

Diagnosis and Treatment Options for Complex Regional Pain Syndrome (CRPS)

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Introduction

- **CRPS (formerly known as Reflex Sympathetic Dystrophy [RSD]) is a chronic disease, most often resulting from trauma, characterized by pain of varying intensity**
- **Early diagnosis and appropriate treatment are important**
- **CRPS is underdiagnosed and undertreated by the medical community**

What Is CRPS?

- **CRPS is a debilitating chronic pain syndrome characterized by varying degrees of:**
 - **Pain and skin hypersensitivity**
 - **Vasomotor skin changes**
 - **Sweat disturbance/ edema**
 - **Motor disturbances**
 - **Trophic changes**
- **CRPS often follows a musculoskeletal trauma, surgery, or immobilization.**

Bogduk N. *Curr Opin Anesthesiol.* 2001;14(5):541-546.

Harden RN, Bruehl SP. In: *Complex Regional Pain Syndrome: Treatment Guidelines.* Milford, CT: RSDSA Press; 2006:1-11.

Challenges

- **Natural course and pathophysiology remain poorly understood¹**
- **Inflammation, vasodysregulation, and axonal injury have recently been implicated in the pathogenesis of CRPS²**
- **Therapies remain controversial due to lack of controlled trials³**
- **Diagnosis is made by exclusion of other causes.**
- **Associated with significant morbidity and loss of quality of life⁴**

1. Jänig W. In: Harden, Baron, Jänig. *Complex Regional Pain Syndrome*. 2001:3-15.

2. Oaklander AL. *Pain*. 2009;139:239-240.

3. Bogduk N. *Curr Opin Anaesthesiol*. 2001;14:541-546.

4. Raja SN et al. *Anesthesiology*. 2002;96:1254-1260.

Linda Lang

RSDSA Board member and co-author of *Living with RSDS*

“Consider, too, that in publicizing RSD, we generally focus on the pain, not the disabilities that come with it—the legs and hands that no longer work, the bones that become osteoporotic, the joints that become locked, the muscles that become spastic....There is an awful lot we leave out—how a productive member of society can become too disabled to work or take care of her children. We don’t discuss the tremendous personal losses—families, friends, jobs that RSD wrecks.”



Terminology: RSD vs. CRPS

- Traditional term = RSD
- More comprehensive term = CRPS
 - Complex regional pain syndrome (CRPS)
 - Includes disorders not related to sympathetic nervous system dysfunction

Galer BS, et al. In: *Loeser, ed. Bonica's Management of Pain.* 2001: 388-411.

Harden RN, Bruehl SP. In: *Complex Regional Pain Syndrome: Treatment Guidelines.* Milford, CT: RSDSA Press; 2006:1-11

Terminology: RSD vs. CRPS

- **Types**
 - **CRPS 1 = RSD**
 - **CRPS 2 = Causalgia (involves major nerve injury)**
 - **CRPS-NOS (Not Otherwise Specified) = partially meets CRPS criteria; not better explained by other condition**

Galer BS, et al. In: *Loeser, ed. Bonica's Management of Pain.* 2001: 388-411.

Harden RN, Bruehl SP. In: *Complex Regional Pain Syndrome: Treatment Guidelines.* Milford, CT: RSDSA Press; 2006:1-11

Epidemiology

- Incidence 26.2 per 100,000 person years¹
- Age: common in younger adults
 - Mean 41.8 years
 - Mean age at time of injury 37.7 years
- Mean duration of symptoms before pain center evaluation = 30 months
- 3.4 times more frequent in females than males¹
- Usually involves a single limb in the early stage²

1. De Mos M. *Pain*. 2007;129;12-20.

2. Galer BS, et al. In: Loeser. Ed. *Bonica's Management of Pain*. 2001;388-411.

CRPS Epidemiology

- **Prospective epidemiology links CRPS with nerve injury, asthma, migraine, osteoporosis, NOT with somatization or psychiatric disease**
- **There may be as many 50,000 new cases a year^{1,2}**

1. de Mos M, de Bruijn AG, Huygen FJ, et al. *Pain*. 2007 May;129(1-2):12-20.

2. de Mos M, Huygen FJ, Dieleman JP, et al. *Pain*. 2008 Oct 15;139(2):458-66.

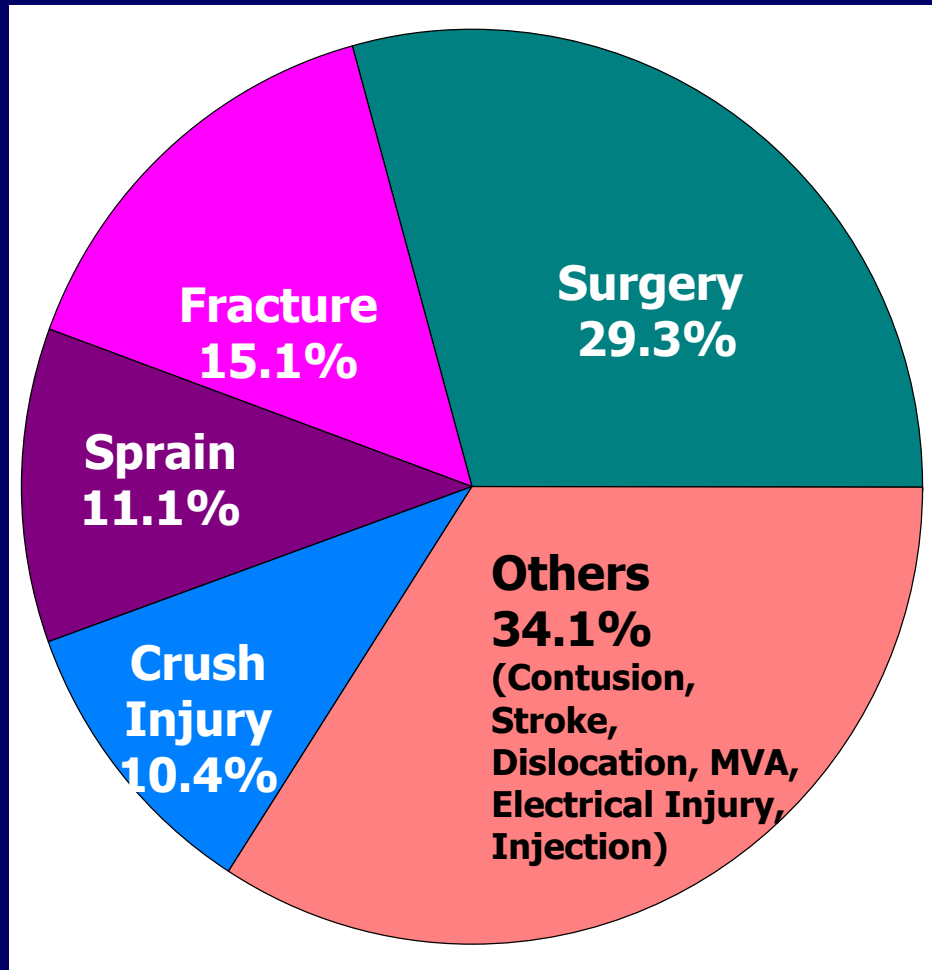
Surgery and Trauma

Common inciting factors

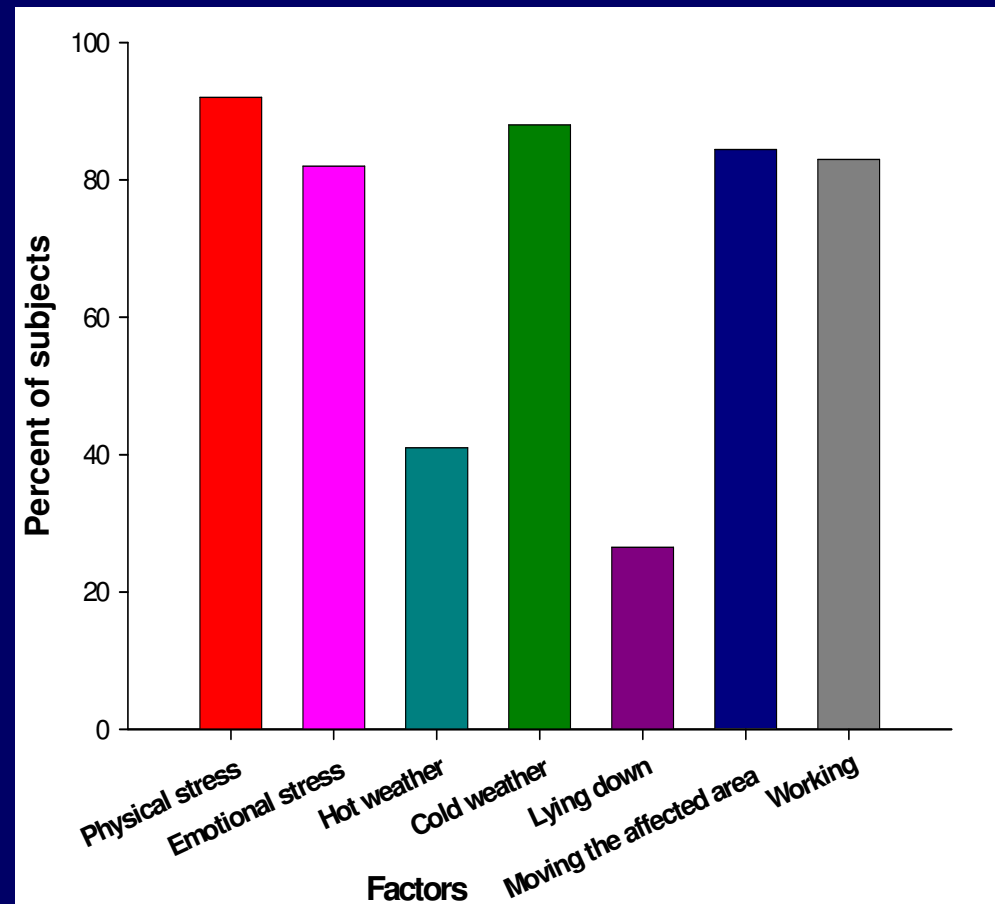
- **Post-surgery**
 - **20% of CRPS patients seen in pain clinics have treatment history of prior surgery, mostly orthopedic in the involved body region**
 - **Smaller prospective studies suggest 11% to 18% of patients following fracture or total knee arthroplasty may develop CRPS-I**

CRPS: A web-based survey

Inciting event



Factors associated with increased pain



Spread of Symptoms

- **More than 77% of respondents report spreading of symptoms to a region other than the site of the original disease¹**
- **The exact frequency of spread of CRPS-I is not available in published literature²**
- **A pattern called 'Independent Spread' is estimated to occur in 6.4% of CRPS-I patients²**
- **Other investigators agree that spread is not uncommon**

1. Sharma A, Agarwal S, Broatch J, Raja SN. *Reg Anesth Pain Med.* 2009;34:110-115.

2. Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ. *Pain.* 2000 Dec 1;88(3):259-266.

Remission

- **Remission of CRPS is difficult to predict based on demographic and clinical characteristics.**
- **The correlation between remission and improvement with sympathetic blocks suggests CRPS patients with sympathetically-maintained pain are more likely to achieve remission.**
- **Remission is often transient, with most experiencing recurrence of symptoms.**

Lesley M, et al. Remission and Recurrence of Complex Regional Pain Syndrome: Analysis of a Web-based Survey. Abstract.

http://www.rsds.org/3/research/Lesley_Mazloomdoost_Agarwal.html

Quality of Life Issues¹

- **Employment**
 - **60% rated themselves as disabled**
 - **Only 16% were employed full-time**
- **Sleep**
 - **94% said that their pain affects sleep**

Clinical Features

CRPS describes an array of painful conditions that are characterized by a continuing regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion.

The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings.

The presence of a group of symptoms has been tested for optimal sensitivity and specificity. The syndrome shows variable progression over time.

Diagnostic Criteria

- **Continuing pain, which is disproportionate to any inciting event**
- **There is no other diagnosis that better explains the signs and symptoms**

Diagnostic Criteria

Symptoms and Signs

Report *three of the four* symptoms following and display at the time of evaluation *at least two or more* of the signs:

1. Sensory

- ***Allodynia***: pain from a stimulus that does not normally provoke pain or
- ***Hyperesthesia***: increased sensitivity to a sensory stimulation

2. Vasomotor

- **Temperature asymmetry (2°C) and/or skin color changes and/or skin color asymmetry**

Diagnostic Criteria

Symptoms and Signs

3. Sudomotor/Edema

- **Edema and/or sweating changes**

4. Motor/Trophic

- **Decreased range of motion and/or motor dysfunction and/or trophic changes (hair, nail, skin)**

Swelling/Edema



Vasomotor Changes



Abnormal Sweating



Motor Disturbance: Dystonia



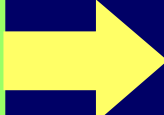
Differential Diagnoses

- Diabetic and other small-fiber peripheral neuropathies
- Entrapment neuropathies
- Thoracic outlet syndrome
- Discogenic disease
- Deep vein thrombosis
- Cellulitis
- Vascular insufficiency
- Lymphedema
- Erythromelalgia

Psychological Aspects

- **Pain can cause symptoms of psychologic distress, including**
 - **Anxiety**
 - **Depression**
 - **Posttraumatic Stress Syndrome**
 - **Fear**
 - **Anger**

Treatment Guidelines

- 1. Physiotherapy**
 - 2. Pain management**
 - 3. Psychological therapy**
- 

Sequential progression through functional restoration pathway

Stanton-Hicks M, et al. *Pain Practice*. 2002;2:1-16.

Harden RN, Swan M, Costa BR, et al. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford CT: RSDSA Press;2006:12-24.

Treatment Guidelines

Physical therapy (PT), Occupational therapy (OT), and Rehabilitation therapy (RT) are crucial to patient's progression

- **Assessment of patient's motivation**
- **Goal setting**
- **Adequate analgesia, encouragement, and education**

Stanton-Hicks M, et al. *Pain Practice*. 2002;2:1-16.

Harden RN, Swan M., Costa BR, et al. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford CT: RSDSA Press;2006:12-24.

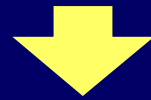
Overall Evidence Gaps

Based upon literature

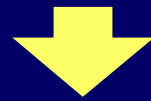
- **Inadequate evidence of efficacy; lack of multiple high quality RCTs**
- **Small sample sizes**
- **Follow-up periods variable**
- **Few studies on QOL and function, not used as primary outcome**
- **Few studies compare interventional therapies to other treatments or placebo**

Functional Restoration: General Steps

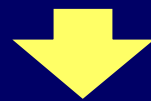
Reactivation, contrast baths, desensitization, and exposure therapy



Flexibility, mobilization, edema control, isometric strengthening, and correction of postural abnormalities



Stress loading, isotonic strengthening, range of motion, postural normalization, and aerobic conditioning



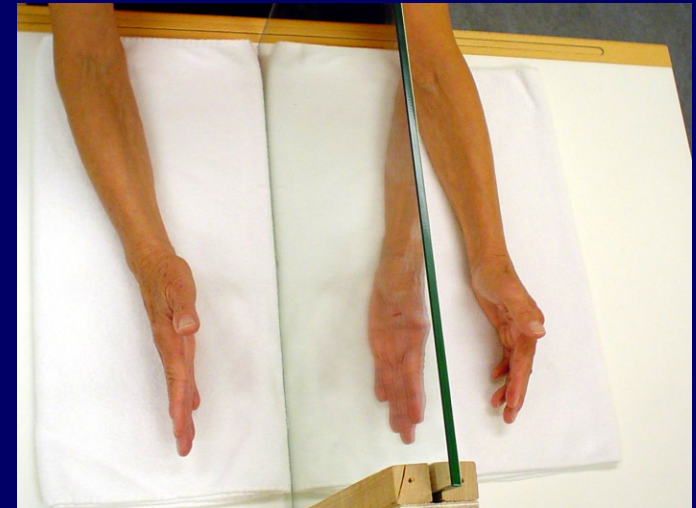
Ergonomics, movement therapy, normalization of use, and vocational and functional rehabilitation

Therapeutic Options for Pain Management

- **Pharmacologic therapy**
 - **Intravenous ketamine**
 - **Intrathecal baclofen**
- **Sympathetic neural blockade**
- **Psychological intervention**
- **Complementary therapy**
 - **Mirror therapy**
- **Spinal cord stimulation**

Mirror Therapy for CRPS

- Exercise of cardinal movements of the affected limb while viewing an image of their unaffected limb in a mirror for 30 minutes daily has been shown to improve pain, motor function, and edema¹
- Sensory discrimination training while looking toward the affected body part but seeing the opposite part of the body in the mirror also decreased pain and increased tactile acuity²



Cacchio C et al. *N Eng J Med.* 2009;361(6);634-636.; Moseley GL, et al. *Pain.* 2009;144;314-319.

Evidence-based Practice Recommendations

- **Treatments for CRPS-I supported by evidence of efficacy and little likelihood for harm are:**
 - **Topical DMSO cream**
 - **IV bisphosphonates**
 - **Limited courses of oral corticosteroids**
- **Despite some contradictory evidence, physical therapy and calcitonin (intranasal or intramuscular) are likely to benefit patients with CRPS-I**

Pharmacotherapy Guide

Symptoms/ Signs	Treatment(s)
Mild-to-moderate pain	Simple analgesics, sympathetic nerve blocks
Severe/intractable pain	Opioids, nerve blocks, IV ketamine
Inflammation, edema	Steroids, NSAIDs
Depression, anxiety, insomnia	Sedatives, antidepressants, anxiolytics
Allodynia, hyperalgesia	Anticonvulsants, lidocaine patch
Osteopenia, immobility, trophic changes	Calcitonin, bisphosphonates
Vasomotor disturbances	Calcium channel blockers, sympatholytics, and/or blocks
Spasticity	Baclofen

Harden RN. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press;2006:25-36.; Schwartzman RJ. *Pain*. 2009;147:107-115.

Role of Opioids

- **Only one controlled trial evaluating controlled-release morphine in CRPS; showed no difference (only 8-day trial)¹**
- **Methadone may have a special place because it blocks NMDA receptor**
- **The use of opioid therapy should be linked to increased participation in the functional restoration process, as with all medications or interventions²**

1. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. *Anesth Analg*. 2001;92:488-495.

2. Harden RN. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press; 2006:25-36.

Pharmacologic Pain Therapy

- **Most medications used for neuropathic pain are used to treat pain in CRPS, such as antidepressants, anticonvulsants, and opioids**
- **Other medications:**
 - **IV alendronate (bisphosphonate)**
 - **Topic dimethyl sulfoxide**
 - **Topical clonidine**
 - **Topical ketamine**
 - **IV bretylium**
 - **IV ketanserin**
 - **IV phentolamine**
 - **IV lidocaine**
 - **Intranasal calcitonin**

Schwartzman RJ, et al. *Pain Med.* 2009;10:401-411.; Raja SN, et al. *Anesthesiol.* 2002;96:1254-1260.; Kingery WS. *Pain.*1997;73:123-139.

Intravenous Ketamine

High dose

Anesthetic doses of ketamine have been used successfully in treatment of CRPS. However, these findings have not been tested in randomized trials

Kiefer RT. *Pain Med.* 2008;9:1173-201.

Low dose

Intravenous ketamine at low doses (25-30 mg/hr in 70 kg adult) resulted in significant pain relief but no functional improvement

Sigtermans MJ. *Pain.* 2009;145:304-11.

Schwartzman RJ. *Pain.* 2009;147:107-115

Interventional Pain Therapy

- **Minimally Invasive Therapies**
 - **Sympathetic/Somatic nerve blocks**
 - **IV Regional nerve blocks**



- **More Invasive Therapies**
 - **Epidural/Plexus Catheter Blocks**
 - **Neurostimulation**
 - **Intrathecal Drug Infusion**



- **Surgical Therapies**
 - **Sympathectomy**
 - **Motor Cortex Stimulation**

Burton A. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press; 2006:51-62.; Velasco F. *Pain*. 2009;147:91-98.

Minimally Invasive Therapies

The choice of the nerve block should depend on the presence or absence of a demonstrable sympathetic component to the pain (SMP) in the patient.

- Patients with SMP may benefit from sympathetic, IV regional, and somatic nerve blocks.
- For patients without SMP, a somatic block or epidural infusion may be indicated to optimize analgesia for PT.

More Invasive Therapies

- Spinal cord stimulation may result in
 - Pain reduction
 - Subjective improvement of health status
 - Objective improvement of functional status remains to be proven

Van Rijn MA, et al. *Pain*. 2009;143:41-47.; Stanton-Hicks M, et al. *Pain Practice*. 2002;2:1-16.; Burton A. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press; 2006:51-62..

More Invasive Therapies

- **Intrathecal drug delivery**
 - **Role of intrathecal opioids or combination therapies have not been studied well and should be used with caution**
 - **Intrathecal baclofen might offer patients with CRPS associated dystonia pain relief and increased quality of life**

Van Rijn MA, et al. *Pain*. 2009;143:41-47.; Stanton-Hicks M, et al. *Pain Practice*. 2002;2:1-16.; Burton A. In: *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press; 2006:51-62..

Intrathecal Baclofen

- Dystonia in CRPS that can not be treated by more conservative measures can be alleviated through intrathecal baclofen
- In patients with dystonia, baclofen possibly improves pain, disability and quality of life

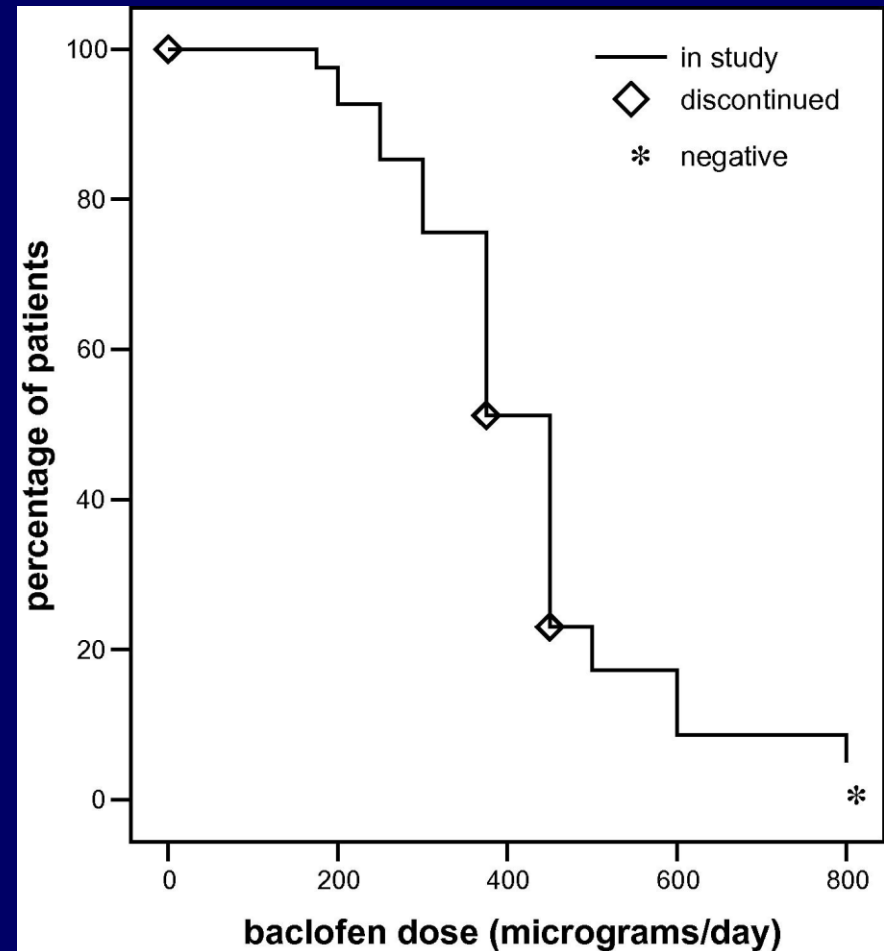
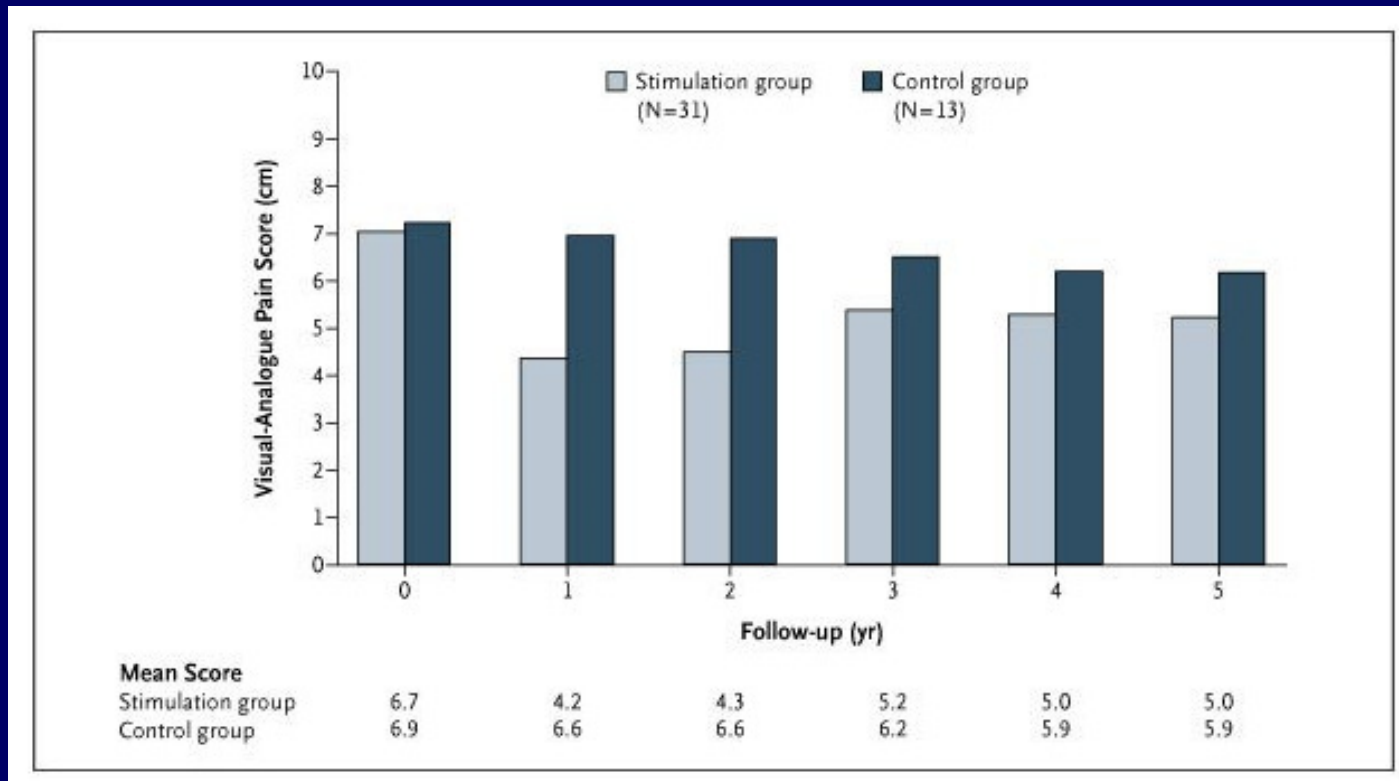


Fig 2. Van Rijn. *Pain*. 2009;143:41-47.


Spinal Cord Stimulation

- Spinal cord stimulation (SCS) has a modest, time-limited effect on pain scores but no effect on health-related quality of life



Kemler MA. *N Engl J Med.* 2006 Jun;354(22):2394-2396.; Kemler MA. *J Neurosurg.* 2008;108:292-298.

Psychological Intervention

- **Patient/family education**
 - **Pathophysiology/disuse issues**
 - **Psychophysiologic interactions**
 - **Self-management focus**
- 
- **Psychological evaluation**
 - **Cognitive, behavioral, and emotional response**
 - **Comorbidities**
 - **Response of family and friends**

Psychological Intervention

- **Psychological pain management evaluation**
 - **Relaxation training with feedback**
 - **Constructive self-talk**
 - **Behavioral intervention**
 - **Family intervention**
 - **Constructive social support**

Prevention

- **Vitamin C**
 - **In doses of 0.5-1gm Vitamin C daily, it has been shown to decrease the incidence of CRPS after foot and ankle surgery¹ as well as following wrist fracture²**
 - **Vitamin C appears to be a simple and cost-effective way of limiting the incidence of CRPS and can be considered in at-risk patients**

1. Besse JL. *Foot and Ankle Surgery*; 2009; 15: 179-82.

2. Zollinger PE. *J Bone Joint Surgery Am*; 2007; 89: 1424-31

Prognosis

- **Difficult to predict**
- **Earlier intervention may be more likely to be successful**
- **Some patients experience reduced symptoms or apparently full recovery**
- **Some patients continue to experience significant disability**

Conclusions

- **CRPS is a chronic pain syndrome**
- **Not all patients have the same set of symptoms**
- **Early diagnosis and appropriate treatment may be associated with faster recovery**
- **Ideal treatment should be multidisciplinary**
- **Consider prevention for high risk surgery**

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Galer BS, Schwartz L, Allen RJ. In: Loeser. Ed. *Bonica's Management of Pain*. 2001: 388-411.

**Harden RN, Bruehl SP. Eds. *Complex Regional Pain Syndrome: Treatment Guidelines*. Milford, CT: RSDSA Press; 2006.
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Stanton-Hicks M, Jänig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995;63:127-133.

Stanton-Hicks M, Baron R, Boas R, et al. Complex Regional Pain Syndrome: guidelines for therapy. *Clin J Pain*. 1998;14:155-166.