



Current state of the art in therapy of neuropathic spinal cord injury pain

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Disclosures



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- Grünenthal
- Novartis Pharma
- Teva Pharmaceuticals
- Astellas
- Mitsubishi Pharma

Agenda



- Classification of SCI pain
- Mechanisms of SCI neuropathic pain
- Evidence-based treatment

Danish Pain Research Center



SCI rehabilitation centers



Neuropathic pain

SCI pain

Central poststroke pain

Chemotherapy-induced painful polyneuropathy

Diabetic painful polyneuropathy

Chronic postsurgical neuropathic pain

Pain physiology and thermal sensory integration

Pharmacological treatment

Swiss Spinal Cord Injury Cohort study

- Community-based survey in Switzerland (traumatic and non-traumatic SCI)
- “What causes you the most problems since your spinal cord injury?”
- The International Classification of Functioning, Disability and Health (ICF).

- 3,144 eligible subjects
- 1,762 respondents to the open-ended question
- 256 (14.5%) reported 1 problem, 1,506 (85.5%) reported 2 to 4 problems.

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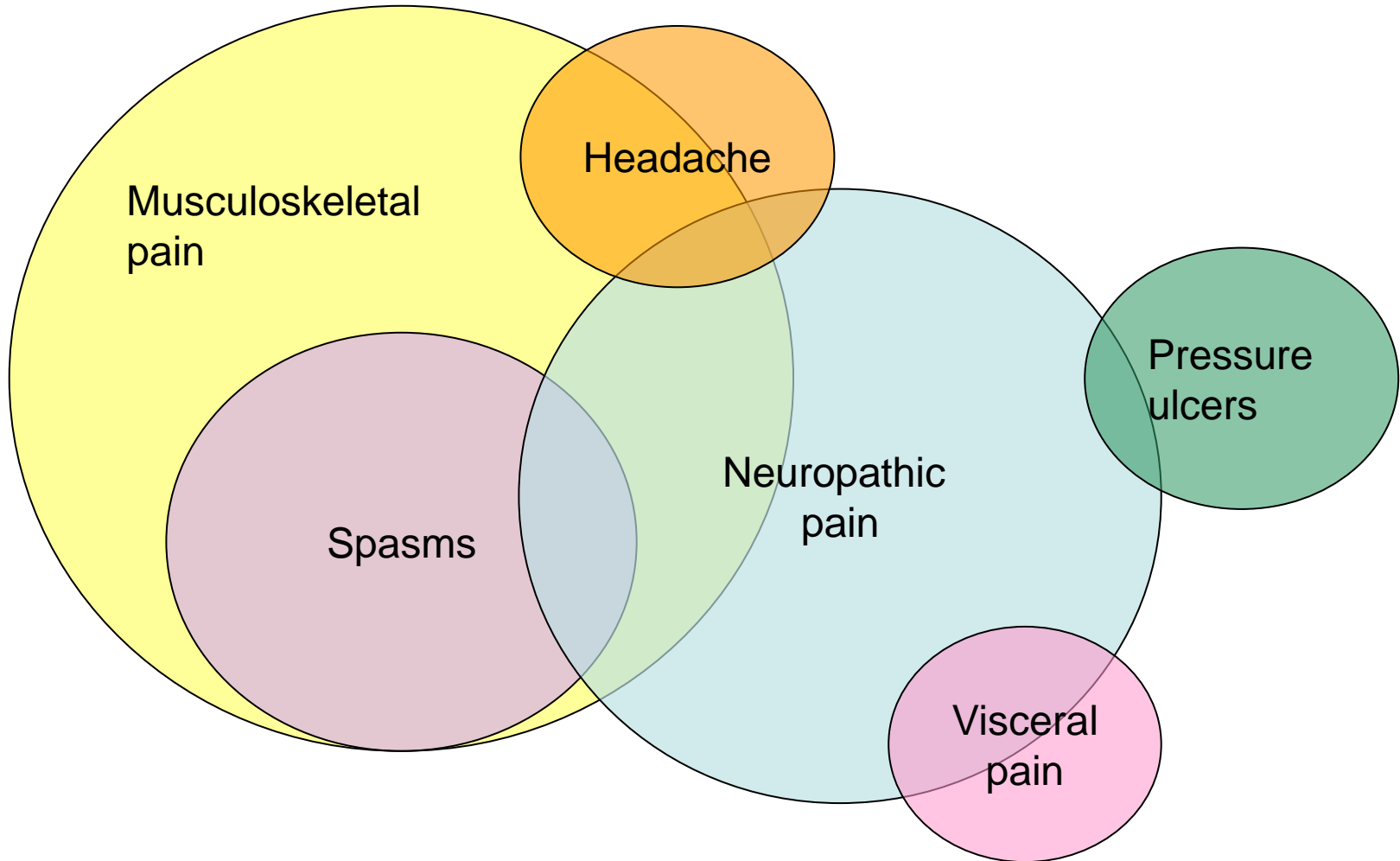
| ICF Category | Problem, n | Percentage |
|----------------------|------------|------------|
| Sensation of pain | 438 | 25% |
| Urination functions | 379 | 22% |
| Toileting | 364 | 21% |
| Defecation functions | 350 | 20% |
| Walking | 168 | 10% |

The International Spinal Cord Injury Pain (ISCIP) Classification

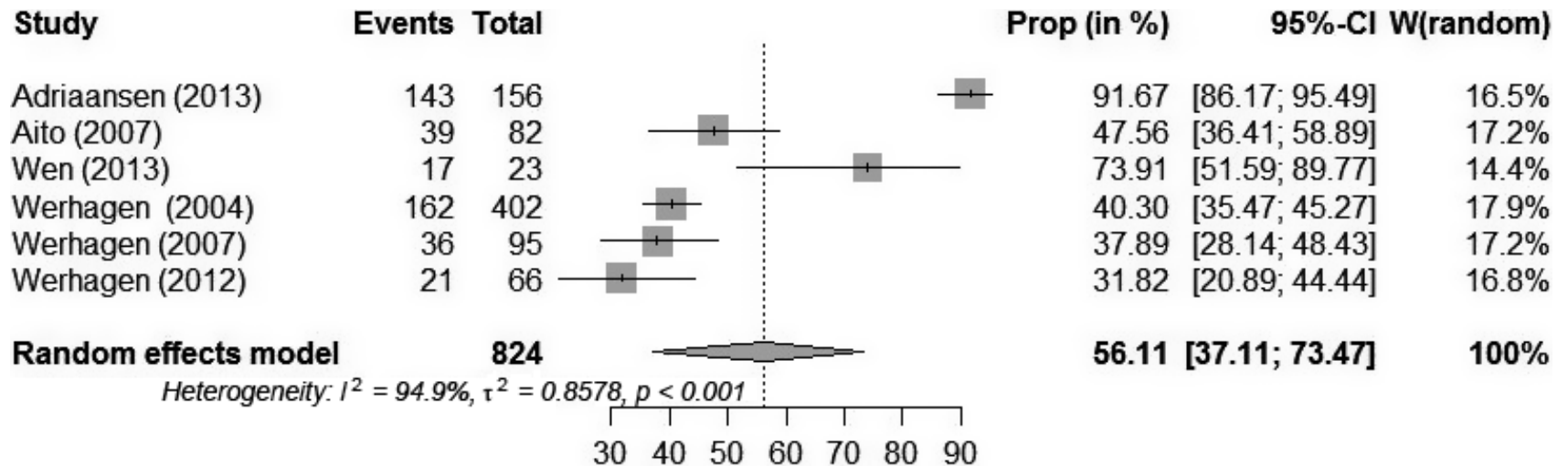
| Tier 1: Pain type | Tier 2: Pain subtype |
|---|---|
| <p>Nociceptive pain</p> <p>(Pain arising from activation of nociceptors, Loeser and Treede Pain 2008)</p> | <p>Musculoskeletal</p> <p>Visceral</p> <p>Other nociceptive</p> |
| <p>Neuropathic pain</p> <p>(Pain arising as a lesion or disease of the somatosensory system, Jensen et al. Pain 2011)</p> | <p>At-level SCI pain</p> <p>Below-level SCI pain</p> <p>Other</p> |
| <p>Other pain</p> | |
| <p>Unknown pain</p> | |



Chronic pain in SCI



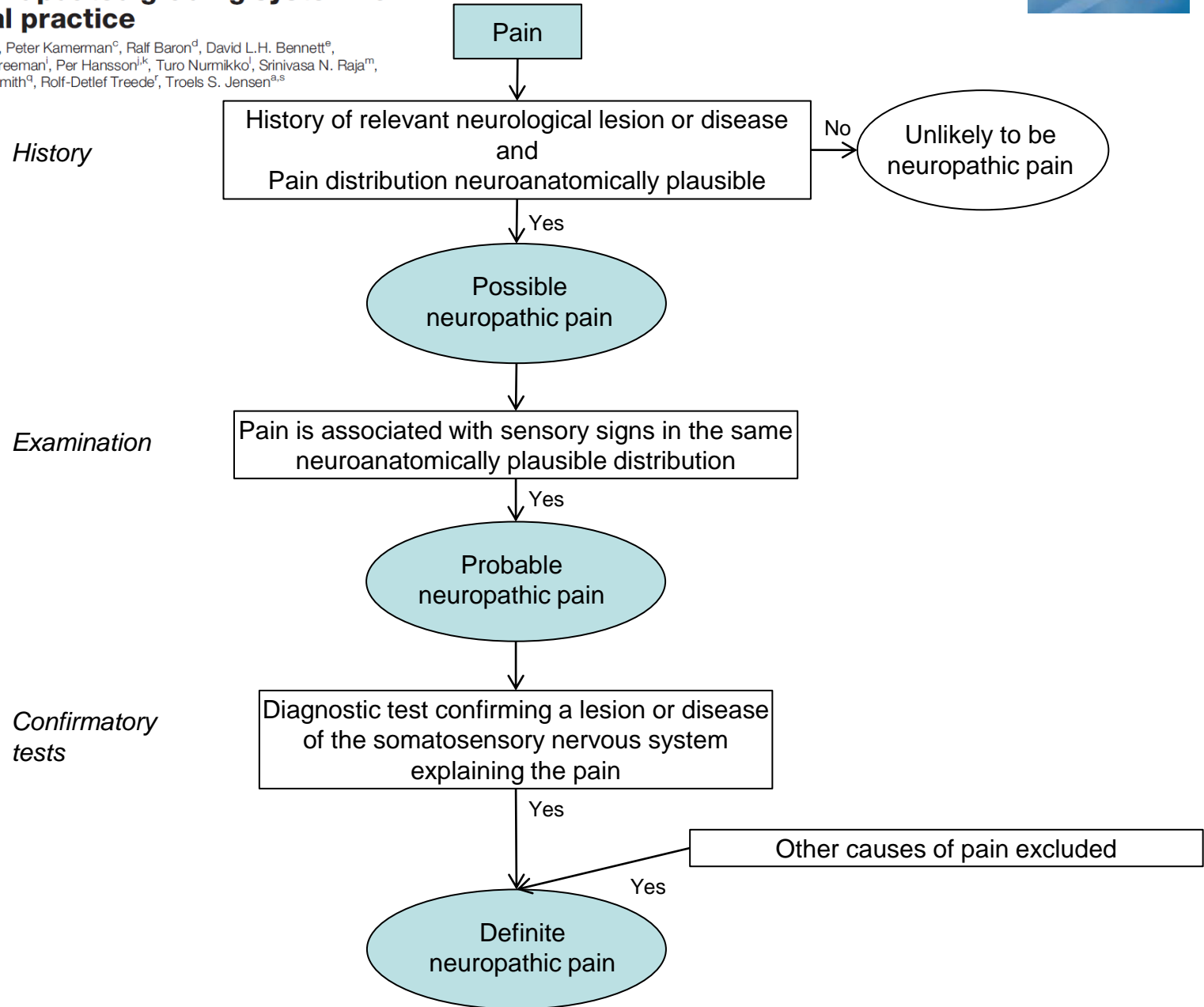
Neuropathic pain prevalence in chronic SCI (>6 months)





Neuropathic pain: an updated grading system for research and clinical practice

Nanna B. Finnerup^{a,*}, Simon Haroutounian^b, Peter Kamerman^c, Ralf Baron^d, David L.H. Bennett^e,
Didier Bouhassira^{f,g}, Giorgio Cruccu^h, Roy Freemanⁱ, Per Hansson^{j,k}, Turo Nurmikko^l, Srinivasa N. Raja^m,
Andrew S.C. Rice^{n,o}, Jordi Serra^p, Blair H. Smith^q, Rolf-Detlef Treede^r, Troels S. Jensen^{a,s}



Red flag conditions

| | |
|------------------|---|
| Musculoskeletal | Fracture or dislocation, heterotopic ossification, contracture |
| Dermatologic | Pressure ulcer, ingrown nail |
| Cardiovascular | Abdominal aortic aneurysm, aortic dissection, myocardial infarction, infection and deep vein thrombosis |
| Respiratory | Pulmonary embolism, deep vein thrombosis, infection or pneumonia |
| Urinary | Urinary tract infection or pyelonephritis, renal or bladder calculi, urinary retention, testicular torsion and epididymitis |
| Pelvic | Ovarian cysts, endometriosis and other genitourinary conditions |
| Gastrointestinal | Stool impaction, constipation, acute abdomen, appendicitis and cholecystitis |
| Neurologic | Peripheral neuropathy, syringomyelia |
| Other | Malignancy |

Review Article

PHANTOM BODY PAIN IN PARAPLEGICS: EVIDENCE FOR A CENTRAL "PATTERN GENERATING MECHANISM" FOR PAIN

RONALD MELZACK and JOHN D. LOESER

*Department of Psychology, McGill University, Montreal, Que. (Canada) and
Department of Neurological Surgery, University of Washington, School of Medicine,
Seattle, Wash. 98195 (U.S.A.)*

(Accepted May 24th, 1977)

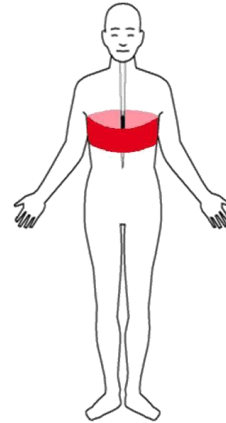
INTRODUCTION

Phantom body pain in paraplegic patients is the most mysterious of all pain phenomena. It has been traditionally assumed [45] that the essential cause of pain in any part of the body is activity in the receptor-fiber units that innervate it. In this paper, however, we shall describe paraplegic patients who had undergone removal of an entire section of the spinal cord (segmental cordectomy) in the attempt to alleviate phantom body pain, yet they still suffered severe pain in the denervated areas of the body.

Neuropathic pain following SCI

- **At-level**

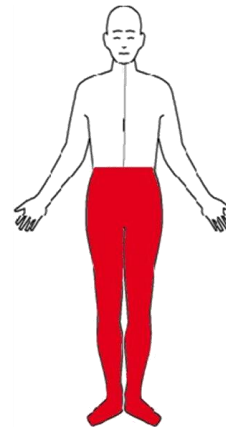
Peripheral and/or central neuropathic pain
Early onset



- Within the dermatome of the neurological level and three dermatomes below this level
- All dermatomes in cauda equina

- **Below-level**

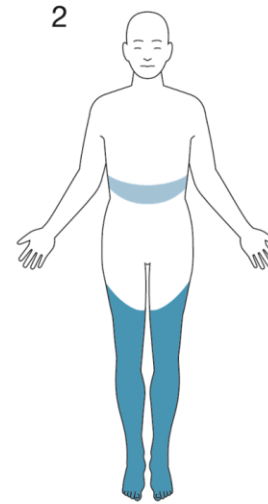
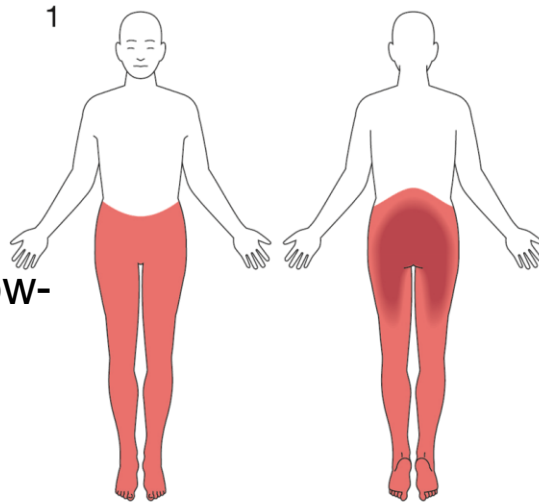
Central neuropathic pain
Later onset (up to 12 months)
Sensory hypersensitivity predictor



- More than three dermatomes below the neurological level but may extend to the “at-level” region

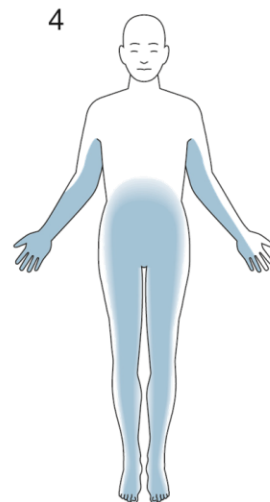
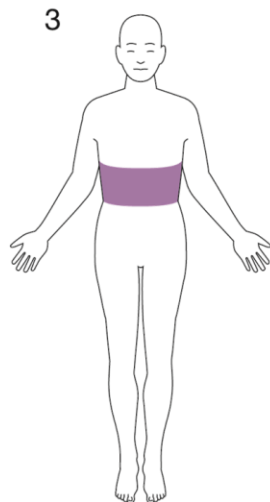
Different SCI pain “phenotypes”

Gradual onset of below-level burning pain

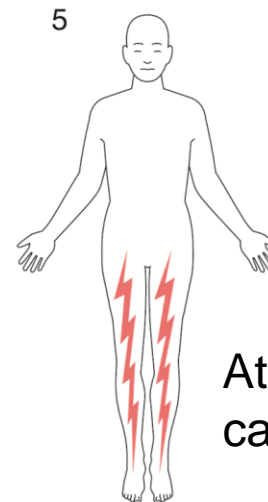


At-level evoked pain below-level spontaneous pain in complete SCI

Squeezing pain as “an armor”

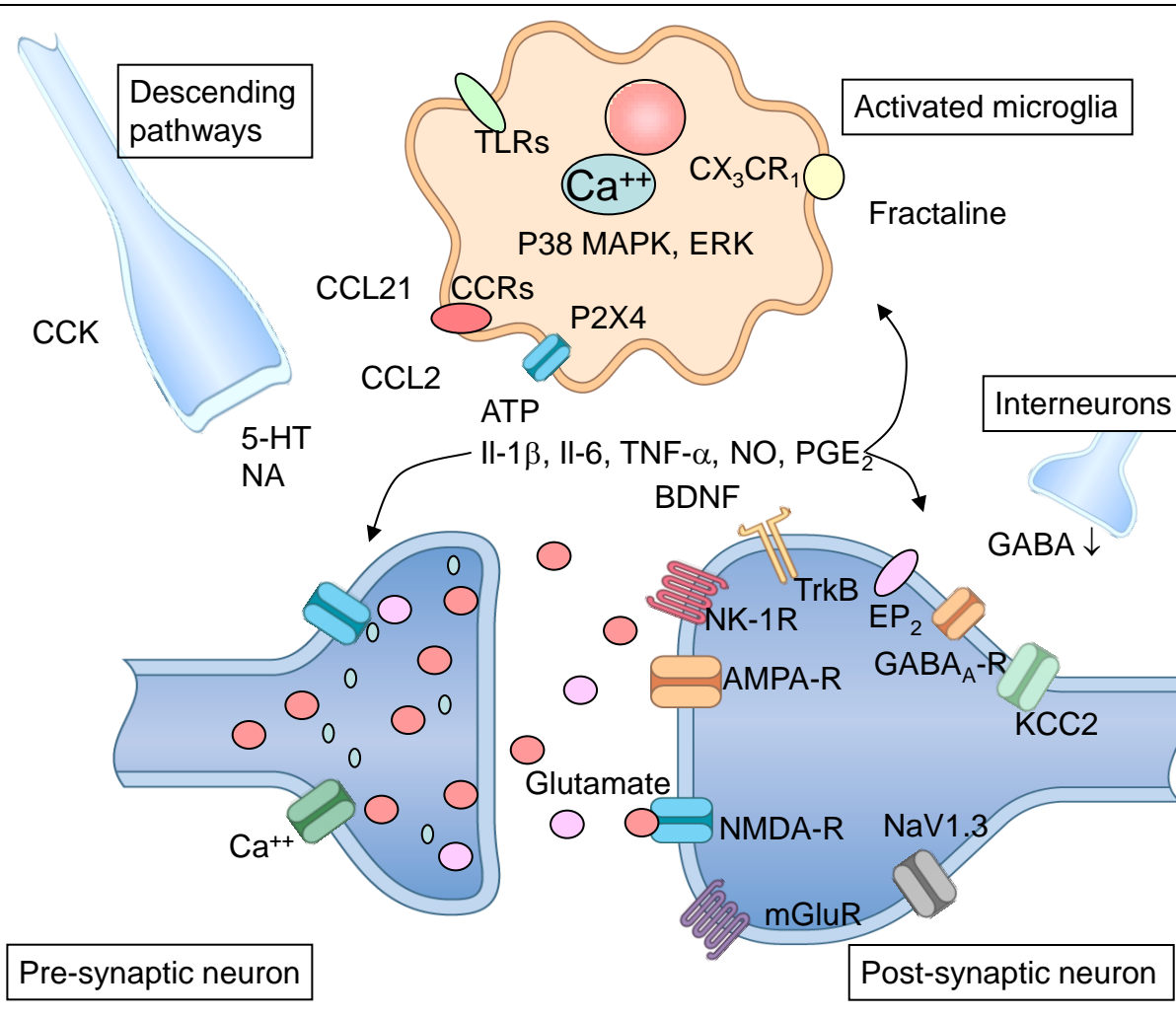


Diffuse evoked pain in incomplete SCI



At-level shooting pain in cauda equina lesion

Mechanisms



Electrophysiological

- Ion channel dysregulation
- Neurotransmitter systems

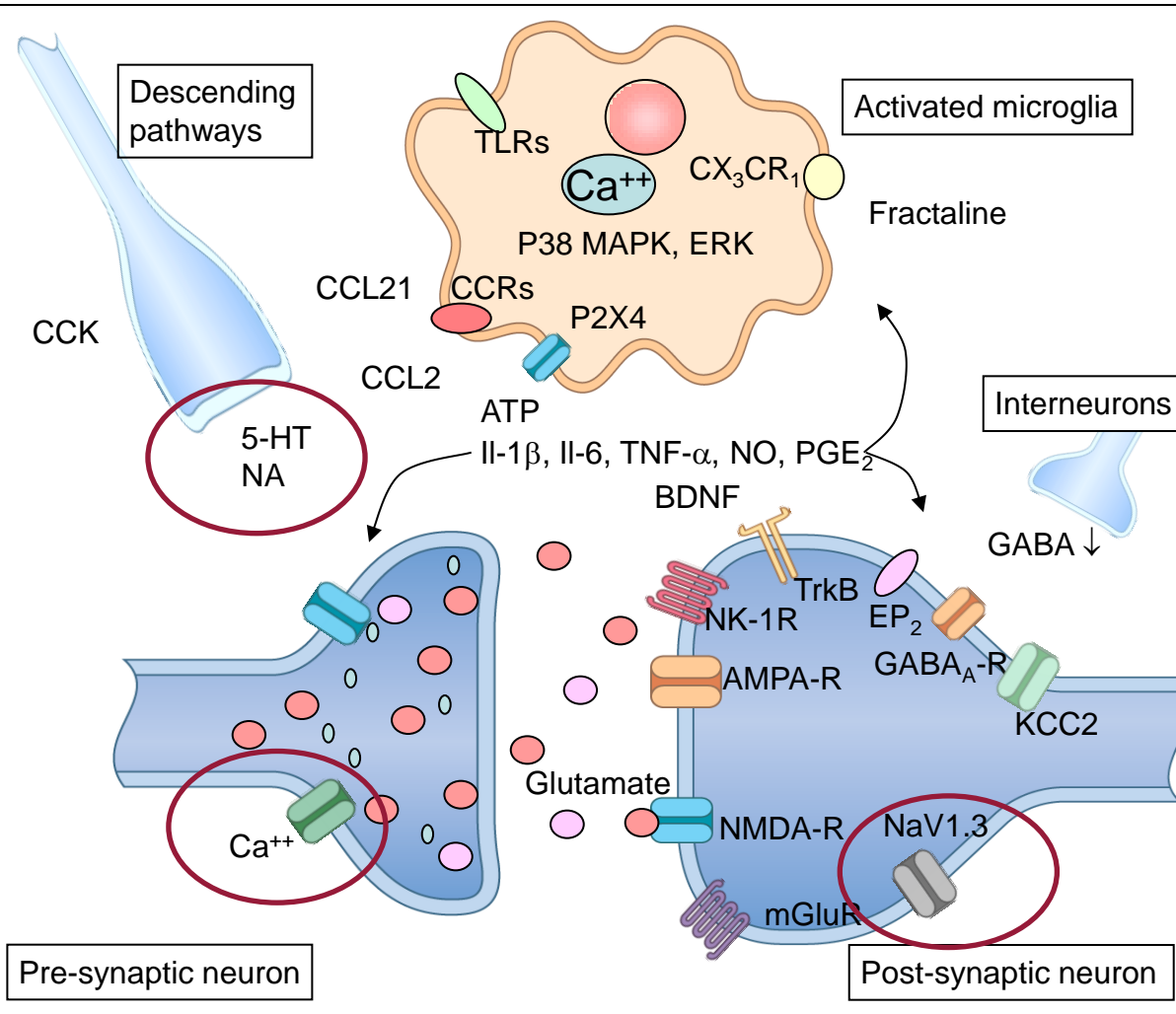
Neuroimmune activation

- Microglia, astrocytes
- Inflammatory substances

Structural mechanisms

- Structural reorganization
- Aberrant sprouting
- Dendritic spine dysgenesis
- Rewiring of local dorsal horn circuitry

Mechanisms



Electrophysiological

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Mechanisms

- Spinal cord hyperexcitability

Druckman and Lende 1965; Edgar et al. 1993; Falci et al. 2002; Finnerup et al. 2003; Chun et al. 2011; Letivan et al. 2015

- Decreased descending pain inhibition

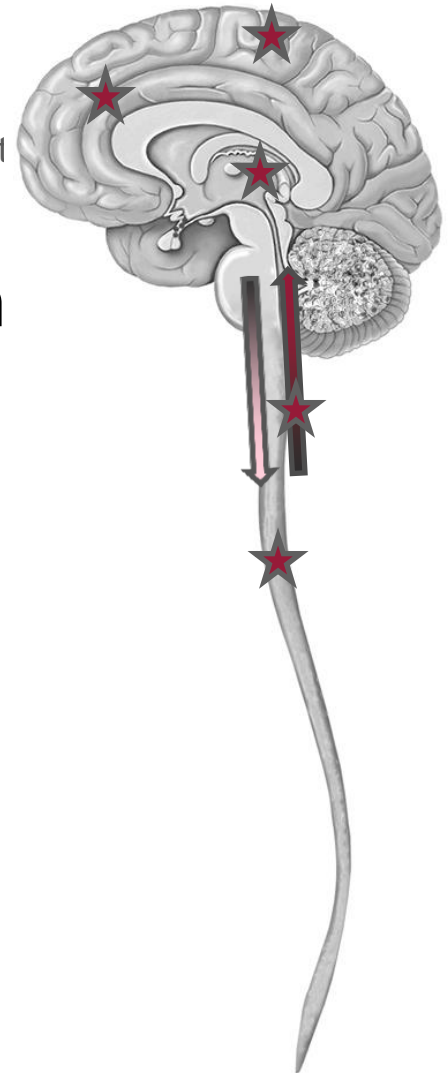
Xiao-Jun et al. Pain 1994; Albu et al. Pain 2015; Gruener et al. Pain 2016

- Preserved and hyperexcitable spinothalamic tract

Wasner et al. 2008; Zeilig et al. 2013; Finnerup et al. 2014; Widerström-Noga et al. 2015

- Brain: thalamus, SI cortex, anterior cingulate cortex, prefrontal cortex

Lenz et al. 1994, Pattany et al. 2002; Stanwell et al. 2010; Gustin et al. 2014; Widerström-Noga et al. 2015, Jutzeler et al. 2016



Treatment of SCI pain

1950s: “Bilateral prefrontal lobotomy .. The patient continues to experience the burning pain ... but does not complain unless questioned directly”

Botterell et al. Proc R Soc Med 1954

1970s: Carbamazepine and phenytoin available. “Drugs and alcohol are effective only so long as the sensorium is clouded”

Hohmann GW. Clin Orthop Relat Res. 1975

2016: Several RCTs on pharmacological and interventional treatment in SCI pain

Drug - max. daily dose

Reference

Size and outcome

N=100

Antidepressants

Amitriptyline 150 mg

Rintala et al. 2007



Positive

Duloxetine 120 mg

Vranken et al. 2011



Negative

Anticonvulsants

Gabapentin 3600 mg

Rintala et al. 2007



Gabapentin 3600 mg

Levendoglu et al. 2004



Pregabalin 600 mg

Vranken et al. 2008



Pregabalin 600 mg

Siddall et al. 2006



Pregabalin 600 mg

Cardenas et al. 2013



Lamotrigine 400 mg*

Finnerup et al. 2002



Levetiracetam 3000 mg

Finnerup et al. 2009



Valproate 2400 mg

Drewes et al. 1994



Opioids

Tramadol 400 mg

Norrbrink et al. 2009



Cannabinoids

Dronabinol 20 mg

Rintala et al. 2010



Sativex spray

NCT01606202



Palmitoylethanolamide (PEA)

Andresen et al. 2016



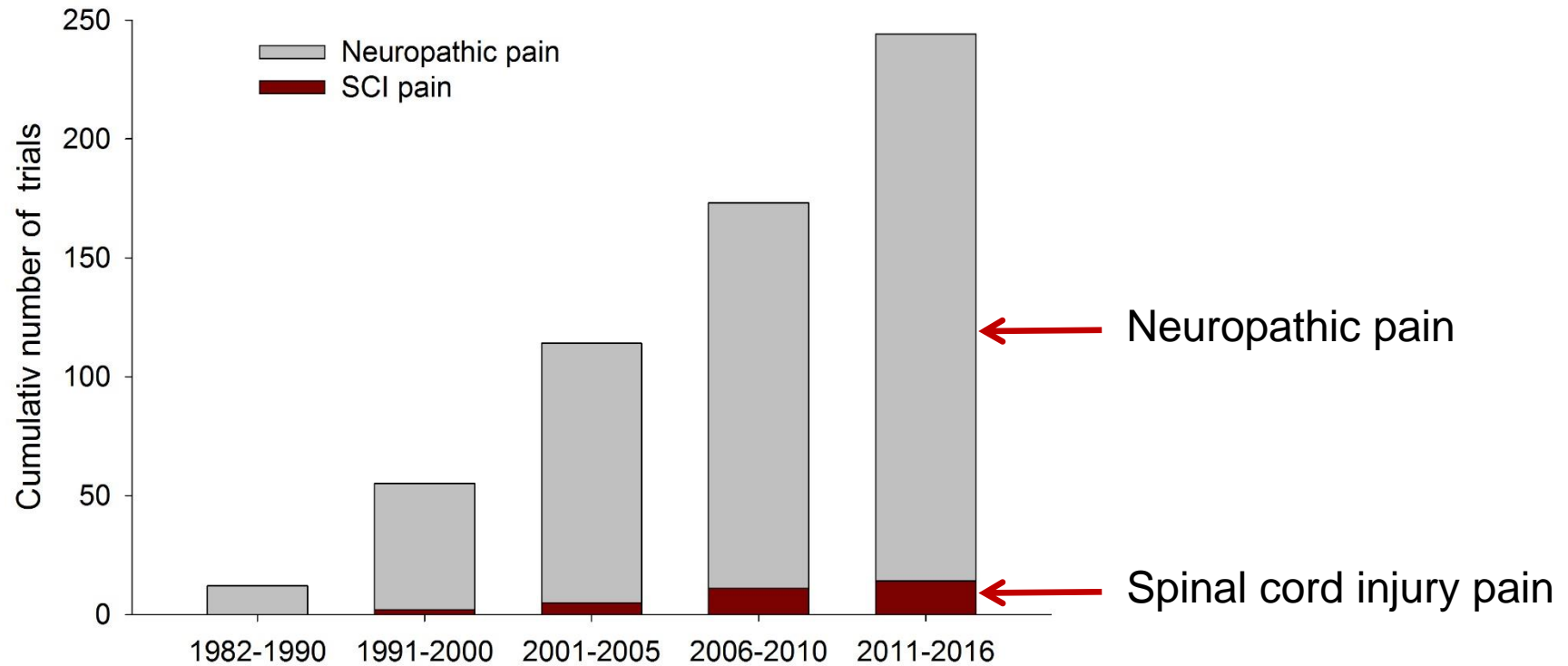
Botulinum toxin type A

Han et al. 2016



1/2 papers retracted for plagiarism and academic fraud

Randomized controlled trials

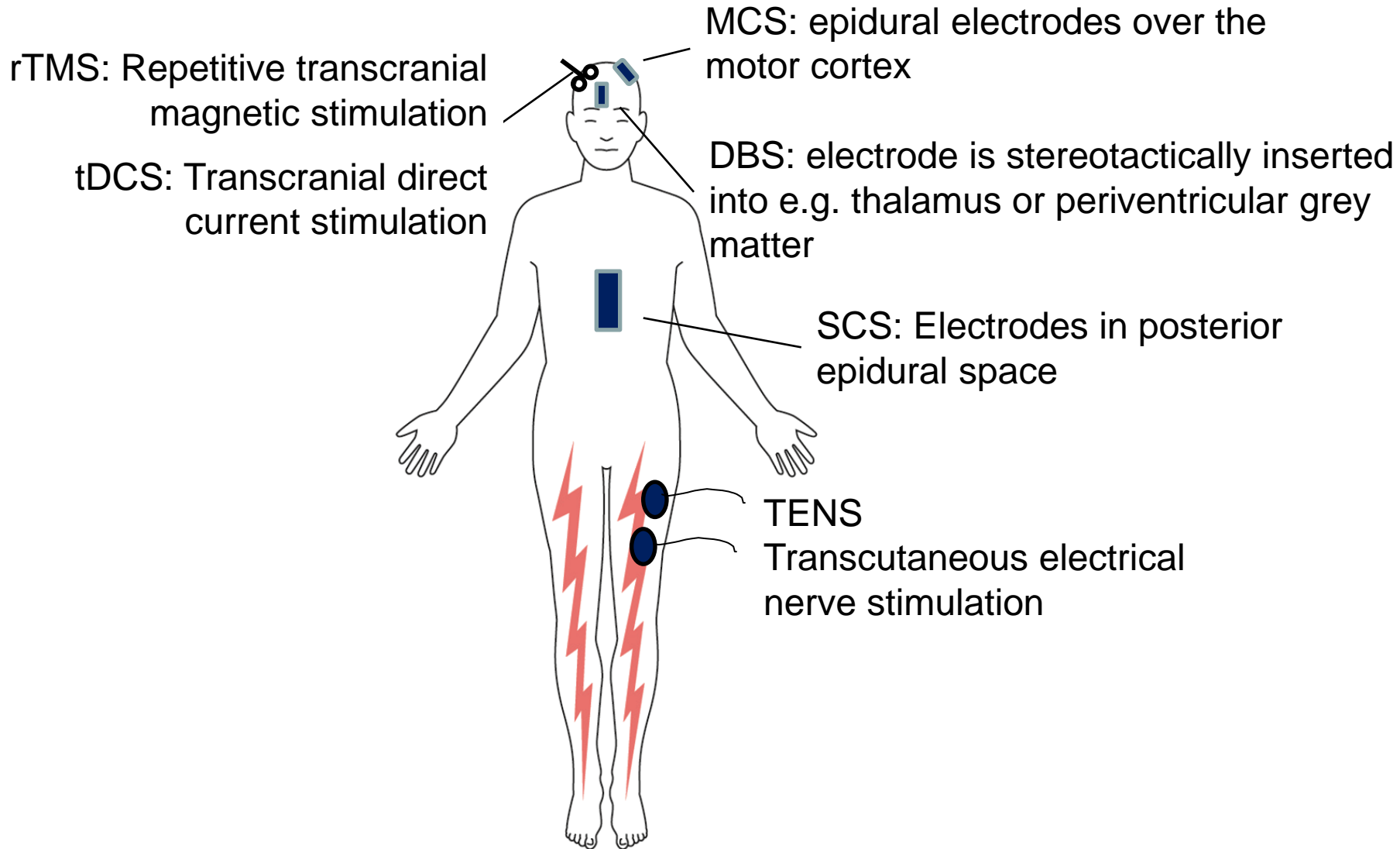


Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

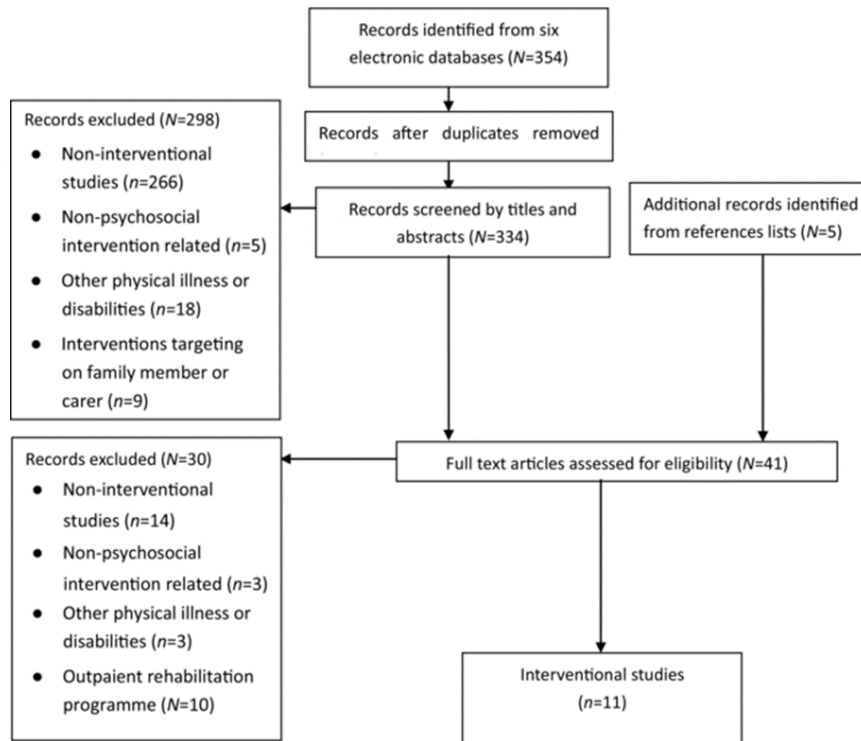
Nanna B Finnerup, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace*

| GRADE classification | Drugs | Recommendations |
|-----------------------|---|---|
| STRONG FOR | Gapabentin Gabapentin ER/enacarbil Pregabalin SNRIs duloxetine/venlafaxine TCAs | First-line First-line First-line First-line First-line |
| WEAK FOR | Capsaicin 8% patches Lidocaine patches Tramadol BTX- A (SC) Strong opioids | Second-line (PNP) Second-line (PNP) Second-line Third-line; specialist use (PNP) Third line |
| INCONCLUSIVE | Carbamazepine, Lacosamide, Lamotrigine, Oxcarbazepine, Topiramate, Zonisamide, SSRI antidepressants, NMDA antagonists, Tapentadol, Capsaicin cream, Topical clonidine | |
| WEAK AGAINST | Cannabinoids Valproate | |
| STRONG AGAINST | Levetiracetam Mexiletine | |

Neurostimulation



Psychosocial interventions in SCI pain



4 randomized controlled trials
7 non-randomized controlled trials

- Psycho-education
- Relaxation
- Cognitive restructuring or appraisal training
- Social skills training or communication training
- Problem solving or coping skills training
- Body awareness training or mindfulness

Improved short-term cognitive appraisal and psychosocial adaptation

Patients' experiences

- Resistance or fear of using pain-relieving drugs
- Worries about side effects
- Requests for complementary treatment and knowledge of how to live with pain
 - Warmth (hot baths, sauna, warm clothes)
 - Avoiding stress
 - Distracting activities
 - Physical activity
 - Balance between activity and rest

CanPain SCI Clinical Practice Guidelines: Recommendations for treatment

First-line therapy

Pregabalin

Gabapentin

Amitriptyline

Second-line therapy

Tramadol

Lamotrigine (for incomplete SCI)

Third-line therapy

Transcranial direct current stimulation (tDCS)

Combined visual illusion and tDCS

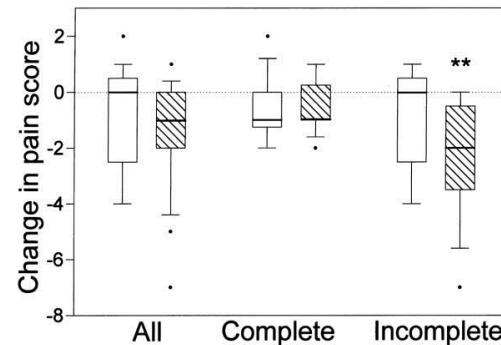
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Finnerup et al. Pain 2002

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PAIN[®] 155 (2014) 2263–2273

PAIN[®]

www.elsevier.com/locate/pain

The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study



Dyveke T. Demant^a, Karen Lund^b, Jan Vollert^c, Christoph Maier^c, Märtha Segerdahl^{d,e}, Nanna B. Finnerup^b, Troels S. Jensen^b, Søren H. Sindrup^{a,*}

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CanPainSCI Working group – Canadian Clinical Practice guidelines

Guy SD et al. Spinal Cord 2016;54:S14-S23

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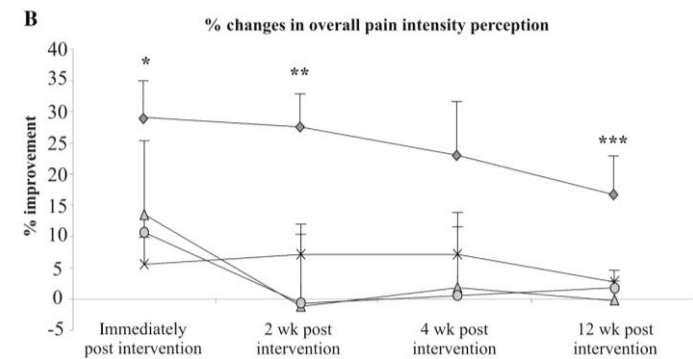
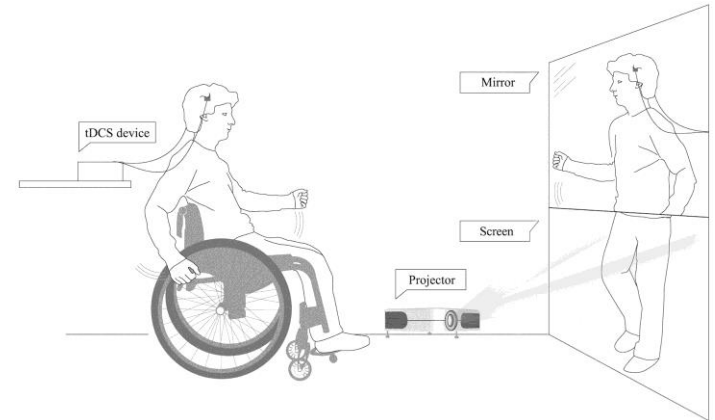
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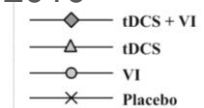
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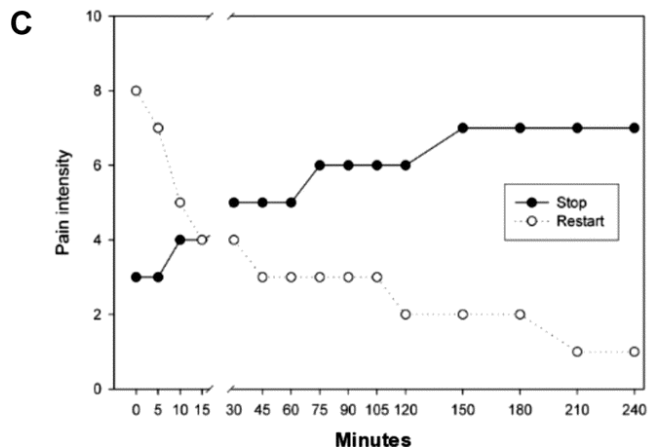
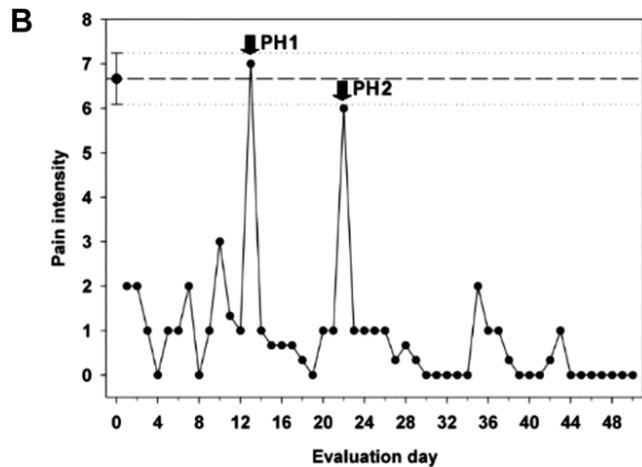
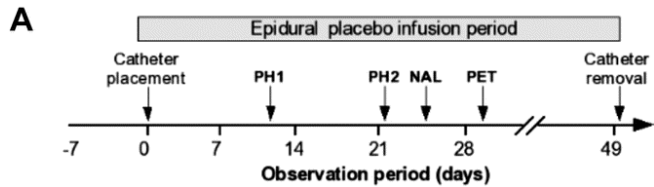
Soler et al. Brain 2010



CanPainSCI Working group – Canadian Clinical Practice guidelines

Guy SD et al. Spinal Cord 2016;54:S14-S23

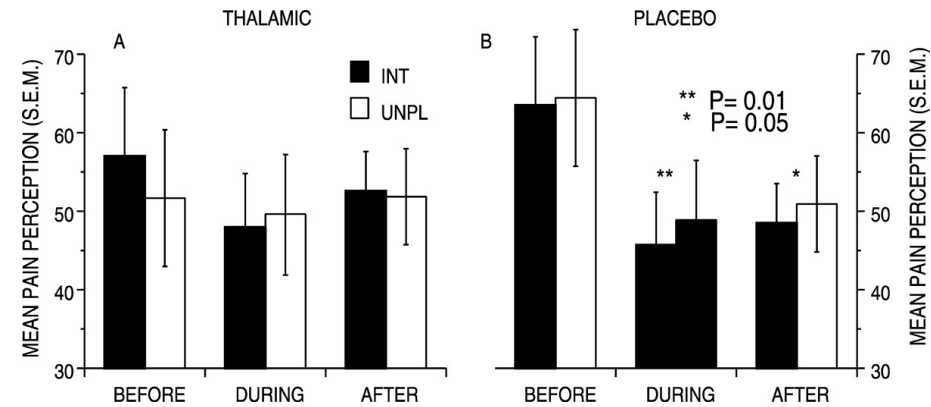
Epidural and DBS placebo analgesia in chronic pain patients



6 patients: Neuropathic pain (trigeminal neuralgia (2), trigeminal postsurgical pain, central (thalamic) pain, postsurgical left eye orbit pain, plexus avulsion)

DBS - Thalamic stimulator for >2 years

Pre-experiment subjective rating: 25-75% pain relief



Placebo-related decreases in rCBF in medial thalamus.

Acknowledgements

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Lars Werhagen, Cecilia Norrbrink, Katarzyna Trok, Fredrik Piehl

Karolinska Institute, Sweden

Mark P Jensen

University of Washington, USA

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