20 mg/d
- Outcome: CRPS scores at 1-mo, blinded assessments
- Success: at least 2-pt reduction

Kalita J et al., QJM, 2006; 99: 89

Oral Steroids





Continued low dose Methylprednisolone (10 mg) for and additional month can prevent recurrence

Kalita J, et al. QJ Med, 2006; 99: 89
Kalita J, et al. Pain Physician. 2016; 19: 565

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Mirror Therapy

- Mismatch between motor intent and sensory feedback of real movement?
- Reorganization of the primary sensory cortex?
- n=48 acute stroke survivors
- Budapest criteria
- Mirror: visualize arm in the mirror during standardized arm movements
- Control: same movements but with mirror covered
- 4-wks of daily treatment (30min-hr)
- Baseline, EOT and 6-mo

Cacchio A,et al., Neurorehabil Neural Repair. 2009; 23: 792

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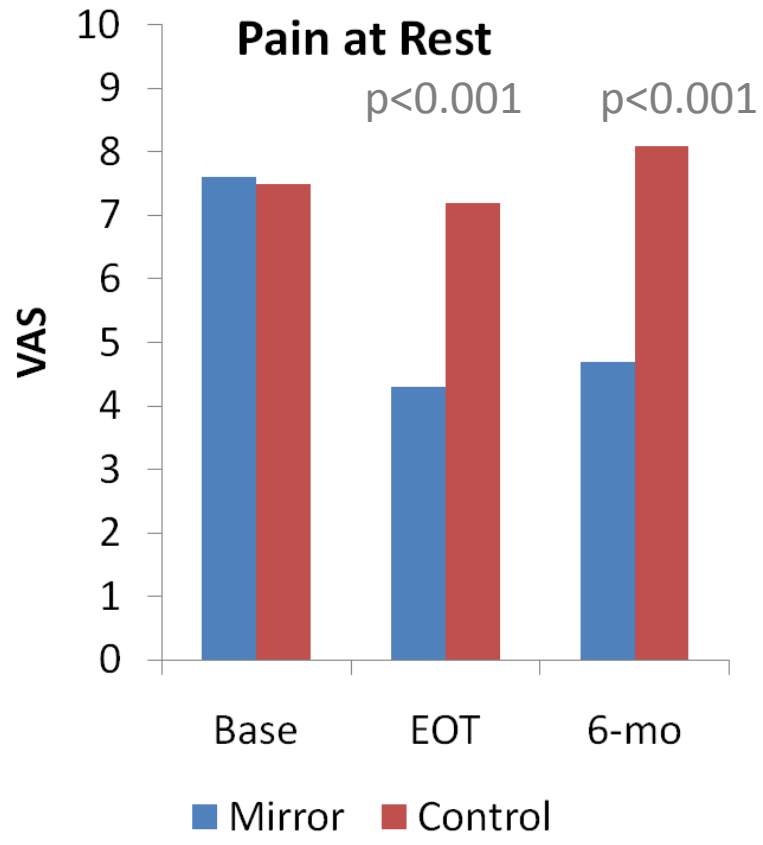
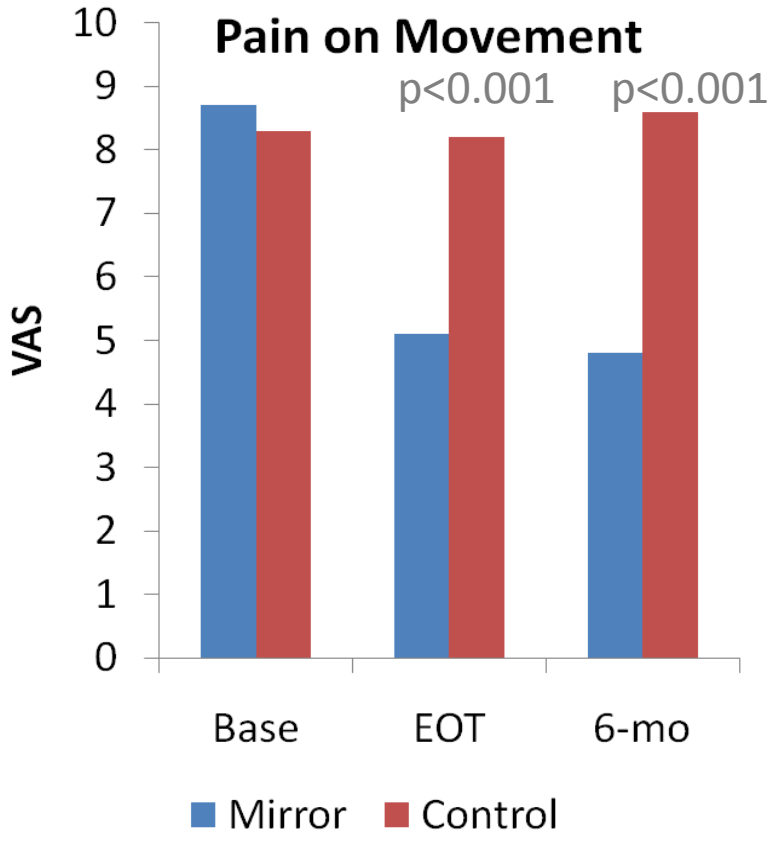
Mirror Therapy





Cacchio A,et al., Neurorehabil Neural Repair. 2009; 23: 792

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Central Post-Stroke Pain Syndrome

Central Post Stroke Pain Syndrome

- Central post stroke pain (CPSP) is characterized as a constant or intermittent pain occurring after stroke located in areas of the body that have sensory abnormalities.

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Lateral Medullary Stroke

- AKA Wallenberg Syndrome
- Described in 1895
- *Spontaneous pain*
- Loss of sensation on ipsilateral face and contralateral limbs

Wallenberg A. Arch *f* Paychiat U Nervenkr, Berlin. 1895; 27: 671-673

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Thalamic Syndrome

Described by Dejerine and Roussy (1906)

- Slight hemiplegia
- Disturbance of superficial and deep sensibility
- Hemiataxia and hemistereognosia
- Intolerable pain
- Choreoathetoid movements

Dejerine J, Roussy J. Rev Neurol. 1906; 14: 521-532

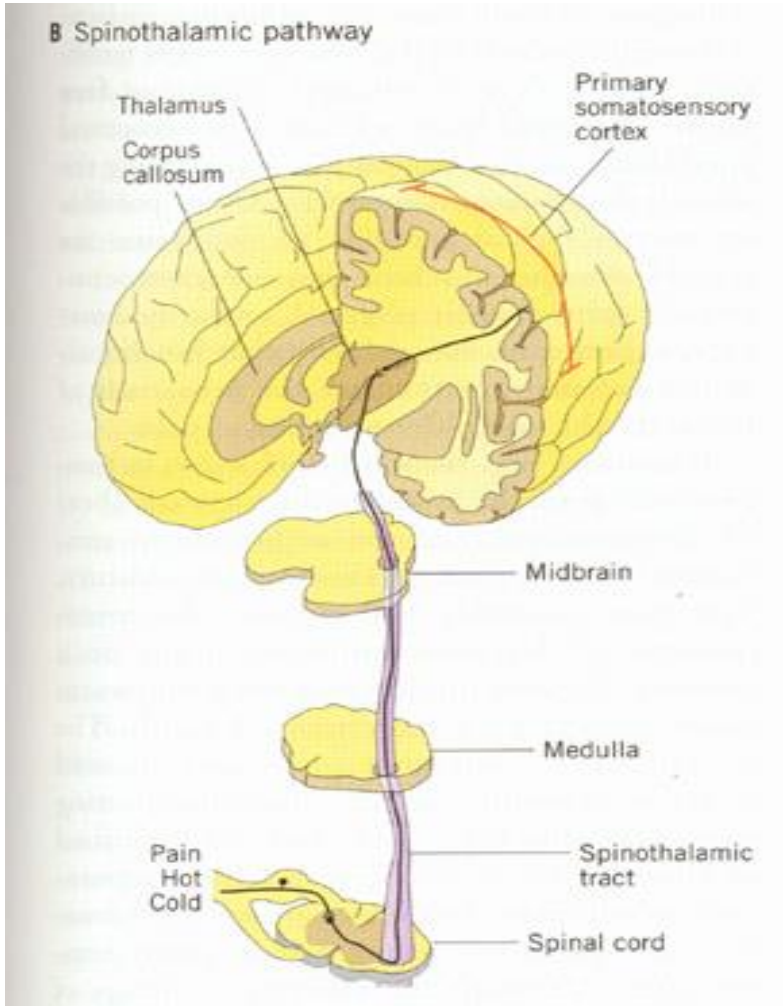
Thalamic Pain?

- 1911: Head and Holmes narrowed down the essential lesion site for the syndrome to the “lateral nucleus of the thalamus”
- 1923: Pieron suggested that a similar pain syndrome might be caused by cortical injury
- 1927: Foix described a case of a pain syndrome induced by pure cortical damage.
- 1935: Davison and Schick found lesions in thalamus, cortex or brainstem in 11 patients with stroke and pain.

Central Pain

- 1969: Cassanari and Pagni report that pain can follow a stroke damaging any part of the spinothalamic or thalamocortical paths.

Not every patient with injury in these tracts has pain



Cassinari V, Pagni CA. Central pain. A Neurosurgical Survey. 1969

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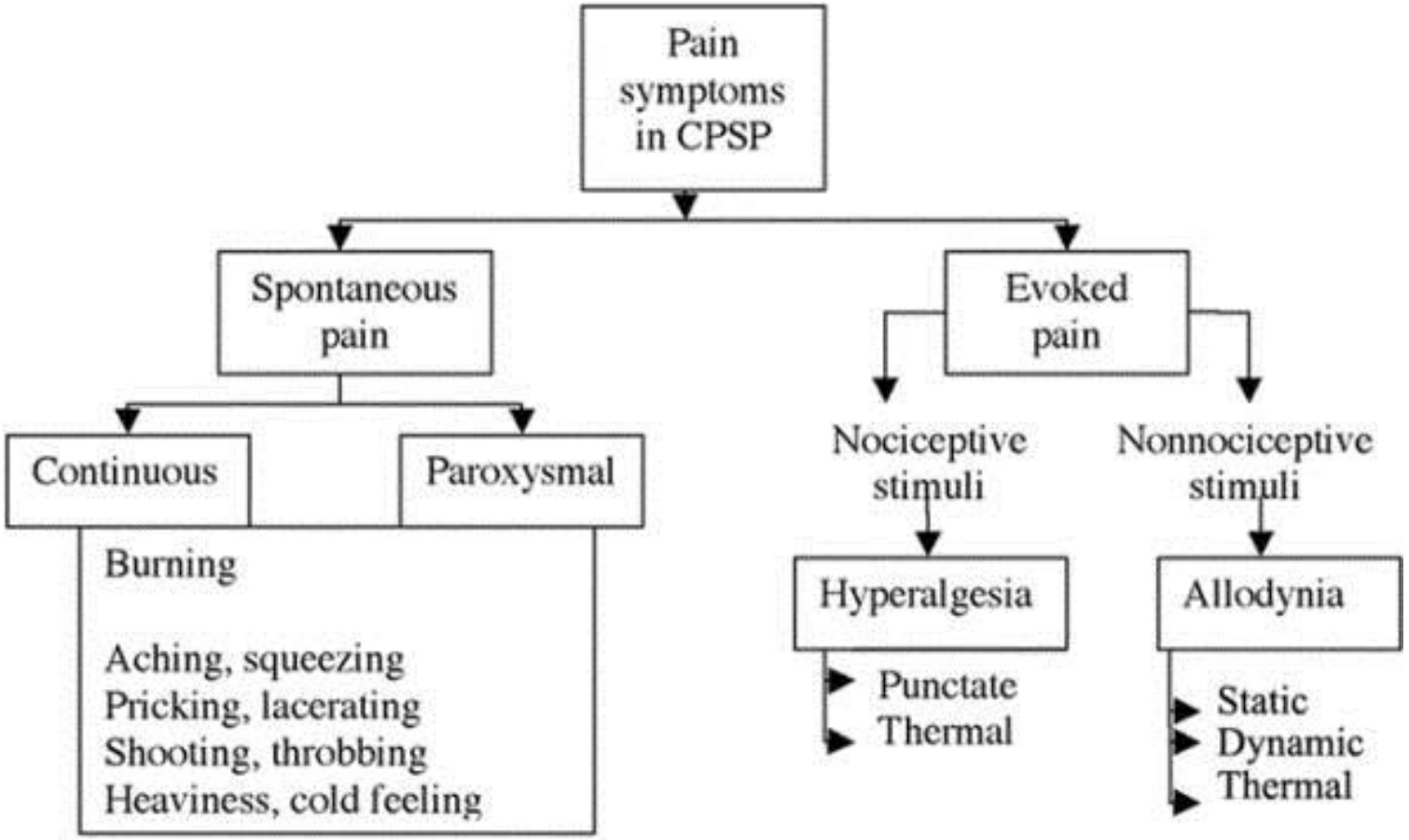
CPSP Epidemiology

- Less commonly seen in stroke than in multiple sclerosis or SCI.
- Occurs in 8% of stroke patients
- 9% of patients with thalamic hemorrhage
- Moderate to severe pain occurs in 5%
- Time of onset can very after stroke:
  - From 1 week to 6 years
  - 63% of cases develop pain with 1 month
  - Few cases have pain at the time of stroke

Bowsher D. Neurol Neurosurg Psychiatry. 1996; 61: 62-69
Leijon G., et al. Pain. 1989; 36: 13-25
Andersen G., et al. Pain. 1995; 61: 187-193

CPSP Symptoms



Kumar B., et al. Anesth Analg. 2009; 108: 1645-1657.

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CPSPS Symptoms – character of pain

Burning	47 – 59%
Aching	30 – 41%
Lacerating	7 – 26%
Pricking	6 – 30%

Leijon G, et al. Pain. 1989; 36: 13-25
Bowsher D. J Neurol Neurosurg Psychiatry. 1996; 61: 62-69

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Symptoms – Factors influencing pain

Factors that increase pain		Factors that decrease pain	
Movement	70%	Movement	19%
Cold	48%	Cold	7%
Warmth	22%	Warmth	30%
Touch	44%	Rest	37%
Emotion	19%		
Other	15%		

Leijon G, et al. Pain. 1989; 36: 13-25

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CPSPS Signs - Allodynia

No allodynia	28%
Tactile only	52%
Movement only	22%
Thermal only	20%
Tactile & thermal	9%
Tactile & movement	12%
Thermal & movement	1%

Bowsher D. Neurol Neurosurg Psychiatry. 1996; 61: 62-69

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CSPS Signs - Hyperpathia

Pin Prick response	%
Normal	4
Hypoalgesia	37
Hyperalgesia	59

Patients with Thalamic lesions more likely to have hyperalgesia

Boivie J et al. Pain. 1989; 37: 173-185

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CPSP – Motor Deficits

Hemiplegia	None	52%
	Moderate	37%
	Severe	11%
Ataxia	None	38%
	Moderate	58%
	Severe	4%
Choreoathetosis		4%

Leijon G, et al. Pain. 1989; 36: 13-25

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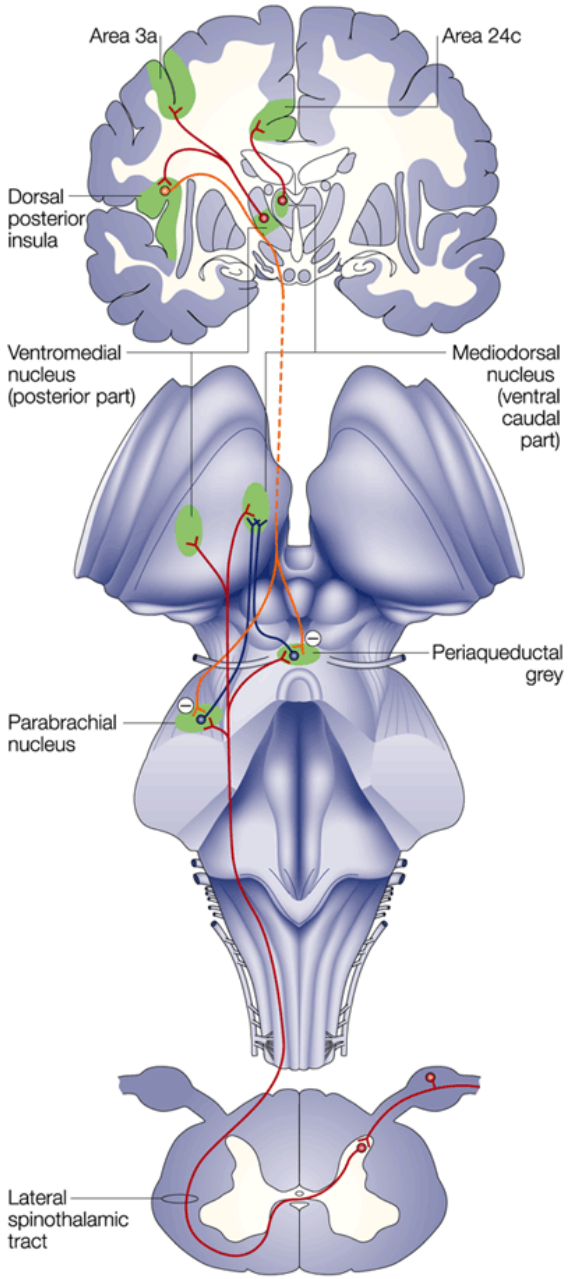
Pathophysiology

- Loss of aminergic modulation
- Central dishibition - loss of GABAergic activity
- Central Excitation – burst activity in thalamus
- Alterations of NMDA/glutamate system
- Abnormal central modulation
- Thermosensory inhibition

Harvey RL. Top Stroke Rehabil. 2010; 17: 163-172

Lamina I sensory pathway

- Thermosensory inhibition
- Abnormal central modulation



Craig AD. Nature Rev Neurosci. 2002; 3: 655-666

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Pathophysiology
Necessary components?

The entire puzzle has yet to be solved

- Injury to spino-thalamo-cortical tracts
- Maladaptive CNS neuroplasticity
- Pain perception is closely linked to the emotional state of the individual and the behavioral drive that signals a homeostatic imbalance.

CPSP treatment

Physiotherapeutic

- Contrast baths
- Desensitization
- Gentle ROM and strengthening exercises
- Ergonomics
- Movement therapy and normalization of use
- Functional restoration

Psychotherapeutic

- Patient and family education
- Psychological evaluation
- Psychological pain management intervention

Pharmacology

- Oral Pharmacology
- Invasive (motor cortex stimulation)

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Management

Phamacological management of CPSP often becomes a practice of trial and error……

…..but knowing some of the pharmacology helps with making decisions

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Noradrenergic agents

- Amitriptyline (up to 75 mg)
  - Reduced pain in 67% of patients with CPSP (vs 7% in placebo)
  - Among patients with thalamic strokes
    - 17% developed pain on amitriptyline
    - 21% developed pain on placebo

Leijon G, Bovie J. Pain. 1989; 36: 27-36

Serotonin Reuptake Inhibitors

- Fluvoxamine (up to 125 mg)
  - Mean change in VAS score from 7.7 to 6.0
  - Open-labeled trial (N=31).
  - More effective in patients with pain < 1 year.
  - Effect on pain was independent of effects on depression.

Shimodozono M, et al. Intern J Neurosci. 2002; 112: 1173-1181

Membrane stabilizing agents

- Carbemazepine (up to 800 mg daily)
  - 36% response (vs 7% placebo)
- Phenytoin
- IV Lidocaine
- Mexilitine (400-800 mg/day)
  - 30% effective but not well tolerated

Leijon G, Bovie J. Pain. 1989; 36: 27-36
Attal N, et al. Neurology. 2000; 54: 564-574

Anti-Glutamate Medications

- IV Ketamine
  - 48% report pain reduction by 40% lasting less than one hour
- Dextromethorphan
  - Negative in one trial using standard dose
- Lamotrigine
  - 40% reported > 2 point reduction on pain scale

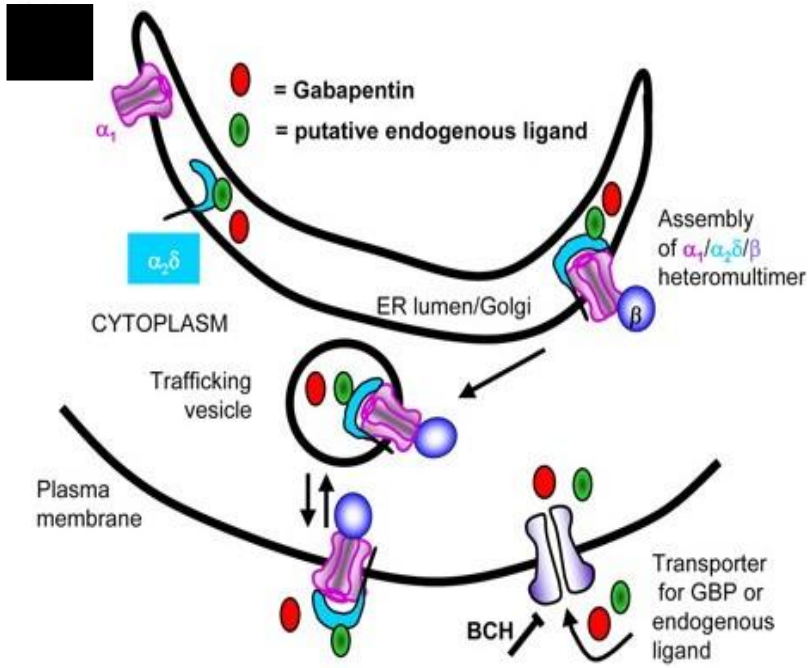
Yamamoto T et al. Pain. 1997; 72: 5-12
McQuay HJ et al. Pain. 1994; 59: 127-133
Vestergaard K et al. Neurology. 2001; 56: 184-190

GABA Agonist Medications

- IV Thiopental
  - 56% reported a significant pain reduction
  - Oral amobarbital was not effective
- IV Propofol
  - Reduced pain in 71% of patients with CPSP
- Intrathecal Baclofen (50-100 mcg)
  - 75-86% reported decrease pain after single bolus
- Intrathecal Medazolam

Yamamoto T et al. Pain. 1997; 72: 5-12
Canavero S, et al. J Neurol. 1995; 242: 561-567
Taira T, et al. J Neurol Neurosurg Psychiatry. 1994; 57: 381-382.

Gabapentin and Pregabalin



- These are structural analogs of GABA
- Acts via voltage gated N-type calcuim channels (binds to the $\alpha_2\delta$ subunit)
- May increase endogenous GABA by increasing activity of glutamic acid decarboxylase

Frese A, et al. Clin J Pain. 2006; 22: 252-260.

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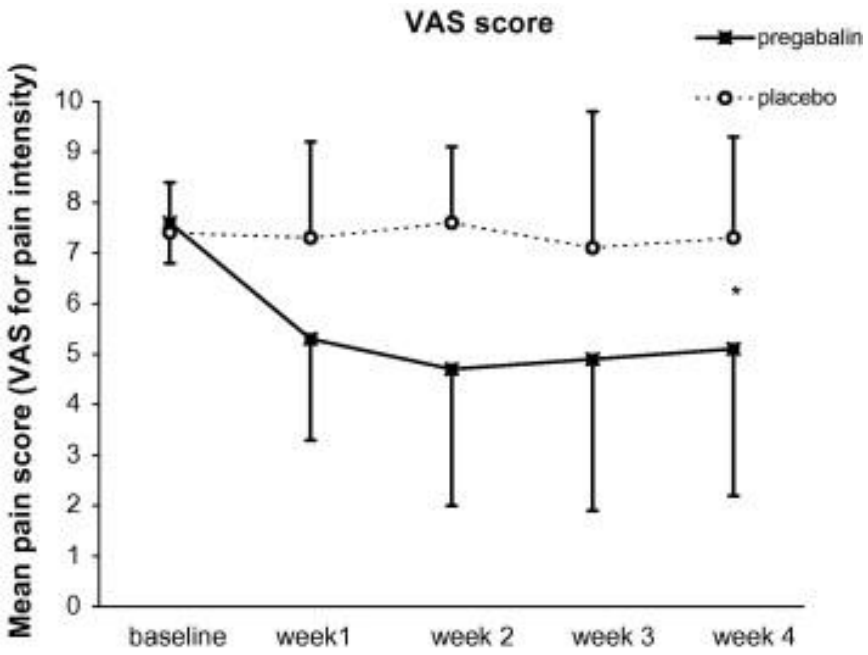
Pregabalin (150 mg to 600 mg)



- 40 patients with Central pain (12 with stroke) randomized to Pregabalin or placebo
- Change in mean VAS pain score from 7.6 to 5.1
- Improved SF-36 pain score
- No significant change in pain related disability (PDI)

Vrankin JH, et al. Pain. 2008; 136: 150-157.

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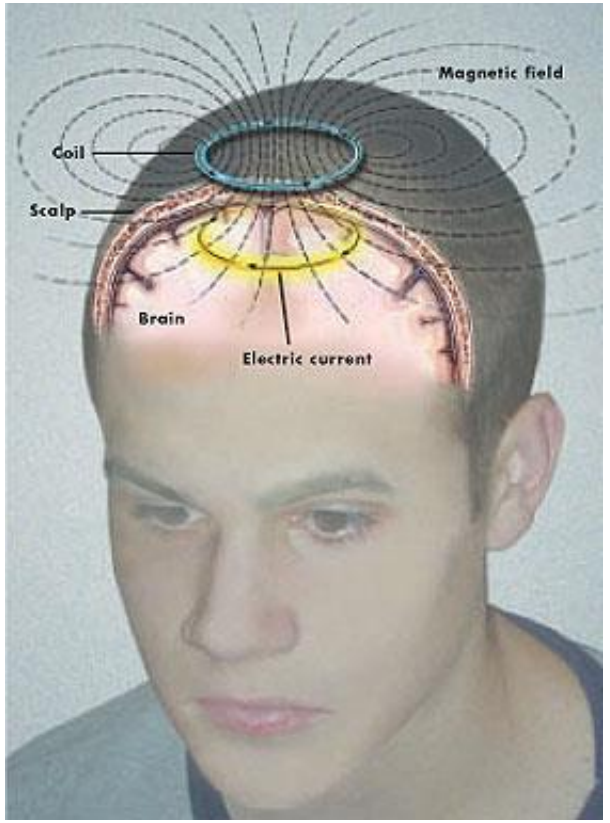
Transcutaneous Electrical Nerve Stimulation (TENS)

- 1/3 of patients have immediate pain reduction
- 1/3 cannot tolerate the stimulation
- Only 1/4 experience long term benefits

Leijon G, Bovie J. Pain. 1989; 38; 187-191

CNS Stimulation

- Transcranial Magnetic Stimulation (TMS)
  - High frequency rTMS for 5 minutes over motor cortex can reduce central pain transiently (3 hours).
  - Daily sessions for 5 days can lead to prolonged pain reduction (up to a month)
  - Cochrane review (N=249): 12% reduction in pain (VAS reduction by 0.77 points)



Lefaucheur LH, et al. J Neurol Neurosurg Psychiatry. 2004; 75: 612

O'Connell NE, et al. Cochrane reviews. 2018; 4: Cd008208

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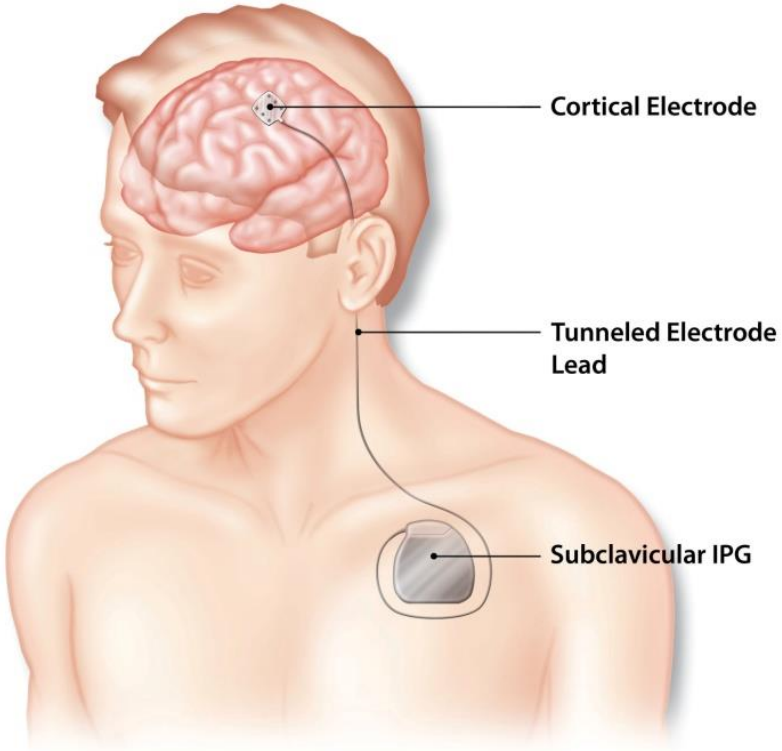
CNS Stimulation



- Motor Cortex Stimulation (MCS)
  - Implanted epidural electrode
  - Subthreshold stimulation over M1 cortex representing muscles underlying painful region
  - Only 25% of patients achieve >70% pain relief
  - 54% achieve 40-50% pain relief
  - 45% maintain 40-50% pain relief at 1 year

Fontaine D, et al. J Neurosurg 2009; 110: 251

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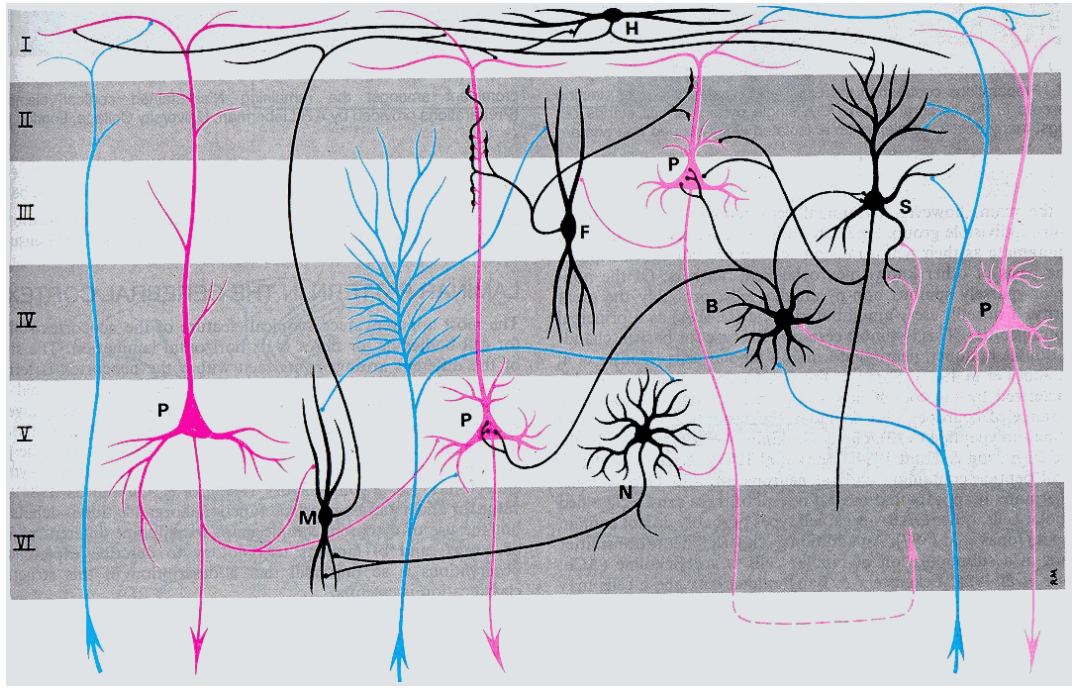
CNS Stimulation



- Mechanism of MCS on central pain
  - Orthograde stimulation of intracortical interneurons to S1 cortex or cingulate
  - Antegrade stimulation of neurons from SI and/or Thalamus
  - Corticospinal stimulation of spinal primary afferents and spinothalamic tract
  - High inhibitory input from non-injured hemisphere

Tsubokawa T, et al. J Neurosurg. 1993; 78: 393-401
Garcia-Larrea L, et al. Pain. 1999; 83: 259-273
Canavero S, Bonicalzi V. Acta Neurochirugica-suppl. 2007; 97: 27-36
Morishita T, Inoue T. Front Hum Neurosci. 2016; eCollection

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CNS Stimulation

- MCS and Central Pain – Factors Predicting success:
  - Intact or nearly intact Coroticospinal motor function
  - Mild sensory loss
  - Absence of thermal sensory threshold alteration in painful area
  - Positive response to Barbiturate, Ketamine or Propofol test
  - Negative response to Morphine test
  - Positive response to rTMS

Canavero S, Bonicalzi V. Acta Neurochirugica-suppl. 2007; 97: 27-36

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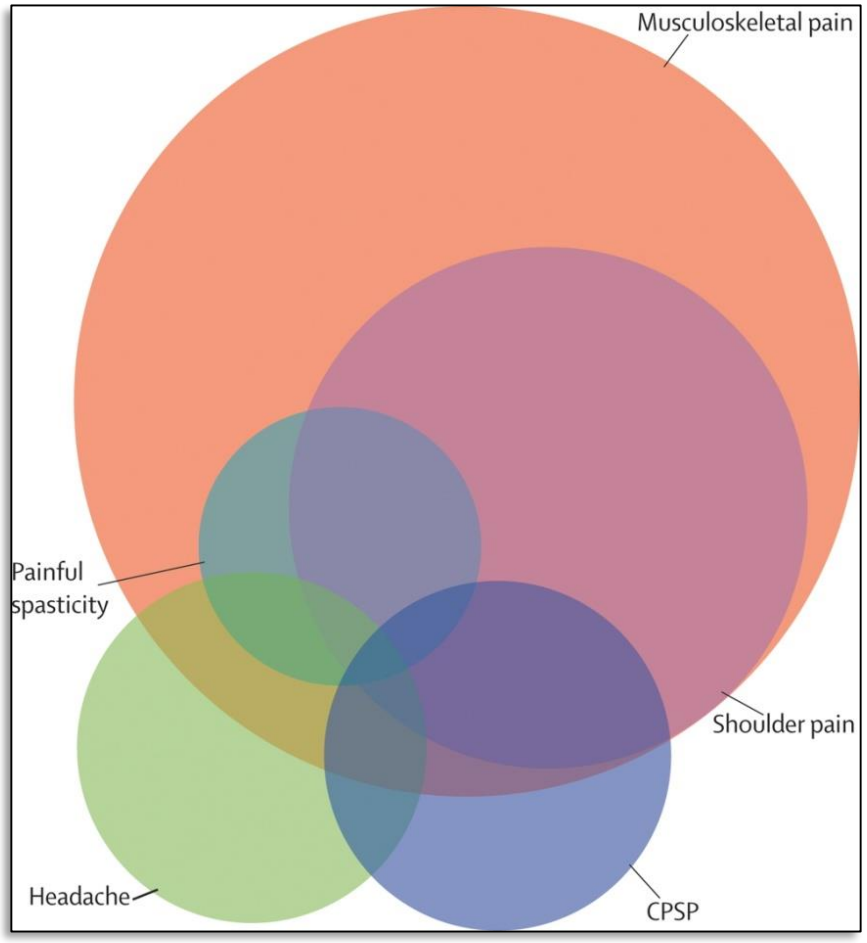
Pain in Stroke



Klit H, et al. Lancet Neurol 2009; 8: 857-68.

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Thank you! (part 2)

References

1. Chae J. Poststroke complex regional pain syndrome. Top Stroke Rehabil. 2010; 17: 151-162
2. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007; 8: 326-331
3. Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. QJM. 2006; 99: 89-95
4. Kalita J, Misra UK, Kumar A, Bhoi SK. Long-term prednisolone in post-stroke complex regional pain syndrome. Pain Physician. 2016; 19: 565-574.
5. Cacchio A, DeBlasis E, De Blasis V, et al. irror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. Neurorehab Neural Repair. 2009; 23: 792-799
6. Wallenberg A. Akute Bulbaraffektion (Embolie der arteria cerebelli post inf sinistra). Archives fur Psychiatry Paychiat U Nervenkr. 1895;27:504–540
7. Dejerine J, Roussy G. Le syndrome thalamique. Rev Neurol. 1906;14:521–532
8. Head H, Holmes G. Sensory disturbances from cerebral lesions. Brain. 1911;34:102–254.
9. Davison C, Schick W. Spontaneous pain and other subjective sensory disturbances. Arch Neurol Psychiatry. 1935;34:1204–1237.
10. Cassinari V, Pagni CA. Central Pain. A Neurological Survey. Cambridge: Harvard University Press; 1969
11. Bowsher D. Central pain: clinical and physiological characteristics. J Neurol Neurosurg Psychiatr. 1996;61:62–69.
12. Leijon G, Boivie J, Johansson I. Central poststroke pain: neurological symptoms and pain characteristics. Pain. 1989;36:13–25.
13. Andersen G, Vestergaard K, Ingeman-Neilsen M, et al. Incidence of central post stroke pain. Pain. 1995;61:187–193
14. Kumar B, Kalita J, Kumar G, Misra UK. Central poststroke pain: a review of pathophysiology and treatment. Anesth Analg. 2009; 108: 1645-1657
15. Leijon G, Boivie J, Johansson I. Central post-stroke pain--neurological symptoms and pain characteristics. Pain. 1989; 36: 13-25
16. Boivie J, Leijon G, Johansson I. Central post-stroke pain--a study of the mechanisms through analyses of the sensory abnormalities. Pain. 1989; 37: 173-185
17. Leijon G, Boivie J. Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine. Pain. 1989; 36: 27-36
18. Harvey RL. Central poststroke pain. Top Stroke Rehabil. 2010; 17: 163-172.
19. Craig AD. How do you feel? Interoception: the sense of the physiological system of the body. Nature Rev Neurosci. 2002; 3: 655-666

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References

20. Shimodozono M, Kawahira K, Kamishita T, et al. Reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. Int J Neurosci. 2002; 112: 1173-1181
21. Attal N, Gaude V, Brasseur L, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. Neurology. 2000; 54: 564-574
22. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T. Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain. 1997; 72: 5-12
23. McQuay HJ, Carroll D, Jadad AR, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled crossover trial with integral n-of-1 design. Pain. 1994; 59: 127-133
24. Vestergaard K, Andersen G, Gottrup H, et al. Lamotrigine for central poststroke pain: a randomized controlled trial. Neurology. 2001; 56: 184-190
25. Canavero S, Bonicalzi V, Pagni CA, et al. Propofol analgesia in central pain: preliminary clinical observations. J Neurol. 1995; 242: 561-567
26. Taira T, Tanikawa T, Kawamura H, et al. Spinal intrathecal baclofen suppresses central pain after a stroke. J Neurol Neurosurg Psychiatry. 1994; 57: 381-382
27. Frese A, Husstedt IW, Ringelstein EB, Evers S. Pharmacologic treatment of central post-stroke pain. Clin J Pain. 2006; 22: 252-260
28. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain. 2008; 136: 150-157
29. Leijon G, Boivie J. Central post-stroke pain--the effect of high and low frequency TENS. Pain. 1989; 38: 187-191
30. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry. 2004;75(4):612-616
31. O'Connell NE, Marston L, Spencer S, et al. Non-invasive brain stimulation techniques for chronic pain. The Cochrane database of systematic reviews. 2018;4:Cd008208.
32. Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. J Neurosurg. 2009; 110: 251-256
33. Tsubokawa T, Katayam Y, Yamamoto T. et al. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg. 1993; 78: 393-401
34. Garcia-Larrea L, Peyron R, Mertens P, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 1999; 83: 259-273
35. Canavero S, Bonicalzi V. Extradural cortical stimulation for central pain. Acta Neurochir Suppl. 2007; 97: 27-36
36. Morishita T, Tooru I. Brain Stimulation Therapy for Central Post-Stroke Pain from a Perspective of Interhemispheric Neural Network Remodeling. Front Hum Neurosci. 2016; 10: doi: 10.3389/fnhum.2016.00166, ePub

Questions?