



Complex Regional Pain Syndrome- Pharmacology Update

Jordi Perez, MD, PhD

Director, Alan Edwards Pain Management Unit

Edwards Chair in Clinical Pain

Associate Professor, Dept Anaesthesia.



Disclosure

Jordi Perez MD, PhD declares the following COI related to this presentation

- 1. Relationships with for-profit and/or non-profit organizations:
 - Speakers Bureau/Honoraria: **Cannopy Growth and Cannimed**
 - Grant/Research Support: **N/A**
 - Other: **N/A**
- 2. Off-Label Use:
 - Many of the analgesic options presented are used off label for pain management in the context of CRPS
 - Interventional approaches are used off label for pain management



Learning Objectives

At the conclusion of this presentation, participants will be able to ...

1. Appraise the importance of early diagnosis and treatment of Complex Regional Pain Syndromes(CRPS).
2. Understand the different pathophysiological mechanisms suggested in CRPS development and maintenance.
3. Recognize the importance of a pain pharmacist in the management of chronic pain within the context of CRPS treatment.

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CRPS: Basic concepts

1. Complex regional pain syndrome (CRPS) is a life-altering condition that usually affects the extremities after a trauma or nerve injury.
2. Prevalence of approximately 5.4-26.2 per 100,000 person/years.
3. Differs from other chronic pain syndromes by presenting autonomic dysfunction, persistent regional inflammatory changes, and a lack of dermatomal distribution.
4. It has been historically difficult to diagnose, arduous to treat, and the physiologic mechanism behind its development and maintenance have not been clearly defined.



Shim H, et al. Complex regional pain syndrome: a narrative review for the practising clinician. Br J Anaesth. 2019

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CRPS: Basic concepts



1. **Nomenclature:** "Reflex sympathetic or neurovascular dystrophy", "Algodystrophy", "Algoneurodystrophy", "Sudecks's atrophy", "Sympathetically-maintained pain", "Shoulder-hand disease", "Causalgia", "CRPS type I and II"

2. **Patophysiology:**

- a) Peripheral nervous system
- b) Ischemia reperfusion
- c) Central nervous system
- d) Autonomous nervous system
- e) Bone demineralization
- f) Immunologic influence
- g) Genetic predisposition
- h) Psychological variables



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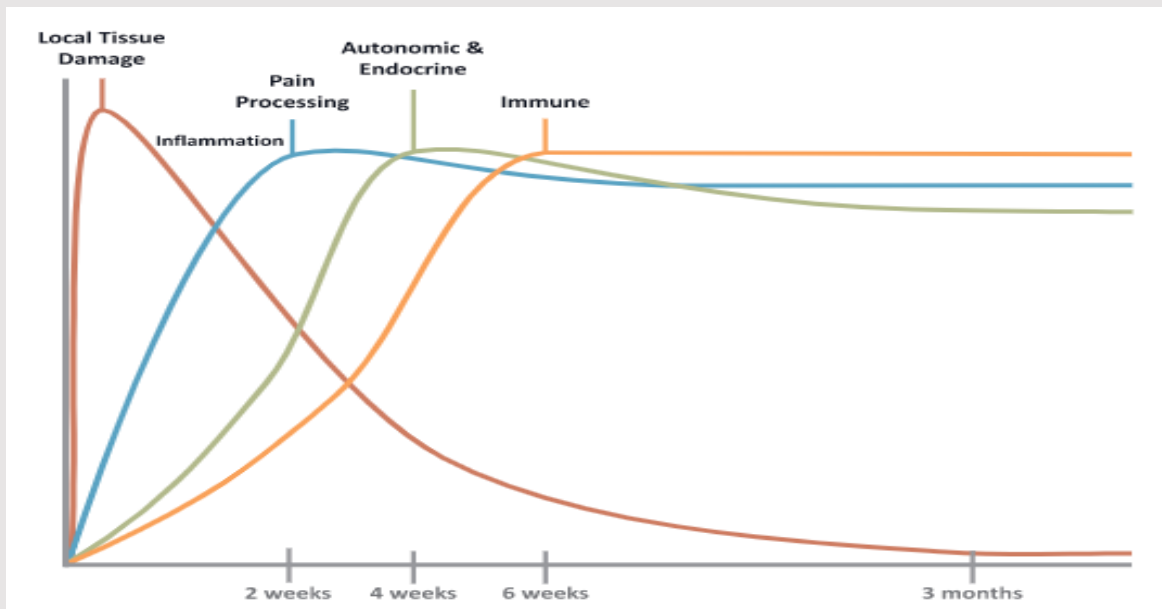


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CRPS: Pathophysiology



Marc Russo M. et al. A new hypothesis for the pathophysiology of complex regional pain syndrome, Medical Hypotheses. 2018

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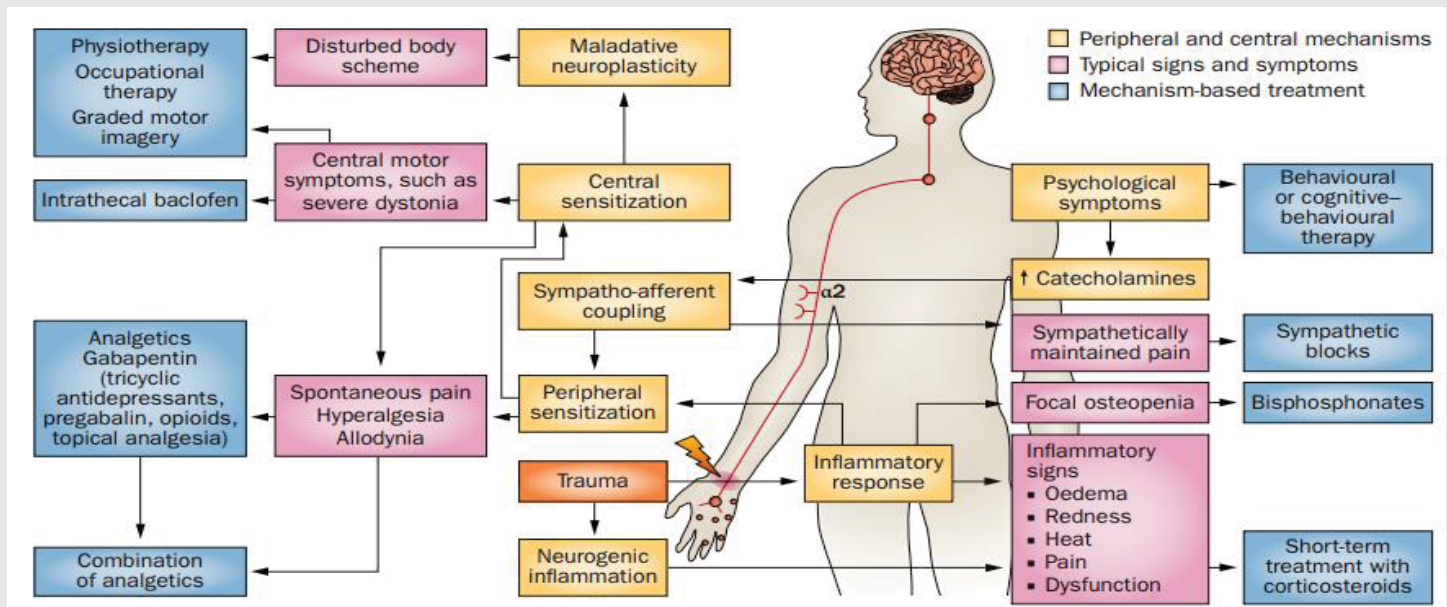


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CRPS: Symptom-targeted drug therapy



Gierthmühlen J, et al. Mechanism-based treatment in complex regional pain syndromes. *Nat Rev Neurol*. 2014

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CRPS: Presentation

Inciting event:

- d) Fractures of upper extremities
- e) The more distal the higher the risk
- f) Fractures requiring surgery increase the risk



FRACTURE



SPRAIN/STRAIN



SOFT TISSUE INJURY



LIMB IMMOBILIZATION



MEDICAL OR SURGICAL PROBLEM

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CRPS: Presentation

Inciting event:

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FRACTURE



SPRAIN/STRAIN



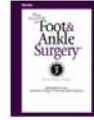
SOFT TISSUE INJURY



Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

The Journal of Foot & Ankle Surgery 000 (2021) 1–7



Original Research

Effect of Perioperative Vitamin C on the Incidence of Complex Regional Pain Syndrome: A Systematic Review and Meta-Analysis

Ishith Seth, MD^{1,2}, Gabriella Bulloch, BMSc³, Nimish Seth, MBBS(Hons)⁴, Adrian Siu, MD², Stephanie Clayton, MSc², Kirk Lower, BSc², Sasha Roshan, FRACS, FAOrthA⁵, Naveen Nara, FRACS, FAOrthA⁶



LIMB IMMOBILIZATION



MEDICAL OR SURGICAL PROBLEM

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CRPS: Presentation

Common presentation

(constellation of symptoms, including sensory abnormalities, autonomic signs, trophic changes and motor dysfunction)

- Pain out of proportion of the inciting event
 - Pain is often neuropathic, spreads without dermatomal pattern
- Increases in skin temperature, nail and hair growth, and erythema
 - Then slowed hair growth, nails become brittle, and muscle weakness begins.
 - Skin temperature can decrease, resulting in a “cold limb”.
 - Pain is usually triggered by mechanically, thermal stimuli and psychological factors.

Swelling that comes and goes along with pain, usually one-sided



Temperature of the affected hand or foot feels hot to the touch



Agony & out of proportion pain not improving as expected



Redness or purple discoloration of the affected hand or foot



Tremors in the affected hand or foot, sometimes with weakness



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CRPS Diagnosis

Table 1 Diagnostic criteria for CRPS (Budapest criteria)¹⁷ (A–D must apply)[†]

A) The patient has continuing pain which is disproportionate to any inciting event		<input type="checkbox"/>
B) The patient has at least one sign in two or more of the categories		<input type="checkbox"/>
C) The patient reports at least one symptom in three or more of the categories		<input type="checkbox"/>
D) No other diagnosis can better explain the signs and symptoms		<input type="checkbox"/>
Category	Sign (you can see or feel a problem)	Symptom (the patient reports a problem)
1 'Sensory'	Allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or hyperalgesia (to pinprick))	<input type="checkbox"/>
2 'Vasomotor'	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	If you notice temperature asymmetry: must be >1°C <input type="checkbox"/>
3 'Sudomotor/oedema'	Oedema and/or sweating changes and/or sweating asymmetry	<input type="checkbox"/>
4 'Motor/trophic'	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)	<input type="checkbox"/>

Royal College of Physicians, UK. 2018

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CRPS: Initial Treatment

The evidence for the effectiveness of many of the treatment modalities for CRPS is lacking strength, and further research is required.

Swelling that comes and goes along with pain, usually one-sided

Temperature of the affected hand or foot feels hot to the touch

Agony & out of proportion pain not improving as expected

Redness or purple discoloration of the affected hand or foot

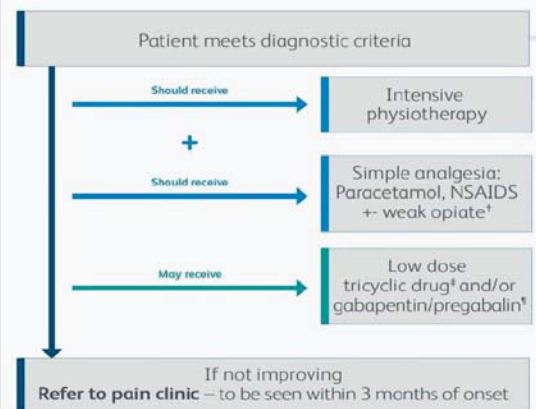
Tremors in the affected hand or foot, sometimes with weakness

CRPS (complex regional pain syndrome) affects the hand or the foot after injuries or surgeries. If found late, it is harder to treat. CRPS screening & treatment should **START NOW.**

Nerve meds like Gabapentin, Pregabalin, & Duloxetine are important to start early

Opioid meds are helpful to support work-outs

Work-outs with early, appropriate, & intensive physical therapy is the key treatment for CRPS



* Diagnosis becomes more reliable >6 weeks after the triggering trauma/operation occurred, and can often not be made before 4 weeks
[†] Eg codeine/dihydrocodeine
[‡] Eg nortriptyline/Imipramine/amitriptyline 10–20mg nocte
[†] Titrate up to therapeutic levels

Royal College of Physicians, UK. 2018

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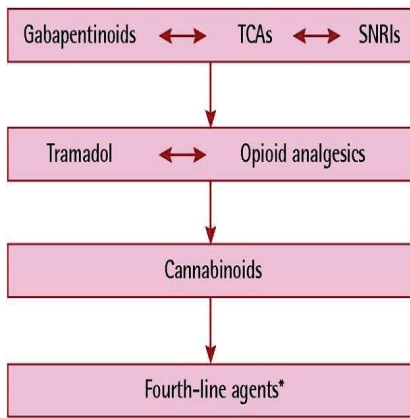
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CRPS: Initial Treatment

The evidence for the effectiveness of many of the treatment modalities for CRPS is lacking strength, and further research is required.



Consider adding additional agents sequentially if there is partial but inadequate pain relief^f

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

- Pregabalin 50 to 300 mg BID
- Gabapentin 100 to 1200mg TID
- Nortriptyline 10 to 50mg qHS
- Duloxetine 30 to 90 mg qAM
- Tramadol 25mg to 400 mg a day

SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant.

*Fourth-line agents include topical lidocaine (second-line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, and botulinum toxin.

Moulin, D. E., (2014). Pain Research and Management

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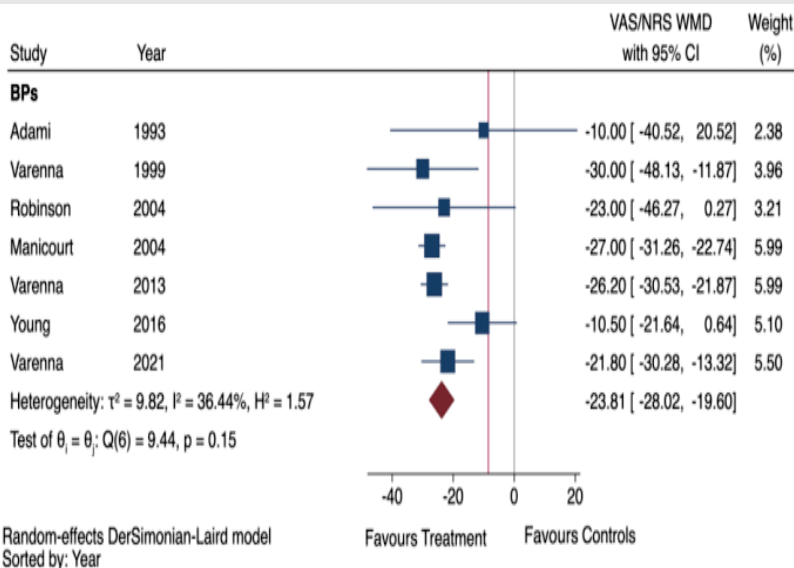


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CRPS: Pharmacy treatment



“**Bisphosphonates** have a consistent effectiveness in terms of reducing pain across studies, and also benefits with respect to other symptoms (allodynia and hyperalgesia) are also suggested. Most RCTs with bisphosphonates used i.v. formulations

MUHC PROTOCOL FOR PAMI-CRPS

- IV Pamidronate 60mg
- Lab test previous mandatory
 - Liver function
 - Kidney function
 - Electrolytes (Ca)
 - Vitamin D

Fassio A, et al. Pharmacological treatment in adult patients with CRPS-I: A systematic review and meta-analysis of randomised controlled trials. Rheumatology 2022

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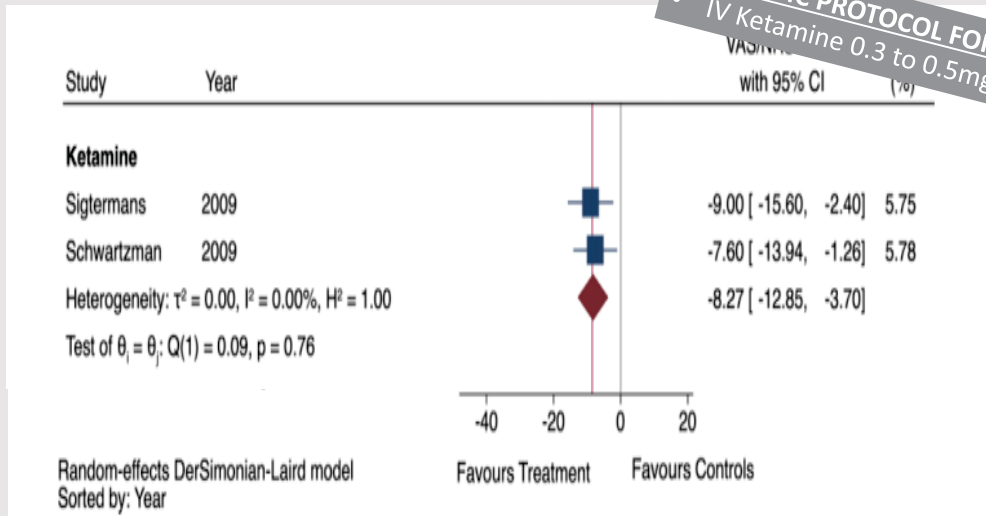


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CRPS: Pharmacy treatment



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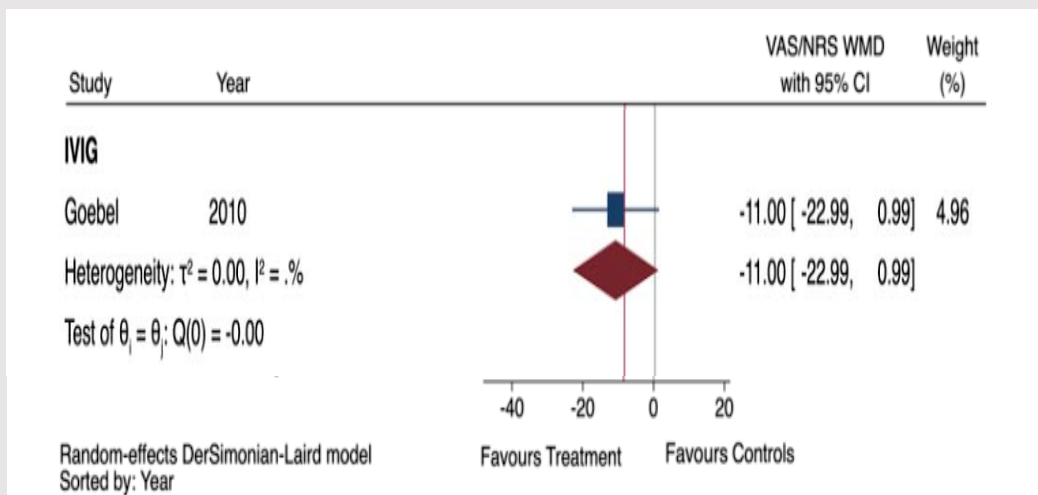


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CRPS: Pharmacy treatment



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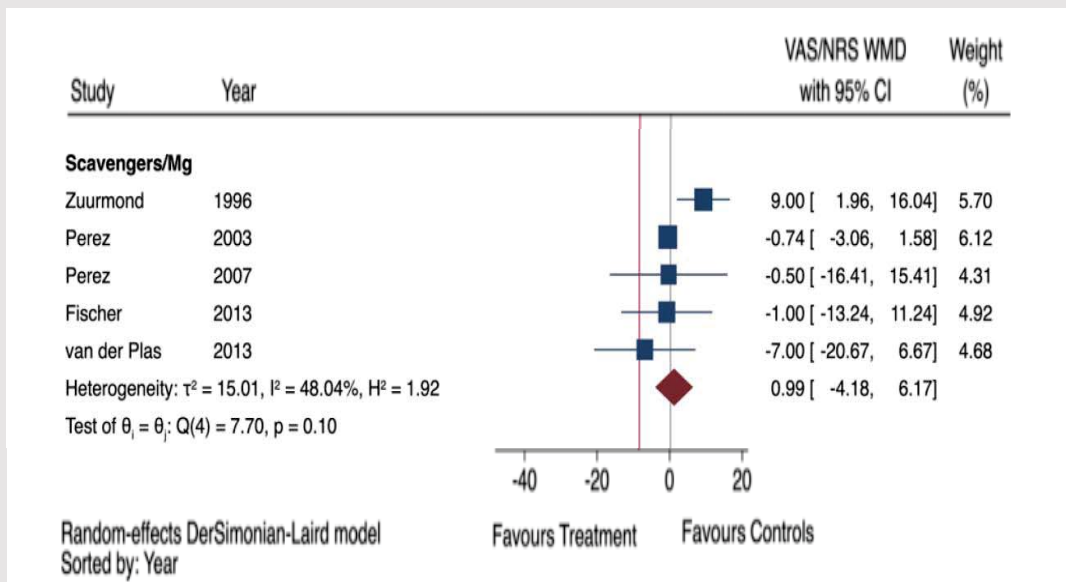


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CRPS: Pharmacy treatment



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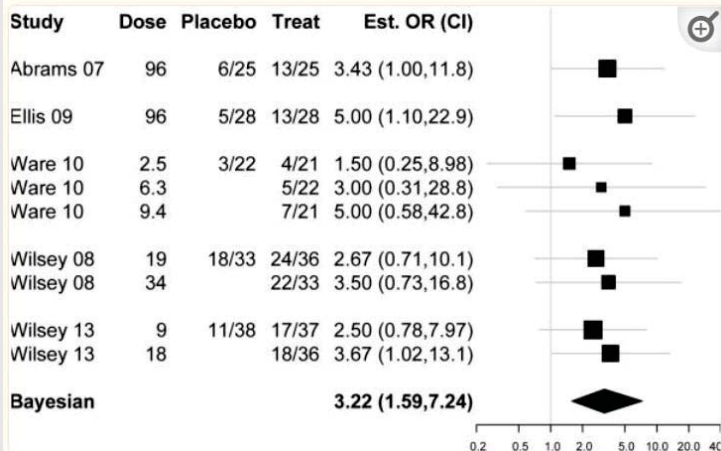
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CRPS: Pharmacy treatment

Andreae MH, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain*. 2015



- Inhaled cannabis appears to provide short term relief from chronic neuropathic pain for one in five to six patients treated.

- Our novel Bayesian hierarchical model allowed the synthesis of all available patient data from five RCT with disparate design and outcome reporting.

- Pragmatic long term studies are needed to confirm the safety and effectiveness of inhaled cannabis for chronic neuropathic pain in the community.

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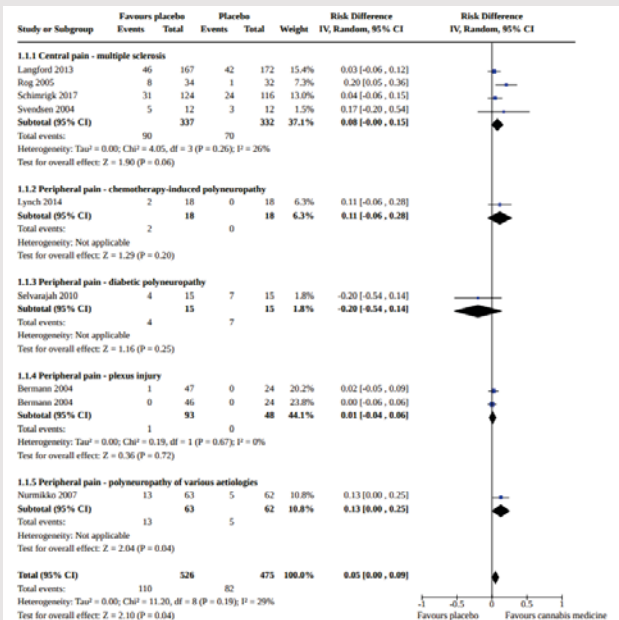


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CRPS: Pharmacy treatment



Mücke M, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018

- The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms.
- The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes.

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CRPS: Pharmacy treatment

Journal of Pain Research Dovepress
open access to scientific and medical research

Open Access Full Text Article CASE REPORT

Treatment of chronic regional pain syndrome type I with palmitoylethanolamide and topical ketamine cream: modulation of nonneuronal cells

This article was published in the following Dove Press journal:
Journal of Pain Research
20 March 2013

Jan M Keppel Hesselink¹
David J Kopsky²

CLINICAL REPORT

A Novel Compound Analgesic Cream (Ketamine, Pentoxifylline, Clonidine, DMSO) for Complex Regional Pain Syndrome Patients

Pain Practice, Volume 16, Issue 1, 2016 E14-E20

Marc A. Russo, MD; Danielle M. Santarelli, PhD
Hunter Pain Clinic, Broadmeadow, New South Wales, Australia

Journal of Pain Research Dovepress
open access to scientific and medical research

ORIGINAL RESEARCH

5% Lidocaine-mediated plaster for the treatment of chronic peripheral neuropathic pain: complex regional pain syndrome and other neuropathic conditions

This article was published in the following Dove Press journal:
Journal of Pain Research
6 October 2016
Number of times this article has been viewed

Enrique Calderón¹
María Eloisa Calderón-Seoane²
Rafael García-Hernández³
Luis Miguel Torres⁴

IASP[®] PAIN[®] 146 (2009) 18–25
www.elsevier.com/locate/pain

Research papers

Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine

Philip M. Finch^{a,b,*}, Lone Knudsen^b, Peter D. Drummond^b

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CRPS: Pharmacology Update – Conclusions



- ✓ CRPS remains poorly understood, misdiagnosed and undertreated.
- ✓ Evidence-based treatment is unsatisfactory.
- ✓ Pain relief is crucial to facilitate physical recovery.
- ✓ Patients referred to pain clinics have exhausted 1st line treatments.
- ✓ Open and bidirectional collaboration between pain physicians and pharmacists is crucial to provide relief by offering “out of the box” options.

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Thank You!

