Complex Regional Pain Syndrome: Thoughts & Progress

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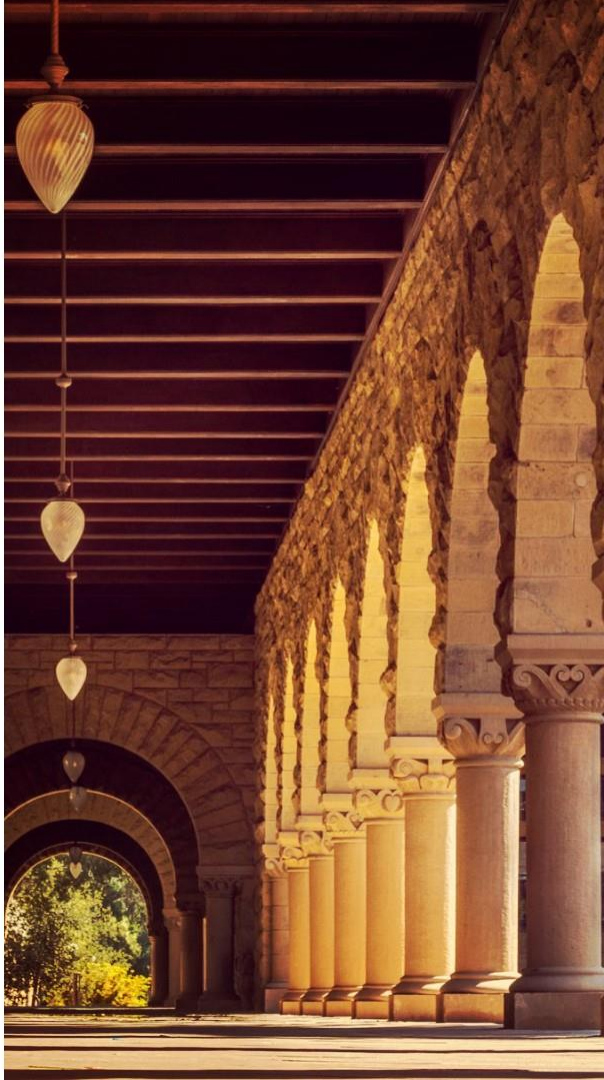


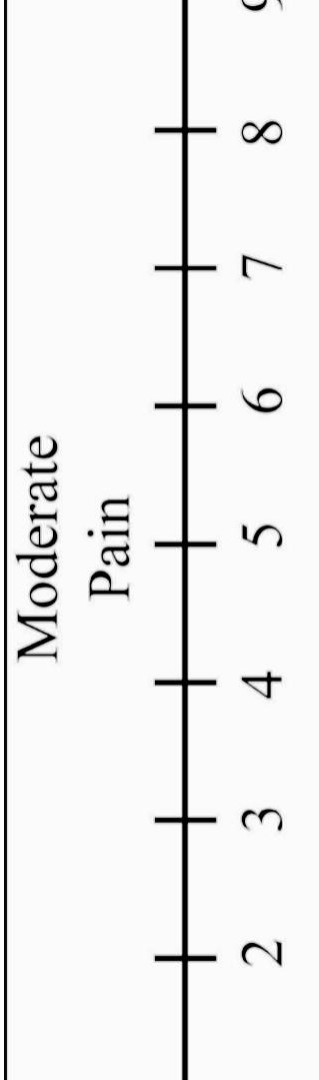
Disclosures

None

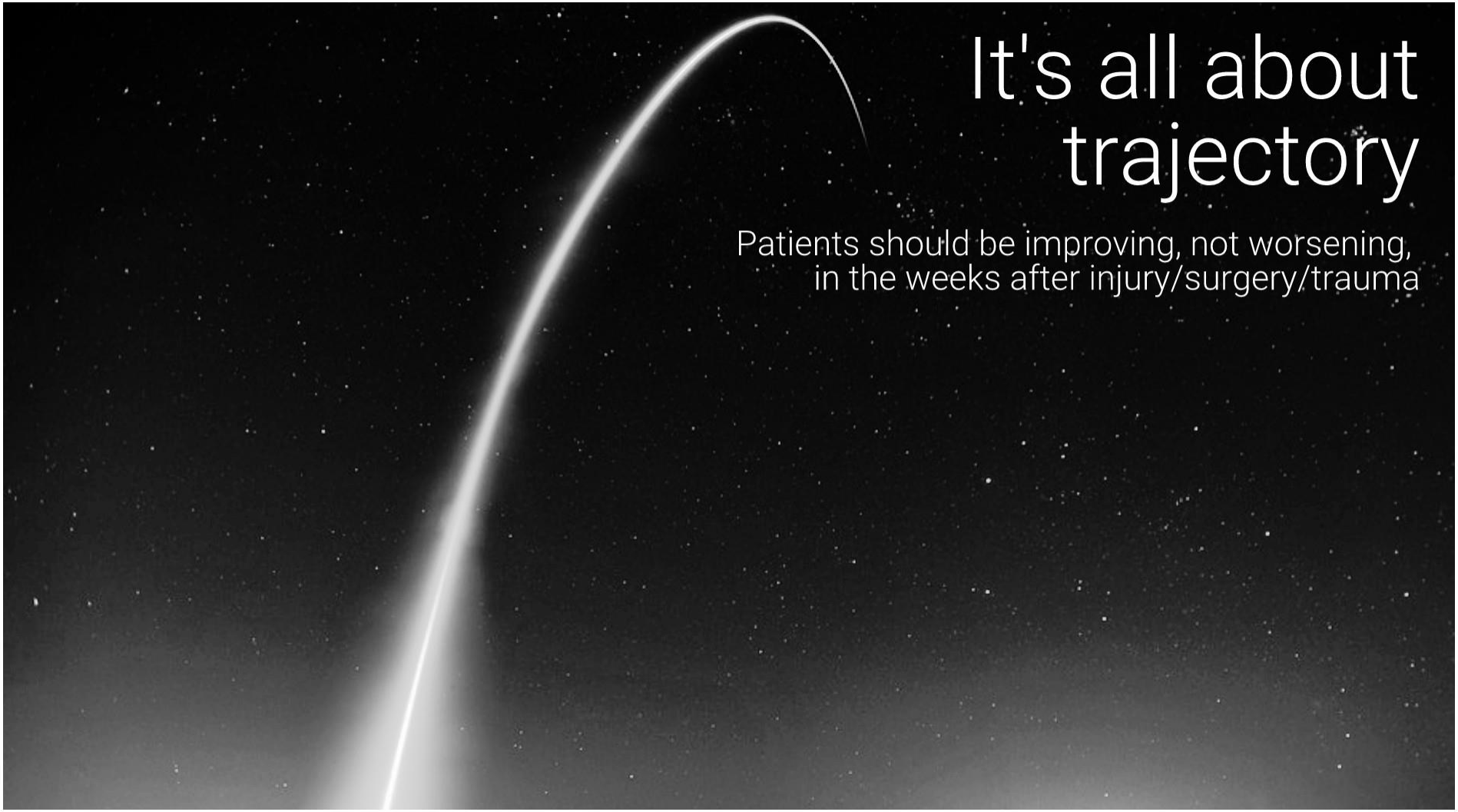
Off-label use of drugs will be discussed


CHRONIC POST-SURGICAL PAIN
IMAGING
PHYSICAL THERAPY
NERVE BLOCK
RADICULOPATHY
SPINAL CORD
PSYCHOLOGY
FIBROMYALGIA
OPIOIDS
PAIN
NEUROPATHIC
NSAIDS
SURGERY
100 MILLION AMERICANS
ACUPUNCTURE
COSTS $635 BILLION
AUTOIMMUNITY
ALLODYNIA
QUALITY OF LIFE
MECHANISMS
INFLAMMATION
LOW BACK PAIN
MULTIDISCIPLINARY

But what is PAIN?




When is acute pain no longer acute pain?



It's all about trajectory

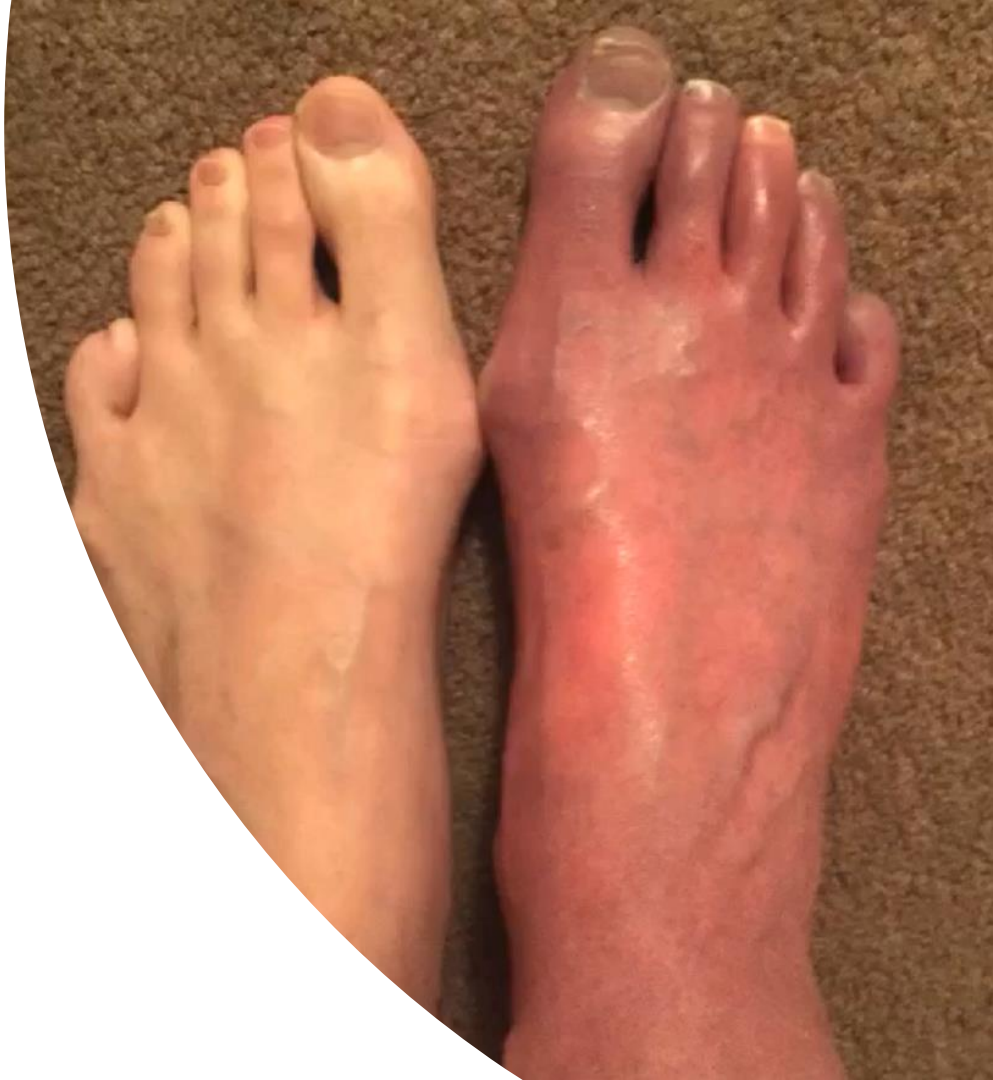
Patients should be improving, not worsening,
in the weeks after injury/surgery/trauma

Not all chronic post-injury pain is the same

28 year old female

Twisted ankle

Persistent pain, swelling, redness, warmth of right foot



Complex Regional Pain Syndrome (CRPS)

A form of chronic pain affecting the limbs often resulting from minor trauma or surgery

Sensory

Pain

Sudomotor

Edema

Sweating

Hair or nail growth changes

Vasomotor

Temperature changes

Color change

Motor

Loss of ROM

Tremor

Weakness

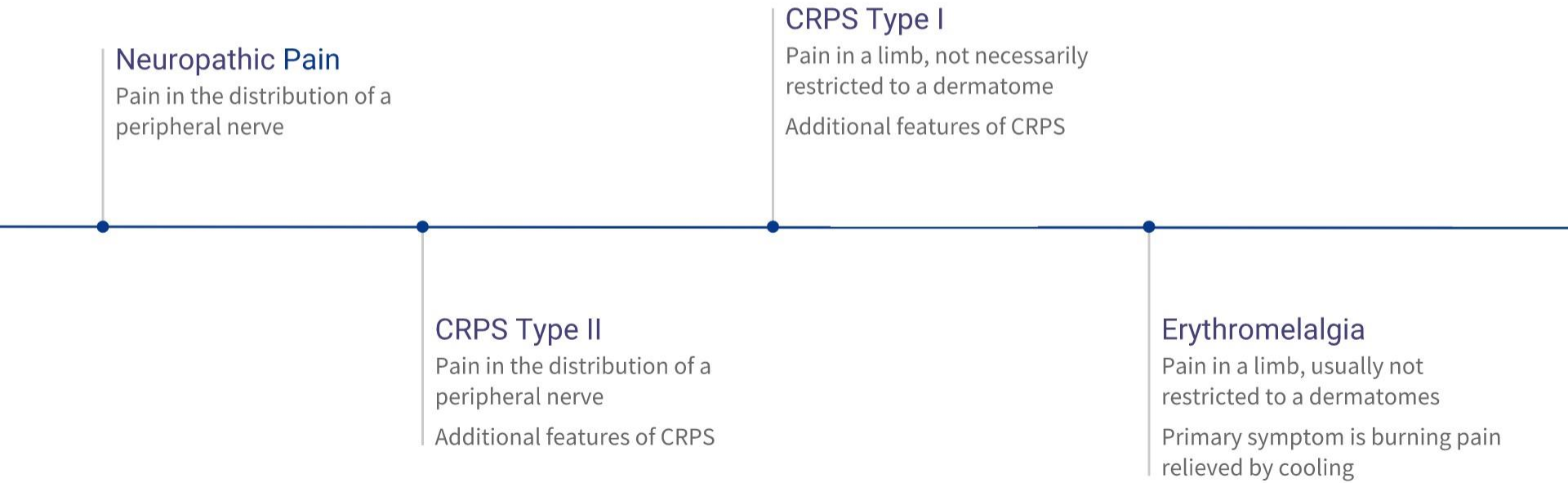
Based on the Budapest Diagnostic Criteria (Harden et al. 2010)

CRPS Distinction Based on Etiology

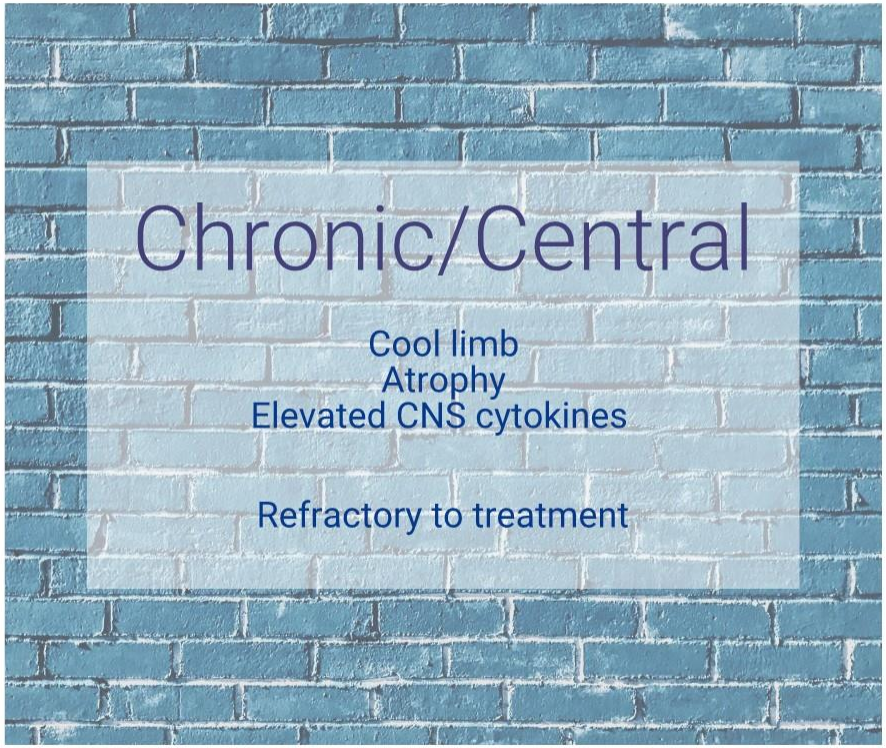
Type I: No “major” nerve lesion

Type II: Detectable nerve injury

A Disease Spectrum for Peripheral Pain

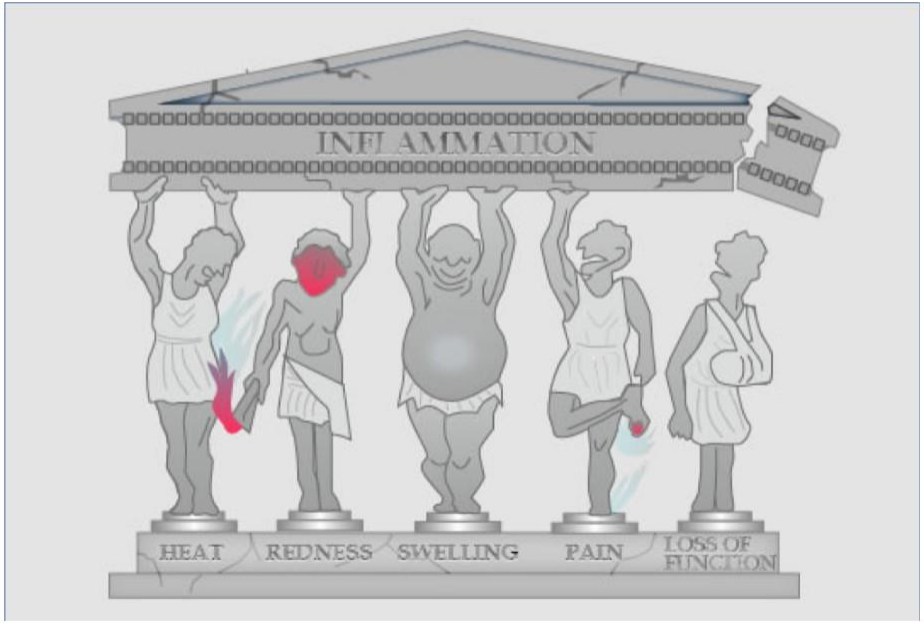


CRPS consists of two phases



Isn't it normal to have post-injury inflammation?

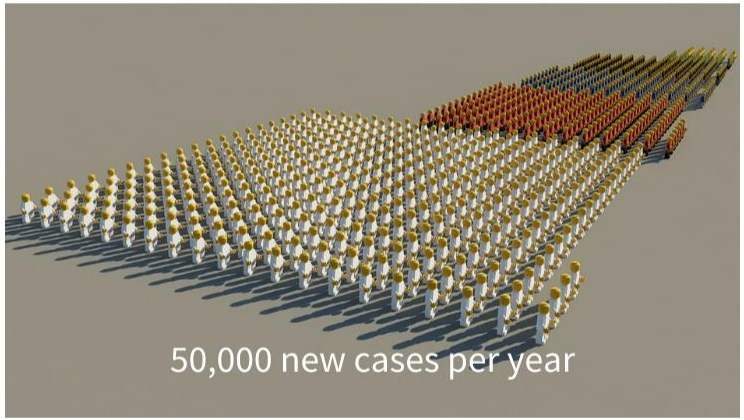
Four classical signs of inflammation described by Celsus (circa 30 BC-30 AD)



Japan Science & Technology Agency, 2012.

Clinical considerations for CRPS

5-26 cases per 100,000 per year



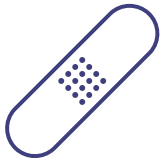
Underrecognized?

Underdiagnosed?

Birklein et al. Neurology 2015; Sandroni et al. Pain 2003; de Mos et al. Pain 2007

Risk factors for the development of CRPS

Female gender (3:1) 

History of trauma or surgery 

Genetics 

Cast “tightness” after injury 

What is up with cast "tightness"?

Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial

Paul E Zollinger, Wim E Tuinebreijer, Robert W Kreis, Roelf S Breederveld

Lancet 1999; **354:** 2025–28

Characteristic	RSD (n=18)	No RSD (n=101)
Sex		
Male	1 (6%)	24 (24%)
Side of fracture		
Right	7 (39%)	48 (47·5%)
Left	11 (61%)	53 (52·5%)
Dominance		
Yes	10 (56%)	48 (47·5%)
No	8 (44%)	53 (52·5%)
Fracture type		
23-A	7 (39%)	68 (67%)
23-B+C	11 (61%)	33 (33%)
Reduction	11 (61%)	59 (58%)
Complaints in plaster	12 (67%)	18 (18%)
Therapy		
Vitamin C	4 (22%)	50 (50%)
Placebo	14 (78%)	51 (50%)

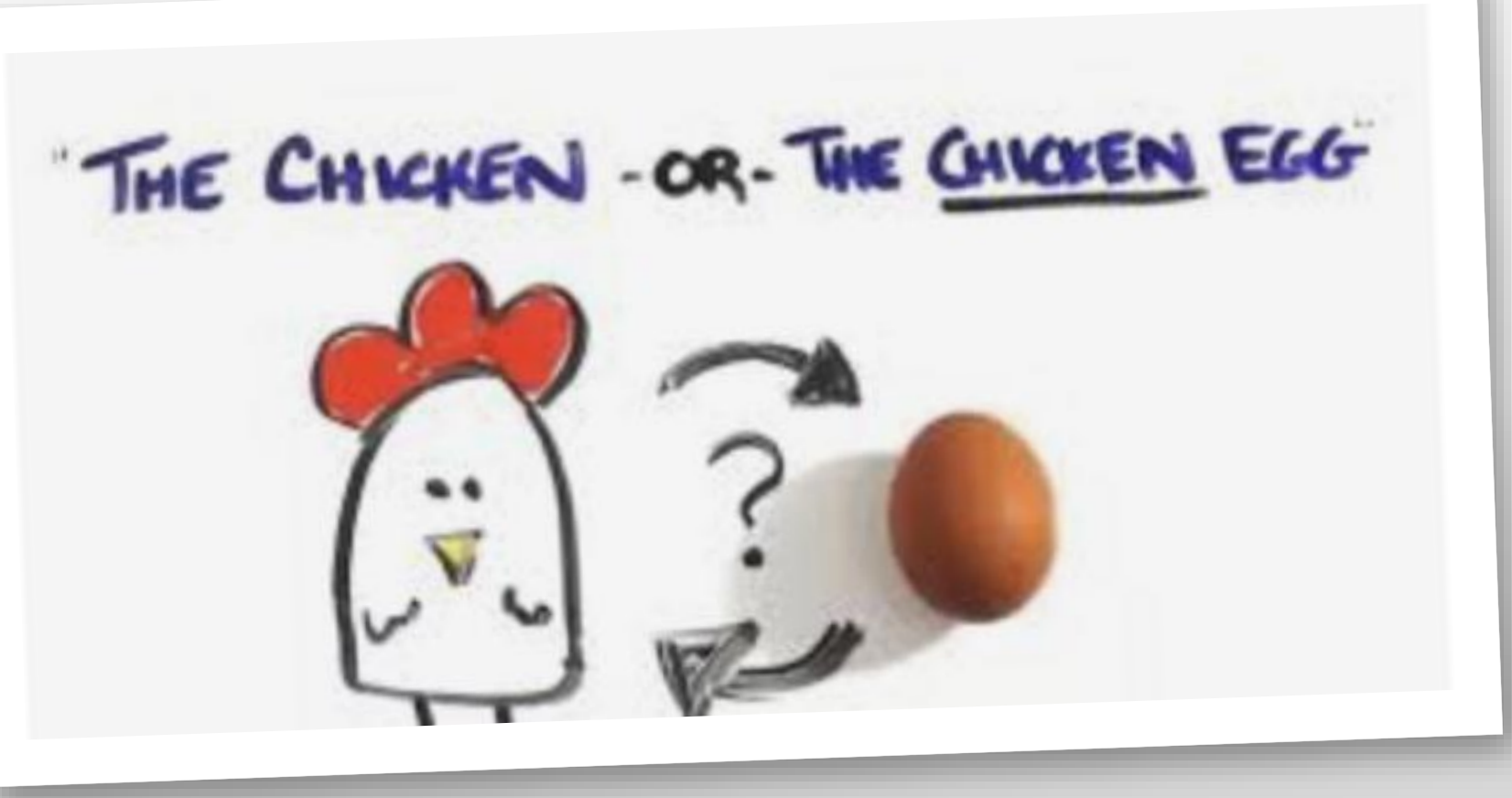
Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures?

A Randomized, Controlled, Multicenter Dose-Response Study

By P.E. Zollinger, MD, W.E. Tuinebreijer, MD, PhD, MSc, MA, R.S. Breederveld, MD, PhD, and R.W. Kreis, MD, PhD

TABLE III Results of Logistic Regression Analysis

	Odds Ratio (95% Confidence Interval)	P Value
Cast-related complaints	5.73 (2.11 to 15.57)	0.001
Vitamin C overall	0.22 (0.08 to 0.58)	0.020
Vitamin C 200 mg	0.38 (0.11 to 1.30)	0.122
Vitamin C 500 mg	0.14 (0.03 to 0.68)	0.014
Vitamin C 1500 mg	0.16 (0.03 to 0.77)	0.022


"THE CHICKEN -OR- THE CHICKEN EGG"
?

Acute

Peripheral

Chronic

Central

The mechanisms underlying CRPS are diverse

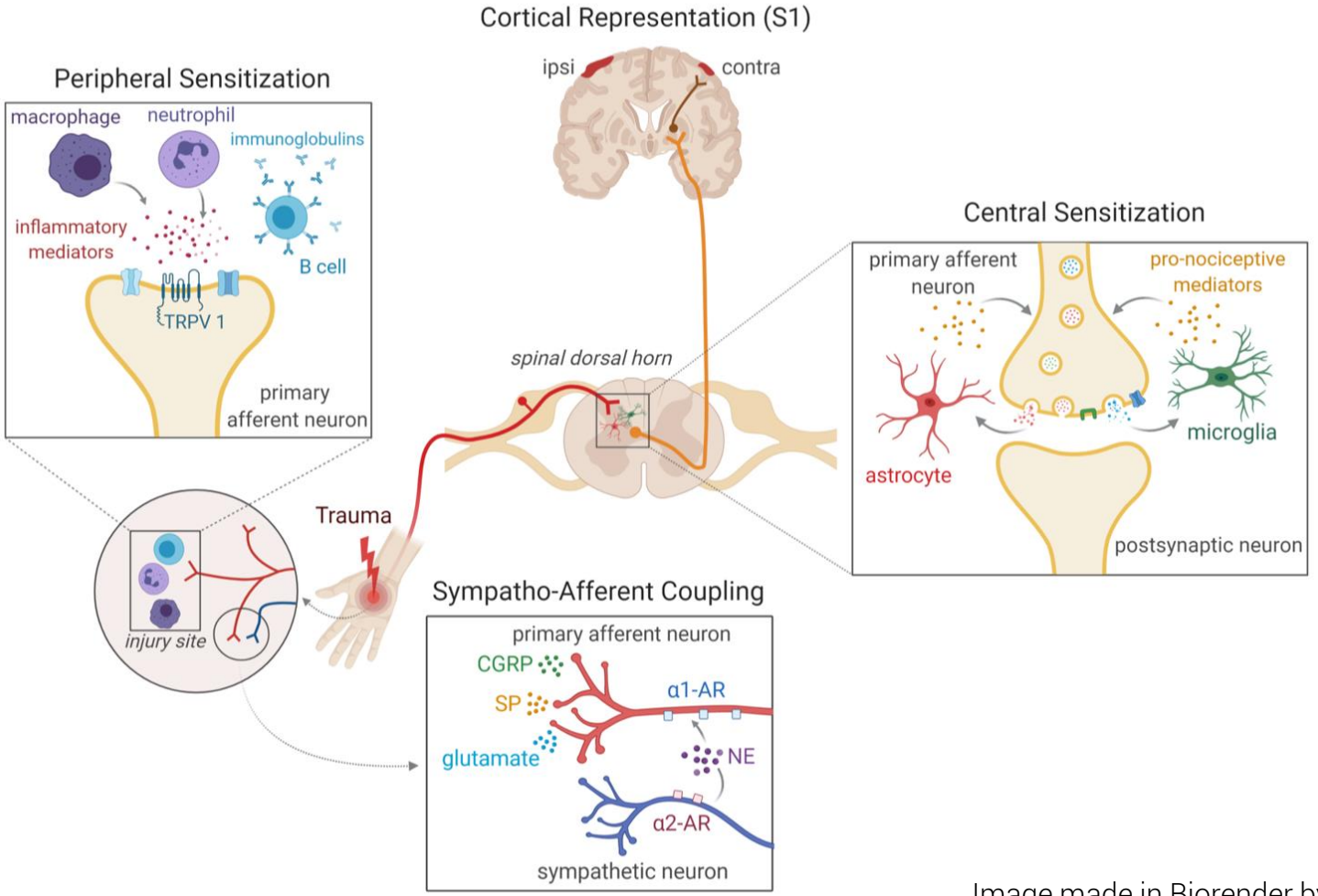
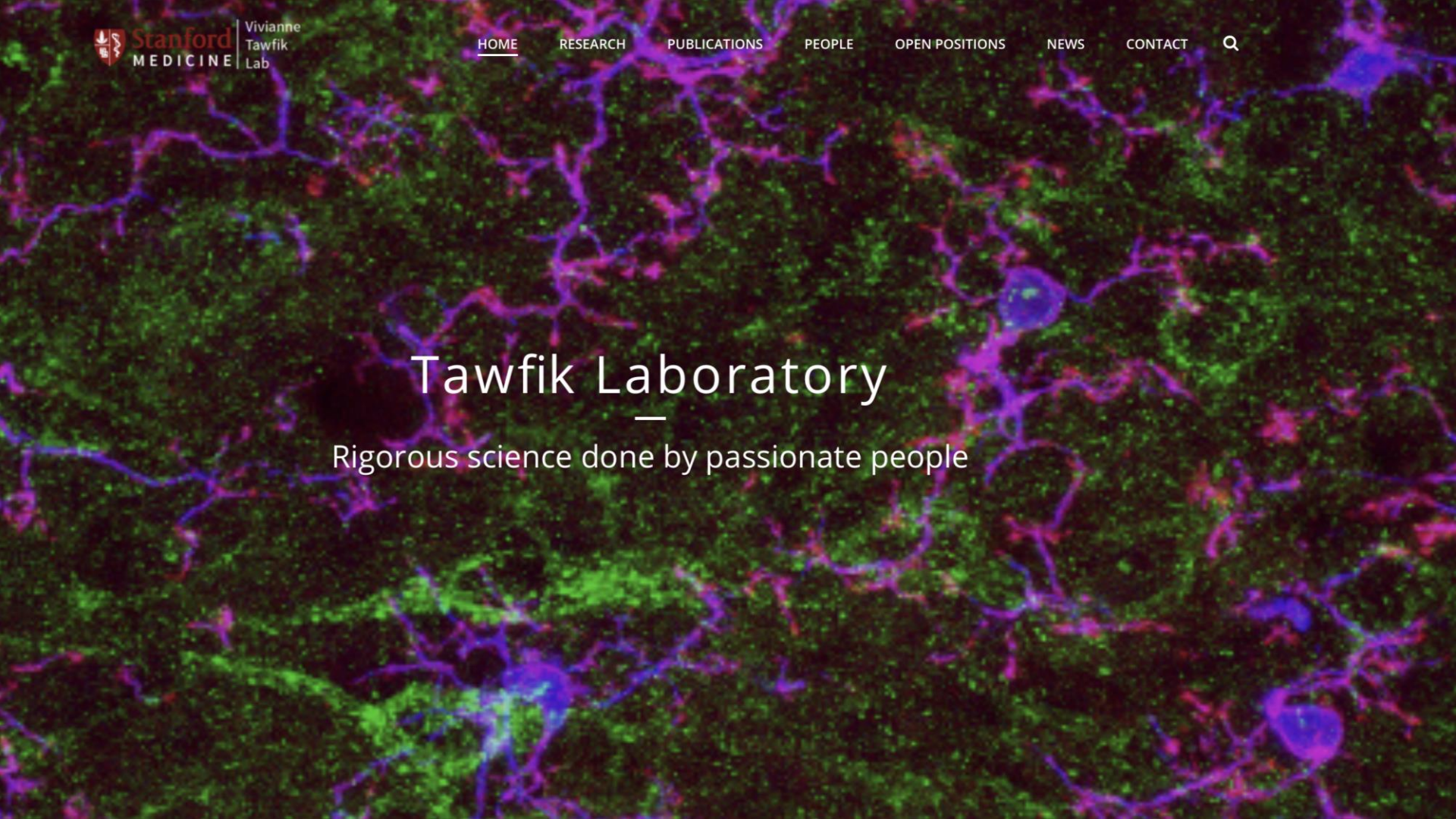


Image made in Biorender by Claire Jordan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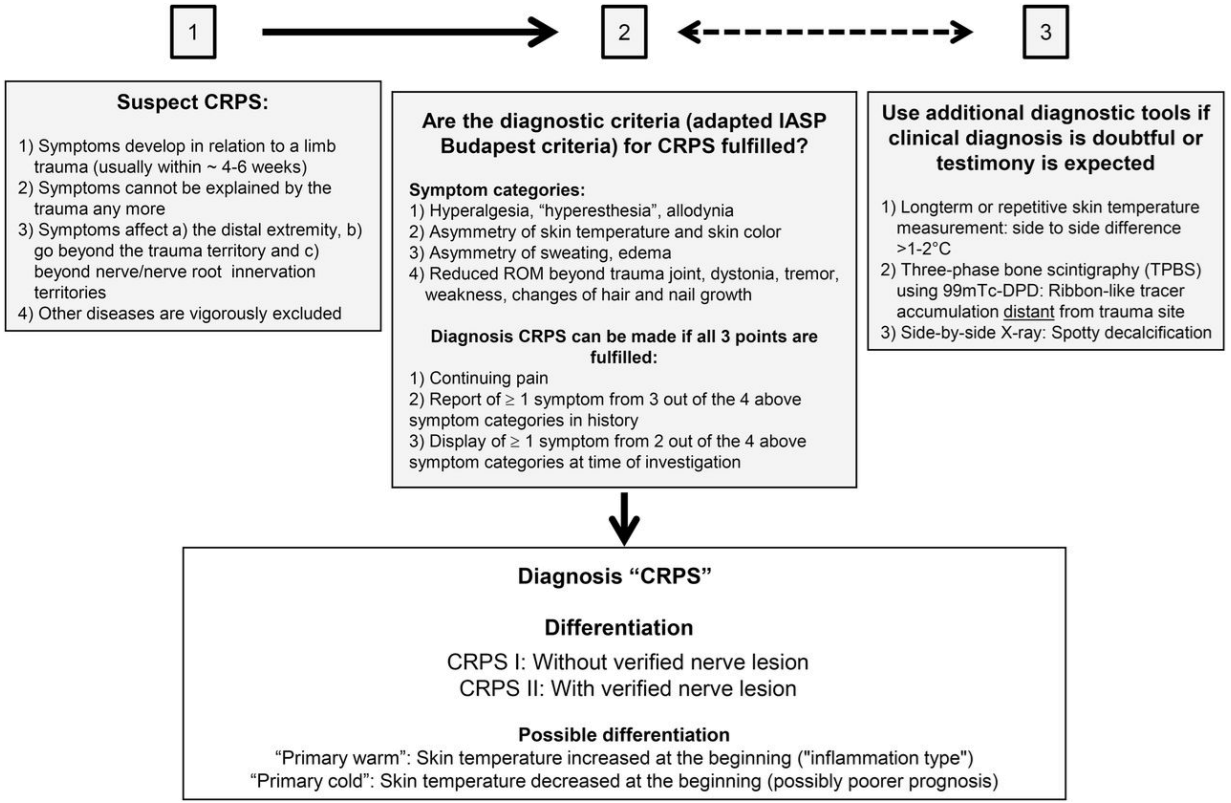
Rigorous science done by passionate people

CRPS Diagnosis: Budapest Criteria

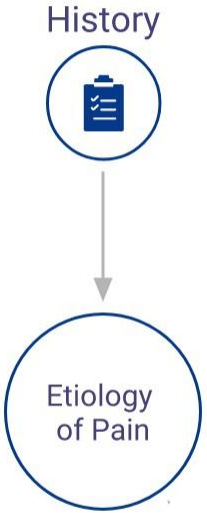
	Symptoms (3 or more)	Signs (2 or more)
Sensory	☐ Report hyperesthesia	☐ Hyperalgesia to pinprick
	☐ Report allodynia	☐ Allodynia to light touch, temperature, deep pressure, or joint movement
Vasomotor	☐ Report temperature asymmetry	☐ Temperature asymmetry (> 1 degree Celsius)
	☐ Report skin color change	☐ Skin color changes
	☐ Report skin color asymmetry	☐ Skin color asymmetry
Sudomotor	☐ Report edema	☐ Edema
	☐ Report sweating changes	☐ Sweating changes
	☐ Report sweating asymmetry	☐ Sweating asymmetry
Motor	☐ Report decreased ROM	☐ Finding reduced ROM
	☐ Report weakness, tremor, dystonia	☐ Finding weakness, tremor, or dystonia
	☐ Report trophic changes	☐ Finding trophic changes in hair, nail, or skin

Diagnostic Approach to CRPS?



Birklein F. Neurology 2015

How do we distinguish the cause of peripheral pain?



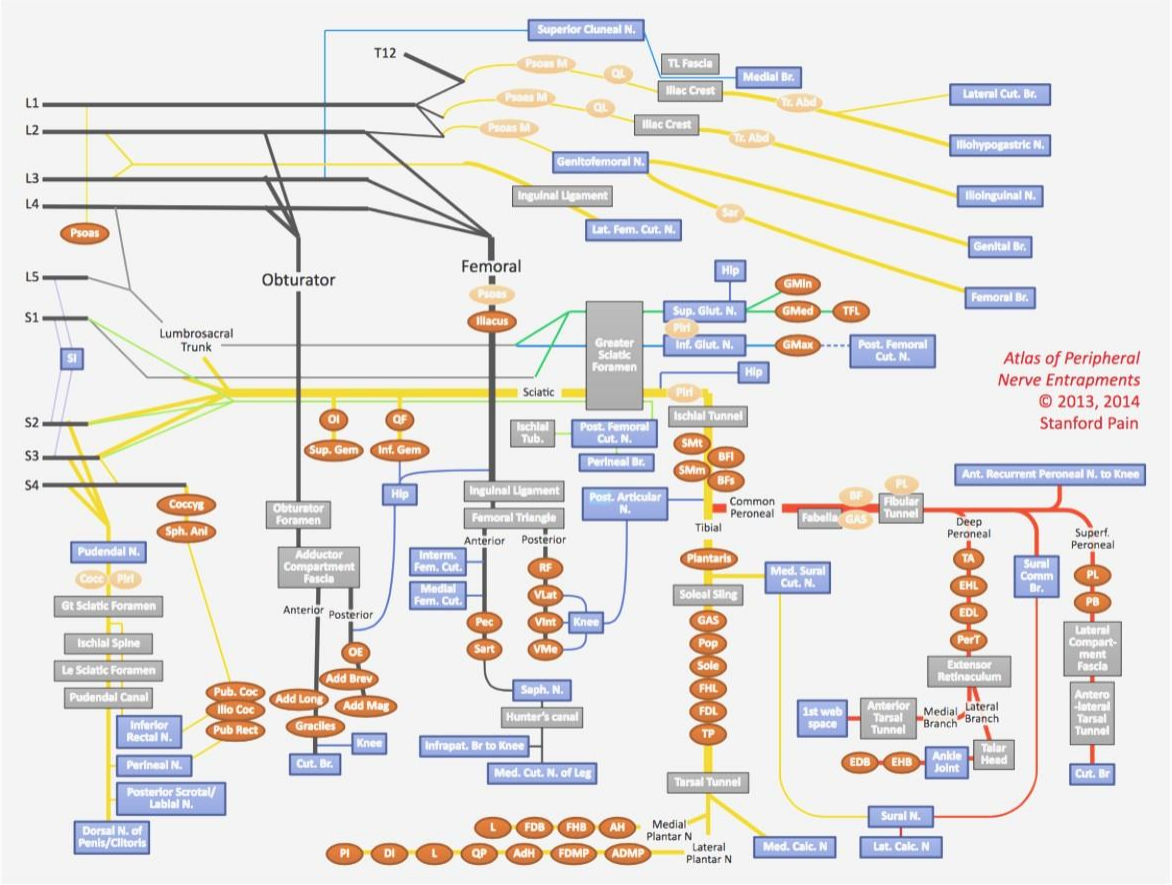
How can imaging help the Pain Physician?

Pain is subjective

Physical exam does not always make the diagnosis clear

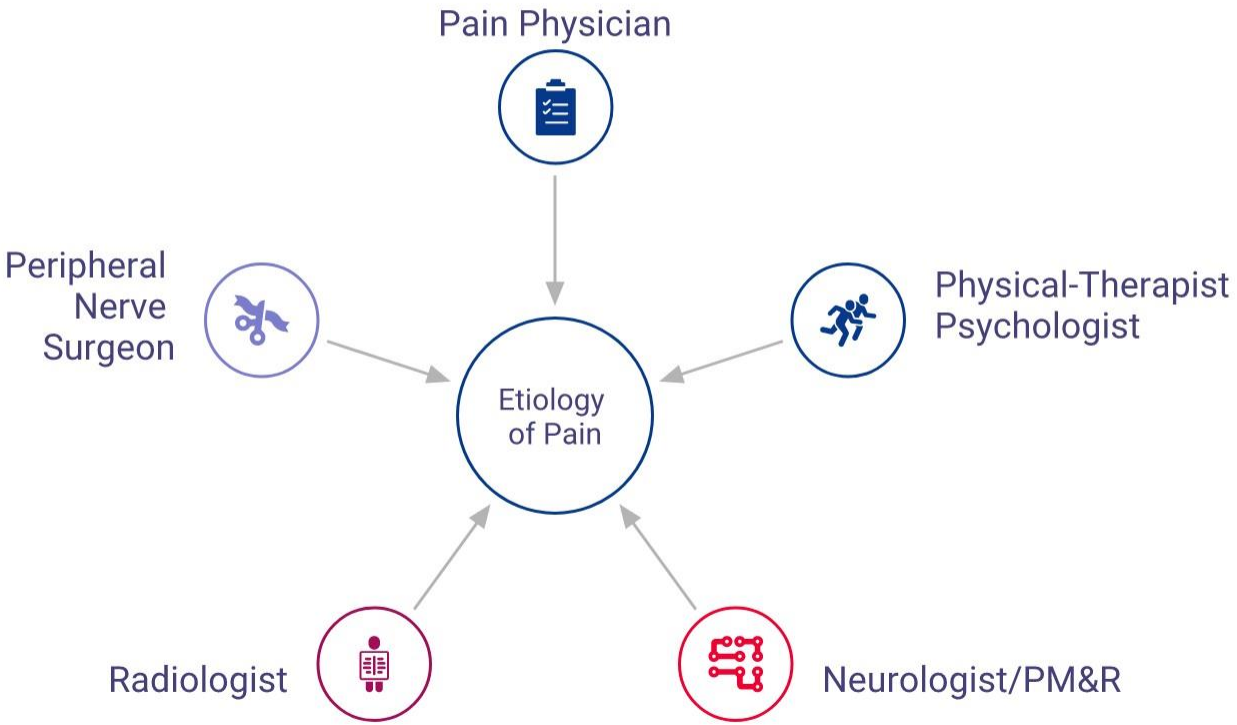
There are many peripheral nerves

An image is worth a thousand words...



MR Neurography- An Approach to “See” Pain?

Does an interdisciplinary team change treatment?



Interdisciplinary evaluation of peripheral pain

- Patients seen in Pain Clinic or Ortho/Plastics “hand” clinic with limb pain
- Referred for MR neurography to evaluate possible peripheral nerve involvement
- Discussed at biweekly interdisciplinary “Nerve Team” conference
- Further work-up or management plans suggested

Case series participants

TABLE 1 | Demographics and patient characteristics.

Number of participants	58
Male	17 (29%)
Female	41 (72%)
Age current (years)	51 ± 16
Age at symptom onset (years)	44 ± 16
Female	42 ± 16
Male	48 ±16
Duration of symptoms (years)	9 ± 16
Race	
White	44 (76%)
Asian	3 (5%)
Black or African American	1 (2%)
Native Hawaiian or Pacific Islander	1 (2%)
American Indian or Alaska Native	1 (2%)
Other	5 (9%)
Unknown	4 (7%)

Numbers are reported as n (%) or average ± standard deviation.

Johnson E et al. Front Pain Res. 2021.

Characteristics of presentation

TABLE 2 | Presenting features and inciting event.

Limb affected	**% patients**
Upper (unilateral)	13 (22%)
Lower (unilateral)	38 (66%)
Upper (bilateral)	2 (3%)
Lower (bilateral)	5 (9%)
Initiating event*	**% patients**
Surgery	25 (43%)
Trauma (no fracture or diagnosed injury)	13 (22%)
Fracture	7 (12%)
Sprain	3 (5%)
Other	5 (9%)
Unknown	14 (24%)

Numbers are reported as n (%).
**Several patients listed both "fracture and surgery" or "trauma and surgery" as their inciting event and therefore totals do not add up to 100%.*

Johnson E et al. Front Pain Res. 2021.

Diagnostics performed

TABLE 3 | Diagnostics performed.

Diagnostic test	% patients
MR neurography	58 (100%)
Nerve block	47 (81%)
EDX	26 (45%)
Standard MRI	24 (41%)
PET/MR study	15 (26%)
NMR bone scan	1 (2%)

Numbers are reported as n (%).

Johnson E et al. Front Pain Res. 2021.

Findings on MR neurography

TABLE 4 | MR neurography findings in all patients and in the subset who underwent surgery as a treatment option.

Radiologic findings*	% patients	% patients who underwent surgery as a treatment
Signal alteration	35 (60%)	12 (57%)
Caliber change	15 (26%)	8 (38%)
Impingement/focal deviation/fat obliteration	13 (22%)	3 (14%)
Mass or mass-like lesion	4 (7%)	3 (14%)
Trauma/disruption	1 (2%)	1 (5%)
None	17 (29%)	5 (24%)
>1 finding	22 (38%)	8 (38%)

**Note that there were 58 patients total and 21 patients who underwent surgery, however, a portion of patients met criteria for more than one radiologic finding and therefore totals do not add up to 100%.*
Numbers are reported as n (%).

Johnson E et al. Front Pain Res. 2021.

Team management changes diagnosis

TABLE 9 | Comparison between referral diagnosis and diagnosis after nerve team evaluation.

		Diagnosis after interdisciplinary nerve team evaluation					
		CRPS I	**CRPS II**	**CRPS NOS**	**Neuropathy***	**Joint dysfunction**	**Total**
Referral diagnosis	CRPS I	**3**	6	0	1	0	10
	CRPS II	1	**1**	0	0	0	2
	CRPS NOS	2	4	**0**	0	0	6
	Neuropathy*	1	0	0	**9**	0	10
	Neuropathy NOS	0	0	0	2	0	2
	Limb pain	0	2	0	5	1	8
	Joint pain	0	5	0	7	0	12
	Pain NOS	0	1	0	5	2	8
	Total	7	19	0	29	3	58

**Neuropathy of a specified peripheral nerve. NOS, not otherwise specified.*

Values in bold and highlighted represent the diagnoses that did not change after interdisciplinary nerve team evaluation.

Treatments provided

TABLE 10 | Treatment and management.

Intervention	% patients
Medication changes	55 (95%)
Physical/occupational therapy	45 (78%)
Pain psychology	45 (78%)
Intravenous infusion (e.g., Ketamine)	23 (40%)
Surgery	21 (36%)
Pulsed Radiofrequency neuromodulation	7 (12%)
Botox injection	7 (12%)
Cryoablation	6 (10%)
Spinal cord stimulator	6 (10%)
Peripheral nerve stimulator	5 (9%)

Numbers are reported as n (%).

Surgery for peripheral limb pain

Of patients who underwent surgery:

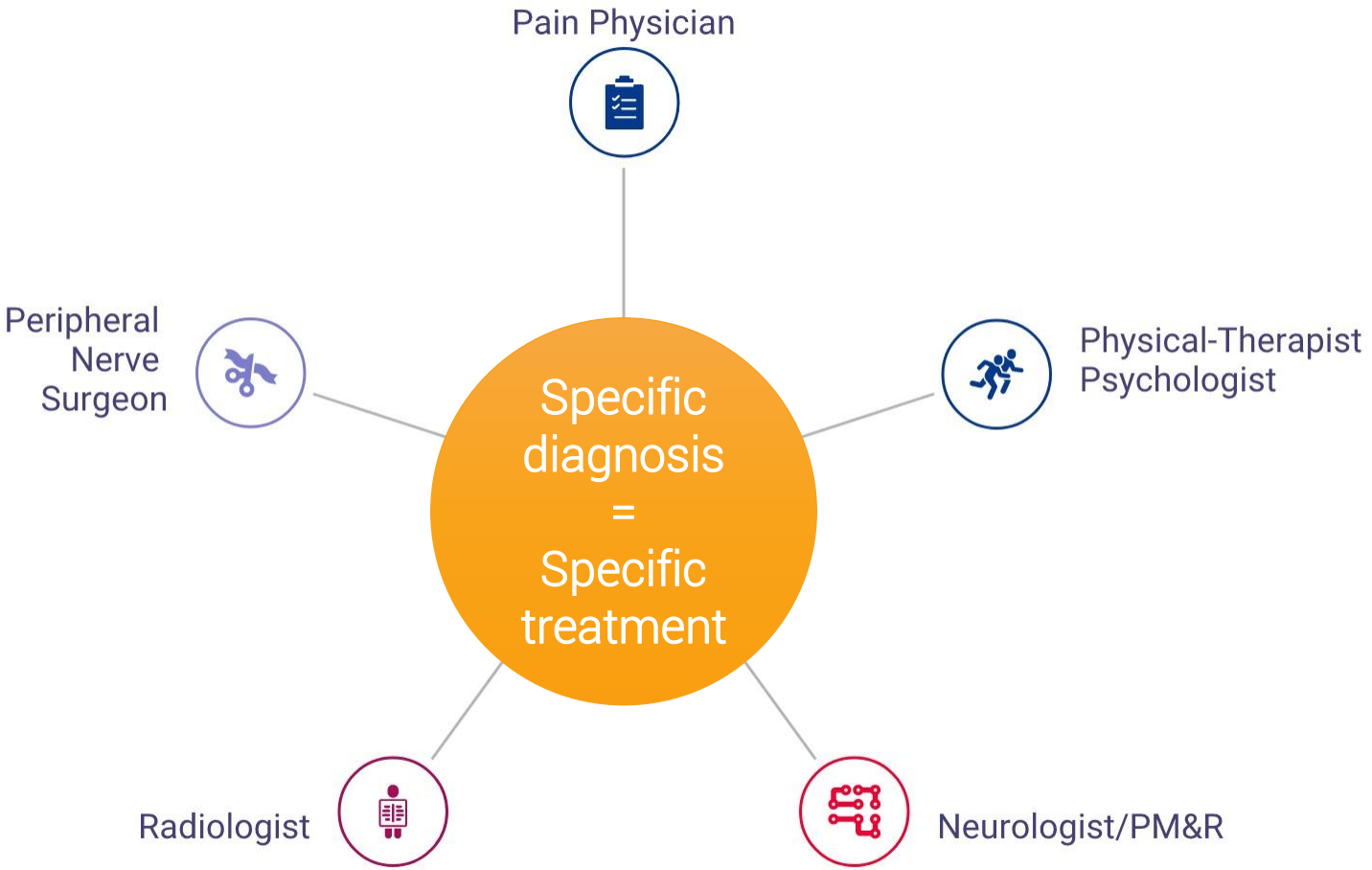
- 83% had positive findings on MRN
- 44% had more than one category of radiologic abnormality on MRN
- 100% had improvement in pain after ultrasound-guided block prior to surgery

I have CRPS and I need to have surgery: What do I do?

- Work with your Pain Management physician and anesthesiologist to develop a plan for managing post-operative pain
  - Increase or re-start anti-neuropathic medications (gabapentin, nortriptyline) the week prior to surgery and continue for 3-6 months after
  - Stop LDN 3-5 days prior to surgery
  - Consider Regional Anesthesia (nerve block)
  - Consider intra-operative and/or post-operative ketamine (if available)

- Take Vitamin C 500 mg daily x 50 days

- Start PT/OT when clinically stable/able


Pain Physician
Peripheral Nerve Surgeon
Physical-Therapist Psychologist
Specific diagnosis = Specific treatment
Radiologist
Neurologist/PM&R

Treatment for CRPS *must* be multidisciplinary

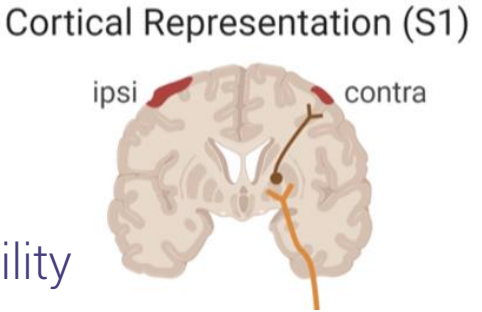
- Medications
- Physical therapy
- Hand therapy
- Education
- Pain Psychology
- Interventions as appropriate

Medication options for CRPS:

- Steroids (early)
- Bisphosphonates (early)
- Anti-neuropathics
- Ketamine
- Low-dose naltrexone
- Other…

Please consult your physician

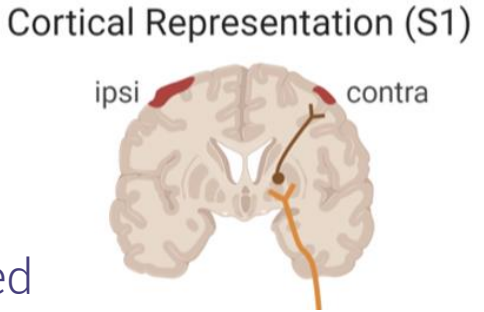
Targeting cortical representation: Physical therapy



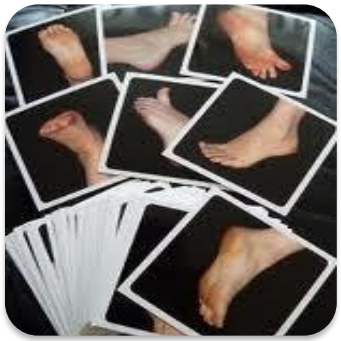
- Effectiveness of physiotherapy interventions for pain and disability associated with CRPS type I and II
    - 18 randomized clinical trials (RCTs) included with a total of 739 participants
    - Lack of high-quality evidence
    - Most included trials were at “high” risk of bias (either blinding not done, patients not randomly assigned…)

Smart et al. Cochrane Database of Systematic Reviews. 2016.

Targeting cortical representation: Physical therapy II

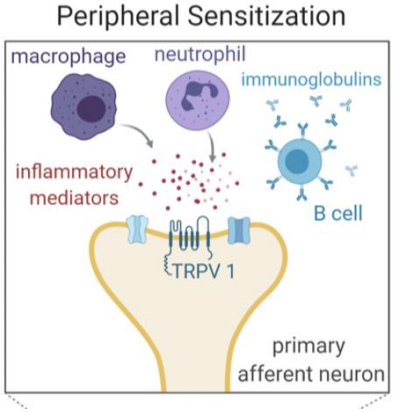


- Graded Motor Imagery (GMI)
  - 2 weeks of limb laterality recognition + 2 weeks of imagined movements + 2 weeks of mirror box therapy
  - Four trials compared GMI to control interventions
  - Overall improvements in pain and function reported immediately after the intervention and at 12-week follow-up



Smart et al. Cochrane Database of Systematic Reviews. 2016.

Targeting peripheral inflammation: Steroids



- **Steroids** decrease post-traumatic inflammation

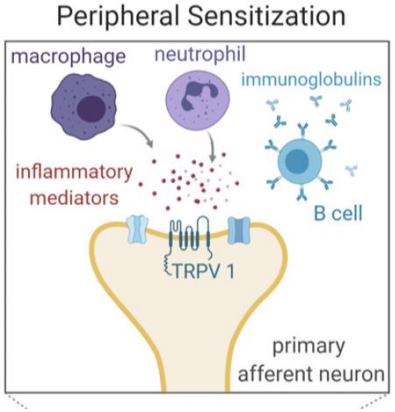
- Probably most useful in the early/acute phase
  - within 6-9 months of initial injury

- No optimal dose reported
  - Prednisolone 100 mg per day with a 25% reduction q 4 days (Birklein et al. Neurology 2015)

  - My practice has been **prednisone** three week taper starting with 6 tabs daily (30 mg) and decreasing by 1 tab daily q3 days (6 tabs daily x 3 days, 5 tabs daily x 3 days, 4 tabs daily x 3 day etc...) until off. (Atalay et al. Pain Physician 2014)

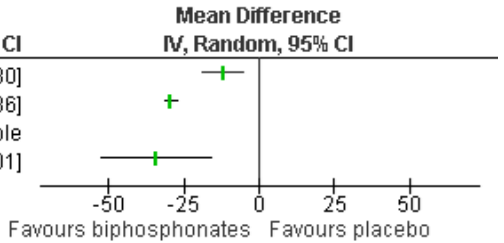
Please consult your physician

Targeting peripheral inflammation: Bisphosphonates



- **Bisphosphonates** reduce bone turnover
  - Shown most effective in early/acute phase
    - Within 1 year of initial injury
  - Highest efficacy in those with documented osteopenia
  - Also likely decrease CRPS-associated inflammation

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Adami 1997 (1)	36	9	10	48	6	10	-12.00 [-18.70, -5.30]
Manicourt 2004 (2)	18.11	3.6	20	47.5	2.9	20	-29.39 [-31.42, -27.36]
Robinson 2004 (3)	0	0	0	0	0	0	Not estimable
Varenna 2000 (4)	22.3	20.2	15	56.4	31.4	17	-34.10 [-52.19, -16.01]



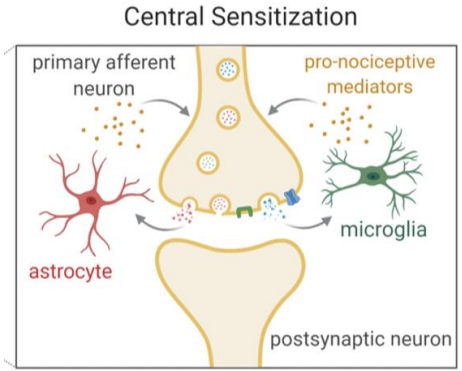
(1) IV alendronate
(2) oral Alendronate
(3) IV Pamidronate (data not available)
(4) IV Clodronate

35-40 mg daily x 8 weeks

Please consult your physician

O'Connell et al. Cochrane Database of Systematic Reviews. 2013.

Targeting central neuroinflammation: Ketamine



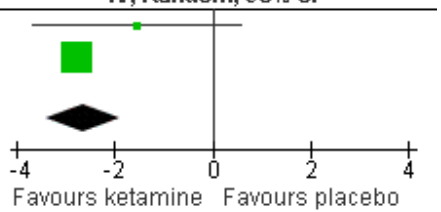
- **Ketamine** likely acts to decrease central excitatory signal

- Schwartzman 2009
  - Ketamine 0.35 mg/kg/hr over 4 hours x 10 working days
  - Stanford "outpatient protocol"

- Sigtermans 2009
  - Ketamine 22.2 mg/hr (mean) continuously for 4.2 days
  - Stanford "inpatient protocol"

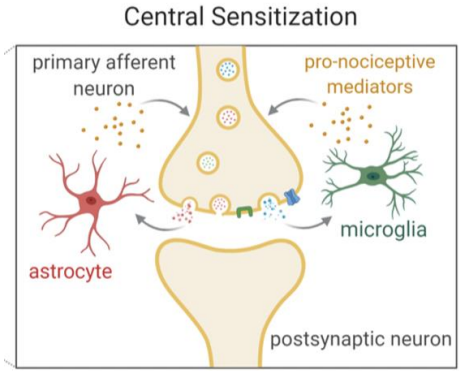
	ketamine			placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Schwartzman 2009	6.06	2.7	9	7.61	1.897	10	11.2%	-1.55 [-3.67, 0.57]
Sigtermans 2009	2.68	0.51	30	5.45	0.48	30	88.8%	-2.77 [-3.02, -2.52]
Total (95% CI)			**39**			**40**	**100.0%**	**-2.63 [-3.39, -1.88]**

Heterogeneity: Tau² = 0.15; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 6.83 (P < 0.00001)



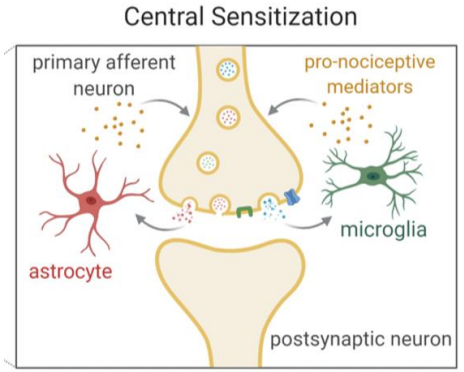
O'Connell et al. Cochrane Database of Systematic Reviews. 2013.

Targeting central neuroinflammation: Ketamine II



- My own anecdotal impression of ketamine:
  - About 1/3 of patients have no improvement
  - About 1/3 of patients have improvement during infusion, dissipates within minutes-hours of turning off infusion
  - About 1/3 of patients have lasting improvement
- Those who ultimately get the most significant improvement are the ones who get relief at lower doses (10-25 mg/hr)

Targeting central neuroinflammation: LDN



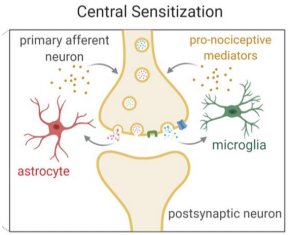
- Low-dose naltrexone (LDN) may act on the TLR4 receptor on microglia to decrease neuroinflammation
- Standard dose is 50 mg, used for opioid addiction and alcohol dependence
- "Low dose" is 4.5 mg, needs to be compounded because standard tablet is 50 mg

  Stanford dose is LDN 4.5 mg at night, 2 hours prior to bedtime

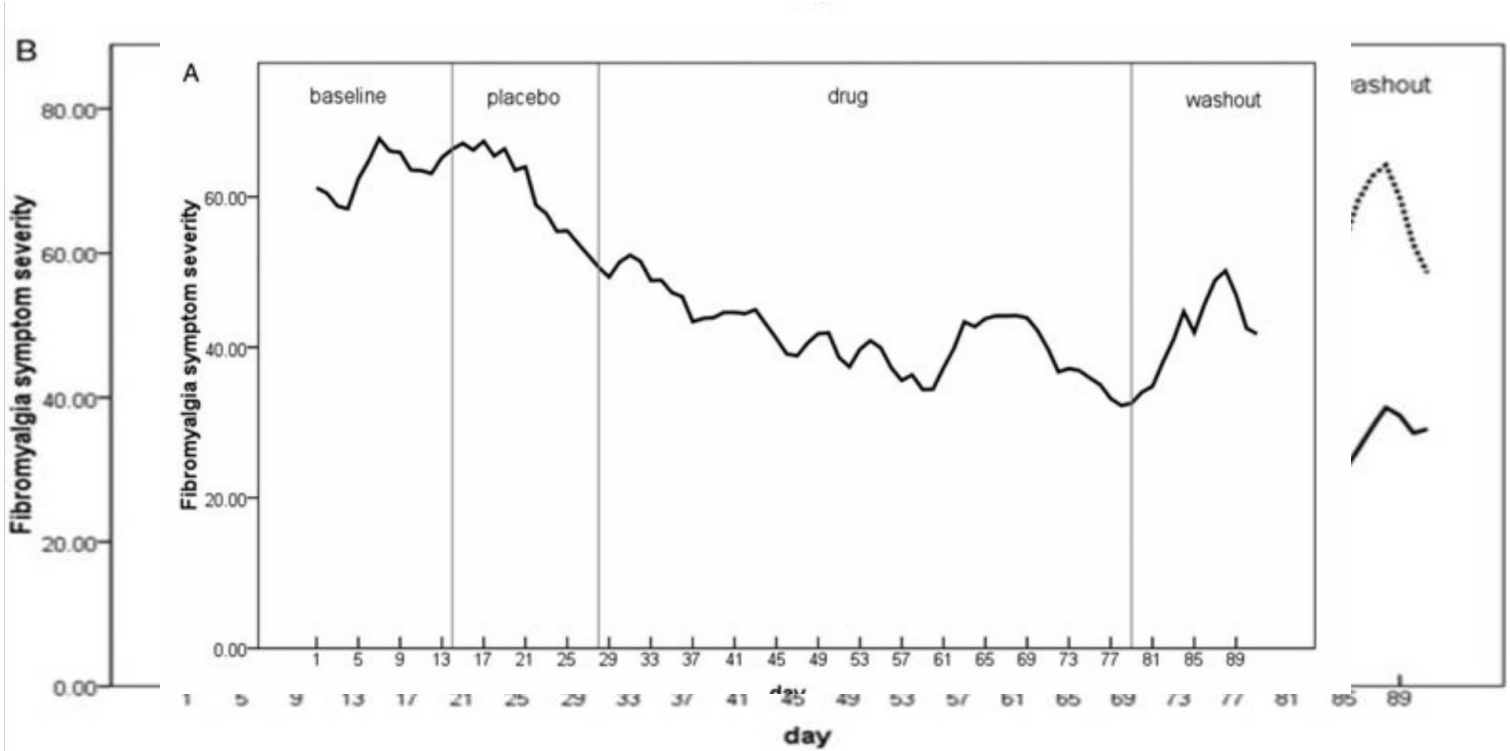
- Occasional start lower (1 mg at night) or go higher (maximum 9 mg at night)

Please consult your physician

Targeting central neuroinflammation: LDN II

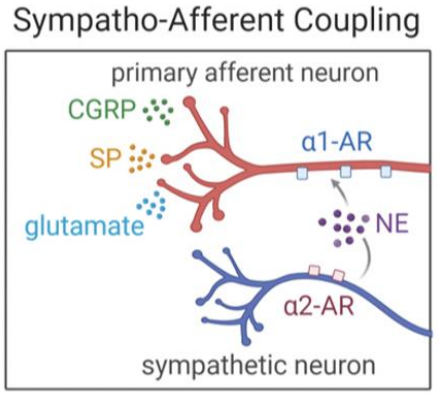


LDN may be more effective for fibromyalgia with a fatigue component



Younger & Mackey, Pain Med 2009.

Targeting the sympathetic nervous system: Sympathetic blocks

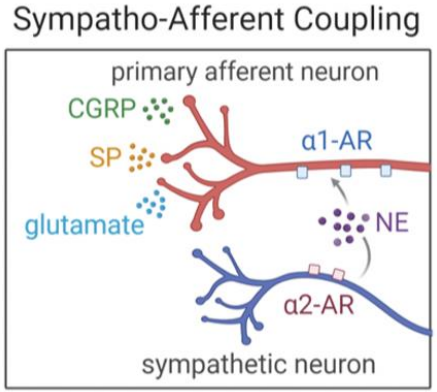


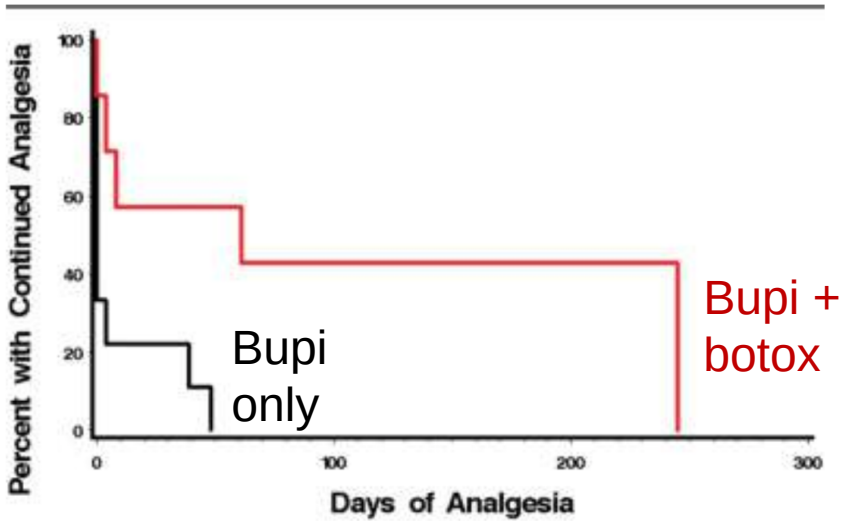
- **Overactivity of the SNS is thought to contribute to CRPS**
- Possible mechanism is through decreasing local sensitivity to epinephrine
- Reviewed 12 studies (n = 461 total)
- Overall quality of the evidence was low to very low with most studies showing no effect at follow up of local anesthetic sympathetic blockade
- Anecdotally I have had some luck doing these in "series"
  - 3 blocks each 3 weeks apart

O'Connell et al. Cochrane Database of Systematic Reviews. 2013.

Targeting the sympathetic nervous system: Sympathetic blocks II

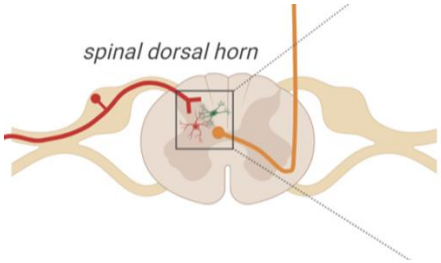
- Patients received (in random order) lumbar sympathetic block with bupivacaine only vs. bupivacaine + 75 U Botox





Carroll I, Clark JD, Mackey SM. Ann Neurol. 2009.

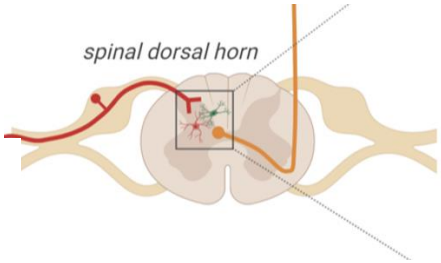
Targeting the dorsal root ganglia: Neuromodulation

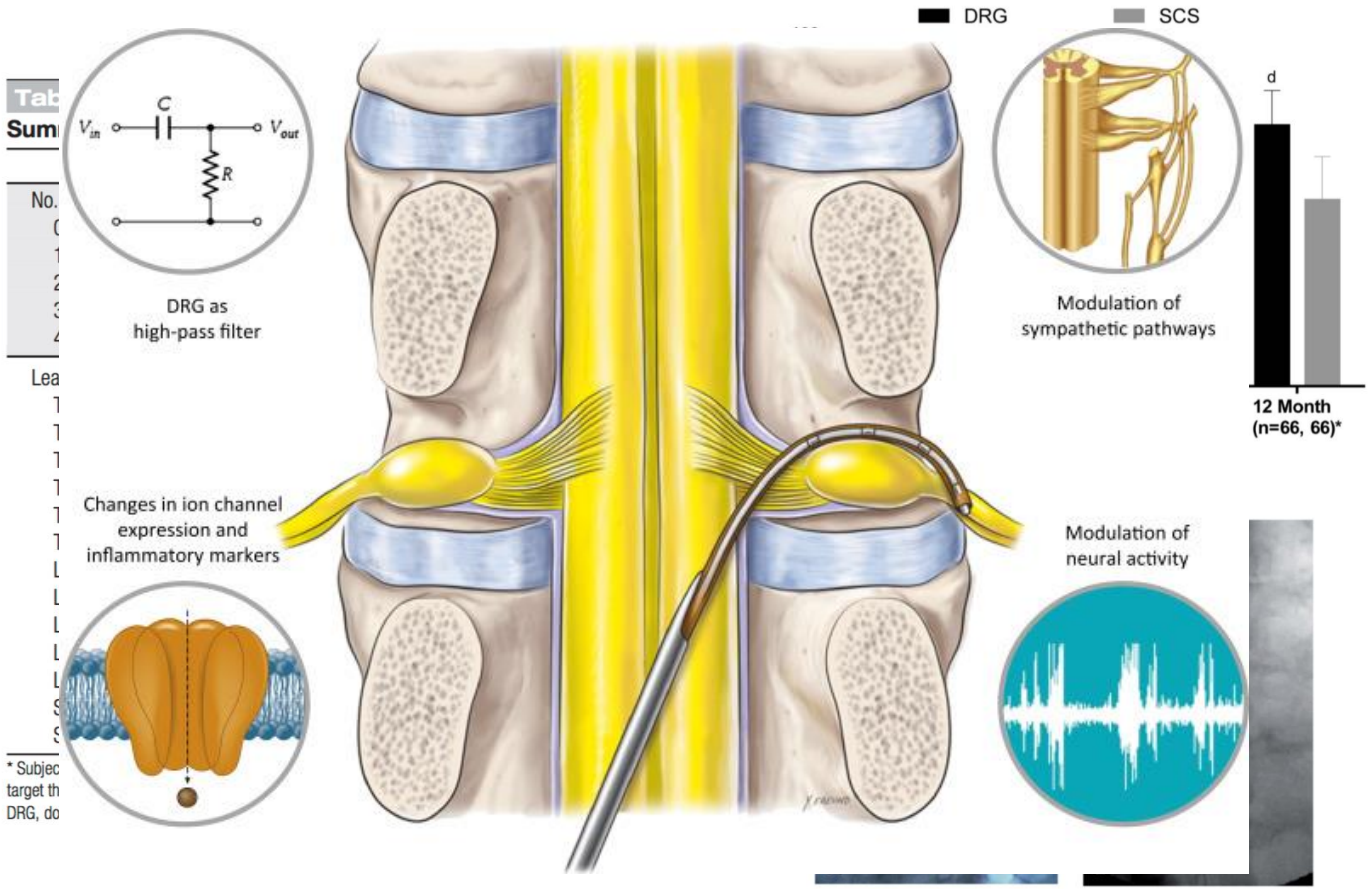


- 152 patients with CRPS in the lower extremities
- Primary end point: composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and adverse events.
- Dorsal root ganglion stimulation also demonstrated greater improvements in quality of life and psychological disposition.
- Largest prospective, randomized comparative effectiveness trial to date, the results show that DRG stimulation provided a higher rate of treatment success with less postural variation in paresthesia intensity compared to SCS

Deer T et al. Pain 2017.

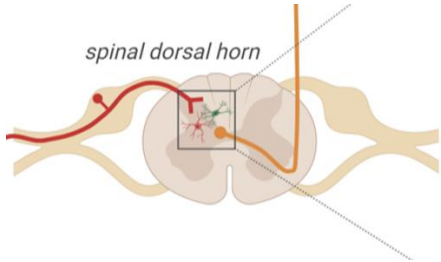
Targeting the dorsal root ganglia: Neuromodulation





Deer T et al. Pain 2017.

Ongoing DRG clinical trials



1	☐	Recruiting	Comparative Study in Patients With Refractory Chronic Lower Limb Neuropathic Pain and/or Back Neuropathic Pain.	• Pain, Neuropathic	• Other: Spinal Cord Stimulation, association of both (DUAL), Dorsal Root Ganglion stimulation	• Poitiers University Hospital Poitiers, France
2	☐	Completed Has Results	A Study to Confirm the Safety of High Frequency **DRG** Stimulator in Patients With Chronic Lower Limb Pain	• Failed Back Surgery Syndrome • Complex Regional Pain Syndrome (CRPS)	• Device: GiMer Medical MN 1000 External Stimulator	• China Medical University Hospital Taichung, Taiwan
3	☐	Active, not recruiting	TARGET Post-Approval Study	• Complex Regional Pain Syndrome (CRPS)	• Device: Dorsal Root Ganglion (**DRG**) Stimulation (Axium™ Neurostimulator System) • Device: Dorsal Root Ganglion (**DRG**) Stimulation (Proclaim™ Neurostimulator System)	• Arizona Pain Specialists Scottsdale, Arizona, United States • Spanish Hills Interventional Pain Specialists Camarillo, California, United States • California Orthopedics & Spine Larkspur, California, United States • (and 42 more...)
4	☐	Active, not recruiting	Intermittent vs. Continuous Dorsal Root Ganglion Stimulation	• Pain, Intractable • Pain, Chronic	• Device: Dorsal Root Ganglion Stimulation (**DRG**-S)	• Spine and Pain Institute NY New York, New York, United States
5	☐	Unknown †	Study to Evaluate the Effectiveness of **DRG** Stimulation for Discogenic Low Back Pain	• Discogenic Low Back Pain	• Device: Dorsal Root Ganglion Stimulation	• Rijnstate Ziekenhuis, Velp Velp, Arnhem, Netherlands
6	☐	Not yet recruiting	Intermittent Dosing of Dorsal Root Ganglion Stimulation as an Alternate Paradigm to Continuous Low-Frequency Therapy	• CRPS (Complex Regional Pain Syndromes) • Radiculopathy • Peripheral Neuropathy	• Device: **DRG** stimulation 20 Hz 30/90 • Device: **DRG** stimulation 5 Hz 30/90	
7	☐	Not yet recruiting	Prediction of Recruitment Potential of Participating Centers in Clinical Trials by Standardized Translation of Selection Criteria and Queries From **DRG** Database	• Multicenter Clinical Study		• Department of Public Health - Hôpital Ambroise Paré Boulogne-Billancourt, Hauts-de-Seine, France

- CRPS
- Discogenic Low Back Pain
- Failed Back Surgery Syndrome
- Neuropathic pain
- Peripheral Neuropathy
- Radiculopathy

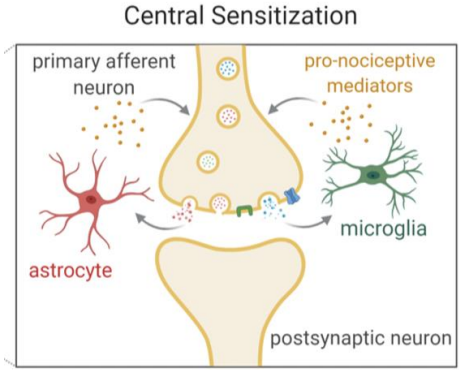
Slide source: Dr. Michael Leong.

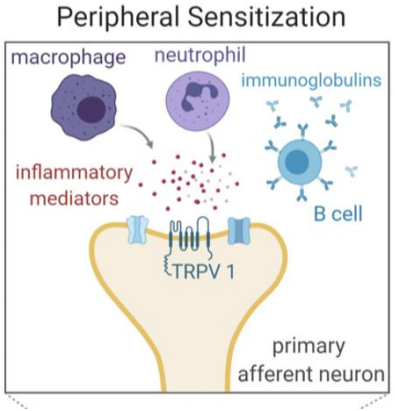
Targeting autoimmunity: HCQ?

- There are likely autoimmune mechanisms underlying CRPS
  - Auto-antibodies to β2-AR and M2 muscarinic receptors found in CRPS patients
  - IgG from patients with CRPS can "transfer" symptoms to mice

- Some clinical data supports the use of steroids, IVIG (high dose), thalidomide and other immune modulators

- Hydroxychloroquine (HCQ) is an antimalarial and immunosuppressive used in the treatment of RA and SLE





Please consult your physician

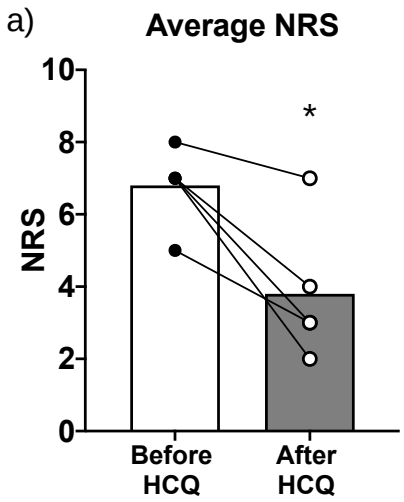
Patients treated off-label with HCQ for refractory CRPS

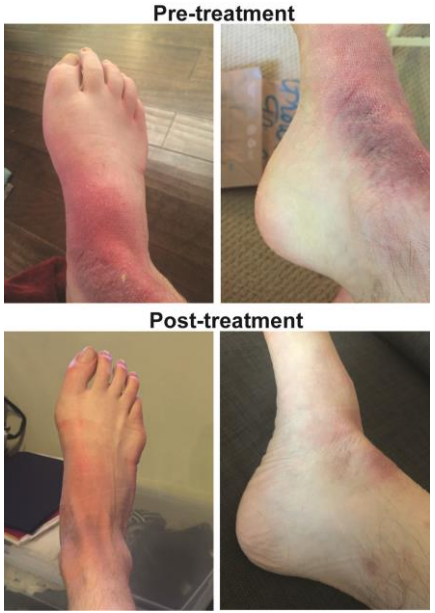
Table 1

Clinical characteristics of patients prescribed HCQ for refractory CRPS.

Patient number	Current age	Gender	Age at symptom onset (y)	Symptom duration (y)	CRPS type	HCQ duration
1	21	F	14	7	2	1 mo
2	40	F	35	4	1	7 mo
3	42	F	39	2	1	8 mo
4	62	F	55	6	2	9 mo
5	47	F	21	25	1	1.5 y
6	37	F	31	5	2	3 y
7	25	F	17	8	2	3 y
Avg (SD)	39 (13)	N/A	29 (14)	8 (8)	N/A	17 (14) mo

Avg, average; CRPS, complex regional pain syndrome; F, female; HCQ, hydroxychloroquine.

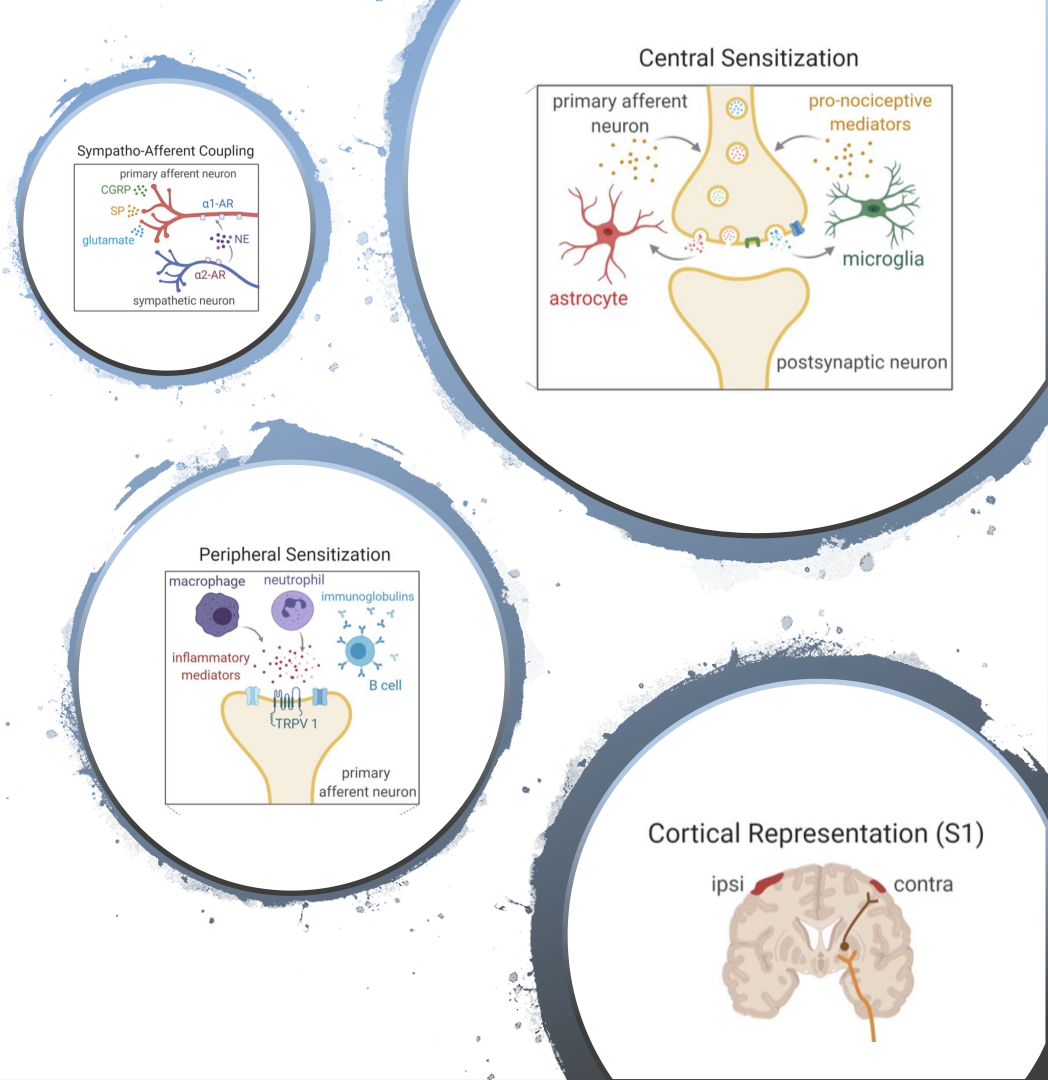




Haight E et al. Pain Reports, 2020

Summary

- CRPS most commonly occurs in the distal extremities after minor trauma or injury
- Looks like “usual healing” but inflammation and pain persist beyond expected timeframe
- Treatment must be multidisciplinary for best outcomes



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