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# Complex Regional Pain Syndrome/RSD: Diagnosis and Management

Reflex Sympathetic Dystrophy  
2016, Orange County, CA

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# Disclosure and disclaimer

- I have no actual or potential conflict of 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.

# Introduction

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



# What is CRPS / RSD

- Syndrome characterized by a continuing pain that is disproportionate to the usual course of any trauma or lesion.
- Usually starts after a trauma



# 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?

# Cause of CRPS

- Some examples where patients have presented with CRPS with a known cause:
- Thoracic outlet syndrome – CRPS of the arm
- Peroneal nerve entrapment – CRPS of the leg
- Autoimmune dysfunction
- Traumatic injury to a nerve – surgery or non-surgical
- Gastrointestinal issues?

# How to explain CRPS to others

- Severe nerve pain condition due to nerve damage
- Constant severe pain with flare ups
- Worst pain known to mankind – worse than amputation of a digit or cancer pain
- No approved treatment

# CRPS - types

- CRPS I : no specific nerve damage can be identified
- CRPS II: a specific nerve is damaged
- The symptoms are the same.
- Its important for the physician to identify which type because some of the treatments can be tailored

# Diagnosis of CRPS

# Diagnosis of CRPS

- Please make sure that it really is CRPS
- Under the umbrella of Neuropathic pain conditions, CRPS is one of them
- There are other neuropathic pain conditions that may look like CRPS.

# Signs and Symptoms of CRPS 1

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

# 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



# What Complex Regional Pain Syndrome is not.....

- There is no such thing as Amplified Pain Syndrome.
- It is not in your head, it is a real pain
- Children are not making it up.



Swelling

Color  
change



Swelling

Shiny skin

Nails growth faster,  
brittle, ridged

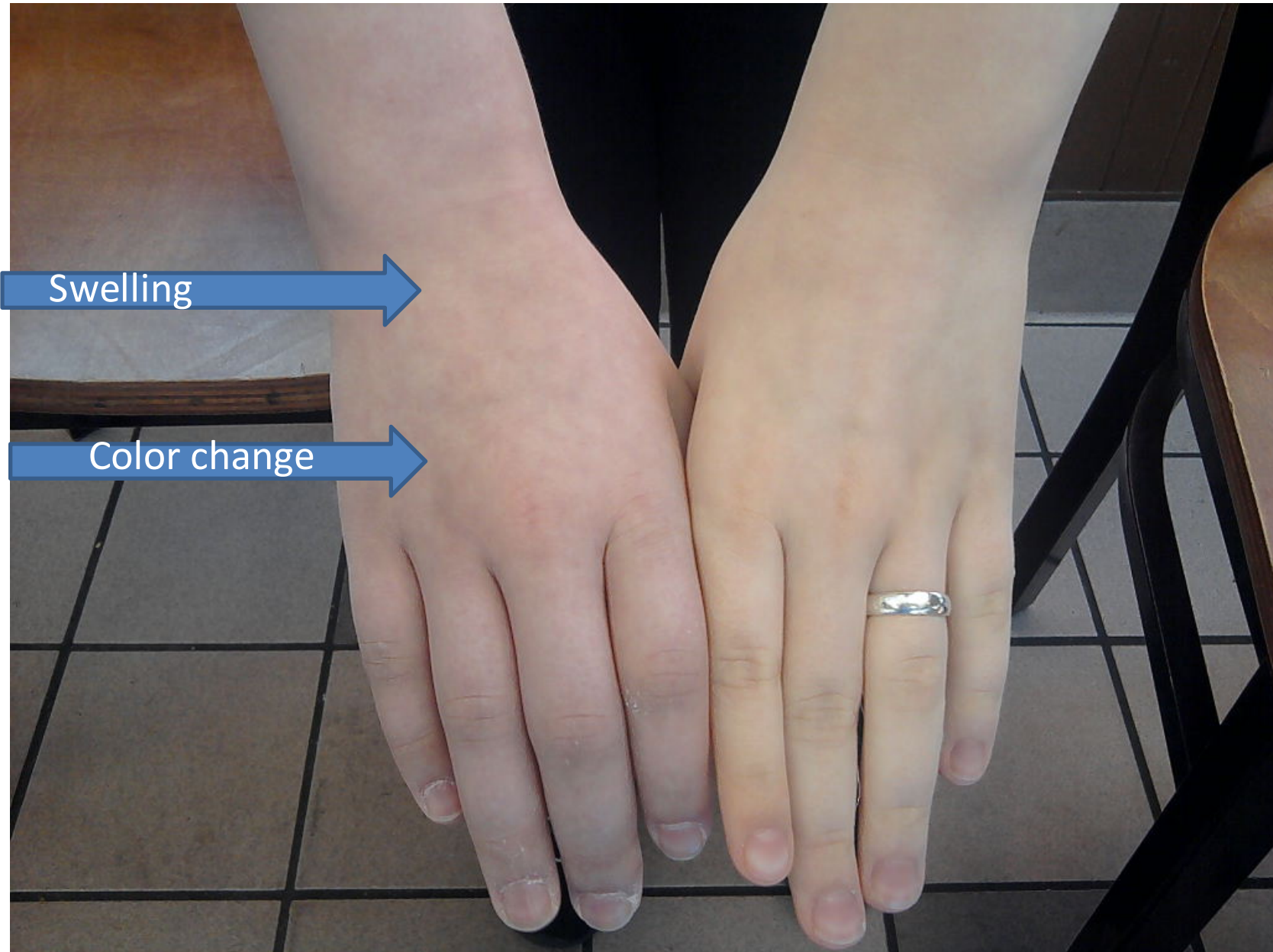
# Best Diagnostic tool

- A good history and thorough physical examination
- A typical evaluation with me lasts 4 hours to 5 hours

# Helpful tips when seeing a Physician

- Write a timeline of your medical history
- List of medications tried and reason why they failed
- List of current medications and how much do they help
- Take pictures of the area comparing both sides





# 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.

# Tests that MAY be helpful in understanding the cause of the pain

- Vitamin D level
- Heavy metals
- Mold exposure
- Regular blood work



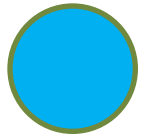
# Grading of treatment

-  Effective
-  Worth trying
-  Use caution
-  Nerdy stuff

# What happens in CRPS / RSD



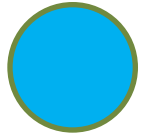
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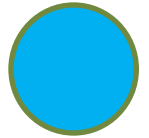
# CENTRAL SENSITIZATION

Key concept to understanding all  
chronic pain

# Central Sensitization

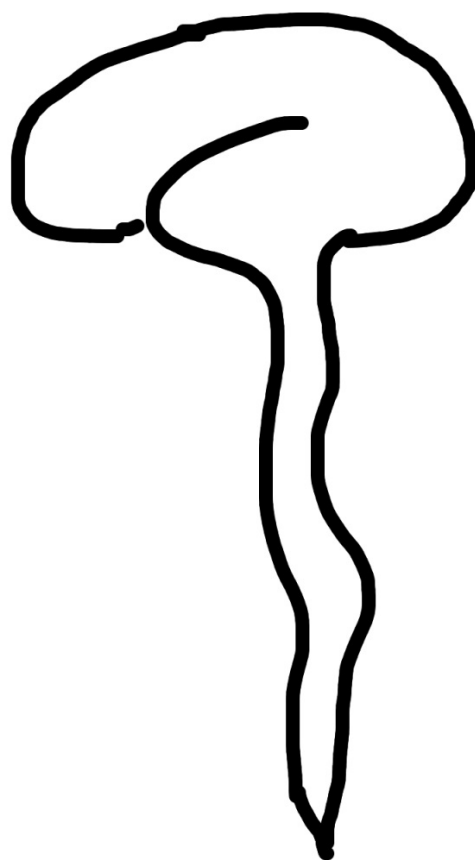
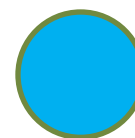


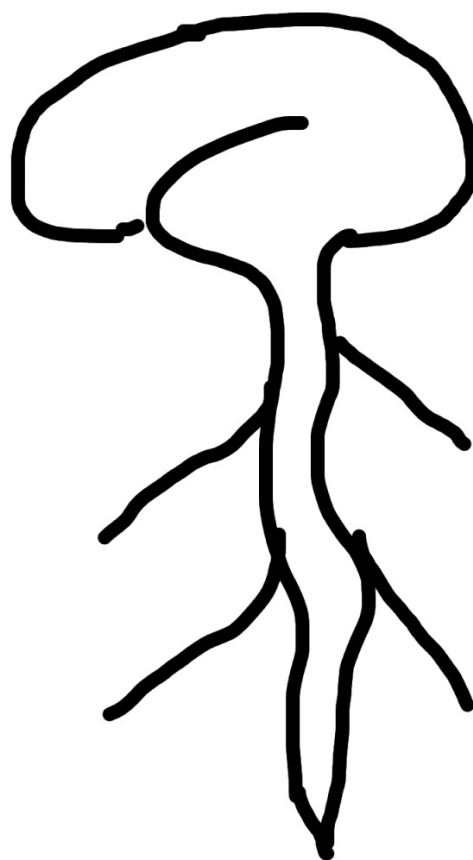
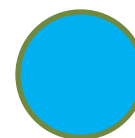
- As the spinal cord and brain is flooded with a barrage of pain signals, the nerves in brain and spinal cord become hyper-sensitized

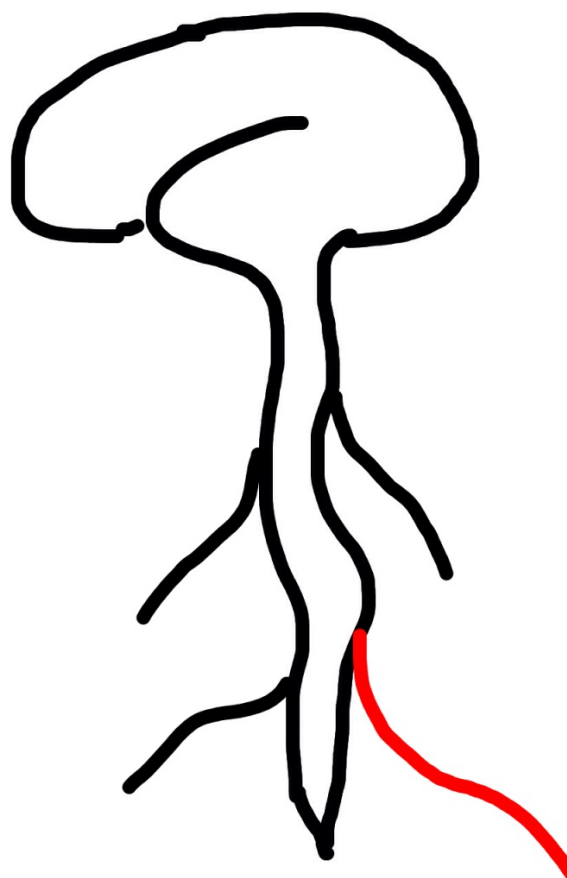
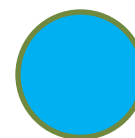


# Central Sensitization

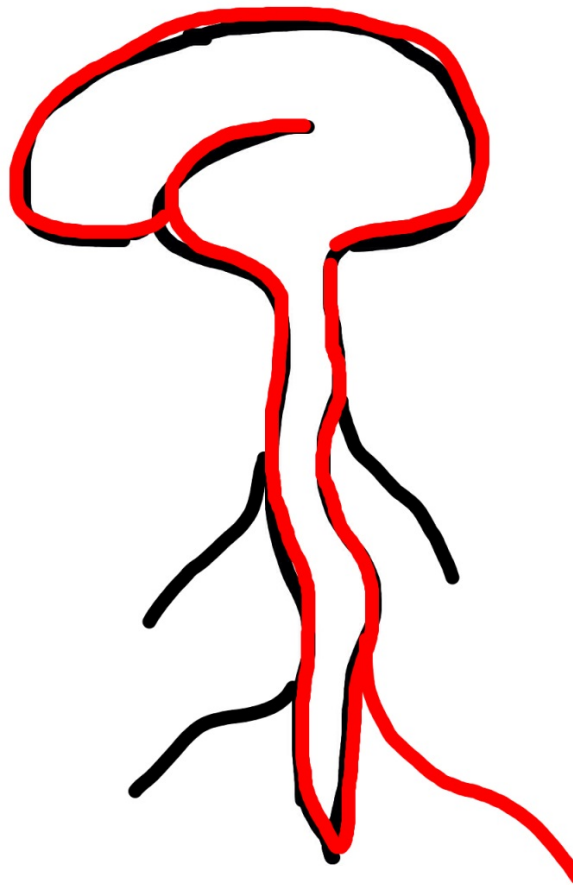
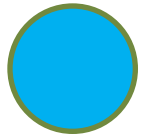
- A normal sensation (e.g. touch) produces an abnormal response (like pain) because the brain and spinal cord are sensitized
- Definition: Increase in the excitability of neurons within the central nervous system (CNS) so that normal inputs produce abnormal responses

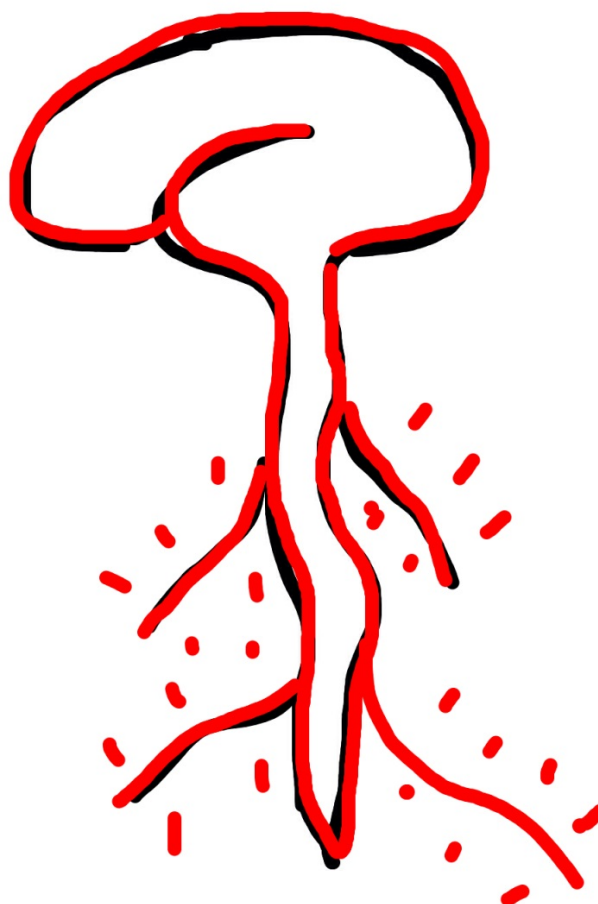
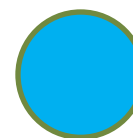


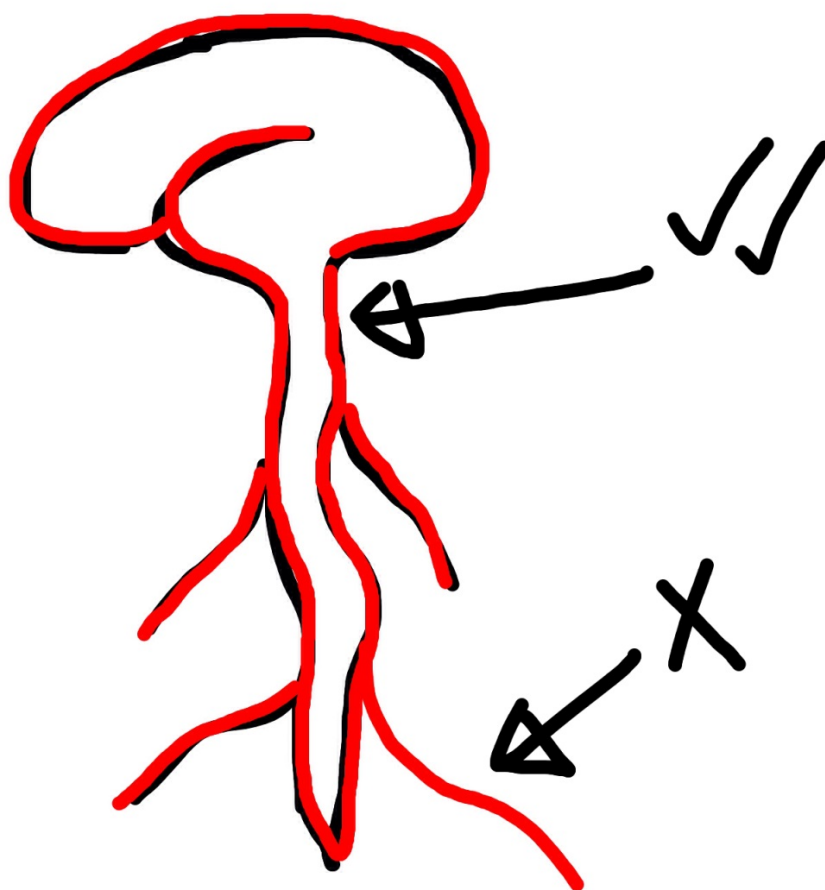
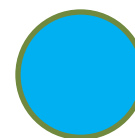










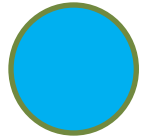


# Spreading



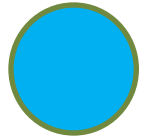
- In long standing cases of CRPS, some patients develop similar symptoms in other areas of the body
- This is usually a result of increasing Central Sensitization.
- As the central nervous system become more and more sensitized, normal sensations to other parts of the body are felt as painful sensations.

# Central Sensitization



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

# Central Sensitization: Activated Glial Cells



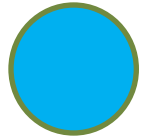
- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function

# Glia



Courtesy Jarred Younger, PhD

Sonja Paetau, University of Helsinki

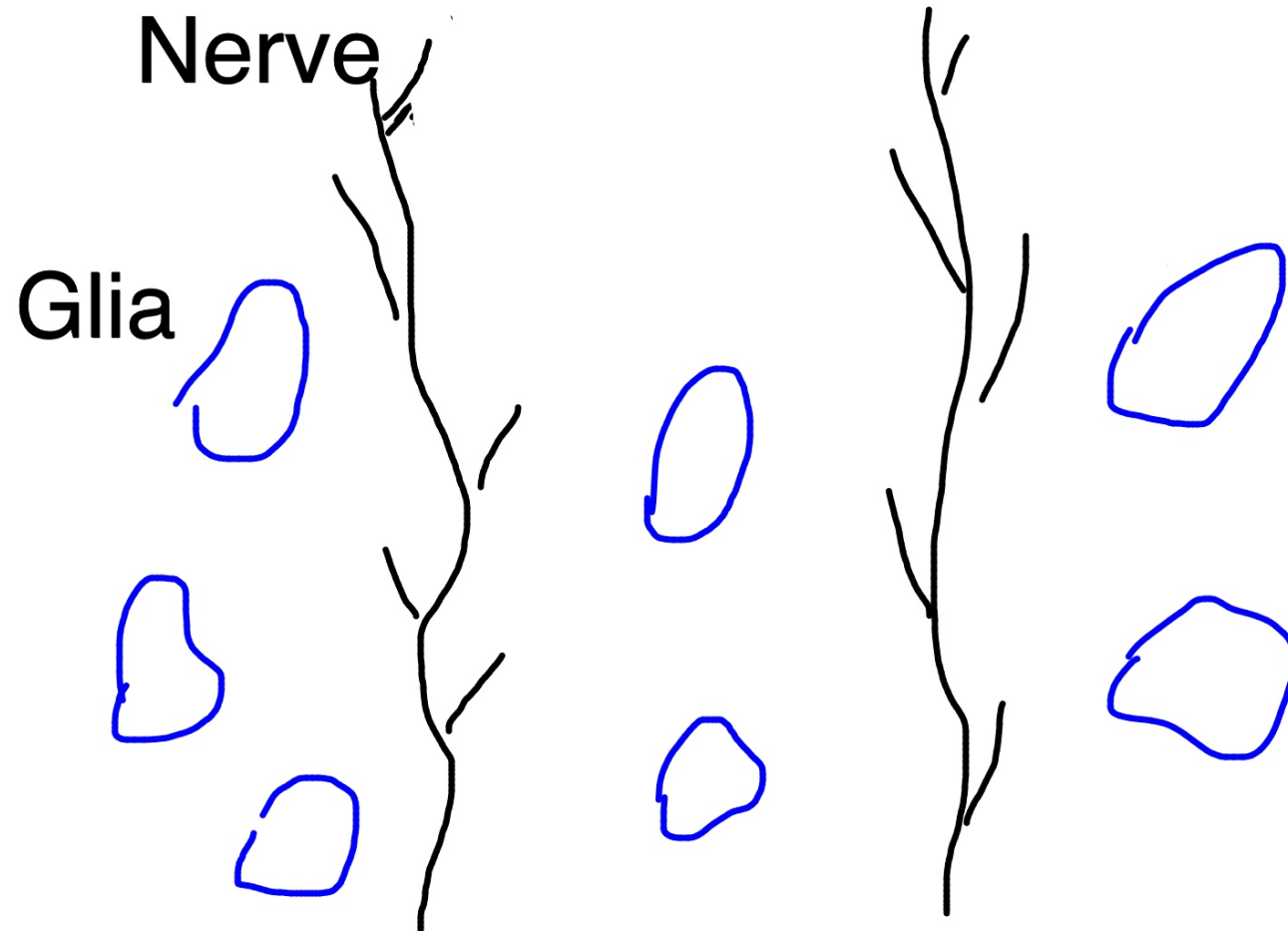


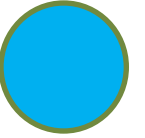
# Central Sensitization: Activated Glial Cells

- 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 and inflammation and pain

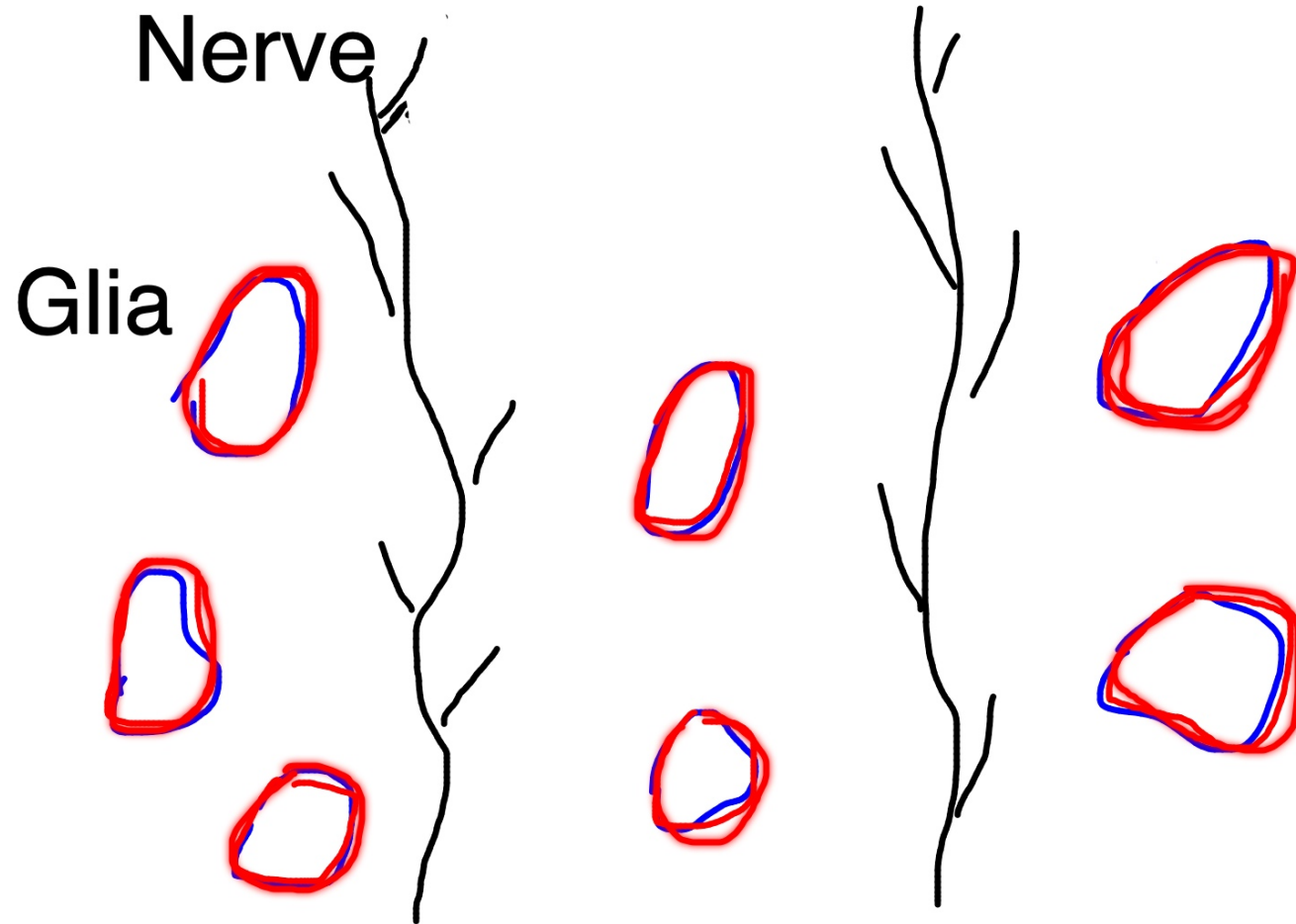


# Glia and nerves under normal conditions

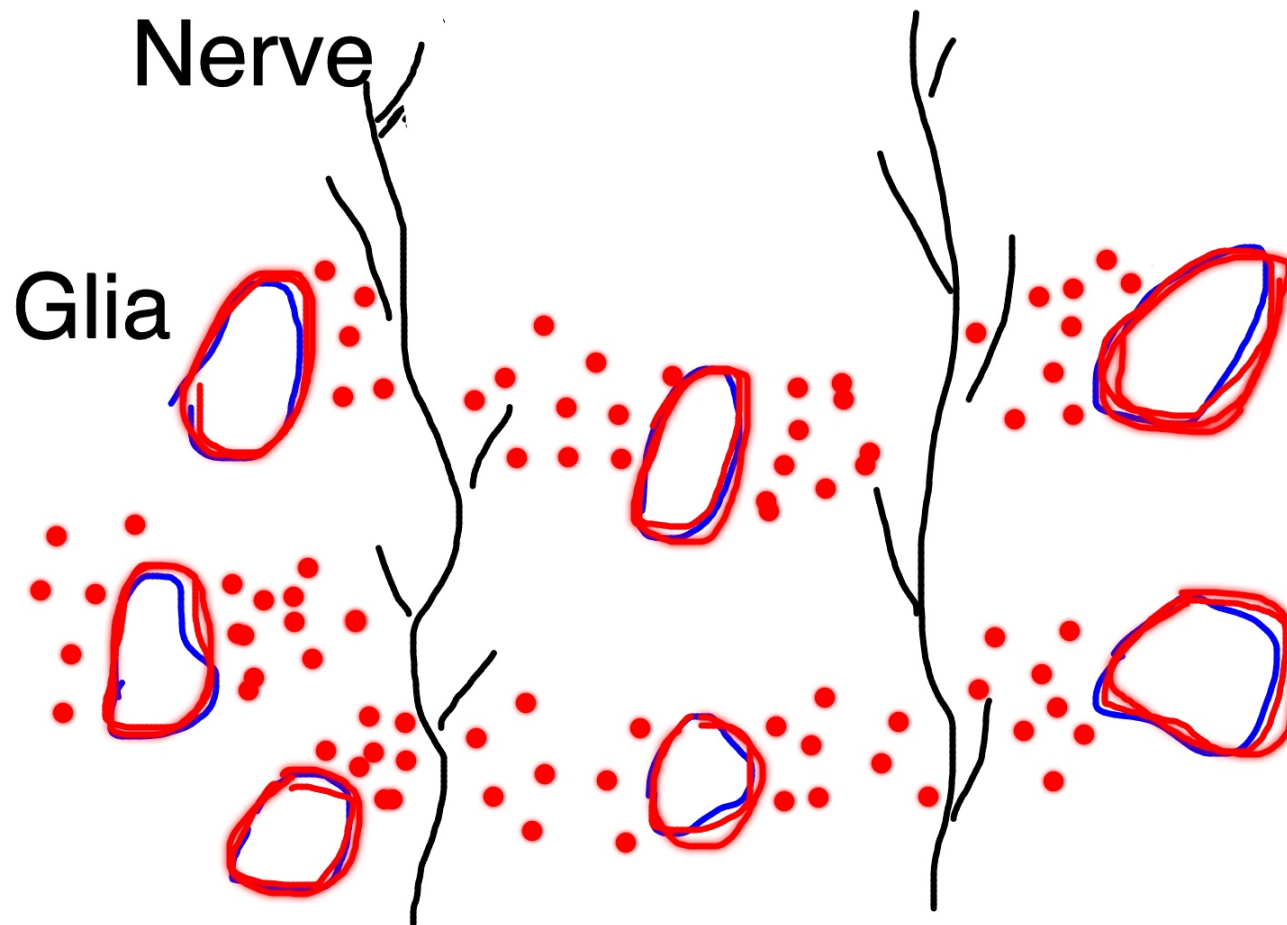




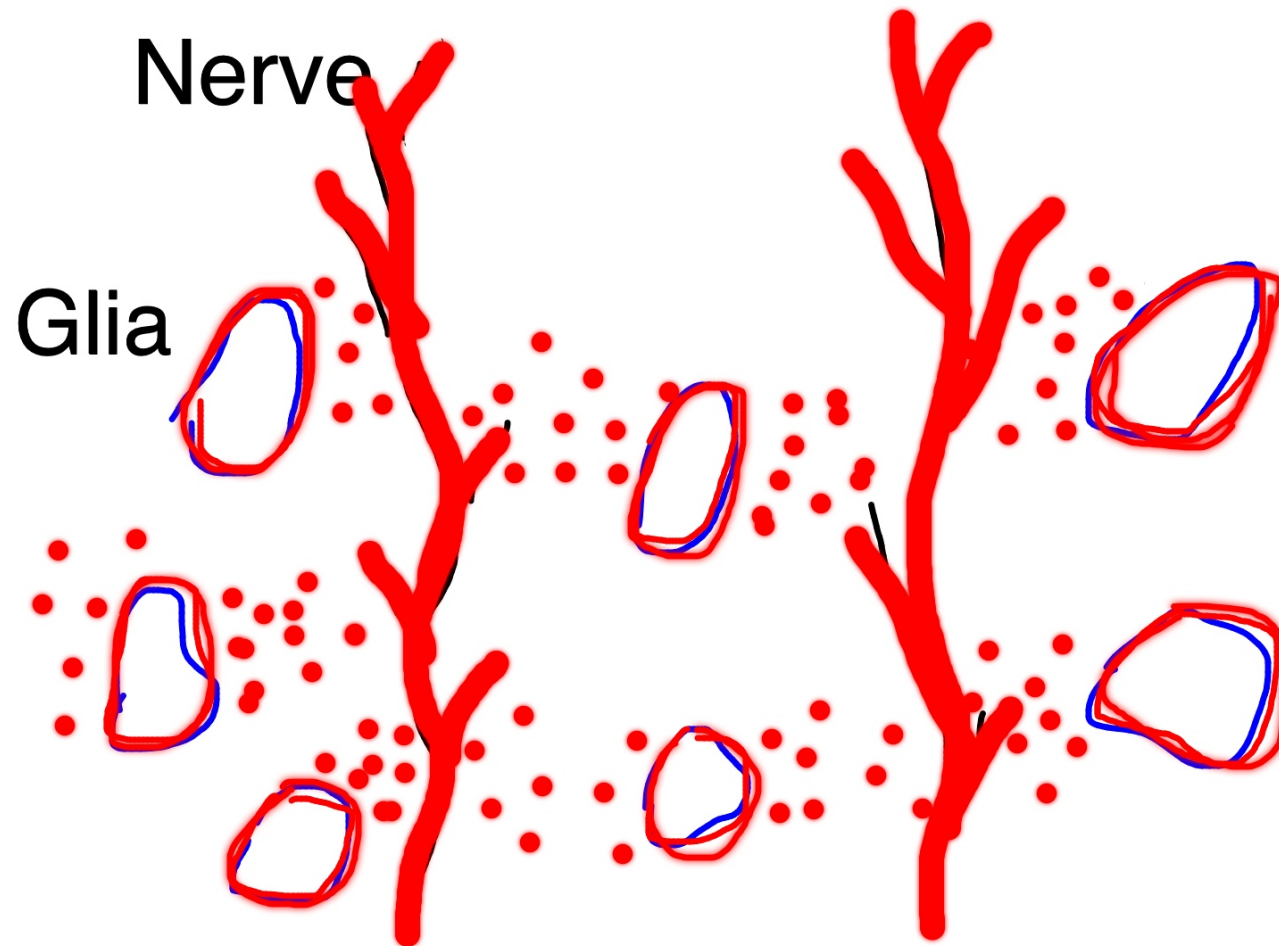
# Activated Glia



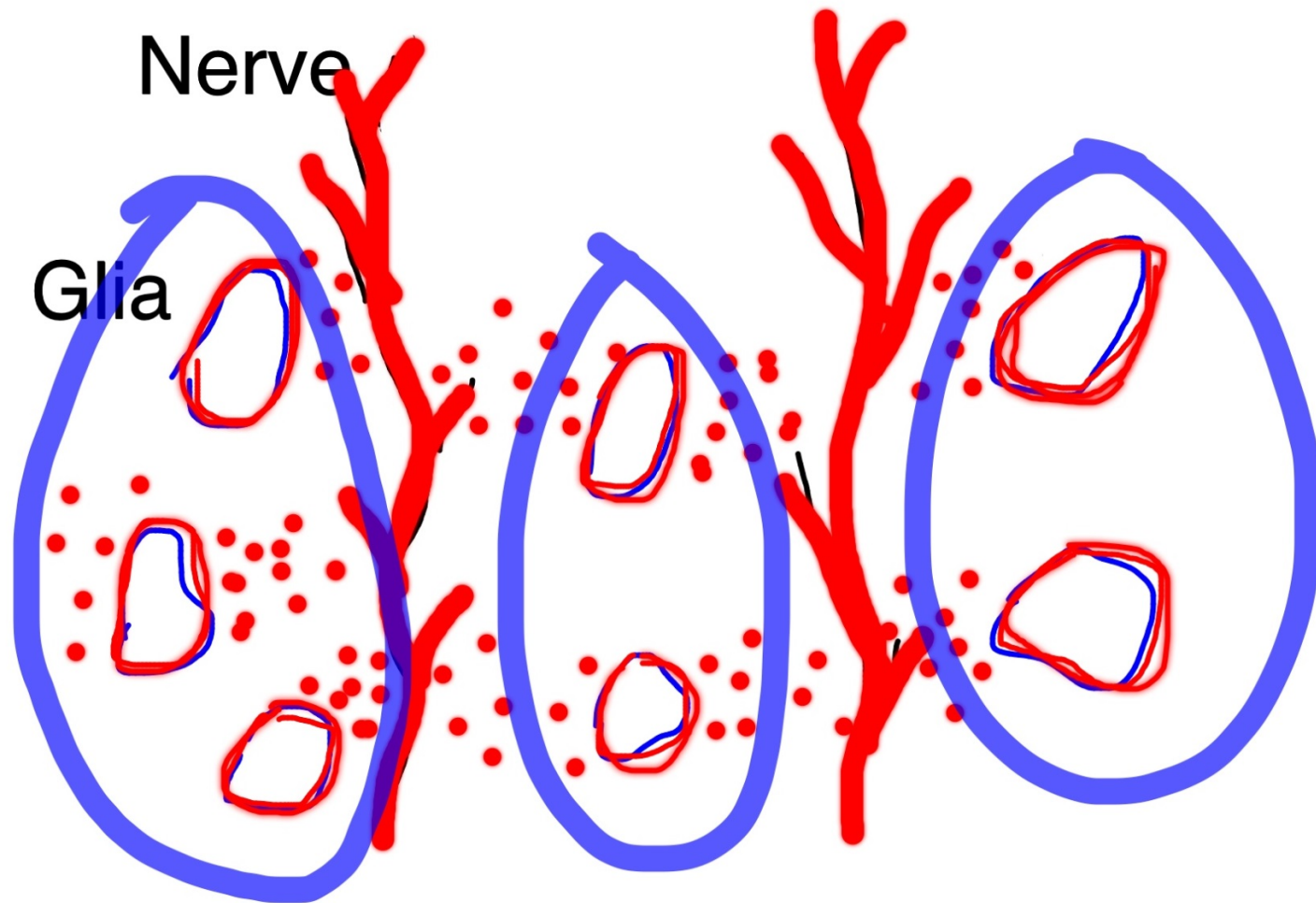
# Chemicals released by activated Glia



# Nerve inflammation

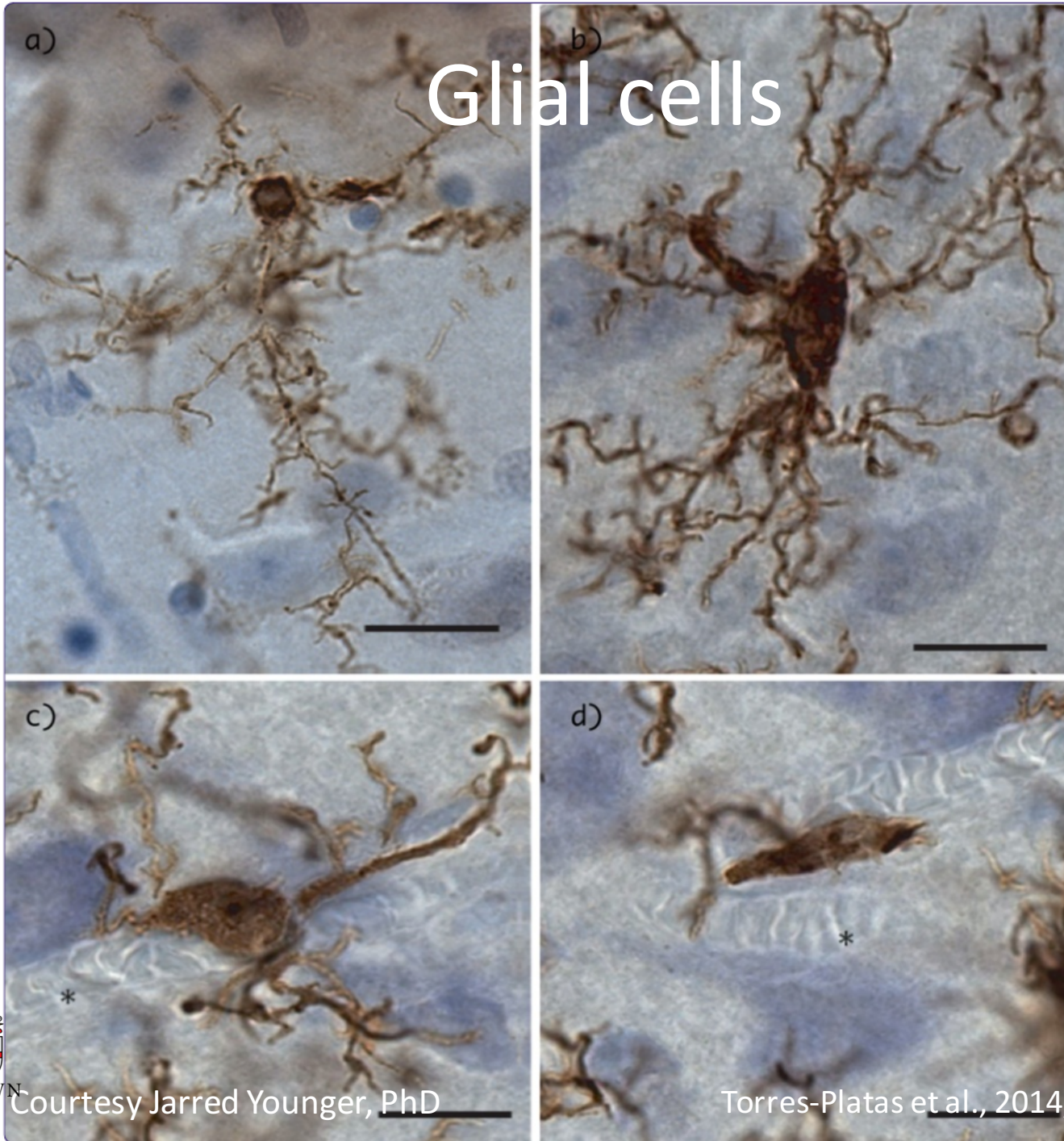


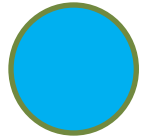
The problem is with the glia cells





# Glial cells





- Management of Complex Regional Pain Syndrome should be directed towards what's causing the nerves to become inflamed and not just the nerves.
- Thus, it makes sense to treat the glial cell activation



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# Management

Complex Regional Pain Syndrome  
(CRPS)

Reflex Sympathetic Dystrophy (RSD)





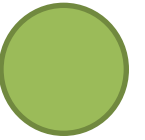
# Basic guidelines in treating CRPS

- Start treatment immediately, even if you suspect CRPS
- Must be evaluated by a Pain Medicine specialist or a physician who is very familiar with it, to start appropriate therapy
- Multidisciplinary approach - team work (??)

# Start low, go slow

# Grading of treatment

-  Effective
-  Worth trying
-  Use caution
-  Nerdy stuff

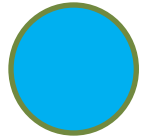


# Ketamine

A useful drug vindicated

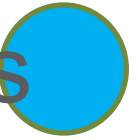


# Central Sensitization



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

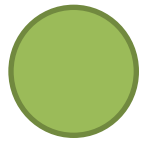
# Central Sensitization - NMDA receptors



- CRPS - activation and proliferation of NMDA receptors
- Activation of the NMDA receptors makes the Central Nervous system more responsive to pain signals 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



# 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)

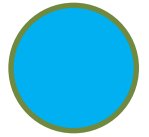


# Factors that are important in getting the best out of a ketamine infusion



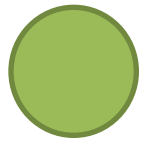
- Ketamine infusions are good only if done in conjunction with other therapies





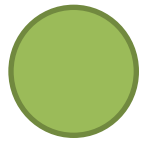
# Low dose Ketamine in CRPS

- Administered in sub-anesthetic doses – 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



# 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



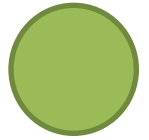
## IV Ketamine - boosters

- 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 may be done after 2 weeks for 2 days
- Then, for one day every 4 to 8 weeks depending on the severity, chronicity and response

# 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.
- Nausea, vomiting, colorful dreams, hallucinations, headache

# Ketamine sublingual (Troche)



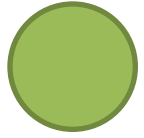
- Only for acute flare up. Not for regular use.
- Take 10mg in your cheek or under tongue every 1 hour till relief or for a total of 40mg to 50mg

10mg 1 hour 10 mg 1 hour 10mg 1 hour 10mg

# Ketamine oral



- Oral ketamine – don't bother
- Unpredictable effects



# Bisphosphonates

Class of drugs used to treat bone loss.

# Bisphosphonates

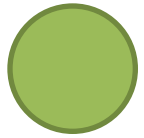
- Commonly used to treat osteoporosis (bone loss)
- Osteoblasts – cells that build bone. They use vitamin D
- Osteoclasts – break down bone
- Bisphosphonates destroy osteoclasts thus helping osteoblasts do their job of making bone



# Bisphosphonates

- Osteoblasts (bone building cells) Vitamin D to function
- It seems like improving healthy bone development either by improving osteoblasts functioning or by destroying osteoclasts (bone destroying cells) helps CRPS

# 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.

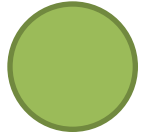
Pradeep Chopra, MD

# Neridronate



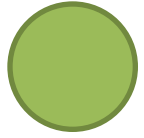
- Very similar to alendronate (Fosamax<sup>®</sup>), Pamidronate (Aredia<sup>®</sup>)
- Very small trial.
- Very select group of patients.
- Only patients who had bone changes were studied.
- Better studies being done which are more realistic

# Vitamin D

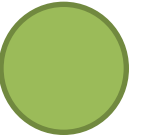


- Vitamin D promotes Calcium absorption in the gut
- Helps bone development
- Helps muscle and immune function
- Reduces inflammation

# Vitamin D

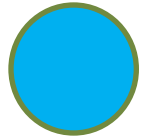


- Rather than seek treatments with bisphosphonates, work towards improving vitamin D levels first
- Really very important to check and make sure that vitamin D levels are adequate



# FREE RADICAL SCAVENGERS

# Free Radicals – what are they?



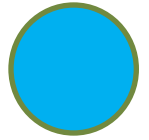
- Human body is made up of cells
- Cells are made up of atoms
- Atoms are made up of electrons and protons (1:1)

# Free radicals

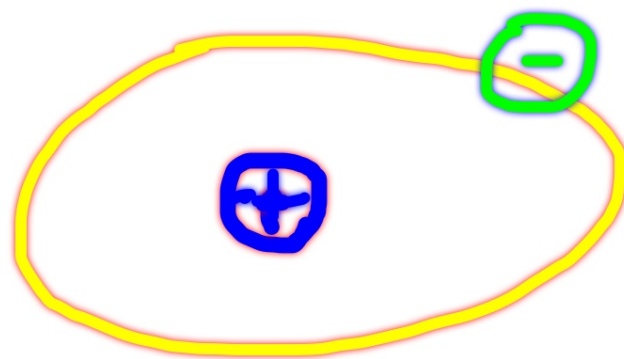
- The increased sympathetic nerve activity in the area cause blood vessels to constrict, hence the cold, pale limb.
- Reduced blood flow, tissue damage and increased acid production
- This causes increased production of free radicals which increase pain in the area.



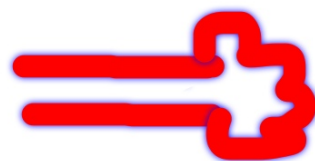
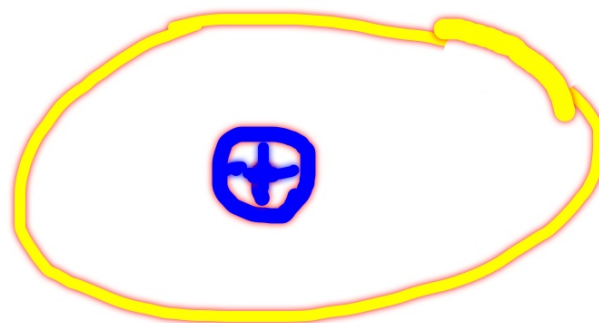
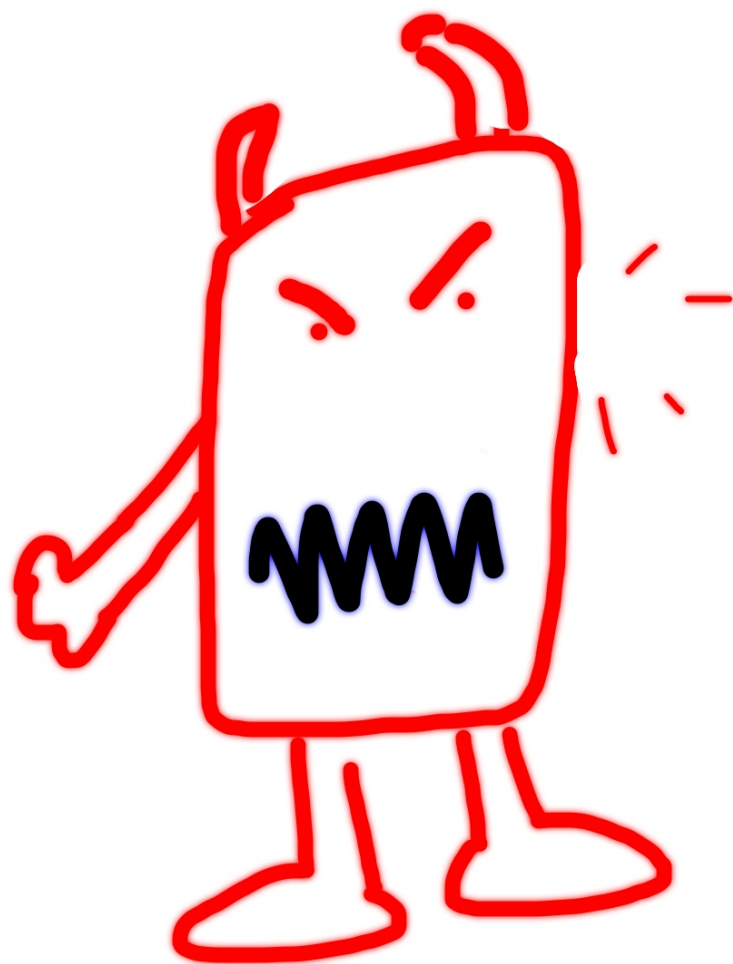
# Free Radicals – what are they?



- 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



I AM A HAPPY  
MOLECULE



FREE RADICAL

Free Radicals attack and rob electrons from other cells to satisfy themselves



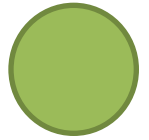
# Free Radical scavengers (Antioxidants)



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

# Alpha Lipoic acid (ALA)

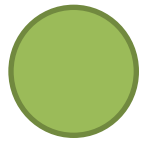
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- Free Radical scavenger
- Promising results in diabetic neuropathy and other polyneuropathies
- No trials in CRPS
- Has been approved in Germany for treating neuropathic pain

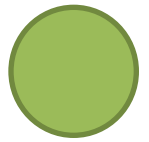
Kapoor S, Foot Ankle Spec, 2012 Aug;5(4); 228-9

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



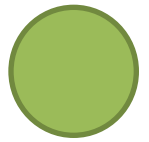
# Vitamin C

- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg for 45 days to 50 days was shown to prevent development of CRPS
- ? Any value to using it in established CRPS, certainly helpful in prevention





# DMSO 50% - Dimethyl Sulphoxide

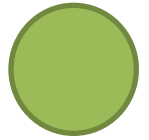


- Topical use only.
- Particularly helpful for 'warm' CRPS
- CRPS less than 1 year - three month course of DMSO applied 5 times topically every day
- CRPS more than 1 year – One month trial course of DMSO everyday.
- If trial helps, then continue

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

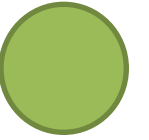
Zakmond WW, Langendijk PN, Bezemer PD, Brink HE, Lange JJ de, Loenen AC van. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand* 1996;40(3):364-7.

# N- Acetyl Cysteine (NAC)



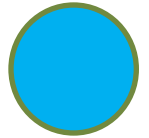
- Useful for cold allodynia
- N-Acetylcysteine 600mg three times a day for three months
- Start low, go slow





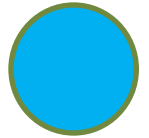
# Low Dose Naltrexone

LDN



# Low Dose Naltrexone (LDN)

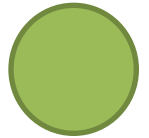
- Competitive antagonist of opioid receptors
- Clinically used for 30 years for addiction
- Suppressive effects on the CNS microglia, which....
- Attenuates production of pro-inflammatory cytokines and neurotoxic superoxides (chemicals that cause inflammation)



# 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

# 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.

# Case of CRPS treated with LDN

CRPS with dystonia  
before LDN



CRPS after 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.






# Sensory Deprivation Therapy



- No studies done for chronic pain
- Good experience in patients with CRPS
- Usually 60 minute sessions.
- Centers in most places, try Google

# Grading of treatment

-  Effective
-  Worth trying
-  Use caution
-  Nerdy stuff

# Oxytocin

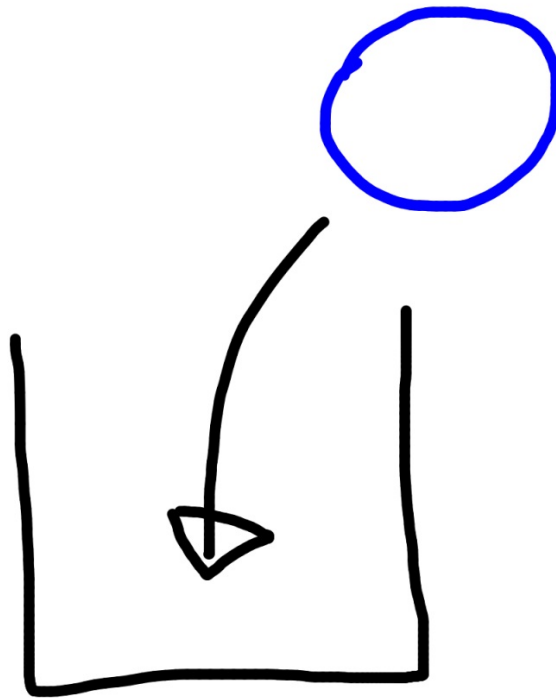


- Chemical produced naturally in the brain
- Taken as a nasal spray, sublingual
- Especially helpful in flare ups (acute pain)
- Two mechanisms by which oxytocin reduces pain
  - Directly on the spinal cord to turn down pain signals
  - By releasing endorphins (morphine produced by the body).

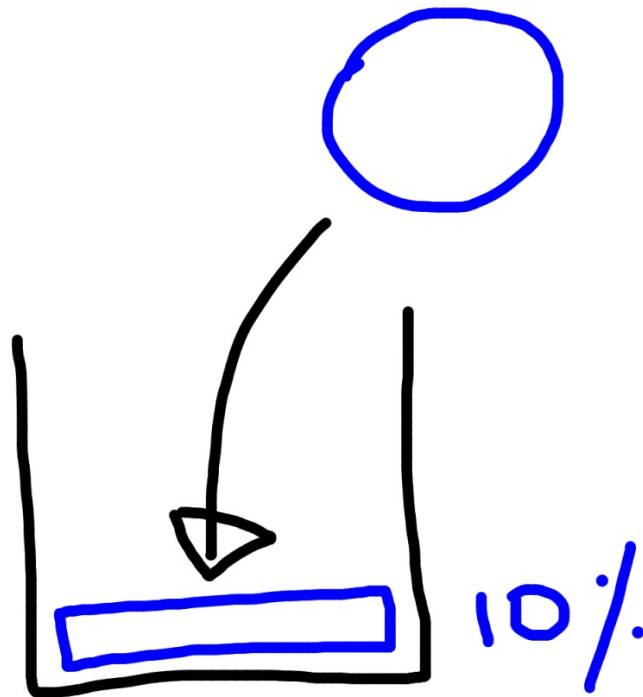
# NC10 rule

Expectations from different therapies

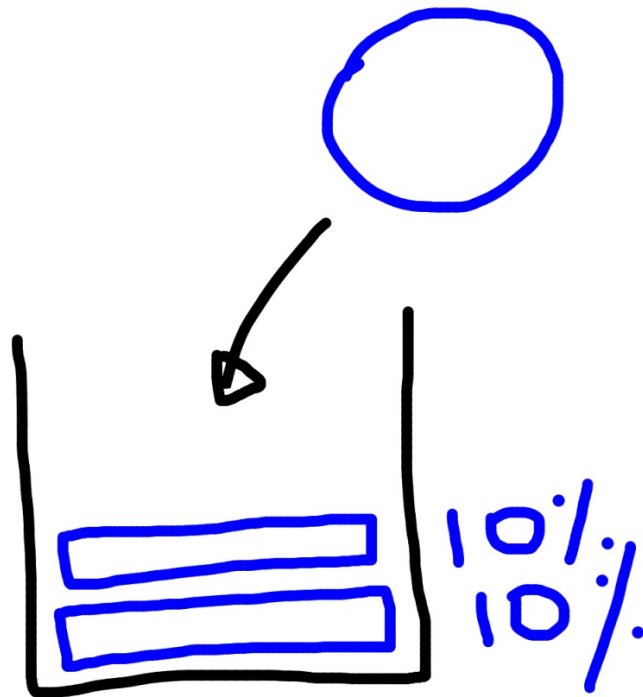
# NC10 rule



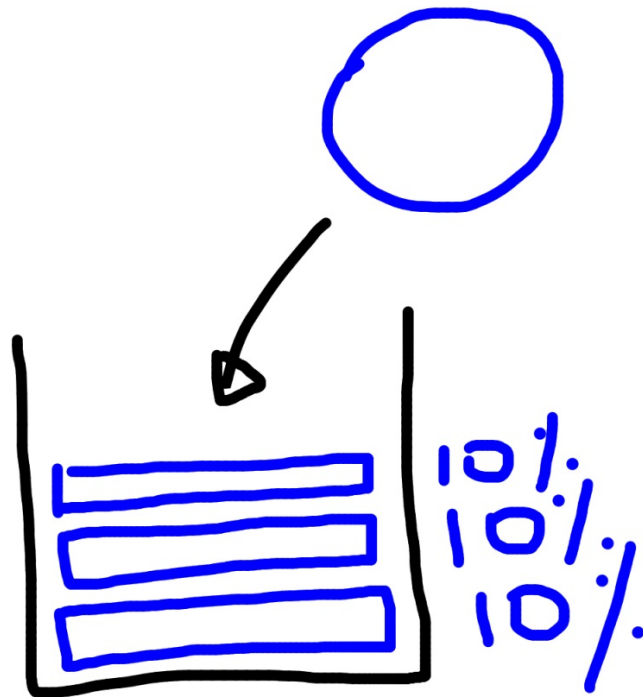
# NC10 rule



# NC10 rule

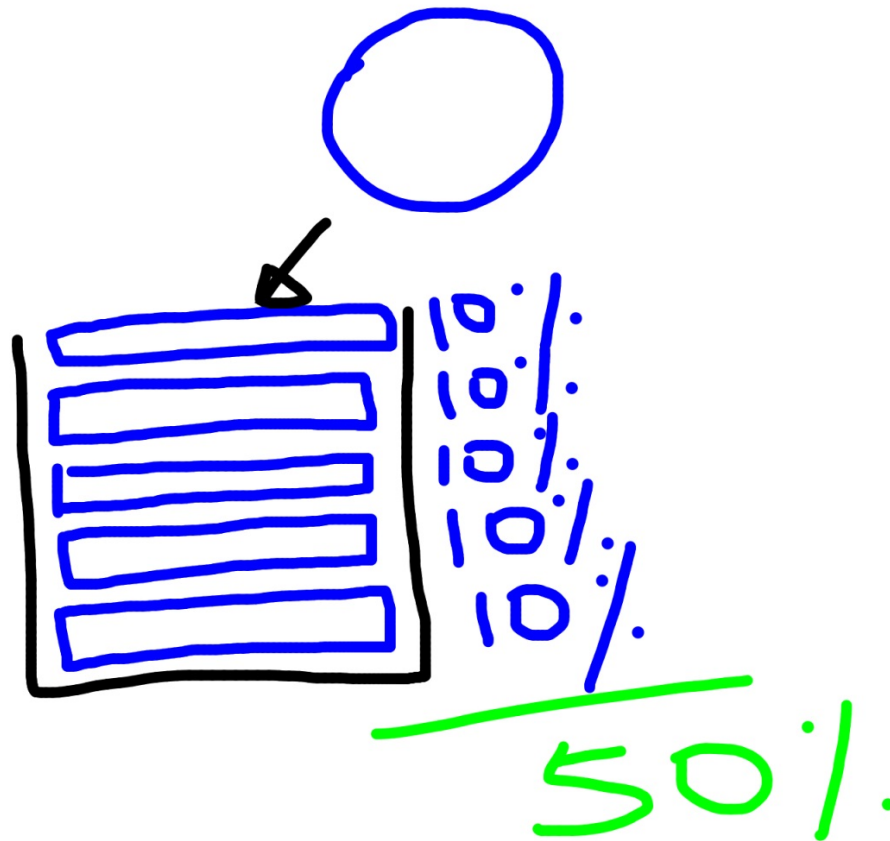


# NC10 rule





# NC10 rule



# Spinal Cord Stimulator (SCS)

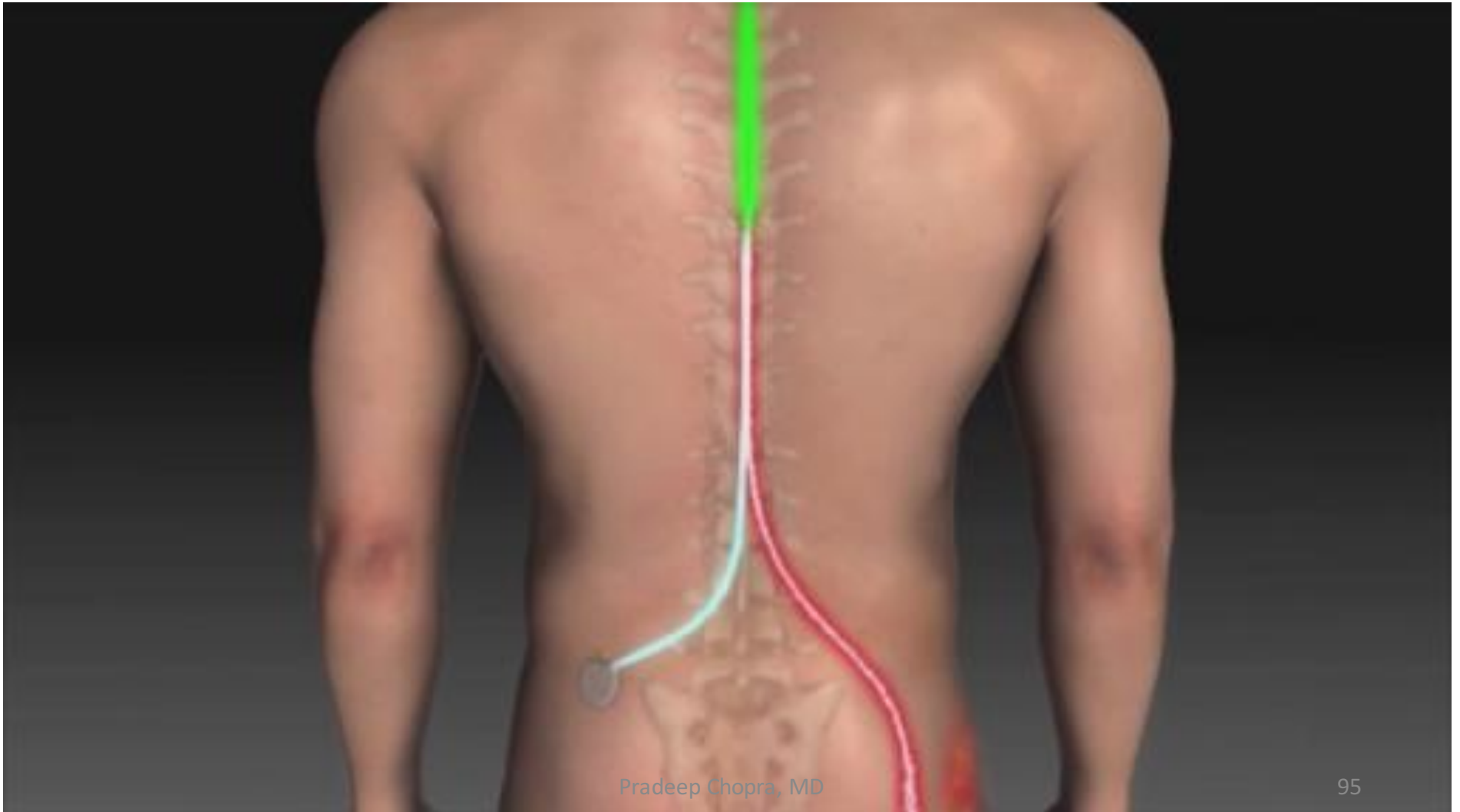


- An electrode is inserted surgically into the epidural space and connected to an implanted generator
- The electrode produces an electrical current is felt as a tingling sensation and suppresses pain.
- Mechanism of action unknown
- Painful and expensive

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



# Spinal Cord Stimulator (SCS)



- Marius A. Kemler, M.D., Ph.D. Henrica C. W. De Vet, Ph.D. Gerard A. M. Barendse, M.D. Frans A. J. M. Van Den Wildenberg, M.D., Ph.D. And Maarten Van Kleef, M.D., Ph.D. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 108:292–298, 2008
- 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 (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.

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.

# 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
- Expensive






# Sympathetic Nerve blocks

- Stellate ganglion blocks for upper extremity
- Lumbar sympathetic blocks for lower extremity
- No good data on long term efficacy of these blocks
- Very risky procedures
- No diagnostic or therapeutic value
- Temporary at best

Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain 1998;14(3):216-26.

 and SC, Beyer A, Romer AW, Galle-Rod A, Peter K, Schops P. Continuous axillary brachial plexus analgesia with low dose morphine in patients with complex regional pain syndromes. Eur J Anaesthesiol 2000;17(3):185-8.

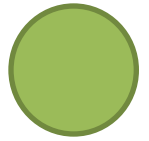
# Electrical stimulation



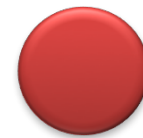
- Different therapies available that involve electrical stimulation of nerves.
- Very unhelpful
- May try a TENS unit.



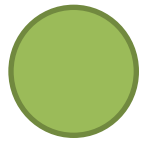
# Commonly used medications



- Gabapentin
- Pregabalin (Lyrica™)
- Milnacipran (Savella™)
- Amitriptyline
- Don't really make a significant difference but may be worth trying
- Duloxetine (Cymbalta™) - avoid



# Physical therapy modalities



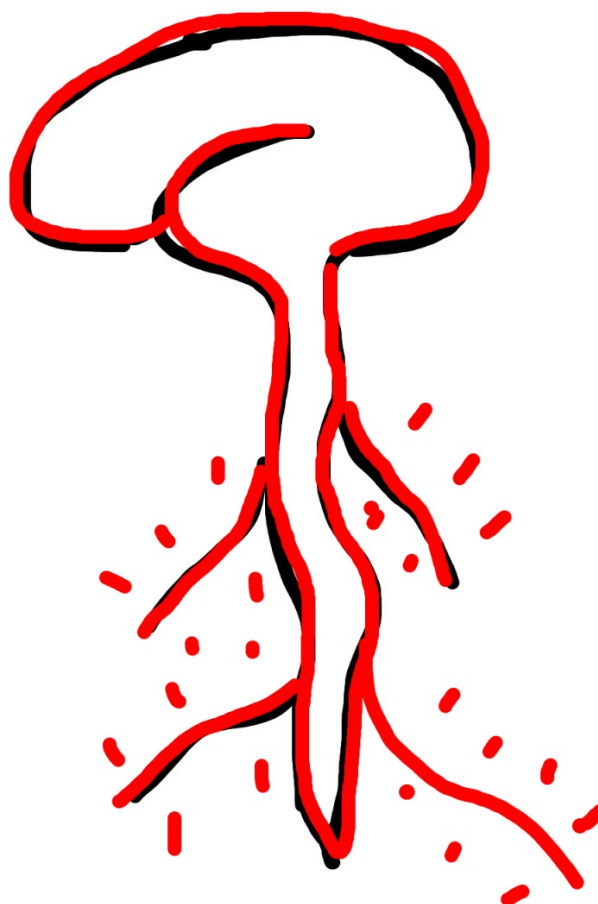
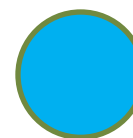
# Physical movement

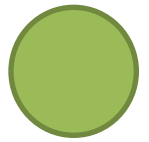
- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- "No pain, no gain" – nonsense

# Desensitization



- Desensitization exercises have been recommended for a long time for CRPS
- Rice bowl, rubbing with a piece of cloth, paraffin bath, etc.
- Worsens Central Sensitization
- No literature to support the use of desensitization exercises.

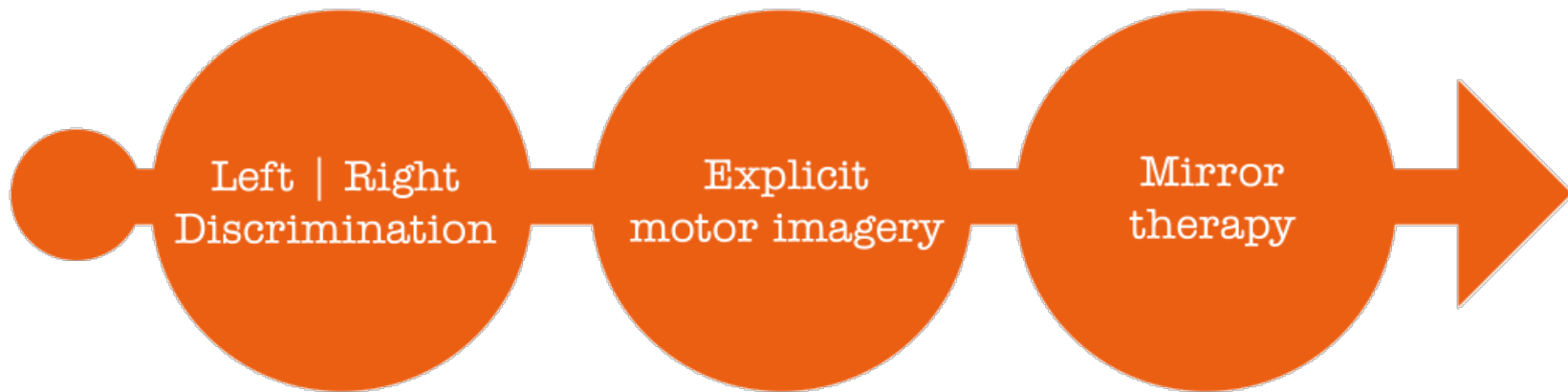




# Motor Imagery

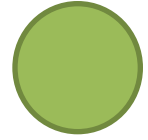
- Early stages: Mirror therapy is useful only in the early stages of the condition
- Later stages: A graded learning concept is required in chronic cases.

# Three stages of Graded Motor Imagery delivered sequentially



- Left / right discrimination
- Explicit Motor imagery
- Mirror therapy

# Graded Motor Imagery

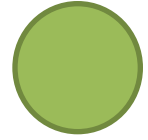


1. App 'Recognise' on iTunes or Google Play
2. Explicit motor imagery and left/right discrimination using the app Recognise
3. Mirror therapy

[www.gradedmotorimagery.com](http://www.gradedmotorimagery.com)



# Graded Motor Imagery



- Rehabilitation program to treat complex pain
- Broken down into three unique stages of treatment techniques, each exercising the brain in different ways.
- [www.gradedmotorimagery.com](http://www.gradedmotorimagery.com)

# Addiction to opioids

How real is the monster?



# Addiction



- A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations
- Note: it is a disease. It is not related to a specific drug



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# Addiction



- Addiction is a disease that has nothing to do with pain.
- Its unfair to use the words addiction and pain medicine in the same sentence.



- In a study of 1,100 patients “the incidence of drug abuse events and aberrant drug related behaviors was relatively low” (Passik et al. *Journal of Pain and Symptom management.*)
- Incidence of abuse or addiction in chronic pain patients was 3.2% and.....  
.....0.19% in patients who had no history of substance use (Fishbain, et al in *Pain Medicine*, 2008)

# Addiction

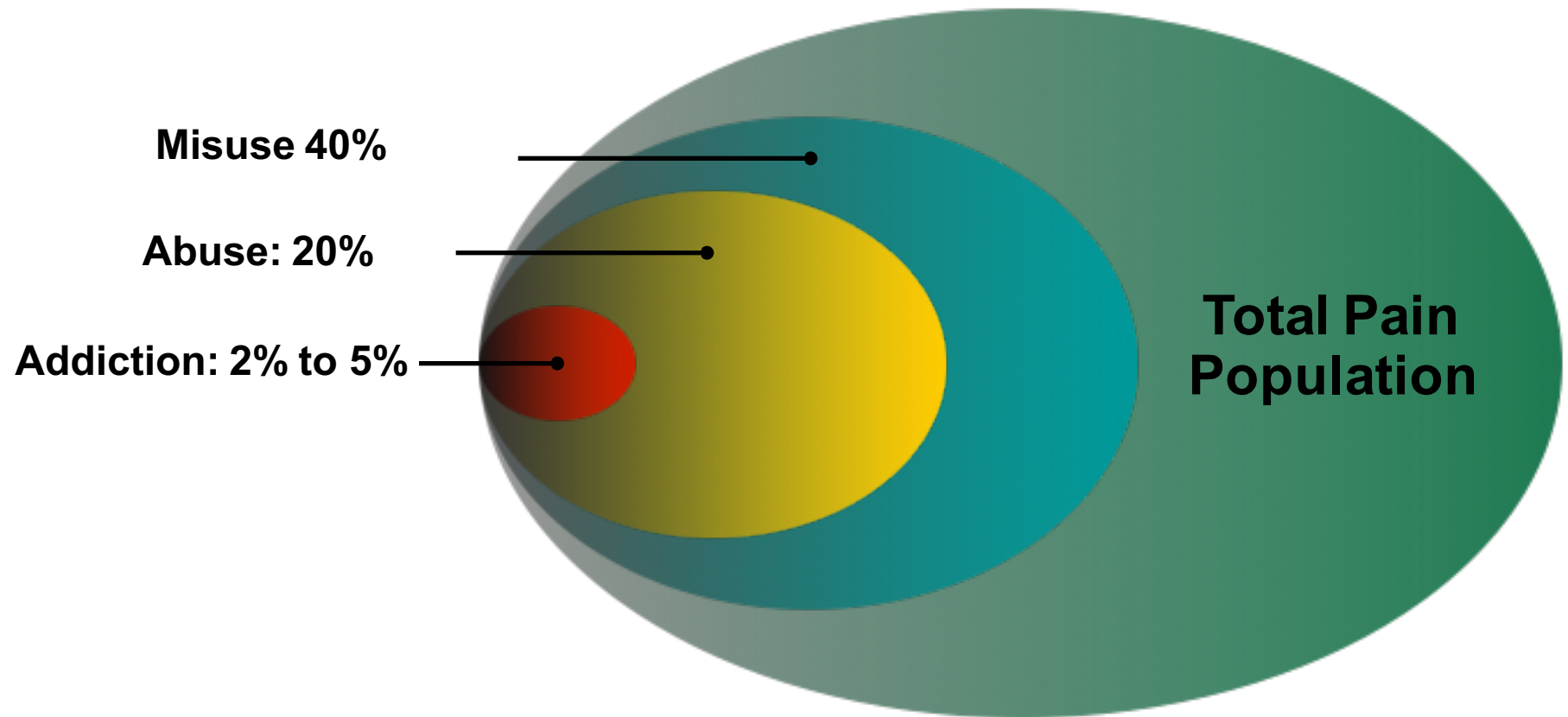


- Most of the news media sensationalize deaths due to addiction with prescription drugs.....

..... the truth is that people die of OVERDOSE or they have taken non-prescription drugs along with their prescription drugs

- Addiction is a disease not a habit.

# Prevalence of Misuse, Abuse, and Addiction





## FDA fights drug overdoses with new labels for prescription painkillers

🕒 21:50 PM, Sep 10, 2013

In the United States, a person dies every 19 minutes from a prescription drug overdose. Many of those deaths are attributed to a family of painkillers known as opioids.



## Orphaned by prescription drug overdoses

🕒 23:26 PM, Dec 13, 2012

CNN's Dr. Sanjay Gupta goes to Kentucky to visit the victims of the prescription drug epidemic -- kids.



## Prescription drug overdoses on the rise

🕒 17:29 PM, Nov 14, 2012

In a new documentary, "Deadly Dose," Dr. Sanjay Gupta investigates the rise of prescription drug overdoses in the U.S.



## Accidental prescription drug overdoses

🕒 17:11 PM, Nov 13, 2012

CNN's Dr. Sanjay Gupta and former President Bill Clinton on the problem of accidental prescription drug overdoses.

Pradeep Chopra, MD





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Pradeep Chopra, MD



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# ‘Addiction’ and ‘pain management’ should never be used together

- Why not use suicides and antidepressants in the same sentence?
- 1 in 3000 will attempt suicide when started on antidepressants
- 1 in 1000 will make a serious attempt at suicide
- Yet, we never use the words suicide and antidepressants in the same sentence

Simon GE<sup>1</sup>, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry. 2006 Jan;163(1):41-7.



# Deaths

- Smoking tobacco more >480,000 per year<sup>1</sup>
- Alcohol 88,000 per year<sup>2</sup> + 10,000 drinking and driving
- Prescription painkiller OVERDOSE 16,000<sup>3</sup> (2013)

1. [http://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/health\\_effects/tobacco\\_related\\_mortality/](http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/)
2. <http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm>
3. <http://www.cdc.gov/drugoverdose/data/index.html>

Taking opioids for pain is not as bad as  
we thought



# Opioids and CRPS

- Taking opioids in CRPS:
  - They sensitize the patient to pain (increase Central Sensitization)
  - They are not very effective for the nerve pain part of CRPS
  - Takes away the option to try LDN

# What to avoid in CRPS

- Immobilization – cast, brace
- Trauma
- Needle stick – unless absolutely necessary

# Gastrointestinal system and CRPS

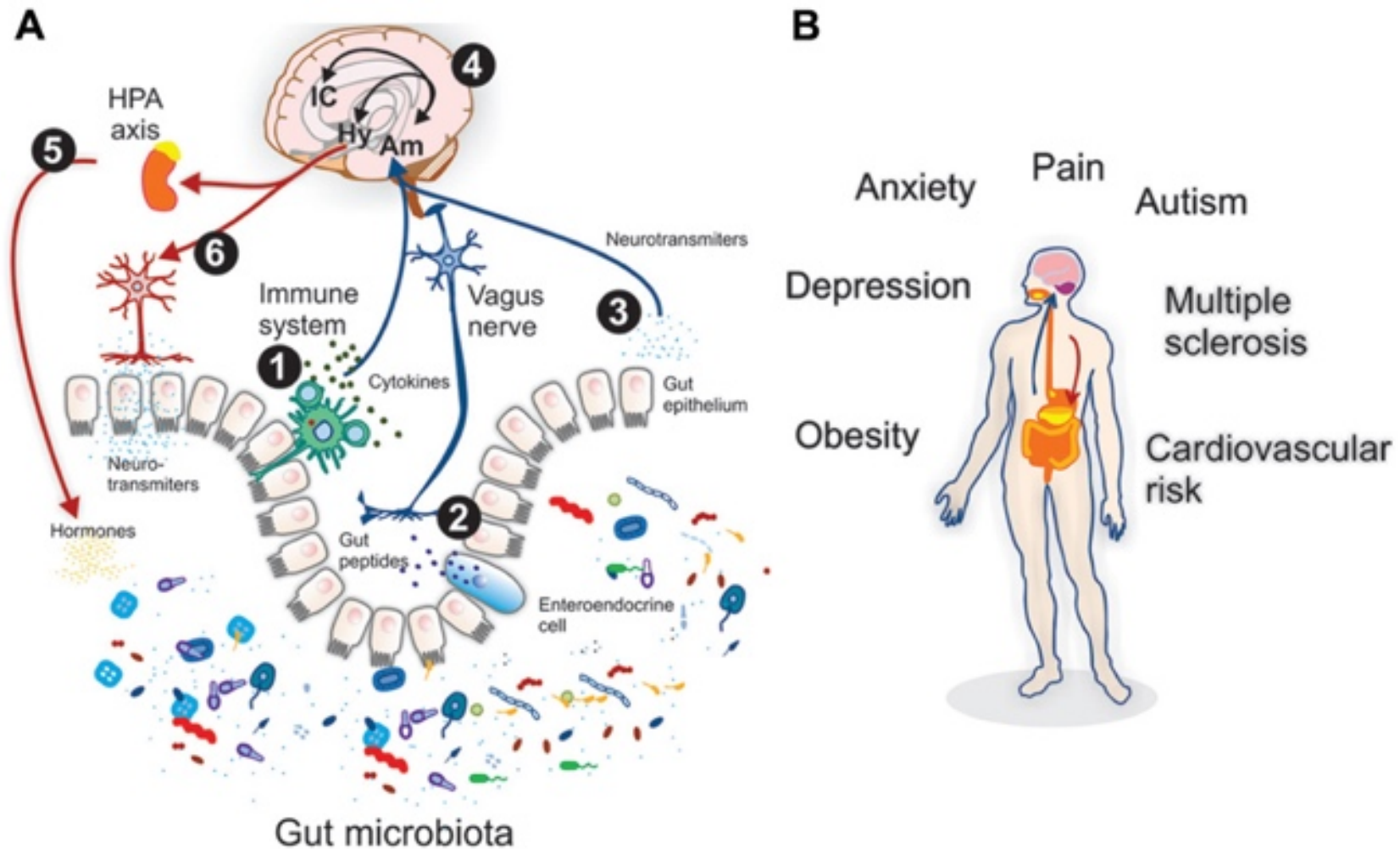
How our foods may affect our pain

# 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.

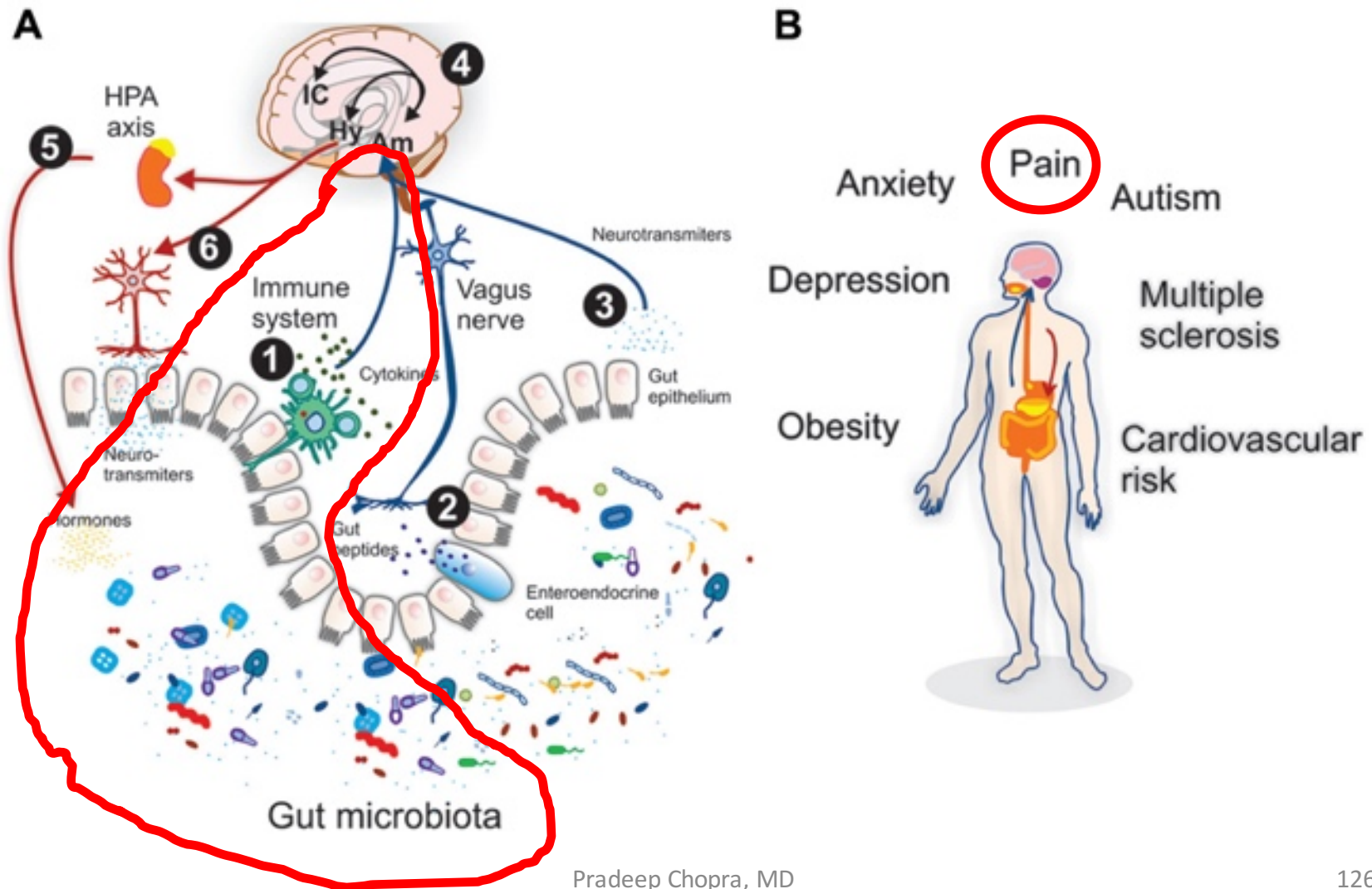


# Gastrointestinal system (GI system) and CRPS



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

# 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

- 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
- TLR4 receptor activity is increased. This has been associated with inflammation.
- TLR4 is one of the receptors where LDN works.

# Gastrointestinal system (GI system) and CRPS

- Are we destroying our 'friendly' bacteria with our artificial foods, preservatives, chemicals, antibiotics?
- SIBO – Small Intestine Bacterial Overgrowth – talk to Gastroenterologist
- We need more research in to this

# 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

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; ¶Department of Psychology, Washington University, St. Louis, Missouri; #Department of Psychology, Washington University, St. Louis, Missouri; \*\*Department of Psychology, Washington University, St. Louis, Missouri; ††Department of Neurology, Washington University, St. Louis, Missouri; ‡‡Department of Neurology, Washington University, St. Louis, Missouri.

# 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.
- 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

# Children and RSD

- Parents should research the physician's philosophy and training before taking their child
- If the physician or center offers only physical therapy and psychological treatment as their main treatment – avoid going there

# Sleep and fatigue

- Problems with having a high sympathetic nerve activity ( high flight and fight mechanism) in CRPS:
- POTS
- Sleep issues
- Fatigue



# Postural Orthostatic Tachycardia Syndrome (POTS)

# POTS

- Dizziness and racing heart – usually with changing posture
- Brain fog
- Fatigue
- Anxiety

# Dizziness and Palpitations

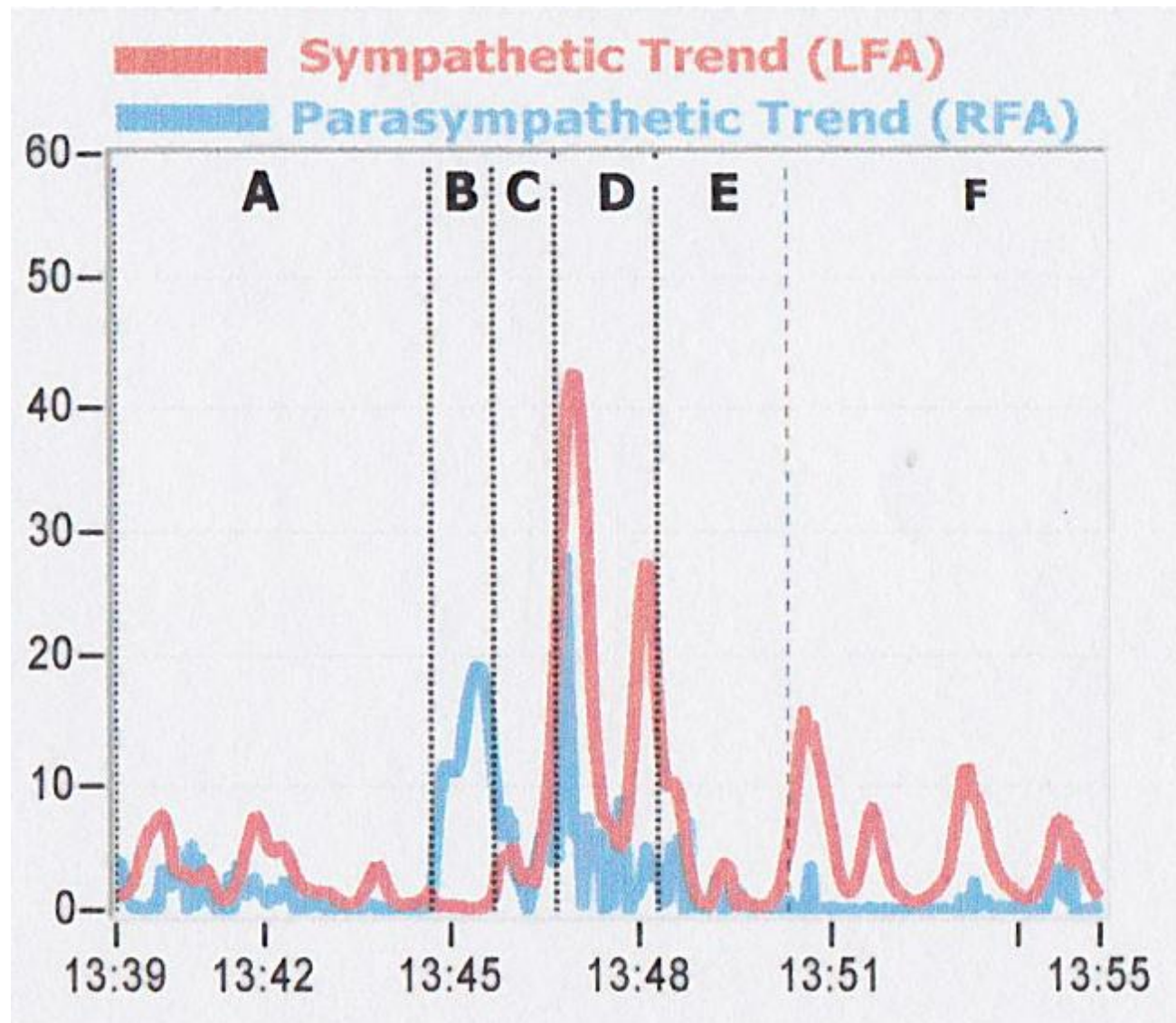
- Increase in heart rate by 30 beats/ min or increase to 120 beats/ minute
- Increase salt intake, fluids, compression leggings
- Medications

# Sleep and CRPS

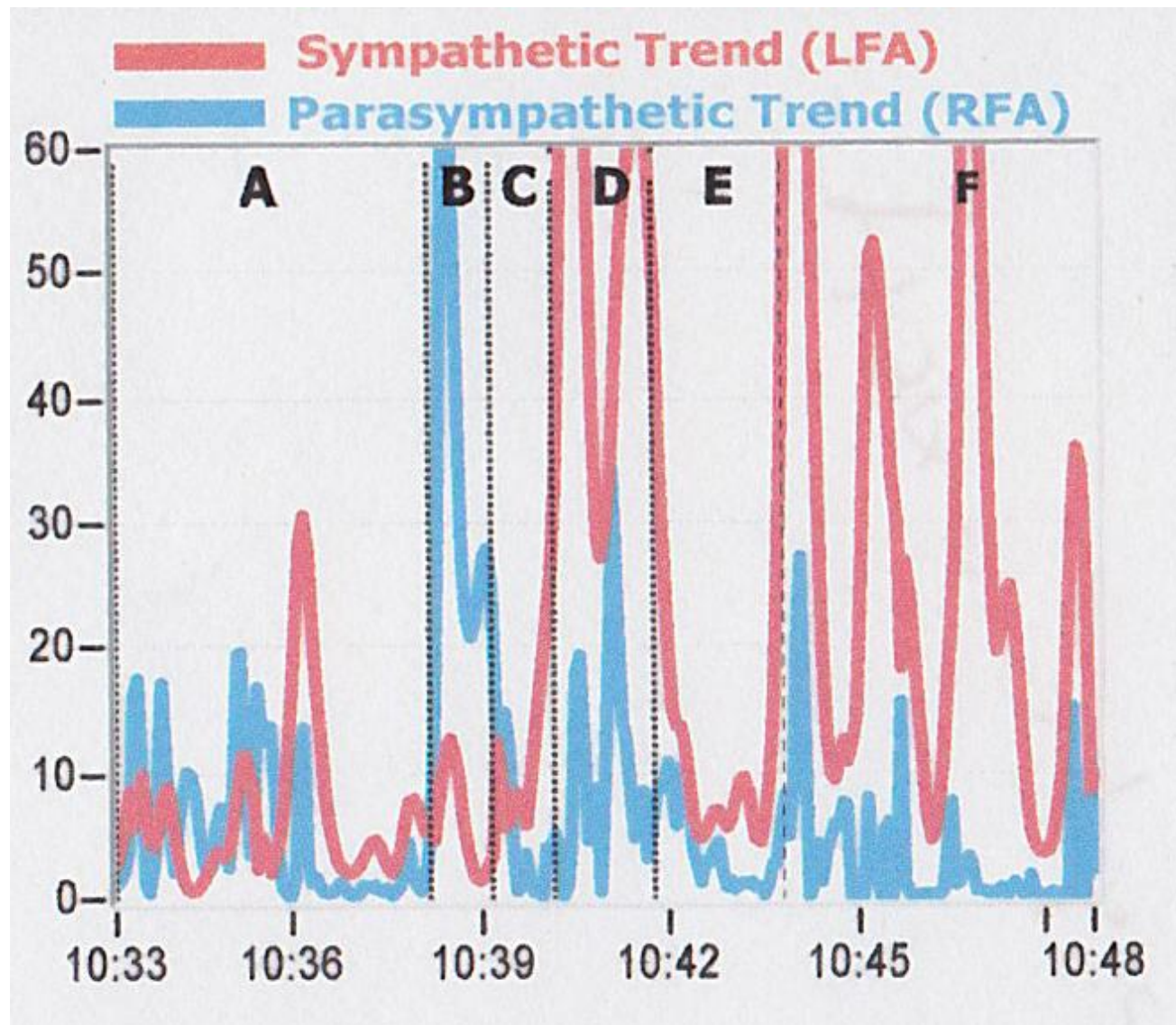
# Sleep and CRPS

- 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.

# Brain activity during sleep - normal

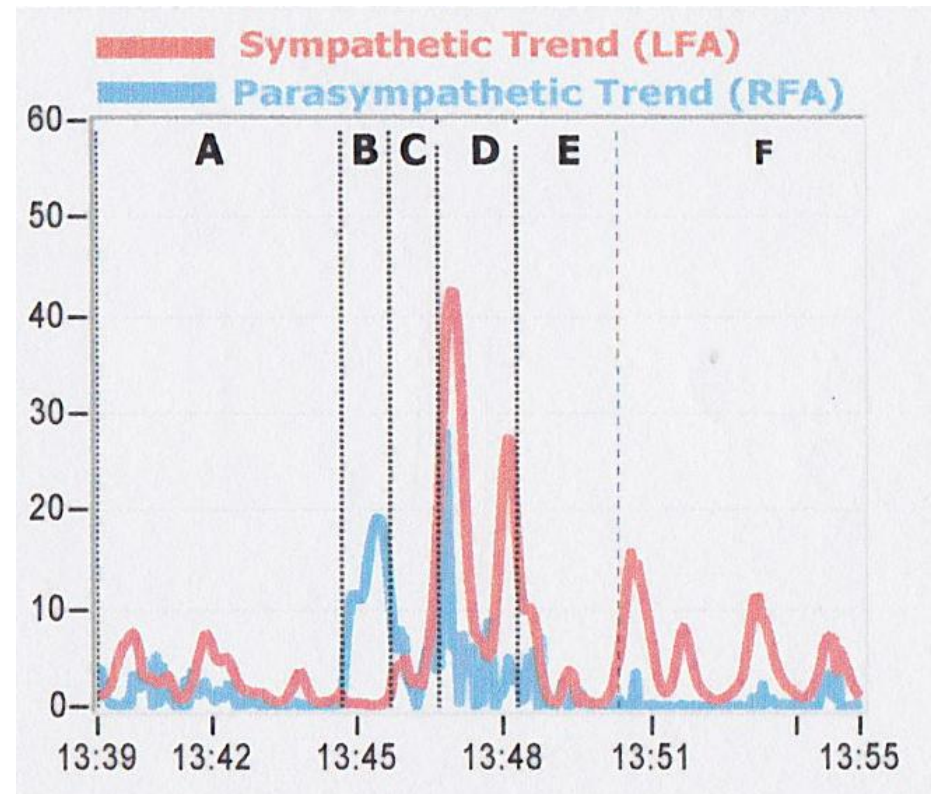
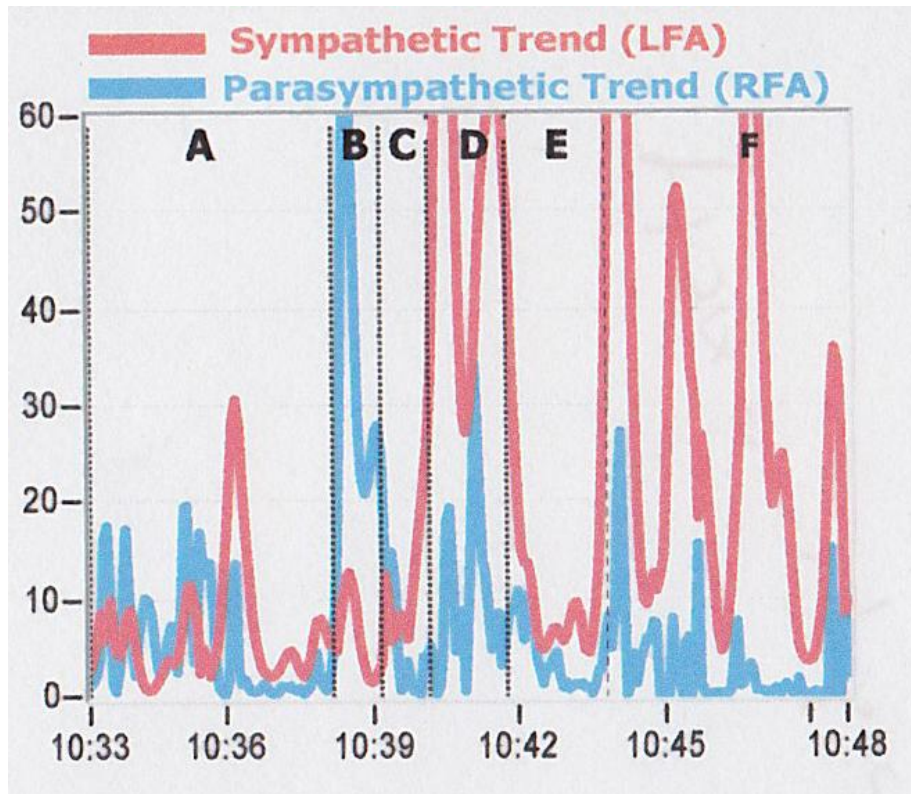


# Brain activity during sleep – in CRPS





# Non-restorative sleep





# Non-restorative sleep

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

# Fatigue and CRPS

# Fatigue and CRPS

- Chronic pain
- Poor sleep as a result of pain
- Non-restorative sleep
- Postural Orthostatic Tachycardia Syndrome (POTS)
- 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
- Supplement cocktail of ubiquinone, carnitine, vitamin B complex

# Mast cells and CRPS

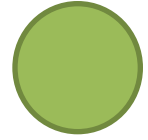
# Mast cells and CRPS

- We know that there is inflammation of the nerves that causes CRPS
- Mast cells found in blood can cause inflammation. Part of the neuro-immune system
- Mast cells release potent inflammatory chemicals (proinflammatory and neuropeptides)

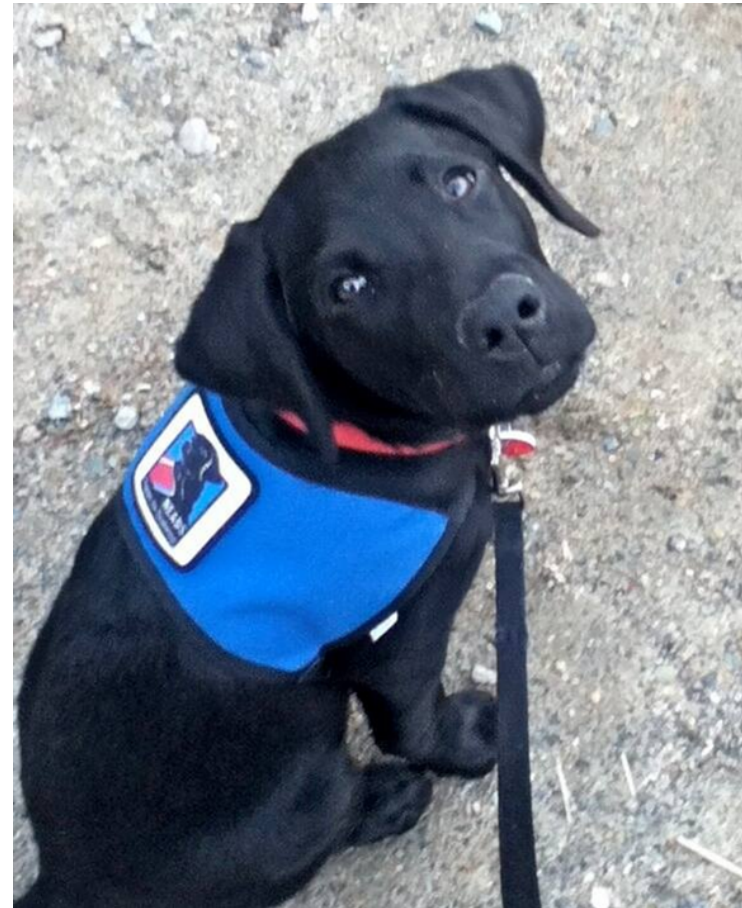
# Mast cells and CRPS

- Antihistamines:
  - Common cold medicines – Benadryl, zyrtec, claritin
  - Zantac
- Cromolyn Sodium
- Ketotifen

# 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





# 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.

# Breast feeding with CRPS

- Check with doctor about which drugs can be taken.



# 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

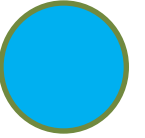
# Needle stick injuries

- 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

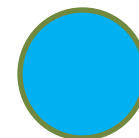
- Ask for a sign over the bed that the affected limb is not to be touched.
- Avoid loud sounds, bright lights
- Cage over the affected limb
- Have a friend or family member to make sure that the area with CRPS is not touched

# The future



# Adenosine receptors

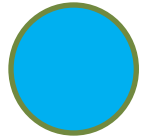




# Adenosine A3 agonists

- A3 receptors are found in nerves and glial cells
- Hence there is a lot of interest in researching A3 drugs for nerve pain.
- There 2 prototypes that have advanced to phase II and III trials (for psoriasis, rheumatoid arthritis and liver cancer)

Dilip K. Tosh,<sup>†</sup> Amanda Finley,<sup>§</sup> Silvia Paoletta. In Vivo Phenotypic Screening for Treating Chronic Neuropathic Pain: Modification of C2-Arylethynyl Group of Conformationally Constrained A3 Adenosine Receptor Agonists. [dx.doi.org/10.1021/jm501021n](https://doi.org/10.1021/jm501021n) | J. Med. Chem. 2014, 57, 9901–9914



# Adenosine receptors agonists

- Growing evidence that drugs acting on adenosine receptors A1, A2A, A2B, A3 can be promising for treating chronic pain
- Several drugs that work on the A3 receptor have been shown to be neuroprotective and anti-inflammatory.
- Promising clinical trials.

# Subcutaneous Ketamine – a future possibility

- Continuous subcutaneous infusion
- Home infusion on a more regular basis
- Not as expensive
- Subcutaneous Ketamine has been used for managing cancer pain at home



# Tadalafil (Cialis)



- Treatment of cold CRPS resulted in significant reduction of temperature difference between affected and unaffected limbs

Groeneweg et al., BMC Musculoskeletal Disorders, 2008, 9:143

# Tocilizumab (TCZ)

- Tocilizumab (Actemra™) is recombinant humanized anti-human IL-6 receptor monoclonal antibody
- IL-6 (Interleukin 6) is one of the cytokines that cause pain in CRPS
- Approved for treatment of Rheumatoid arthritis
- Not studied in CRPS
- Why not?

# Thalidomide

- Suppresses TNF-alpha (a cytokine that cause inflammation)
- 42 patients were administered Thalidomide.
- 31% showed a moderate to significant response

Rajkumar SV, Fonseca R, Witzig TE. Complete resolution of reflex sympathetic dystrophy with thalidomide treatment. Arch Intern Med. 2001;161:2502–2503.

Ching DW, McClintock A, Beswick F. Successful treatment with low-dose thalidomide in a patient with both Behcet's disease and complex regional pain syndrome type 1: case report. J Clin Rheumatol. 2003;9:96–98

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- Iris Gilmore
- Ron Gilmore



- RSDSA - [www.rsds.org](http://www.rsds.org)
- Finding help for living with CRPS is a team effort
- Support these organizations as much as you can.

# Thank you

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