Low Dose Naltrexone

Mechanisms of Action and Clinical Applications

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Disclosures

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Consultant: Salix (Resistor)

Off label use of medicine: Discussed in context of published research and FDA IND applications for research. Not encouraged for general practice.

Naltrexone

- Anti-opioid
- Approved by the FDA in 1985 to treat opiate dependence (Revia®, Depade® and extended-release Vivitrol®
- Dose of 50mg–100mg daily for opiate dependence

Anti-opioids

- Mu opioid receptor antagonists:
  - Naltrexone
  - Methyl-naltrexone
  - Alvimopan
- Kappa opioid receptor agonists:
  - Fedotozine; Asimadoline and ADL 10-0101
- Combined Mu antagonist/delta agonist
  - Eluxadoline (MuDelta)

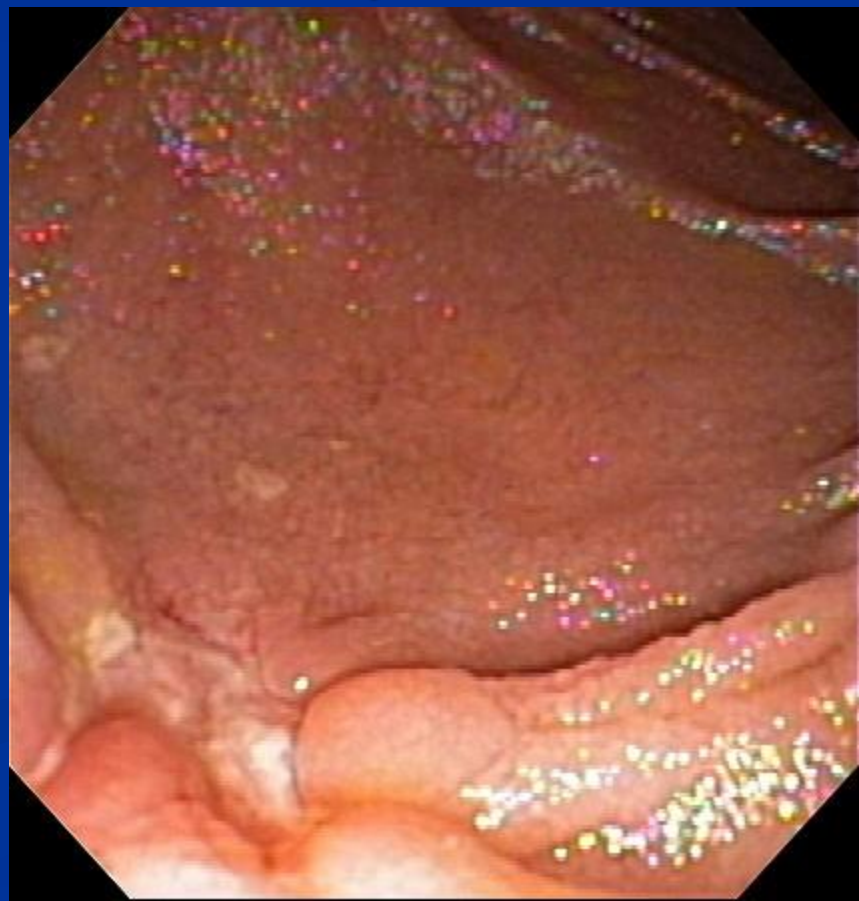
LDN: Modulator of Opioid & Receptor Activity (MORA)

- LDN = low dose naltrexone (2.5-10 mg/d)
- Ultra low dose 0.001 mg in Oxytrex
- 1979-81: MOA studied (Zagon – Penn State)
- 1985: Rx for AIDS (Bihari)
- Mid 90's: Rx for MS (Bihari)
- Other MORAs: Relistor; Xylazine

Zagon et al. Science 1983;221:671-3.

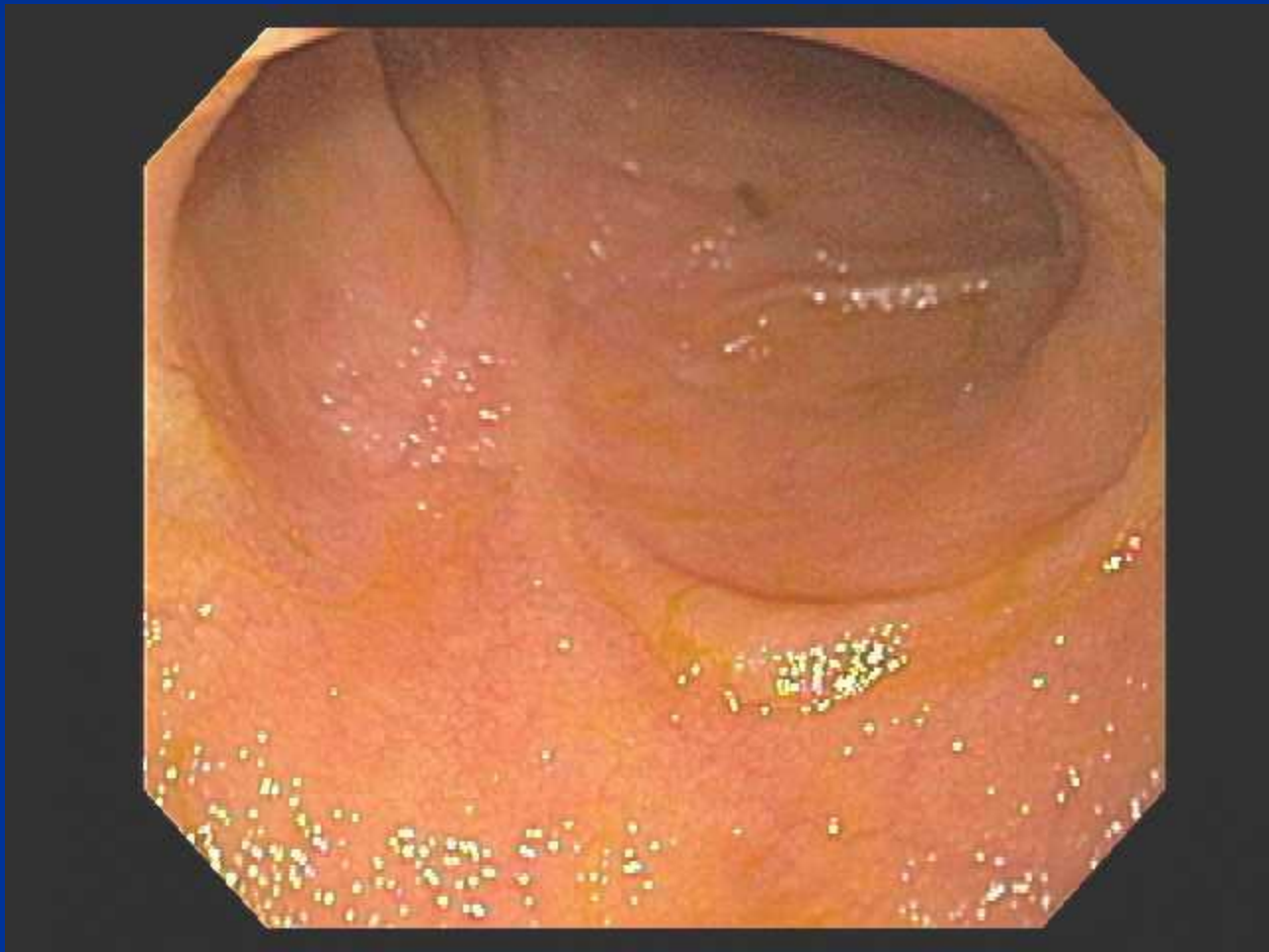
Case 1

- 40 y.o. WF with Crohn's disease – s/p total colectomy, recurrence in ileum 4 yrs later
- Failing infliximab: diarrhea and fatigue



Case 1

- Addition of LDN 4.5 mg
- Endoscopic and sx'ic remission within 2 mo



Case 2

- 60 y.o. WF with 3 yr Hx RLS, constipation and halitosis
- LBT: methane excretor
- Rifaximin 550 mg TID 14 days
- Naltrexone 2.5 qHS
- Remission 3 years

St. Louis experience

- 264 patients in 5 years (through 10/13)
- 5 disorders
  - SIBO – second phase Rx – 108
  - IBS (with negative LBT) – 83
  - CIC – 27
  - Crohn's disease – 34
  - Ulcerative colitis – 12

Weinstock . EMR search: 6/08 – 9/13.

LDN Treatment for Diseases

Published Studies

- Crohn's Diseases
- Irritable bowel
- Multiple Sclerosis
- Fibromyalgia
- Complex regional pain syndrome
- Cancer

Submitted Studies

- Ulcerative colitis

Patient-Reported

- Ankylosing Spondylitis
- Epstein-Barr Syndrome
- Hepatitis C
- Lung Cancer
- Rheumatoid Arthritis
- Lupus Erythematosus
- Parkinson's Disease
- Ulcerative Colitis

Placebo effect and Perceptions

"Therapeutic reports with controls tend to have no enthusiasm and reports with enthusiasm tend to have no controls"

Endorphins

- Endorphins produced in most cells
  - Regulate cell growth including immune cells
  - Disorders of the immune system can occur with unusually low levels of these endorphins
- Met-Enkephalin is the most influential endorphin

Endogenous "opioids"

- Peptides
- B-endorphin, enkephalins, endomorphin, dynorphin
- Distribution
  - CNS and PNS
  - GI tract
    - Myenteric plexus
    - Mucosal plexus
    - Endocrine cells of intestinal mucosa

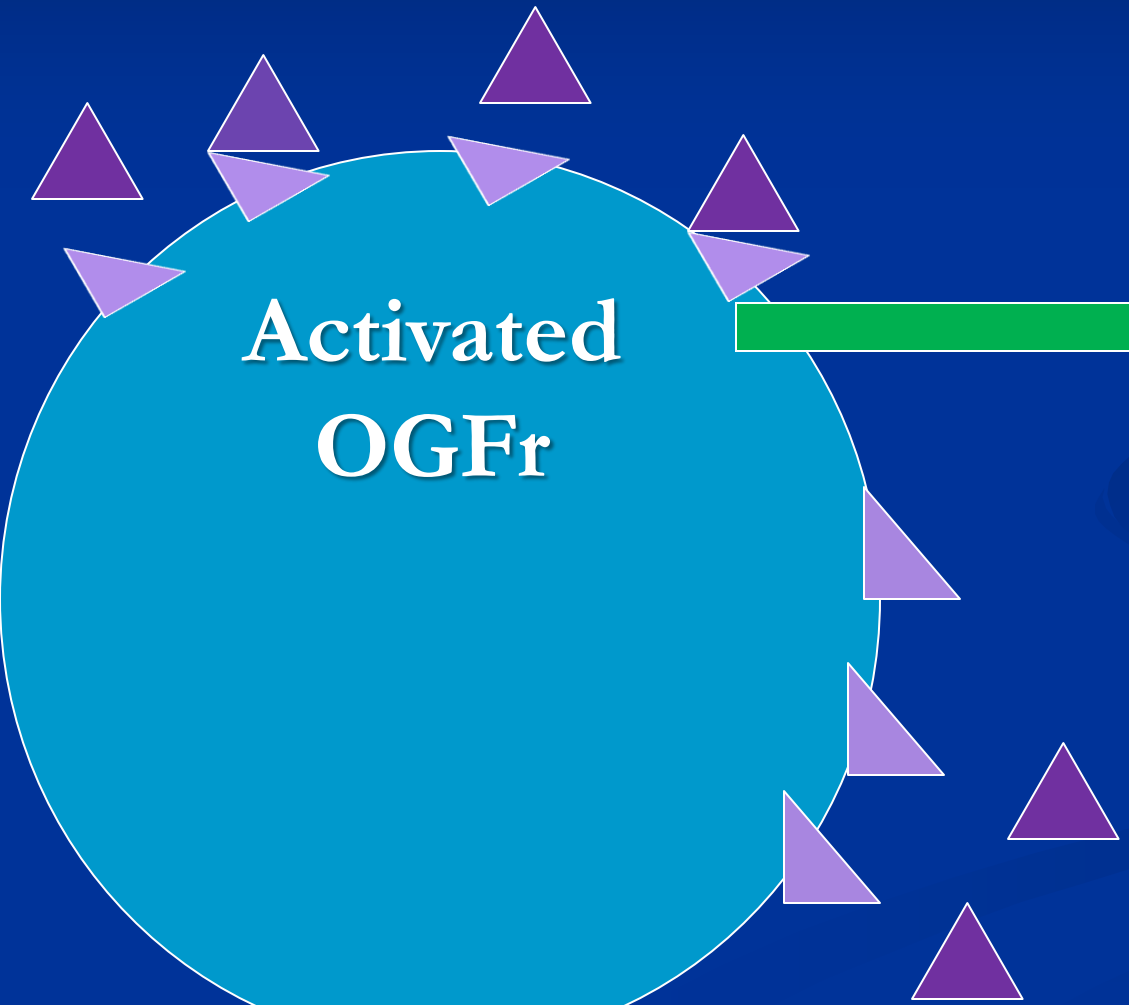
Opioid Growth Factor (OGF)

- Met-Enkephalin = Opioid Growth Factor
- OGF binds to the Opioid Growth Factor Receptor (OGFr)
- Two elements are required for health: opioid production and cell interaction

LDN MOA

- Naltrexone displaces endorphins bound to **OGF** receptors
- Affected cells become deficient in **OGF** and results in:
  - Receptor production and sensitivity is increased to capture more **OGF**
  - Production of **OGF** is increased to compensate for the perceived shortage of **OGF**

OGF & OGFr



- Lymphocytes production controlled
- Endothelial cell barrier maintained

Narcotics, LPS, Thrombin & OGFr

"Breaking Bad"

Src and pY production leads to endothelial cell barrier disruption

LDN MOA

- Naltrexone displaces endorphins from **OGFr**

- Cells become deficient in **OGF** ⇒
  - OGFr production increased
  - OGFr sensitivity increased

LDN & OGFr

Cells perceive OGFr reduction

LDN MOA

- LDN blocks OGFr only for a few hours
- This leads to a rebound effect
  - Production and utilization of OGF is greatly increased.

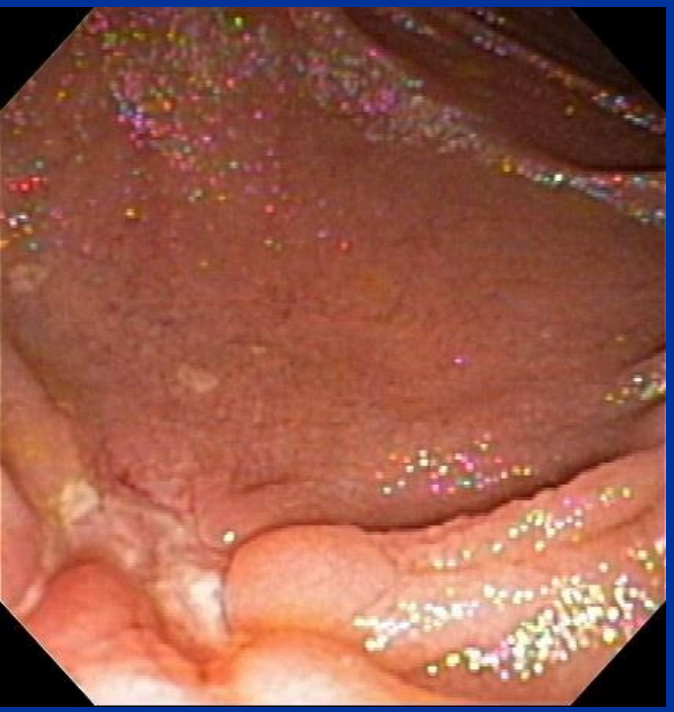
LDN & OGFr

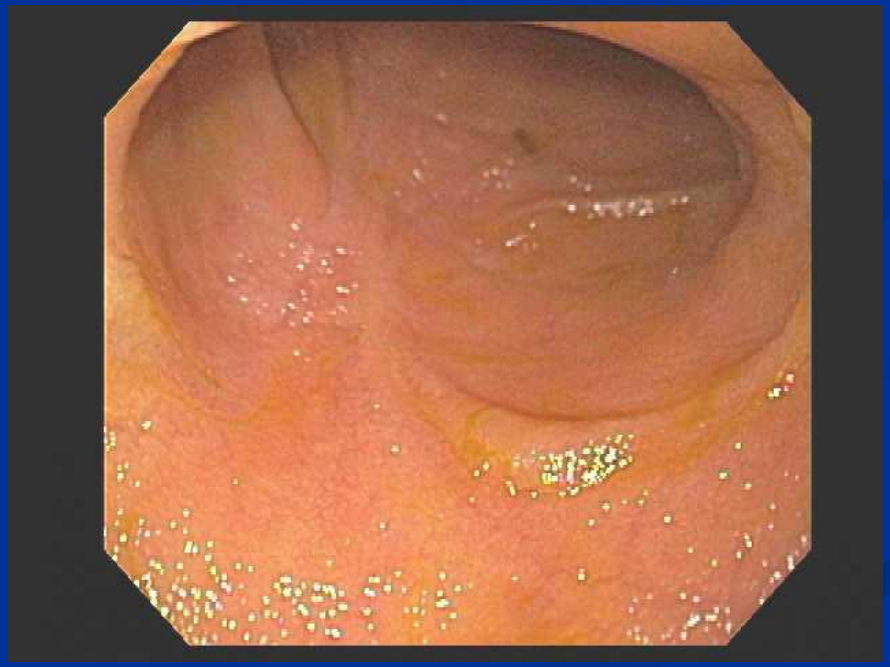
More OGF and OGFr lead to decreased T- and B-cell activity and less permeability

LDN MOA

- LDN blocks the OGF receptors only for a few hours – leads to a *rebound effect*; in which both the production and utilization of OGF is greatly increased.
- Endorphins now interact with the more-sensitive and more-plentiful receptors and assist in regulating cell growth and immunity

Crohn's disease





Weinstock 2013.

Crohn's disease

- Smith. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol 2007;102:820-828.
- Shannon. Low-dose naltrexone for treatment of duodenal Crohn's disease in a pediatric patient. Inflamm Bowel Dis 2010;16:1457.
- Smith. Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study. J Clin Gastroenterol 2013;47:339-345.

Crohn's disease - RCT

- LDN as adjunctive therapy
- Biologic therapy was an exclusion
- 88% of LDN (N=18) had 70-point decrease in CDAI scores vs. 40% of control (N=16)
- After 12 wks, 78% of LDN had response in CD endoscopy index severity score vs. 28% controls
- 33% of LDN had endoscopic remission vs. 8% controls

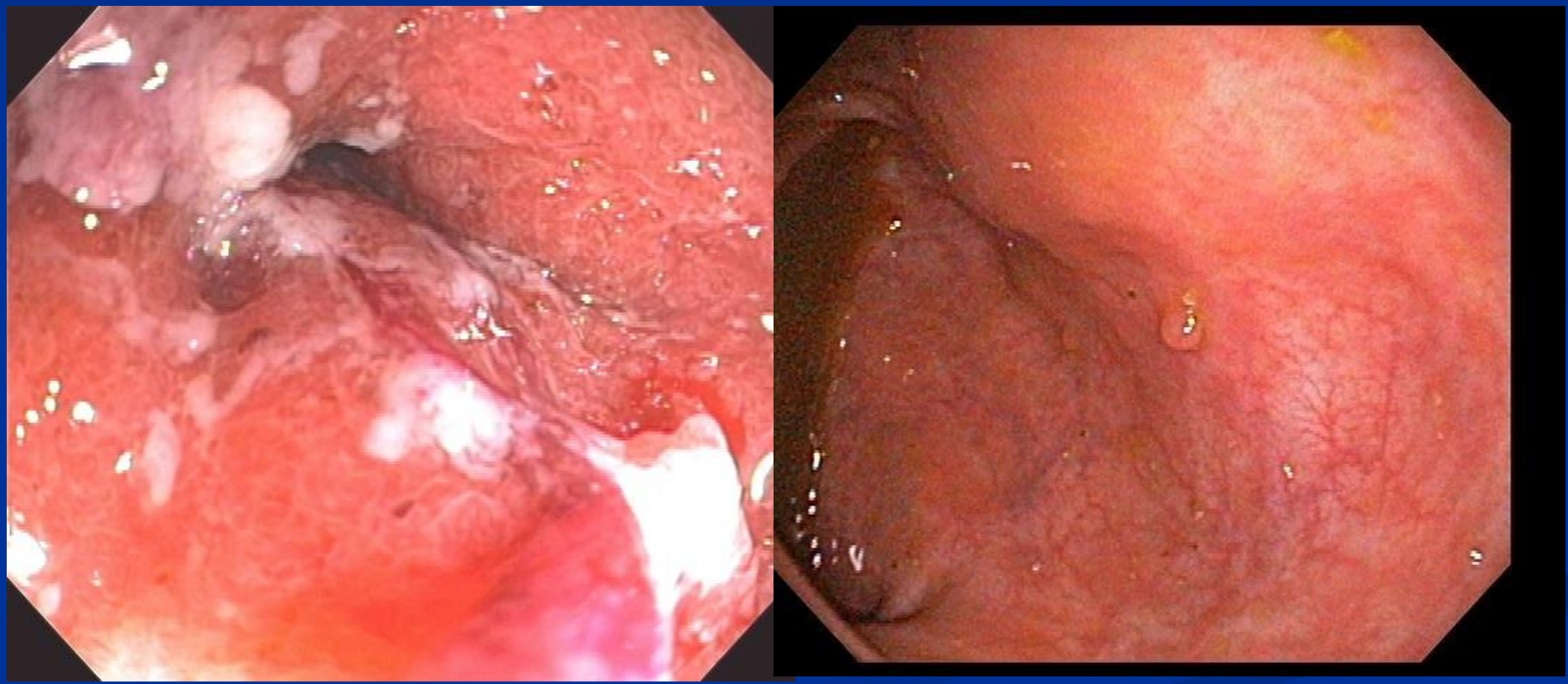
Smith et al. Dig Dis Sci 2011;56:2088-2097.

Crohn's disease

- Open label study: 4.5 mg LDN in moderate to severe CD (N=33)
- Failing 5-ASA followed by 6-MP and/or IFX
- LDN Rx: 40 ±43 wks (max 200 wks)
- 5 withdrew d/t adverse events (mild-moderate)
- Positive clinical response in 15/33 pts
- 11 of 15 responders: C-scope before and after Rx: 8 complete healing, 1 partial healing and 2 unchanged

Weinstock 2013.

Ulcerative colitis



Weinstock 2013.

Ulcerative colitis

- Open label study: 4.5 mg LDN in moderate to severe UC (N=12)
- Failing 5-ASA followed by 6-MP and/or IFX
- LDN Rx: 46 ±75 wks (max 270 wks)
- 1 withdrew d/t insomnia
- Positive clinical response in 6/12 pts
- 2 of 6 responders: C-scope before and after Rx
  - 2 complete healing

Weinstock 2013.

IBS and LDN

- N=42 IBS; Open-label Rx 0.5 mg/day/4 wks
- Evaluation every 4 wks
- Pain-free days and global scores
- Global improvement in 76%
- Weekly # pain-free days increased from 0.5/-1 to 1.25+/2.14 (P=0.011)

Kariv. Dig Dis Sci 2006;51:2128-33.

Idiopathic IBS – St. Louis preliminary report

- N=13 IBS; Open-label Rx 2.5 mg/day
- IBS-d 3; IBS-a 5; IBS-c
- 2 markedly improved
- 5 moderately improved
- 2 unchanged
- 3 markedly worse

Ploesser J, Weinstock LB, Thomas E.
Internat J Pharm Compound 2010:171-173.

IBS-SIBO – St. Louis preliminary report

- N=85 IBS; Open-label Rx 58 w 2.5 mg/day and 27 w 2.5 mg twice a day
- 18% markedly improved
- 38% moderately improved
- 11% mildly improve
- 27% unchanged
- Rest worse

Ploesser J, Weinstock LB, Thomas E.
Internat J Pharm Compound 2010:171-173.

Chronic constipation – St. Louis preliminary report

- N=12; Open-label Rx 2.5 mg twice a day
- 58% markedly improved
- 1% moderately improved
- 25% mildly improve
- 1% unchanged

Ploesser J, Weinstock LB, Thomas E.
Internat J Pharm Compound 2010:171-173.

LDN and MS: 1st study

- 6 mo trial in 40 pts
  - 1° end points: safety and tolerability
  - 2° outcomes: efficacy on spasticity, pain, fatigue, depression and QOL
- 5 dropouts and 2 major AEs
- Significant reduction of spasticity resulted
- Disability progressed in 1
- Beta-endorphins increased during trial

Gironi et al. Mult Scler 2008;14:1076-83.

LDN and MS Mental QOL

- DB, PC, double-masked, X-over study: 8 wks 4.5mg/qHS LDN on QOL
- N=80
- 20 drop outs - multiple reasons (not AE)

Cree et al. Ann Neuro 2010;68:145-50.

LDN and MS Mental QOL (cont.)

- Mental component general health survey:
  3.3-pt improvement ($p = 0.04$)
- Mental health inventory:
  6-pt improvement ($p < 0.01$)
- Pain effects scale:
  1.6-pt improvement ($p = .04$)
- Perceived deficits questionnaire:
  2.4-pt improvement ($p = 0.05$)
- LDN improved MS QOL. Subject dropout reduced statistical power

LDN and MS QOL: negative short study

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- 17-week R, DB, PC parallel-group, crossover : 96 pts with relapsing-remitting or secondary progressive disease

- Primary outcome: scores of physical & mental health obtained in the middle and end of study

Sharafaddinzadeh et al. Mult Scler. 2010;16:964-9

LDN and MS QOL: negative short study

- No diff in pain, energy, emotional well-being, social, cognitive, sexual functions, role limitation due to physical and emotional problems, health distress
- LDN is a relatively safe therapeutic option but efficacy is under question and probably a long duration trial is needed in the future

Sharafaddinzadeh et al. Mult Scler. 2010;16:964-9

MS – latest LDN study

- A randomized placebo-controlled, crossover-design study of the effects of low dose naltrexone on the multiple sclerosis quality of life inventory

- This study is complete but not yet published

Zagon et al, 2013

LDN and Fibromyalgia

- Single-blind, X-over trial baseline (2 wks), placebo (2 wks), drug (8 wks), washout (2 wks)
- N=10 women
- Daily symptom severity daily
- q2wk testing for mechanical, heat and cold pain sensitivity

Younger and Mackey. Pain Med 2009;10:663-72

LDN and Fibromyalgia (cont.)

- LDN reduced FMS symptoms in all 10 pts with a greater than 30% reduction of symptoms over placebo
- Mechanical and heat pain thresholds were improved by the drug
- AE: insomnia & vivid dreams rare (minor and transient)
- Increased ESR assoc. w/ greatest reduction of symptoms

Younger and Mackey. Pain Med 2009;10:663-72

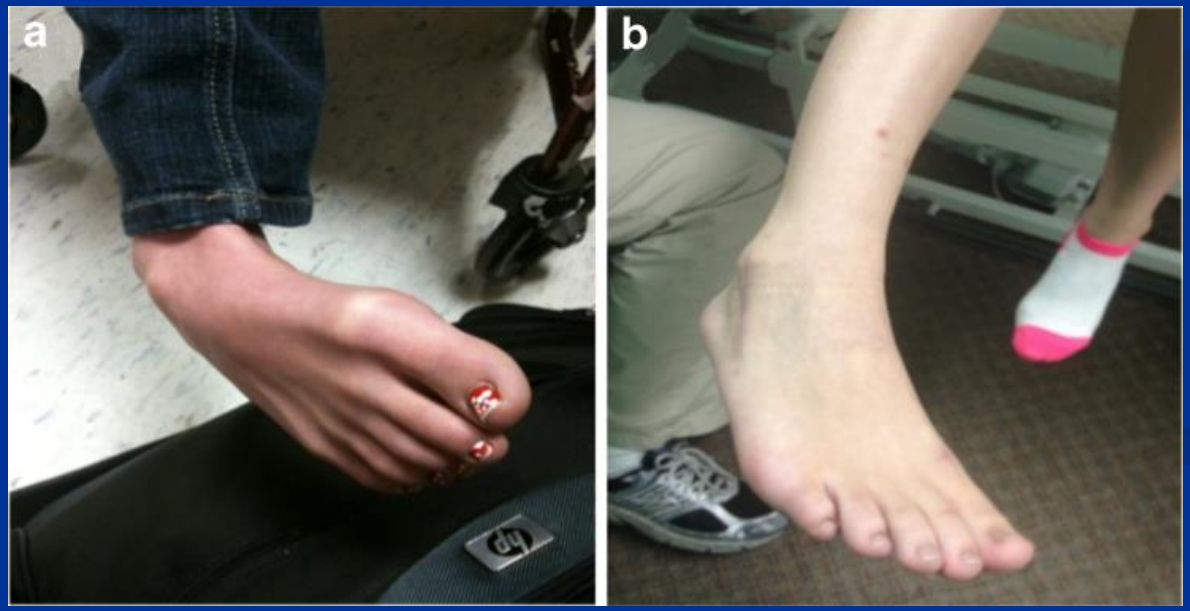
Complex Regional Pain Syndrome

- Reflex Sympathetic Dystrophy or Neurovascular Dystrophy
- Severe pain, swelling & changes in extremities
- Spreads throughout the body in 92%
- Neurogenic inflammation, pain sensitization vasomotor dysfx & aberrant response to tissue injury

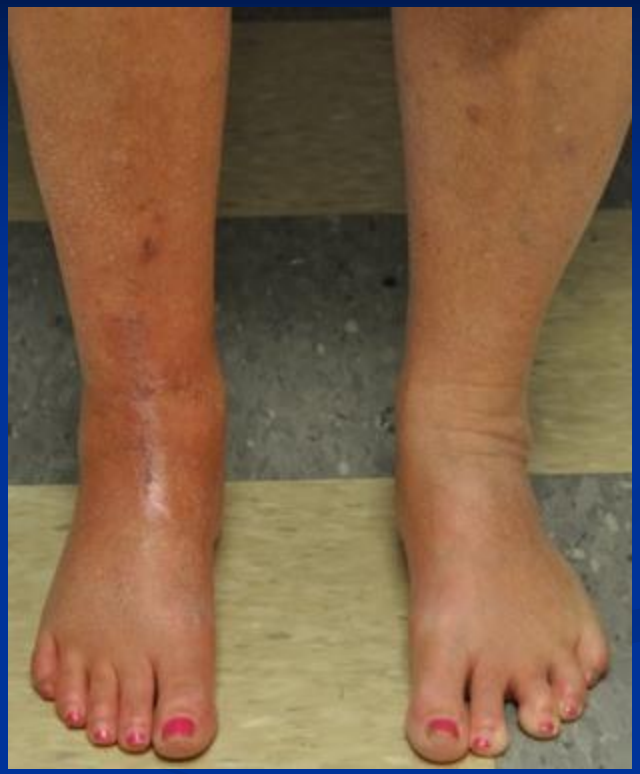
Complex Regional Pain Syndrome

Report:
2 cases with improvement with LDN

Chopra. Neuroimmune Pharmacol 2013;8:470-6.



Complex Regional Pain Syndrome



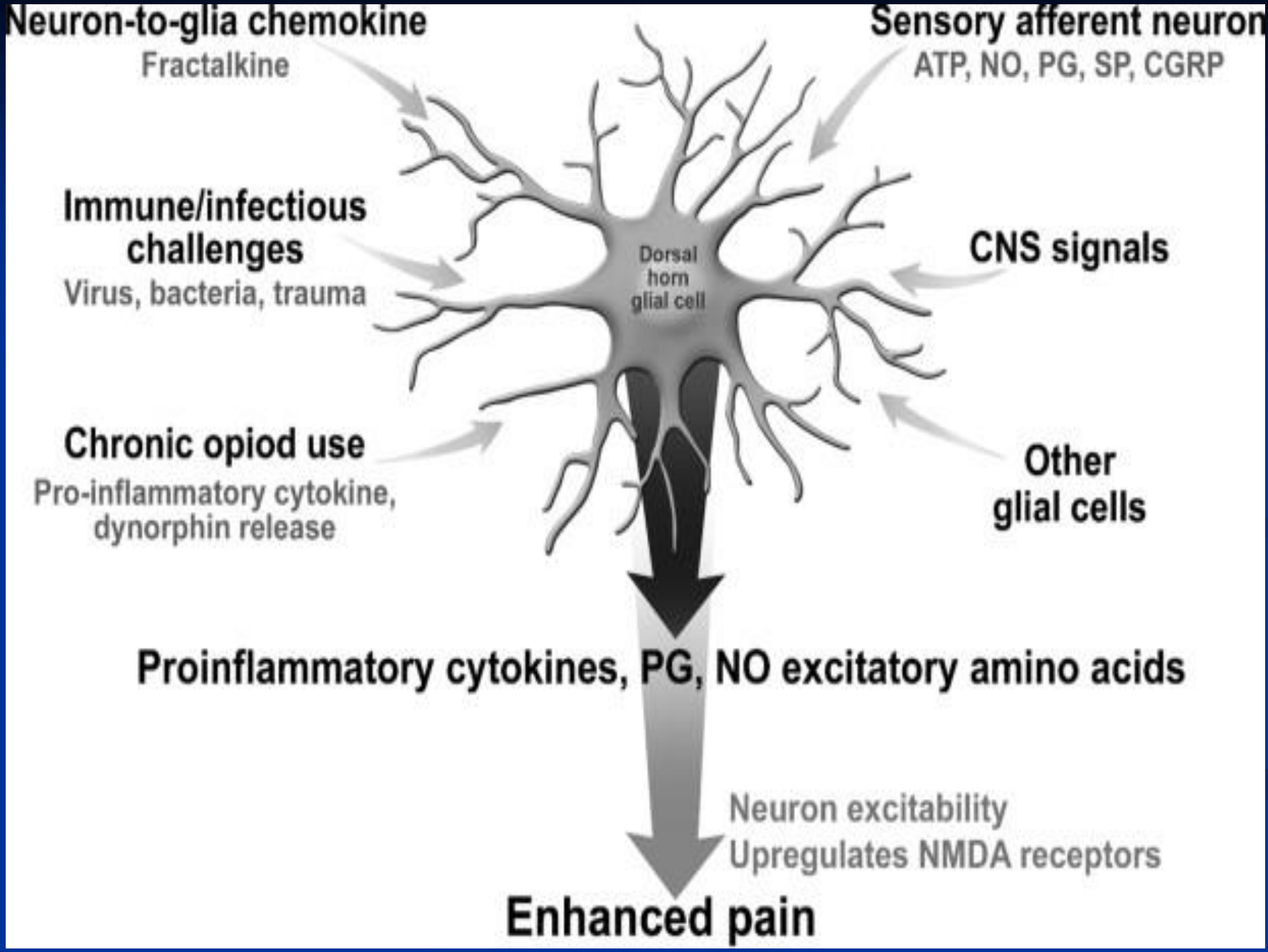
42 y.o. WF

12 yr Hx of CRPS
pain, flushing, shiny
painful skin

Only help with versed
during sympathectomy
Narcotics made pain worse
Was on 2800 mg Neurotin & 8 Viocodin/d

40 y.o. WF w CRPS

- Currently on alprazolam, Wellbutrin 450 mg and occ Tramadol
- 4.5 mg LDN prescribed
- “I am thrilled as I usually have more CRPS pain with weather changes. It snowed here in Indiana and I have minimal pain which is strangely wonderful “


Neuron-to-glia chemokine
Fractalkine
Sensory afferent neuron
ATP, NO, PG, SP, CGRP
Immune/infectious challenges
Virus, bacteria, trauma
Dorsal horn glial cell
CNS signals
Chronic opiod use
Pro-inflammatory cytokine, dynorphin release
Other glial cells
Proinflammatory cytokines, PG, NO excitatory amino acids
Neuron excitability
Upregulates NMDA receptors
Enhanced pain

Narcotic inflammatory pathways

- Increased neuron excitability and up-regulate N-methyl-D-aspartic acid (NMDA) receptors lead to enhanced pain
- Activation of this mechanism by release of:
  - Adenosine triphosphate, Nitric oxide, Prostaglandins, Substance P and Calcitonin g–related polypeptide
- Worsened by immune challenges or infections

Cancer and LDN

Publications by Zagon et al.

General changes in cancer cells

- Ovarian cancer
- Breast cancer
- Head and neck cancer
- Prostate cancer

Cancer and LDN: tissue model

- Opioid receptor blockade in ovarian CA cells
- Short-term Met(5)]-enkephalin and receptor responsible for MAO of NTX on cell proliferation
- NTX up-regulated OGF and OGFr at translational level
- Required p16 and/or p21 cyclin-dependent inhibitory kinases
- Not dependent on cell survival (necrosis, apoptosis)

Donahue RN, McLaughlin PJ, Zagon IS. Exp Biol Med 2011;236:1036-50.

Basic science studies of cancer

- Donahue RN. The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. Gynecol Oncol 2011;122:382-8.
- Donahue RN. Cell proliferation of human ovarian cancer is regulated by the opioid growth factor-opioid growth factor receptor axis. J Physiol Regul Integr Comp Physiol. 2009;296:R1716-25.
- Avella DM.The opioid growth factor-opioid growth factor receptor axis regulates cell proliferation of human hepatocellular cancer. Am J Physiol Regul Integr Comp Physiol. 2010;298:R459-66.
- McLaughlin PJ. Growth inhibition of thyroid follicular cell-derived cancers by the opioid growth factor (OGF) - opioid growth factor receptor (OGFr) axis. BMC Cancer. 2009;9:369
- McLaughlin PJ. Modulation of the opioid growth factor ([Met(5)]-enkephalin)-opioid growth factor receptor axis: novel therapies for squamous cell carcinoma of the head and neck. Head Neck 2012;34:513-9.
- Zagon IS. Opioid growth factor - opioid growth factor receptor axis inhibits proliferation of triple negative breast cancer. Exp Biol Med 2013;238:589-99

Human study with cancer

- Pancreatic cancer – combined in 3 pts with I.V. alpha-lipoic acid - stabilization and/or regression of metastatic disease (4, 5 and 39 months)
- One of the 3 patients also had reversal of signs and symptoms concomittant B-cell lymphoma

Berkson et al. Integr Cancer Ther. 2007;6:293-6.

LDN side effects

- 10% in CD studies
- 40% in GI disorder study
  - 67% return of AE surveys
  - Included many IBS patients
- Oral methyl-naltrexone should have low AE profile

Ploesser J, Weinstock LB, Thomas E.
Low Dose Naltrexone: Side Effects and Efficacy in Gastrointestinal Disorders.
Internat J Pharm Compound 2010:171-173.

LDN side effects: neurologic

- Anxiety 15.7%
- Drowsiness 11.6%
- Headache 11.6%
- Insomnia 8.3%
- Muscle pain 8.3%
- Vivid dreams 5.0%
- Mood change 3.3%
- Trouble concentration 1.7%

Ploesser J, Weinstock LB, Thomas E. Internat J Pharm Compound 2010:171-173.

LDN: additional side effects

- Nausea 12.4%
- Abd. Pain 11.6%
- Diarrhea 8.3%
- Anorexia 8.3%
- Rash, hot flashes, weight gain 0.1% each

Ploesser J, Weinstock LB, Thomas E.
Low Dose Naltrexone: Side Effects and Efficacy in Gastrointestinal Disorders.
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Conclusions

- "Breaking Bad": Endorphins good, Narcotics bad
- High quality studies are needed
- Methyl-naltrexone is a promising treatment for several GI and SIBO related conditions
- Methyl-naltrexone should have lower AE profile but does not cross BBB so it may not be effective for all MORA-responsive disorders