PainWeek®

Low Dose Naltrexone: An Alternative to Treating Neuropathic Pain

Neel Mehta, MD

Disclosure

- Grant/Research Support: Nevro
- Honoraria: Nevro
- Off-label use will be discussed in this presentation.

Learning Objectives

- Describe the role of low dose naltrexone in the treatment of neuropathic pain.
- Recognize novel treatments in development and emerging evidence for role of currently available or repurposed treatments in the treatment of neuropathic pain.
- Describe where these novel or re-emerging treatments fit within current evidence based treatment algorithms.

Self-Assessment Question 1

What mechanism of action does LDN work on?

A. Inhibition of Pro-inflammatory Cytokines
B. Increase Endogenous Enkephalin and Endorphins
C. Antagonize Toll-Like Receptor 4
D. All of the Above
E. None of the Above

Self-Assessment Question 2

What dose range is LDN effective at?

A. 1-4.5mg
B. 100-500mcg
C. 2-25mcg
D. 50mg
E. A-C only

Common Use of Naltrexone

- 1963 naltrexone is an opioid antagonist first synthesized
- 1984 approved for opioid dependence
- 1995 approved for alcohol abuse disorders
- Typical dosages for opioid addiction is **50.0-100.0** mg daily, and 50mg tablets (ReVia, Depade) available commercially

Expanded Clinical Uses of LDN

- Fibromyalgia
- Crohn’s disease
- Multiple sclerosis
- Complex regional pain syndrome
- Neuropathic pain
- Cancer
- Hailey-Hailey disease
- Diabetic neuropathy
- Psychiatric conditions

Low Dose Naltrexone (LDN)

- Naltrexone and its active metabolite 6-β-naltrexol competitive antagonists at:
  - μ-opioid and κ-opioid receptors
  - lesser extent at δ-opioid receptors

- Low-dose Naltrexone is using a sub-therapeutic dose of naltrexone for that used in opioid addiction. Typical dosages range around 1mg-6mg, typically 4.5mg.

- At low dosages, naltrexone exhibits a paradoxical effect which includes analgesia and anti-inflammatory actions.

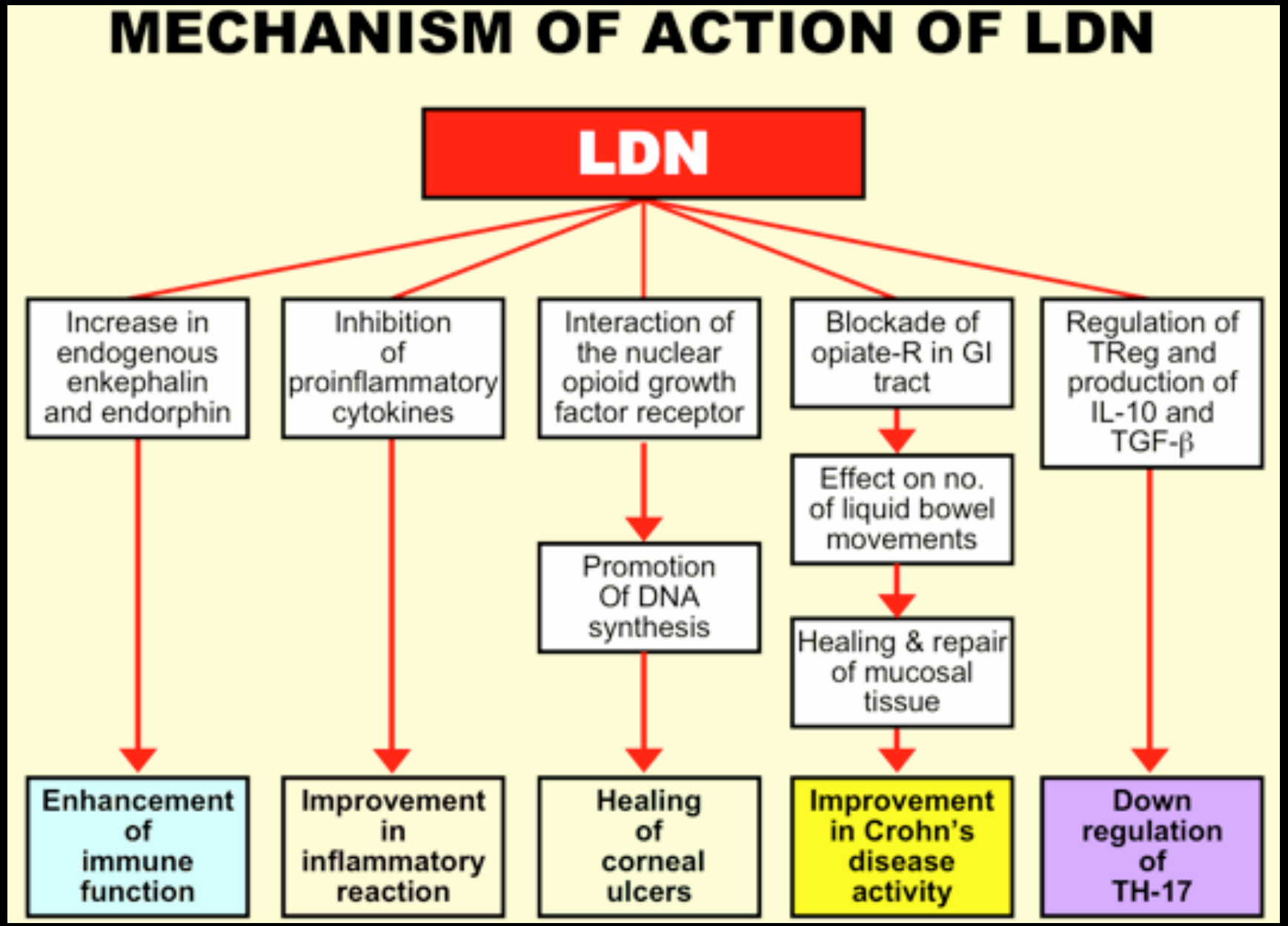
  - Cannot use with typical μ-opioid
    - However I have used with buprenorphine, tramadol before

LDN Mechanism of Action

1. Inhibiting opioid receptors at low doses might cause the body to increase production of endorphins and upregulate the immune system

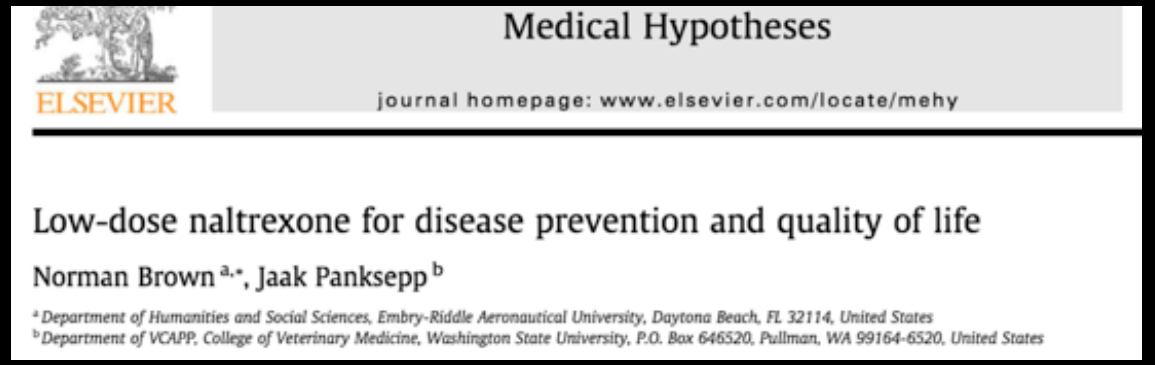
2. Antagonize Toll-like receptor 4 that are found on macrophages, including microglia, and any reported anti-inflammatory effects

– Microglia are found in central nervous system immune.
  - When activated, they produce inflammatory and excitatory products causing pain
  - pro-inflammatory cytokines
  - substance P
  - nitric oxide
  - and excitatory amino acids


MECHANISM OF ACTION OF LDN
LDN
Increase in endogenous enkephalin and endorphin
Inhibition of proinflammatory cytokines
Interaction of the nuclear opioid growth factor receptor
Blockade of opiate-R in GI tract
Regulation of TReg and production of IL-10 and TGF-β
Effect on no. of liquid bowel movements
Promotion Of DNA synthesis
Healing & repair of mucosal tissue
Enhancement of immune function
Improvement in inflammatory reaction
Healing of corneal ulcers
Improvement in Crohn's disease activity
Down regulation of TH-17

Mechanism of Action: “Opioid Rebound” Hypothesis

- LDN produces a small and transient opioid blockade, causing upregulation of endogenous opioids and opioid receptors.
- As compared to dosages of 0.5mg/kg, doses of 0.08mg/kg will only block mu opioid receptors for a few hours
  - Hence, if taken at night, patient will theoretically wake up with a rebound of their own endogenous opioid systems.
- Animal studies show that LDN elevate mu opioid receptor density, and in MS patients, increase the circulating beta-endorphins.



Mechanism: Dextro-Naltrexone

- The glial cell theory of naltrexone is supported by research on dextro-naltrexone.
- The commercially used naltrexone is the levo enantiomer of naltrexone, which has the affinity for opioid antagonism.
- Dextro-naltrexone is active at microglia receptors but has no activity at opioid receptors.
- Theoretically, higher dosages can be used with higher levels of microglial suppression,
- Can be co-administered with opioid analgesics.

Ultra-Low Dose Naltrexone (UDN)

- Microgram, nanogram, and picogram doses, that are co-administered with opioid analgesics with the goal of increasing pain relief and reducing side effects.

- 25-100mcg general range
  - Ok to use with opioids

  - Ultra-low-dose naltrexone (range of 2 to 25 ug) was researched as a possible combination therapy therapy with opioids
    - improve efficacy, increase duration, and alleviate tolerance and withdrawal, and decrease addiction.

UDN and Opioids

- Chindalore, et al., 2005: 350-patient Phase II clinical trial comparing (oxycodone+ultra-low-dose naltrexone) and oxycodone showed better and longer analgesia.

- Crain and Shen 1995; Powell et al., 2002: alleviation of opioid tolerance with ultra low-dose naltrexone

- Further studies showed a marginal difference between combination therapy with opioid and ULDN and opioid alone.

Evidence in Various Disease States

Fibromyalgia

Arthritis Rheum. 2013 Feb;65(2):529-38. doi: 10.1002/art.37734.

Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels.

Younger J[1], Noor N, McCue R, Mackey S.

- Randomized, double-blind, placebo-controlled, crossover study with 31 women.
- Participants received 4.5mg of oral naltrexone daily during the drug phase of the trial.
- Results: 28.8% reduction in baseline pain with LDN versus 18% reduction with placebo (P=0.045), with improved mood. No improvement in fatigue or sleep
- 32% of participants med the criteria for positive response (significant reduction in pain scale plus reduction in fatigue or sleep problems) during LDN versus the 11% response rate during placebo therapy (P=0.05)
- No difference in tolerability or side effect profile.

Crohn’s Disease

Cochrane Database Syst Rev. 2014 Feb 21;(2):CD010410. doi: 10.1002/14651858.CD010410.pub2.

Low dose naltrexone for induction of remission in Crohn's disease.

Segal D[1], Macdonald JK, Chande N.

- Primary outcome was induction of clinical remission defined by a Crohn's disease activity index.
- Two studies (total 46 subjects).
  - One study for efficacy and safety of 12 weeks of LDN (4.5mg/day) treatment compared to placebo in adult patients (N=34).
    - Remission reported in 30% vs. 18%, no statistically significant, however there was a clinical and endoscopic response.
  - 2nd study for 8 weeks of LDN of 0.1mg/kg, max 4.5mg/day treatment compared to placebo in pediatric patients (N=12),
    - 25% of LDN achieved clinical remission compared to 0% in the placebo-controlled group.
- -Conclusion is that there is insufficient evidence to conclude the efficacy of LDN.

Multiple Sclerosis

Mult Scler. 2010 Aug;16(8):964-9. doi: 10.1177/1352458510366857. Epub 2010 Jun 9.

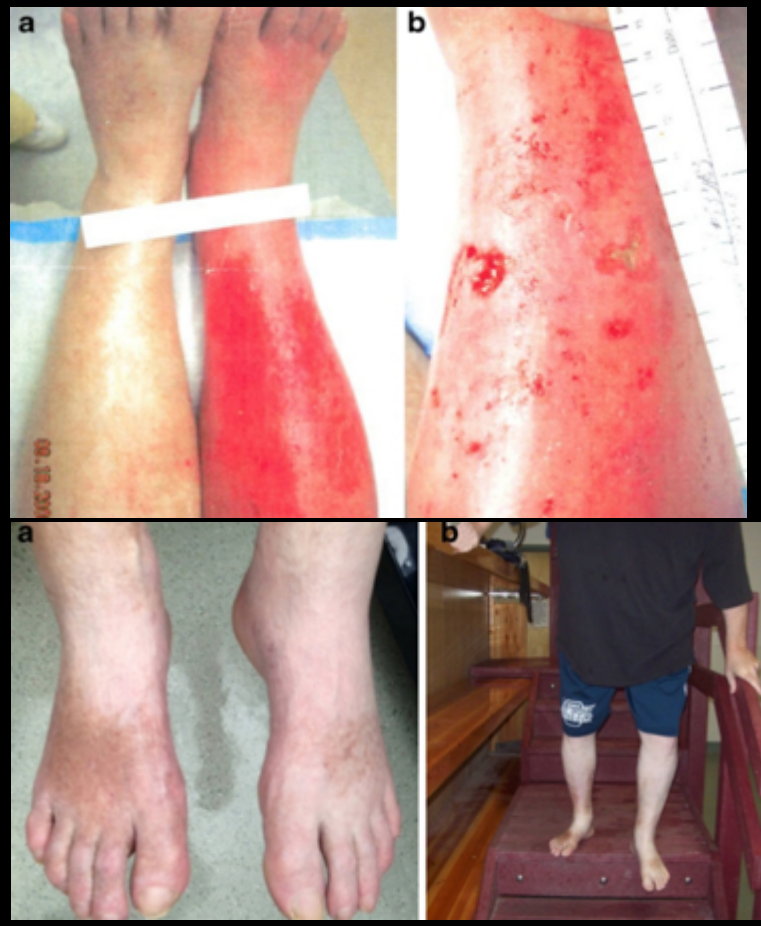
The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial.

Sharafaddinzadeh N[1], Moghtaderi A, Kashipazha D, Majdinasab N, Shalbafan B.

- 17 week randomized, double-blind, placebo-controlled, parallel-group, crossover-design clinical trial conducted in two universities.
- 96 patients with relapsing-remitting or secondary progressive MS for longer than 6 months duration
- Primary outcome was comparison of the scores of physical and mental health
- No statistically significant difference in overall QoL
- Conclusion: LDN is a safe therapeutic option for MS, but efficacy is unknown

Case 1: Complex Regional Pain Syndrome (CRPs)

- 48-year-old male with right leg injury and infection
- CRPS spread to upper extremities by 2007, with blisters and ulceration in his right lower extremity.
- By 2009, he was no able to ambulate without assistance.
- Failed opioids, pregabalin, duloxetine, ketamine.
- Started on 4.5mg LDN nightly
- Improvement in color, temperature, allodynia, edema, physical activity, energy levels, dystonic spasms, with NRS from 8/10 to 5-6/10 (2 months after initiation)



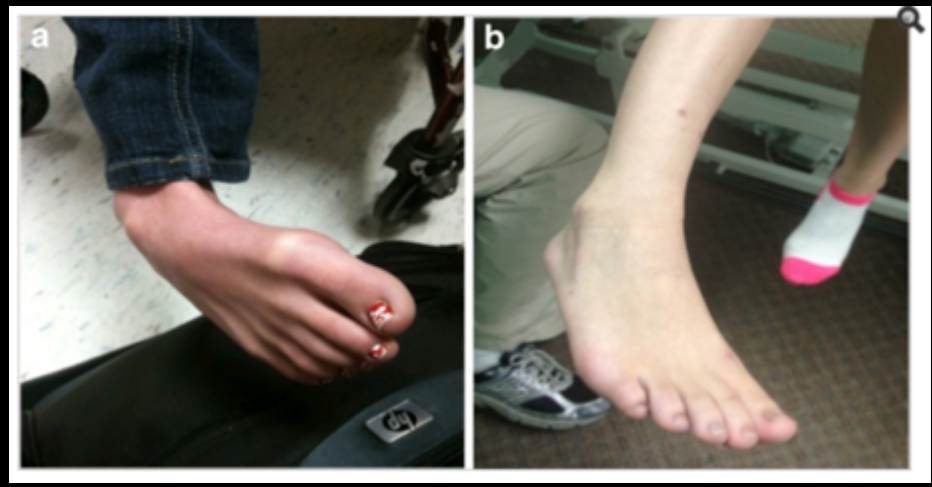
J Neuroimmune Pharmacol. 2013 Jun; 8(3): 470–476. PMCID:
Published online 2013 Apr 2.
doi: 10.1007/s11481-013-9451-y

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

Pradeep Chopra and Mark S. Cooper

Case 2: Complex Regional Pain Syndrome (CRPS)

- 12-year-old female with EDS, dysautonomia, seizures, gastritis, mitochondrial dysfunction, asthma, with repeated right shoulder dislocations and right ankle dislocations.
- CRPS of the right lower extremity in 2009, and spasms in the upper extremities in 2009. Associated with color change, temperature change, allodynia, nail distortion.
- She was started on LDN of 3mg daily and sublingual ketamine. The LDN was increased to 4.5mg, with NRS dropping from 7-10/10 to 3-5/10.
- No spreading of CRPS despite multiple surgical procedures, and CRPS symptoms have resolved completely as of 18 months post treatment initiation.



J Neuroimmune Pharmacol. 2013 Jun; 8(3): 470–476. PMCID
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Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN)

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Case Report: Diabetic Neuropathy

Off-Label, Low-Dose Naltrexone for Refractory Painful Diabetic Neuropathy
Debasish Hota, MD, DM Anand Srinivasan, MD Pinaki Dutta, MD, DM Anil Bhansali, MD, DM Amitava Chakrabarti, MD, DM. *Pain Medicine*, Volume 17, Issue 4, 1 April 2016, Pages 790–791, https://doi.org/10.1093/pm/pnv009
Published: 25 November 2015

- 76-year-old male with a 30-year history of type-2 diabetes and 7 years of diabetic neuropathic symptoms presented in the endocrinology clinic with complaints of burning pain in both legs below the mid-calf level
- 4mg LDN qhs showed 90% improvement in pain followed for 2 years

- Case Report: Diabetic Neuropathy
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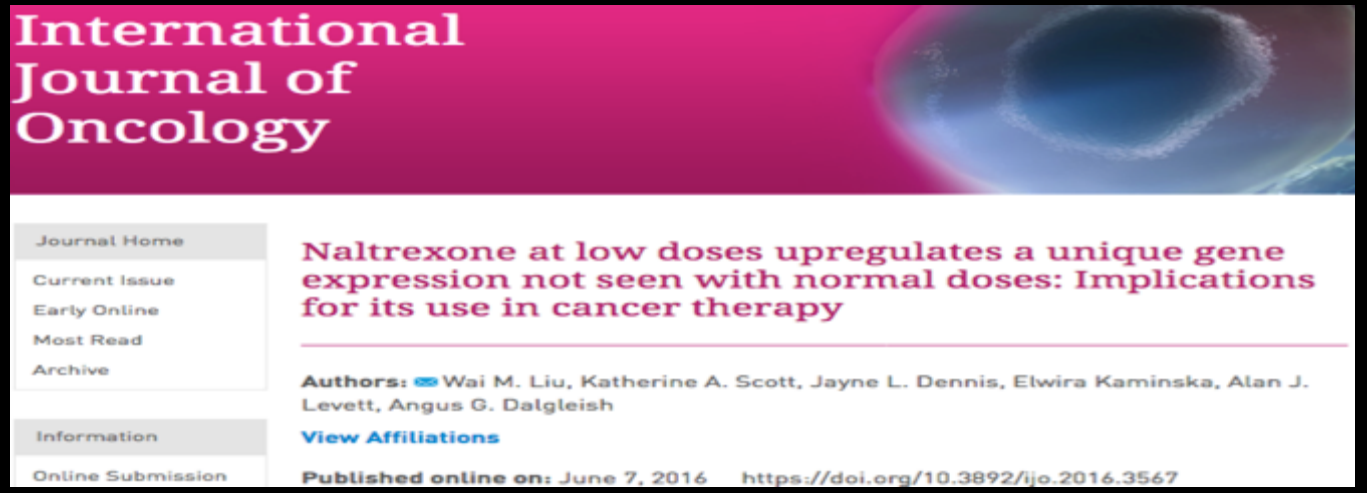
Neuropathic Corneal Pain

- Ophthalmology. 2017 Nov;124(11S):S34-S47. doi: 10.1016/j.ophtha.2017.08.004.
- Neuropathic Corneal Pain: Approaches for Management.
- Dieckmann G1, Goyal S2, Hamrah P3.

- Mentioned as 2nd line of algorithm for treatment
- Dosing similar to Fibromyalgia (1-4.5mg)
- No evidence cited

LDN and Cancer



Opioid Growth Factor, LDN, Cancer

- LDN inhibits cell proliferation *in vivo*
- Established a tissue culture model of LDN and HDN using short-term and continuous opioid receptor blockade, respectively, in human ovarian cancer cells
- Found duration of opioid receptor blockade determines cell proliferative response.
- Also detected in cells representative of pancreatic, colorectal and squamous cell carcinomas.
- The opioid growth factor (OGF; [Met^5]-enkephalin) and its receptor (OGFr) were responsible for mediating the action of NTX on cell proliferation.

Case Series in CHOIR

- 27 patients with chronic “central” pain given LDN (1-4.5mg)
- A retrospective chart review confirmed use of LDN at Time 1 (31 and 60 days after LDN) and Time 2 (61 and 90 days after LDN prescription).
- Wilcoxon Signed Rank Test (WSRT) analyses suggested that patients taking LDN reported significantly lower average pain scores, lower “lowest” pain scores, and improved physical function from baseline to Time 2 ($p < 0.05$).
- Depression scores were also significantly reduced from baseline to Time 1 and from baseline to Time 2 ($p < 0.05$).
- The significant findings of decreased average pain scores and depression and improved physical function

Journal of Pain April 2016 Volume 17, Issue 4, Supplement, Page S79 A novel glial cell inhibitor, low dose naltrexone, reduces pain and depression, and improves function in chronic pain: A CHOIR study. K. Noon, J. Sturgeon, M. Kao, B. Darnall, S. Mackey

Improved Energy or Pain Relief?

- Patients getting LDN given Dolo-test before and after 2-6 months of LDN.
- 26 patients on LDN and no other new treatment.
- Results: The mean percentage reduction in VAS was calculated:
  - Pain: 17%; problems with light physical activities: 12%; strenuous physical activities: 10%; job problems: 8%; reduced energy and strength: 23%; low spirit: 13%; reduced social activity: 15%; sleep problems: 12%
- Pain relief associated with more energy and strength
  - highest change in score, even higher than pain.

A. Bendiksen. Pain Clinic, Friklinikken, Give, Denmark
Low Dose Naltrexone (LDN): New in the treatment of chronic pain syndromes. What really matters – reduced pain or increased energy? Abstract. Journal of the Neurological Sciences 357 (2015)

Future Directions

- Assess the antiallodynic synergistic interaction between gabapentinoids and naltrexone in rats.
- Oral administration of pregabalin (ED_{50} = 2.79 ± 0.16 mg/kg) or gabapentin (ED_{50} = 21.04 ± 2.87 mg/kg) as well as intrathecal naltrexone (ED_{50} = 0.11 ± 0.02 ng) reduced in a dose-dependent manner tactile allodynia in rats.
- Maximal antiallodynic effects (~100%) were reached with 30 mg/kg of pregabalin, 300 mg/kg of gabapentin or 0.5 ng of naltrexone.
- Co-administration of pregabalin or gabapentin and naltrexone in a fixed-dose ratio (1:1) remarkably reduced spinal nerve ligation-induced tactile allodynia showing a synergistic interaction.
- Combinations of pregabalin or gabapentin and ultra-low doses of naltrexone are able to reduce tactile allodynia in neuropathic rats with lower doses that those used when drugs are given individually and with an improved side effects profile.

Drug Dev Res. 2017 Dec;78(8):371-380. doi: 10.1002/ddr.21409. Epub 2017 Sep 3.
Ultra-Low Doses of Naltrexone Enhance the Antiallodynic Effect of Pregabalin or Gabapentin in Neuropathic Rats.
Pineda-Farias JB[1], Caram-Salas NL[2], Salinas-Abarca AB[1], Ocampo J[3], Granados-Soto V[1].

Future Directions

- 10-week, single-blind, crossover trial
- Tested immune effects of eight weeks of oral administration of (LDN).
- 8 women average age of 46 years, symptom severity of 62 out of 100, and symptom duration of 14 years.
- LDN was associated with reduced plasma concentrations of interleukin (IL)-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-27, interferon (IFN)-α, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, and granulocyte-colony stimulating factor (G-CSF).
- 15% reduction of FM-associated pain and an 18% reduction in overall symptoms.
- LDN treatment in fibromyalgia is associated with a reduction of several key pro-inflammatory cytokines and symptoms.

Biomedicines. 2017 Apr 18;5(2). pii: E16. doi: 10.3390/biomedicines5020016.
Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia.
Parkitny L[1], Younger J[2].

Contrave: A combination product of naltrexone sustained release (SR) and bupropion SR

- The mechanism by which the combination of naltrexone SR/bupropion SR induces weight loss is not understood.
- Research on CNS pathways that regulate food intake and body weight has identified the hypothalamic melanocortin system and the mesolimbic reward system. These systems are the target of this combination.
- Pro-opiomelanocortin (POMC)-producing neurons in the hypothalamus release α–melanocyte-stimulating hormone (MSH) and β-endorphin. α–MSH mediates the anorectic effect of POMC, whereas β-endorphin is responsible for autoinhibitory feedback, which inactivates the anorectic effect.
- Bupropion can be used to stimulate the POMC neurons, whereas **naltrexone can be used to block the autoinhibitory feedback that is associated with a decline in weight reduction**.
- Might also regulate the mesolimbic reward pathways, which may lead to further weight reduction by modulating reward values and goal-oriented behaviors

The Bad: Increased Opioid Sensitivity?

- Thought that LDN is an opioid antagonist, and may cause withdrawal when used with opioids
- Is there a chance of hyper excitability of the mu receptor?
- Case report of patient on LDN4.5mg for MS, became obtunded after 5mg of oxycodone

Am J Emerg Med. 2017 Aug;35(8):1209.e3-1209.e4. doi: 10.1016/j.ajem.2017.04.012. Epub 2017 Apr 6.
Potential drug interaction with opioid agonist in the setting of chronic low-dose opioid antagonist use.
Leonard JB, Nair V, Diaz CJ, Penoyar JB, Goode PA.

Opioid Tolerance with LDN usage

Case report: Emergency surgery Pain Medicine News December 2015

Robert Bolash, Elizabeth Casserly

- 48-year-old man admitted for perforated duodenal ulcer with intra-abdominal free air.
- LDN 1.5mg for 3 years due to chronic abdominal pain following an open repair of an abdominal aortic aneurysm
- Given IV opioid
  - I.V. fentanyl 4,500 mcg per day and Hydromorphone to 47mg per day
  - Acute pain remained uncontrolled.

- Observed that an opiate-naive patient was refractory to the analgesic, sedative, or respiratory depressant effects of I.V. opiates with liberal dose escalation.

Popularity and the Norwegian Effect

- Unique experiment, unprecedented “tsunami” like increase powered by the population
- On February 27th, 2013, TV2, the biggest TV channel in Norway aired a documentary on LDN. Patients featured had severe multiple sclerosis and claimed that LDN all but normalized their function status.
- A survey of the Norwegian Prescription Database showed that the number of LDN users rose from less than 20 in 2012 to more than 15000 in 2013 and 2014.
- In 2014, 20% of all physicians and 71% of GPs registered in Norway prescribed LDN at least once.
- Among patients collecting more than 4 LDN prescriptions a year, annual average opioid consumption was reduced by 41 defined daily doses per person (or 46%), with no increase in the number of NSAIDs, acetaminophen, or other analgesics. Fear of interaction or therapeutic effect?


Some claim it can cure everything
from cancer to multiple sclerosis.
0:55 / 22:02

Lack of Evidence and Future Direction

- Why is there a lack of high quality, large scale trials?
- LDN is off patent, cheap, and no financial incentive to finance large scale trials.
- Significant grass roots movement

Practicalities

- No set guidelines for prescribing in the United States.
- Usual dosages 1-4.5mg/day. May start anywhere within that range and titrate up or down.
- No evidence as to what the ideal dosage is.
- Low toxicity and side effect profile: vivid dreams, sleep disturbance, nausea, abdominal pain, joint pain, headaches.
- Available from compounding pharmacies and ~$40/month

Obtaining LDN/UDN

- Need compound pharmacy
- I use Belmar pharmacy (but there are many more!)
  - Scorable tablet vs capsule
  - Lowest price ($36 for 60 tabs)
  - Direct patient to Low Dose Naltrexone website
- Part of my multimodal therapy

- Caution that research is limited
  - Some evidence in fibromyalgia, Multiple sclerosis
  - LDN websites can make pseudoscience claims about treating HIV and cancer

The World's Largest LDN Survey

Everyone can take part anonymously
with the **FREE** Health Tracker App

Please tell your patients about the LDN App!

- Jill Brook M.A.

This free smartphone app guides patients to track their response to LDN, while anonymously donating their data so that we can accelerate research. It's an invaluable tool for guiding patient-provider discussions about optimal dosing, as it tracks side effects, pain, sleep, quality of life, and more.

You can find it in the App Store or Google Play Store.

Please participate in this worldwide citizen science initiative!

LDN Health Tracker App

www.ldnresearchtrust.org/ldn-health-tracker-app

Conclusion

- LDN and UDN have unique properties and growing popularity
- No set dosing
- Relatively harmless and cheap
- Easy to trial
- Multimodal therapy

Self-Assessment Question 1 Answer

What mechanism of action does LDN work on?

A. Inhibition of Pro-inflammatory Cytokines
B. Increase Endogenous Enkephalin and Endorphins
C. Antagonize Toll-Like Receptor 4
D. All of the Above
E. None of the Above

D. All of the above

Self-Assessment Question 2 Answer

What dose range is LDN effective at?

A. 1-6mg
B. 100-500mcg
C. 2-25mcg
D. 50mg
E. A-C only

E. Doses are generally 1-6mg for LDN, 2-500mcg for ULDN. 50mg is the dose for addiction treatment

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