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Complex Regional Pain Syndrome: Diagnosis and Management

Reflex Sympathetic Dystrophy
2015 Denver, CO

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- 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
- Training and Fellowship, Harvard Medical school in Pain Medicine
- Assistant Professor – Brown Medical School, Rhode Island



Grading of treatment

-  Effective
-  Worth trying
-  Use caution
-  Nerdy stuff

Diagnosis of CRPS

What is CRPS / RSD

- Complex Regional Pain Syndrome formerly Reflex Sympathetic Dystrophy
- Syndrome characterized by a continuing pain that is disproportionate to the usual course of any trauma or lesion.
- Usually starts after a trauma, immobilization.

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. Unexplained and diffuse
- Severe pain
- Temperature, color change.
- Edema
- Area of pain larger than the primary injury
- Limited range of motion

Signs and Symptoms of CRPS

2

- Allodynia - pain on light touch
- Creepy, crawly sensation to touch - dysesthesia
- Nail growth changes (faster, distorted), hair growth changes (coarser, darker, rapid growth, hair falling), skin changes (atrophy of skin), skin lesions

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

Muscle symptoms in CRPS

- Muscle spasms
- Dystonia
- Tremors
- Myoclonus

Other symptoms

- Loud or even normal sounds can set off pain
- Bright lights or normal lights can set off pain.



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Color, temperature and swelling



Swelling



Hair growth



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Best Diagnostic tool

- A good history and physical examination
- A repeat examination may be done to come to a diagnosis because of the fleeting nature of some of the symptoms (color change, temperature asymmetry)

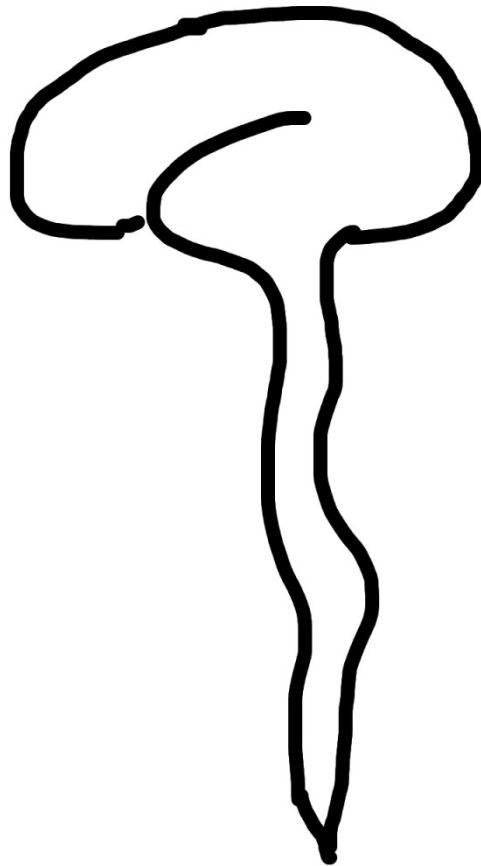
Tests that are **not** helpful for diagnosing CRPS

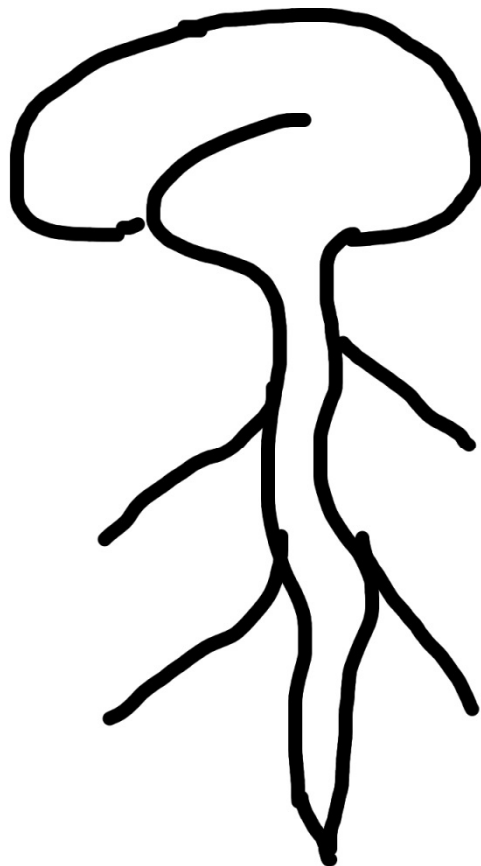
- Imaging techniques – x-ray, MRI, fMRI, Three phase bone scan, bone density
- Blood tests
- Skin biopsy
- Sympathetic nerve tests – sweat test, sympathetic skin response,
- Nerve tests – EMG, nerve conduction,
- The tests MAYBE used if another diagnosis is suspected.

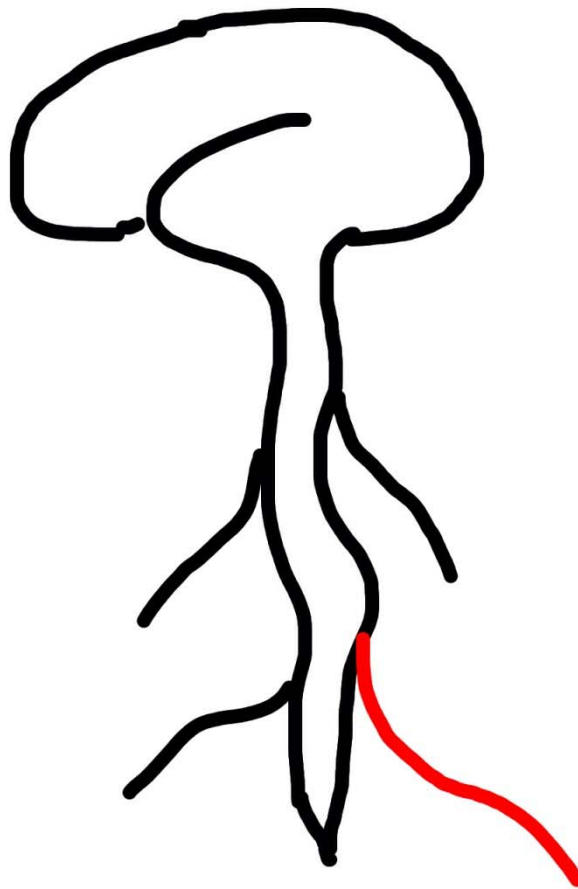
Nerve entrapment

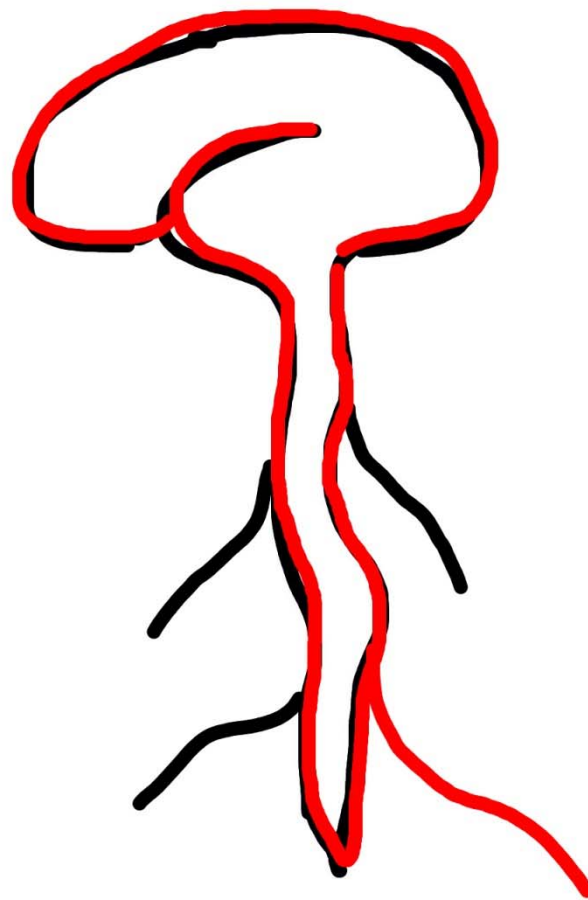
- Often seen after a cast is put on or trauma causing dislocation or fracture
- May cause pain either right away or after some time with chronic pressure over the nerve

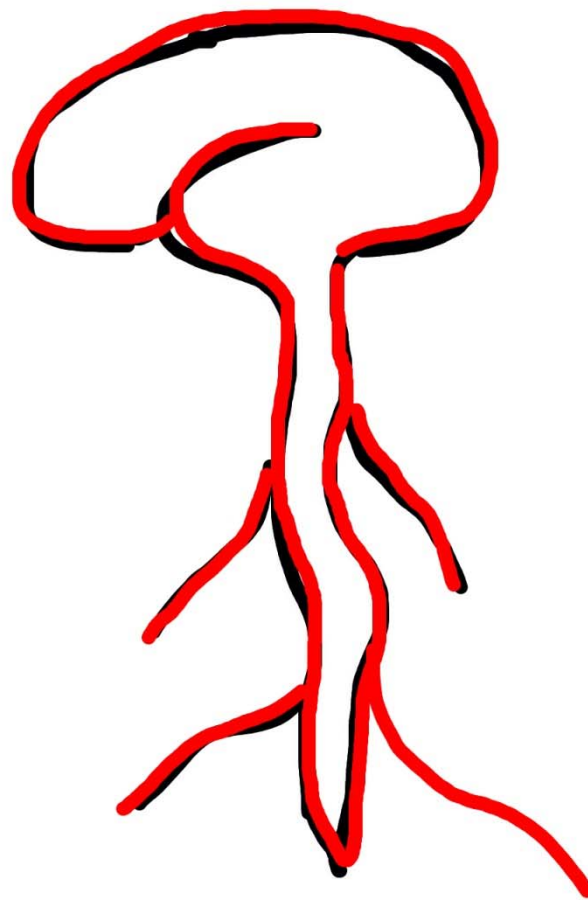
What happens in CRPS / RSD

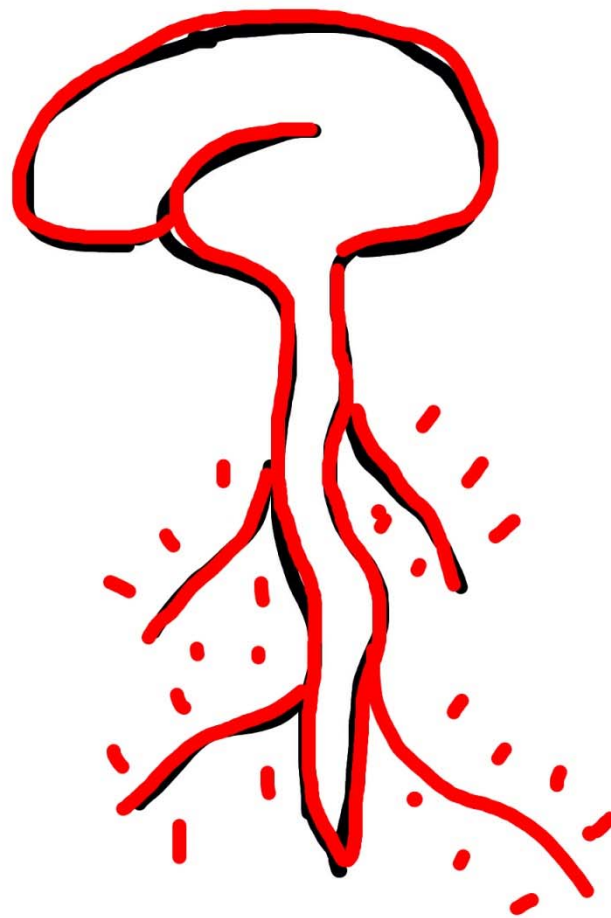


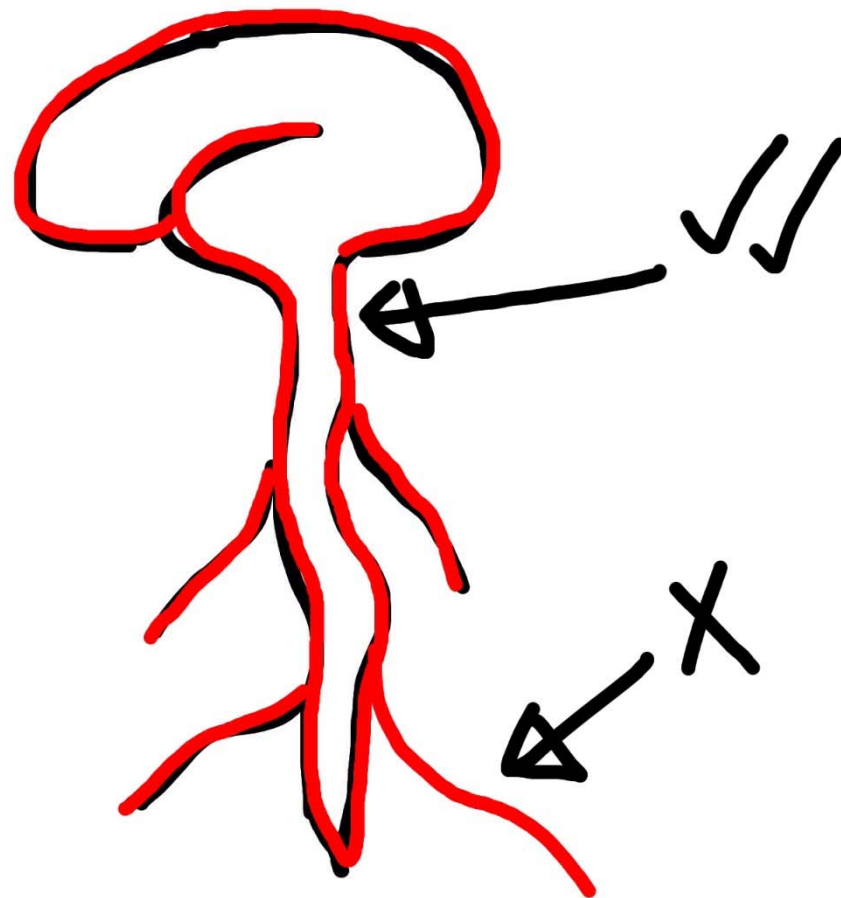










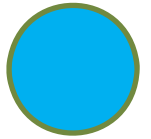




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CENTRAL SENSITIZATION

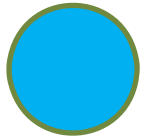
Key concept to understanding all
chronic pain



Central Sensitization

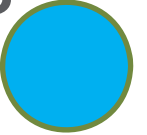
- Definition: Increase in the excitability of neurons within the central nervous system (CNS) so that normal inputs produce abnormal responses

Central Sensitization



- As the spinal cord and brain is flooded with a barrage of pain signals, the nerves in these structures become hyper-sensitized
- Two things happen in Central Sensitization:
 1. NMDA receptors are activated
 2. Glial cells are activated

Central Sensitization - NMDA receptors

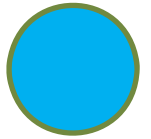


- Central Sensitization causes activation and proliferation of a certain receptor called NMDA receptor
- Activation of the NMDA receptors makes the Central Nervous system more responsive to pain signals and decreases sensitivity to opioids



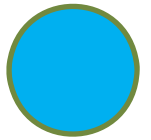
Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 10:23–36

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
- In CRPS with Central Sensitization, 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



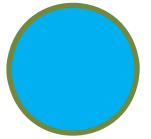


Central Sensitization: Glia

- Activated glial cells release chemicals (cytokines) that cause nerve inflammation
- Treatments used towards de-activating glia maybe useful for managing CRPS
- Treatments that we know of are: medications and exercise /Physical Therapy
- Opioids / narcotics increase glial cell activation



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



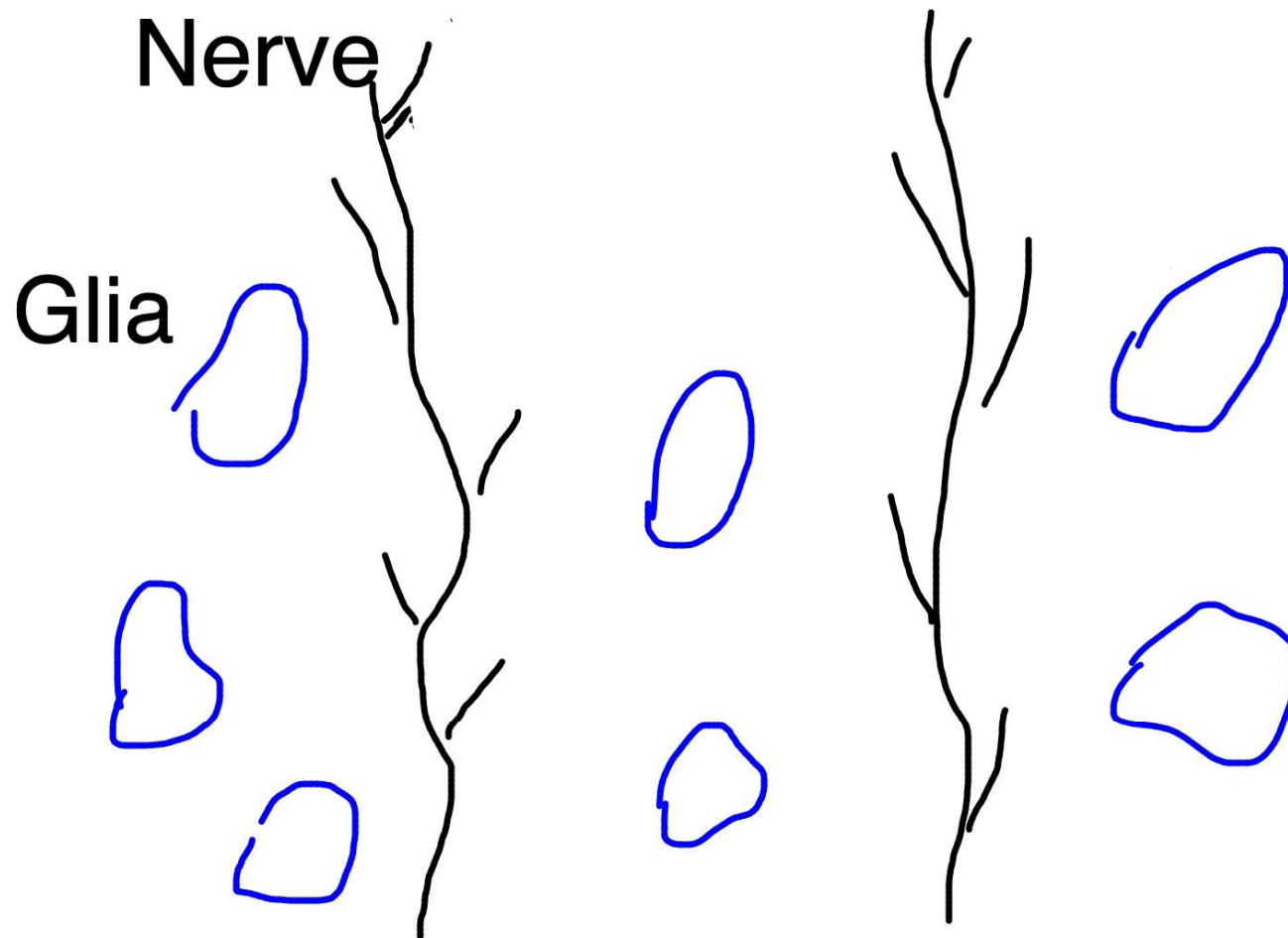
Glial cell attenuators

- Drugs that decrease glial cells activation are still in experimental stages, but there are some that are used clinically
- Pentoxifylline
- Tetracyclines - Minocycline, Doxycycline
- Ibudiblast – Used for the last 20 years in Japan and Korea for asthma and stroke. Glial cell attenuator. Neuroprotective.

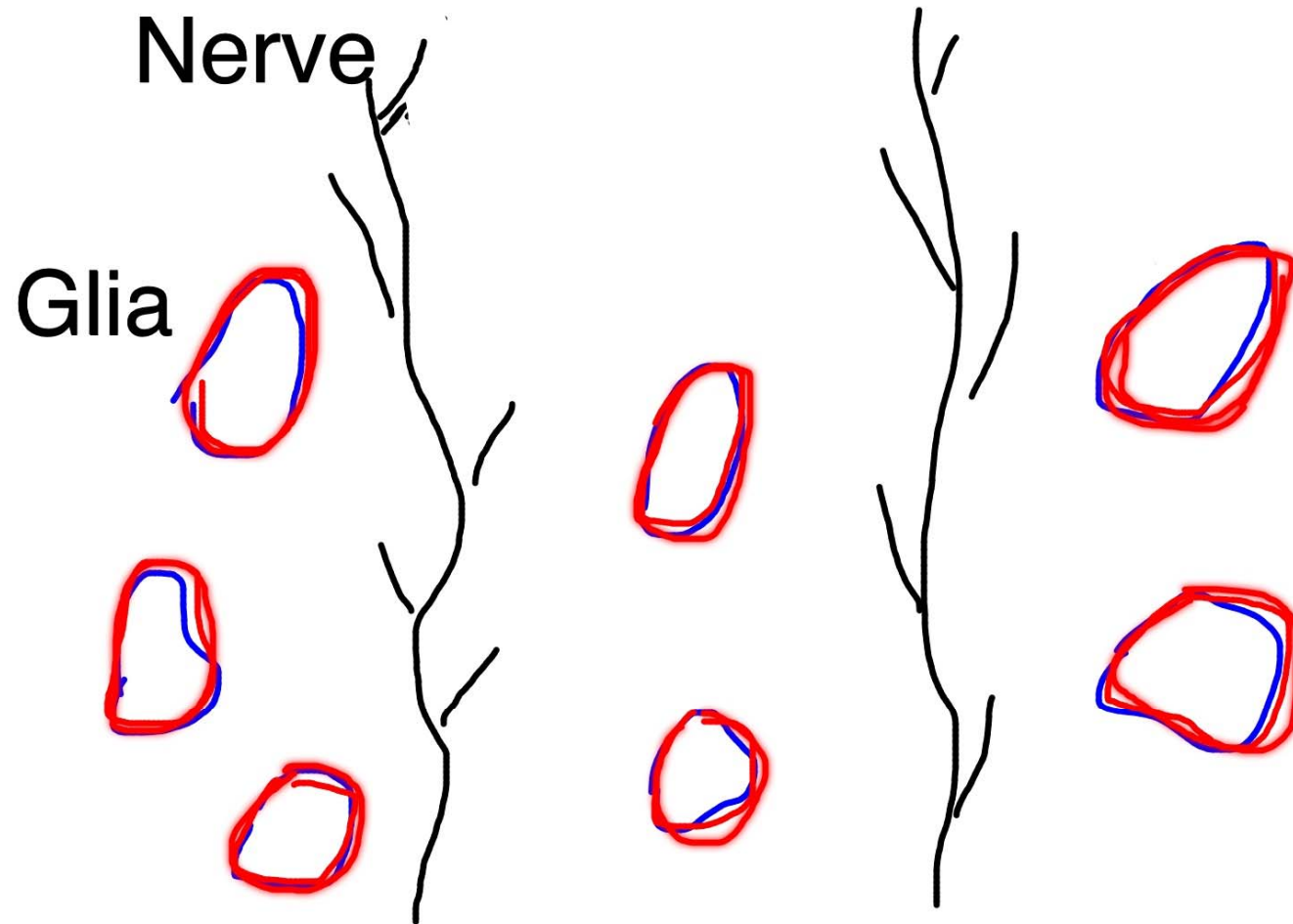


Watkins LR, Maier SF (2003) Glia: a novel drug discovery target for clinical pain. Nat Rev Drug Discov 2:973–985

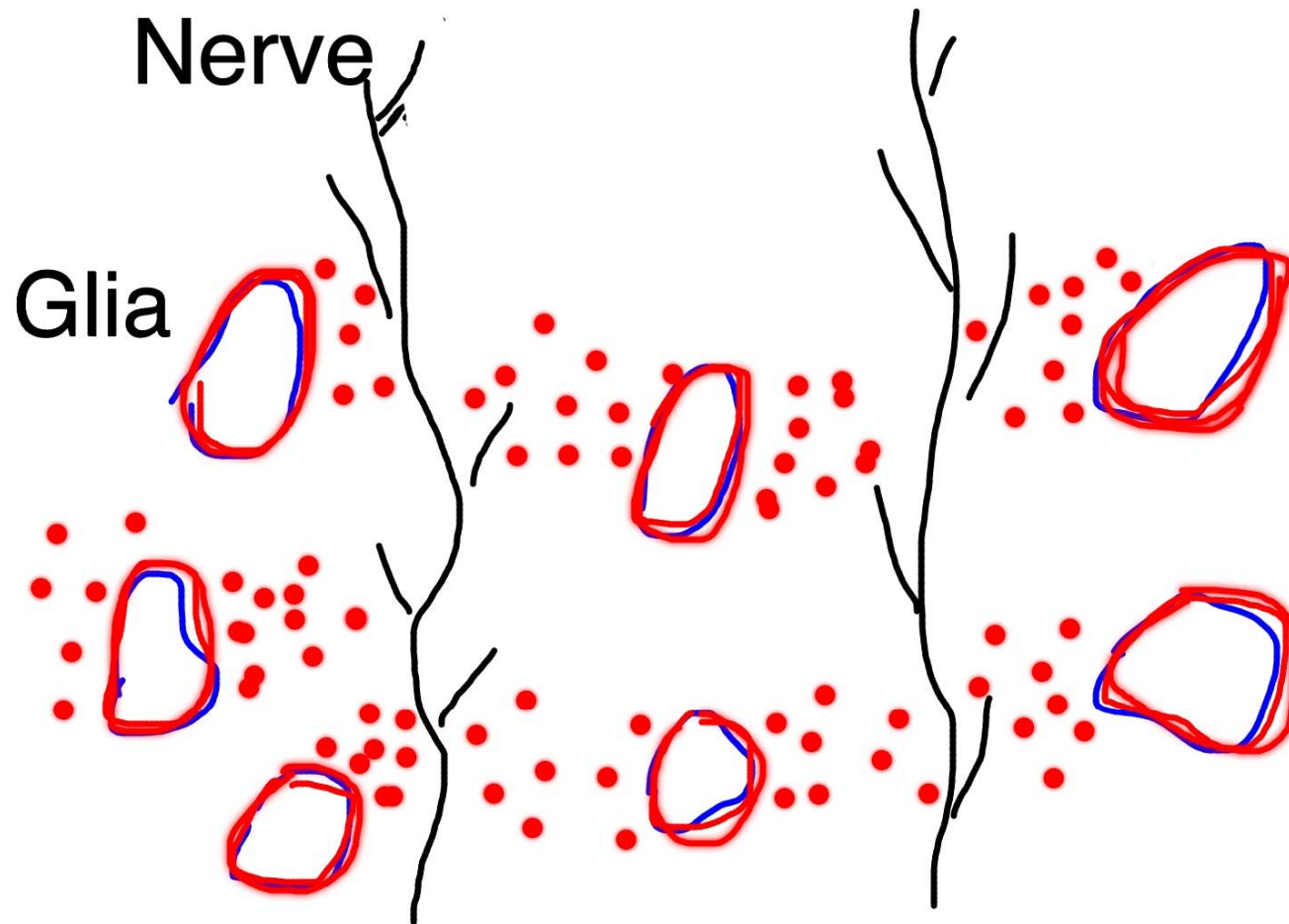
Glia and nerves under normal conditions



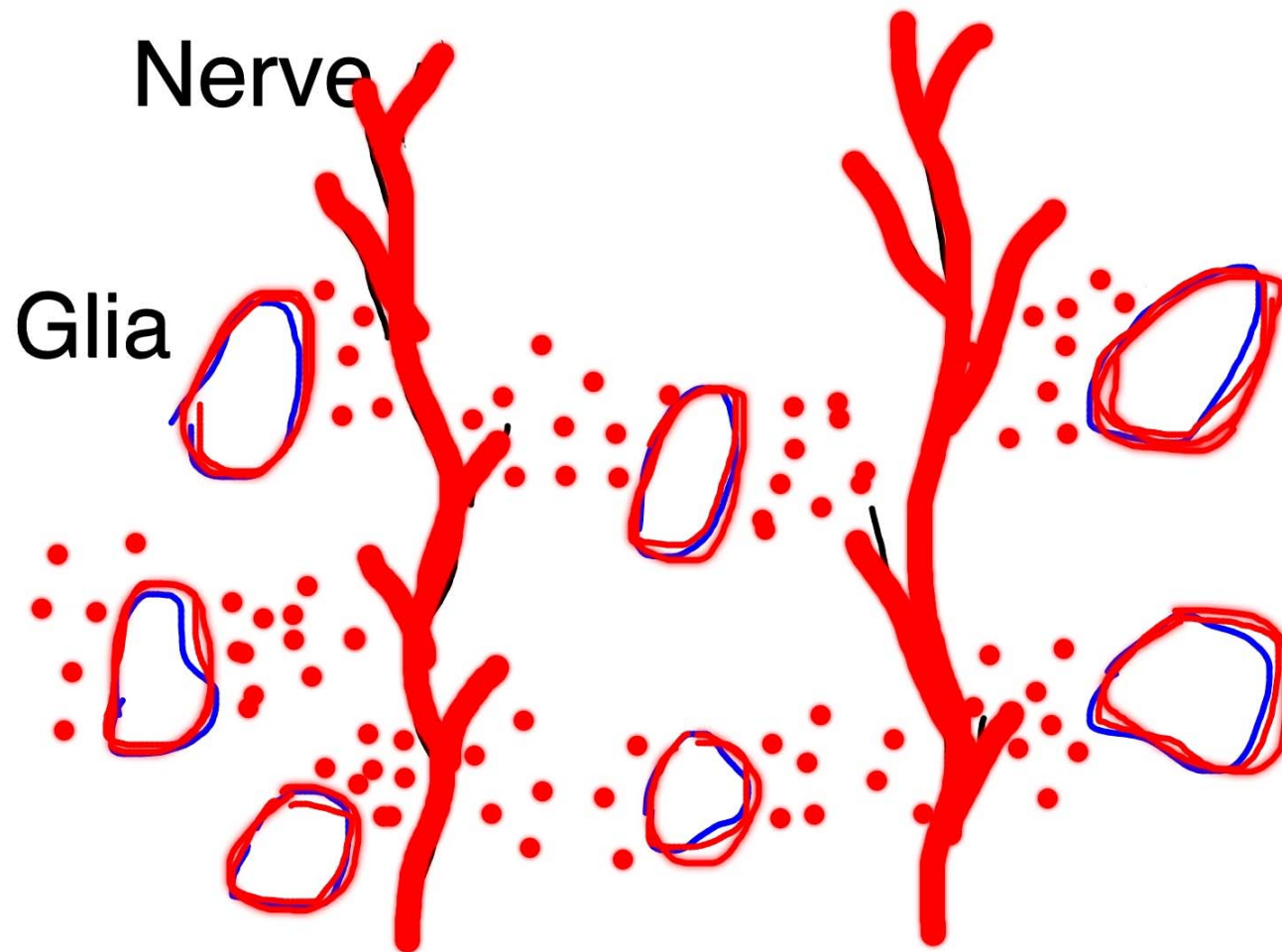
Activated Glia



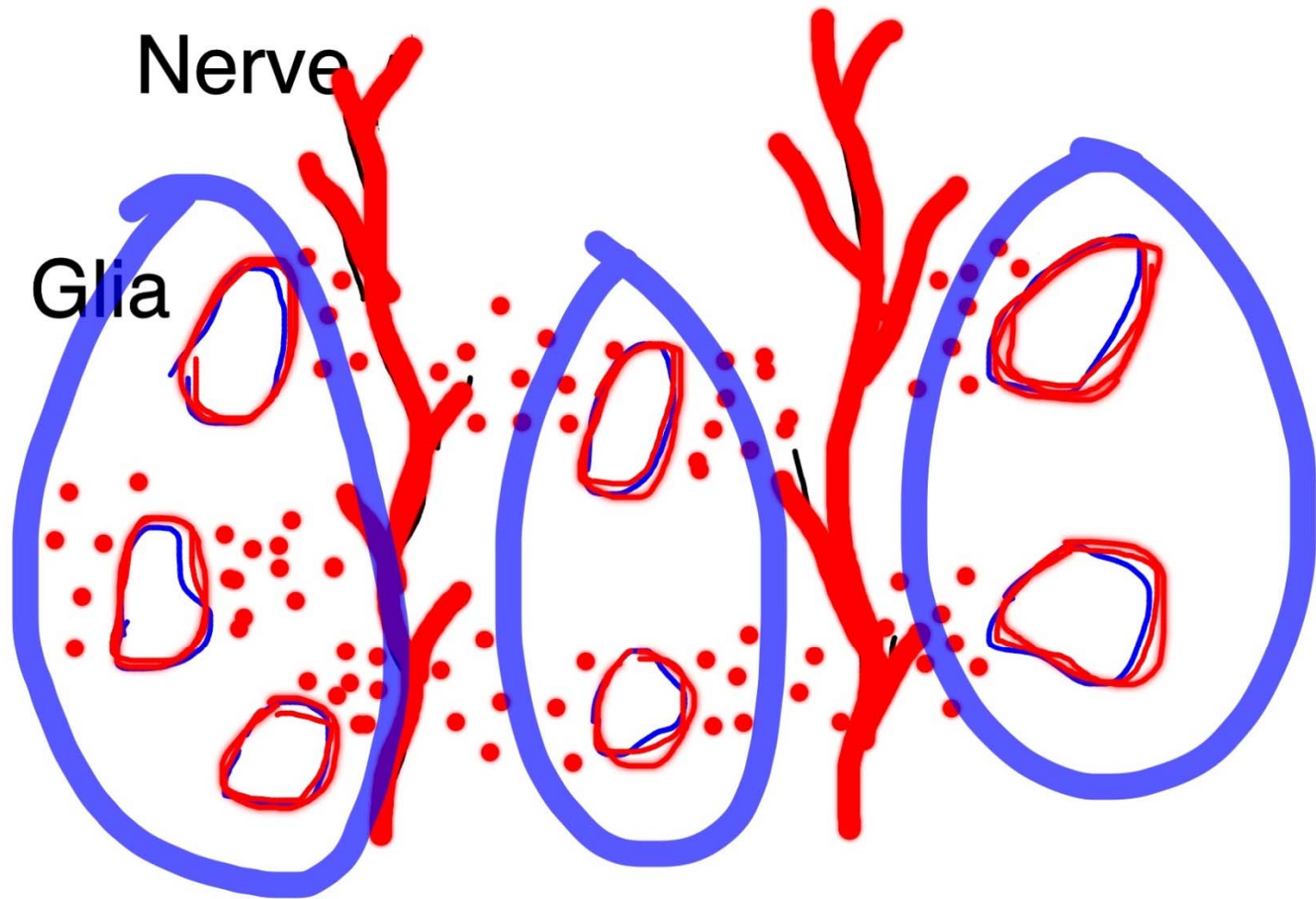
Chemicals released by activated Glia

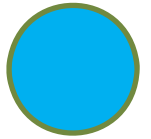


Nerve inflammation



The problem is with the glia cells





Autoimmunity

- The relationship between Central Nervous System and the immune system is incompletely understood.
- Auto-antibodies (IgG) against the autonomic nervous system and peripheral nerves have been shown
- Cytokines modulate pain by affecting the nervous system and the immune system



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Management

Complex Regional Pain Syndrome
(CRPS)

Reflex Sympathetic Dystrophy (RSD)

Basic guidelines in treating CRPS

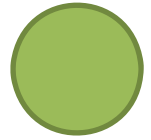
- Start treatment immediately, even if you suspect CRPS
- Must be evaluated by a Pain Medicine specialist or a physician who is very familiar with it, to start appropriate therapy
- Treatment should be directed towards restoration of function
- Multidisciplinary approach - team work

- Management of Complex Regional Pain Syndrome should be directed towards the cause of the neuro-inflammation and not just the nerves.
- Thus, it makes sense to treat the glial cell activation or the autoimmune condition

- Start low, go slow

Grading of treatment

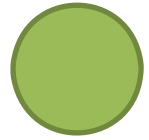
-  Effective
-  Worth trying
-  Use caution
-  Nerdy stuff



Bisphosphonates

Class of drugs used to treat bone loss.

Calcium regulating drugs – in refractory cases



- 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

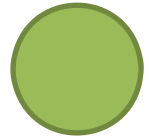


Forouzanfar T, Koke AJ, Kleef M van, Weber WE. Treatment of complex regional pain syndrome type I. Eur J Pain 2002;6(2):105-22.

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.

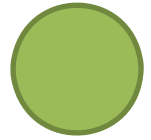
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Neridronate

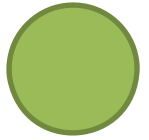


- Very similar to alendronate (Fosmax[®]), Pamidronate (Aredia[®])
- Very small trial.
- Very select group of patients.
- Only patients who had bone changes were studied.
- Better studies being done which are more realistic

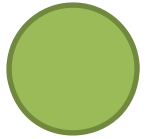
Bisphosphonates



- It's worth trying a bisphosphonate in CRPS especially if there are bone changes.
- Bone changes can be seen on an MRI or even an x-ray.



Ketamine

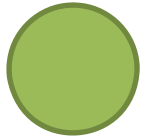


Ketamine

- CRPS - activation and proliferation of NMDA receptors
- Strong NMDA Receptor blocker
- One of the safest anesthetic drugs
- Powerful analgesic even at low doses
- Poor absorption when administered orally.
- Effective as IV or submucosal (Troche)

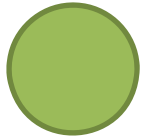


Factors that are important in getting the best out of a ketamine infusion



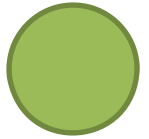
- How long does the ketamine stay in the body i.e. how long are the receptors blocked
- How much is needed to keep most of the receptors blocked
- Minimize trauma while delivering the infusion
- Ketamine infusions are good only if done in conjunction with other therapies, especially exercise

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
- Administration: IV, sublingual, nasal
- 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

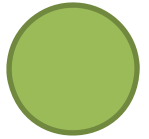




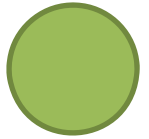
Ketamine – out patient

- Increasing dose of ketamine over 10 days
- Start at a low dose, increase everyday
- Usually start to see some relief by day 4 or 5
- If no relief by day 5 or 6, stop
- Infusion done over 4 to 5 hours
- Full standard monitoring
- Qualified personnel must be present at all times

Ketamine protocols in CRPS



- Low dose protocol:
- Loading dose: a low dose IV ketamine administered over a few hours (usually 4 hours). It is increased everyday over the next 10 days based on the response.
- Booster dose: Low dose IV ketamine is repeated for 1 or 2 days after 2 weeks and then again at 4 weeks to 6 weeks tailored to patient's response



IV Ketamine - boosters

- Very important part of the treatment protocol
- As the effect of the initial ketamine wears, 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
- Sometimes, it may be necessary to do a 2 day booster.

Ketamine infusions

- Must be done under strict ASA (American Society of Anesthesiologists) standard monitoring
- Continuous oxygen levels, heart rate, EKG
- Intermittent (every 15 minutes) blood pressure, conscious level
- Very quiet room
- Dark room

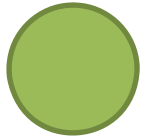
Ketamine infusions

- Avoid talking, television, music, etc
- Avoid any visual and sound stimulation
- Dreams, hallucinations – to a mild degree imply effective dose.
- Triggered by loud sounds and light
- Rest of the day – avoid loud traffic, spend the day at home in a quiet, dark room

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



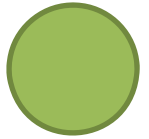
- Oral ketamine – don't bother
- Unpredictable effects

Severe RSD with skin lesions



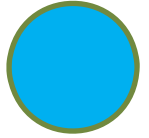
IV ketamine





FREE RADICAL SCAVENGERS

Free Radicals – what are they?

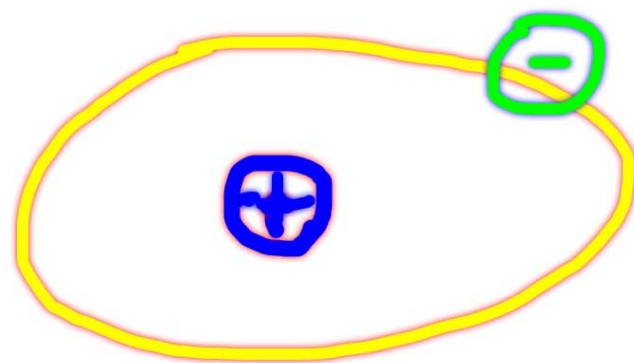
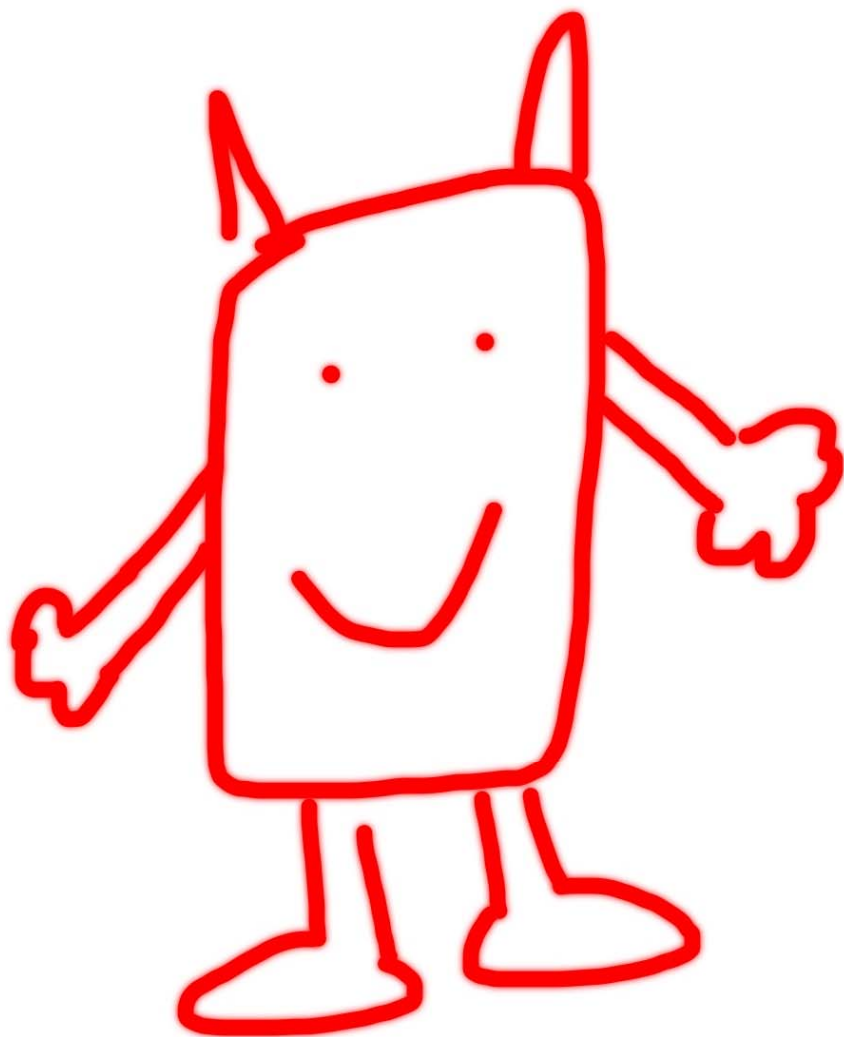


- Human body is made up of cells
- Cells are made up of molecules
- Molecules are made up of atoms
- Atoms are made up of electrons and protons (1:1)

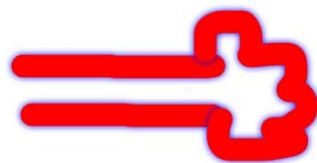
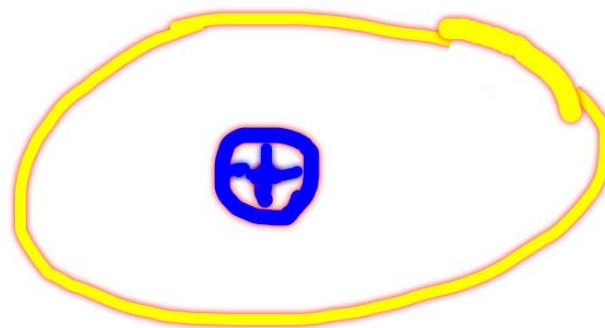
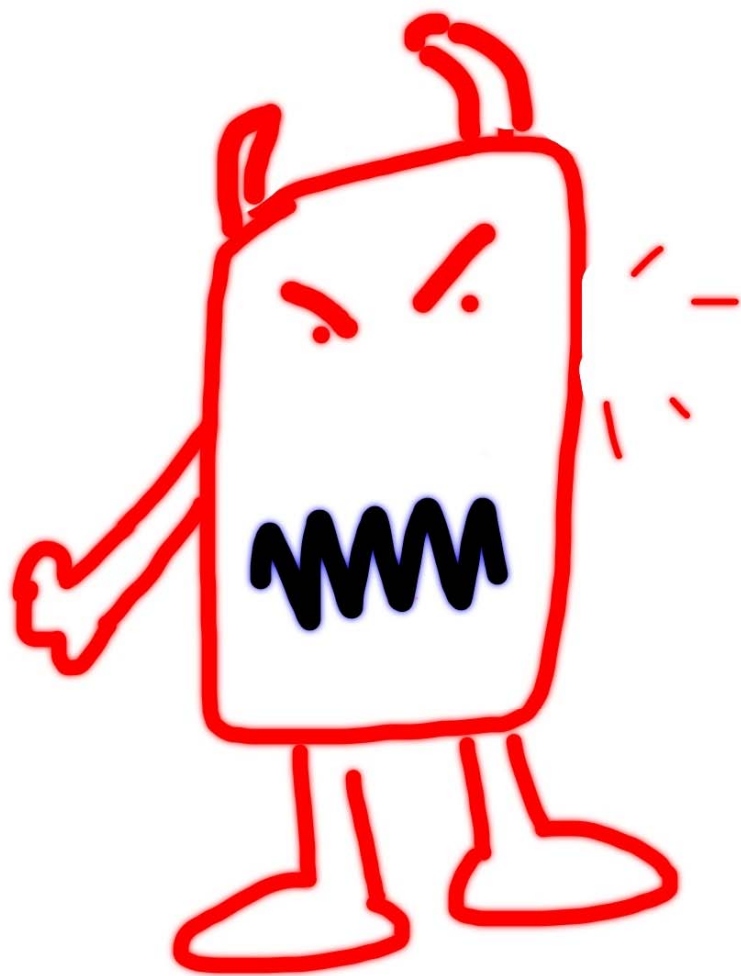
Free Radicals – what are they?



- When molecules 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 energy from other cells to satisfy themselves

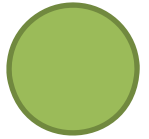


Free Radical scavengers (Antioxidants)

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

Alpha Lipoic acid (ALA)

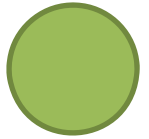
1



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

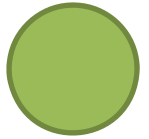
Kapoor S, Foot Ankle Spec, 2012 Aug;5(4); 228-9

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, Dysautonomia
- Effective when taken as IV (Intravenous)
- May be taken orally
- Dose: 600mg to 1200mg per day
- Start low, go slow



Vitamin C

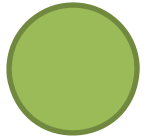
- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg for 45 days to 50 days was shown to prevent development of CRPS
- ? Any value to using it in established CRPS, certainly helpful in prevention



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

N- Acetyl Cysteine (NAC)



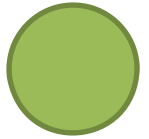
- Useful for cold allodynia
- N-Acetylcysteine 600mg three times a day for three months
- Start low, go slow



Grading of treatment

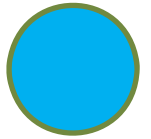
-  Effective
-  Worth trying
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- Start low, go slow



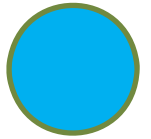
Low Dose Naltrexone

LDN



Low Dose Naltrexone (LDN) 1

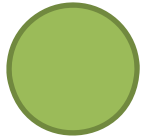
- Competitive antagonist of opioid receptors
- Clinically used for 30 years for addiction
- Suppressive effects on the CNS microglia, which....
- Attenuates production of pro-inflammatory cytokines and neurotoxic superoxides (chemicals that cause inflammation)



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 12 weeks
- To avoid all opioids or tramadol.

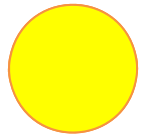
Case of CRPS treated with LDN

CRPS with dystonia
before LDN



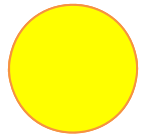
CRPS after LDN





Muscle spasms


- Magnesium
- Diazepam (Valium®), Alprazolam
- Flexeril
- Tizanidine
- Baclofen




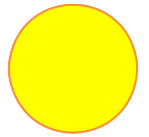
Muscle Relaxants

- Not very helpful for muscle symptoms of CRPS
- Baclofen and diazepam may have some benefit
- Intrathecal (spinal pump) baclofen is not helpful

Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990;40(1):57-61.

 tia KP, Bhatt MH, Marsden CD. The causalgia-dystonia syndrome. Brain 1993;116 (Pt 4):843-51.

 en JJ van, Beek WJ van de, Vein AA, Dijk JG van, Middelkoop HA. Clinical aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. Neurology 2001;56(12):1762-5.



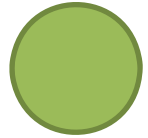
Magnesium

- IV magnesium: small study with 8 patients, administered IV magnesium over 5 days, for 4 hours each day.
- Significant decrease in pain
- Improvement in quality of life

Collins et al., Pain Medicine, 2009, 10:930-940



Magnesium



- Magnesium down regulates NMDA receptor (responsible for CRPS)
- Study done with IV magnesium was very positive for helping CRPS
- Blood tests for Magnesium levels are not accurate
- Recommend Chelated Magnesium






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

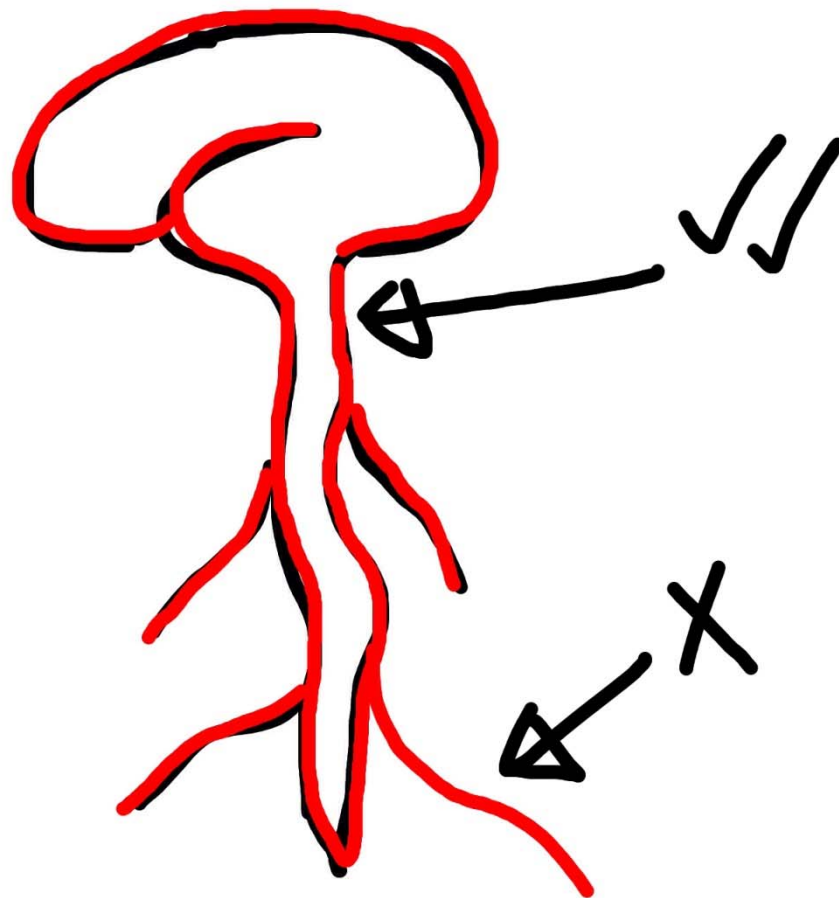
Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain 1998;14(3):216-26.

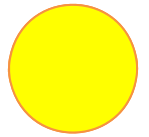
 Mid SC, Beyer A, Romer AW, Galle-Rod A, Peter K, Schops P. Continuous axillary brachial plexus analgesia with low dose morphine in patients with complex regional pain syndromes. Eur J Anaesthesiol 2000;17(3):185-8.

Electrical stimulation



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





Hyperbaric Oxygen

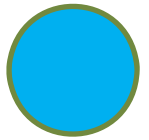
- No good evidence that it helps in the long term
- Anecdotal reports (mostly from hyperbaric centers)
- Different types of HBOT – high pressure and low pressure
- Expensive

[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

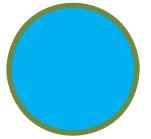


BROWN



Toll like receptors TLR4

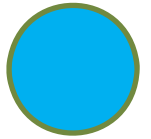
- TLR4 is predominantly expressed by microglia
- Its expression is upregulated under neuroinflammatory conditions.
- TLR4 have been shown to be a key glial activation receptor in initiation and maintenance of neuropathic pain
- Opioids cause glial cell activation by acting on the TLR4 receptors leading to a cascade of pro-inflammatory cytokines
- Opioid antagonists (naloxone, naltrexone) block TLR4 signalling



Opioids

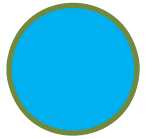
- Counterproductive for CRPS
- Activate glia through a receptor that is distinct from classical opioid receptors called Toll-like receptors (TLR4)
- Opioid induced activation of glia induces them to release neuroexcitatory pro-inflammatory cytokines, suppressing opioid analgesia





Opioids

- Repeated exposure to opioids leads to enhanced pro-inflammatory cytokine release from glia (Johnston et al)
- Blocking such opioid induced glial activation enhances acute opioid analgesia and suppresses the development of opioid tolerance. (Hutchinson, Johnson)



Opioids and CRPS and Glia

- Opioids taken chronically have been shown to increase glial cell activation
- Glia play a key role in developing tolerance to opioids.
- Increased tolerance to opioids leads to increasing the dose of opioids which, in turn, cause further glial cell activation
- Similarly, drugs that decrease glial cell activation also increase the effectiveness of opioids.

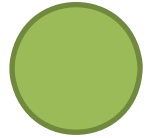
Opioids

- In summary, taking long term opioids for CRPS is not a good idea.
- Maybe okay to take it for a short term to get over a flare up

Neuropathic pain medications

- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Duloxetine (Cymbalta®)
- Milnacipran (Savella®)

Gabapentin and pregabalin

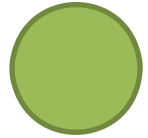


- May help some patients with CRPS
- Gabapentin –Slow acting drug.
- Pregabalin (Lyrica™)– no evidence that it helps CRPS but a trial course may be tried
- If there is no difference in 8 weeks, taper it off.


Seaton MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 2000;99(3):557-66.


Vos AC van de, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type I [ISRCTN84121379]. BMC Neurol 2004;4(1):13.

Antidepressants



- Tricyclic antidepressants (TCA) well studied in neuropathic pain, not CRPS
- Reuptake blockers of serotonin and noradrenaline (Amitriptyline, nortriptyline) – work well
- Selective noradrenaline blockers (desipramine)
- SSRI (Prozac[®], Zoloft[®])– do not work well

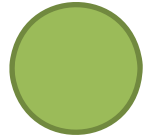
 Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. Pain 1992;48(1):29-36.

 Raj S, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59(7):1015-21.

Antidepressants (SNRI's)

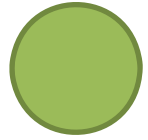
- Increase nor - epinephrine levels in the central nervous system
- Increased nor-epinephrine levels help in modulating pain signals
- Milnacipran (Savella TM) increases nor-epinephrine by 3 times as compared to duloxetine (Cymbalta TM)

Antidepressants (SNRI's)



- Milnacipran (Savella®) – approved for fibromyalgia
- No studies for CRPS
- A trial of Milnacipran may be considered
- Avoid Duloxetine (Cymbalta®)

Clonidine



- Alpha2 adrenergic agonist – used for treatment of high blood pressure
- Transdermal patch more effective than oral
- Effective for hyperalgesia and allodynia (Davis et al)

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



Kerns 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

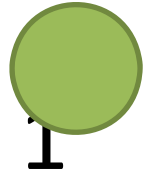


Kemler MA, Barendse GA, Kleef M van, Wildenberg FA van den, Weber WE. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. J Neurosurg 1999;90(1 suppl):79-83.

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.

Skin Lesions in RSD



- Often go undiagnosed. Little information on skin lesions
- Different types of skin lesions.
- Bullae or raised skin lesions filled with fluid
- Ketamine cream 5% applied topically works well

Skin lesions

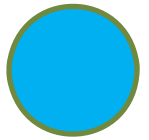


Pradeep Chopra, MD



Mast Cell Activation Syndrome

MCAS



Mast cells

- Found in blood and tissue.
- Release histamine and inflammatory mediators (e.g. cytokines)
- Mast cells contribute to pain in inflammatory pain conditions
- Chronic pain conditions such as Interstitial Cystitis, chronic pancreatitis – 3 times as many mast cells.



Mast Cell Activation Syndrome (MCAS)

- Common in CRPS
- Affects most symptoms
- Chronic fatigue,
- feeling cold (common), feeling hot
- Sweats – unexplained
- Weight gain
- Itchy – comes and goes,
- Rash – unpredictable, unprovoked,



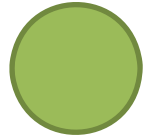
Mast Cell Activation Syndrome (MCAS)

- Sores, poor wound healing,
- Eyes – gritty, increased water, difficulty focusing
- Mouth – burning mouth
- Stomach – intestinal pain
- Bladder pain
- Inflammatory chemicals released by mast cells cause nerves to become inflamed.

Mast Cell Activation Syndrome (MCAS)

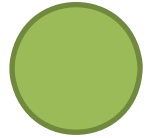
- Inflammatory chemicals released by mast cells cause nerves to become inflamed.
- Tingling, numbness
- Tics, tremors,
- Brain fog

Management of MCAS



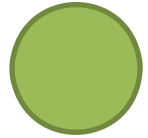
- Anti-histamine blockers:
 - Most cold medicines
 - Ranitidine, famotidine
- Cromolyn
- Ketotifen
- Low histamine diet
- Certain drugs like NSAID's (Ibuprofen etc), opioids increase MCAS

Physical Therapy



- Critical part of the treatment
- Non weight bearing exercises
- Aqua therapy
- Start low, go slow
- Physical Therapy must be gentle in the beginning and stay below pain threshold and not overly exacerbate pain
- Low impact, move joints, move muscles.

Physical Therapy - two types



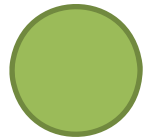
- **Pain Focused:** Patients who have recently developed CRPS – PT should focus more on pain
- **Time based:** Patients who have had CRPS for a while (Chronic) – PT should be more time based

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.

Service Dogs

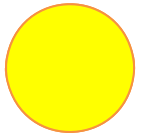


- Trained to each person's physical impairments
- help with functioning and independence
- Constant companion, will often sense its owners pain and will comfort them both physically and emotionally
- Can sense distress and call for help
- Service dogs give patients a feeling of security allowing them to be more active physically and socially
- Provide stability while walking, open and close doors, switch on and off lights



Other treatments

Oxytocin



- Chemical produced naturally in the brain
- Taken as a nasal spray
- 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).

Vitamin D



- There is a very clear connection between chronic pain and low vitamin D levels.
- Low Vitamin D levels are very common
- Low Vitamin D levels cause osteomalacia (softening of the bones).
- Bisphosphonates help prevent loss of bone mass and help CRPS in some cases.

Tadalafil (Cialis)

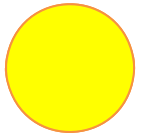


- Treatment of cold CRPS resulted in significant reduction of temperature difference between affected and unaffected limbs
- Long term effect unknown

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



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



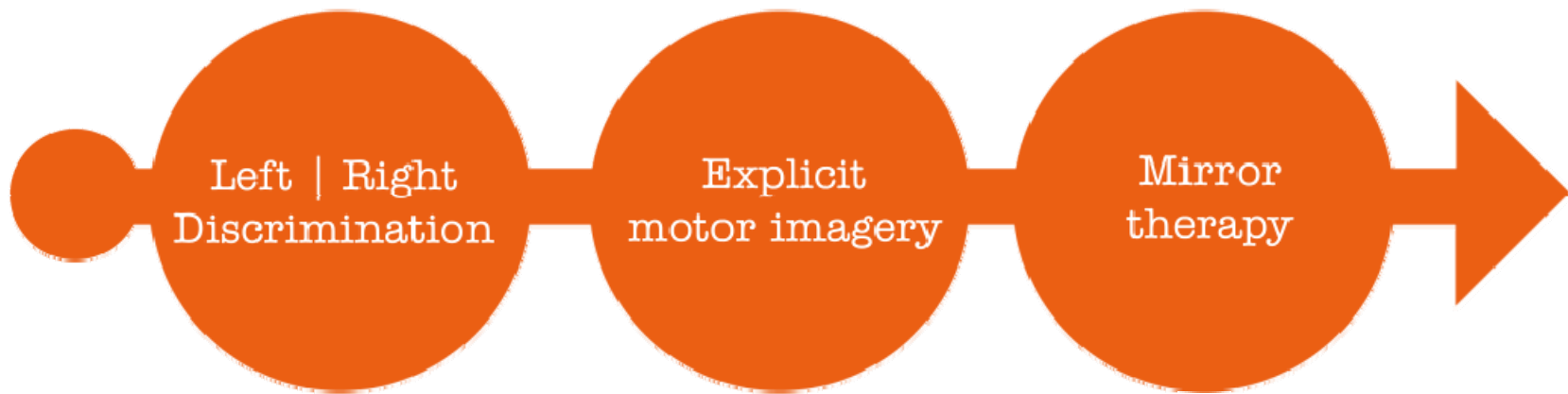
- No studies done for chronic pain
- Good experience in patients with CRPS
- Usually 60 minute sessions.
- Centers in most places, try Google

Graded Motor Imagery



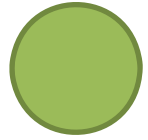
- Rehabilitation program to treat complex pain
- Broken down into three unique stages of treatment techniques, each exercising the brain in different ways.
- www.gradedmotorimagery.com

Three stages of Graded Motor Imagery delivered sequentially



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

Graded Motor Imagery



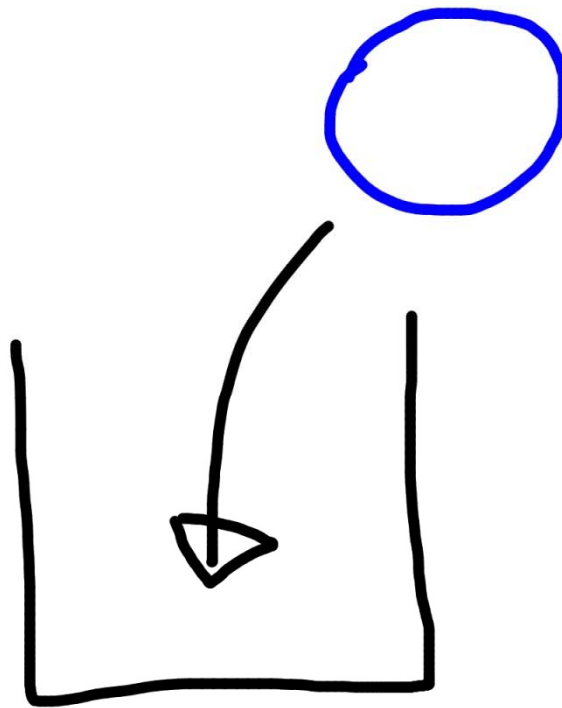
1. App 'Recognise' on iTunes or Google Play
2. Explicit motor imagery and left/right discrimination using the app Recognise
3. Mirror therapy

www.gradedmotorimagery.com

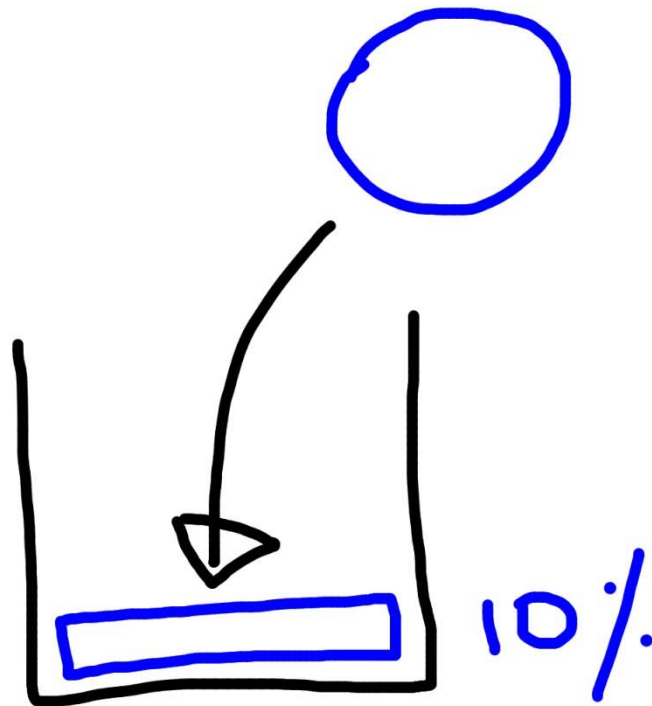
NC10 rule

Expectations from different therapies

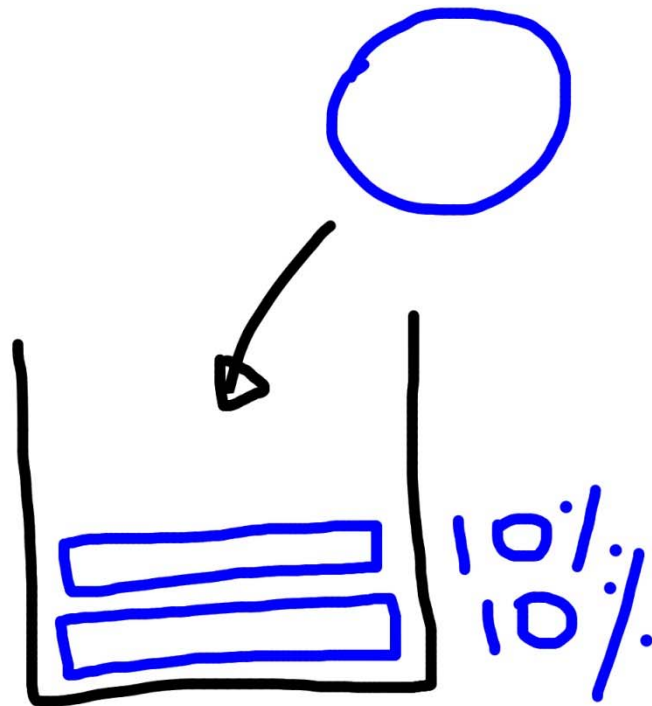
NC10 rule



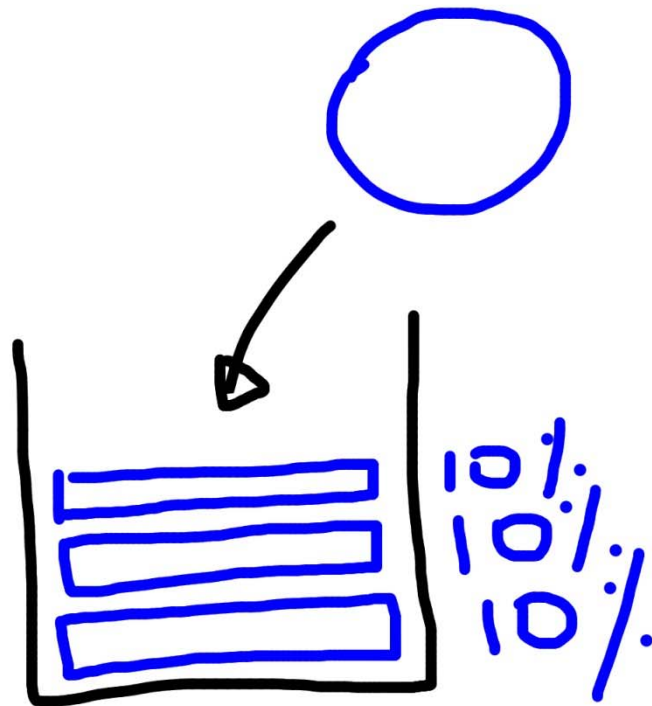
NC10 rule



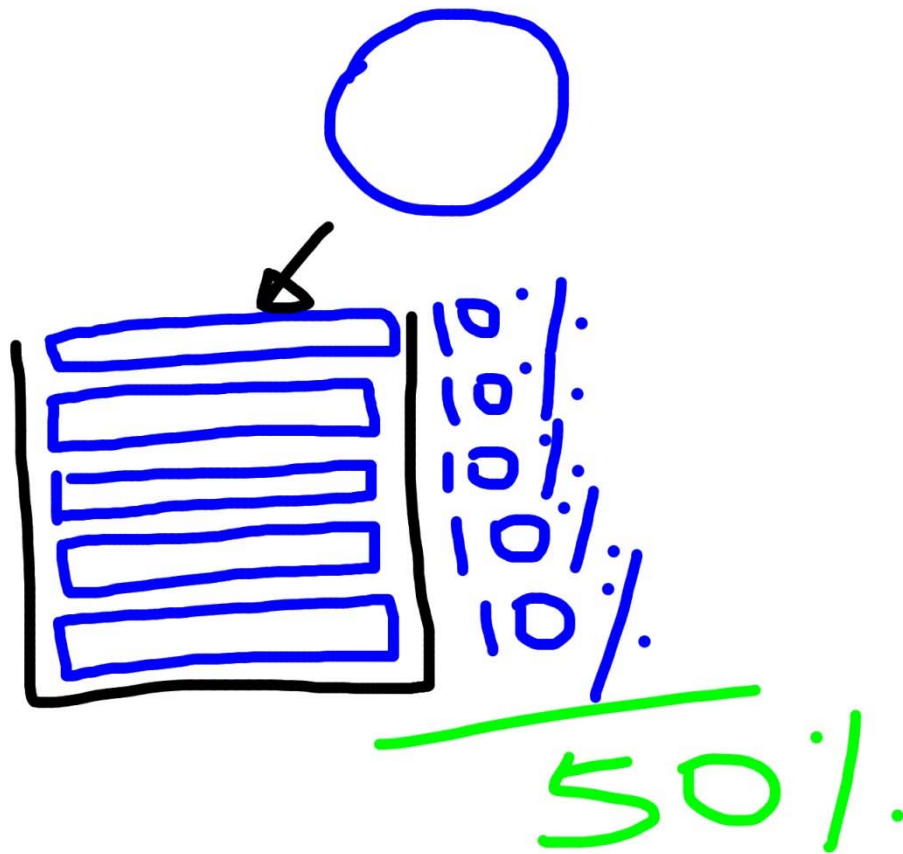
NC10 rule



NC10 rule



NC10 rule



CRPS in children

Children and CRPS 1

- Children develop the same symptoms
- 58% to 93% of cases of RSD in children will resolve with proper treatment
- Relapses following apparent healing are often observed (10% to 48%)
- More common in girls

Children and CRPS ₂

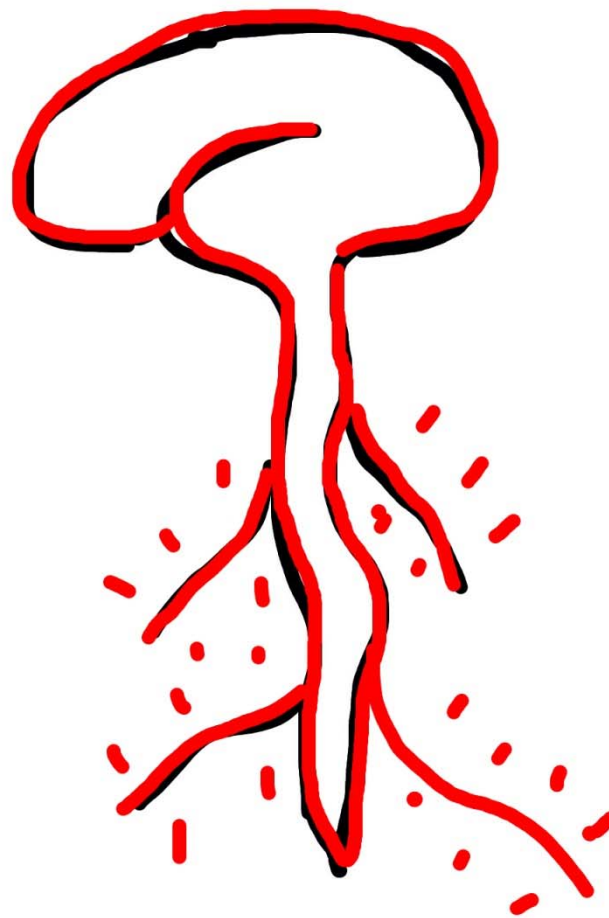
- It is often labeled as a behavioral disorder, conversion disorder and parents are labeled as having Munchausen's syndrome
- Very important that parents pay close attention to the child's complaints
- See a specialist who has experience with treating CRPS in children

Children and RSD 4

- Often associated with other conditions such as
 - Ehler's Danlos Syndrome (EDS)
 - Mitochondrial disorder
 - Nerve entrapment
 - Autoimmune dysfunction

Needle stick trauma

- Avoid 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.
- Let them know that the veins are ‘difficult’. CRPS patients have thin and friable veins
- For those undergoing regular infusions (IV fluid rehydration or IV Ketamine) should consider a chest port
- PICC line is not a good option



Dizziness and Palpitations

- POTS (Postural Orthostatic Tachycardia Syndrome)
- Dizziness and racing heart – usually with standing up
- Increase in heart rate by 30 beats/ min or increase to 120 beats/ minute
- Increase salt intake, fluids, compression stockings
- Medications

Sleep in Complex Regional Pain Syndrome

- Non-restorative sleep – constant activity of the ‘flight and fight mechanism’ (sympathetic nerves)
- Beta blocker – propranolol, betaxolol

Adenosine receptors

Adenosine receptors agonists

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

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,[†] Amanda Finley,[§] 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

Tailoring treatments for CRPS

- Autoimmune
- Bones
- Nerve damage
- Nerve entrapment

Thank you

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