

# Update on Complex Regional Pain Syndromes (CRPS)



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Director

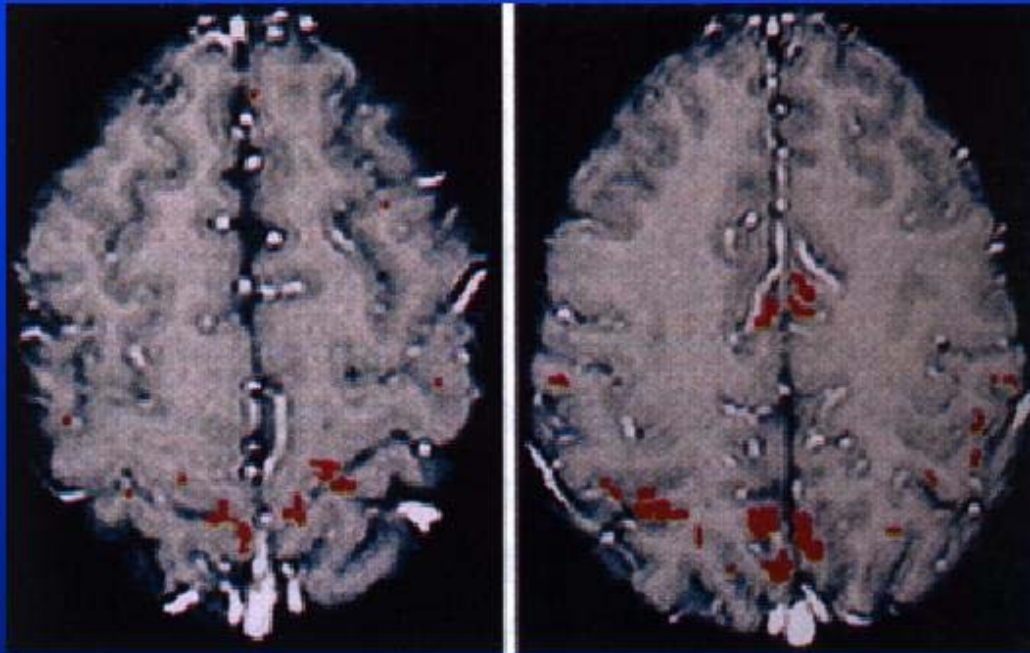
California Pain Medicine Centers at UCLA:  
Center for the Rehabilitation of Pain Syndromes (CRPS)  
Reflex Sympathetic Dystrophy Institute  
Johns Hopkins Annual Pain Meeting 2004

“We met with a small number of men who were suffering from a pain which they described as burning or mustard red-hot or as red-hot file rasping the skin....

“...The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperaesthetic, so that a touch or tap of the fingers increases the pain. Exposure to the air is avoided with a care which seems almost absurd...”

“...The seat of burning pain is very various... its intensity varies from a most trivial burning to a state of torture which hardly can be credited but which is the cause of a considerable economy until the general health is seriously affected...”

# fMRI in CRPS



Courtesy of Ali Rezai, M.D., Ph.D.

# Functional MRI

- Widely available instruments and increasingly applied technology
- No radiation
- Better spatial and temporal resolution than PET and SPECT
- Anatomic and functional imaging performed at same setting
- A practical and unique tool for assessing neurological disorders

# PICTURES OF CRPS with SMP

- Widespread prefrontal activity
-  cingulate activity
-  contralateral thalamic activity

# Functional Imaging of Pain: The Chronic Pain State

- Relative **hypoperfusion of contralateral thalamus** in chronic peripheral or central neuropathic pain-

Hsieh JC et al. Pain 1995; 63:225-36; Peyron R et al. Pain 1995; 62: 275-86

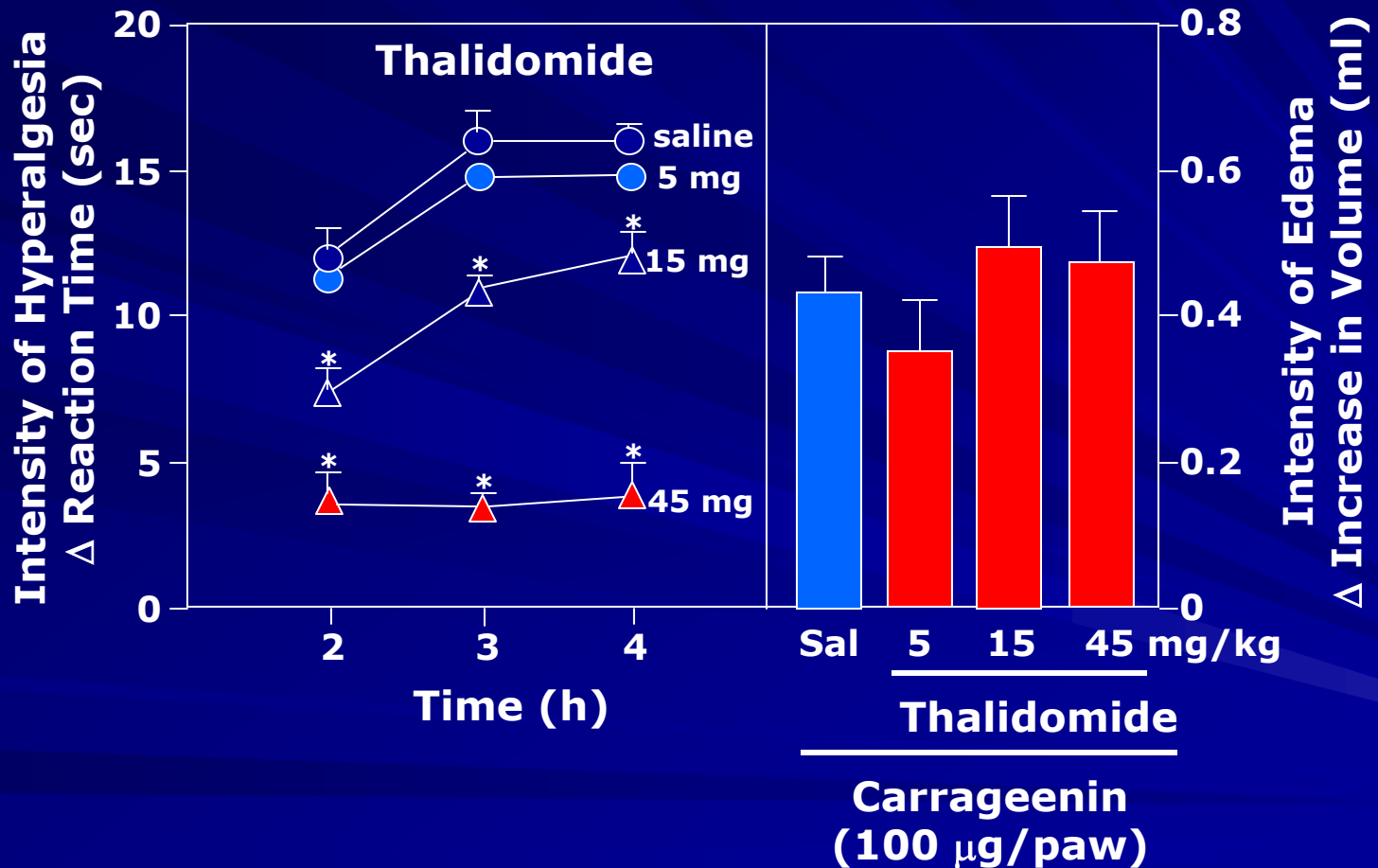
- This hypoperfusion was reduced with effective analgesic treatment
- Paradoxical **decrease in perfusion of ACC** with allodynia (adaptive mechanism ?)

# Functional Imaging: Pain Circuitry

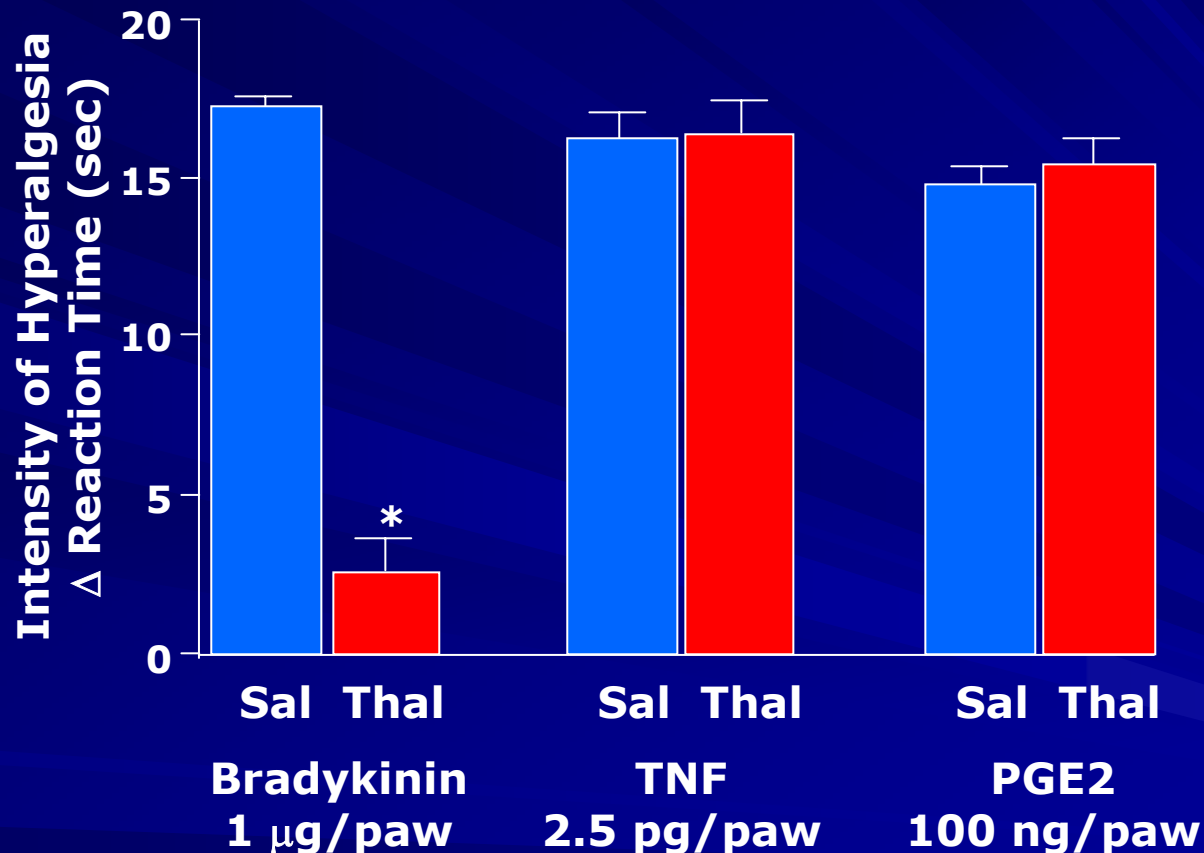
- Evolving understanding of pain circuits
- There is no one region for the expression of pain
- The interaction of multiple areas is involved in the “pain experience”
- Primary Somatosensory Cortex S1
- Secondary Somatosensory Cortex S2
- Insular Cortex
- Cingulate Cortex (Anterior)
- Frontal Cortex (orbitofrontal, DLPFC)

# **THALIDOMIDE: Analgesia**

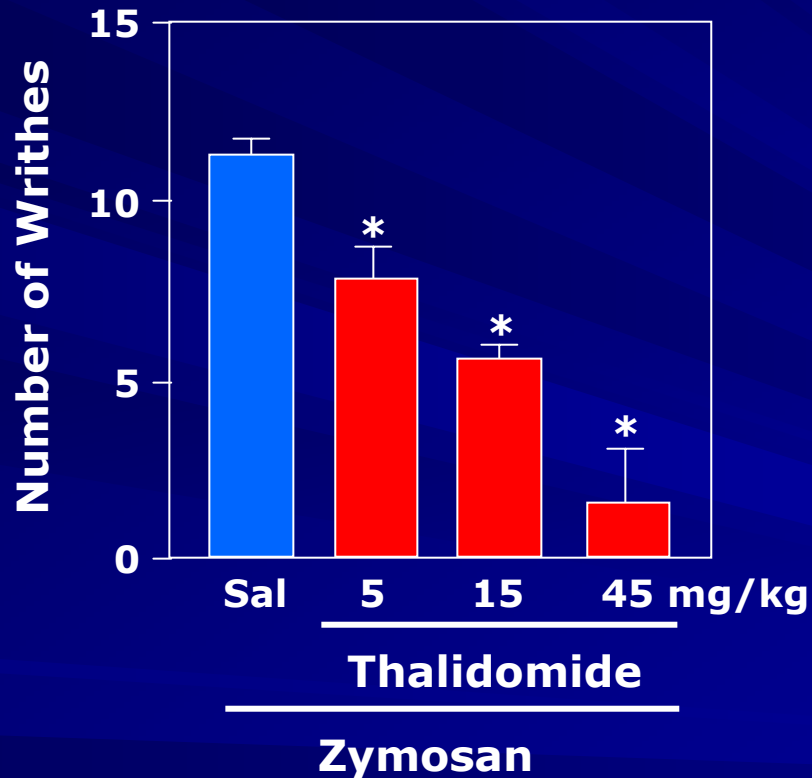
# Thalidomide Inhibits Carrageenin-induced Hyperalgesia but not Edema in Rats



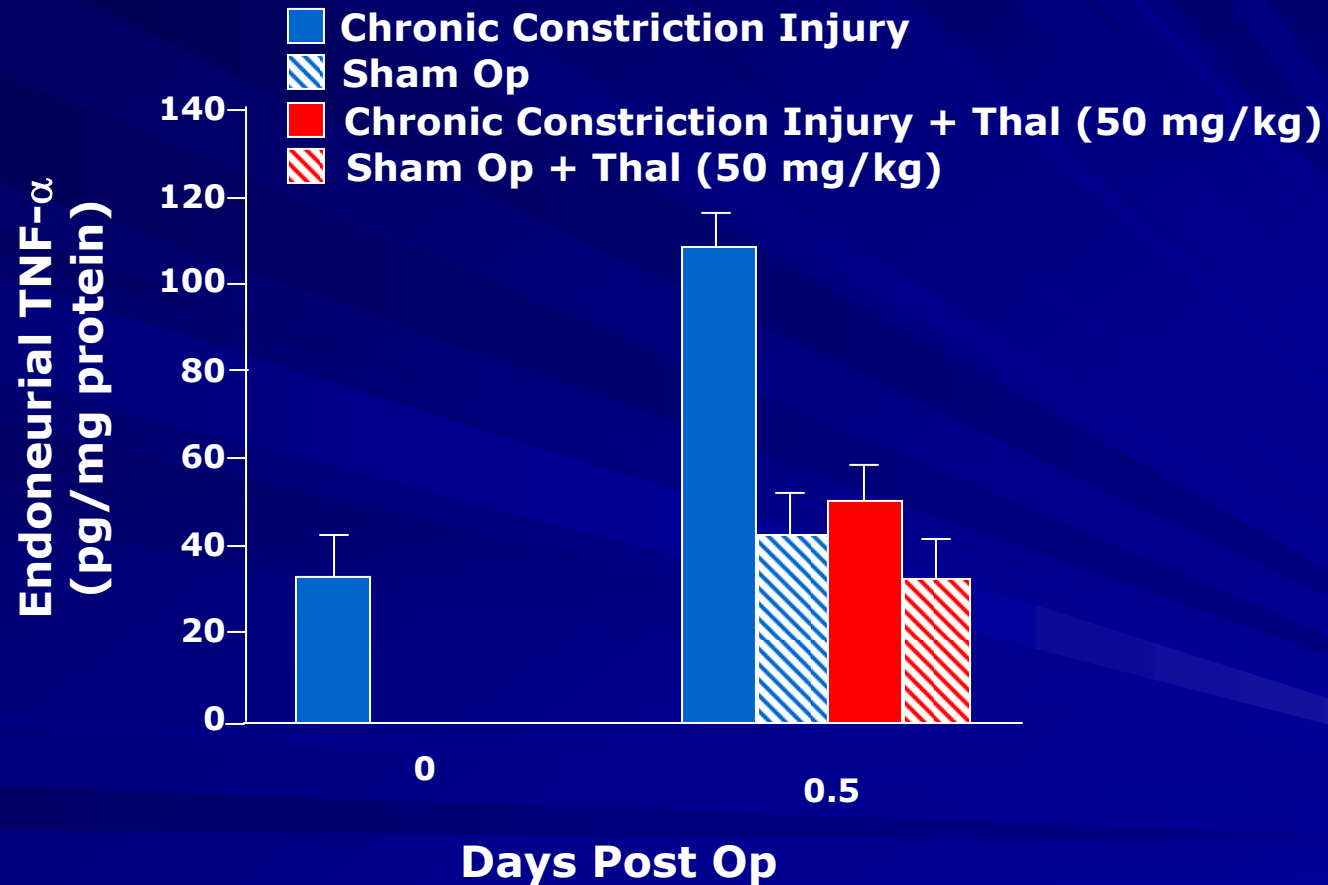
# Thalidomide Inhibits Hyperalgesia Induced by Bradykinin but not by TNF or PGE2



# Thalidomide Inhibits Zymosan-Induced Writhing and TNF- $\alpha$ Production in Mice



# Thalidomide Inhibits TNF- $\alpha$ Production Caused by Constriction of Rat Sciatic Nerve

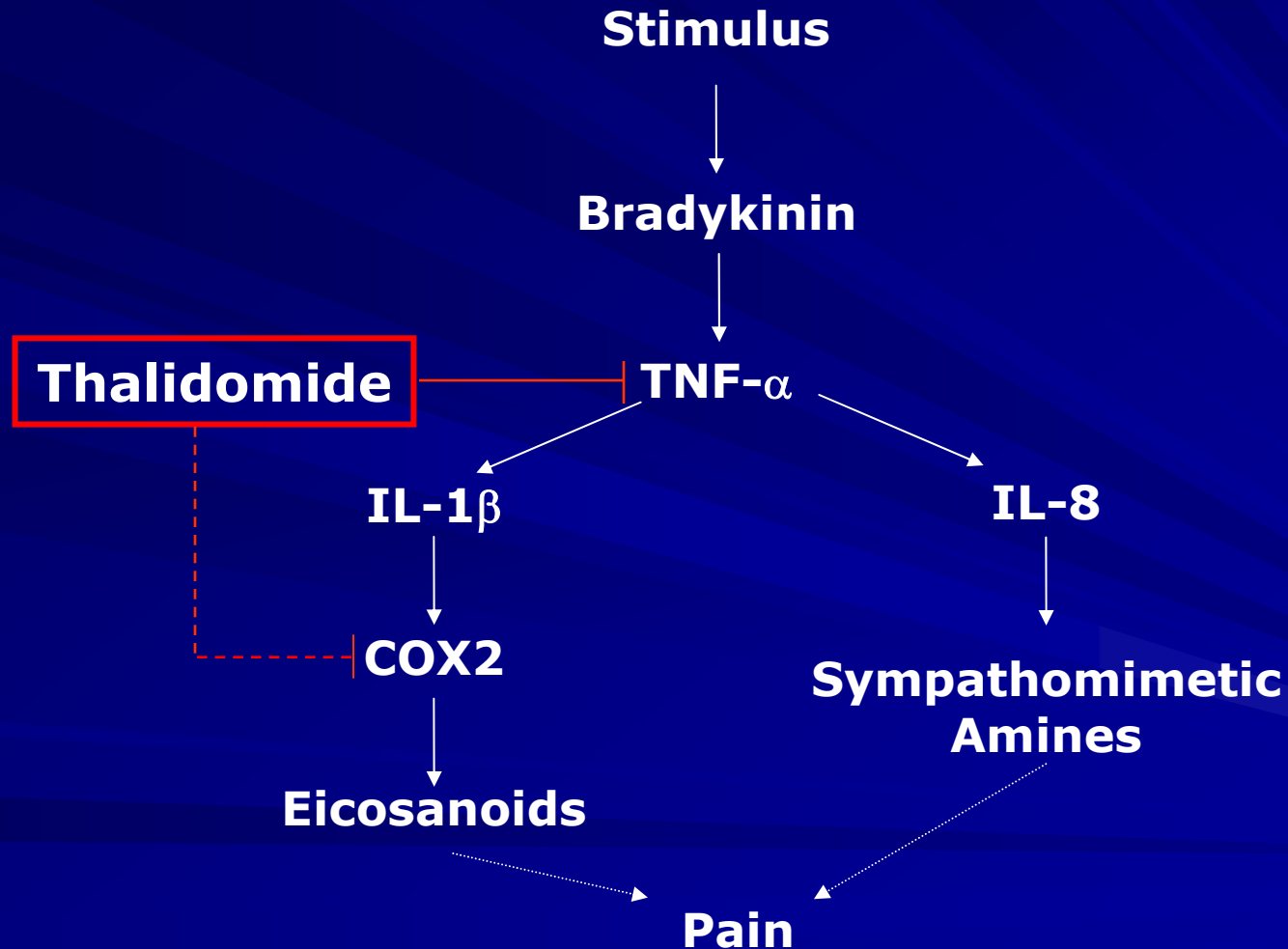


# Thalidomide Inhibits Thermal Hyperalgesia and Mechanical Allodynia in Rat CCI Model

## **Thalidomide (50 mg/kg/day p.o.):**

- **Reduced thermal hyperalgesia by 50-80% on days 5-9 after surgery.**
- **Prevented the increased sensitivity to von Frey hair stimulation for 7 days after surgery.**

# Model for Analgesic Effect of Thalidomide



# Summary of Thalidomide Activities

## Monocytes

**TNF- $\alpha$ , IL-12, GM-CSF, COX-2**

**IL-10**



## T cells

**IL-2, IFN- $\gamma$ , proliferation**

**Th1/Th2**



## Angiogenesis



## Hyperalgesia



# Questions

- What is the optimal dose range?
- What is the optimal time course?
- How long is the residual effect?
- Would there be more profound effects noticed in patients treated earlier?
- What is the long term effect on CRPS?
- What are the best adjuvants to thalidomide in treating CRPS?
- Which patients have the highest probability of success?

# Conclusion

- Continued/expanded study into efficacy and tolerability of thalidomide in patients with CRPS warranted
  - Multicenter, randomized, controlled, double-blind trial to investigate both the change in pain and the increase in functionality

# Thalidomide Analogs

- Studies in progress
- Better side effect profile?
- Fewer side effects allow more aggressive dosing
- Await outcome of studies

# Ketamine

# Ketamine

- Allodynia and hyperalgesia can be related to central sensitization and increased N-methyl-D-aspartate (NMDA) receptor activity
- Ketamine is an NMDA receptor Antagonist

# Ketamine Coma

## RJ Schwatzman

- Performed in Germany
- 18 patients thusfar
- All with severe refractory CRPS

# Ketamine Coma Technique

- Average five days duration
- .7 to .8 mg/kg per hour IV
- Concurrent use of IV Midazolam

# Ketamine Coma Results

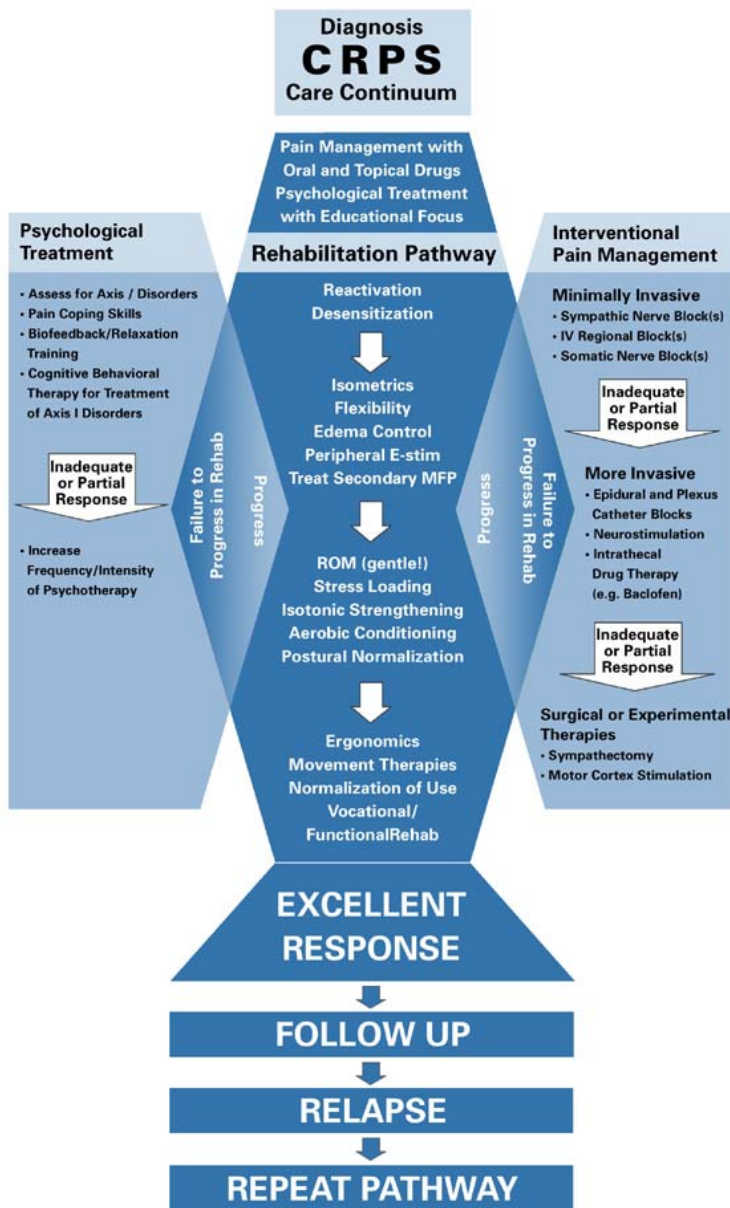
- 6/18 relief without need for retreatment
- 12/18 relief with variable duration (requiring retreatment)
- Side-effects not as severe as expected with ketamine for anesthesia

# Outpatient Low dose Ketamine infusion

RJ Schwatzman

- 40-80 mg daily over 4 hours for 10 days
- 29 subjects
- Decreased shooting, sharp burning, heavy, color change, temperature change, posture change, spasm

# Interdisciplinary Clinical Pathway



- Interdisciplinary treatment: simultaneous and time-contingent
- “Therapeutic options in response to patient’s clinical progress in rehabilitation pathway”
- Failure to Progress necessitates more advanced pain management and psychological approaches

Diagnosis  
**CRPS**  
Care Continuum

Pain Management with  
Oral and Topical Drugs  
Psychological Treatment  
with Educational Focus

**Psychological  
Treatment**

- Assess for Axis / Disorders
- Pain Coping Skills
- Biofeedback/Relaxation Training
- Cognitive Behavioral Therapy for Treatment of Axis I Disorders

Inadequate  
or Partial  
Response

- Increase Frequency/Intensity of Psychotherapy

Failure to  
Progress in Rehab

**Rehabilitation Pathway**

Reactivation  
Desensitization



Isometrics  
Flexibility  
Edema Control  
Peripheral E-stim  
Treat Secondary MFP



ROM (gentle!)  
Stress Loading  
Isotonic Strengthening  
Aerobic Conditioning  
Postural Normalization



Ergonomics  
Movement Therapies  
Normalization of Use  
Vocational/  
Functional Rehab

**Interventional  
Pain Management**

- Minimally Invasive**
- Sympathetic Nerve Block(s)
  - IV Regional Block(s)
  - Somatic Nerve Block(s)

Inadequate  
or Partial  
Response

- More Invasive**
- Epidural and Plexus Catheter Blocks
  - Neurostimulation
  - Intrathecal Drug Therapy (e.g. Baclofen)

Inadequate  
or Partial  
Response

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

Failure to  
Progress in Rehab

**EXCELLENT  
RESPONSE**



**FOLLOW UP**



**RELAPSE**



**REPEAT PATHWAY**

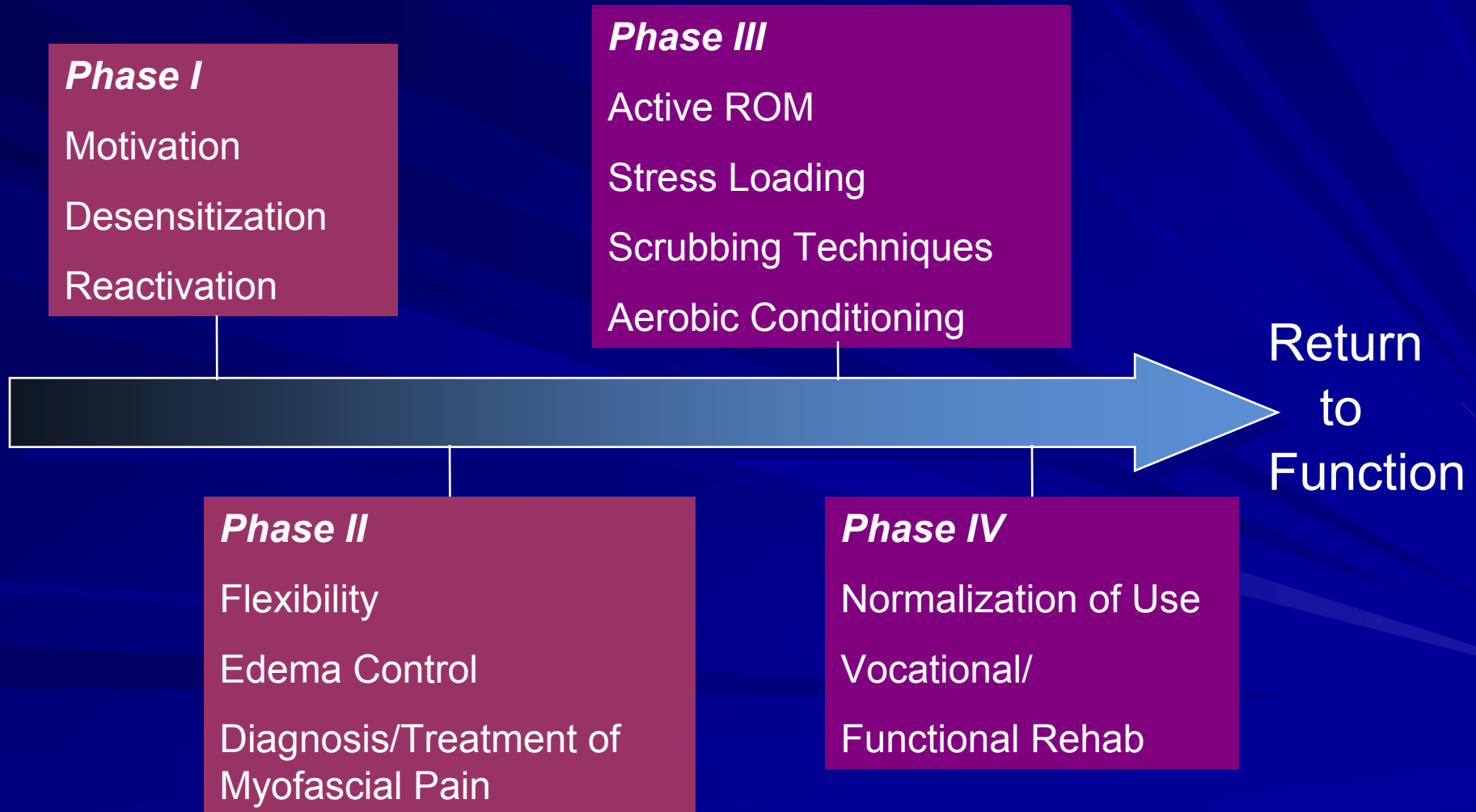
# Treatment: 3 Core Elements

- Rehabilitation
- Pain management
- Psychological treatment

# Rehabilitation

- Mainstay of CRPS treatment
- Physiotherapeutic Algorithm based on:
  - motivation
  - desensitization
  - mobilization
- Pain management and psychological measures facilitate progression through rehabilitation pathway

# Highlights of Recommended Rehabilitation Algorithm



# Psychological Treatment

**Early in Disease Process:  
(4-6 weeks of onset)  
Education**



**Disease Progression:  
(6-8 weeks of significant symptoms)**

- Assessment and treatment of Axis I Disorders (e.g. depression, anxiety)
  - Pain Coping Skills
- Biofeedback/Relaxation Training

# Pain Management Continuum

## Initial Treatment

- Oral and topical medications

## Partial or Inadequate Response: Minimally Invasive

- Sympathetic nerve blocks
- Intravenous regional blocks
- Somatic blocks

## Partial or Inadequate Response: More Invasive

- Epidural/Plexus catheter blocks
- Neurostimulation
- Intrathecal drug delivery

# Pain Management: Fundamental to Successful Rehabilitation

“Because time is of the essence, failure to progress should be seen as a trigger to introduce regional anesthesia or neuromodulatory methods to support the progressive rehabilitation.”

— Dr. Michael Stanton-Hicks  
*Cleveland Clinic Foundation*

# Pharmacologic Management of Neuropathic Pain

<b>Drug class</b>	<b>Example</b>
Antidepressants (Tricyclic)	Amitriptyline, desipramine, nortriptyline, imipramine, doxepin
Antidepressant (SSRI)	Fluoxetine, Sertraline, Paroxetine, Citalopram, cis-citalopram
Anticonvulsants	gabapentin, topiramate, DPH, lamotrigine Carbamazepine & ox, levetiracetam
Antidysrhythmics and local anesthetics	Lidocaine, mexilitine
Topical formulations	Capsaicin, EMLA cream, aspirin
GABA agonists	Baclofen
NMDA receptor Antagonists	Ketamine, Dextromethorphan
Alpha Agonists and Mixed	Clonidine, tizanadine, tramadol
Anti-Inflammatories	COX-2 Inhibitors, Traditional NSAIDS

# Pharmacological treatment of neuropathic pain:

- Match symptoms to the medication
- Utilize side-effects to the patient's benefit
- Gently titrate
  - Titrate to either effect or side effect
- Only make one change at a time
- Multiple mechanisms of action make sense

# Are We Paying a High Price for Surgical Sympathectomy? A Systemic Literature Review of Late Complications

- 135 Articles reporting on 22,458 patients and 42,061 procedures
- Indications: 84.3% Hyperhidrosis Others with Neuropathic Pain
- Complications: Compensatory Hyperhidrosis (52.3%), Gustatory sweating (32.3%), Phantom sweating (38.6%), Horner's Syndrome (2.4%)

# Are We Paying a High Price for Surgical Sympathectomy? A Systemic Literature Review of Late Complications

- Neuropathic Pain occurred in 11.9% of patients
- Neuropathic complications occurred three times more often if neuropathic pain was the indication (25.2% vs. 9.8%)

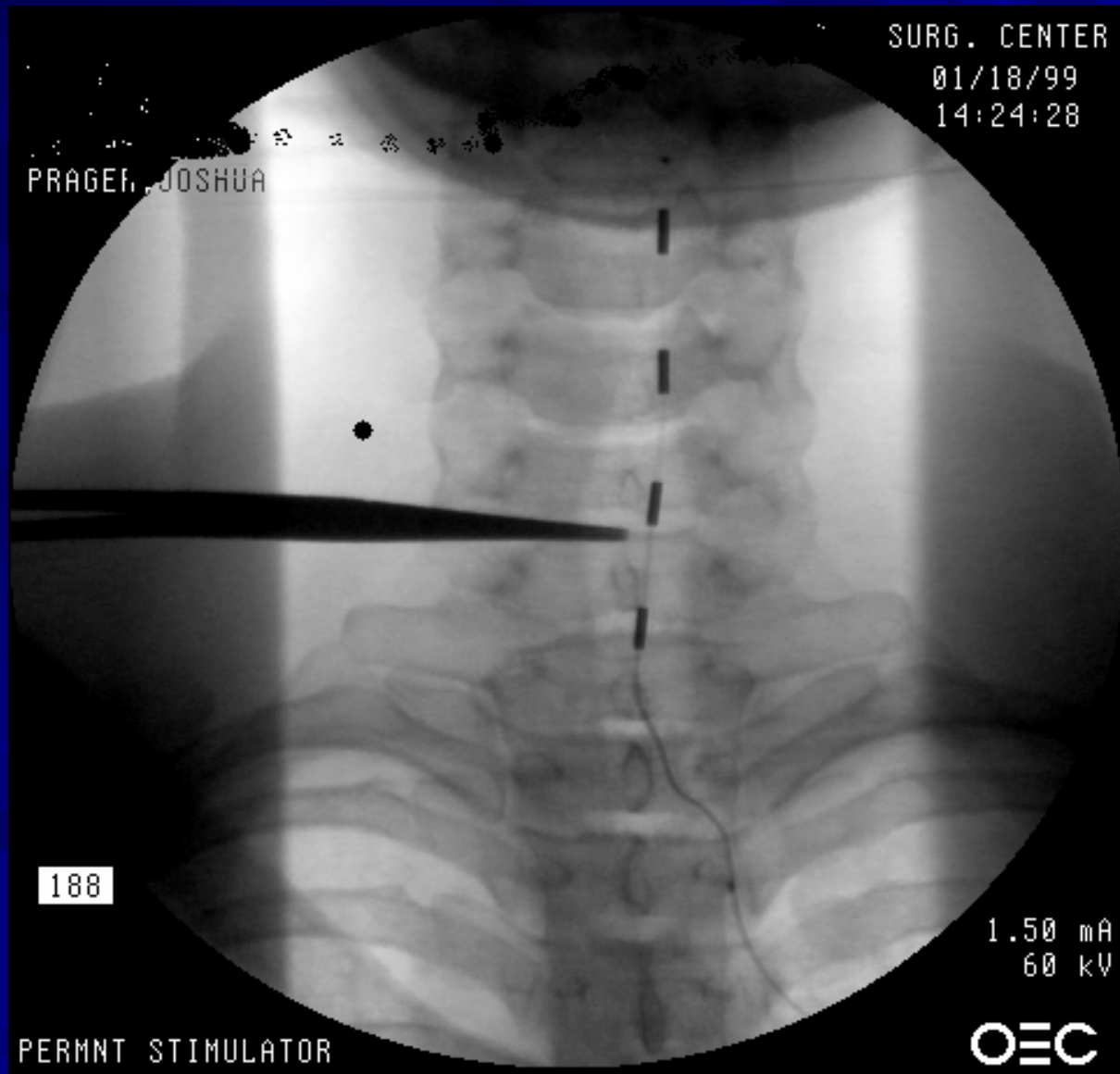
# Neurostimulation

- Spinal cord stimulation (SCS)
  - Type I and Type II
- Peripheral nerve stimulation (PNS)
  - Consider in Type II if symptoms limited to single nerve distribution

SCS: Implantable Pulse Generator or Radiofrequency System, PNS: Radiofrequency System

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

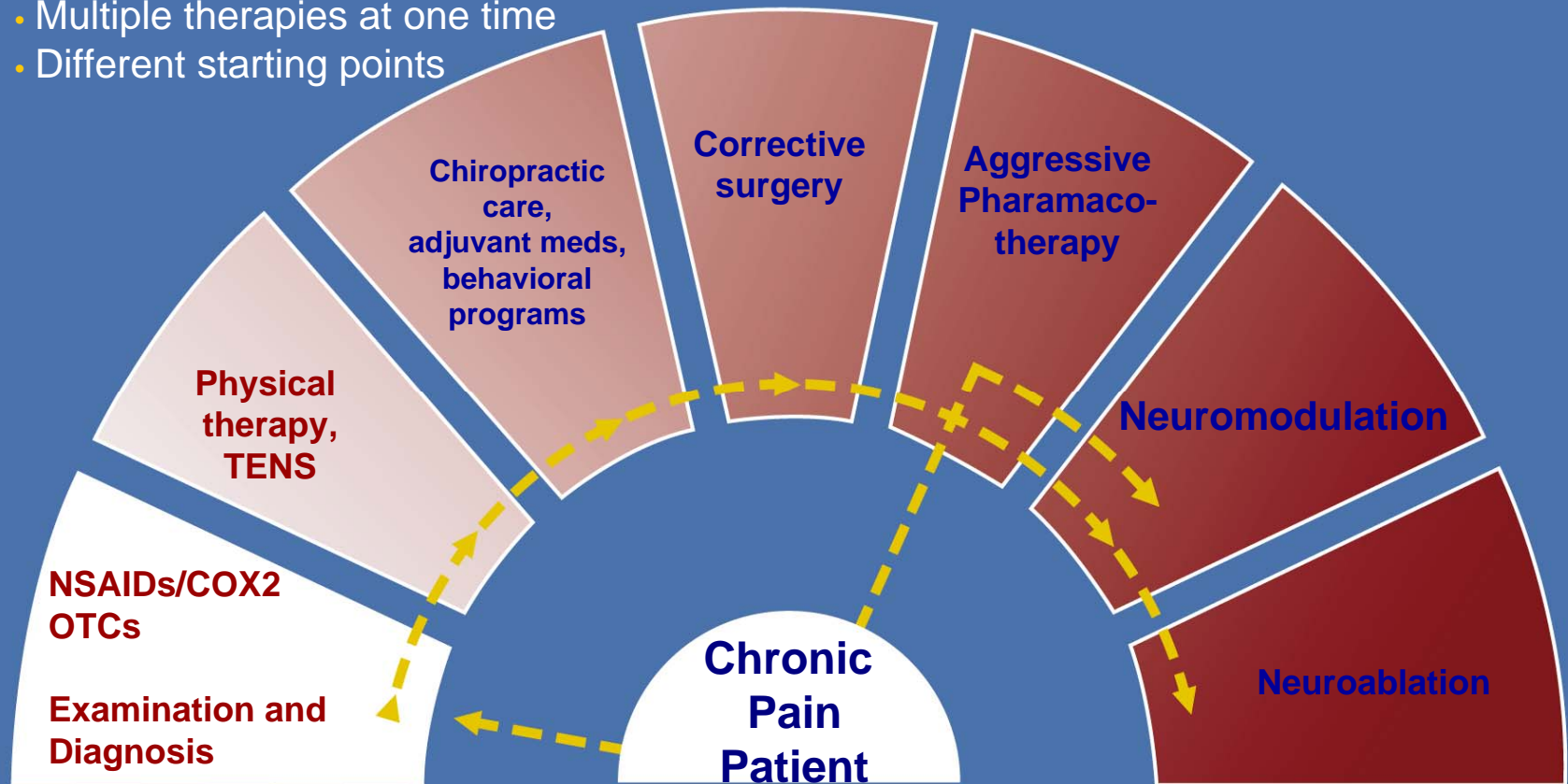
# Cervical Spinal Cord Stimulation



# Pain Management Continuum

## A Flexible Approach

- Different time frames
- Multiple therapies at one time
- Different starting points



# Spinal Cord Stimulation as a Temporary Treatment for Complex Regional Pain Syndrome

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# Patient Selection

- Objective evidence of pathology
- Inadequate pain relief and/or intolerable side effects from more conservative therapies
- Psychological evaluation
- Absence of drug-seeking behavior

# Prophylaxis for surgery in CRPS patients

- Ipsilateral epidural catheter place under fluoroscopy
- Low dose local anesthetic and fentanyl
- 19 patients thusfar
- No recurrence with surgery

# Complex Regional Pain Syndromes

- ❖ CRPS are nervous system disorders.
- ❖ The key to treatment is functional restoration.
- ❖ Peripheral destructive procedures do not address the central component of the syndromes.