

Low Dose Naltrexone and chronic pain

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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
- No financial interest in any pharmaceutical company or otherwise

Introduction

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

LDN and chronic pain

- Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), Neuropathic pain
- Ehlers Danlos Syndrome (EDS), Connective Tissue disorder
- Fibromyalgia

LDN and chronic pain

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Complex Regional Pain
Syndrome (CRPS)
or
Reflex Sympathetic Dystrophy
(RSD)

What is CRPS / RSD

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

How common is RSD?

-
- USA: estimated to be 50,000 new cases per year

Signs and Symptoms of CRPS 1

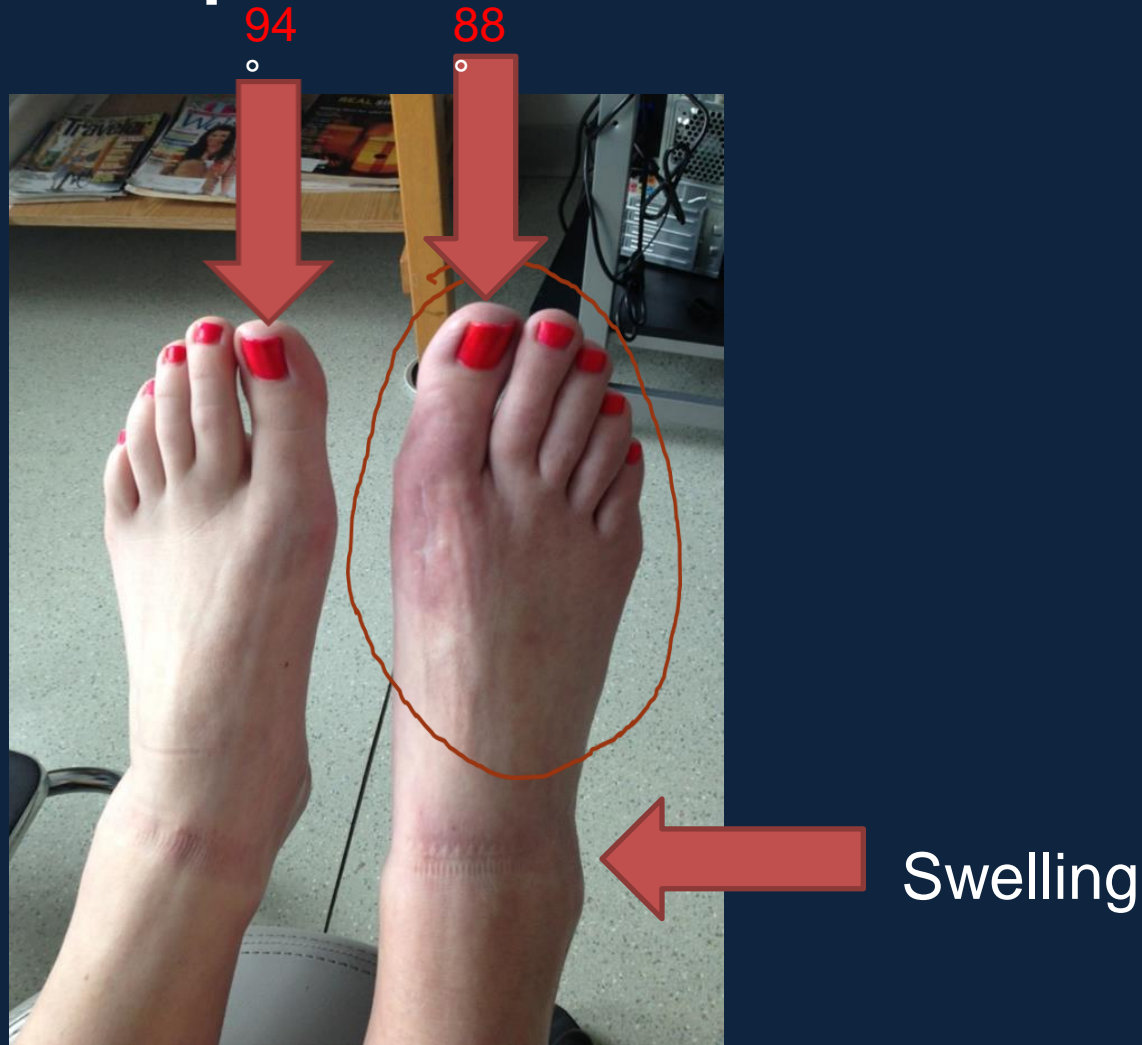
- Pain starts in one limb but can present in the trunk (spine, abdomen, perineum)
- Constant pain, even at rest with intermittent exacerbations. Unexplained and diffuse
- Severe pain - burning, tearing, shooting
- Temperature, color change.
- Edema
- Area of pain larger than the primary injury
- Limited range of motion

Signs and Symptoms of CRPS

2

- Allodynia - pain on light touch
- Hyperalgesia - increased pain to mildly painful stimulus
- Trophic changes - nail growth changes (faster, distorted), hair growth changes (coarser, darker, rapid growth, hair falling), skin changes (atrophy of skin), skin lesions

Color, temperature and swelling













Bilateral CRPS







CENTRAL SENSITIZATION

Key concept to understanding all
chronic pain

Central Sensitization

- The increased excitability is due to a barrage of signals from the peripheral nociceptors.
- This barrage alters the strength of the synaptic connections between the neurons in the spinal cord.
- Low threshold neurons activated by light touch of the skin begin to activate neurons in the CNS that normally respond to noxious stimulus.
- Hence a simple touch of the skin feels painful.
- Although the pain feels as if it originates in the periphery, it actually is a result of abnormal sensory processing in the CNS.

GLIA

The final frontier in understanding
disease

Glia

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- Glia constitute 70% to 80% of all cells in the CNS
- Perform immune surveillance under basal conditions
- Glia when activated release pro-inflammatory cytokines

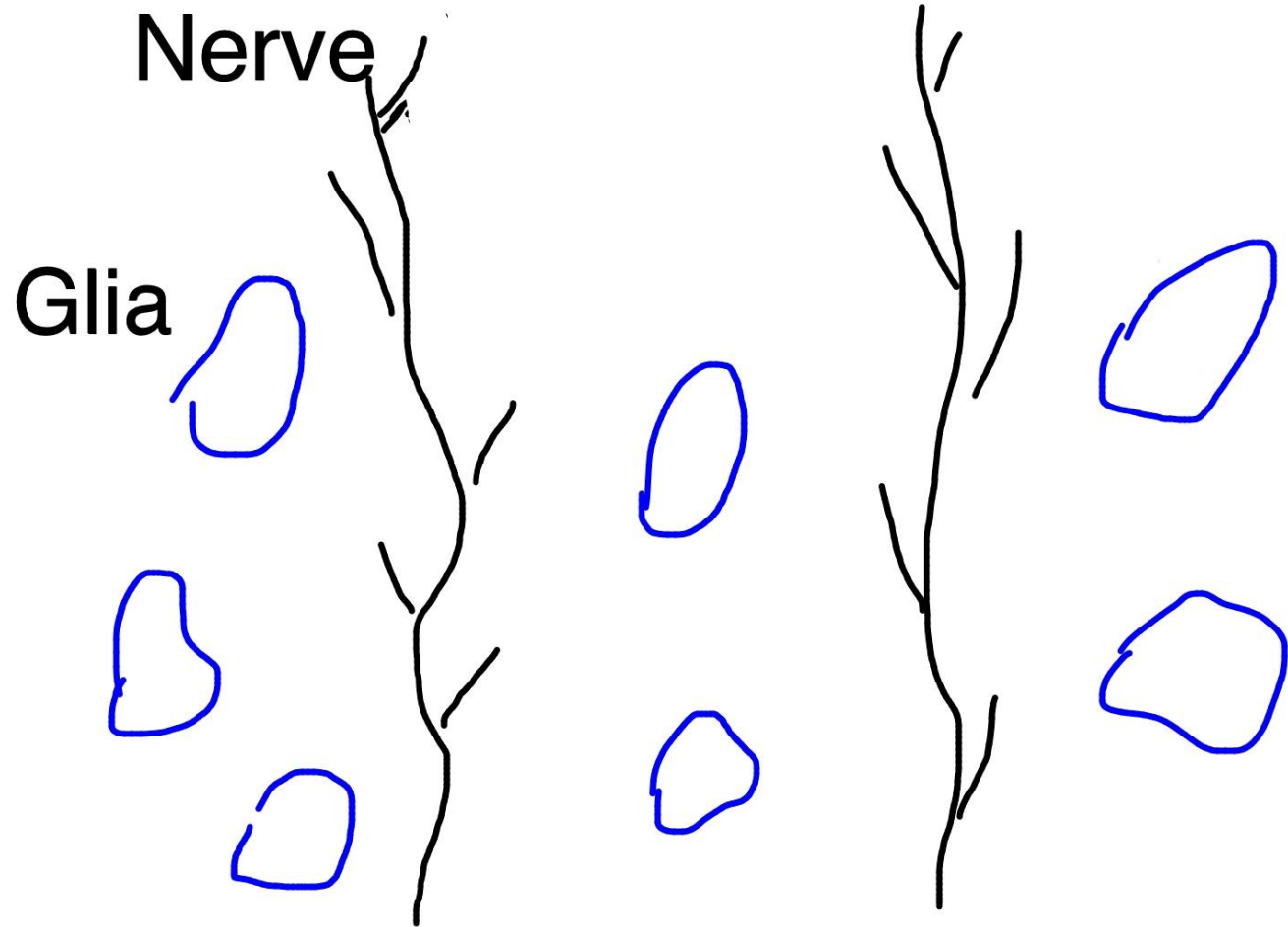
Glia – Activated

- Create and maintain neuropathic pain
- Compromise the efficacy of opioids

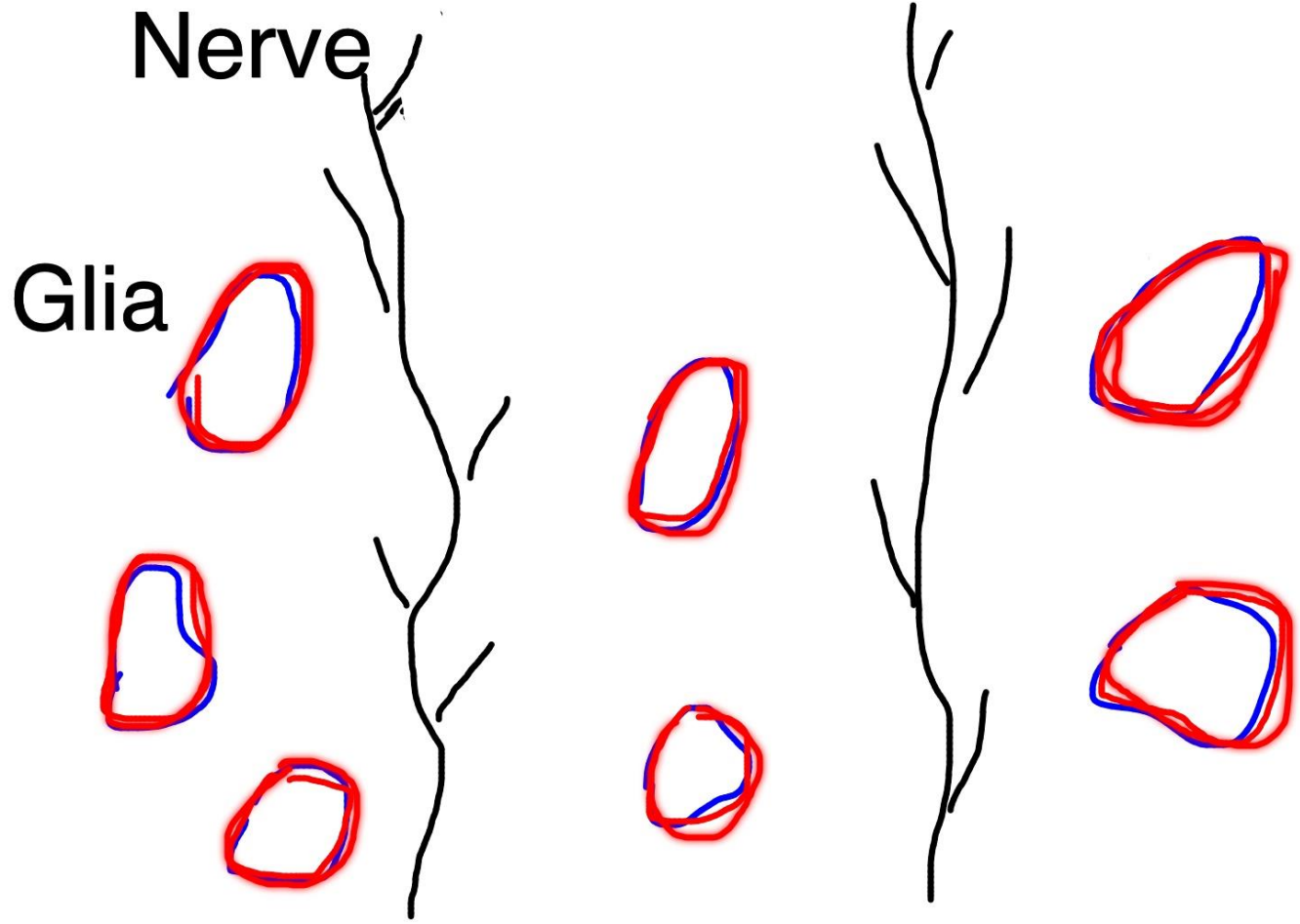
Activated Glia and Neuropathic Pain

- When activated – glia release a variety of substances (proinflammatory cytokines, chemokines, etc.)
- These substances in turn cause neuroinflammation
- This is a shift in our understanding of chronic pain from neural signalling to a cellular mechanism

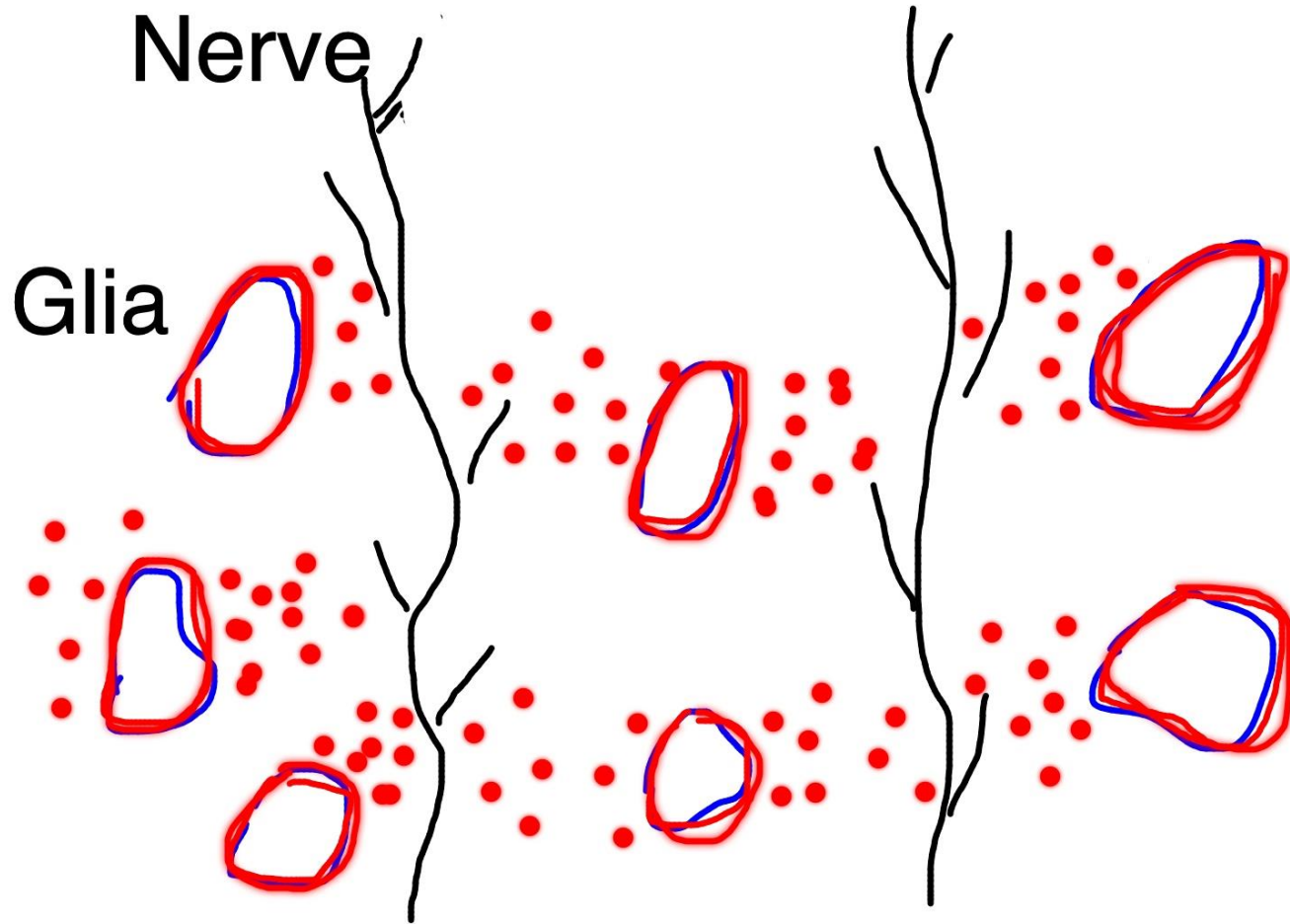
Glia and nerves under normal conditions



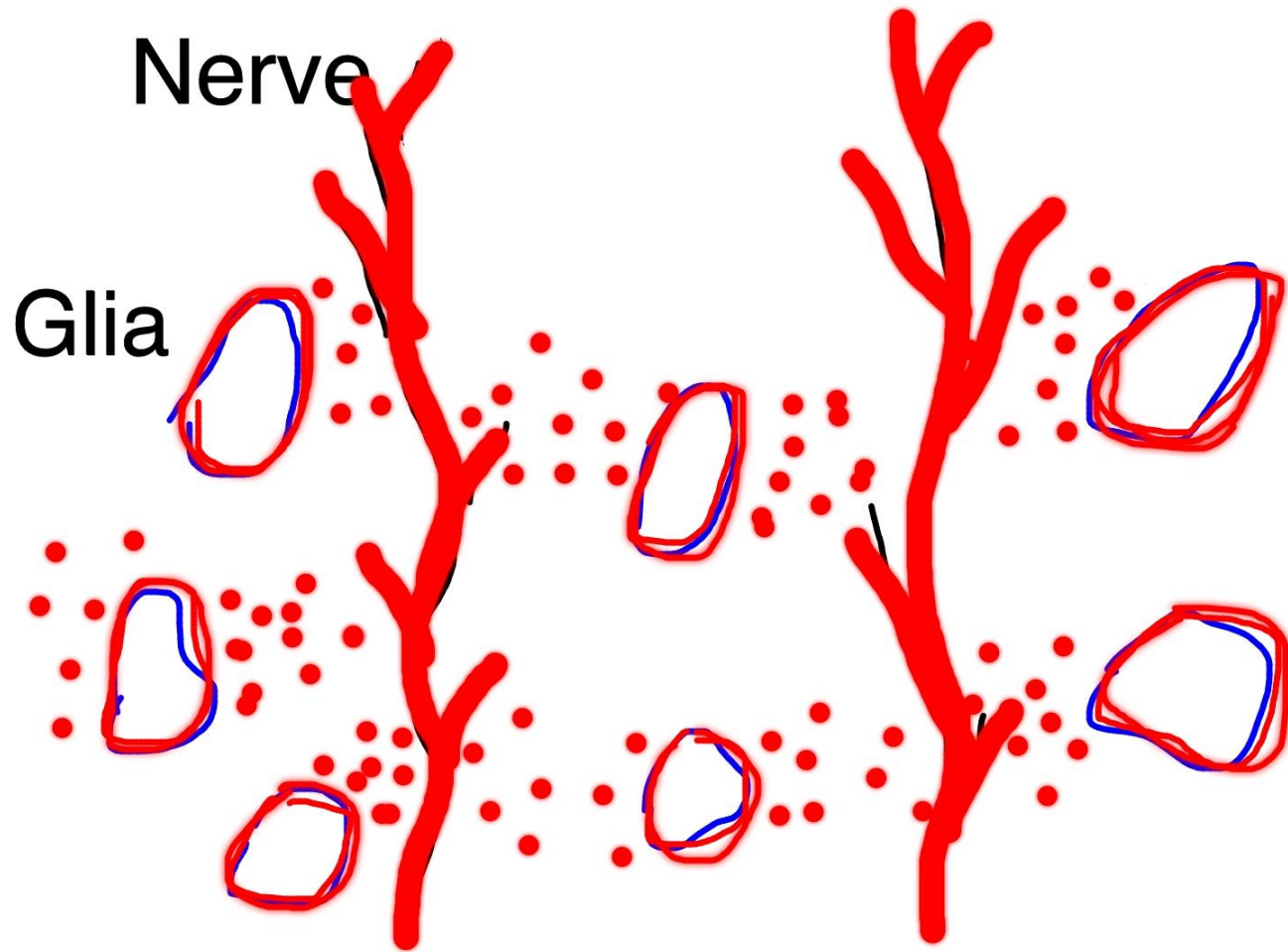
Activated Glia



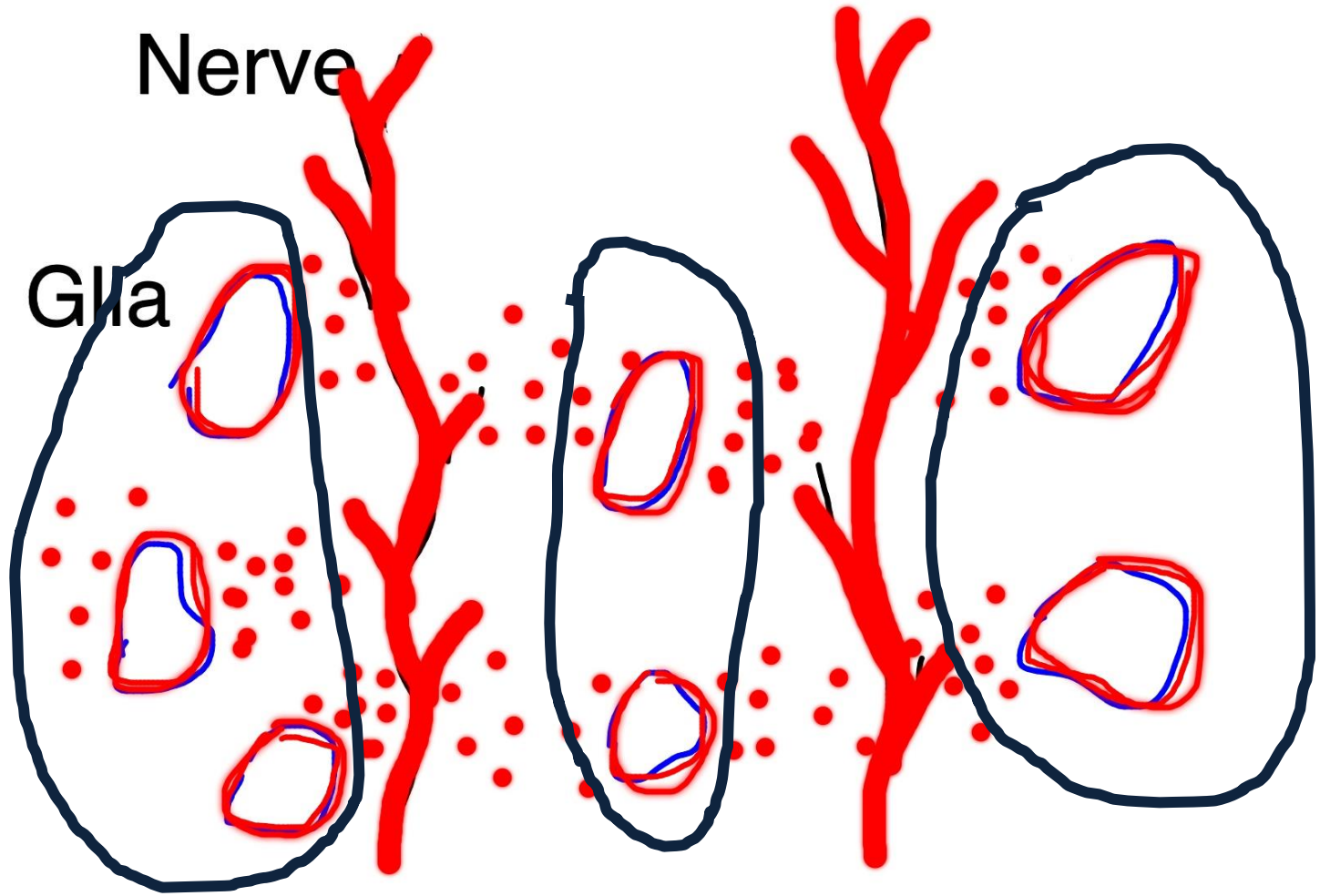
Chemicals released by activated Glia



Nerve inflammation - Central Sensitization



The problem is no longer in the nerves. Its in the cells (Glia cells)

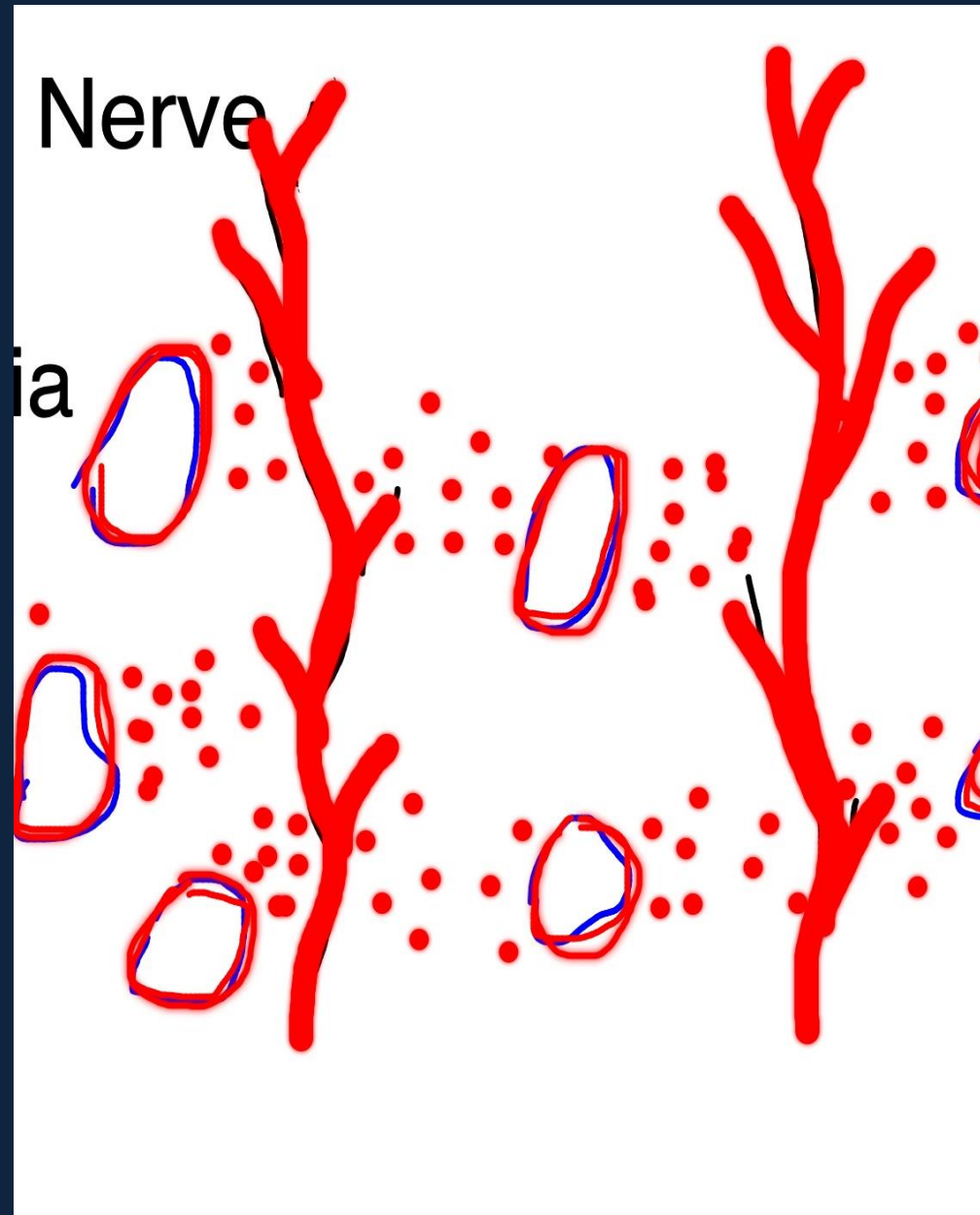


Toll like receptors TLR4

- 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

- Activate glia
- Increased Central Sensitization



Opioids

2

- 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)

Low Dose Naltrexone

LDN

Low Dose Naltrexone (LDN) 2

- Reduction of pro-inflammatory cytokines can be achieved with low doses of naltrexone (Liu et al, Greeneltch et al, Tsai et al)
- Effect not mediated by opioid receptor activity
- Potentially mediated by activity on Toll Like Receptors 4 (TLR4)

Low Dose Naltrexone (LDN)

2

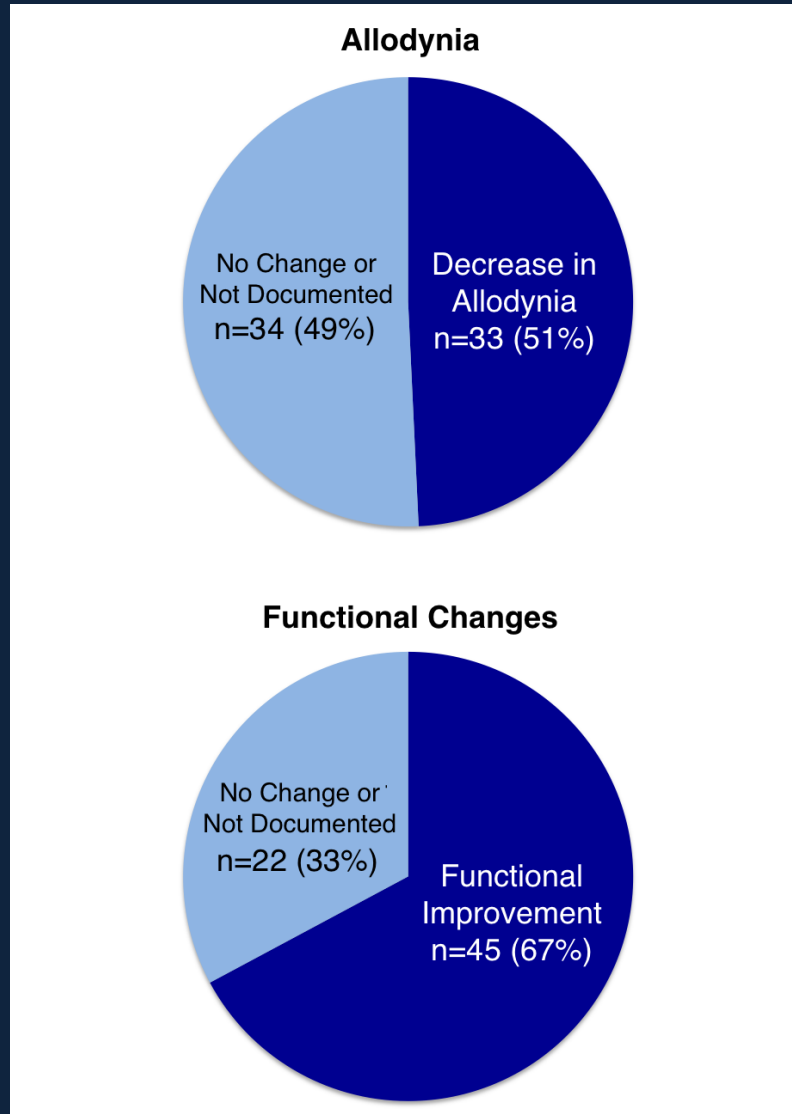
- There are several theories as to how LDN may work.
 1. Transiently blocks opioid receptor leading to positive feedback production of endorphins (Zagnon)
 2. LDN increases production of OGF (opioid growth factor) as well as number of and density of OGF receptors by intermittently blocking the opiate receptor. Increased in OGF repairs tissue and healing.
 3. Effect not mediated by opioid receptor activity. Potentially mediated by activity on Toll Like Receptors 4 (TLR4)

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

Pradeep Chopra • Mark S. Cooper

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

LDN and CRPS





RESEARCH

Open Access

Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats

Theresa-Alexandra M Mattioli¹, Brian Milne^{1,3} and Catherine M Cahill^{*1,2,3}

Conclusion: Taken together, we demonstrate a positive correlation between the prevention of analgesic tolerance and the inhibition of spinal gliosis by treatment with ultra-low dose naltrexone. This research provides further validation for using ultra-low dose opioid receptor antagonists in the treatment of various pain syndromes.

Case of RSD treated with LDN

RSD with dystonia
before LDN



RSD after LDN



Severe RSD with skin lesions



CRPS treated with LDN



Ehlers Danlos Syndrome (EDS)

Connective tissue disorders

Incidence of Ehlers Danlos Syndrome

- Incidence of EDS is 1%
- Number of cases of EDS in the USA is 3.1 million
- Entire population of Iowa or Mississippi or Kansas

Ehlers Danlos Syndrome

1

- EDS is a group of inherited disorders
- Affects connective tissue (‘connects’)
- Connective tissue is found in skin, joints and blood vessels
- Very flexible, unstable joints (‘Double jointed’), stretchy skin and many other symptoms



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Pain in EDS₁

- Recurrent dislocations of joints
- Muscle pain – weak muscles, muscle spasms
- Ligament tear and injury
- Neuropathic pain, Complex Regional Pain Syndrome (CRPS)
- Unstable spine
- Tethered cord syndrome

Ehlers Danlos Syndrome and LDN

1

- LDN in EDS patients helps in two ways:
- Helps lower pain, tolerate pain
- It also helps with stability of the connective tissue
- Patients report feeling ‘more put together’

Fibromyalgia

Centrally Sensitized pain

Fibromyalgia

- Chronic widespread pain
- Allodynia (pain to normal touch)
- Fatigue, poor sleep, joint stiffness

Published in final edited form as:

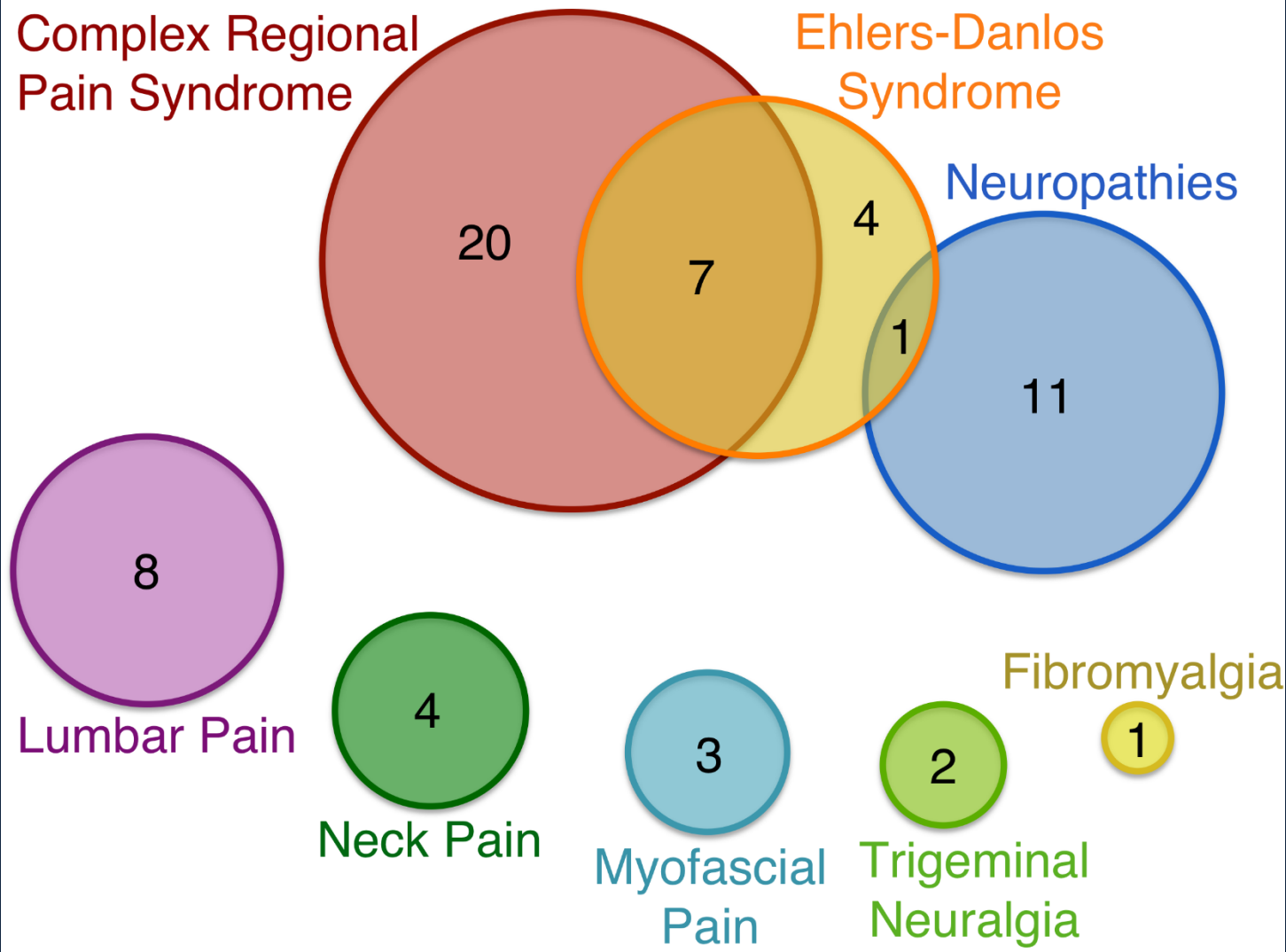
Pain Med. 2009 ; 10(4): 663–672. doi:10.1111/j.1526-4637.2009.00613.x.

Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study

Jarred Younger, PhD and Sean Mackey, MD, PhD

School of Medicine, Department of Anesthesia, Division of Pain Management, Stanford University, Palo Alto, California, USA

Results—Low-dose naltrexone reduced fibromyalgia symptoms in the entire cohort, with a greater than 30% reduction of symptoms over placebo. In addition, laboratory visits showed that mechanical and heat pain thresholds were improved by the drug. Side effects (including insomnia and vivid dreams) were rare, and described as minor and transient. Baseline erythrocyte sedimentation rate predicted over 80% of the variance in drug response. Individuals with higher sedimentation rates (indicating general inflammatory processes) had the greatest reduction of symptoms in response to low-dose naltrexone.

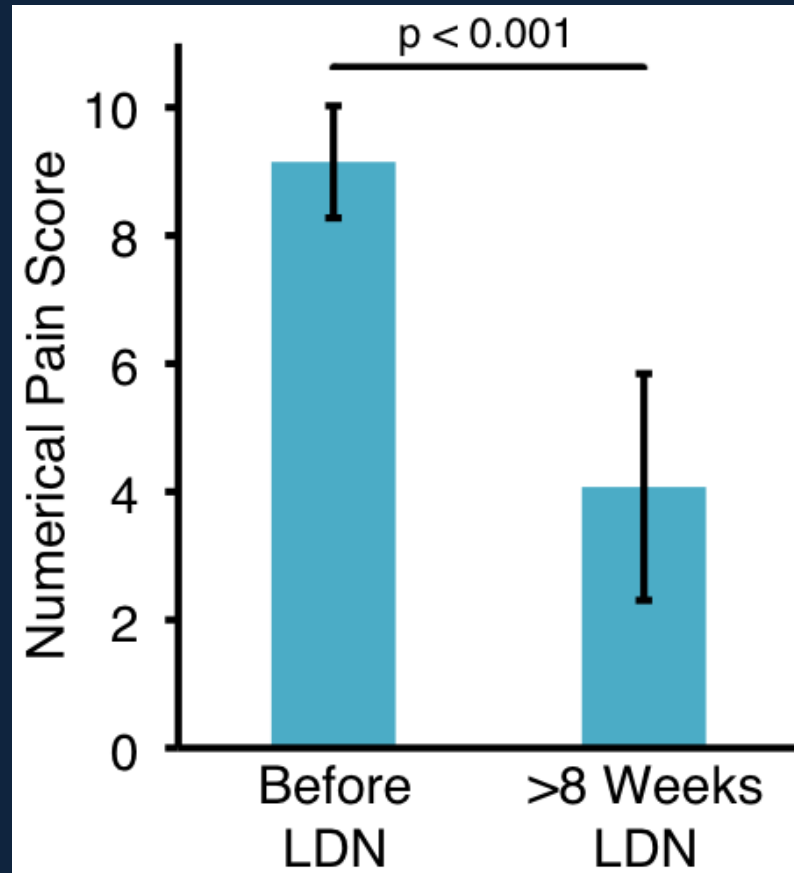


Other Pain Disorders = 6

Total # Patients = 67

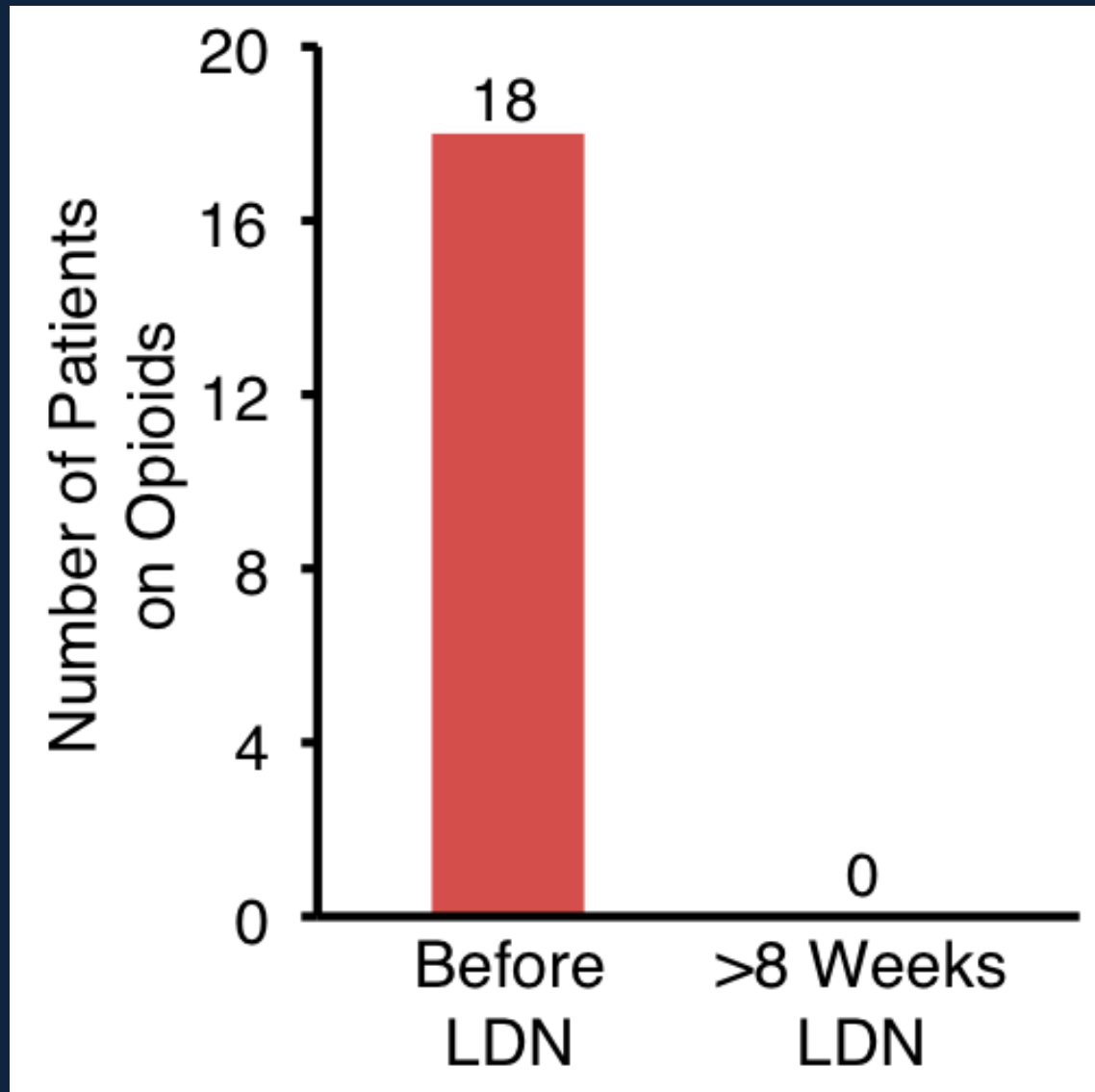
Average Dose:	Prescribing LDN
Standard Deviation:	(mg/day)
Most Common Dose:	4.5
Minimum Dose:	1
Maximum Dose:	6

Pain Scores for All Patients



Average change in pain score = **5.15** points (SD = 1.32)

Opioid Use



Patients who discontinued LDN before 1st follow-up: 3/67
Patients who discontinued LDN after 1st follow-up: 1/67

Reason for discontinuation: No pain relief

Mary C. Olmstead · Lindsay H. Burns

Ultra-low-dose naltrexone suppresses rewarding effects of opiates and aversive effects of opiate withdrawal in rats

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toward a CPP. *Conclusions:* Ultra-low-dose NTX coadministration blocks the acute rewarding effects of analgesic doses of oxycodone or morphine as well as the anhedonia of withdrawal from chronic administration.

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