

# Complex Regional Pain Syndrome (CRPS) Diagnosis and Management

Nashville, 2017


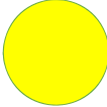


# Introduction


- Pain Medicine specialist with a special interest in complex pains in adults and children
- Assistant Professor (Clinical) – Brown Medical School, Rhode Island, USA

# Disclosure and disclaimer

- I have no actual or potential conflict of financial interest in relation to this presentation or program
- This presentation will discuss “off-label” uses of medications
- Discussions in this presentation are for a general information purposes only. Please discuss with your physician your own particular treatment. This presentation or discussion is NOT meant to take the place of your doctor.

# Grading of treatment

- Effective 
- Worth trying 
- Use caution 
- Science 



How do you know if you  
have CRPS?



# How to confirm a diagnosis of CRPS

- See a specialist who treats CRPS [ not someone “its crps, I do not treat it” or “I do not know what it is, probably CRPS”]
- Look for the features of CRPS yourself. The diagnosis of CRPS depends on very specific criteria
- [www.rsdsa.org](http://www.rsdsa.org) is good place to start with
- The symptoms of CRPS can mimic other nerve pain conditions.



# Cause of CRPS

- Although by definition CRPS does not have a known cause
- Its just that we have not found the cause
- But what if we can identify a cause?
- Obviously, something is wrong
- Sometimes we can identify what is wrong and sometime we can't



# Diagnosis of CRPS





# Signs and Symptoms of CRPS

- Pain starts in one limb
- It can present in the trunk (spine, abdomen, chest wall, pelvis)
- Constant pain, even at rest with intermittent exacerbations.
- Temperature difference between two sides
- Color difference – comes and goes
- Swelling – comes and goes
- Area of pain larger than the primary injury



## Early and chronic stages

- The temperature difference is much more obvious in the early stages but as it becomes chronic, the difference may not be as obvious
- The color difference is much more obvious in the early stages
- Swelling is random and does not imply severity of the condition.



# Signs and Symptoms of CRPS

- Pain or uncomfortable sensation to touch
- Nail growth changes (faster, distorted),
- hair growth changes (coarser, darker, rapid growth, hair falling),
- skin changes – thin and shiny
- skin lesions – pin point lesions to blisters
- Increased sweating

# Color difference



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# Hair growth





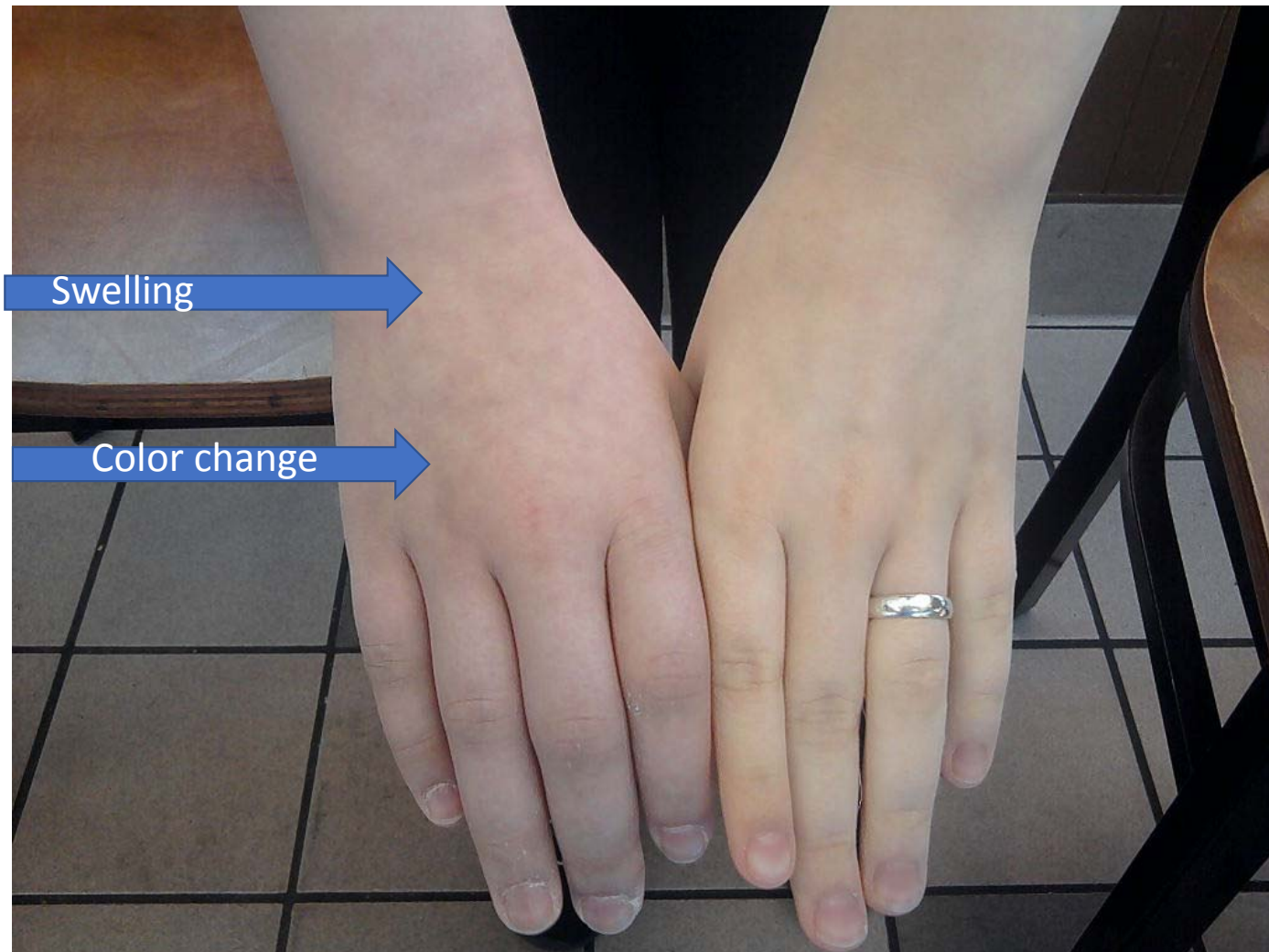
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Swelling

Nails growth faster,  
brittle, ridged







# Tests that are not helpful for diagnosing CRPS

- Imaging techniques – x-ray, MRI, fMRI, Three phase bone scan, bone density
- Blood tests
- Skin biopsy
- Sympathetic nerve tests – sweat test, sympathetic skin response,
- Nerve tests – EMG, nerve conduction,
- The tests MAYBE used if another diagnosis is suspected.

Atkins RM, Tindale W, Bickerstaff D, Kanis JA. Quantitative bone scintigraphy in reflex sympathetic dystrophy. Br J Rheumatol 1993;32(1):41-5.

Todorovic-Tirnanic M, Obradovic V, Han R, Goldner B, Stankovic D, Sekulic D, et al. Diagnostic approach to reflex sympathetic dystrophy after fracture: radiography or bone scintigraphy? Eur J Nucl Med

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# Best Diagnostic tool

- A good history and thorough physical examination
- The symptoms change over time - they become less



# CENTRAL SENSITIZATION

Key concept to understanding all chronic pain

# Central Sensitization

- The nervous system in our body becomes sensitized because of the constant barrage of pain signals



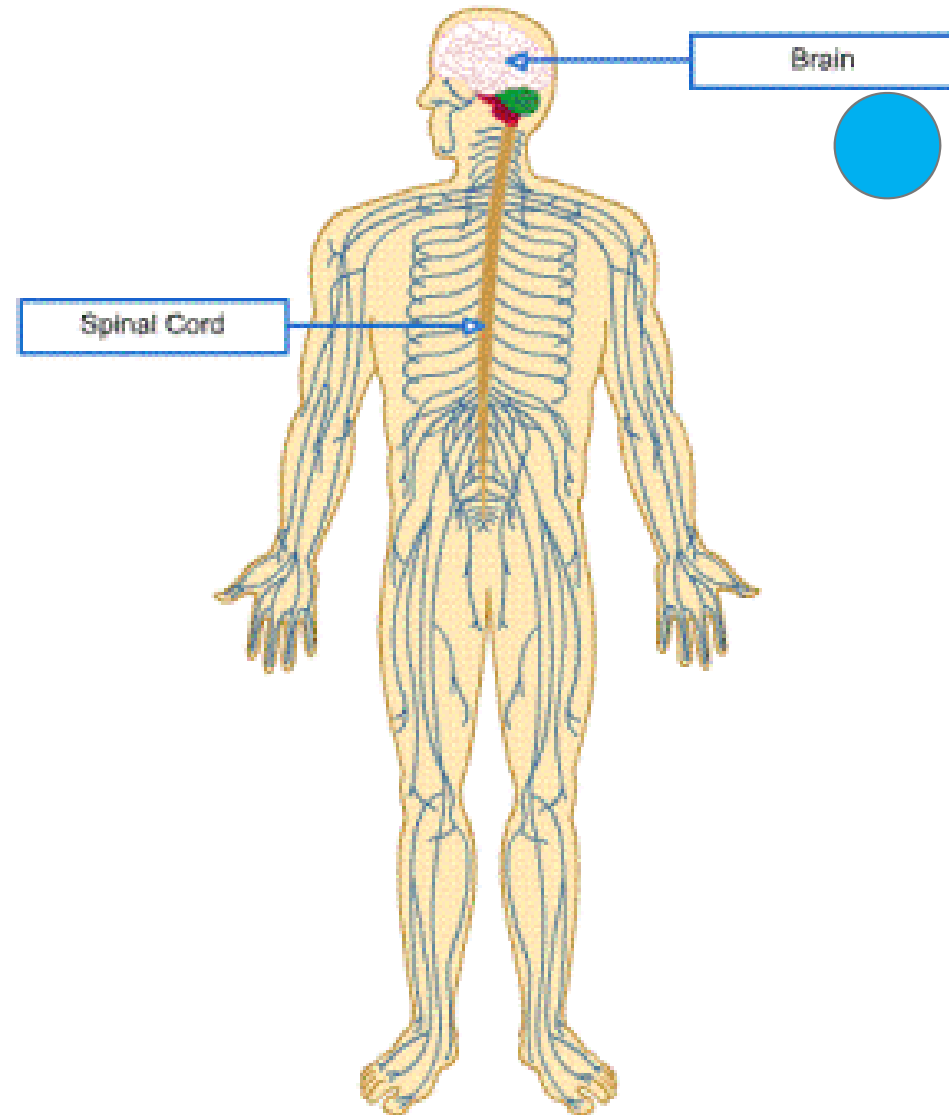
# Central Sensitization

- A normal sensation (e.g. soft touch) produces an abnormal response (like pain) because the brain and spinal cord are sensitized
- Definition: Increase in the excitability of neurons within the central nervous system (CNS) so that normal inputs produce abnormal responses

# Central Nervous System

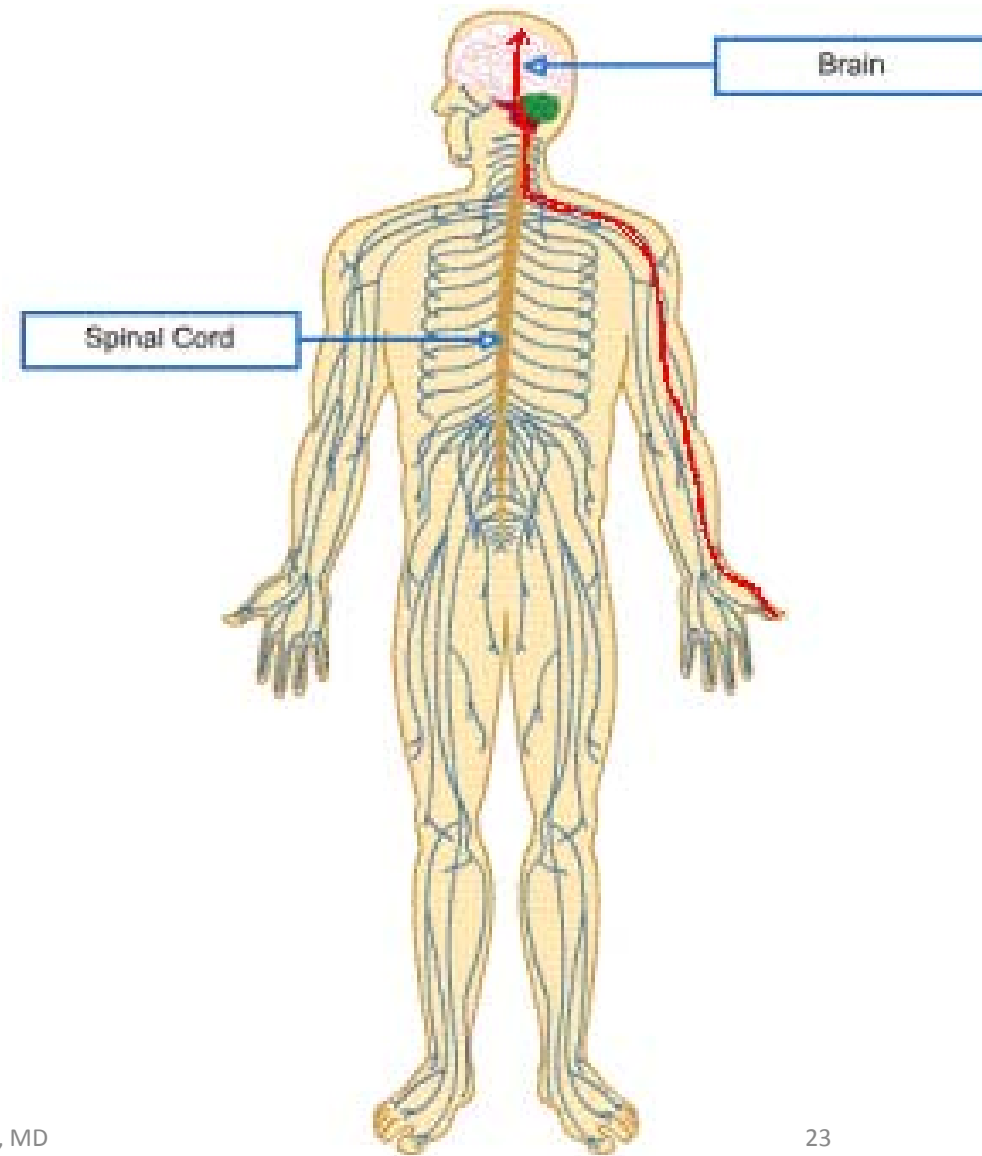
- The Central Nervous system (CNS) is made of 2 parts:

1. Brain
2. Spinal cord



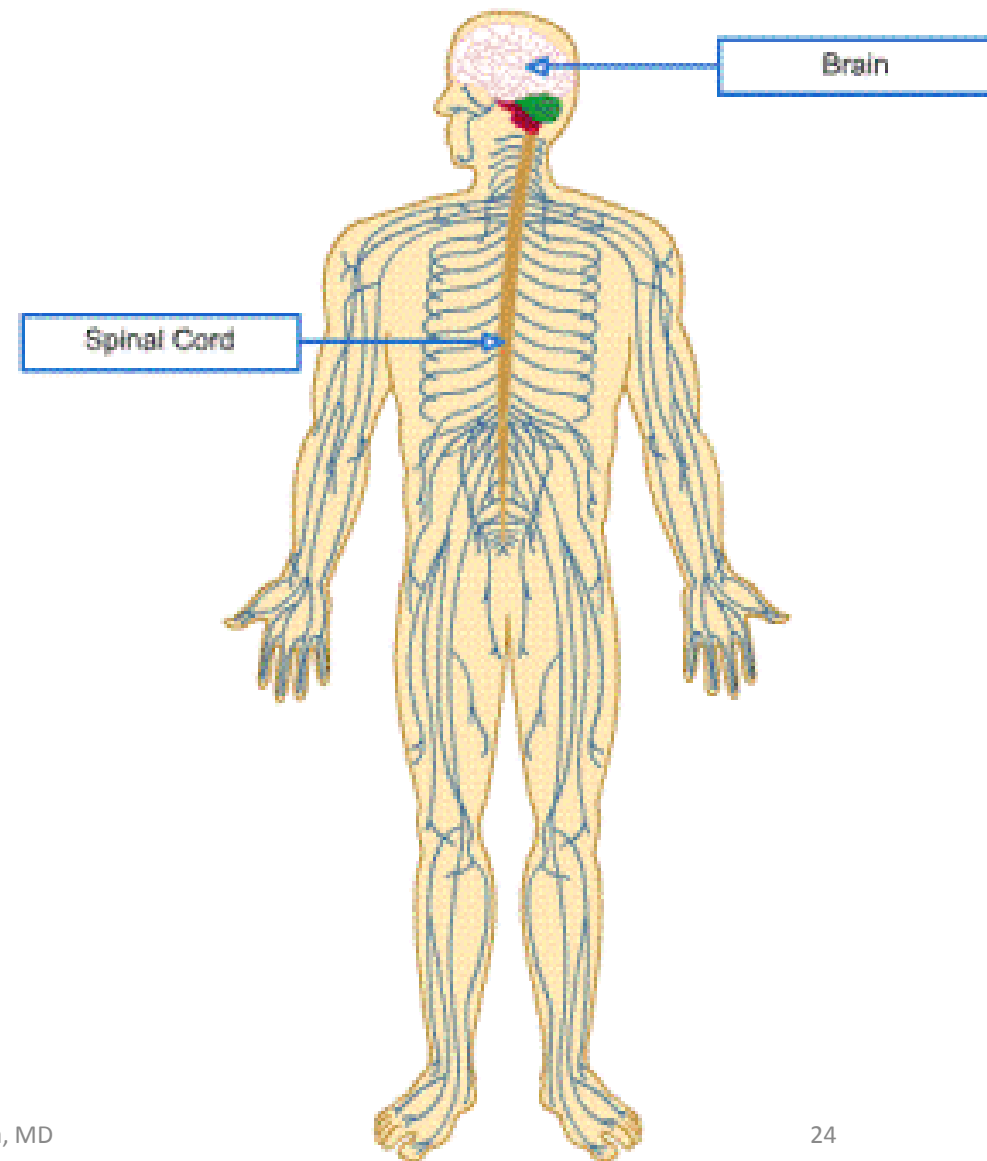
# Normal pain

- Normally, an injury will cause pain and the signals are sent to the brain
- In the brain, the signal gets an emotional component and we sense pain



# Normal pain

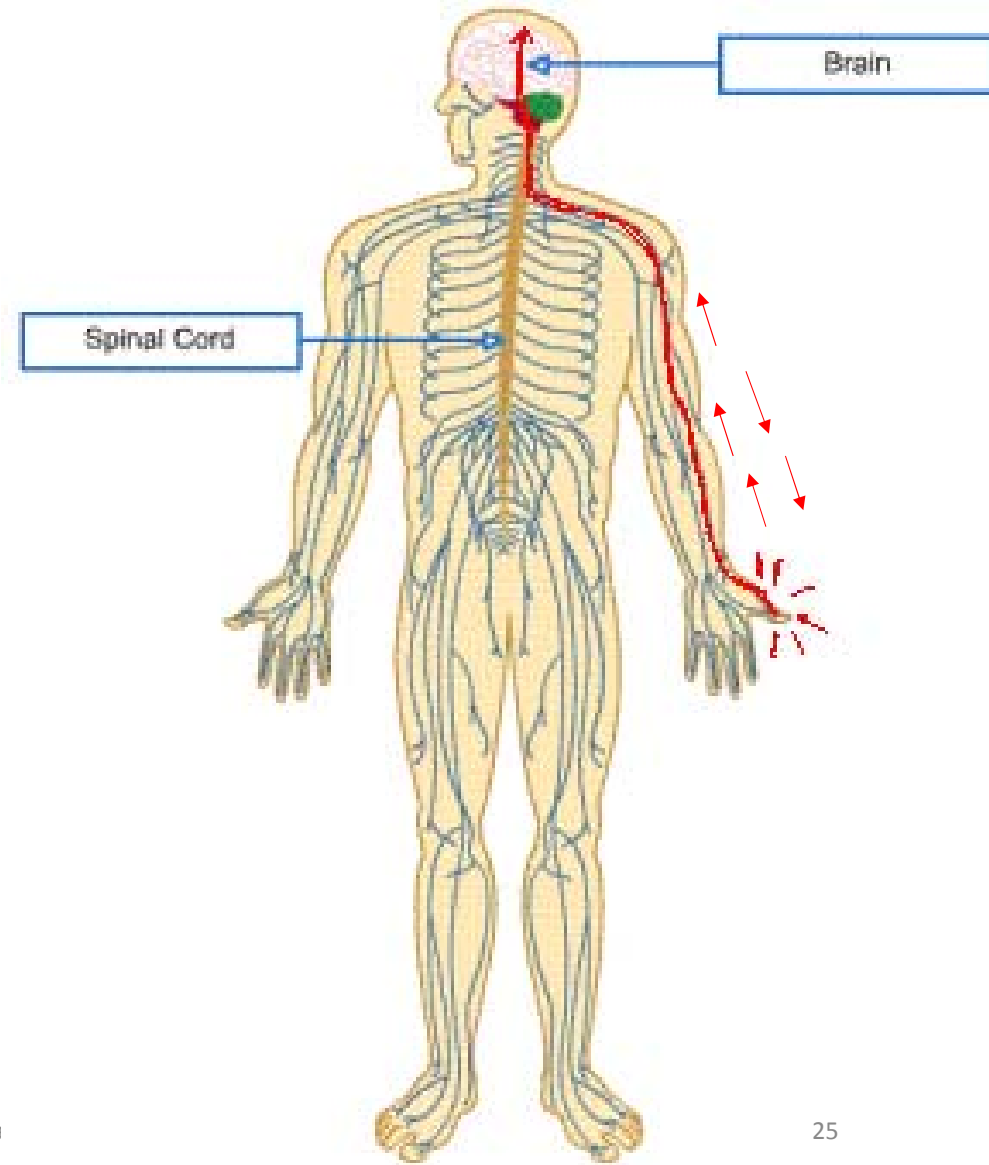
- Once the injury heals, the signals stop and everything returns to normal





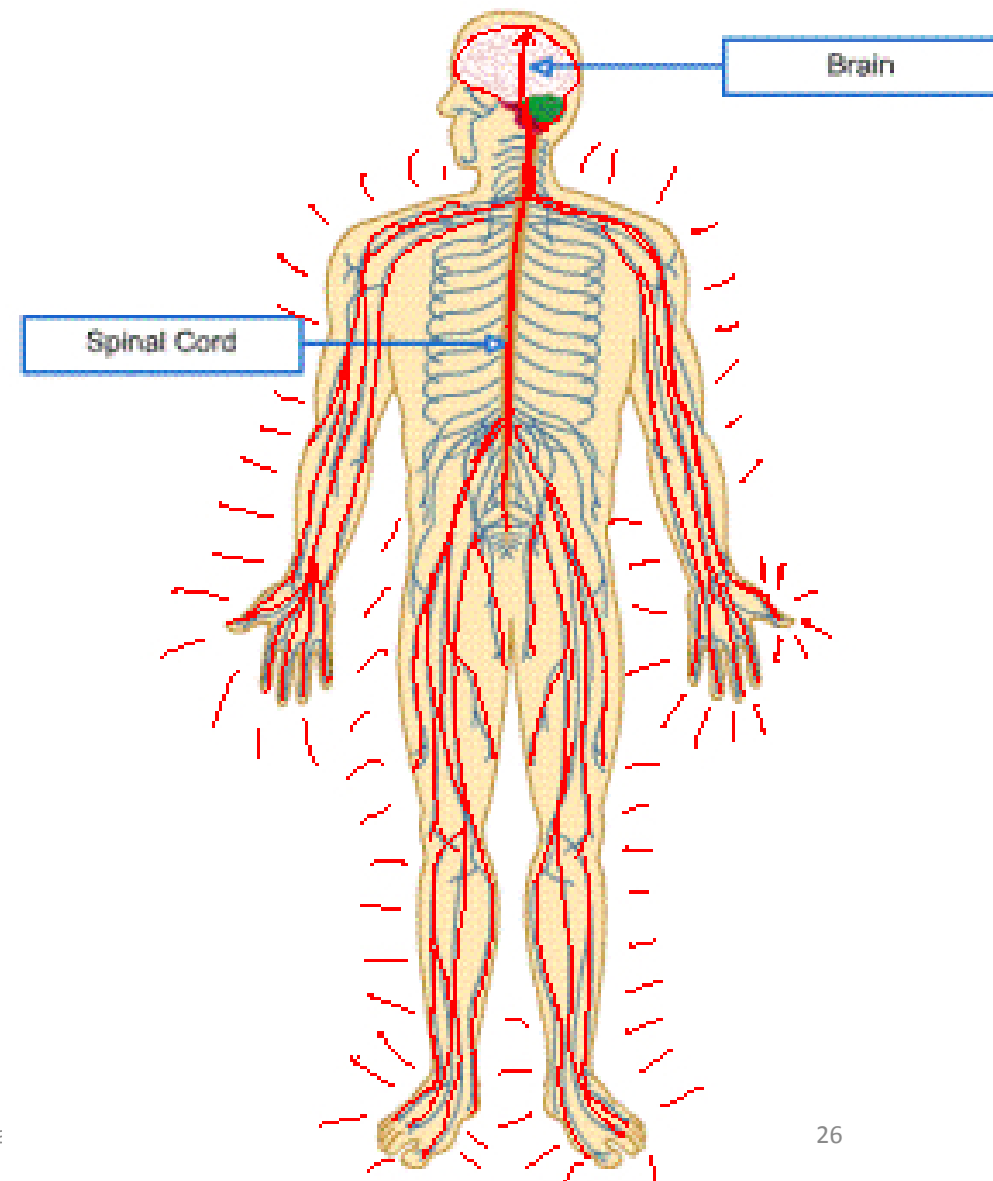
# CRPS

- In CRPS, the pain signals continue even after the injury heals
- The brain also tries to send signals down to suppress the pain signals
- In CRPS, there is a constant barrage of pain signals travelling up and down



# Central Sensitization

- The constant barrage of signals travelling up and down the brain and spinal cord makes the nervous system sensitive
- This is called Central Sensitization
- Hence, normal touch or a minor injury anywhere in the body, magnifies the pain greatly

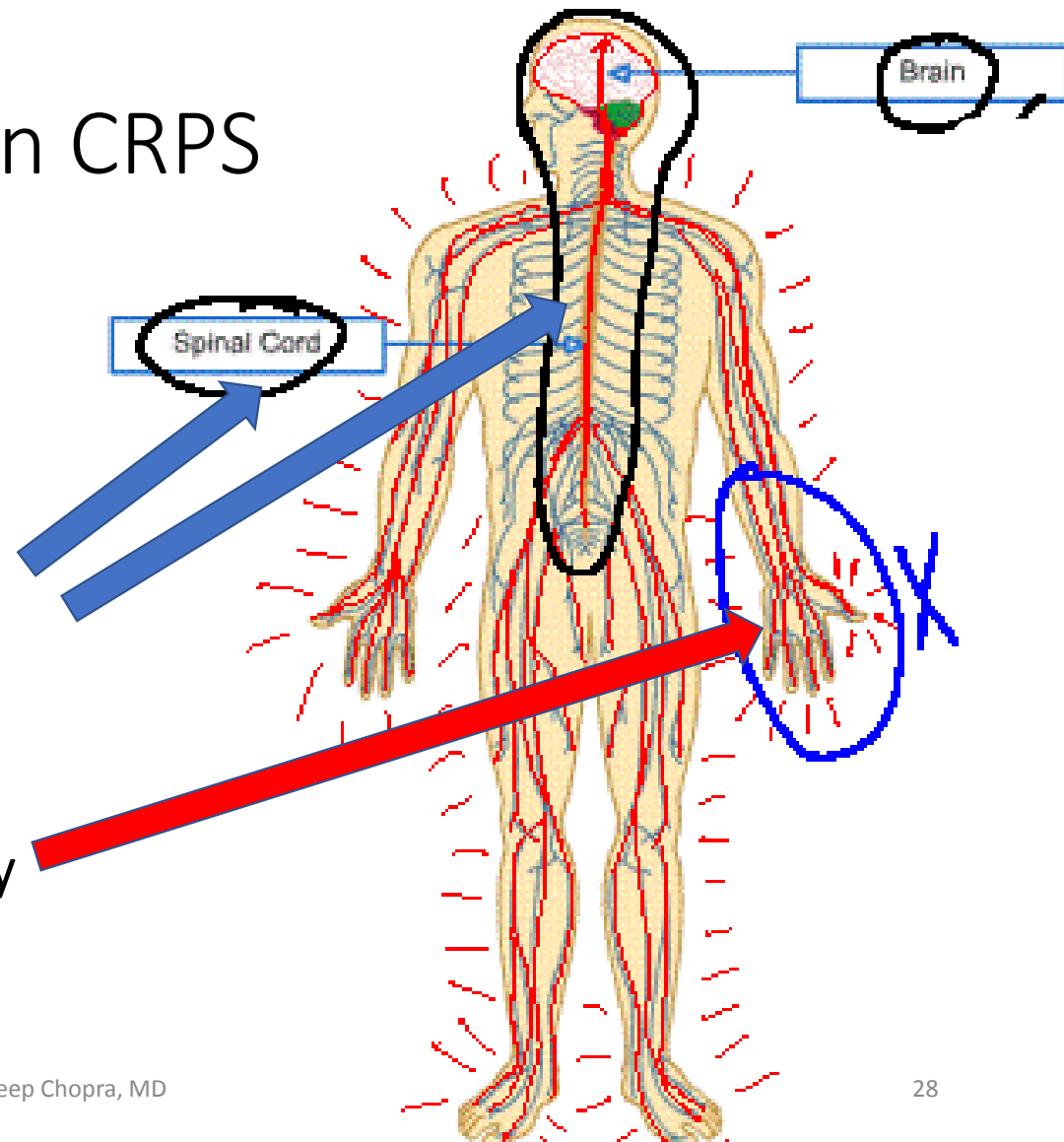


# Central Sensitization

- Normal sounds may trigger pain
- Normal lights may trigger pain
- Slightest change in weather (barometric pressure) can trigger pain

# Central Sensitization in CRPS

- In CRPS, the problem lies in the Central Nervous system
- Any treatment for CRPS, should be to treat it at the level of the Central Nervous system
- Treating the pain at the periphery may not help and may even make the pain worse



# What really happens in CRPS /Central Sensitization

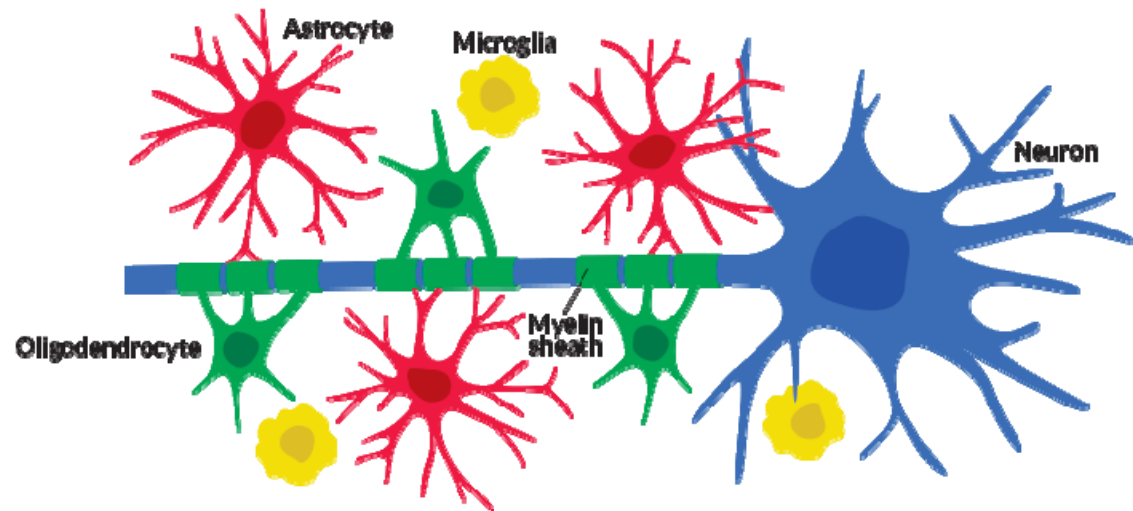


# Central Sensitization

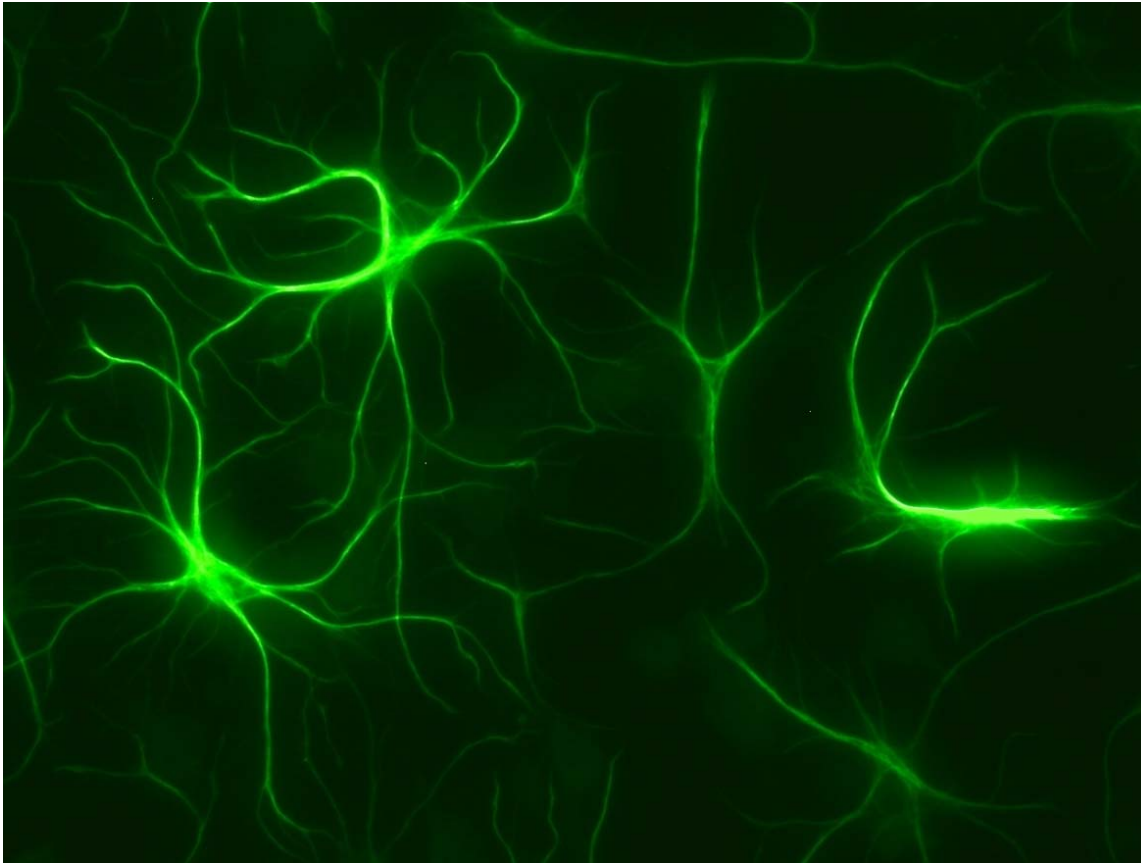
- Two things happen in Central Sensitization:
  1. Glial cells get activated
  2. NMDA receptors are activated

# Central Sensitization: Activated Glial Cells

- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function



This is what glial cells look like



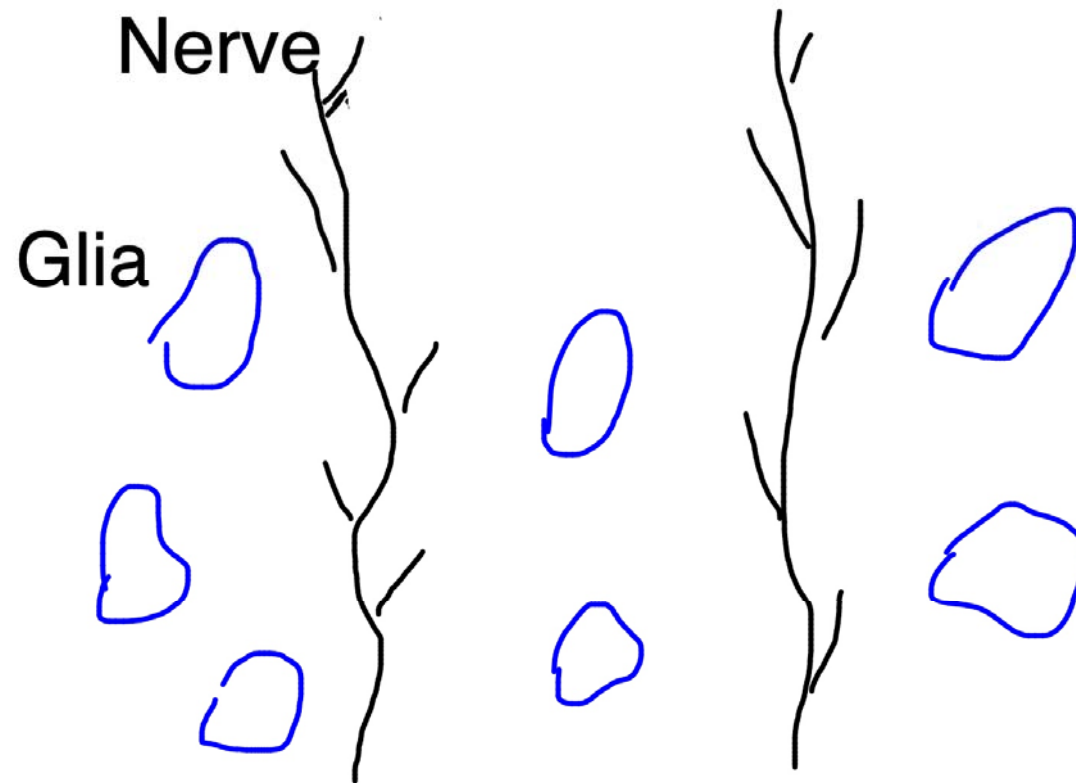
Courtesy Jarred Younger, PhD

Pradeep Chopra, MD

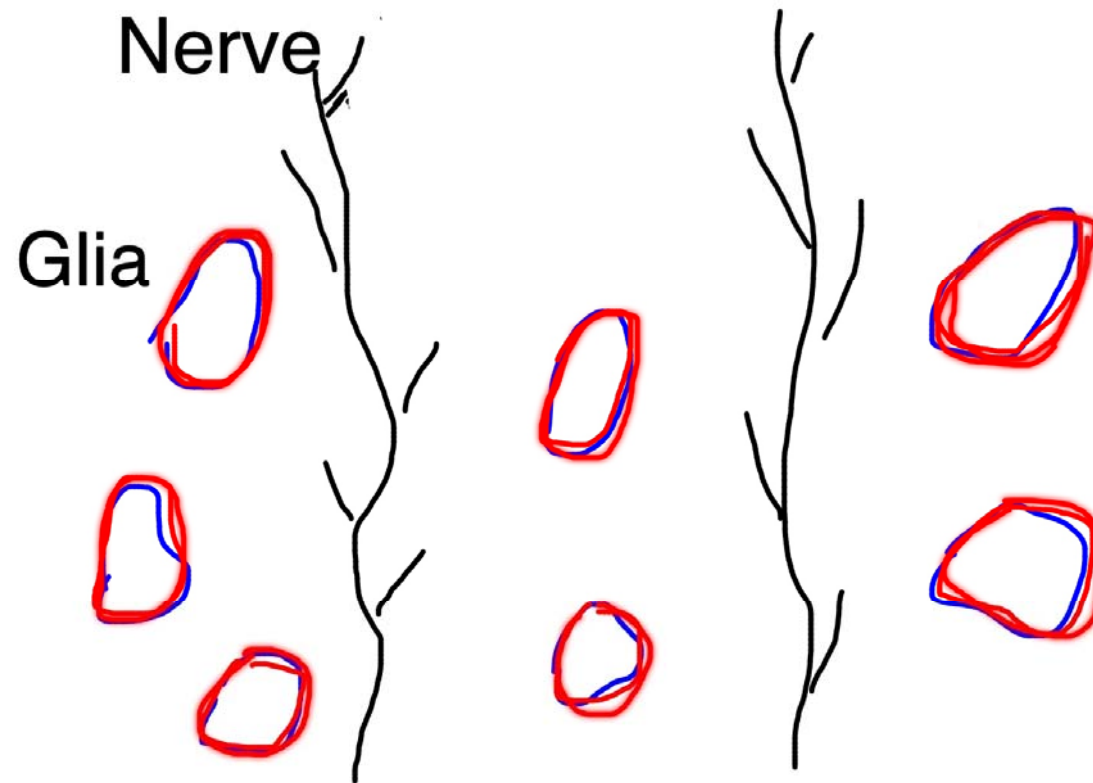
Sonja Paetau, University of Helsinki



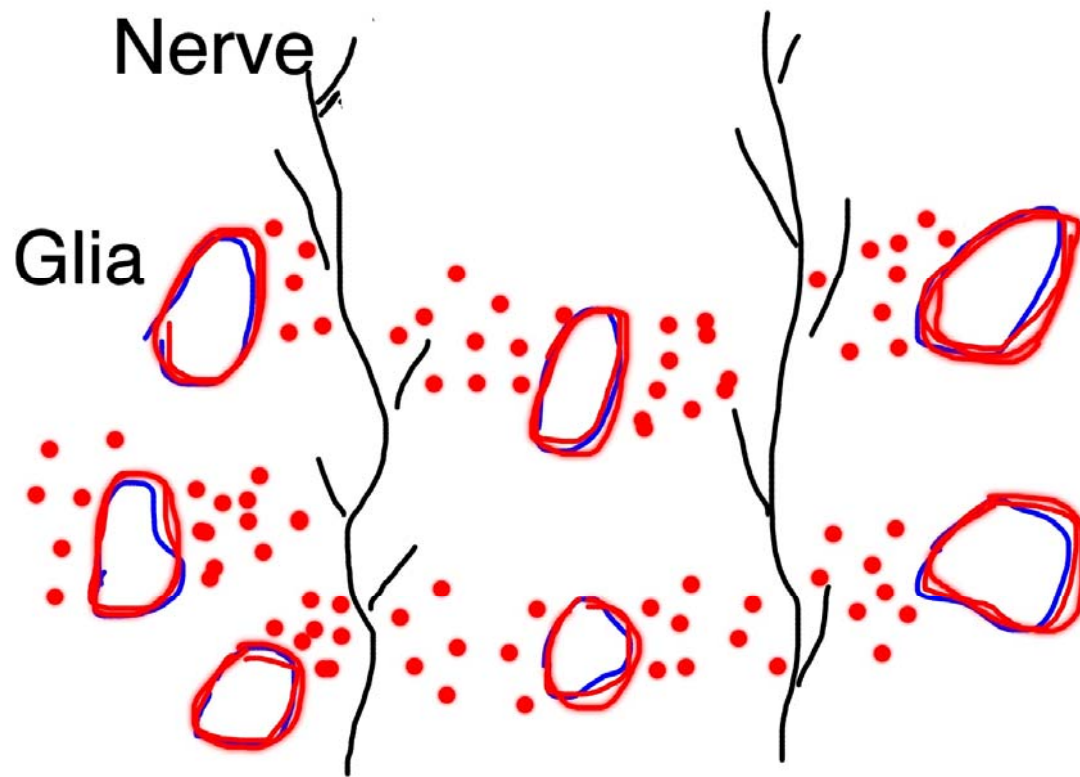
## Glia and nerves under normal conditions



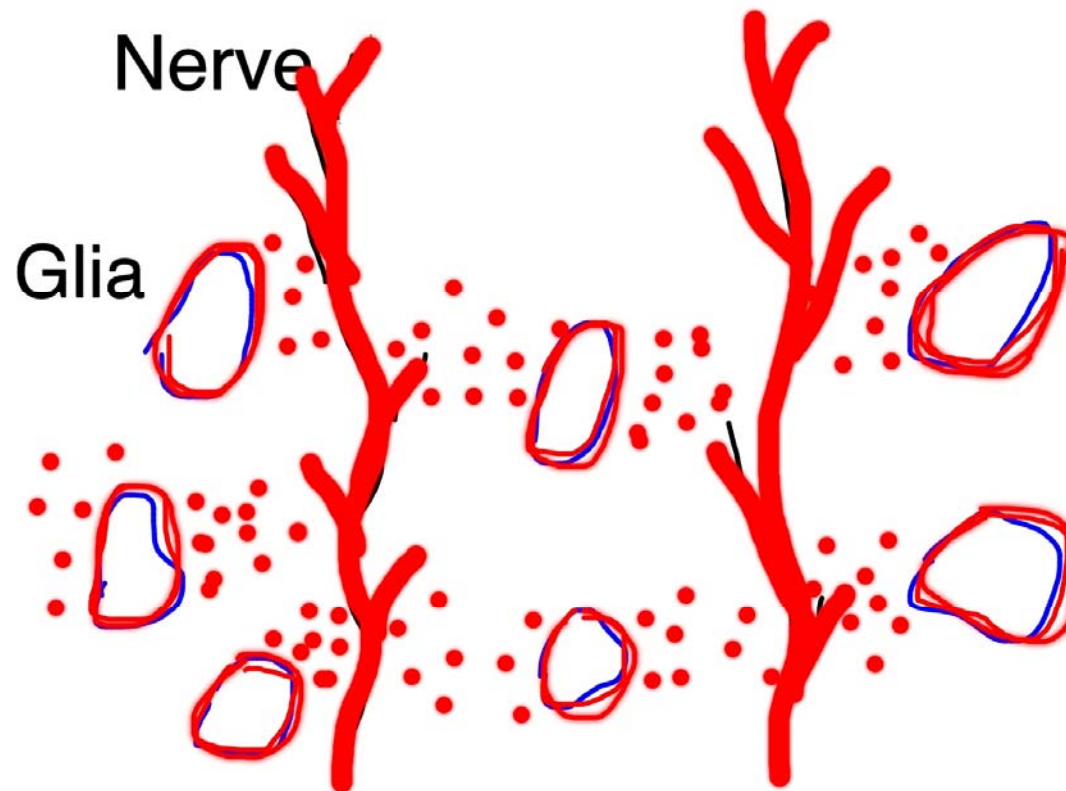
# Activated Glia



## Chemicals released by activated Glia



# Nerve inflammation

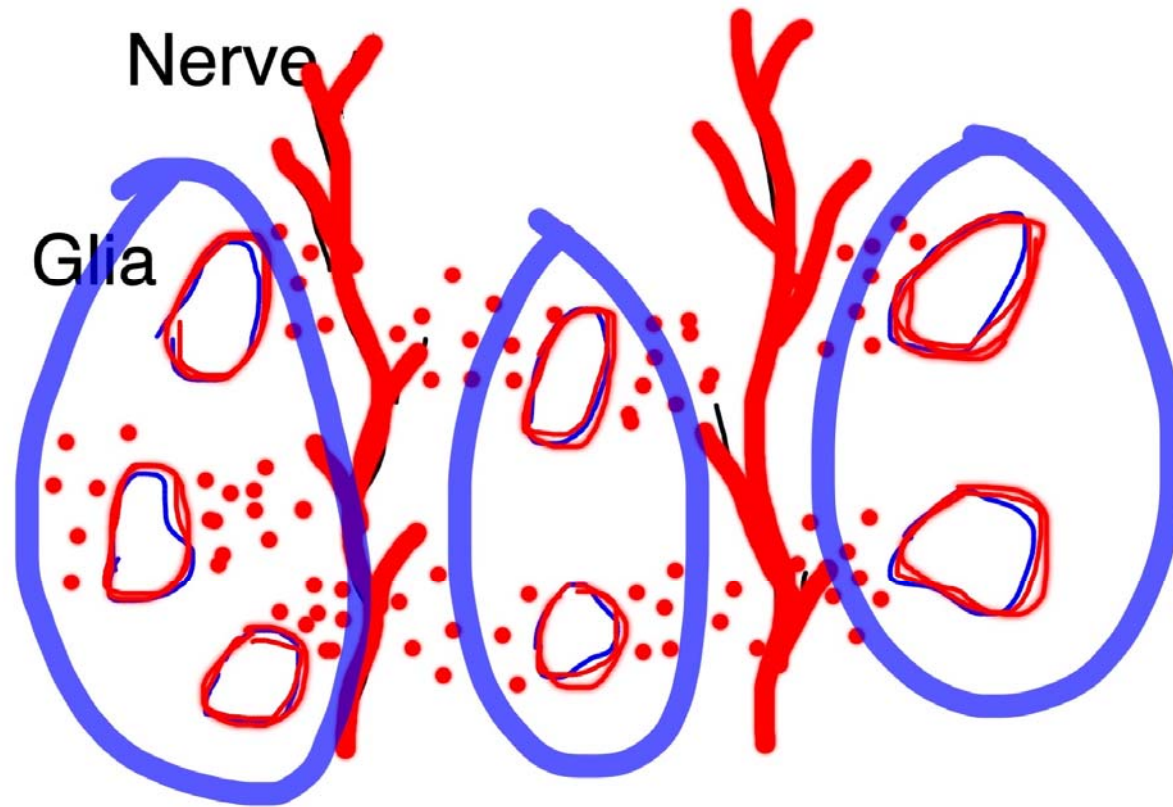




## Central Sensitization: Activated Glial Cells

- In CRPS these glial cells are activated.
- Activated glia release certain chemicals (Cytokines) that cause nerves to become inflamed
- Glial cells are an important link between the nervous system and the immune system, inflammation and pain

The problem is with the glia cells





# Spreading

- In long standing cases of CRPS, some patients develop similar symptoms in other areas of the body
- This is usually a result of increasing Central Sensitization.
- As the central nervous system become more and more sensitized, normal sensations to other parts of the body are felt as painful sensations.



# Treat the inflammation

- Management of Complex Regional Pain Syndrome should be directed towards what's causing the nerves to become inflamed
- Treating just the nerves does not reduce inflammation of the nerves (that is why nerve blocks, spinal cord stimulators or any form of electricity does not work).



# Management

Complex Regional Pain Syndrome (CRPS)

Reflex Sympathetic Dystrophy (RSD)

# Basic guidelines in treating CRPS

- Start treatment immediately, even if you suspect CRPS
- Must be evaluated by a physician who is very familiar with it, to start appropriate therapy
- Multidisciplinary approach - team work.

# Management of CRPS – step A

- The first step to do is to confirm if it is CRPS.
- Very often patients are told that it is CRPS because a cause of the pain could not be found
- The criteria for diagnosis of CRPS very specific

# Management of CRPS – step B

- The next thing to do is to determine if its CRPS I or CRPS II

# CRPS I and CRPS II

- In CRPS I – we do not know the exact nerve that is damaged
- In CRPS II – limited to a specific nerve distribution
- Some of the treatments are common to both
- In CRPS II, fixing the cause of the nerve damage may help

## CRPS-NOS (not otherwise specified)

- CRPS-NOS (not otherwise specified): partially meets CRPS criteria;
- not better explained by any other condition. Usually used for patients who had CRPS but now present with some features and do not meet all the criteria.

# Management of CRPS – possible causes of CRPS I

- Unknown
- Autoimmune dysfunction
- Gastrointestinal (?)

# CRPS II

This was the first CRPS discovered, even before CRPS I





## CRPS II

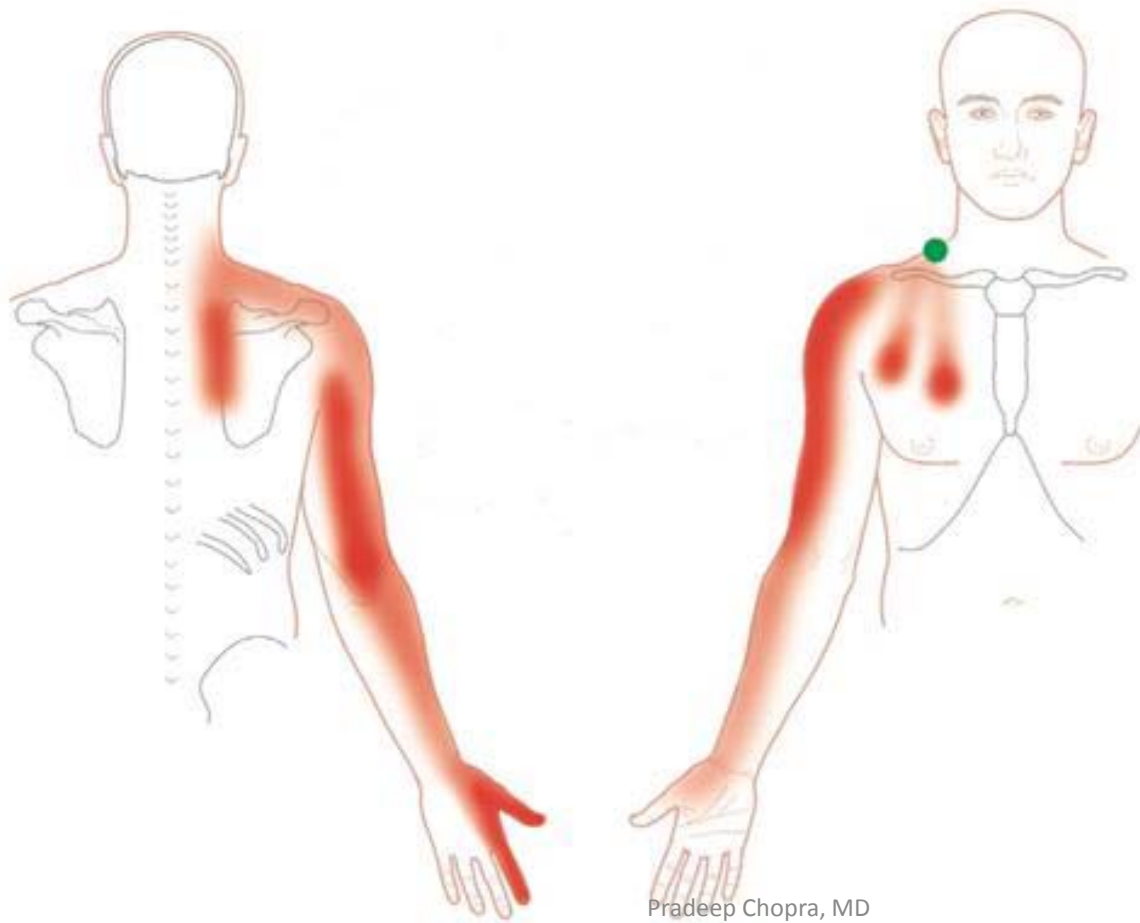
- Most of the symptoms are similar to CRPS I
- There is a major nerve damage that can be identified
- A careful examination may identify the nerve affected



## Some examples of CRPS II

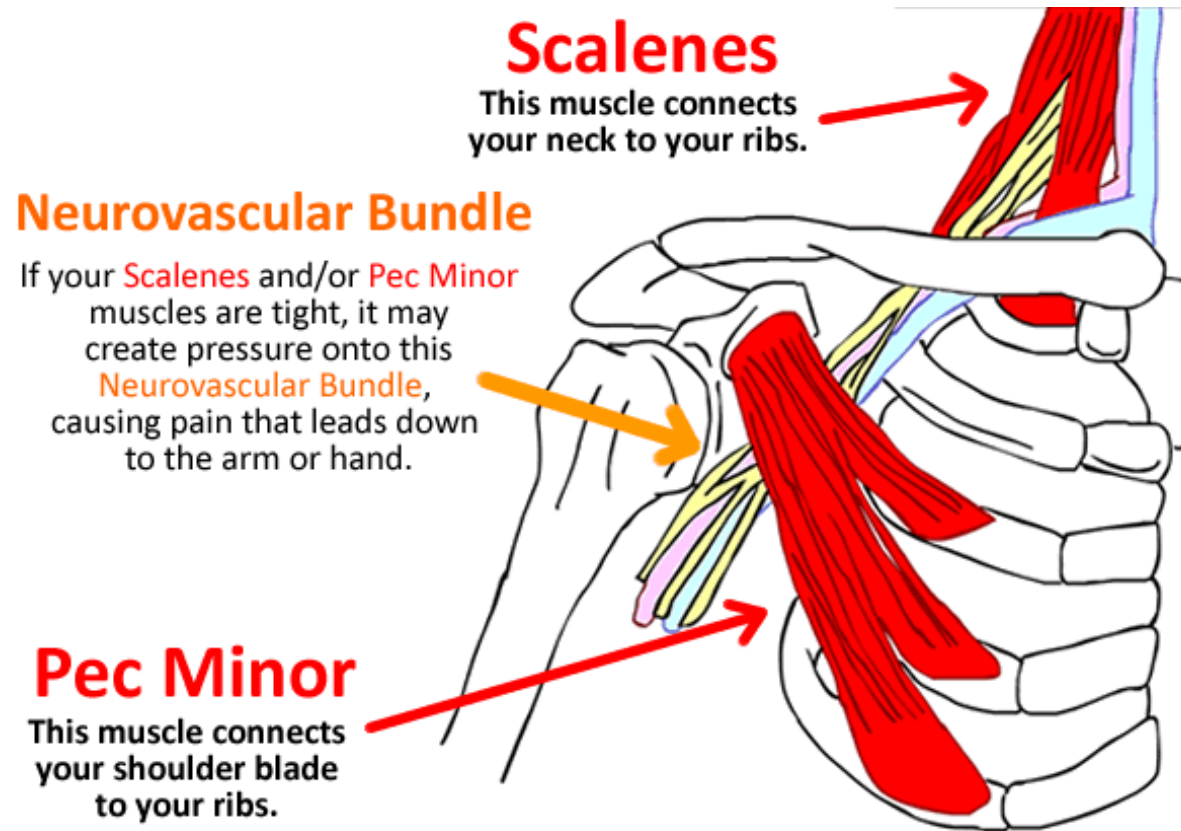
- Arms – Thoracic outlet syndrome, ulnar nerve entrapment
- Legs – Common Peroneal neuralgia,
- Scarring after a nerve injury.
- Ehlers Danlos Syndromes – diffuse neuroinflammation from recurrent subluxations and dislocations.

# Pain patterns in Thoracic Outlet syndrome



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# Thoracic Outlet Syndrome





# CRPS II from Thoracic Outlet Syndrome

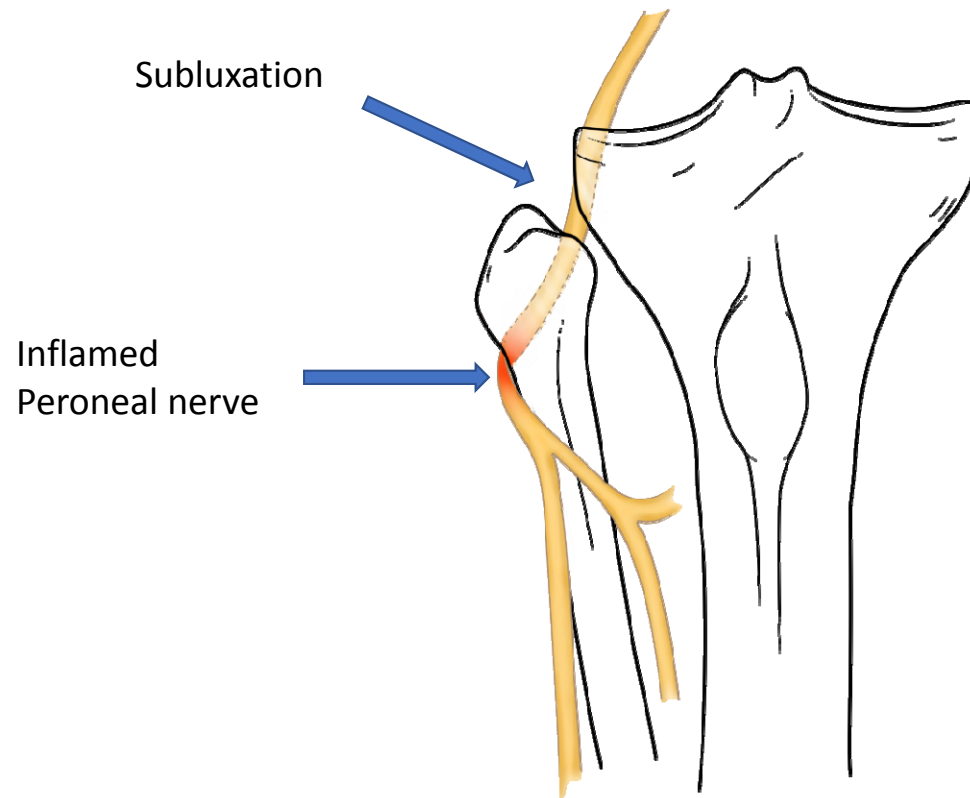
- Physical therapy
- Botox
- Kinesio taping
- Surgical correction - if all else fails



## An example of CRPS II in the leg

- Symptoms of CRPS II may develop in the leg after impingement of the Common Peroneal nerve
- This nerve lives below and just outside the knee

# CRPS II in the leg



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# Dysautonomia (maybe a complication of CRPS)

POTS – Postural Orthostatic Tachycardia syndrome



# Symptoms

- Dizziness – especially when standing up
- Heart racing
- Fatigue
- Headaches
- Cold hands and feet
- Poor concentration “brain fog”

# POTS - Postural Orthostatic Tachycardia syndrome

1. Lie down for 5 minutes – check blood pressure and pulse
2. Stand up – check blood pressure and pulse
3. Keep standing for 10 minutes - check blood pressure and pulse

## POTS - Postural Orthostatic Tachycardia syndrome

- Increase in heart rate by 30 beats/min within 10 minutes of standing
- heart rate of 120 beats / min within the first 10 minutes of standing
- No significant change in blood pressure
- Syncope or almost syncope (fainting)
- In children an increase of 40 beats/minute

# Treatment of POTS

- Increase oral salts
- Increase oral electrolyte fluids
- Cardiologist
- Midodrine
- Propranolol
- Mestinon

# Mast Cell Activation Syndrome (May be a complication of CRPS)

## MCAS

# Mast Cell Activation Syndrome (MCAS)

- Rashes, hives, itchy
- Fatigue, tiredness
- Muscle pain
- Bone and joint pain
- Abdominal pain – cramping, urgency, diarrhea
- Flushing especially after a hot shower
- Bladder pain – interstitial cystitis

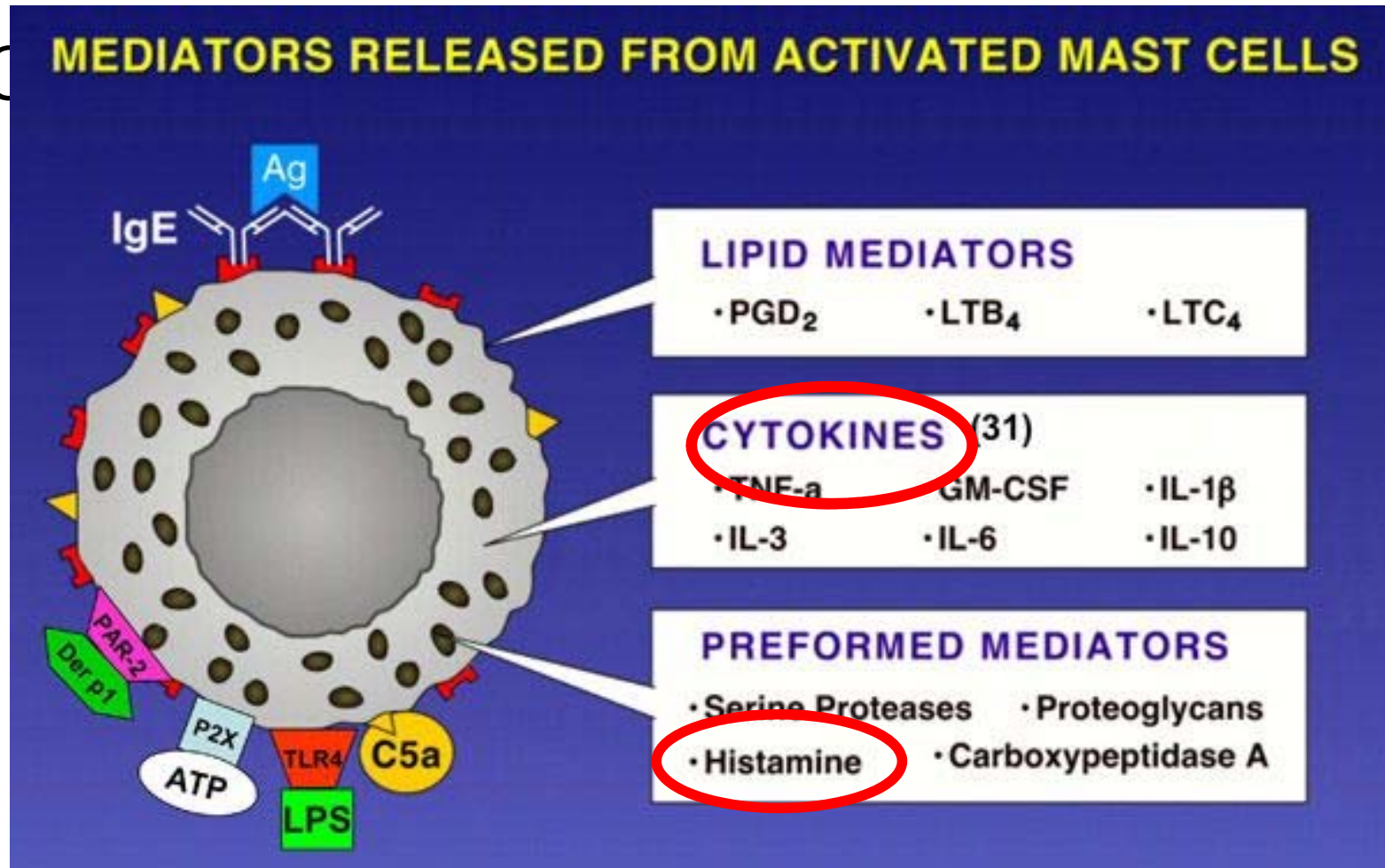
Jonathan J. Lyons, MD<sup>1</sup>, Guangping Sun, MD<sup>1</sup>, Kelly D. Stone, MD, PhD<sup>1</sup>, Celeste Nelson, CRNP<sup>1</sup>, Laura Wisch, MSN<sup>1</sup>, Michelle O'Brien, RN, BSN<sup>1</sup>, Nina Jones, RN, BSN<sup>2</sup>, Andrew Lindsley, MD, PhD<sup>3</sup>, Hirsh D. Komarow, MD<sup>1</sup>, Yun Bai, MS<sup>1</sup>, Linda M. Scott, MS, CRNP<sup>1</sup>, Daly Cantave, MSN<sup>4</sup>, Irina Maric, MD<sup>5</sup>, J. Pablo Abonia, MD<sup>3</sup>, Marc E. Rothenberg, MD,

MD<sup>3</sup>, Lawrence B. Schwartz, MD, PhD<sup>6</sup>, Joshua D. Milner, MD<sup>1</sup>, and Todd M. Wilson, DO<sup>1</sup>. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol. 2014 May ; 133(5): 1471–1474. doi:10.1016/j.jaci.2013.11.039

# Mast cells

- Cells in blood
- Normally present in blood
- Contain histamine, cytokines and a bunch of other chemicals
- Involved in allergy, wound healing and protection against infection

MC



Courtesy Ann Maitland, MD



# Mast Cell Activation Syndrome (MCAS)




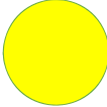

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<https://mastcellblog.wordpress.com/mastcell/>

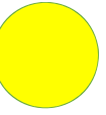
# Management of Mast Cell Activation Syndrome (MCAS)

- Anti-histamine:
  - Diphenhydramine, cetirizine (H1 blockers)
  - Ranitidine, famotidine (H2 blockers)
- Cromolyn
- Montelukast (Singulair™)
- Low histamine diet

# Start low, go slow

# Grading of treatment

- Effective 
- Worth trying 
- Use caution 
- Scientific 



# Commonly used medications

- Gabapentin
- Pregabalin (Lyrica <sup>TM</sup> )
- Milnacipran (Savella<sup>TM</sup>)
- Amitriptyline or nortriptyline
- Duloxetine (Cymbalta<sup>TM</sup>) - avoid



## Other commonly used pain medications

- Acetaminophen / paracetamol
- Non steroidal anti-inflammatory drugs (NSAID) like ibuprofen, naproxen
- Steroids
- Not very helpful in CRPS. They may help a little when taken with other medications



## Other commonly used pain medications

- Topical creams – useless and expensive
- Remember the pain is in the Central Nervous System (brain and spinal cord) not the limb



# Ketamine



# Central Sensitization

- Two things happen in Central Sensitization:
  1. Glial cells are activated
  2. NMDA receptors are activated

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# Central Sensitization - NMDA receptors

- In CRPS there is activation and proliferation of NMDA receptors

Activation of the NMDA receptors makes the Central Nervous system  
increases pain and

- decreases sensitivity to opioids

Milligan ED, Watkins LR (2009) Pathological and protective roles of  
glia in chronic pain. Nat Rev Neurosci 10:23–36

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# Ketamine

- Ketamine is a good NMDA Receptor blocker
- One of the safest anesthetic drugs
- Powerful analgesic even at low doses
- Poor absorption when administered orally.
- Effective as IV or sublingual (Troche) or nasal

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Medicine 2004;5(3):263-75.

Braden Ghossein MD

# Ketamine infusion – good news

- FDA is considering approving Ketamine infusions for the treatment of depression
- Once it gets approved, it should be covered by insurance
- More and more centers are now offering ketamine infusions

# Factors that are important in getting the best out of a ketamine infusion



- Ketamine infusions are good only if done in conjunction with other therapies



# Low dose Ketamine in CRPS

- Administered in sub-anesthetic doses – ketamine blocks NMDA receptors without causing too many side effects
- In CRPS it decreases Central Sensitization
- Rough estimates – 85% show improvement in daily activities, reduction in their medications and improved lifestyles
- It is not a cure. It is to be done along with other therapies

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Medicine 2004;5(3):263-75. Pradeep Chopra, MD



# Ketamine – out patient

- Increasing dose of ketamine over 10 days – loading dose
- Start at a low dose, increase everyday
- Infusion done over 4 to 5 hours
- Full standard monitoring
- Qualified personnel must be present at all times with the patient





## IV Ketamine - boosters

- Very important part of the treatment protocol
- As the effect of the initial ketamine wears off, the glial cells begin to get activated again.
- Boosters for one day or two days every 4 to 8 weeks depending on the severity, chronicity and response
- The protocol has to be customized to each patient



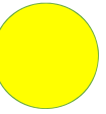
# Ketamine side effects

- Most of the side effects are temporary and short lived and reversible.
- We do not know of any long term side effects of ketamine infusions.
- Temporary side effects: Nausea, vomiting, colorful dreams, hallucinations, headache



# Ketamine oral

- Oral ketamine – don't bother
- Unpredictable effects



# Opioids

- Very little role in CRPS
- Opioids increase glial cell activation which increases central sensitization
- Maybe helpful at low doses if there is associated structural pain.



# Low Dose Naltrexone

## LDN



## Low Dose Naltrexone (LDN)

- Competitive antagonist of opioid receptors
- Clinically used for 30 years for addiction
- Suppresses glial cell activation, which....
- Attenuates production of pro-inflammatory cytokines and neurotoxic superoxides (chemicals that cause inflammation)



## Low Dose Naltrexone (LDN)

- There are several theories as to how LDN may work.
  1. Transiently blocks opioid receptor leading to positive feedback production of endorphins (Zagnon)
  2. LDN increases production of OGF (opioid growth factor) as well as number of and density of OGF receptors by intermittently blocking the opiate receptor. Increased in OGF repairs tissue and healing.
  3. Naltrexone blocks the effect of TLR4 (Toll Like receptors) which decreases glial cell activation



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## Low Dose Naltrexone (LDN)

- Dose can vary anywhere between 1.75mg to 4.5mg
- May cause insomnia, mild headaches initially.
- Patients report increased physical activity, flare ups not as acute, better tolerance to pain.
- Recommend a trial of at least 6 months
- To avoid all opioids or tramadol.
- Has to be made by a compounding pharmacy
- Inexpensive

## Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN)

Pradeep Chopra · Mark S. Cooper

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**Abstract** Complex Regional Pain Syndrome (CRPS) is a neuropathic pain syndrome, which involves glial activation and central sensitization in the central nervous system. Here, we describe positive outcomes of two CRPS patients, after they were treated with low-dose naltrexone (a glial attenuator), in combination with other CRPS therapies. Prominent CRPS symptoms remitted in these two patients, including dystonic spasms and fixed dystonia (respectively), following treatment with low-dose naltrexone (LDN). LDN, which is known to antagonize the Toll-like Receptor 4 pathway and attenuate activated microglia, was utilized in these patients after conventional CRPS pharmacotherapy failed to suppress their recalcitrant CRPS symptoms.

**Keywords** Chronic pain · Complex regional pain syndrome · CRPS · Reflex sympathetic dystrophy · RSD · Neuropathic pain · Naltrexone · Fixed dystonia · Allodynia · Vasomotor · Ulceration · Dystonic spasms · Conversion disorder · Functional movement disorder · LDN

### Introduction

Complex Regional Pain Syndrome (CRPS) is a

dysfunctions. One of the characteristic symptoms of this condition is that the pain is out of proportion to the initial injury. Diagnoses of CRPS are often delayed because it is under recognized (Binkley 2012). If effective treatments are given early enough in progression of the disease, there is reduced chance for the spread of regional pain, autonomic dysfunction, motor changes, and negative sensory symptoms, such as hypoalgesia (Marinus et al. 2011). As CRPS progresses, it becomes refractory to sympathetic nerve blocks, conventional analgesics, anticonvulsants and antidepressants.

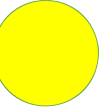
During neuroimmune activation, TLR4 (Toll-Like Receptor 4) is upregulated in microglia, resident immune cells of the central nervous system (Watkins et al. 2009). After transection of the L5 spinal nerve in the rat, TLR4 expression is increased in spinal microglia. This correlates with the rodent developing neuropathic pain (Tanga et al. 2005). From a post-mortem analysis of a CRPS patient, activated microglia and astroglia in the central nervous system (CNS) have been implicated in the generation of CRPS symptoms (Del Valle et al. 2009).

Activation of TLR4 in both microglia and CNS neurons augments the production of pro-inflammatory cytokines via the NF- $\kappa$ B pathway (Millington et al. 2009). L

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# Low Dose Naltrexone (LDN)

- <https://www.ldnresearchtrust.org>
- This website has more information on LDN



# Sensory Deprivation Therapy

- Isolation tank.
- Warm water with high quantities of EPSOM salt
- Subject floats on the water because of the high salt content
- No lights or sounds in the room
- All external stimulation to the Central Nervous system (brain and spinal cord) is cut off.
- Very helpful for Central Sensitization

# Sensory Deprivation Therapy





# Spinal Cord Stimulator (SCS)

- An electrode is inserted surgically into the epidural space and connected to an implanted generator
- The electrode produces an electrical current is felt as a tingling sensation and suppresses pain.
- Mechanism of action unknown
- Painful and expensive
- No great benefit after a few years
- Dorsal root ganglion stimulator - new

Kemler MA, Barendse GA, Kleef M van, Vet HC de, Rijks CP, Furnee CA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618-24.

Bennett DS, Alo KM, Oakley J, Feler CA. Spinal cord stimulation for complex regional pain syndrome I (RSD): a retrospective multicenter experience from 1995 to 1998 of 101 patients. Neuromodulation 1999;2:202-10.

# Spinal Cord stimulator



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# Spinal Cord Stimulator (SCS)

- 25% to 50% of patients develop complications requiring further surgery.
- In a huge study SCS reduced pain and improved quality of life but did not improve function for up to 2 years after implantation.
- From 3 years after implantation there was no difference between those who had it implanted and those who did not

Kemler MA, Barendse GA, Kleef M van, Wildenberg FA van den, Weber WE. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. J Neurosurg 1999;90(1 suppl):79-83.

Calvillo O, Racz G, Didie J, Smith K. Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity. Acta Orthop Belg 1998;64(1):57-63.

Kemler MA, Vet HC de, Barendse GA, Wildenberg FA van den, Kleef M van. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol 2004;55(1):13-8.

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# Desensitization

- Rice bowl, rubbing with a piece of cloth, paraffin bath, etc.
- Desensitization exercises have been recommended for a long time for CRPS
- The idea of desensitization came from treating mental conditions such as phobias
- Pain in CRPS is real pain, not a mental condition
- Worsens Central Sensitization, harmful for CRPS



# CRPS and Physiotherapy in Children

- Some centers force children to undergo severe physical therapy without controlling their pain first.
- If the child does not improve, doctors blame it on the child's mental condition or the parents who advocate for them
- This approach has left long term psychological trauma on these children
- The same standards are not applied to adults



# Physical therapy modalities



# Physical movement

- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- "No pain, no gain" – does not apply here

# Mental Health

- The cause of CRPS is NOT a psychiatric condition.
- It is definitely NOT in your head.
- Move away from providers who even suggest that
- CRPS, like all chronic conditions causes a feeling of despair and anxiety – reasonable to see a mental health provider for that

These are not manifestations of a psychological condition



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# Graded Motor Imagery



## Stage 1: Left/Right discrimination – Graded Motor Imagery

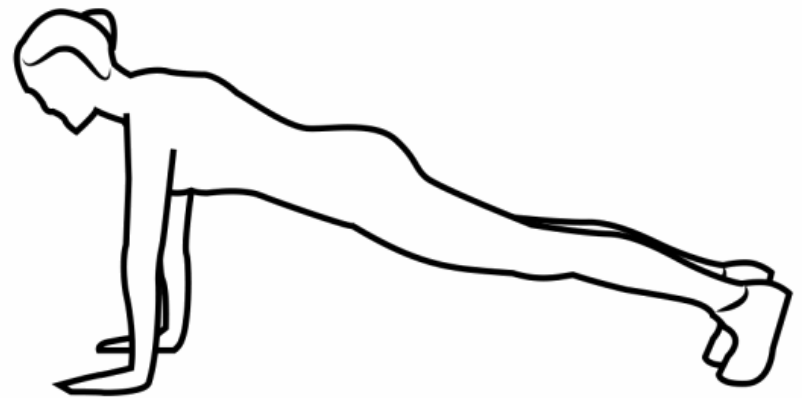
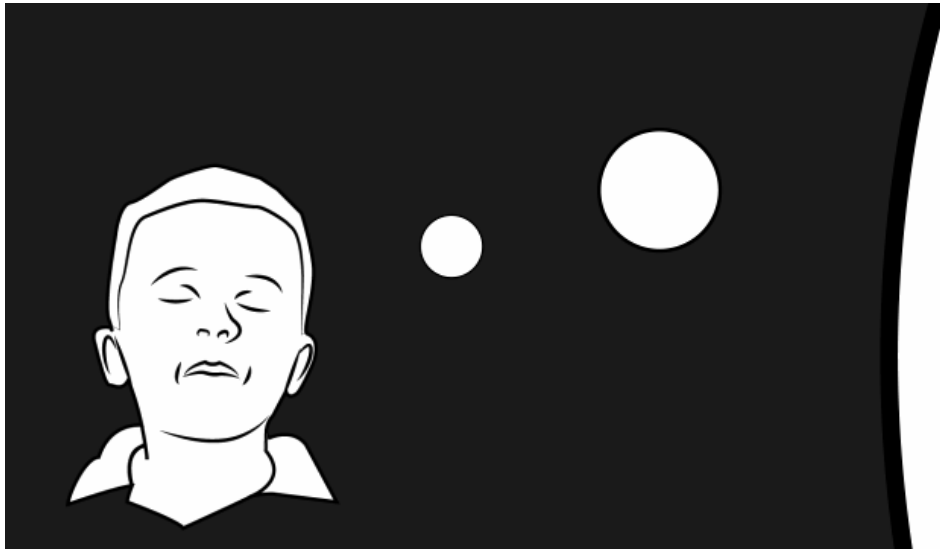
- In CRPS, people often lose the ability to identify left or right images of their painful body parts.
- This ability is important for normal recovery from pain
- The good news is that the brain is plastic and changeable.
- The 'Recognise' app helps regain this ability





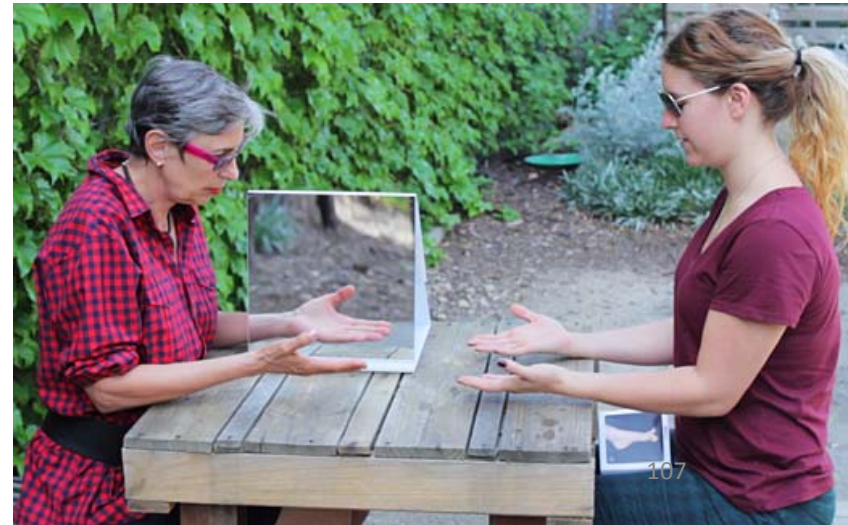
## Stage 2: Explicit Motor Imagery - Graded Motor Imagery

- The process of thinking about moving without actually moving
- Imagined movement can actually be hard work if you are in pain.
- 25% of our brain is made of 'mirror neurons' – they start firing when you think of moving or even watch someone else move
- Imagining movements before actually moving you use the same neurons that you would use when you actually move



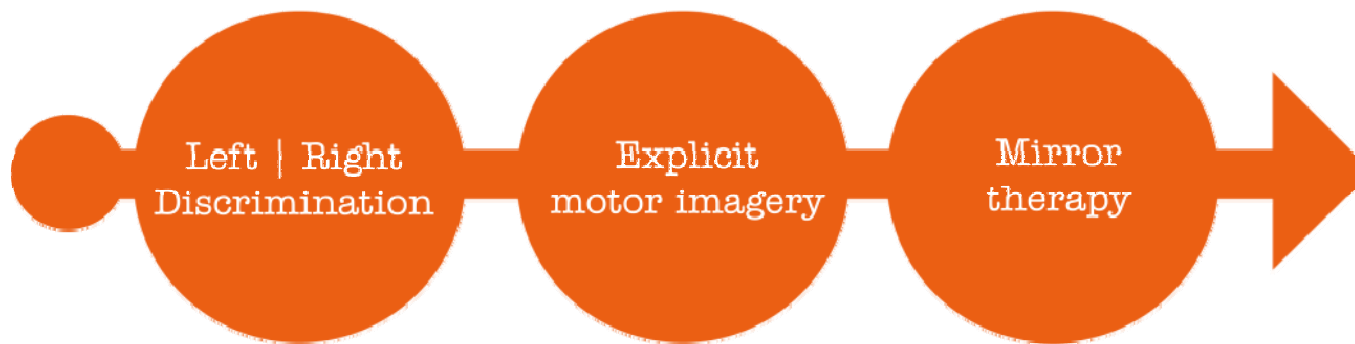
## Stage 3: Mirror therapy- Graded Motor Imagery

- By hiding the affected limb behind a mirror, you can trick the brain into believing that the reflection of the normal hand is the affected limb.
- In your brain you are exercising the affected limb as you move the normal limb.





# Three stages of Graded Motor Imagery delivered sequentially



- Left / right discrimination
- Explicit Motor imagery
- Mirror therapy
- [www.gradedmotorimagery.com](http://www.gradedmotorimagery.com)

# Gastrointestinal system and CRPS

How our foods may affect our pain

# Gastrointestinal system (GI system) and CRPS

- We have millions of bacteria living in our intestines (GI system)
- Bacteria within the gut are vital to nutrient breakdown and absorption.
- Bacteria remove toxins and help maintain a functional immune system.
- These bacteria are in direct contact with nerves.
- The GI system is also known as the 'second brain'

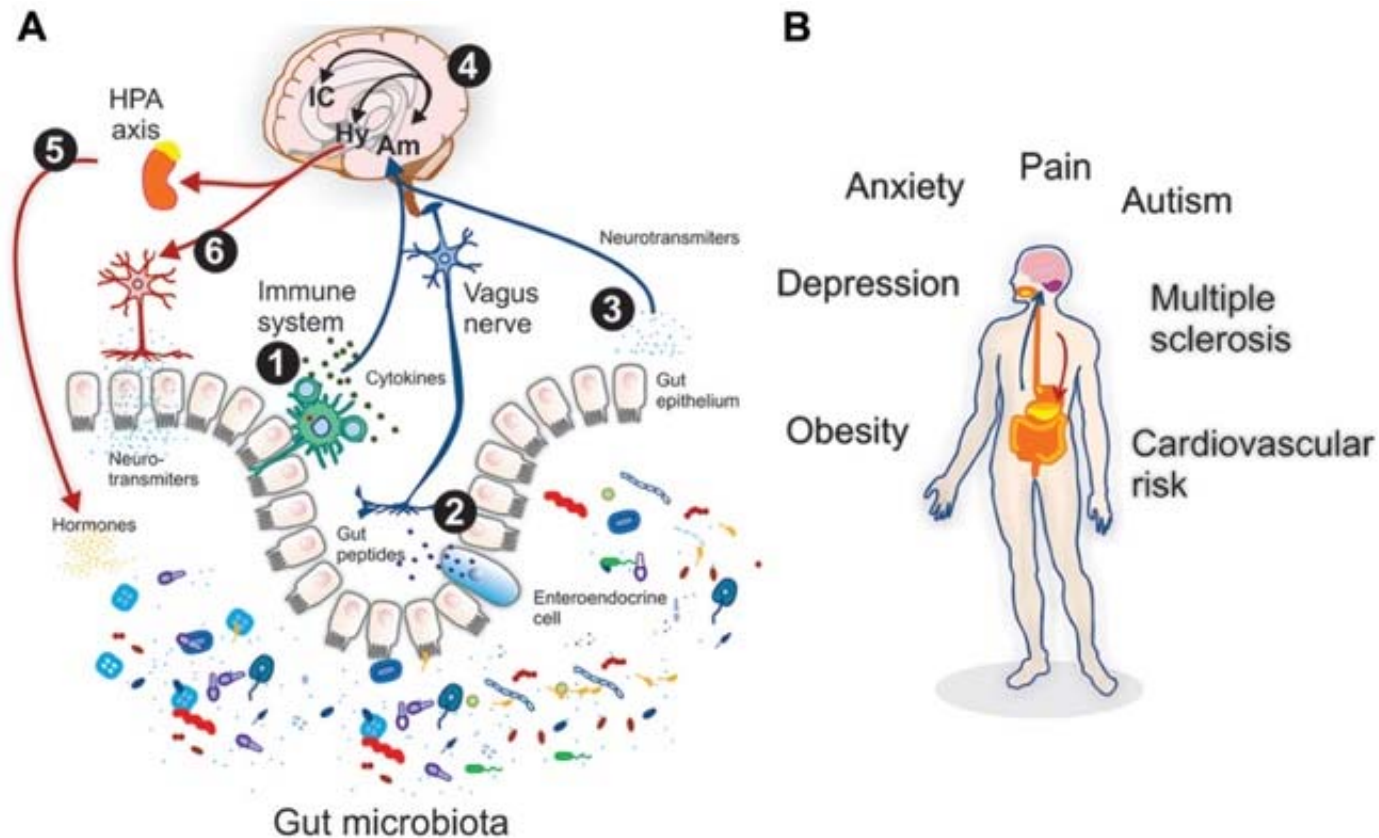
# Gastrointestinal system (GI system) and CRPS

- In CRPS the diversity of bacteria is less (normally, approximately 1000 different types of bacteria)
- This causes GI inflammation, the lining of the intestines is damaged, and increased production of pro-inflammatory cytokines (chemicals that trigger pain)
- TLR4 receptor activity is increased. This has been associated with inflammation.
- TLR4 is one of the receptors where LDN works.

Erin R. Reichenberger a, Guillermo M. Alexander b, Marielle J. Perreault b, Jacob A. Russell c, Robert J. Schwartzman b, Uri Hershberg a,1, Gail Rosen. Establishing a relationship between bacteria in the human gut and Complex Regional Pain Syndrome. Brain, Behavior, and Immunity 29 (2013) 62–69

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# Gastrointestinal system (GI system) and CRPS

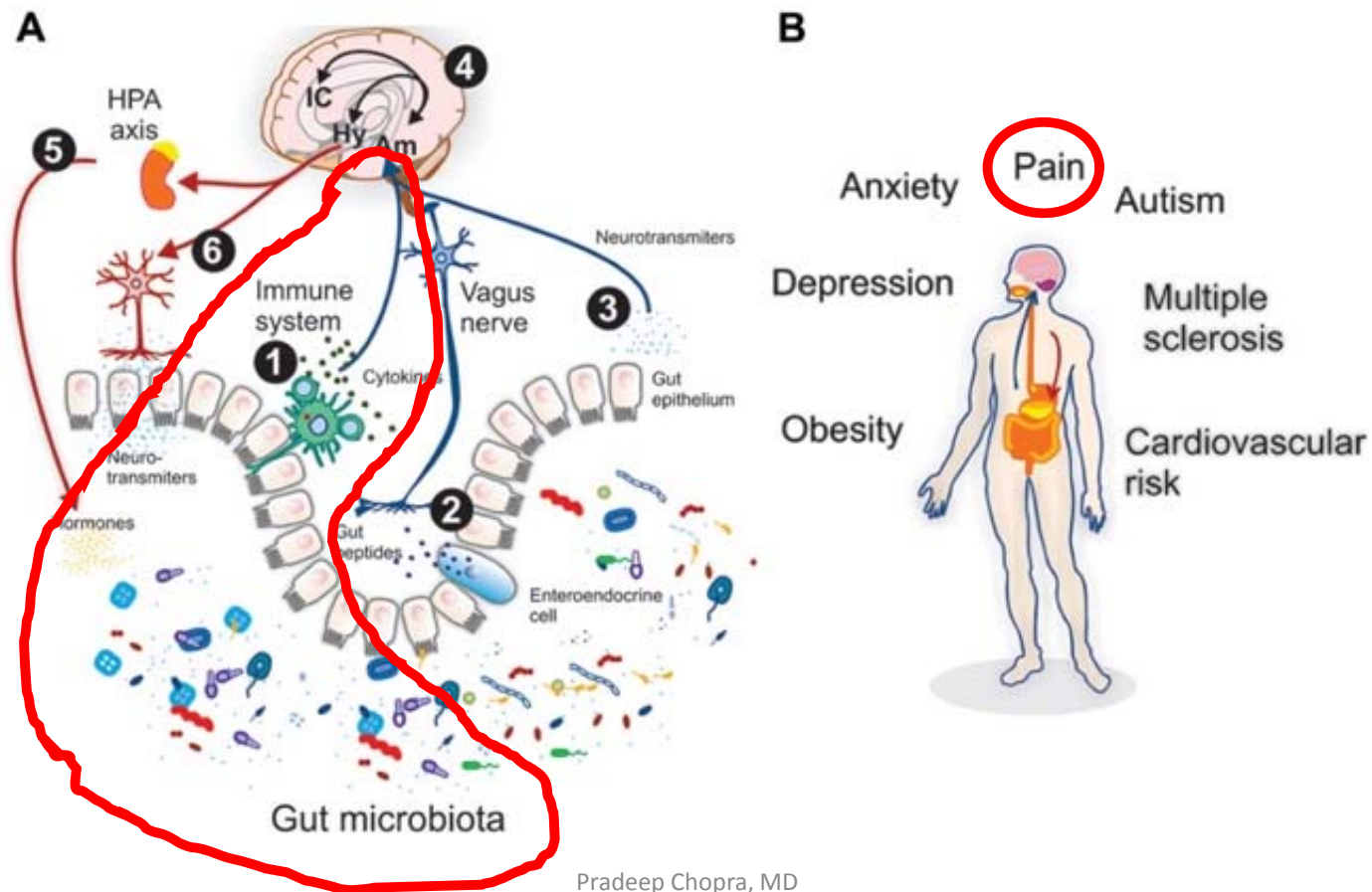


Augusto J. Montiel-Castro<sup>1,2\*</sup>, Rina M. González-Cervantes<sup>2,3</sup>, Gabriela Bravo-Ruiseco<sup>2</sup> and Gustavo Pacheco-López. The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality. *Front. Integr. Neurosci.*, 07 October 2013 <http://dx.doi.org/10.3389/fnint.2013.00070>. Review Article

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# Gastrointestinal system (GI system) and CRPS



# Gastrointestinal system (GI system) and CRPS

- These nerves are directly stimulated by the bacteria to develop an immune response and release of cytokines.

# Gastrointestinal system (GI system) and CRPS

- Overgrowth of bacteria in the small intestine causes an inflammatory response in the intestine.
- SIBO – Small Intestine Bacterial Overgrowth – talk to Gastroenterologist
- Bloating, abdominal pain, fatigue, weakness,
- Autoimmune dysfunction, CRPS
- The test for SIBO is an easy breath test.

## Identification and Treatment of New Inflammatory Triggers for Complex Regional Pain Syndrome: Small Intestinal Bacterial Overgrowth and Obstructive Sleep Apnea

Leonard B. Weinstock, MD, FACG,\*†‡ Trisha L. Myers, PA-C,‡ Arthur S. Walters, MD,§ Oscar A. Schwartz, MD,\*|| Jarred W. Younger, PhD,¶||#\*\* Pradeep J. Chopra, MD,††‡‡ and Anthony H. Guarino, MD‡‡

Complex regional pain syndrome (CRPS) is evoked by conditions that may be associated with local and/or systemic inflammation. We present a case of long-standing CRPS in a patient with Ehlers-Danlos syndrome in which prolonged remission was attained by directing therapy toward concomitant small intestinal bacterial overgrowth, obstructive sleep apnea, and potential increased microglia activity. We theorize that cytokine production produced by small intestinal bacterial overgrowth and obstructive sleep apnea may act as stimuli for ongoing CRPS symptoms. CRPS may also benefit from the properties of low-dose naltrexone that blocks microglia Toll-like receptors and induces production of endorphins that regulate and reduce inflammation. (A&A Case Reports. 2015;XXX:00–00.)

Complex regional pain syndrome (CRPS), formally known as reflex sympathetic dystrophy, is a neuropathic pain disorder that may fail to respond to current therapy including a variety of medications, nerve blocks, and ketamine infusions.<sup>1,2</sup> The incidence of CRPS is uncertain because there are few epidemiological studies. In a Mayo Clinic study, the rate was 5.46 per 100,000 person-years compared with a 6-fold larger study in the Netherlands where the rate was 26.2 per 100,000 person-years.<sup>3,4</sup> A marked female predominance was noted in each study. A familial occurrence of CRPS has been described.<sup>5</sup> The natural history of CRPS varies widely. The Mayo Clinic reported that 56 of the 74 patients with CRPS for 1 month to 5 years had complete remission after various treatments. Spontaneous remission was observed when the initial symptoms were mild.<sup>3</sup> By way of comparison, there were no remissions in 656 Drexel University patients who had CRPS for 1 to 46 years.<sup>6</sup> Pain had only modest improvement with their treatments. No spontaneous remissions occurred in 102

Dutch database patients who had CRPS for 2.1 to 10.8 years.<sup>7</sup> Progressive disease was reported in 16%, and permanent disability was present in 31% of the Dutch patients.

Pathophysiologic consequences of cytokine release, microglia activation, central sensitization, and autonomic nervous system dysfunction result in regional pain along with vasomotor, motor/trophic, and sudomotor/edema dysfunction.<sup>1,2,8,9</sup> Microglia cells are an integral part of the anatomic framework of the nervous system with attachments to astrocytes.<sup>10</sup> They act as neuromodulators, which alter central nervous cell and spinal sensory neuron excitability. Various syndromes marked by hyperalgesia including fibromyalgia and CRPS may be mediated by microglia cell activation as a consequence of proinflammatory cytokines.<sup>11,12</sup> Events known to trigger the onset of CRPS include bone fractures, sprains, trauma (injections, nerve injury, surgery, burns, and frostbite), nerve injury, infection, pregnancy, myocardial infarction, and stroke.<sup>1,2</sup> Some of these triggers may be associated with local and/or systemic inflammation.<sup>13–17</sup> In stroke-associated CRPS, inflammation from the stroke has been theorized as one of several possible pathophysiologic mechanisms.<sup>17</sup>

In light of the complex pathophysiology of CRPS and that no single therapy is completely effective, it is desirable to identify the triggers that contribute to the condition.

From the Departments of \*Anesthesia and †Internal Medicine, Washington University School of Medicine, St. Louis, Missouri; ‡Specialists in Gastroenterology, LLC, St. Louis, Missouri; §Department of Neurology, Vanderbilt University, Nashville, Tennessee; ||Sleep and EEG Laboratory, Barnes Jewish West County, BJC Medical Group Center for Sleep Medicine, St. Louis, Missouri; ¶Pharmaceutical Research and Development, Bristol-Myers Squibb, Princeton, New Jersey; \*\*Department of Neurology, University of Michigan, Ann Arbor, Michigan; ††Department of Neurology, University of California, San Francisco, California; ‡‡Department of Neurology, University of Texas at Austin, Austin, Texas.



# Bisphosphonates

Class of drugs used to treat bone loss.

# Bisphosphonates

- Commonly used to treat osteoporosis (bone loss)
- Osteoblasts – cells that build bone. They use vitamin D
- Osteoclasts – break down bone
- Bisphosphonates destroy osteoclasts thus helping osteoblasts do their job of making bone

# Bisphosphonates

- It seems like improving healthy bone development either by improving osteoblasts functioning or by destroying osteoclasts (bone destroying cells) helps CRPS
- They decrease cells that cause inflammation and pain (TNF, IL-1, IL-6)



# Bisphosphonates

- Clodronate (300mg) daily IV for 10 days – pain, swelling, movement range in acute CRPS
- Alendronate (7.5mg) once IV - pain, swelling, movement range in acute CRPS
- Pamidronate 60mg IV
- Use in long standing cases

Forouzanfar T, Koke AJ, Kleef M van, Weber WE. Treatment of complex regional pain syndrome type I. Eur J Pain 2002;6(2):105-22.

Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997;56(3):201-4.

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# Neridronate

- Very similar to alendronate (Fosamax®), Pamidronate (Aredia®)
- Very small trial.
- Very select group of patients.
- Only patients who had bone changes were studied.
- Better studies being done which are more realistic

Varenni M, Adami S, Rossini M. Treatment of CRPS I with neridronate: a randomized, double blind, placebo controlled study. Rheumatology. Doi 110.1093/rheumatology/kes312 274,299

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# Vitamin D

- Vitamin D promotes Calcium absorption in the gut
- Helps bone development
- Helps muscle and immune function
- Reduces inflammation



# FREE RADICAL SCAVENGERS

Antioxidants



# Free Radicals – what are they?

- Human body is made up of cells
- Cells are made up of atoms
- Atoms are made up of electrons and protons (1:1)

# Free radicals

- The increased sympathetic nerve activity in the area cause blood vessels to constrict, hence the cold, pale limb.
- Reduced blood flow, tissue damage and increased acid production
- This causes increased production of free radicals which increase pain in the area.

# Free Radicals – what are they?

- When tissues break up, some electrons are left free to float around.
- These unbalanced molecules are called free radicals
- These unbalanced molecules become very unstable and attack another molecule or electron to grab onto for stability.
- In our body, when these unstable electrons attack other molecules to achieve stability they damage human cells – nerves, muscles



# Free Radical scavengers (Antioxidants)

- Alpha Lipoic Acid
  - Vitamin C
  - DMSO (Dimethyl sulphoxide) – cream or lotion
  - N-Acetyl Cysteine (NAC)
- 
- They are available over the counter



# Alpha Lipoic acid (ALA) 1

- Free Radical scavenger
- Promising results in diabetic neuropathy and other polyneuropathies
- No trials in CRPS
- Has been approved in Germany for treating neuropathic pain

Kapoor S, Foot Ankle Spec, 2012 Aug;5(4); 228-9

Snedecor SJ, Sudarshan L, Cappelleru JC etc al. 2013 Pain Pract, Mar 28





# Alpha Lipoic acid (ALA)

- Its also helps with autonomic neuropathy (common in CRPS) POTS
- Effective when taken as IV (Intravenous)
- May be taken orally
- Dose: 600mg to 1200mg per day
- Start low, go slow



# Vitamin C

- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg was shown to prevent development of CRPS
- Vitamin C 500mg/day may help in patients who have developed CRPS
- No value to going higher than 500mg / day

Zollinger Paul, Tuinebereijer, Keir R, Breederveld, 1999, Lancet  
Jae Hun Kim<sup>1</sup>, Yong Chul Kim<sup>2</sup> *International Journal of Medical  
Sciences*  
2017; 14(1): 97-101. doi: 10.7150/ijms.17681

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# DMSO 50% - Dimethyl Sulphoxide

- Topical use only.
- Particularly helpful for 'warm' CRPS
- CRPS less than 1 year - three month course of DMSO applied 5 times topically every day
- CRPS more than 1 year – One month trial course of DMSO everyday.
- If trial helps, then continue

Geertzen JH, Bruijn H de, Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75(4):442-6.

Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, Lange JJ de, Loenen AC van. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand 1996;40(3):364-7.

Proctor, Glenn MD




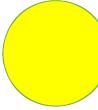


# N- Acetyl Cysteine (NAC)

- Useful for cold allodynia
- N-Acetylcysteine 600mg three times a day for three months
- Start low, go slow

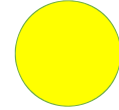
Perez RS, Zuurmond WW, Bezemer PD, Kuik DJ, Loenen AC van, Lange JJ de, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* 2003;102(3):297-307

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# Grading of treatment

- Effective 
- Worth trying 
- Use caution 
- Nerdy stuff 

# Oxytocin

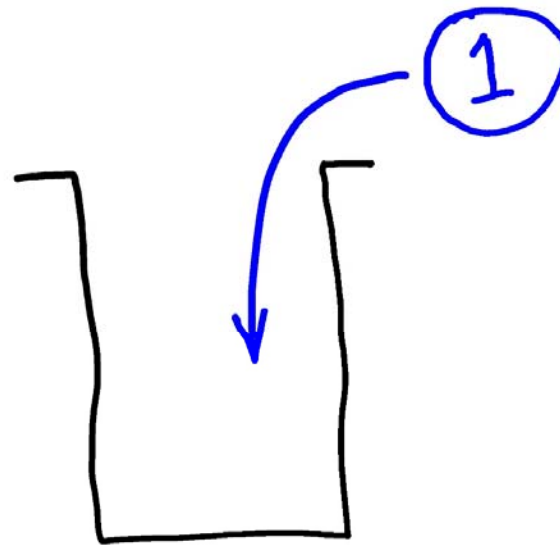


- Chemical produced naturally in the brain
- Taken as a nasal spray, sublingual
- Especially helpful in flare ups (acute pain)
- Two mechanisms by which oxytocin reduces pain
  - Directly on the spinal cord to turn down pain signals
  - By releasing endorphins (morphine produced by the body).

# NC10 rule

Expectations from different therapies

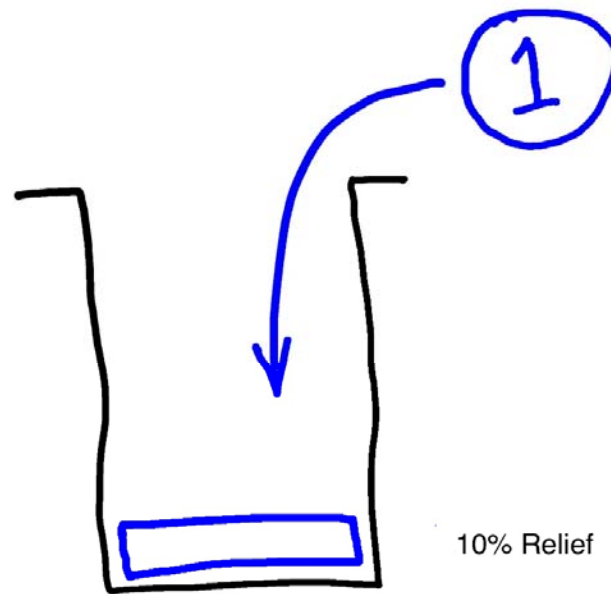
# NC 10 rule



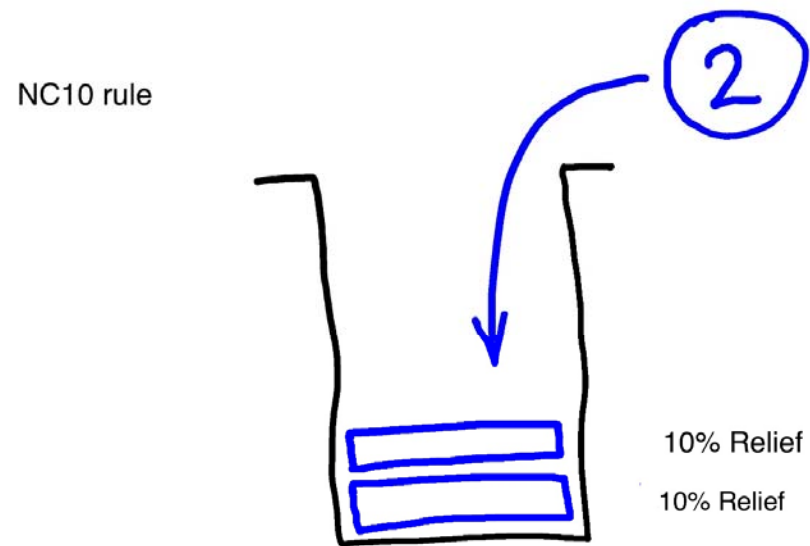


# NC 10 rule

NC10 rule

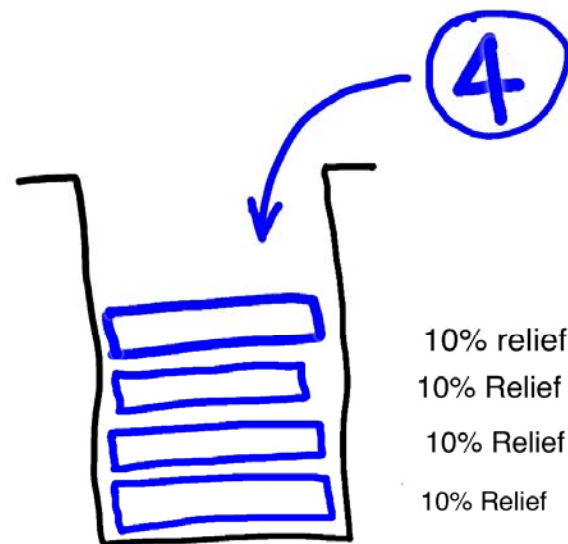


# NC 10 rule



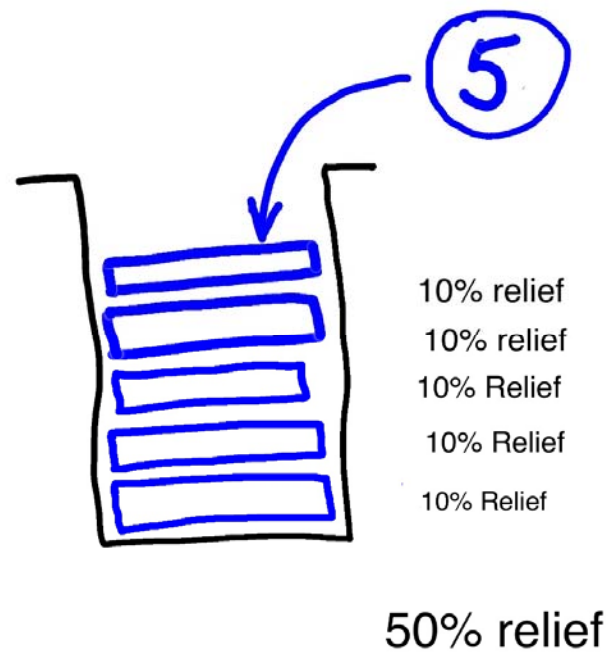
# NC 10 rule

NC10 rule



# NC 10 rule

NC10 rule



# Pain receptor behavior

- When we take a drug for pain for a long time there is downregulation of the receptors, which means....
- The body's response to the drug is not as good.
- If we stop the drug for sometime, the receptors are upregulated, which means....
- Restarting the drug gets a better response at a lower dose.

# Pain receptor behavior - drug rotation

- Ideally, a person could switch between drugs of a different class.
- For example, a patient on opioids for some months can take a 'drug holiday' for a few weeks to months.
- During this time, they can try medicinal marijuana (if legal) or ketamine (sublingual) or NSAID's
- After some time restart opioids at a lower dose.



# Hyperbaric Oxygen

- No good evidence that it helps in the long term
- Anecdotal reports (mostly from hyperbaric centers)
- Different types – high pressure and low pressure
- Waste of time and money

[Kiralp MZ](#), [Yildiz S](#), [Vural D](#), [Keskin I](#), [Ay H](#), [Dursun H](#). [J Int Med Res](#). 2004 May-Jun;32(3):258-62.  
Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome

# Physical therapy modalities



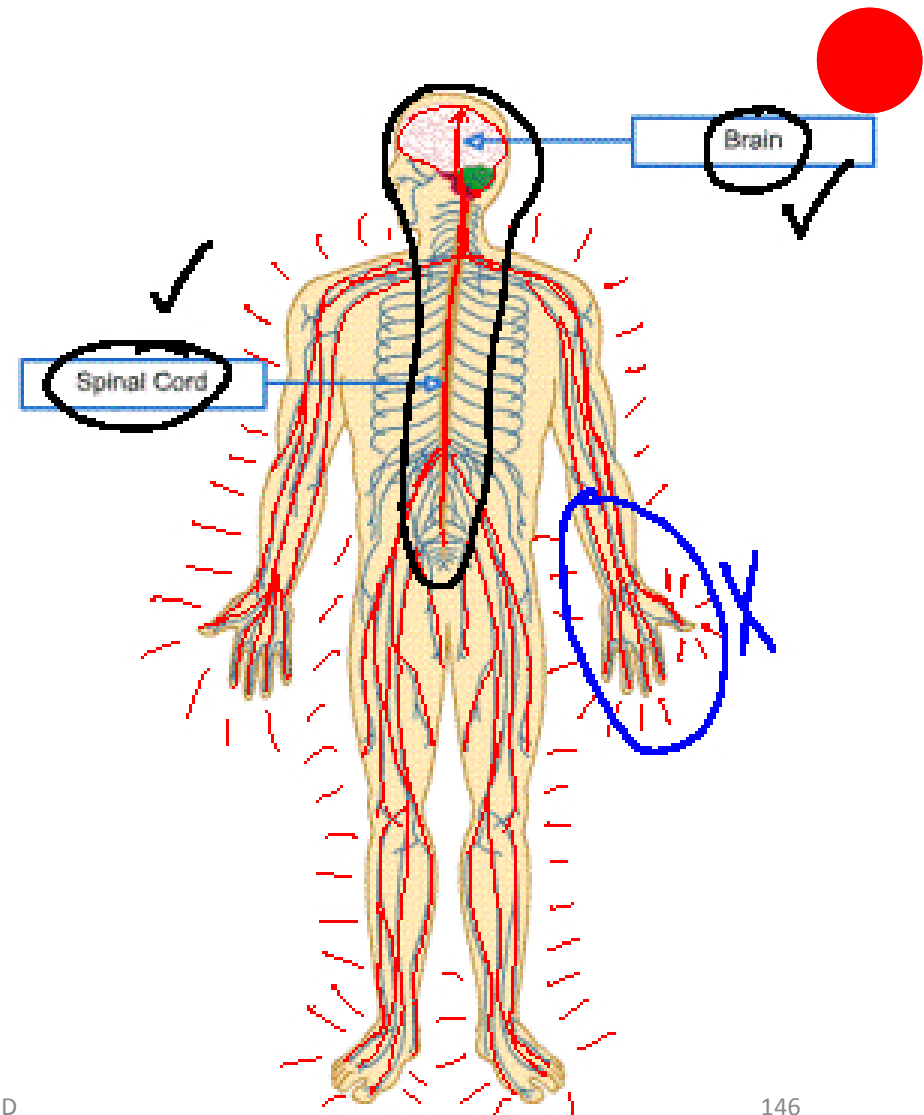


# Physical movement

- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- "No pain, no gain" – nonsense

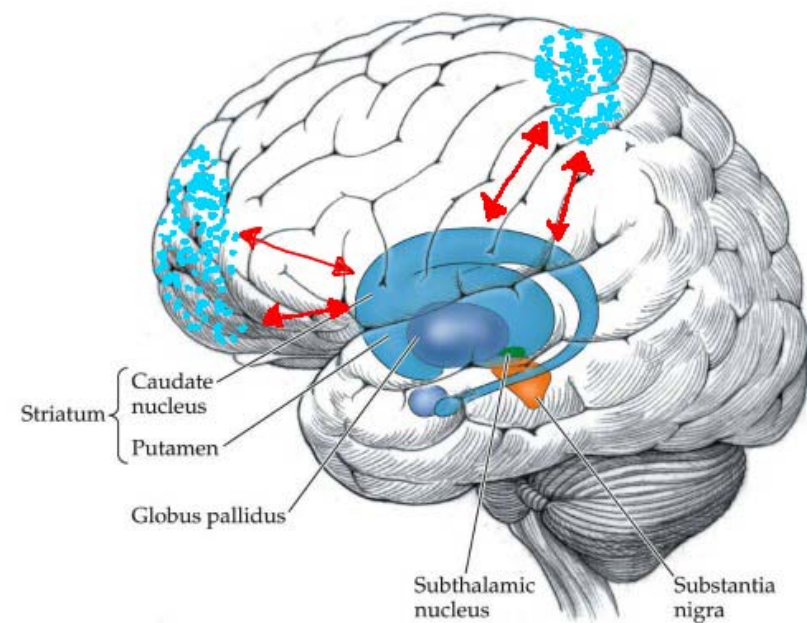
# Avoid desensitization

- The source of the pain is in the brain and spinal cord.
- Repetitive rubbing of the painful limb will only worsen Central Sensitization
- The pain in CRPS is real, it is not a phobia



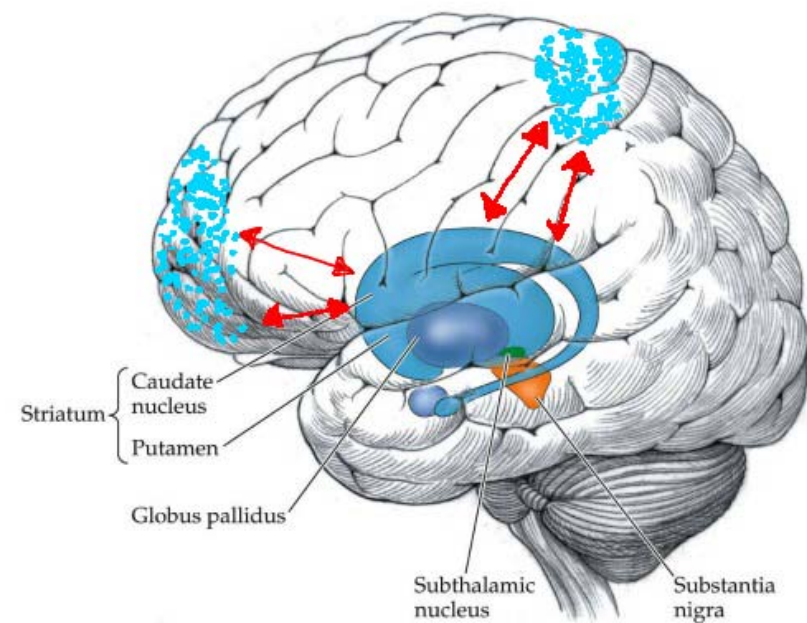
# Basal Ganglia

- Basal ganglia are part of the brain
- It is associated with different parts of the brain that control movement, cognition and emotion, body perception
- One of the chemicals it uses is dopamine.



# Basal Ganglia

- In CRPS – there is reduced dopamine
- Levodopa (Sinemet™) can increase dopamine and may help movement disorders in CRPS



# Muscle dysfunction in CRPS

- Significant muscle issues such as dystonia, tremors, persistent flexion postures of fingers and toes.
- Dystonia is unrelated to Central sensitization and is unlikely to respond to ketamine
- A trial of Baclofen or sinemet may be helpful

# Fatigue and CRPS

# Fatigue and CRPS

- Poor sleep as a result of pain
- Non-restorative sleep
- Muscle spasms, dystonia

# Fatigue

- Good sleep hygiene – no caffeine, no laptops, smart phones, quiet dark room, comfortable bed, warm room, no hypoglycemia
- Take a pain medicine rather than a sedative
- Beta blockers for non-restorative sleep, POTS
- It could be secondary mitochondrial dysfunction
- Mineral supplement of ubiquinone, carnitine, vitamin B complex



# Sample mixture of mineral supplements for fatigue

Ubiquinone	300mg PO QD
Riboflavin (B <sub>2</sub> )	100mg PO QD
Acetyl-L-Carnitine	416 mg PO QD
Thiamine (B <sub>1</sub> )	300mg PO QD
Pyridoxine (B <sub>6</sub> )	50mg PO QD
Cobalamin (B <sub>12</sub> )	50 mcg PO QD
Creatine	2g PO QD
Mannitol (filler)	1.834 g

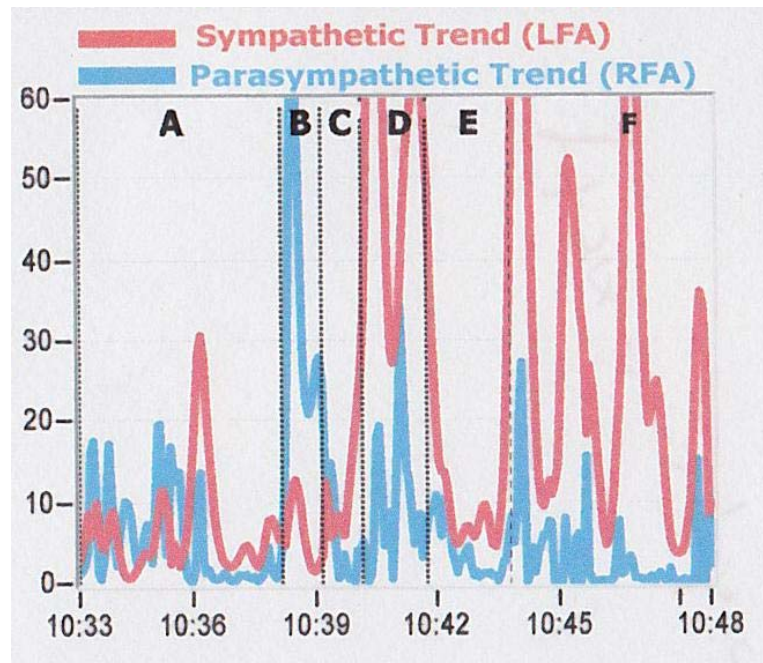
# Sleep

# Sleep and CRPS

- Pain keeps them awake
- If they fall asleep they continue to produce adrenaline (because of CRPS) they have light, dream-filled sleep
- Increased number of sleep disrupting 'arousals'
- Wake up unrefreshed – Non-restorative sleep.

# Non-restorative sleep

Untreated

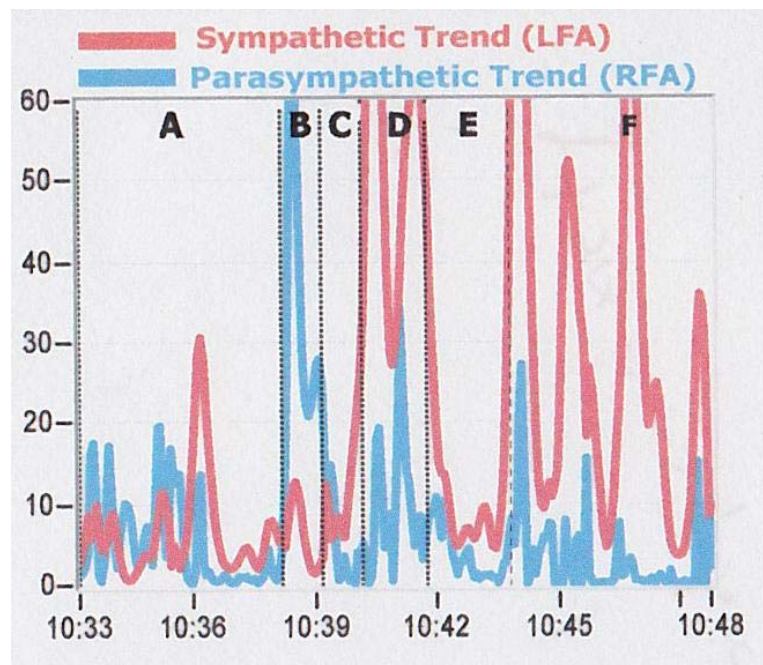


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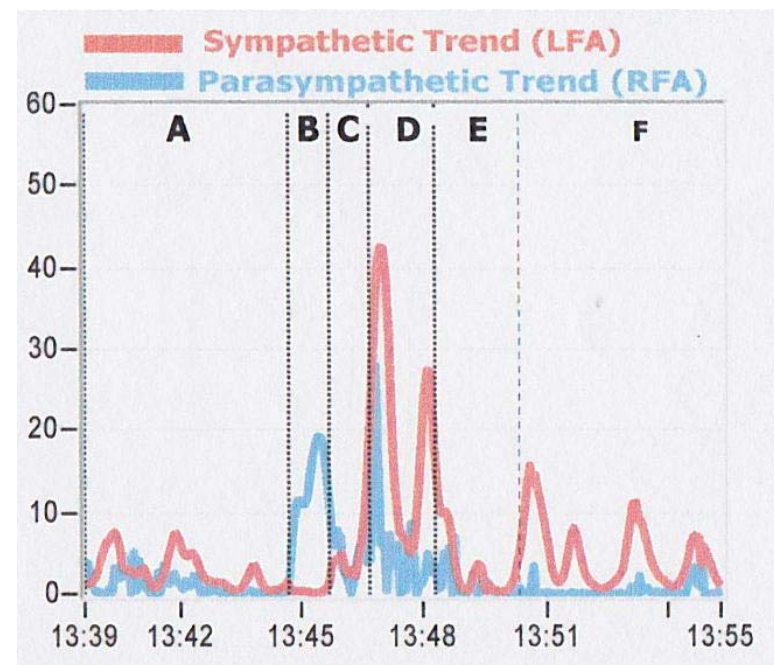
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# Non-restorative sleep

Untreated



After treatment with a beta blocker (Propranolol)



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# Non-restorative sleep

- Good sleep hygiene – comfortable mattress, dark and quite room, no digital lights
- Beta blockers – propranolol
- Alpha blockers – clonidine, guanfacine
- Pain medicines

# Caution

- If someone calls it Amplified Pain Syndrome
- There is no such thing as Amplified pain syndrome, the person is implying that it is 'all in your head'
- Nerve blocks
- Spinal cord stimulators, especially if that is the first and only thing they offer
- Psychiatrist – if that is the main treatment offered.
- You are diagnosed with CRPS within minutes of being seen and no detailed examination of the affected area

# CRPS in children



# Children and RSD 1

- Children develop the same symptoms
- 58% to 93% of cases of RSD in children will resolve with proper treatment

# Children and CRPS

- It's the exact same disease as in adults yet physicians in children's hospitals recommend intense physical therapy and psychiatric treatment as the main treatment.
- No pain treatment is offered
- If they fail to respond to physiotherapy, they are labelled as having a psychological problem – it's the child's fault

# Children and RSD

- It is often labeled as a behavioral disorder, Conversion Disorder
- Concerned Parents are labeled as having Munchausen's syndrome
- To make any of the above diagnosis is very challenging.
- Usually takes years by a Psychologist in conjunction with other treating physicians.

# Children and RSD

- Imperative that all other medical conditions have been ruled out
- Cannot be made by physicians with little or no mental health training.
- Very important that parents pay close attention to the child's complaints

# Children and RSD

- Parents should consult a physician familiar with CRPS because being labeled as a psychological disorder is far more devastating and closes the doors to any further treatment for CRPS
- Very often children have a condition that has not been diagnosed and are labelled as having CRPS

# Children and RSD

- CRPS in children is often associated with other conditions such as
  - Ehler's Danlos Syndrome (EDS)
  - Mitochondrial disorder
  - Nerve entrapment

# Skin Lesions in CRPS – use ketamine ointment



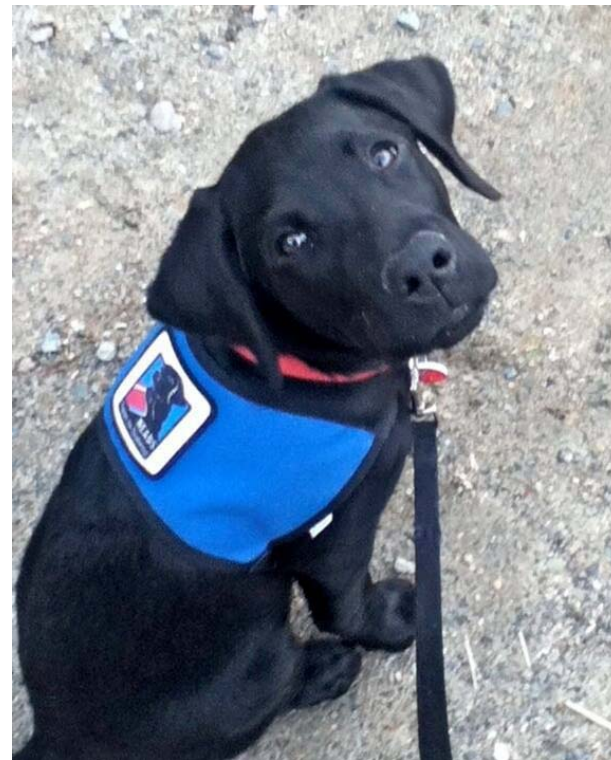
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# Service Dogs

- Help with functioning and independence
- Constant companion, will often sense its owners pain and will comfort them both physically and emotionally
- Can sense distress and call for help
- Service dogs give patients a feeling of security allowing them to be more active physically and socially







## Service Dogs - invaluable

- POTS – they can sense when their owner is having an episode of dizziness or seizure
- CRPS and pain - they protect the limb from being injured or touched
- Helps boost confidence in their owners, making them more independent
- Help with balance, call for help, open doors, switch on lights, pull wheelchairs, anxiety,

# Pregnancy and CRPS

# Pregnancy and CRPS - prenatal

- CRPS not known to affect fertility
- In most cases, CRPS pain gets much better during pregnancy
- Care should be at a high risk pregnancy center
- Discuss with Obstetrician and team about the issues with CRPS

# Pregnancy and CRPS - prenatal

- CRPS pain is usually well controlled during pregnancy
- Most drugs are not approved during pregnancy – confirm with Obstetrician
- May take opioids – stop prior to delivery

# Natural delivery of C-section?

## CRPS and natural delivery

- Prolonged pushing
- Episiotomy incision
- Legs in stirrups
- There is a lot of touching, pushing and moving

# CRPS and C-section

- Surgical incision
- No excessive pushing – causing tissue trauma
- No episiotomy

## CRPS and delivery

- Discuss with Obstetrician about finding a middle ground – if no significant progress after pushing for a period of time, consider C-section
- Opt for epidural or spinal anesthesia, if possible.



# Surgery and Complex Regional Pain Syndrome (CRPS)

# Surgical trauma and Complex Regional Pain Syndrome (CRPS)

- Avoid surgery unless you have to (duh!)
- Start gabapentin or pregabalin 2 weeks before the surgery
- Vitamin C 500 mg one daily. Start 7 days before surgery and continue for 45 days after surgery

# Surgical trauma and CRPS - Intra – operative

- Use intravenous ketamine as part of anesthesia
- Apply topical numbing medicine over IV site before insertion of needle
- IV must be inserted with minimum trauma (first shot, smallest needle possible)
- Epidural or spinal anesthesia, if lower body surgery
- Request that the chart be marked,

# Surgical trauma and CRPS

- Mark in record the area with CRPS that it should be handled with extreme care
- Continue low dose IV ketamine in the recovery room for a few hours – very important
- Continue epidural anesthesia for pain control, if inserted pre op, for at least 24 hours

# Needle stick injuries

- Minimize needle stick injuries as far as possible – combine a blood test from different physicians into one procedure
- Ask that the thinnest needle possible be used.
- Use a topical numbing cream (EMLA® or Synera® patch)
- Let them know that your veins are ‘difficult’. CRPS patients have thin veins
- Ask for the most experienced person to insert IV or blood draw
- For those undergoing regular infusions (IV fluid rehydration or IV Ketamine) should consider a chest port
- PICC line is not a good option

# Hospital

- Ask for a sign over the bed that the affected limb is not to be touched.
- Avoid loud sounds, bright lights
- Cage over the affected limb
- Have a friend or family member to make sure that the area with CRPS is not touched

# Palmitoyl ethanol amide (PEA)

3-135

# PEA

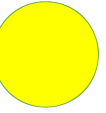
- Palmitoylethanolamide (PEA) or Palmidrol
- Nobel Prize winner Prof. Rita Levi-Montalcini
- Endogenous lipid
- Very good studies to show its usefulness in managing neuropathic pain
- Available as PeaPure, Normast, Pelvilen





# PEA

- Helps with hyperalgesia (severe pain with mildly painful stimulus) and allodynia (pain to touch)
- Mechanism unclear
- It works on the PPAR-alpha receptor and the G-protein coupled receptor 55 (GPR55)
- The PPAR-alpha receptor controls pain and inflammation
- The GPR55 receptor is an endocannabinoid receptor activated by cannabinoids
- Anti-inflammatory
- Prevents mast cell activation (mast cells are important part of inflammation)



# PEA

- Now available in USA
- Comes as pills and ointment.
- Place powder from capsule under the tongue for the first 10 days.
- Ointment works well over small areas

# The Feldenkrais Method

- It is a type of physiotherapy that helps repair impaired connections between the brain and the body
- The Feldenkrais Method teaches new patterns using gentle, slow, repeated movements.
- It uses slow repetition to teach correct and safe movements in CRPS
- Can be done sitting or lying down
- Each session consists of comfortable, easy movements within the limits of safety

# The Feldenkrais Method in CRPS

- It is based on principles of physics, biomechanics and an understanding of learning and human development.
- This method of exercise is excellent for improving limb movements in CRPS
- Can be done sitting or lying down
- Each session consists of comfortable, easy movements within the limits of safety

# The Feldenkrais Method in CRPS

- Can be done sitting or lying down
- Each session consists of comfortable, easy movements within the limits of safety



# The Feldenkrais Method

- <http://www.feldenkrais.com/>

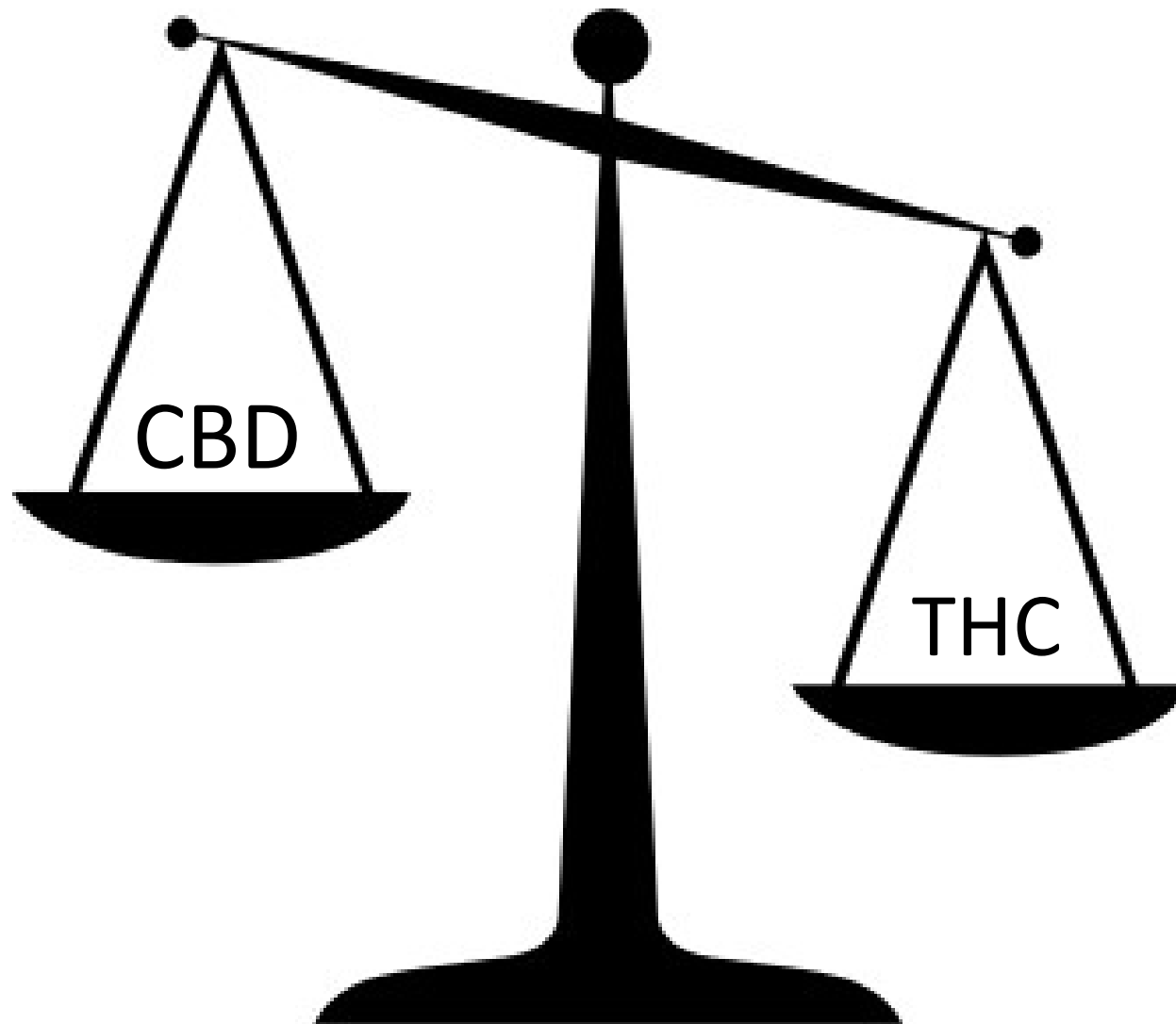
# Medicinal marijuana

- The human body has two types of receptors – CB1 and CB2
- CB1 receptors are found in the brain
- CB2 receptors are found in the rest of the body, immune cells and glia cells in the Central Nervous System
- Chemicals that cause inflammation in the peripheral parts of the body are modulated by cannabinoids. Hence, cannabis applied topically may be helpful

# Medicinal Marijuana

- MM basically contains 2 substances – THC and CBD
- THC works on CB1 and is responsible for the cognitive effects
- CBD works on CB2 and is responsible for pain relief, helps autoimmune dysfunction.
- For MM to work, both THC and CBD have to be together, separating them is not as effective. This is called the Entourage effect.
- One can take MM with a higher concentration of CBD and lower concentration of THC – for pain
- Higher THC and lower CBD for sleep





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# Medicinal Marijuana

- Reasonable choice to try.
- Higher CBD levels and lower THC levels
- Vaporizing, edibles
- Topical over joints and muscles.
- Does not affect Mast Cell Activation Syndrome (MCAS) as much as NSAID's and opioids

# Muscle pain and movement disorder in EDS

# Hope

- Do not give up hope.
- There are many, many success stories.
- Do not look for a 100% cure, look for enough to be functional.
- We seldom 'cure' diseases.
- There is no cure for diabetes, high blood pressure, arthritis, migraines.
- We manage them to be functional.

# CRPS 2013



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- Finding help for living with CRPS is a team effort
- Support RSDSA and its efforts to help people with CRPS

# Thank you

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