Central Post-Stroke Pain

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Central Pain

- “pain associated with lesions of the central nervous system”
- Central post-stroke pain (CPSP)
- Spinal cord injury (SCI)

Nicholson. Neurology 2004; 62(Suppl 2): S30-36.

Central Neuropathic Pain

Panel 2: Common causes of central neuropathic pain

- Ischaemic and haemorrhagic stroke
- Multiple sclerosis
- Spinal cord injury
- Syringomyelia
- Vascular malformations
- Infections (ie, abscess, encephalitis, vasculitis)
- Traumatic brain injury
- Parkinson's disease?

Klit. Lancet Neurol 2009; 8: 857–68

Central post-stroke pain (CPSP)

- Thalamic pain syndrome by Dejerine and Roussey (1906)
- (1) a thalamic lesion,
- (2) slight hemiplegia,
- (3) disturbance of superficial and deep sensibility,
- (4) hemiataxia and hemiastereognosia,
- (5) intolerable pain, and
- (6) choreoathetoid movements

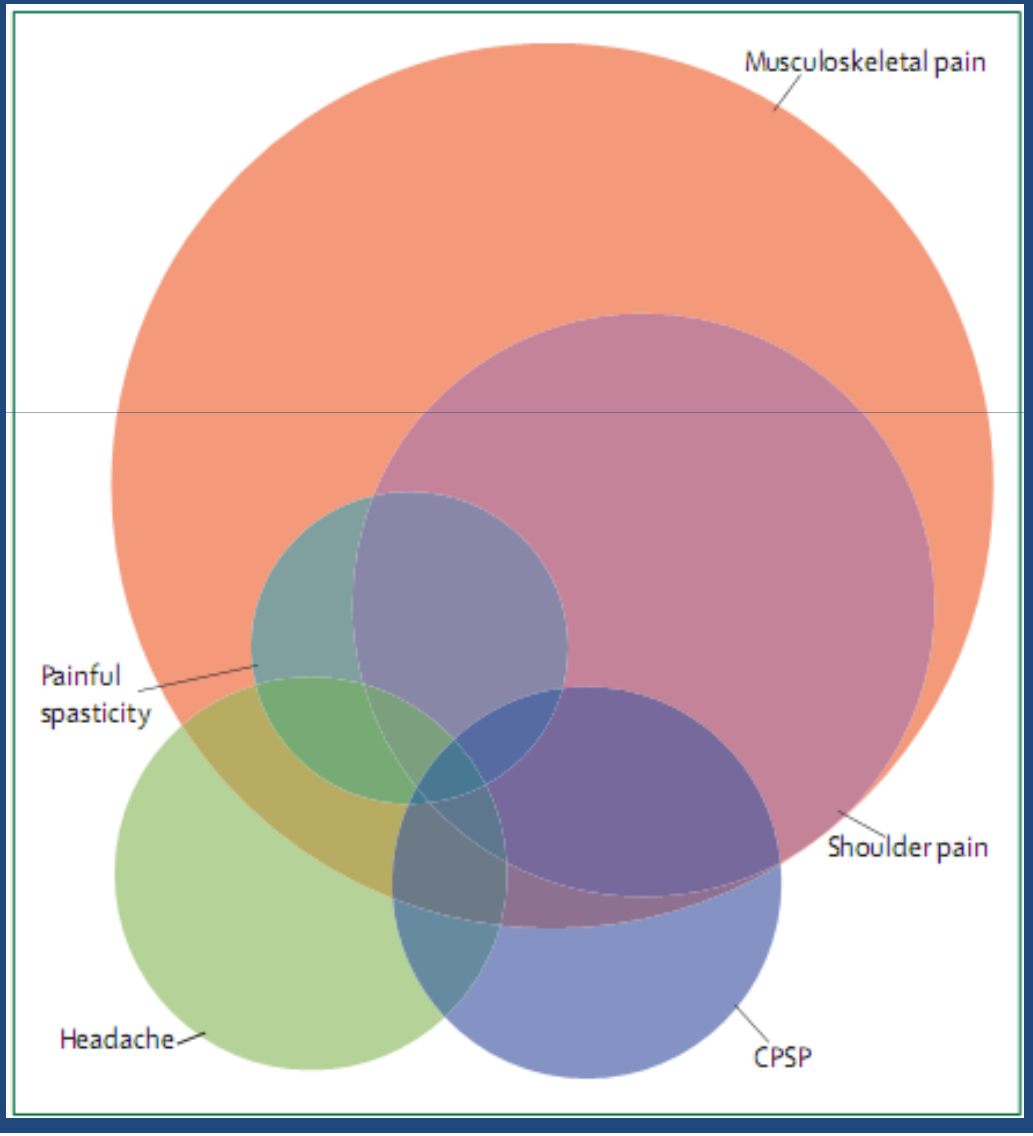
Andersen. Pain, 61 (1995) 187-193

Central post-stroke pain (CPSP)

- pain resulting from a primary lesion or dysfunction of the central nervous system after a stroke
- thalamic & extra-thalamic lesions

Kumar. Anesth Analg 2009;108:1645–57

Common types of chronic pain that can occur after stroke



Klit. Lancet Neurol 2009; 8: 857–68

Locations of stroke producing central poststroke pain

1 sensory cortex;

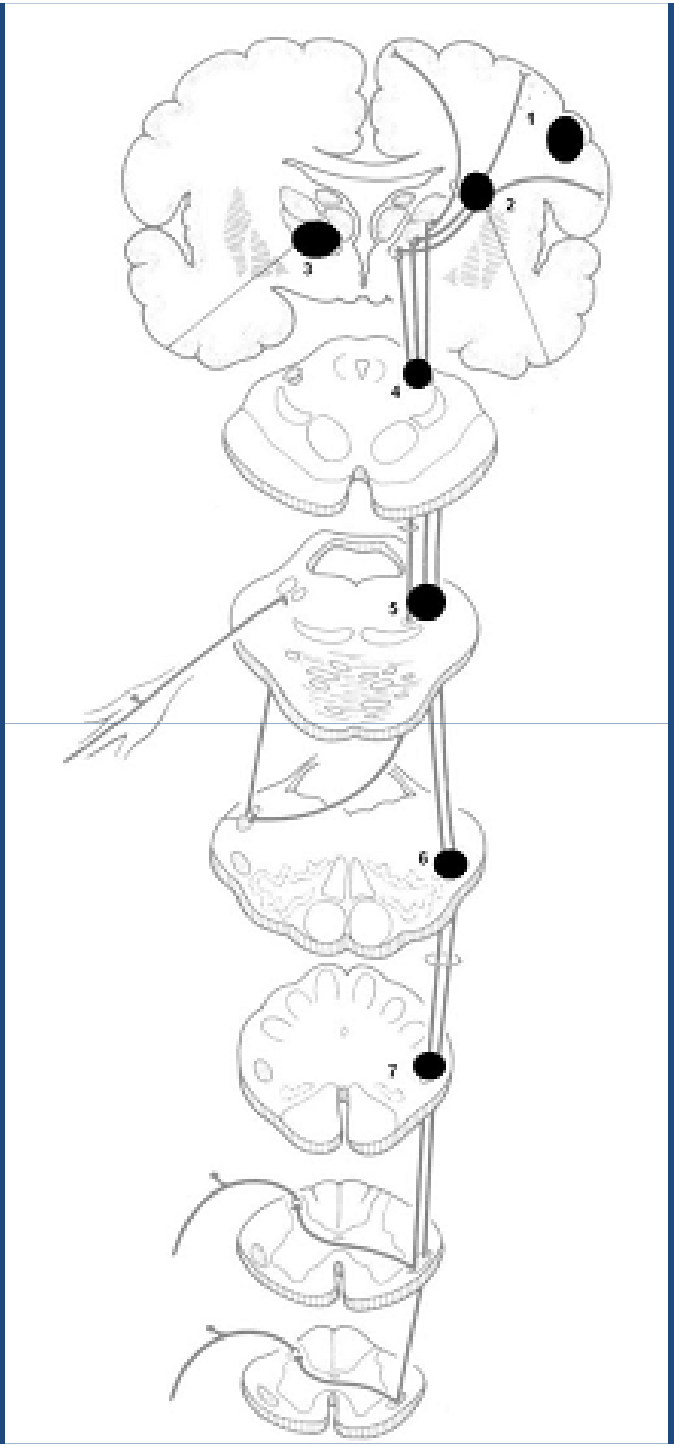
2 thalamocortical projection of spinothalamic sensations;

3 ventral posterolateral nucleus of thalamus;

4 mid-brain;

5 pons

6 and 7 medulla



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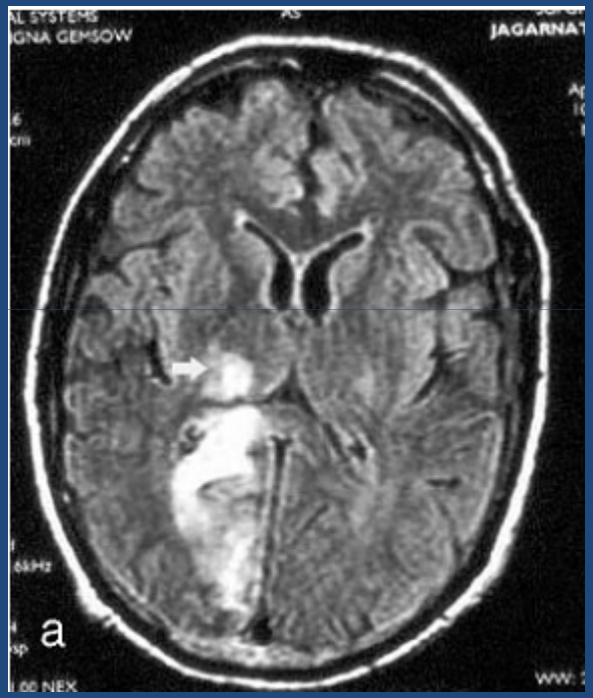
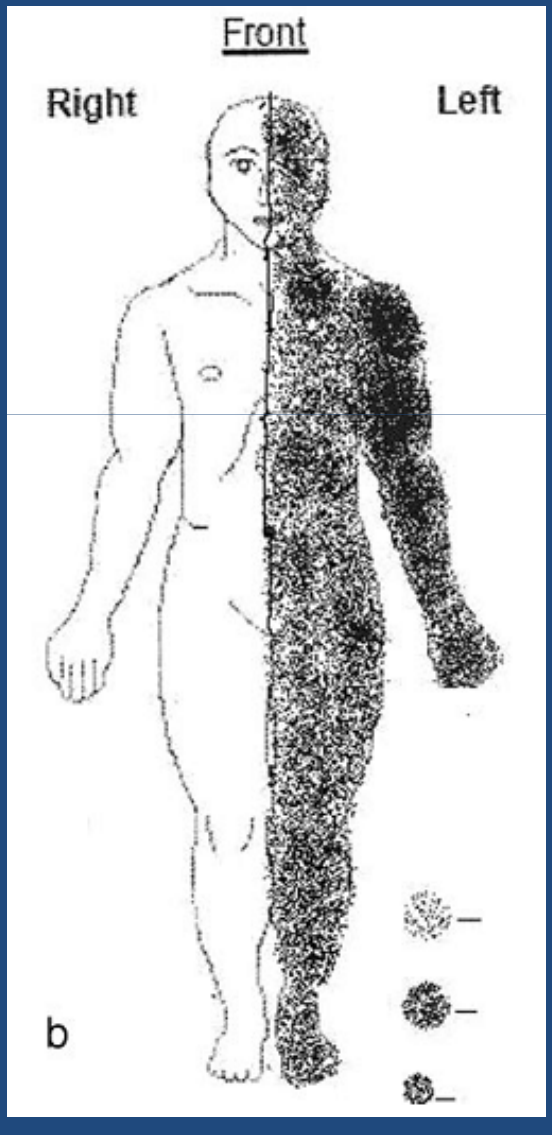
Stroke lesion and Central Poststroke pain localization





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Prevalence of CPSP (1)

- between 8% and 35%
- timing of the study
- variations in inclusion criteria,
- the definition of CPSP

Kumar. Anesth Analg 2009;108:1645–57

Prevalence of CPSP (2)

	Time since stroke	Number of patients	Prevalence of all types of pain	Prevalence of CPSP	Comments
Inpatient rehabilitation multicentre prospective study[21]	Not available	327	Musculoskeletal pain 32·4% (n=106)	4·3% (n=14)	..
Prospective study[22]	12 months	207	..	8% (n=16)	Verified by clinical examination
Stroke register[18]	12 months	253	11% (n=28)	..	..
Acute thalamic infarct verified by CT[8]	Mean 47·5 months (6 months to 9 years)	40	..	8% (n=3) in all patients with thalamic infarct	11% (3 of 27) in patients with sensory dysfunction 17% (3 of 18) in patients with inferolateral infarcts
Questionnaire sent to 1071 elderly individuals (>69 years)[23]	..	72 patients with stroke	..	11% (n=8)	Identified by questionnaire
Stroke unit[17]	3 months	244	55% (n=134)	..	..
Stroke register[16]	16 months	297	All pain 21% (n=62) Stroke-associated pain 8% (n=23)	1% (n=4)	Only patients suspected to have CPSP by interviewers were referred to a neurologist
Outpatient clinic, medullary infarcts: (LMI: n=41; MMI: n=14)[24]	Mean 21 months	55	..	LMI: body 83% (n=34), face 56% (n=23) MMI: body 71% (n=10), face 7% (n=1)	Residual sensory symptoms, not pain
Out-patient rehabilitation clinic[15]	More than 6 months	107	42% (n=45)	12% (n=13)	..
Prophylaxis study of amitriptyline *vs* placebo in patients with acute thalamic stroke[25]	12 months	39	..	18% (pooled; n=7)	Thalamic strokes only Placebo group 21% (4 of 19) Treatment group 17% (3 of 18)
Stroke registry[19]	12 months	140	All pain 49% (n=68) Stroke-associated pain 21% (n=29)	3% (n=4)	..
Patients with LMI identified retrospectively (n=4) and prospectively (n=9), stroke unit[26]	Mean 60 months (2–108 months)	63	..	25% (n=16)	LMI only All patients underwent clinical examination
Severely disabling stroke (Barthel index ≤10), identified by stroke registry and visited at home[20]	12 months	122	Shoulder pain 52% (n=64) Other pain 55% (n=67)	..	..
Postal questionnaire[27]	12 months	119	..	Presumed CPSP 9% (n=11)	CPSP confirmed by clinical examination in 5 of 6 presumed cases (4%)
Inpatient register[28]	24 months	288	15% (n=43)	5% (n=15)	Verified by clinical examination and quantitative sensory tests

..=not applicable. CPSP=central post-stroke pain. LMI=lateral medullary infarct (Wallenberg's syndrome). MMI=medial medullary infarct.

Table 1: **The prevalence of post-stroke pain and CPSP**

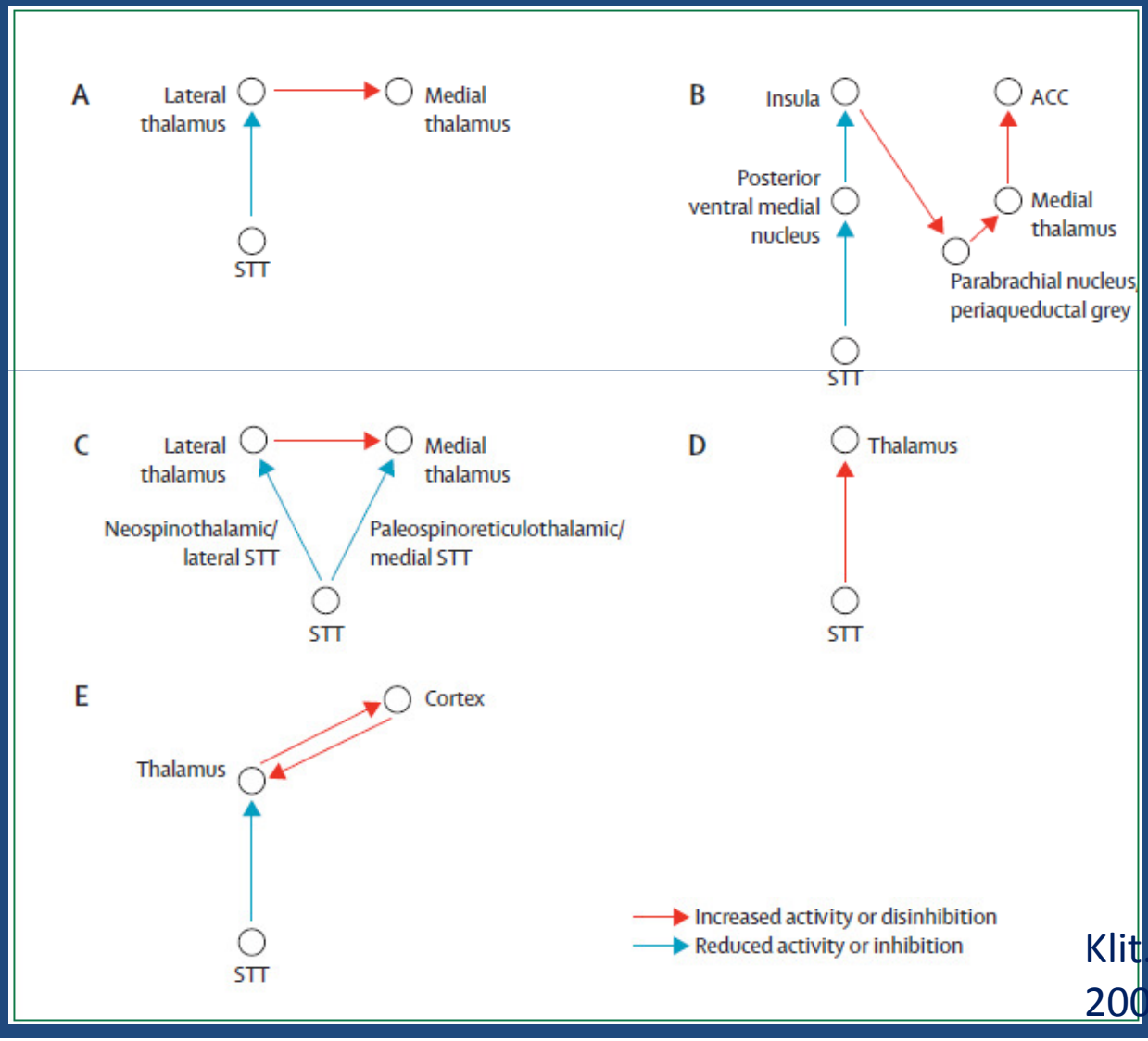
Klit. Lancet Neurol 2009; 8: 857–68

Pathophysiology

- Unclear
- Spinothalamiocortical sensory pathways
- The ventrocaudal (Vc) nuclei of the thalamus, particularly within the ventroposterior inferior (VPI) nucleus
- Subthreshold activation of nociceptive neurons, in which nociceptive neurons fire in response to a normally nonpainful stimulus

Nicholson. Neurology 2004; 62(Suppl 2): S30-36.

Some proposed mechanisms for central pain



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Panel 1: Definition of common pain terms

Pain
An "...unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[10]

Neuropathic pain
Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system[11]

Central neuropathic pain
Pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system[11]

Allodynia
Pain evoked by stimuli that is usually not painful (ie, touch or brush)

Hyperalgesia
An increased response to a stimulus that is normally painful[10]

Paraesthesia
An abnormal but non-painful (and not unpleasant) sensation, either spontaneous or evoked

Dysaesthesia
An abnormal unpleasant sensation, either spontaneous or evoked

Aftersensation
A sensory impression that persists after the stimulus has ceased

Central sensitisation
An "...increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[12]

Klit. Lancet Neurol 2009; 8: 857–68

Clinical features of central pain syndromes

- acronym "**MD HAS CP**"
- **M**uscle pains
- **D**ysesthesias
- **H**yperpathia
- **A**llodynia
- **S**hooting/lancinating pain
- **C**irculatory pain
- **P**eristaltic/visceral pain

Nicholson. Neurology 2004; 62(Suppl 2): S30-36.

Muscle pains

- described as cramping, band-like constriction, as well as crushing

Dysesthesias

- are the most common abnormal sensations in CPSP
- abnormal, unpleasant, and poorly localized
- Centrally evoked dysesthesias are characterized by delayed onset after stimulus (temporal or slow summation), most often resulting in a burning sensation.
- (dysesthesias associated with peripheral nerve injury have no delay in onset after a stimulus is applied)

Hyperpathia

- due to CNS disinhibition, involves a heightened response to noxious stimuli (evoked pain)
- Injury within the spinothalamic tract is believed to give rise to these pathologic sensory phenomena.
- A stimulus such as an EMG/NCV test may evoke intense pain for the patient with hyperpathia.

Allodynia

- is a classic hallmark that is present in more than 50% of patients with post-stroke pain
- interpretation of nonpainful stimuli (e.g., thermal, touch) as being painful or the sensation of pain in a location other than the area stimulated

Shooting/lancinating pain

- is intermittent pain with clear sensory discriminative characteristics
- A patient with this presentation has little difficulty in identifying the location of the pain, unlike the patient with dysesthesias.

Circulatory pain

- is described as pins and needles, stings, jabs, or walking on broken glass.
- This pain may be mistaken for peripheral neuropathy or for a result of poor circulation.

Peristaltic/visceral pain

- may be expressed as bloating, or fullness of the bladder, as well as burning pain with urinary urgency

Panel 3: Diagnostic criteria for CPSP

Mandatory criteria for the diagnosis of CPSP

- Pain within an area of the body corresponding to the lesion of the CNS
- History suggestive of a stroke and onset of pain at or after stroke onset
- Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion
- Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely

Supportive criteria

- No primary relation to movement, inflammation, or other local tissue damage
- Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply
- Allodynia or dysaesthesia to touch or cold

CPSP=central post-stroke pain.

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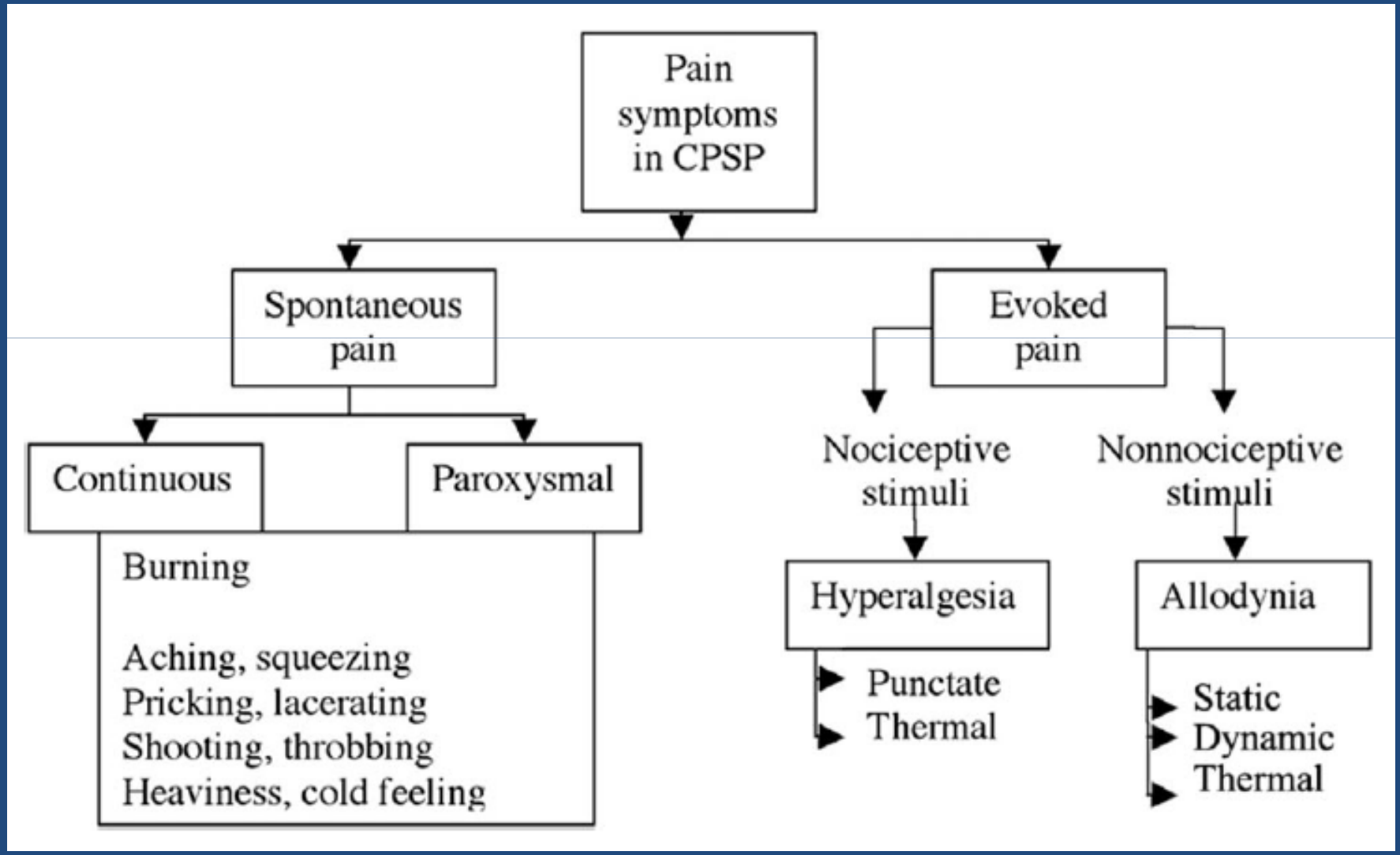
Pain symptoms in central poststroke pain (CPSP)



Kumar. Anesth Analg 2009;108:1645–57

Percentages of the Quality, Onset, and Durations of the Signs and Symptoms of Central Poststroke Pain (CPSP) (1)

Pain quality		Symptom onset		Location of stroke (%)	
Leijon et al.[33] 1989 (n = 27)					
Burning	59%	Immediate	15%	Thalamus	33.33%
Aching	30%	Within 1st month	37%	Brainstem	29.63%
Pricking	30%	1–3 mo	26%	Supratentorial	22.22%
Lacerating	26%	5–12 mo	11%	Not located	14.81%
Shooting	11%	24–34 mo	11%		
Squeezing	11%				
Throbbing	11%				
Other	19%				
Andersen et al.[12] 1995 (n = 207, CPSP = 16)					
Lacerating	50%	Within 1st month	63%	Thalamus	25%
Aching	25%	1–6 mo	19%	Extrathalamic	75%
Burning	19%	>6 mo	19%		
Freezing	19%				
Squeezing	19%				
Other	13%				
Widar et al.[13] 2002 (n = 43)					
Stabbing		Within 1st week	33%	Brainstem	11.62%
Aching		Within 1st month	20%	Thalamus	11.62
Dull aching		2–6 mo	47%	Supratentorial	62.79%
Burning				Not located	13.59%
Bowsher et al.[17] 1998 (n = 73)					
Burning	43.8%			Infratentorial	16.43%
Aching and throbbing and cramps	41%			Thalamic + capsular	36.98%
Electrical	10.9%			Supratentorial	28.76%
				Multiple	17.80%

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Percentages of the Quality, Onset, and Durations of the Signs and Symptoms of Central Poststroke Pain (CPSP) (2)

Pain quality		Symptom onset		Pain distribution	
MacGowan et al.[18] 1997 (n = 63, CPSP 16) Lateral medullary infarction					
Burning	87.5%	2 wk	18.6%	I/L cheek	31.25%
Add. electrical	37.5%	1 mo	51.36%	C/L arm leg	18.7%
Only electrical	12.5%	6 mo	All	C/L arm	12.5%
Cold	75%			I/L cheek, C/L arm leg	37.5%
Mechanical	27.5%				
Kim[72] 2003 (n = 20, Capsular hemorrhage)					
Cold	50%	Simultaneous	15%	Leg	45%
Numb	95%	Within 1 mo	25%	Foot	5%
Aching	20%	2–3 mo	45%	Leg, arm	20%
Swollen	95%	4–6 mo	10%	Leg, trunk	5%
Squeezing	10%	>6 mo	5%	Leg, arm, face	25%
Kim[19] 1999					

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Percentages of the Quality, Onset, and Durations of the Signs and Symptoms of Central Poststroke Pain (CPSP) (3)

Pain characters and percentage Lateral medullary syndrome (n = 41)		Pain characters and percentage Medial medullary syndrome (n = 1 4)	
Cold	17%	Numb	7.1%
Burning	7.3%	Numb, cold	28.5%
Burning, cold	12.2%	Cold, numb, pricky	7.1%
Burning, numb	7.3%	Squeezing, numb, heavy	14.2%
Squeezing	2.4%	Numb and heavy	14.2%
Burning, numb, cold	4.8%		
Burning, numb, pricky	2.4%		
Cold, numb	2.4%		
Cold, numb, pricky	2.4%		
Distributions			
Face	4.8%	Body limb	64.4%
Body limb	29.2%	Face (C/L), Body limb	14.2%
I/L face, body limb	34.1%		
C/L face, body and limb	12.2%		

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Treatment of central pain

- Antidepressants
- Anticonvulsants
- Antiarrhythmics
- Opioids
- N-methyl-D-aspartate (NMDA) antagonists
- Motor cortex stimulation

Hansson. European Journal of Neurology 2004; 11 (Suppl. 1): 22–30.

Drugs Studied in Central Poststroke Pain and Their Mechanism of Action

Drugs	Mechanism
Antidepressants Amitriptyline	Balanced monoamine reuptake inhibition
Anticonvulsants	
Phenytoin	Voltage-gated sodium-channel blockade
Carbamazepine	Voltage-gated sodium-channel blockade
Lamotrigine	Presynaptic voltage-gated sodium-channel inhibition thus reduced release of presynaptic transmitters
Topiramate	Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainase receptors
Gabapentine	Binding to $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Zonisamide	Voltage-gated sodium-channel block
Anesthetics	
Lidocain	Blockade of sodium channels thus preventing ectopic discharges
Mexiletine	Same as lidocain
NMDA receptor antagonist	
Ketamine	NMDA receptor antagonist
Analgesics	
Tramadol	μ opioid-receptor agonist and monoamine
Morphine	Reuptake inhibitor

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Oral Drugs Reported to be Effective in the Treatment of CPSP

TABLE 1. Oral Drugs Reported to be Effective in the Treatment of CPSP

Drug	Reference	No. of Patients Total/CP/(CPSP)	Study Design	Study Level	Dosing Regimen	Outcome Measures	Results	Comments
Amitriptyline	Leijon and Boivie[21]	15/15/15	Double-blind, placebo-controlled, 3-phase, double-dummy, crossover, 4 weeks treatment, 1 week washout amitriptyline vs carbamazepine vs placebo	A	Amitriptyline d 1:25 mg d 2–5: 50 mg d 6–28: 75 mg	1. At least 20% pain-reduction on a 10-step verbal daily pain rating scale d 22–28 2. Patient global rating on d 28	1. Sig better than placebo at weeks 2–4 2. Global rating improved 10/15 vs 1/15 on placebo	Positive effect correlated with a plasma level > 300 nmol/l, not caused by an antidepressive effect
Lamotrigine	Vestergaard et al[50]	30/30/30	Double-blind, placebo-controlled, crossover, vs placebo, 8 weeks treatment, 2 weeks washout	A	Lamotrigine w 1+2: 25 mg w 3+4: 50 mg w 5+6: 100 mg w 7+8: 200 mg	At least reduction > 2 of ongoing pain 0–10 on a Likert scale	12 responders to lamotrigine, 3 to placebo, mean pain score 5 on 200 mg lamotrigine vs 7 on placebo	Also sig reduction of cold induced allodynia, 3 patients withdrawn because of adverse events during lamotrigine treatment
Levorphanol	Rowbotham et al[73]	81/23/5	Double-blind, randomized	A	Low dose (0.15 mg) against high dose (0.75 mg) up to 21 capsules/day	VAS 1–100	36% reduction in high dose and 21% reduction in the low dose	Effect most apparent in peripheral pain, almost no effect in CPSP
Mexiletine	Awerbuch and Sandyk[33]	9/9/8	Open label study	B	d1–3: 150 mg d 4–6: 300 mg following 4 weeks: l0 mg/kg	5-point scale: 1 = no relief 5 = complete relief	At least moderate relief in 8/9 patients	Negative long-term results in a post-study follow-up after lidocaine IV (Attal et al[37])
Phenytoin	Agnew and Goldberg[32]	10/8/8	Open label study	B	Dose increased until side effects occurred	Brief series of charts for pain estimation	3/8 patients with CPSP improved markedly, 2 minimally, 3 worsened	No exact data given about treatment dose, duration, and outcome measures
Fluvoxamine	Shimodozono et al[27]	31/31/31	Open label study	B	Individual dose between 25 and 125 mg	VAS 1–10	Significant decrease from 7.7 to 6.0	Significant result only when stroke was less than 1 year ago
Gabapentin	Attal et al[67]	18/7/2	Open label study	B	d1–3: 600 mg increase every 3 days up to a maximum of 2400 mg, total duration 6 weeks	1. Spontaneous ongoing pain VAS 1–100 2. Paroxysmal pain, number of daily attacks	1. At week 6 sig decline of spont. ongoing pain 2. At week 6 sig reduction of daily painful attacks	No separate data on CPSP patients also sig reduction of brash-induced and cold allodynia
Zonisamide	Takahashi et al[59]	2/2/2	Case series	C	—	—	Two patients with thalamic infarction improved	—

A, randomized placebo-controlled trial; B, uncontrolled trial; C, case series; IV, intravenously; d, day; w, week; vs, versus; sig, significant.

Frese. Clin J Pain 2006;22:252–260

Intrathecal Drugs Reported to be Effective in the Treatment of CPSP

TABLE 2. Intrathecal Drugs Reported to be Effective in the Treatment of CPSP

Drug	Reference	No. of Patients Total/CP/ CPSP	Study Design	Study Level	Dosing Regimen	Outcome Measures	Results	Comments
Baclofen	Taira et al[57]	14/14/8	Open label study	B	Bolus 50–150 µg	10-grade pain score 0 = no pain, 10 = pretreatment pain level	9/14 patients (6/8 CPSP) with best pain score < 5/10	Effect lasting approx. 12–24 h, but no exact data given, also relief of allodynia and hyperalgia, if present

B, uncontrolled trial; IV, intravenously.

Frese. Clin J Pain 2006;22:252–260

Intravenous Drags Reported to be Effective in the Treatment of CPSP

TABLE 3. Intravenous Drags Reported to be Effective in the Treatment of CPSP

Drug	Reference	No. of Patients Total/CP/CPSP	Study Design	Study Level	Dosing Regimen	Outcome Measures	Results	Comments
Lidocaine	Attal et al[75]	16/16/6	Double-blind, placebo-controlled, crossover	A	5 mg/kg IV over 30 minutes	1. Spontaneous pain, VAS 1–100 2. Global assessment of pain relief	1. Sig greater relief of pain for up to 45 min with lidocaine 2. 11/16 > 50% pain relief with lidocaine vs 6/16 with placebo	Also sig reduction of brush-induced allodynia and mechanical hyperalgesia
Propofol	Canavero et al[54]	32/16/7	Double-blind, placebo-controlled, crossover	A	Single IV bolus of 0.2 mg/kg responders: 0.3 mg/kg per h for 6–24 h	VAS 1–10 every 5 min for 30 min	Reduction by > 3 VAS points in 5/7 CPSP patients, 14/16 CP patients vs 0/16 with placebo	In responders allodynia abolished, pain control with prolonged infusion for 6–24 h in 7 patients
Ketamine	Backonja et al[43]	6/3/2	Double-blind, placebo-controlled, crossover	A	250 µg/kg IV over 5 min	Pain rating scale 0–10	Pain relief > 50% in 2/3 patients with CP (both with CPSP) lasting 2–3 hours vs 0/3 with placebo	Continous subcutaneous infusion only in 1 patient with neuropathic pain, discontinued because of side-effects
	Yamamoto et al[20]	23/23/23	Uncontrolled trial d1 morphine d2 thiamylal d3 ketamine	B	5 mg every 5 min, total dose 25 mg	VAS 1–10	Pain relief > 40% in 11/23 patients, 2/23 pain increase, duration < 60 min	No long-term application
Thiamylal	Yamamoto et al[20]	39/39/39	Uncontrolled trial, d1 morphine, d2 thiamylal, d3 ketamine	B	50 mg every 5 min, total dose 250 mg	VAS 1–10	Pain relief > 40% in 22/39 patients, duration > 60 min	No long-term application
Morphine	Yamamoto et al[20]	39/39/39	Uncontrolled trial, d1 morphine, d2 thiamylal, d3 ketamine	B	3 mg every 5 min, total dose 18 mg	VAS 1–10	Pain relief > 40% in 8/39 patients, duration > 60 min	No long-term application
	Attal et al[70]	15/15/6	Placebo-controlled, crossover	A	1. Mean dosage 16 mg IV 2. Mean dosage 93 mg oral	VAS 1–100	1. No sig difference in pain reduction 2. 4 of 14 with long-term efficacy of oral morphine	Sig influence of morphine on allodynia and thermal threshold

A, randomized placebo-controlled trial; B, uncontrolled trial; IV, intravenously; d, day; vs, versus; sig, significant.

Frese. Clin J Pain 2006;22:252–260

TABLE 4. Treatment Recommendation for CPSP Based on Evidence Level

Short term pain control:
- Lidocaine IV 5 mg/kg over 5 minutes
- Propofol IV 0.3 mg/kg per hour

Oral treatment:

Drugs of first choice (based on controlled trials):
- Amitriptyline at least 75 mg per day
- Lamotrigine at least 200 mg per day

Drugs of second choice (based on open studies and experts' opinion):
- Mexiletine up to 10 mg/kg per day
- Fluvoxamin up to 125 mg per day (when stroke is less than one year)
- Gabapentin at least 1200 mg per day

Frese. Clin J Pain 2006;22:252–260

Important Studies on Pharmacological Treatment of Central Poststroke Pain (CPSP)

Kumar. Anesth Analg 2009;108:1645–57

Author	Class	Level	No. of pts	Drugs, dose, duration	Efficacy	Adverse effects
Vestergard et al.[38] 2001	I	B	30	Lamotrigine 25 mg/d increased to 200 mg/day or placebo × 8 wk, followed by 2 wk wash out then crossed over	Median pain score at last week of treatment ↓ to 5 in lamotrigine 200 mg/d and to 7 in placebo ($P = 0.01$)	Lamotrigine 57% vs Placebo 60%. 5 patients developed rash in lamotrigine vs 2 patients in placebo. 3 patients withdrawn from lamotrigine due to rash, headache and pain
Serpell et al.[39] 2002	I for pain III for CPSP	—	Pain ($n = 307$) CPSP (9/307)	Gabapentin: 900 mg/d increased to 1800 or 2400 mg mg/day × 8 wk, gabapentin ($n = 153$), Placebo ($n = 152$)	Improvement in pain score, gabapentin (21%) vs placebo (14%), $P = 0.48$	Dizziness (24% vs 8%) and somnolence (14% vs 5%) Were common in gabapentin compare with placebo
Leijon, Boivie.[33] 1989	II	B	($n = 15$)	Carbamazepine upto 800 mg/d or placebo × 4 wk then 1 wk washout period followed cross over	Carbamazepine better than placebo in relieving pain at 3 wk ($P < 0.05$) over the course of but not at other time points	CBZ resulted vertigo, tiredness, dry mouth, GI disturbance resulting in dose reduction in 4 patients
Leijon et al.[33] 1989	II	B	15	CBZ 800 mg/d vs amitriptyline 75 mg/d or placebo × 4 wk then wash out 1 wk followed by crossover	Pain relief was significantly better in amitriptyline than placebo at 2 wk ($P < 0.01$), 3 wk ($P < 0.05$), and 4 wk ($P < 0.05$)	Tiredness, dry month
Attal et al.[50] 2000	II	B	Central pain (16) CPSP (6/16)	Lidocain 5 mg/kg over 30 min vs saline; after 3 wk oral mexiletine 200 mg/d ↑ to 800 mg/d × 4–12 wk in 12 patients	Moderate to complete pain relief in 69% in lidocain vs 38% in placebo. Oral mexiletine not effective	11 patients in lidocain had side effect (1 withdrawn), vs 5 in placebo. Major side effect light headedness
Bainton et al.[47] 1992	II	B	20	Naloxone 8 mg IV vs normal saline then crossover	Pain relief in naloxone 27.2% vs placebo 44% (nonsignificant) group	Sweating, tremor, salivation, increased, abdominal pain in naloxone group
Attal et al.[46] 2002	II	B	15 pts, CPSP-6	IV morphine mean 16 mg (9–13 mg) vs saline infusion over 30 min. Switched over to oral morphine	Pain relief 46% in morphine 13.6% in placebo group (insignificant)	Higher side effects in morphine 60% vs 40%); somnolence, nausea and vomiting

Lamotrigine

- Class I level B
- 30 pts
- 25 mg/d increased to 200 mg/day or placebo 8 wk, followed by 2 wk wash out then crossed over
- Median pain score at last week of treatment ↓ to 5 in lamotrigine 200 mg/d and to 7 in placebo (*P 0.01)*
- Lamotrigine 57% vs Placebo 60%. 5 patients developed rash in lamotrigine vs 2 patients in placebo. 3 patients withdrawn from lamotrigine due to rash, headache and pain

Vestergard . Neurol 2001

Gabapentin

- Class III
- 9 pts
- 900 mg/d increased to 1800 or 2400 mg/day 8 wk
- Improvement in pain score, gabapentin (21%) vs placebo (14%), *P 0.48*
- Dizziness (24% vs 8%) and somnolence (14% vs 5%) were common in gabapentin compare with placebo

Serpell. Pain. 2002

Carbamazepine (1)

- Class II Level B
- 15 pts
- Carbamazepine upto 800 mg/d or placebo 4 wk then 1 wk washout period followed cross over
- Carbamazepine better than placebo in relieving pain at 3 wk (*P 0.05) over the* course of but not at other time points
- CBZ resulted vertigo, tiredness, dry mouth, GI disturbance resulting in dose reduction in 4 patients

Leijon, Boivie. Pain 1989

Carbamazepine (2)

- CBZ 800 mg/d vs amitriptyline 75 mg/d or placebo 4 wk then wash out 1 wk followed by crossover
- Pain relief was significantly better in amitriptyline than placebo at 2 wk ($P < 0.01$), 3 wk ($P < 0.05$), and 4 wk ($P < 0.05$)
- Tiredness, dry month

Leijon, Boivie. Pain 1989

Lidocaine

- Class II Level B
- 16 pts
- 5 mg/kg over 30 min vs saline; after 3 wk oral mexiletine 200 mg/d 1 to 800 mg/d 4–12 wk in 12 patients
- Moderate to complete pain relief in 69% in lidocain vs 38% in placebo. Oral mexiletine not effective
- 11 patients in lidocain had side effect (1 withdrawn), vs 5 in placebo. Major side effect light headedness

Attal. Neurol 2000

Naloxone

- Class II Level B
- 6 pts
- 8 mg IV vs normal saline then crossover
- Pain relief in naloxone 27.2% vs placebo 44% (nonsignificant) group
- Sweating, tremor, salivation, increased abdominal pain in naloxone group

Bainton. Pain 1992

Morphine

- Class II Level B
- 6 pts
- IV morphine mean 16 mg (9–13 mg) vs saline infusion over 30 min. Switched over to oral morphine
- Pain relief 46% in morphine 13.6% in placebo group (insignificant)
- Higher side effects in morphine 60% vs 40%); somnolence, nausea and vomiting

Attal. Neurol 2002

Important Studies on Invasive Motor Cortex Stimulation in Central Poststroke Pain (CPSP)

Author	Class	No. of patients	Response	Adverse effect
Tsubokawa et al.[56] 1993	III	11	Pain improved in 73% at 1 wk; 45% at 2 yr	Not available
Hosobuchi[73] 1993	III	6	Short-term complete relief 2–3 mo 4 excellent 1:30%	Not significant
Yamamoto et al.[44] 1997	III	28	>12 mo follow up: 36/26 had pain relief	Not significant
Katayama et al.[62] 1998	III	31	Short-term 74% excellent to good response Long-term: good relief in 13/18 (72.2%) without weakness and 2/13 (15.4%) with weakness	Not significant
Nguyen et al.[74] 1999	III	32 (13 CPSP)	Short-term: pain relief in 10; same relief up to 27.3 mo	Not significant
Mertens et al.[75] 1999	III	23 (16 CPSP)	At mean 23 mo follow up pain relief was excellent 25% Good 35% Fair 15%	Method failure 25%
Nuti et al.[76]2005	III	31 (22 CPSP)	Long-term pain relief was excellent 10% Good 42% Poor 35% Negligible 13% Reduced analgesic intake 52% Withdrawal analgesic in 42% Subjective improvement 72%	Not significant

Kumar. Anesth Analg 2009;108:1645–57

Deep Brain Stimulation (DBS)

Table 4 Overall long term rates of success and failure with respect to the two categories of pain; nociceptive and deafferentation

	Success	Failure	Total
Nociceptive	129 (63%)	75 (37%)	204
Deafferentation	103 (47%)	117 (53%)	220

Table 5 Overall long term rates of success and failure with respect to the two sub-categories of deafferentation pain; central and peripheral

	Success	Failure	Total
Central	14 (31%)	31 (69%)	45
Peripheral	89 (51%)	86 (49%)	175

Bittar. Journal of Clinical Neuroscience (2005) 12(5), 515–519

Repetitive Transcranial Magnetic Stimulation (rTMS) (1)

- the pain level was scored on a visual analogue scale before and after a 20 minute session of "real" or "sham" 10 Hz rTMS over the side of the motor cortex corresponding to the hand on the painful side

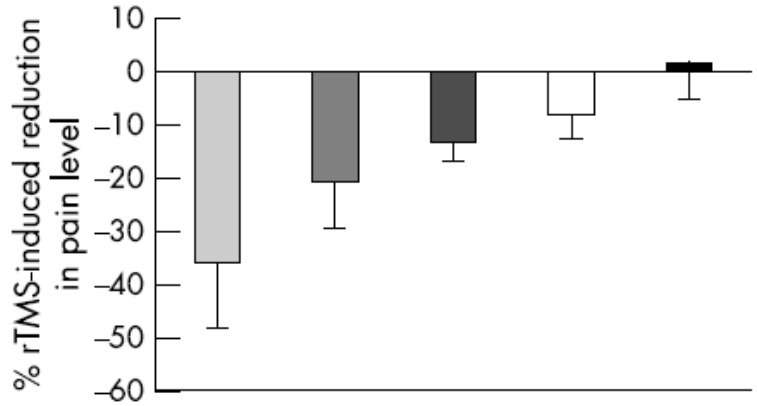

Figure 1 Mean (SEM) % pain reduction on a visual analogue scale induced by a single session of repetitive transcranial magnetic stimulation of the motor cortex (values calculated by subtracting the results obtained using a sham coil from those obtained using a real coil), depending on the type of lesion at the origin of pain. From left: trigeminal nerve lesion, thalamic stroke, brachial plexus lesion, spinal cord lesion, brainstem stroke. Kruskal-Wallis test, $p=0.039$.

Lefaucheur. J Neurol Neurosurg Psychiatry 2004;75:612–616

Repetitive Transcranial Magnetic Stimulation (rTMS) (2)

- 24 pts with post-stroke pain syndrome (PSP)
- 14 received 10 minutes real rTMS over the hand area of motor cortex (20 Hz, 10610 s trains, intensity 80% of motor threshold) every day for five consecutive days v.s. 10 pts with sham stimulation

Table 2 Individual effect on visual analogue scale (VAS) ratings of repetitive transcranial magnetic stimulation (rTMS) immediately after the last session and at two weeks' follow up. Values are n (%)

	After the fifth session			Two weeks after the last session		
Subgroup	Poor	Satisfactory	Good	Poor	Satisfactory	Good
TGN real	4 (28.6)	7 (50)	3 (21.4)	6 (42.9)	5 (35.7)	3 (21.4)
TGN sham	6 (60)	4 (40)	0 (0)	8 (80)	2 (20)	0 (0)
PSP real	3 (21.4)	10 (71.4)	1 (7.2)	5 (35.7)	7 (50)	2 (14.3)
PSP sham	9 (90)	1(10)	0 (0)	10 (100)	0 (0)	0 (0)

PSP, post-stroke pain; TGN, trigeminal neuralgia.

Khedr. J Neurol Neurosurg Psychiatry 2005;76:833–838

Vestibular Caloric Stimulation

- Vestibular caloric stimulation activates the posterior insula which, in turn, inhibits the generation of pain in the anterior cingulate gyrus.
- 9 patients with CPSP
- cold caloric vestibular stimulation v.s placebo
- reduction of pain by 2.58 points on a 10 point scale v.s 0.54 in the placebo group

Mc Geoch. J Neurol Neurosurg Psychiatry 2008;79:1298–301

Take Home Message

- Be alert to what the patients tell us because CPSP might not occur immediately after the stroke onset.
- In most cases of CPCS, the stroke lesions are extrathalamic.
- Amitriptyline would be the drug of choice.
- If amitriptyline fails or is unavailable, then try lamotrigine.
- In intractable cases, short-term pain relief may be achieved by IV lidocaine, propofol, or pentothal.
- DBS and rTMS may be tried in pharmacoresistant CPSP patients.

Thank you for your attention!

Table 1. Evidence Classification Scheme for Therapeutic Interventions

Class 1:

An adequately powered randomized controlled trial with measured outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled trials (RCTs) with masked outcome assessment in representative populations. The following are required:

(a) Randomization concealment.
(b) Primary outcome (s) are clearly defined.
(c) Exclusion/inclusion criteria are clearly defined.
(d) Accurate accounting for dropout and crossovers with numbers sufficiently low to have minimal potential for bias
(e) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate adjustment for differences.

Class II:

Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-c, above or RCT in a representative population that lacks one criteria.

Class III:

All other controlled trials (including well defined natural history controls or patients serves as own controls) in a representative population where outcome assessment is independent of patient treatment.

Class IV:

Evidence from uncontrolled studies, case series or case report or expert opinion.

Rating of recommendation:

Level A: Established as effective, ineffective or harmful; requires at least one class I study or 2 consistent convincing class II studies.

Level B: Probably requires at least 1 convincing class II in overwhelming class III evidence.

Level C: Probably requires at least 2 class III studies.

Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces–revised recommendations 2004. Eur J Neurol 2004;11:577–81.

Epidemiology

- 8% of stroke patients
- the pain is moderate to severe in 5% of patients
- The onset of central pain following a stroke occurs more than 1 month after the stroke in 40% ~ 60% of all patients.
- the median age of CPSP was 57, suggesting that there may be a significant age difference between CPSP patients and the general stroke population (median age 75)→ equivocal

Nicholson. Neurology 2004; 62(Suppl 2): S30-36.

Prevalence of CPSP (2)

- 267 patients who had ischemic and hemorrhagic strokes
- CPSP was found in 16 (8%) patients .
- Pain onset was within 1 month after stroke in 10 (63%) patients,
- between 1 and 6 months in 3 (19%) patients and
- more than 6 months after stroke in 3 (19%) patients

Andersen. Pain, 61 (1995) 187-193

Prevalence of CPSP (3)

- 297 patients who had ischemic and hemorrhagic strokes
- moderate to severe pain in 32% of patients after 4 month
- 21% after 16 month
- At 16 mo, the higher pain intensity correlated with female sex, worse Geriatric Depression Scale score, better Mini Mental State Examination score, and increased glycosylated hemoglobin.

Jonsson. J Neurol Neurosurg Psychiatry 2006;77:590–5

Class I randomised, double-blind, placebo-controlled trials in CPSP

	Dosage (per day)	Outcome	Number of patients	Number of withdrawals	Number needed to treat	Design
Oral and transdermal						
Oral amitriptyline[104]	75 mg	Positive	15 (CPSP)	0	1·7	Three-phase, cross-over
Oral carbamazepine[104]	800 mg	Negative	14 (CPSP)	0	..	Three-phase, cross-over
Oral lamotrigine[105]	200 mg	Positive	30 (CPSP)	10	NA	Cross-over
Oral pregabalin[106]	300–600 mg	Positive	40 (mixed CP: 19 CPSP, 21 SCI)	7	4·0	Parallel, flexible-dose
Transdermal ketamine[107]	50–75 mg	Negative	33 (mixed CP: 15? CPSP)	0	NA	Parallel, three-arm
Intravenous trials						
Morphine[108]	9–30 mg	Negative	15 (mixed CP: 6 CPSP, 9 SCI)	1	NA	Cross-over
Lidocaine[109]	5 mg/kg	Positive	16 (mixed CP: 6 CPSP, 10 SCI)	0	NA	Cross-over
Propofol[110]	0·2 mg/kg	Positive	44 (mixed CP: 22 CPSP)	0	NA	Cross-over
Naloxone[111]	8 mg	Negative	20 (CPSP)	2	NA	Cross-over

..=not applicable. CP=central neuropathic pain. CPSP=central post-stroke pain. NA=not available. SCI=spinal cord injury.

Table 2: **Class I randomised, double-blind, placebo-controlled trials in CPSP**

Klit. Lancet Neurol 2009; 8: 857–68