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Improving Patients' Lives with Low-Dose Naltrexone (LDN):

What We Know, Mechanisms and Evidence

Nat Jones, RPh, FAPC

PCCA Clinical Compounding Pharmacist

Submit your questions to the pharmacy via private Chat.

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The LDN Dilemma

- 40+ years since the patent has expired and yet here we are finding new uses
  - Over 300 different disease states can potentially be treated in part with naltrexone
- It is interesting that we have anecdotally found all of these uses and now have a reverse of the normal research process, in that we find ourselves having to go back and put the legs under the clinical results
- Some experts estimate that 20% of the population could potentially benefit from using LDN

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Product Approval

- Naltrexone was discovered in 1963 by Endo Laboratories
- FDA approved the 50 mg tablet for the treatment of addiction to opioids in 1984 and alcohol use disorders in 1994
- Vivitrol® (naltrexone for extended-release injectable suspension) was FDA approved in 2010 and is indicated for the prevention of relapse to opioid dependence, following opioid detoxification

LDN, Where It Began

- Low-dose naltrexone (LDN) therapy was developed in 1985 by Dr. Bernard Bihari, a Doctor of Internal Medicine, Psychiatry and Neurology
- Dr. Bihari changed his research interest from addiction to AIDs when the AIDs epidemic occurred and discovered that AIDS patients had 20% of the normal endorphin levels of healthy patients
- His key discovery was that 1% of the normal dose of naltrexone caused an unusual effect of a 300% increase in endorphin levels

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LDN, Where It Began

- Dr. Bihari soon found that it not only benefitted AIDs patients but the immune-system normalizing effect of the drug applied to a wide range of autoimmune disorders
- Before his death in 2010, he estimated that there were already between 30-40,000 patients using LDN nationwide
- An explosion of information about LDN has occurred since his death and continues at a rapid pace

How Much Literature?

The Dartmouth Paper

- Amazing references! They reviewed all the literature and only the most important articles are referenced as of the date submitted…
- It provides an overview of the current knowledge on these topics and summarize the key findings published in peer-review sources
- First paper to review ultra low-dose outcomes

Med Sci (Basel). 2018 Sep 21;6(4). pii: E82. doi: 10.3390/medsci6040082.
Low-Dose Naltrexone (LDN)-Review of Therapeutic Utilization.
Toljan K, Vrooman B.

The Dartmouth Paper Reviews

- Pharmacological Properties
  - Mechanism of Action of Low-Dose Naltrexone
  - Mechanism of Action of Very Low-Dose Naltrexone
  - Mechanism of Action of Ultra Low-Dose Naltrexone
- Low-Dose Naltrexone in Clinical Medicine
  - Multiple Sclerosis, Complex Regional Pain Syndrome, Fibromyalgia, Gastrointestinal Tract Diseases, Cancer, Skin Conditions, Other Diseases or States (autism, sclerosis-associated pruritus, ALS, and a variety of pathologies)

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Mechanism of Action (MOA)

- LDN to the contrary of ‘classical’ effect of naltrexone exerting opioid antagonism eliciting a fairly long opioid receptor blockade by standard dosing, the transient opioid receptor blockade ensuing from low-dose use upregulates opioid signaling
- This opens the perspective of LDN as modulating tool of the neuroimmune axis, which further intertwines with the neuroendocrine axis to form a crossroads between CNS and rest of the body
- So, we see an upregulation of the endogenous levels of endorphin and met-enkephalin, also known as opioid growth factor, with concomitant respectively increased μ-opioid, δ-opioid, and ζ-opioid receptor expression (opioid growth factor receptor)

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Mechanism of Action (MOA)

- Low-dose naltrexone disrupts the TRIF portion of the signaling cascade which reduces TNF-α and interferon-β synthesis
- Consequently, activated microglial cells expressing toll-like receptor 4, otherwise a non-constitutive receptor, exert an attenuated pro-inflammatory profile
- The span and importance of neuronal toll-like receptor 4 signaling is still under debate with *ex vivo* and *in vitro* investigations emphasizing its role in neuroinflammation, a role traditionally reserved for glia in the central nervous system (CNS)
- Thus, the attribute “glial attenuator” is occasionally used to describe LDN

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The Dartmouth Paper Reviews

- Very Low-Dose Naltrexone (VLDN) in Clinical Medicine
  - Six-day methadone taper of either 0.125 mg or 0.250 mg VLDN daily and achieved benefits of attenuated withdrawal symptoms, reduced craving, and increased engagement in outpatient treatment at first week follow-up
  - Also, patients without substance abuse history, but who are experiencing adverse effects with LDN, could possibly benefit from lower doses that would qualify as VLDN

40-45% of patients are not going to get off opioids this way but can achieve get 50% reduction in dosage of opioids

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The Dartmouth Paper Reviews

- Ultra Low-Dose Naltrexone (ULDN) in Clinical Medicine
  - Case: a patient suffering from terminal stage of cancer and severe intractable cholestasis pruritus, functionally improved upon introduction of 0.2 mg naloxone in a 24 h-continuous intravenous infusion, her pruritus score dropping from 9/10 to 0–2/10. The ULDN infusion did not reduce her concurrent buprenorphine-based analgesia and even improved her mental condition impacted by high opioid dose.

Med Sci (Basel). 2018 Sep 21;6(4). pii: E82. doi: 10.3390/medsci6040082.
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The Dartmouth Paper Reviews

- Ultra Low-Dose Naltrexone (ULDN) in Clinical Medicine
  - Larger-scale clinical trials with an opioid and ULDN:
    - A combination of oxycodone and 2 mcg or 4 mcg daily naltrexone has been tested respectively against placebo and oxycodone as part of a randomized controlled blinded trial involving 719 patients affected by low back pain
    - All treated groups had significant pain relief compared to placebo, but oxycodone with 2 mcg naltrexone daily proved to be the best modality of the available study treatments
    - Patients receiving that combination reported significantly fewer opioid-related adverse effects such as constipation, somnolence, and pruritus and fewest opioid-withdrawal effects following active treatment cessation

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The Dartmouth Paper Reviews

- Ultra Low-Dose Naltrexone (ULDN) in Clinical Medicine
  - Also studied for:
    - Cholestasis pruritus
    - Osteoarthritis
    - Low back pain
    - Axillary brachial plexus blockade
    - Postoperative pain control following colorectal surgery
    - Postoperative pain control following lumbar discectomy

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Dosing 1.0

Naltrexone Oral Dosing Defined

- Standard oral dosage for various indications is 50 mg once daily (opioid overdose, uremic pruritus, dermatologic, etc.)
- Adults recommended maximum dosages are 150 mg/day PO; 380 mg/dose IM
- Dosages from 0.5 up to 4.5 mg are usually classified as low-dose (some references list 1 mg to 5 mg)
- Dosages of a microgram or less per day have been considered “ultra low-dose” (<0.001 mg)
- Any dose between low-dose and ultra-low-dose is considered “very low-dose” (0.001 – 1 mg)

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Bihari LDN Dosing Protocol

- Start with 1.5 mg po 1 hour prior to bedtime for one week
- Then increase to 3 mg if well tolerated for one week
- Then increase to 4.5 mg as maintenance dose if well tolerated
- Remember, this is an opioid antagonist and would be contraindicated in patients receiving opioid analgesics, partial opiate agonists (e.g., buprenorphine), those with current physiologic opioid dependence, and those in acute opioid withdrawal

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Ploesser J, Weinstock LB, Thomas E. Low dose naltrexone: side effects and efficacy in gastrointestinal disorders. Int J Pharm Compd. 2010;14(2):171-173.

Table. Side Effects of Low Dose Naltrexone in 121 Patients.

	Number of Participants with Side Effects	*Percentage of Participants with Side Effects*
Neurological Side Effects		
Anxiety	19	15.7
Drowsiness	14	11.6
Headache	14	11.6
Dizziness	13	10.7
Insomnia	10	8.3
Muscle pain	10	8.3
Vivid dreams	6	5.0
Mood change	4	3.3
Trouble concentrating	2	1.7
Gastrointestinal Side Effects		
Nausea	15	12.4
Abdominal pain	14	11.6
Diarrhea	10	8.3
Anorexia	10	8.3

Risk of Serious Adverse Events, at Any Dose? None!

- This systematic review and meta-analysis found no evidence of a difference in risk of SAEs for oral naltrexone compared to placebo
- This evidence supports the use of naltrexone in its currently licensed (FDA approved) form and provides solid support to contemporary efforts studying naltrexone where it is currently unlicensed

BMC Med. 2019 Jan 15;17(1):10. doi: 10.1186/s12916-018-1242-0.
Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: a systematic review and meta-analysis.
Bolton M, et al.

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Autoimmune Diseases

- “Autoimmunity, a condition in which the body’s immune system reacts with components of its own cells, appears to be increasing in the United States”
  - https://www.nih.gov/news-events/news-releases/autoimmunity-may-be-rising-united-states
- There are more than 100 autoimmune diseases
  - https://www.aarda.org/diseaselist/
- Prevalence is on the rise
  - https://www.nih.gov/news-events/news-releases/autoimmunity-may-be-rising-united-states

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Prevalence on the Rise

- National Health and Nutrition Examination Survey (NHANES)
  - They found that ANA prevalence for 1988-1991 was 11.0%, while for 1999-2004 it was 11.5%, and for 2011-2012 it was 15.9%. These percentages corresponded to 22, 27 and 41 million affected individuals, respectively.
  - “The reasons for the increases in ANA are not clear, but they are concerning and may suggest a possible increase in future autoimmune disease.”

- Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, Chan EKL, Miller FW. 2020. Increasing prevalence of antinuclear antibodies in the United States. Arthritis Rheum; doi: 10.1002/art.41214 [Online 8 April 2020].

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Disease	Percent of population	US Prevalence	Per 100,000
Rheumatoid arthritis	0.806%	2,580,000	860.00
Hashimoto's autoimmune thyroiditis	0.742%	2,375,100	791.70
Celiac disease	0.703%	2,250,000	750.00
Graves' disease	0.590%	1,887,000	629.00
Diabetes mellitus, type 1	0.450%	1,440,000	480.00
Vitiligo	0.375%	1,200,600	400.20
Rheumatic fever	0.234%	750,000	250.00
Pernicious anemia/atrophic gastritis	0.141%	452,700	150.90
Alopecia areata	0.141%	450,000	150.00
Immune thrombocytopenic purpura	0.068%	216,000	72.00
Multiple sclerosis	0.055%	174,900	58.30
Systematic Lupus Erythematosus	0.030%	96,000	32.00
Temporal arteritis	0.028%	90,000	30.00
Ulcerative colitis	0.028%	90,000	30.00
Crohn's disease	0.023%	75,000	25.00
Scleroderma	0.023%	72,000	24.00
Antiphospholipid syndrome	0.020%	64,500	21.50
Autoimmune hepatitis type 1	0.015%	48,300	16.10

Prevalence of Autoimmune Disease per 100,000

Autoimmun Rev. 2012 Aug;11(10):754-65.
Updated assessment of the prevalence, spectrum and case definition of autoimmune disease
Scott M Hayter, Matthew C Cook

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Looking Ahead

- The use of low-dose naltrexone (LDN) for the treatment and prophylaxis of various bodily disorders is discussed. Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such as autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect.
    - Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. Med Hypotheses. 2009 Mar;72(3):333-7. doi: 10.1016/j.mehy.2008.06.048. Epub 2008 Nov 28. PMID: 19041189.

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    - Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. Med Hypotheses. 2009 Mar;72(3):333-7. doi: 10.1016/j.mehy.2008.06.048. Epub 2008 Nov 28. PMID: 19041189.

Conditions Where LDN Could be of Benefit

- There are over 150 conditions for which LDN could be beneficial
  - https://ldnresearchtrust.org/conditions
- The list includes all the major autoimmune diseases
- Why?
  - Because it is immunomodulatory without decreasing innate immune response to other immune challenges

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What Causes an Autoimmune Disease?

Hallmarks of Autoimmune Disease

- The Trifecta
  - Bacterial proteins
  - Increased GI permeability (inflamed and porous)
  - High-stress event

Microbiome

- Connections between the microbiome and autoimmune diseases
  - **Interactions of microbiota and the immune system have been shown to promote and sustain chronic inflammation and autoimmunity**. In mechanistic studies, microbe-immune cell interactions have been implicated in the initiation of autoimmune rheumatic diseases
    - Best Pract Res Clin Rheumatol. 2020 Feb;34(1):101473. The microbiome in autoimmune rheumatic disease. Maximilian F Konig
  - Several studies have highlighted the role of the microbiome in the pathogenesis of autoimmune **diseases such as systemic lupus erythematosus and rheumatoid arthritis**
    - Clin Exp Immunol. 2019 Jan;195(1):74-85. The microbiome in autoimmune diseases. F De Luca, Y Shoenfeld

Microbiome

- Connections between the microbiome and autoimmune diseases
  - **Complex host-microbiota interactions contribute to systemic autoimmunity outside the gut**. On a molecular level, posttranslational modification of, and cross-reactivity with, autoantigens represent mechanisms of how the microbiota mediates autoimmunity. On a cellular level, translocation of live gut bacteria across a dysfunctional gut barrier allows for direct interactions with immune and tissue cells, instigating autoimmunity systemically.
    - Curr Opin Rheumatol. 2019 Mar;31(2):201-207. The microbiome in systemic autoimmune disease: mechanistic insights from recent studies. Carina Dehner, et al.

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Interplay Between Microbiota and Host

- Interplay between microbiota and host, leading to autoimmune diseases
  - "The perception of the classical link between microbial infection and development of autoimmune disease has evolved to **the more recent concept of the connection between the microbiome/dysbiosis and breaking of immunological tolerance**."
  - **i.e., changes in diversity of microbiome leads to changes in immune function**
    - Curr Opin Rheumatol. 2018 Jul;30(4):403-409. Multiple hit infection and autoimmunity: the dysbiotic microbiota-ACPA connection in rheumatoid arthritis. Lazaros I Sakkas , Dimitrios P Bogdanos

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Autoimmune Disorders Get Started…

- Bacteroides fragilis are part of the normal human colon flora. In a longitudinal analysis of the stool specimens collected from 15 healthy adults, B. fragilis was cultured from 87% of the cohort.
- Bacteroides fragilis plays an intricate role in the human colon and has a beneficial relationship with the host. Still, if there is a breach in the integrity of the mucosal lining either by surgery or trauma, it can cause significant morbidity.
- As the number of B. fragilis come up there is less diversity in the microbiome.

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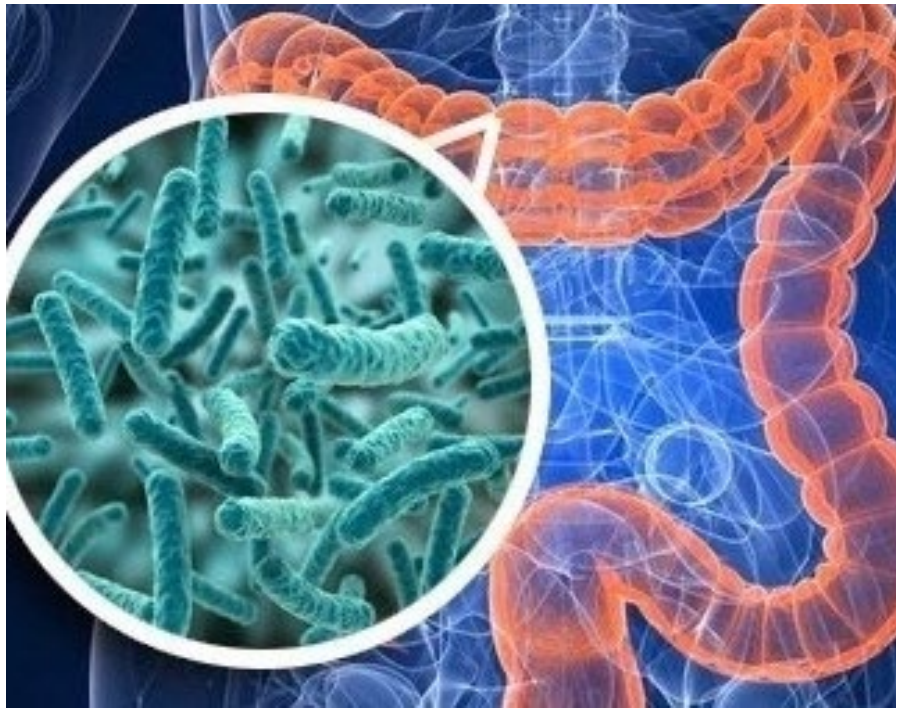
Autoimmune Origins

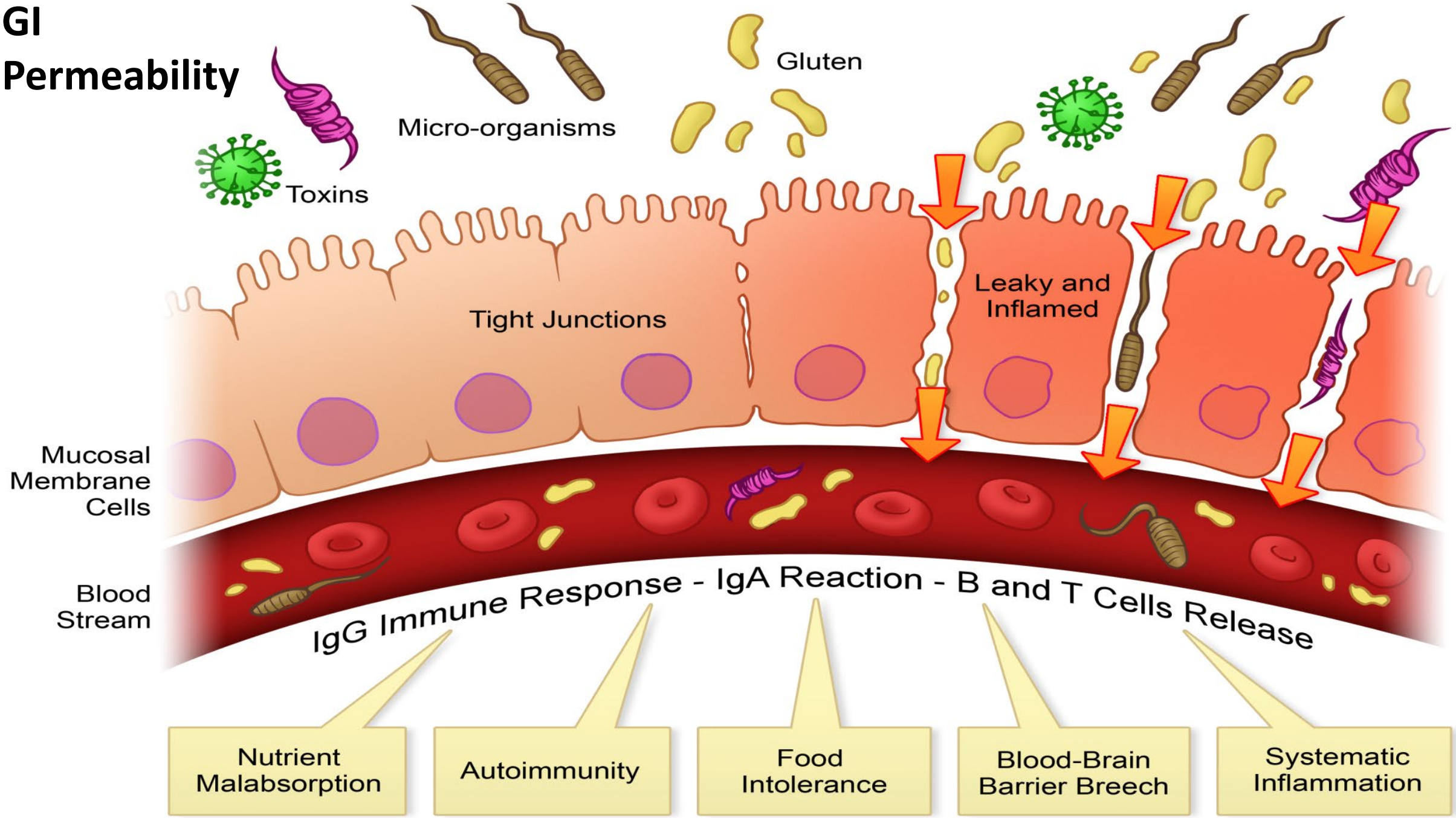
- We show that the immune system of some individuals has been exposed to BfUbb (**Bacteroides Fragilis Ubiquitin**) which has **resulted in the generation of IgG antibodies**. Serum from patients referred for first-time testing to an immunology laboratory for autoimmune disease are more likely to have a high level of antibodies to BfUbb than healthy volunteers. **Molecular mimicry of human ubiquitin by BfUbb could be a trigger for autoimmune disease**.
    - Stewart et al. Antigenic mimicry of ubiquitin by the gut bacterium Bacteroides fragilis: a potential link with autoimmune disease. Clin Exp Immunol. 2018 Nov; 194(2): 153–165. Published online 2018 Sep 17.

Autoimmune Origins

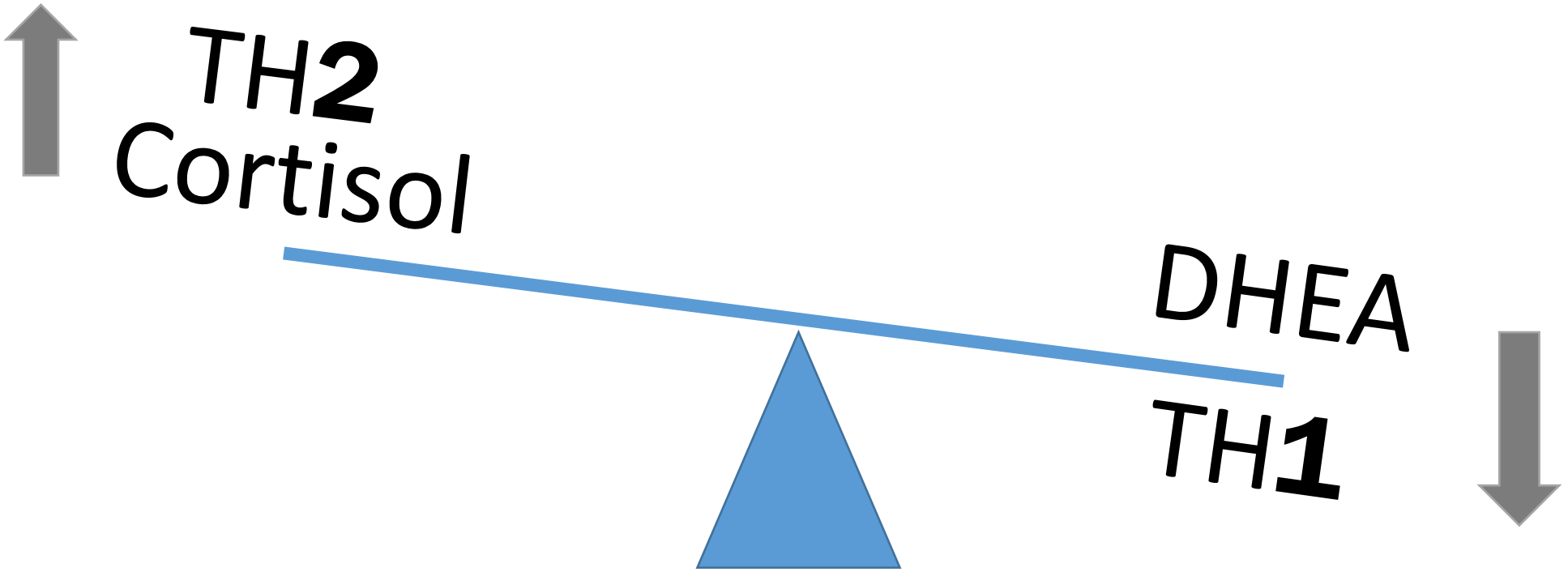
- …that translocation of a gut pathobiont, **Enterococcus gallinarum**, to the liver and other systemic tissues triggers autoimmune responses in a genetic background predisposing to autoimmunity.
  - Vieira, S.M. et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science 09 Mar 2018: Vol. 359, Issue 6380, pp. 1156-1161.



GI Permeability



Immune Imbalance



The World According to Nat…

- A highly processed food diet leads to decreased microbiome diversity
- We have been hearing the importance of elimination of proflammatory foods from our diets, probiotics and gut repair for the last decade or more
- We need to be looking at our patients coming in with constipation, dysbiosis, food sensitivities with the potential of developing an autoimmune problem

High-Stress Event

- The etiology of autoimmune diseases is multifactorial: genetic, environmental, hormonal and immunological factors are all considered important in their development. Nevertheless, the onset of at least 50% of autoimmune disorders has been attributed to “unknown trigger factors.”
- **Physical and psychological stress has been implicated in the development of autoimmune disease**, since numerous animal and human studies demonstrated the effect of sundry stressors on immune function. Moreover, many retrospective **studies found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset**.
    - Stojanovich, L. Marisavljevich, D. Stress as a trigger of autoimmune disease. Autoimmunity Reviews 7 (2008) 209–213

Why Not You?

- The findings of this study are consistent with some **biological evidence linking psychological stress and stressful events to varying impairments of immune function, both of which lend support to a biopsychosocial model in the etiology of autoimmune disease.** Under stress, the activated autonomic nervous system might induce the dysregulation of immune function and disinhibition of inflammatory response via the inflammatory reflex.
- Moreover, patients with **PTSD have been reported to have excessively low cortisol levels,** particularly in the context of early life trauma exposure. The consequence of long-lasting lower cortisol levels **may be amplified production of pro-inflammatory cytokines with accelerated immune cell aging and over-activated immune system**
    - Song H, Fang F, Tomasson G, et al. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA. 2018;319(23):2388–2400.

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And the Usual Suspects…

- PTSD is associated with increased interleukin 6, interleukin 1β, TNFα, and interferon γ levels. This information might be useful for consideration of chronic low-grade inflammation as a potential target or biomarker in PTSD treatment.
    - Passos IC, Vasconcelos-Moreno MP, Costa LG, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015;2(11):1002-1012.

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Any High-Stress Events Lately?

- COVID
  - Quarantine
  - School
  - Illness
- Work
  - Layoffs
  - Work functions
  - Shifts
  - Dual responsibilities
  - Money
- Politics

Trifecta – Remember Me?

Presence of bacterial proteins presenting at the liver (made possible by increased gut permeability) couple that with stress and it can lead to higher chance of autoimmune development

TLR Autoimmune Link

- Data rising predominantly from human patients and animal models of autoimmune disease indicate that, **inappropriate triggering of TLR pathways by exogenous or endogenous ligands may cause the initiation and/or perpetuation of autoimmune reactions and tissue damage**.
- Considering the role of TLRs as a critical link between the innate and the adaptive immune responses, the idea has created that **continuous activation or dysregulation of TLR signaling might contribute to the pathogenesis of autoimmunity**.
    - Toll-Like Receptors in the Pathogenesis of Autoimmune Diseases A. Hosseini, et al., Adv Pharm Bull. 2015 Dec; 5(Suppl 1): 605–614.

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Immune Disorders

- Although TLRs play a key role in the initiation of immune responses to infection, **inappropriate TLR activity and/or recognition of self-ligands are associated with inflammatory conditions and autoimmunity**. For example, increased expression of TLRs has been observed in peripheral B cells from patients with **inflammatory bowel disease**, while recognition of self-DNA complexes by TLR9 mediates pDC activation in **psoriasis**. TLRs have also been implicated in the tumor microenvironment, with TLR activation linked to angiogenesis, tumor proliferation, and immune evasion. Furthermore, some TLR polymorphisms may be associated with development of inflammatory conditions such as **Crohn's disease**. TLRs have, therefore, been investigated as potential therapeutic targets in patients with these diseases…
    - Low dose naltrexone (LDN) enhances maturation of bone marrow dendritic cells (BMDCs), Jingjuan Meng, et al, International Immunopharmacology, 2013

Cytokines and Immune Disorders

- **IL-1 is an important mediator of inflammation and tissue damage in multiple organs, both in experimental animal models of disease and in human diseases**. The IL-1 family consists of two agonists, IL-1α and IL-1β, two receptors, biologically active IL-1RI and inert IL-1RII, and a specific receptor antagonist, IL-1Ra. The balance between IL-1 and IL-1Ra in local tissues plays an important role in the susceptibility to and severity of many diseases.
  - The balance between IL-1 and IL-1Ra in disease, W Arend, Cytokine & Growth Factor Reviews, Volume 13, Issues 4–5, August–October 2002, Pages 323-340

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TLR 4 Implications

- Toll-like receptor 4 (TLR4) signal pathway plays an important role in initiating the innate immune response and **its activation by bacterial endotoxin is responsible for chronic and acute inflammatory disorders** that are becoming more and more frequent in developed countries. Modulation of the TLR4 pathway is a potential strategy to specifically target these pathologies.
  - TLR4 Signaling Pathway Modulators as Potential Therapeutics in Inflammation and Sepsis. Kuzmich NN, Vaccines (Basel). 2017 Oct 4;5(4). pii: E34.

TLR4 Receptor Cells

- Keratinocytes
- Monocytes/macrophages
- Neutrophils
- Myeloid dendritic cells
- Microglia
- Mast cells
- B lymphocytes
- Intestinal epithelium

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Autoimmune Pathophysiology

- **Inflammation is also a cause of autoimmune diseases such as rheumatoid arthritis, in which excess levels of cytokines such as TNF-α, IL-6, IL-1β, and IL-8** are often found. Multiple sclerosis, another autoimmune disease, is caused by chronic inflammation in the central nervous system. Activated NF-κB is found in patients with multiple sclerosis. Elevated levels of other cytokines such as **IL-1α**, IL-2, IL-4, **IL-6**, IL-10, IFN-γ, TGF-β1, TGF-β2, and **TNF-α** have also been found in frozen sections of **central nervous system tissue from multiple sclerosis patients**.
    - The inflammation theory of disease, The growing realization that chronic inflammation is crucial in many diseases opens new avenues for treatment, P Hunter, EMBO reports, Nov 2012: 968-970

Autoimmune Pathophysiology

- Similarly, cerebrospinal fluid samples from patients with **Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis and schizophrenia have been shown to exhibit the overexpression of cytokines and NF-κB**. Likewise, in patients with **diabetes, high levels of CRP, IL-6, IL-1, and TNF-α**—along with abnormal expression of NF-κB—have been observed.
  - The inflammation theory of disease, The growing realization that chronic inflammation is crucial in many diseases opens new avenues for treatment, P Hunter, EMBO reports, Nov 2012: 968-970

LDN and the Inflammatory Cytokines

- Fibromyalgia (FM) - In this 10-week, single-blind, crossover trial we tested the immune effects of eight weeks of oral administration of low-dose naltrexone (LDN). We enrolled

"We found that 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)."

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

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Cytokines and LDN

- Autoimmune Pathophysiology
  - IL-1α, IL-2, IL-4, IL-6,IL-8 IL-10
  - IFN-γ
  - TGF-β1
  - TGF-β2
  - TNF-α
  - Activated NF-κB
- LDN Treatment
  - (IL)-1 , IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-27
  - IFN-γ
  - TGF-β
  - TNFα
  - G-CSF

LDN and Inflammatory Disease States

Arthritic Implications – Preclinical Data

- NTX relieved the severity of arthritis in the CIA rat models at a concentration of 10 mg/kg by regulating T lymphocyte subsets and the expression of cytokines. NTX affected opioid receptors to inhibit the TLR4/NF-κB signaling pathway, regulating the systemic immune response and decreasing osteoclast differentiation, thereby alleviating inflammation and the erosion of articular cartilage along with bone tissue.
    - Xu, Neili, et al, Naltrexone (NTX) relieves inflammation in the collagen-induced- arthritis (CIA) rat models through regulating TLR4/NFκB signaling pathway. International Immunopharmacology, Volume 79, February 2020, https://doi.org/10.1016/j.intimp.2019.106056

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Shared Homology of Toll-Like Receptors

- TLR paralogs are located on cell surfaces or within endosomes and have important roles in the host defense against pathogenic organisms throughout the animal kingdom.
- In humans, ten TLRs respond to a variety of Pathogen-Associated Molecular Patterns (PAMPs), including lipopolysaccharide (TLR4), lipopeptides (TLR2 associated with TLR1 or TLR6), bacterial flagellin (TLR5), viral dsRNA (TLR3), viral or bacterial ssRNA (TLRs 7 and 8) and CpG-rich unmethylated DNA (TLR9), among others.
    - Structure. 2011 Apr 13;19(4):447-59. The structural biology of Toll-like receptors. Istvan Botos, et al.

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Rheumatoid Arthritis (RA) and Cytokines

- Two key pro-inflammatory cytokines in RA are IL-1 and TNFα
- It is well established that TNF and IL-1 are key cytokines in the process of chronic joint inflammation and the concomitant erosive changes in cartilage and bone
- Regulation of these cytokines is of crucial importance in the RA disease
- Rheumatoid arthritis is considered as an Th1-associated disease
    - Madame Curie Bioscience Database [Internet]. Cytokines in the Pathogenesis of Rheumatoid Arthritis and Collagen-Induced Arthritis. Erik Lubberts and Wim B. van den Berg https://www.ncbi.nlm.nih.gov/books/NBK6288/ accessed online 4/28/21

IL-6 and Rheumatoid Arthritis (RA)

- IL-6 is continuously produced in RA can be expected to lead to the best use of this agent (tocilizumab) for RA patients and aid in investigations into the pathogenesis of RA
- IL-6 has been shown to contribute to the production of autoantibodies by acting on plasmablasts
- IL-6 is involved in local inflammation causing joint destruction
- IL-6 blockade strategy may indeed correct immunological abnormalities in RA
    - Biomed Res Int. 2014;2014:698313. Interleukin 6 and rheumatoid arthritis. Yuji Yoshida, Toshio Tanaka

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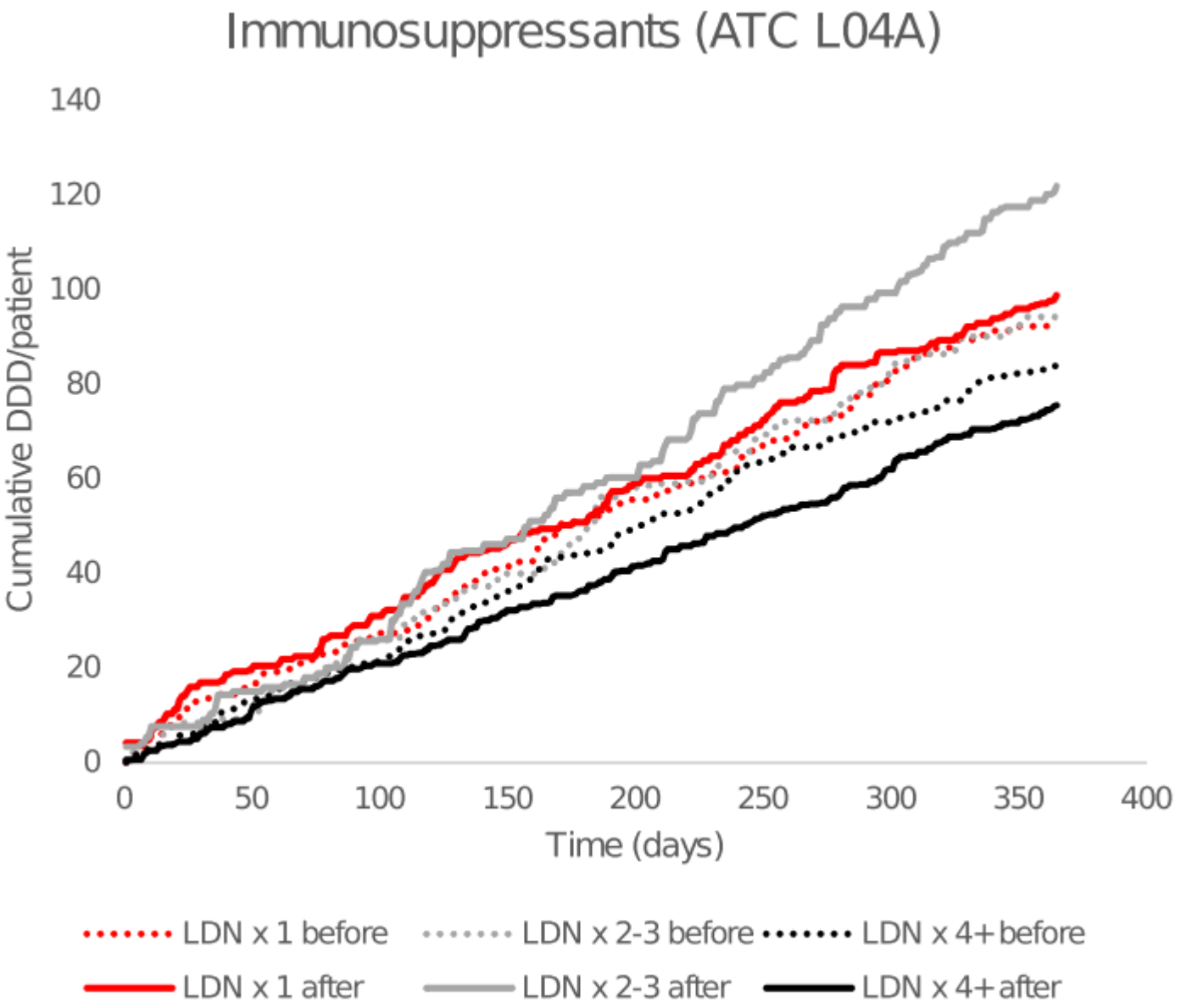
So, It Works?

- In persistent LDN users, there was a 13% relative reduction in cumulative defined daily doses (DDD) of all medicines examined

The results support the hypothesis that persistent use of LDN reduces the need for medication used in the treatment of rheumatic and seropositive arthritis.

α antagonists and opioids. There was a decrease in the number of NSAID users among patients with the least LDN exposure.

- Raknes G, Småbrekke L. Low dose naltrexone: Effects on medication in rheumatoid and seropositive arthritis. A nationwide register-based controlled quasi-experimental beforeafter study [published correction appears in PLoS One. 2019 Oct 1;14(10):e0223545]. PLoS One. 2019;14(2):e0212460.



Cumulative dispensed average defined daily doses (DDDs) of immunosuppressants

Osteoarthritis (OA)

- While age and obesity are considered the primary preventable risk factor for OA, both conditions are associated with abnormal innate immune inflammatory responses that contribute to OA progression
- Toll-like receptor (TLR)4-induced catabolic responses also play a significant role in OA
- The complex interplay between obesity and aging-associated macrophage activation, pro-inflammatory cytokine production from TLR-driven responses, and adipokines leads to a vicious cycle of synovial hyperplasia, macrophage activation, cartilage catabolism, infrapatellar fat pad fibrosis, and joint destruction
    - Curr Rheumatol Rep. 2017 Aug;19(8):45. Innate Immune Responses and Osteoarthritis. Evangelia Kalaitzoglou, et al.

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Osteoarthritis (OA) IL-6 and TNF-α

- It is known that adipose tissue produces and secretes several proinflammatory cytokines, including IL-6 and TNF-α
    - Int J of Inflammation, vol. 2015, Article ID 329792, 8 pages, 2015. "Serum Levels of Proinflammatory Cytokines in Painful Knee Osteoarthritis and Sensitization". Marta Imamura, et al.
- Serum levels of IL-6 and TNF-α are associated with knee cartilage loss in older people suggesting low level inflammation plays a role in the pathogenesis of knee OA
    - Osteoarthritis and Cartilage Volume 18, Issue 11, November 2010, Pages 1441-1447. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Stannus O, et al.

Osteoarthritis (OA) and IL-6

- Joint inflammation is present in the majority of OA patients and pro-inflammatory mediators, such as IL-6, are actively involved in disease progression. Increased levels of IL-6 in serum or synovial fluid from OA patients correlate with disease incidence and severity, with IL-6 playing a pivotal role in the development of cartilage pathology, e.g. via induction of matrix-degrading enzymes.
    - Rheumatology, Volume 59, Issue 10, October 2020, Pages 2681–2694 A roadmap to target interleukin-6 in osteoarthritis. Renske Wiegertjes, et al.

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Systemic Lupus Erythematosus (SLE)

- Is a complex autoimmune disease characterized by the loss of tolerance to self-nuclear antigens
- Clinical sample studies have provided evidence for the involvement of TLRs, including TLR2/4, TLR5, TLR3 and TLR7/8/9, in SLE pathogenesis
    - Acta Pharmacol Sin. 2015 Dec;36(12):1395-407. Toll-like receptors: potential targets for lupus treatment. Yan-wei Wu, et al.

Systemic Lupus Erythematosus (SLE)

- An association between IL-6 and lupus was demonstrated in murine models of SLE and blocking IL-6 improved lupus in all models tested
    - Lupus. 2004;13(5):339-43. Rationale for interleukin-6 blockade in systemic lupus erythematosus. Tackey E, et al.
- Increased serum level of TNF-α is observed in SLE patients and associated with disease activity and certain systemic manifestations
    - Cytokine. 2011 Dec;56(3):537-43. The role of Tumor Necrosis Factor-alpha (TNF-α) in the pathogenesis of systemic lupus erythematosus. Mariana Postal, Simone Appenzeller

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SLE and TLR 7 & 9

- “Other toll-like targets are of interest as well, such as TLR-7 and TLR-9 blockage by hydroxychloroquine, which has been used successfully in inflammatory disorders such as systemic lupus erythematosus and post-Lyme’s arthritis”
- **Erythrocyte sedimentation rate (ESR), a significant predictor of clinical response to LDN**, and our findings that baseline ESR may be associated with LDN response **suggest that other inflammatory conditions, such as rheumatoid arthritis, polymyalgia rheumatica, and lupus, may benefit from LDN which may serve as a concomitant medication when immunomodulatory therapies are not effective or not well tolerated by the patient**
    - Clin Rheumatol. 2014 Apr;33(4):451-9. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Jarred Younger, et al.

LDN for Pain

- Low-dose naltrexone (LDN) has shown promise to reduce symptoms related to chronic pain conditions such as fibromyalgia, inflammatory bowel conditions, and multiple sclerosis. The mechanism of LDN appears to be modulation of neuro-inflammation, specifically, the modulation of the glial cells and release of inflammatory chemicals in the central nervous system.
  - Kim PS, Fishman MA. Low-Dose Naltrexone for Chronic Pain: Update and Systemic Review. Curr Pain Headache Rep. 2020 Aug 26;24(10):64. doi: 10.1007/s11916-020-00898-0. PMID: 32845365.

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LDN for Pain

- Spinal cord levels of BDNF and IL-10 were modulated by low-dose naltrexone. Thus, low-dose naltrexone may be suitable to relieve trigeminal neuralgia; however, the exact mechanisms need to be clarified.
    - Camila Lino de Oliveira, et al. Low-dose Naltrexone Reverses Facial Mechanical Allodynia In A Rat Model Of Trigeminal Neuralgia. Neuroscience Letters, Volume 736, 2020

Low-Dose Naltrexone (LDN) for Pain

- LDN is a novel therapy which has low risk, low side effect profile, and low cost
- Naltrexone is an opioid receptor antagonist medication originally designed and approved for the treatment of opioid addiction at a dose of 50 mg to 100 mg per day
- More recently it has been suggested that low-dose naltrexone may be utilized for the treatment of chronic pain, in an off-label fashion at a much lower dose: 0.5 mg to 4.5 mg/day. Although the exact mechanism is unknown, it is believed that in this lower dose, naltrexone acts as a glial/immune cell modulator, which decreases pain by helping reduce inflammation

  - Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014;33(4):451-459.
  - Toljan K, Vrooman B. Low-dose naltrexone (LDN)—review of therapeutic utilization. Med Sci (Basel). 2018;6(4).

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LDN Anti-Inflammatory Action

- This study showed that LDN:
  - Is inexpensive and well-tolerated
  - Is a promising treatment approach for chronic pain conditions thought to involve inflammatory processes
  - May emerge as the first of many glial cell modulators that could be used to treat chronic conditions
    - Clin Rheumatol. 2014 Apr;33(4):451-9. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Younger J, Parkitny L, McLain D.

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LDN and the Microglia

"Low-dose naltrexone disrupts this signaling cascade with reduced synthesis of the proinflammatory cytokines, consequently attenuating the activated microglial cells and resulting in analgesic and anti-inflammatory effect."

Am Journal Hospice & Palliative Med 2019, Vol. 36(10) 907-912. Pharmacology Update: Low-Dose Naltrexone as a Possible Nonopoid Modality of Some Chronic, Nonmalignant Pain Syndromes. Trofimovitch D, Baumrucker SJ

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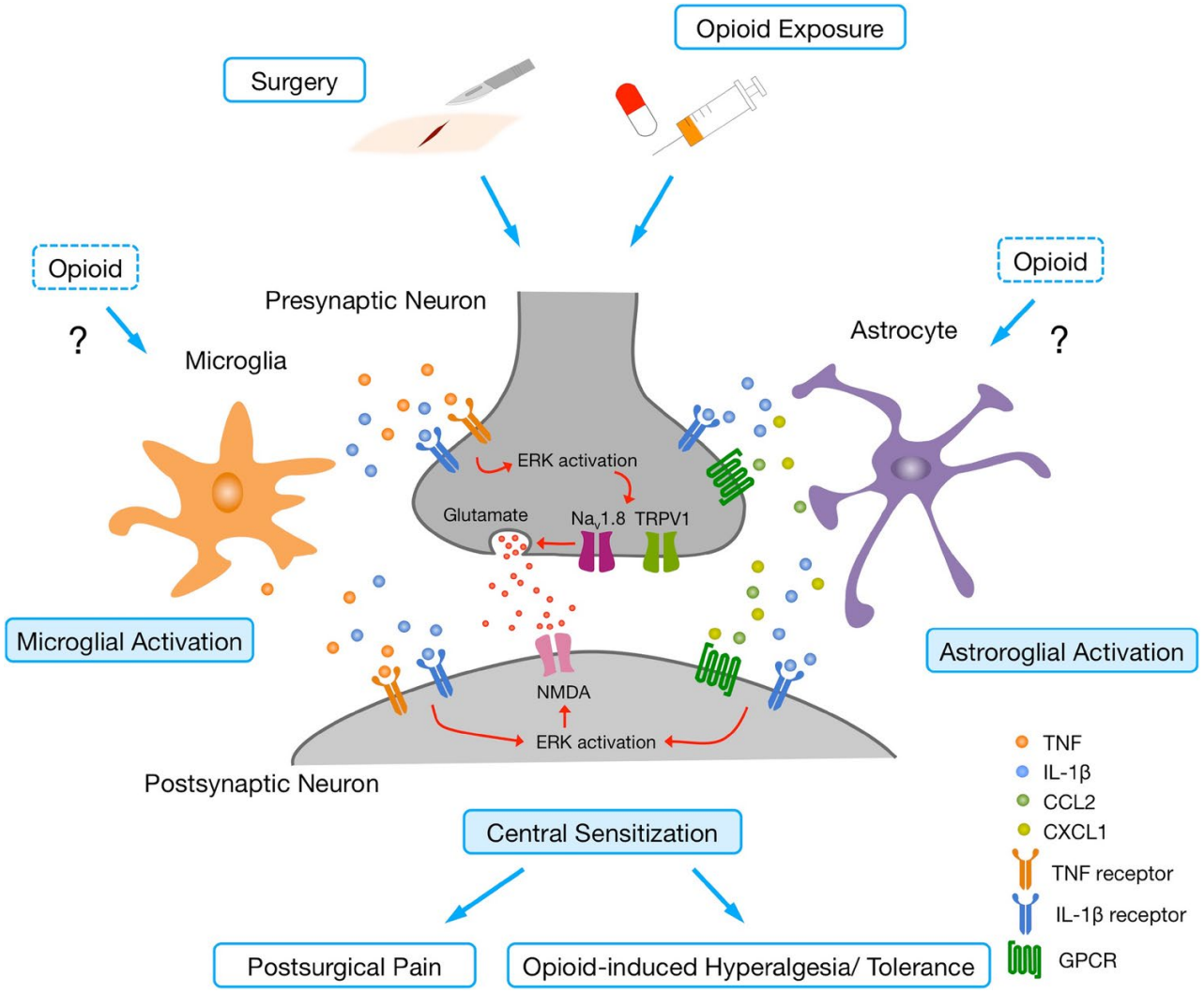
When the Microglia Get Involved



- Activation of central glia (microglia and astrocytes) in the spinal cord by surgery and/or opioids treatment results in secretion of glial mediators including TNF, IL-1β, CCL2, CXCL1, and BDNF which neuromodulate to induce central sensitization
- Central sensitization is a driving force of postsurgical pain as well as opioid-induced hyperalgesia and tolerance

LDN CRPS Case Studies

- Case No. 1
  - A 48-year-old male with a right leg injury in 2006, after complications was eventually diagnosed with CRPS
  - He experienced multiple largely unsuccessful treatments for years and eventually demonstrated significant reuptake in the right foot
  - In 2012, low-dose naltrexone was started and maintained at 4.5 mg per day (1 dose at night)
    - J Neuroimmune Pharmacol. 2013 Jun;8(3):470-6. Treatment of Complex Regional Pain Syndrome (CRPS) using low dose naltrexone (LDN). Chopra P, Cooper MS

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LDN CRPS Case Studies (cont'd)

- Case No. 1 (cont'd)
  - Within 2 months after starting LDN, the patient's dystonic spasms discontinued, although he still had moderate pain in both upper extremities. The patient was able to walk without a cane, which he had used continuously since 2006.
  - His pain was an average of 8 to 10 on the Numeric Rating Scale (NRS) before starting LDN. It dropped down to an average of 5 to 6 on the NRS after starting LDN.
  - After LDN therapy, the patient's pain symptoms have reduced in severity, but not in their distribution. His current mood state is good. No side effects of LDN were noted.
    - J Neuroimmune Pharmacol. 2013 Jun;8(3):470-6. Treatment of Complex Regional Pain Syndrome (CRPS) using low dose naltrexone (LDN). Chopra P, Cooper MS

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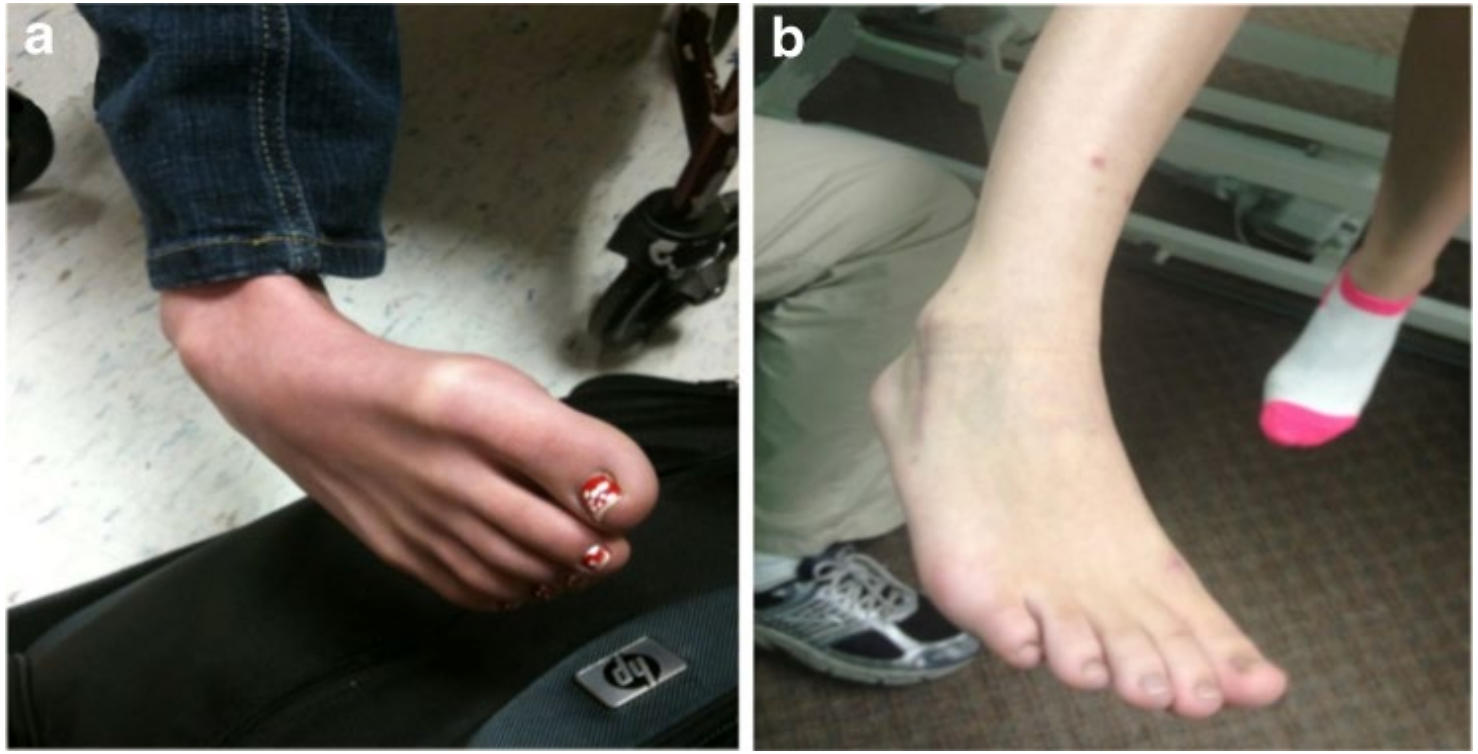
LDN CRPS Case Studies (cont'd)

- Our use of LDN treatment for CRPS patients was motivated by a presumed neuroinflammatory etiology for longstanding CRPS symptoms. The remission of pain and dystonic spasms in Case 1, as well a remission of all CRPS symptoms (including fixed dystonia) in Case 2 provides evidence that a multi-modal interventional approach, which includes low-dose naltrexone (a known glial attenuator), should be considered as a treatment option for the treatment of CRPS patients, particularly those patients with dystonic movement disorders.
    - J Neuroimmune Pharmacol. 2013 Jun;8(3):470-6. Treatment of Complex Regional Pain Syndrome (CRPS) using low dose naltrexone (LDN). Chopra P, Cooper MS

CRPS Cases (cont'd)



J Neuroimmune Pharmacol. 2013 Jun;8(3):470-6. Treatment of Complex Regional Pain Syndrome (CRPS) using low-dose naltrexone (LDN). Chopra P, Cooper MS

Case 2: a- Female patient, currently 12 years old with fixed dystonia, allodynia, and vasomotor abnormalities in the right lower extremity of a CRPS patient (panel a) remitted following treatment with a low-dose naltrexone. b- No symptoms and signs of CRPS after LDN treatment. Two months after surgical reinforcement of the right ankle for Ehlers-Danlos Syndrome (EDS).

LDN for Fibromyalgia

- This prospective study lends further support to the preliminary body of evidence that naltrexone is a well tolerated and likely effective treatment option in the community setting.
  - Metyas S, Chen CL, Yeter K, Solyman J, Arkfeld DG. Low dose naltrexone in the treatment of fibromyalgia. Current Rheumatology Reviews. 2018;14(2):177-180.

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LDN for Fibromyalgia

- When contrasting the condition end points, we observed a significantly greater reduction of baseline pain in those taking low-dose naltrexone than in those taking placebo (28.8% reduction versus 18.0% reduction). Low-dose naltrexone was also associated with improved general satisfaction with life and with improved mood (P = 0.039), but not improved fatigue or sleep.
- The preliminary evidence continues to show that low-dose naltrexone has a specific and clinically beneficial impact on fibromyalgia pain. The medication is widely available, inexpensive, safe and well-tolerated.
  - Arthritis Rheum. 2013 Feb;65(2):529-38. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Jarred Younger, et al.

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LDN and the Microglia

"Together, these chronic constriction injury data support the conclusion that neuron-to-glia signaling through TLR4 is important not only for initiating neuropathic pain, as suggested previously, but also for maintaining established neuropathic pain. Furthermore, these studies suggest that the novel TLR4 antagonists (+)-naloxone and (-)-naloxone can each fully reverse established neuropathic pain upon multi-day administration."

Eur J Neurosci. 2008 Jul;28(1):20-9. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Hutchinson MR, et al.

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Naltrexone and the TLR4

- “The toll-like receptor TLR4 is involved in neuropathic pain and in drug reward and reinforcement
- The opioid inactive isomers (+)-naltrexone and (+)-naloxone act as TLR4 antagonists, reversing neuropathic pain…”
    - Br J Pharmacol. 2016 Mar;173(5):856-69. Pharmacological characterization of the opioid inactive isomers (+)-naltrexone and (+)-naloxone as antagonists of toll-like receptor 4. Wang X, et al.

Multiple Sclerosis and Cytokines

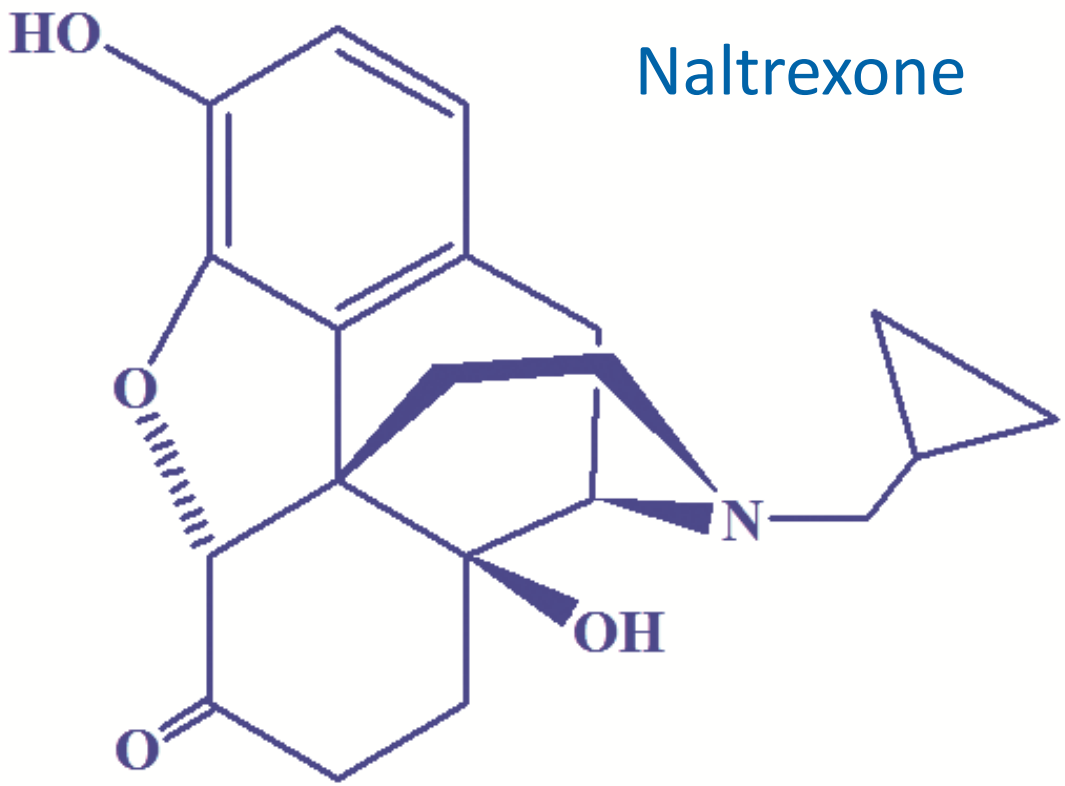
- Th1 and Th17 cells produce the pro-inflammatory cytokines IFNγ and IL-17, respectively, that have been shown to have pathogenic roles in EAE and MS
    - Exp Biol Med (Maywood). 2016 Jan;241(1):71-8. Opioid growth factor and low-dose naltrexone impair central nervous system infiltration by CD4 + T lymphocytes in established experimental autoimmune encephalomyelitis, a model of multiple sclerosis. Leslie A Hammer, et al.

Multiple Sclerosis and LDN

- Regulatory CD4(+) T cells suppress immune reactions and have been demonstrated to be dysfunctional in MS patients. Opioid growth factor (OGF), chemically termed [Met(5)]-enkephalin, is a negative growth factor that interacts with the OGF receptor. The OGF-OGFr axis can be activated through exogenous administration of OGF or a low dosage of naltrexone (LDN), an opioid antagonist.
    - Exp Biol Med (Maywood). 2016 Jan;241(1):71-8. Opioid growth factor and low-dose naltrexone impair central nervous system infiltration by CD4 + T lymphocytes in established experimental autoimmune encephalomyelitis, a model of multiple sclerosis. Leslie A Hammer, et al.

Multiple Sclerosis and LDN

- Serum [Met5]-enkephalin levels were lower in humans with multiple sclerosis relative to non-multiple sclerosis patients, and low-dose naltrexone restored their levels
  - Exp Biol Med (Maywood). 2017 Jan 1:1535370217724791. Serum [Met5]-enkephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. Ludwig MD, Zagon IS, McLaughlin PJ.



Naltrexone

Multiple Sclerosis and LDN

- **There is overwhelming anecdotal evidence, that in low doses naltrexone not only prevents relapses in MS but also reduces the progression of the disease**. It is proposed that naltrexone acts by reducing apoptosis of oligodendrocytes. It does this by reducing inducible nitric oxide synthase activity. This results in a decrease in the formation of peroxynitrites, which in turn prevent the inhibition of the glutamate transporters. Thus, the excitatory neurotoxicity of glutamate on neuronal cells and oligodendrocytes via activation of the alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid class of glutamate receptor is prevented.
  - Med Hypotheses. 2005;64(4):721-4. Low dose naltrexone therapy in multiple sclerosis. Y P Agrawal

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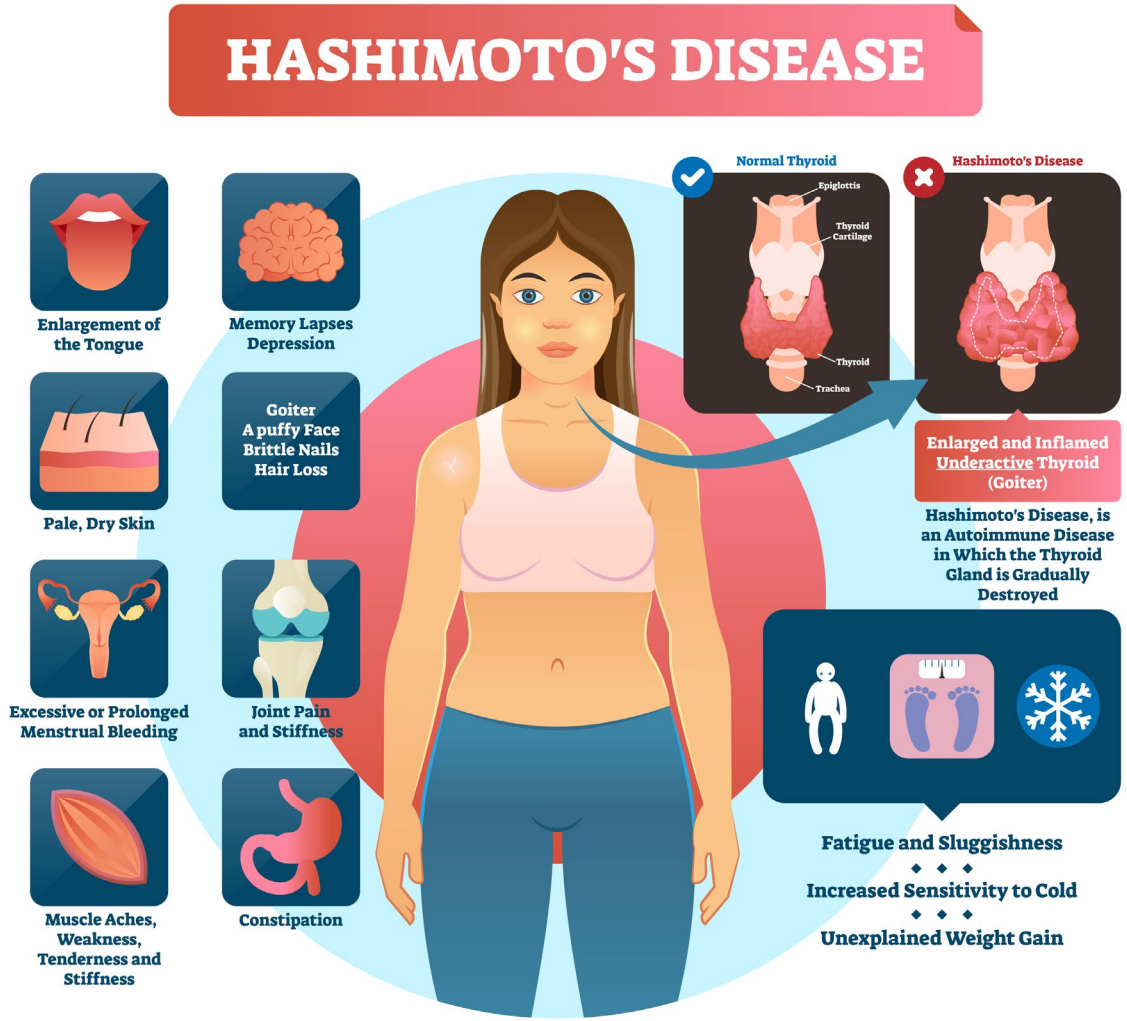
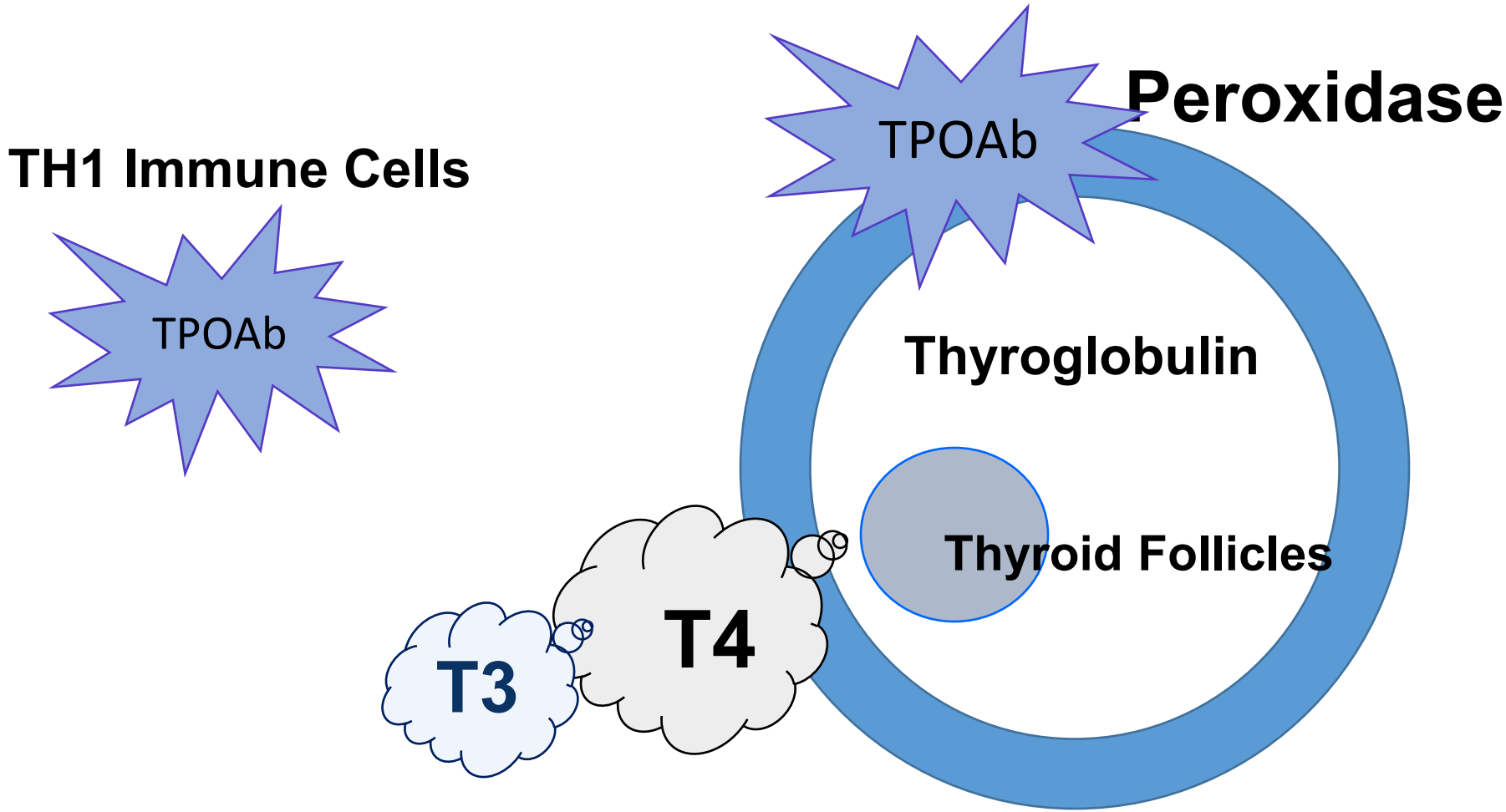
Hashimoto’s

Patients develop antibodies to a variety of thyroid antigens, the most common of which is anti-thyroid peroxidase (anti-TPO). Many also form antithyroglobulin (anti-Tg) and TSH receptor-blocking antibodies (TBII). These antibodies attack the thyroid tissue, eventually leading to inadequate production of thyroid hormone.



Thyroid Antibodies



Clinical Application

- Women are more often affected. The female-to-male ratio is at least 10:1. Although some sources cite diagnosis happening more so in the fifth decade of life, most women are diagnosed between the ages of 30 to 50 years.
- Excessive supplementation can lead to deleterious and morbid effects, such as arrhythmias (the most common being atrial fibrillation) and osteoporosis.

Dysfunctional TH1 and TH2

- Autoimmune thyroid disease (AITD) is **one of the most common organ-specific autoimmune disorders**. It mainly manifests as **Hashimoto's thyroiditis (HT) and Graves' disease (GD)…**dysfunction of these T cells or aberrant expressions of these cytokines can cause the breakdown of immune tolerance and result in aberrant immune responses during the development of AITDs
    - Li Q, Wang B, Mu K, Zhang JA. The pathogenesis of thyroid autoimmune diseases: New T lymphocytes - Cytokines circuits beyond the Th1-Th2 paradigm. J Cell Physiol. 2019;234(3):2204-2216. doi:10.1002/jcp.27180

Does removal of the gland and/or thyroid replacement therapy address the underlying autoimmune disease?

LDN and Hashimoto's

- Case studies published on the LDN Research Trust website
- Survey taken in 2015 of over 2000 readers with Hashimoto's by Izabella Wentz, PharmD, FASCP
  - While only 38 percent of those that tried low-dose naltrexone reported feeling better, those who did see benefits, had some spectacular results
  - Forty-eight percent were able to reduce their thyroid antibodies, 61 percent saw an improvement in mood, 66 percent had more energy, and 40 percent saw a reduction in pain

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MOR and TLR4

- Opioid receptors are known to share a relationship with other receptors throughout the body. However, the interaction between the mu opioid receptor (MOR) and toll-like receptor 4 (TLR4) is of particular interest due to the observed side-effects of pain, inflammation and addiction.
- As a result of TLR4 activation, a higher dosage of opioids is being used to achieve the same result leading to dependence and addiction. While analyzing opioid dependence, the type of opioids used during procedures were also scrutinized for their effects on pain and inflammation.
    - Sai Sripad Kodukula and Si Zeng. Signal Crosstalk Between TLR4 and Opioid Receptor Pathways. Translational Perioperative and Pain Medicine. February 10, 2018

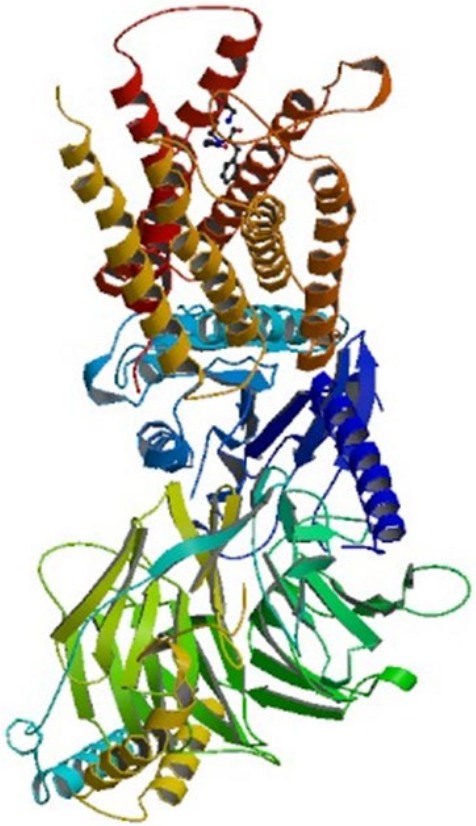
Understanding LDN Interaction with Opioid Receptors

Opioid Receptors

Name	Ligand (Protein)	Location	Function
mu (μ)	Endorphins, Opiates, low affinity for enkephalin	Plasma Membrane	Analgesia, respiration, GI motility, inflammation
Delta (δ)	Enkephalin high affinity	Plasma Membrane	Analgesia, inflammation
Kappa (κ)	Ethylketocyclazocine	Plasma Membrane	Analgesia, diuresis, inflammation
OGFr	[Met^5]-enkephalin	Nuclear Membrane	Growth, healing

Naltrexone

- Binds to all four types of opioid receptors non-specifically, in an antagonistic fashion
- But when it binds to the mu receptor the effect can vary with dosage



Mu Receptor

Mu (μ) Receptors

- Have a low affinity for enkephalin and naltrexone
- Have an opposite effect when it comes to inflammation than that seen in kappa and delta receptors
  - If levels of enkephalin and naltrexone are low they are attracted to the OGF and delta receptors and you get less inflammation
  - If the levels of naltrexone are high it causes inflammation because it goes to the mu receptor

Cell Growth and the OGF

- With normal amounts of enkephalins and endorphins, (produced by most cells in the body) cell growth is normal
- However, **when levels of both enkephalins and endorphins are too low then growth is abnormal and cancer cells can proliferate out of control**
- [Met^5]-enkephalin (a 5 amino acid sequence) is another name for opioid growth factor (OGF)
  - Once on the nuclear receptor it increases production of inhibitory kinases

OGF, LDN, Cancer

- [Met^5]-enkephalin is an endogenous opioid peptide that interacts with the OGF receptor (OGFr) to delay the G(1)/S interface of the cell cycle by modulating cyclin-dependent inhibitory kinase (CKI) pathways
- With an increase in these kinases, cell growth is inhibited
- **LDN in binding to the OGFr inhibits the growth**
- However high doses of naltrexone can stimulate tumor growth (research done using ovarian cancer cells)

Biochem Pharmacol. 2012 Sep 15;84(6):746-55. The opioid growth factor-opioid growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease. McLaughlin PJ, Zagon IS.

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Risk If Naltrexone Dose Is Too High

- Intermittent (or partial) blockade by LDN results in inhibited cell replication
- **The only opioid receptor used in regulating cancer growth is the OGFr**
- The mechanism by which LDN works in normal cells or immune cells may be different than in cancer cells

Biochem Pharmacol. 2012 Sep 15;84(6):746-55. The opioid growth factor-opioid growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease. McLaughlin PJ, Zagon IS.

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LDN in the Gut

- One mechanism is that LDN blocks the release of inflammatory cytokines, decreasing inflammation thus allowing the bowel to heal
- Another mechanism is that LDN acts on the OGF receptor and stimulates healing

Crohn’s Disease

- Several human studies have been published using LDN for Crohn’s disease

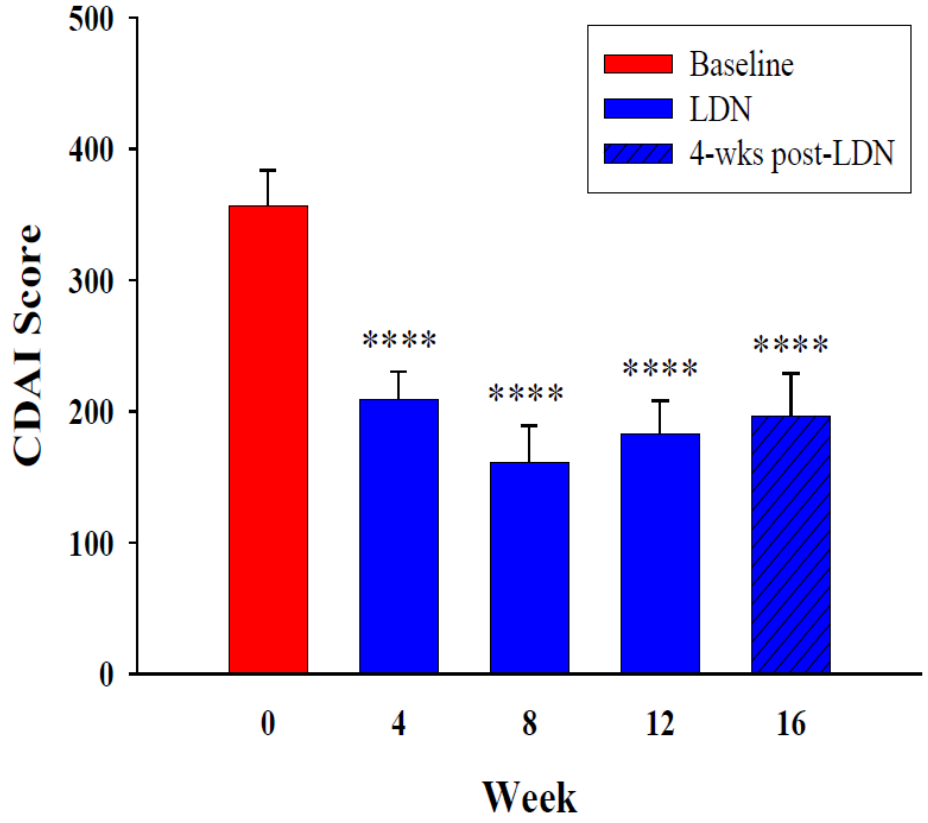
Am J Gastroenterol. 2007 Apr;102(4):820-8. Epub 2007 Jan 11.
Low-dose naltrexone therapy improves active Crohn's disease.
Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS.

Dig Dis Sci. 2011 Jul;56(7):2088-97.
Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial.
Smith JP, Bingaman SI, Ruggiero F, Mauger DT, Mukherjee A, McGovern CO, Zagon IS.

J Clin Gastroenterol. 2013 Apr;47(4):339-45.
Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study.
Smith JP, Field D, Bingaman SI, Evans R, Mauger DT.

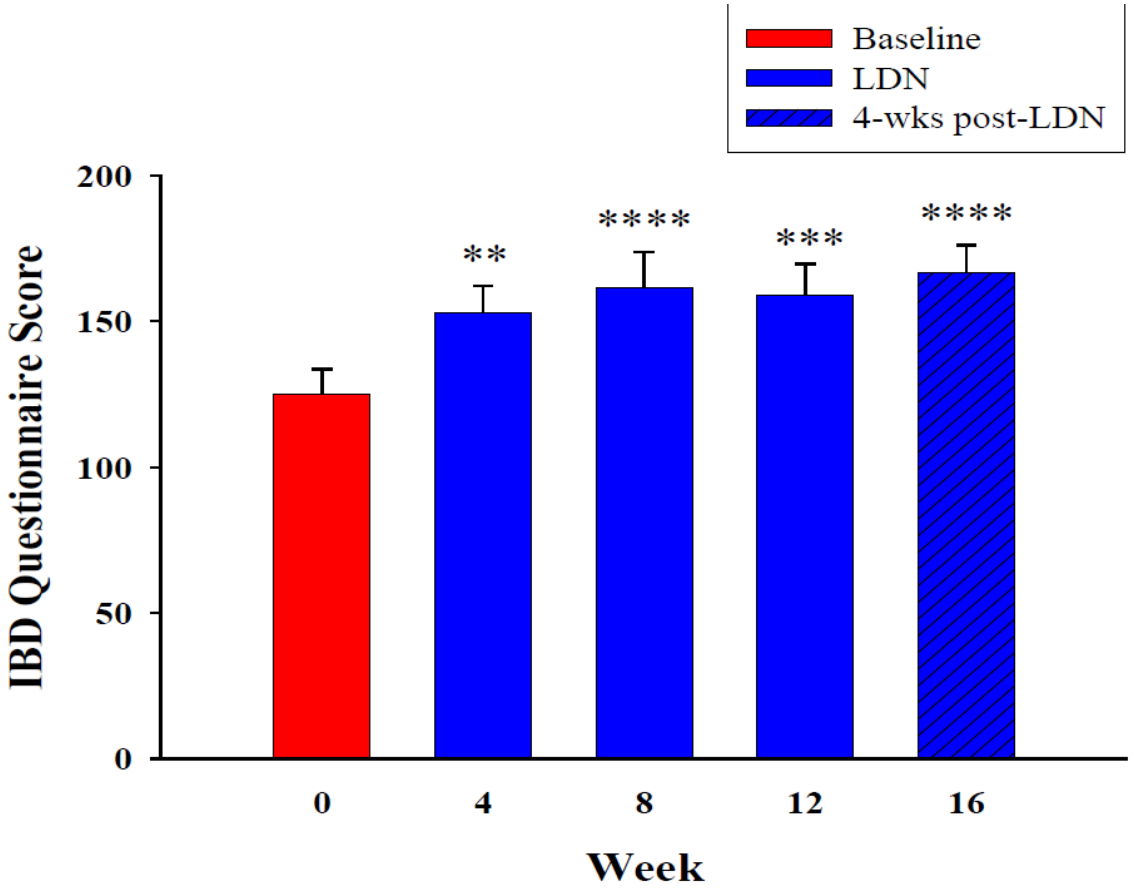
Crohn's Disease

- First Study: (Open Label)
  - Crohn's Disease Activity Index (CDAI) scores declined significantly



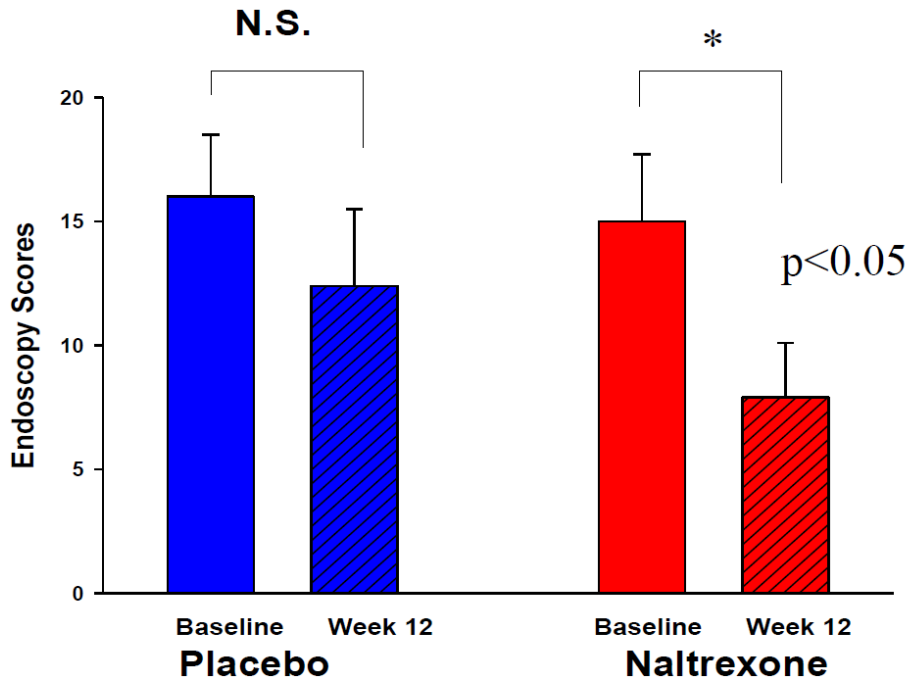
Crohn's Disease

- First Study:
  - IBD Questionnaire scores also improved significantly



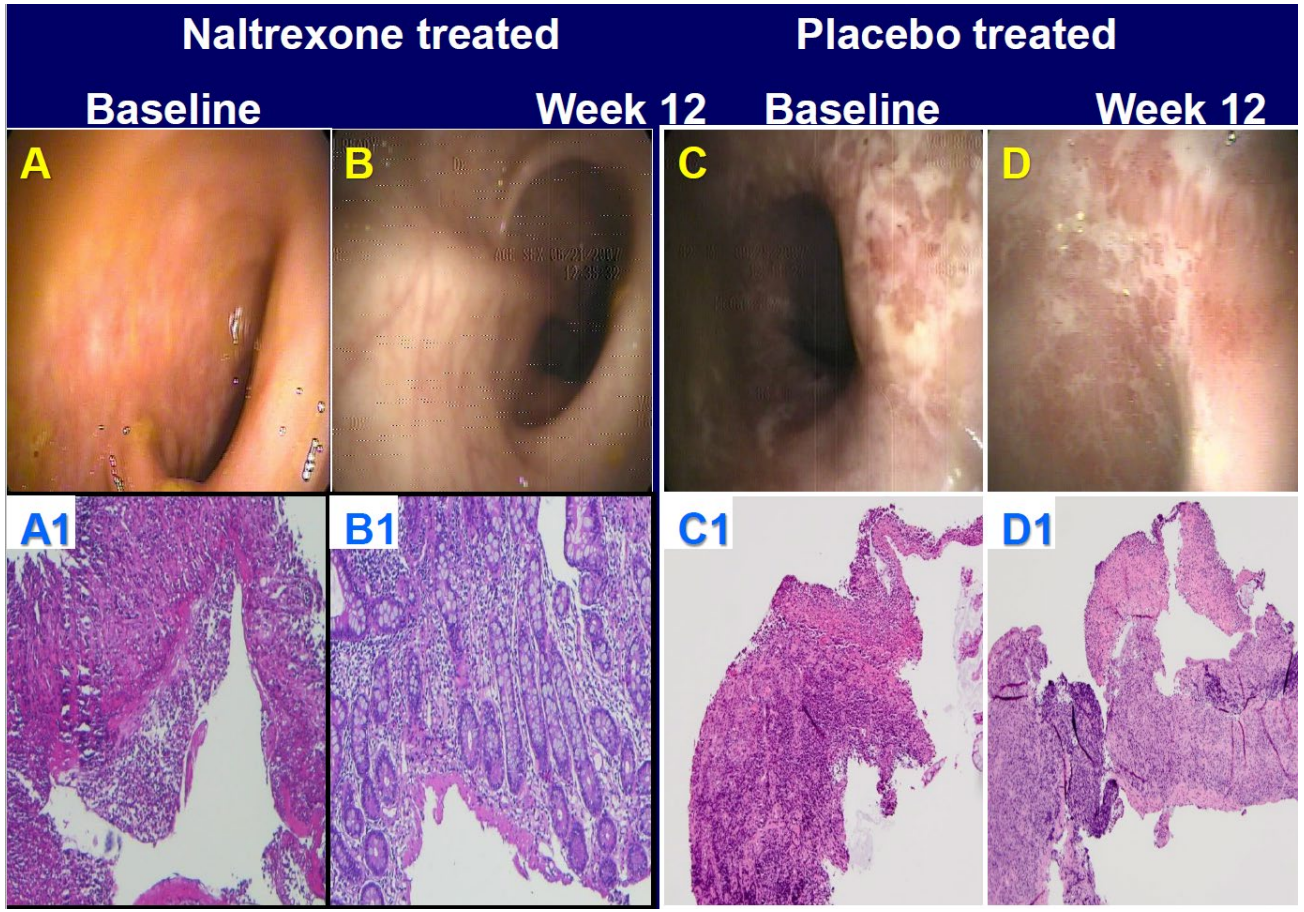
Crohn's Disease

- Phase 2 placebo controlled randomized study
  - First 3 months blinded and then at the
    3 months, open label
  - Colonoscopy and biopsy monitored
- Naltrexone showed significant improvement in CDAI scores
- 44% remission on naltrexone, none on placebo
- Endoscopy improved significantly on NTX and none with placebo



Crohn's Disease

- Phase 2 placebo controlled randomized study
  - Histology improves as well with LDN



Crohn's Disease

- The third study: *Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study.*
  - Children face difficulties with Crohn's that adults don't face
    - Another pediatric therapy consideration is the duration of treatment (life long) and the potential for severe adverse reactions
      - The anti-tumor necrosis factor alpha drugs (biologics) have black box warnings:

> Risk of serious infections leading to hospitalization or death, including TB, bacterial sepsis, invasive fungal infections and infections due to opportunistic pathogens. Also increased risk of cancers, notably lymphoma and hepatosplenic T-cell lymphoma.

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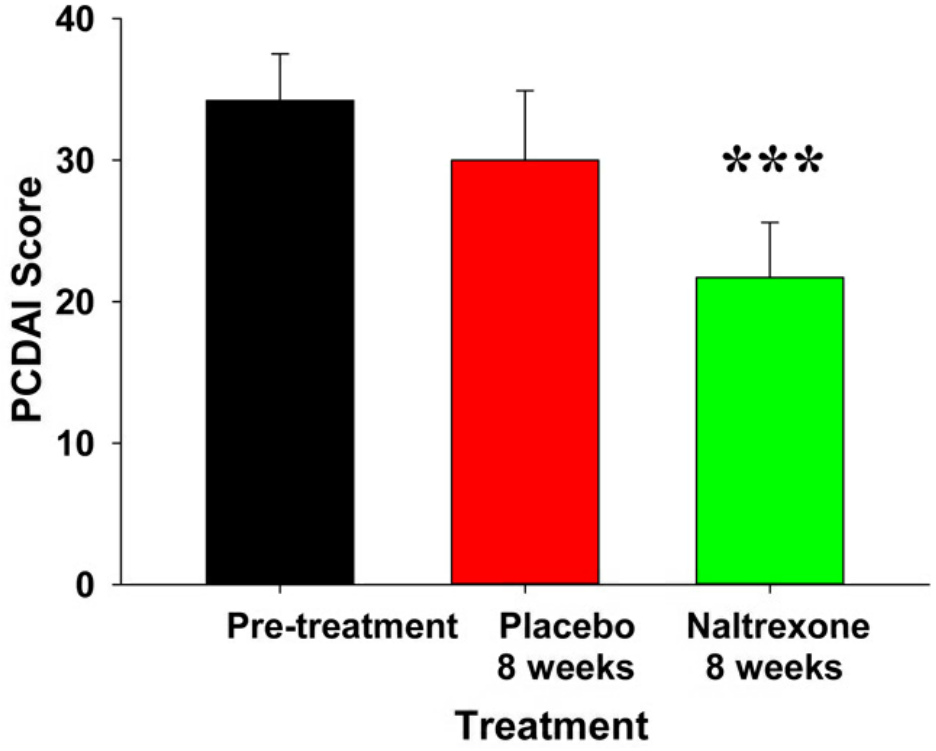
Crohn’s Disease

- The third study: *Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study.*
  - This study concluded:
    - Naltrexone therapy seems safe with limited toxicity when given to children with Crohn's disease and may reduce disease activity
- LDN decreases, but does not eliminate, cytokine production



- The mechanisms by which naltrexone helps in Crohn's disease is likely through:
  - Opioid blockade on inflammatory cells
  - Mucosal healing through the OGFr
  - Augmenting innate immunity

Additional Research on LDN and Inflammatory Bowel Disease

- Lie MRKL, et al. “Low Dose Naltrexone for Induction of Remission in Inflammatory Bowel Disease Patients.” *Journal of Translational Medicine*, BioMed Central, 9 Mar. 2018
- Raknes, Guttorm, et al. “The Effect of Low-Dose Naltrexone on Medication in Inflammatory Bowel Disease: A Quasi Experimental Before-and-After Prescription Database Study.” *Journal of Crohn's & Colitis*, Oxford University Press, 25 May 2018

Low-Dose Naltrexone for Induction of Remission in IBD

- Investigated the potential of LDN to induce clinical response in therapy refractory IBD patients and investigated its direct effects on epithelial barrier function
- 47 patients (19 with UC & 28 with CD) received LDN and were followed prospectively for 12 weeks

Table 2 Medical therapies used prior to start of LDN and concomitantly with LDN

	UC, 19	CD, 28	Combined, 47
Prior and concomitant therapies			
Therapies prior to LDN, N (%)			
5-ASA	17 (89%)	14 (50%)	31 (66%)
Steroids	19 (100%)	28 (100%)	47 (100%)
Immunosuppressives	18 (95%)	27 (96%)	45 (96%)
Anti-TNF	16 (84%)	25 (89%)	41 (87%)
Other	5 (26%)	2 (7%)	8 (15%)
Concomitant therapies at start of LDN, N (%)			
5-ASA	7 (37%)	3 (11%)	10 (21%)
Steroids	6 (32%)	18 (64%)	24 (51%)
Immunosuppressives	8 (42%)	9 (32%)	17 (36%)
Anti-TNF	5 (26%)	3 (11%)	8 (17%)
Other	1 (5%)	2 (7%)	3 (6%)
None	4 (21%)	7 (25%)	11 (23%)

Steroids refer to any form of corticosteroids. Immunosuppressives refer to thiopurines or methotrexate. Other refers to tacrolimus, cyclosporine, thioguanine or blinded trial drugs

anti-TNF anti-tumor necrosis factor, *CD* Crohn's disease, *LDN* low dose Naltrexone, *UC* ulcerative colitis

Lie MRKL, et al. "Low Dose Naltrexone for Induction of Remission in Inflammatory Bowel Disease Patients." Journal of Translational Medicine, BioMed Central, 9 Mar. 2018

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Conclusion

Strengths:

- Most patients achieving clinical remission also showed endoscopic improvements
- Study suggests that naltrexone can have direct beneficial consequences on epithelial barrier cells by stimulating wound healing
- LDN is safe and effective in the treatment of conventional therapy-refractory IBD patients

Weaknesses:

- No effect of LDN on IL-8 production
- No statistical significance in clinical efficacy

Lie MRKL, et al. “Low Dose Naltrexone for Induction of Remission in Inflammatory Bowel Disease Patients.” Journal of Translational Medicine, BioMed Central, 9 Mar. 2018

The Effect of Low-Dose Naltrexone on Medication in Inflammatory Bowel Disease: A Quasi Experimental Before-and-After Prescription Database Study

Examined whether initiation of LDN therapy by patients with inflammatory bowel disease (IBD) was followed by changes in dispensing of relevant medication

First pharmacoepidemiological study on LDN in IBD

Used the Norwegian Prescription Database as data source for identification, inclusion of patients, and outcomes

- Covered the entire Norwegian population over 4 years 2011-2015

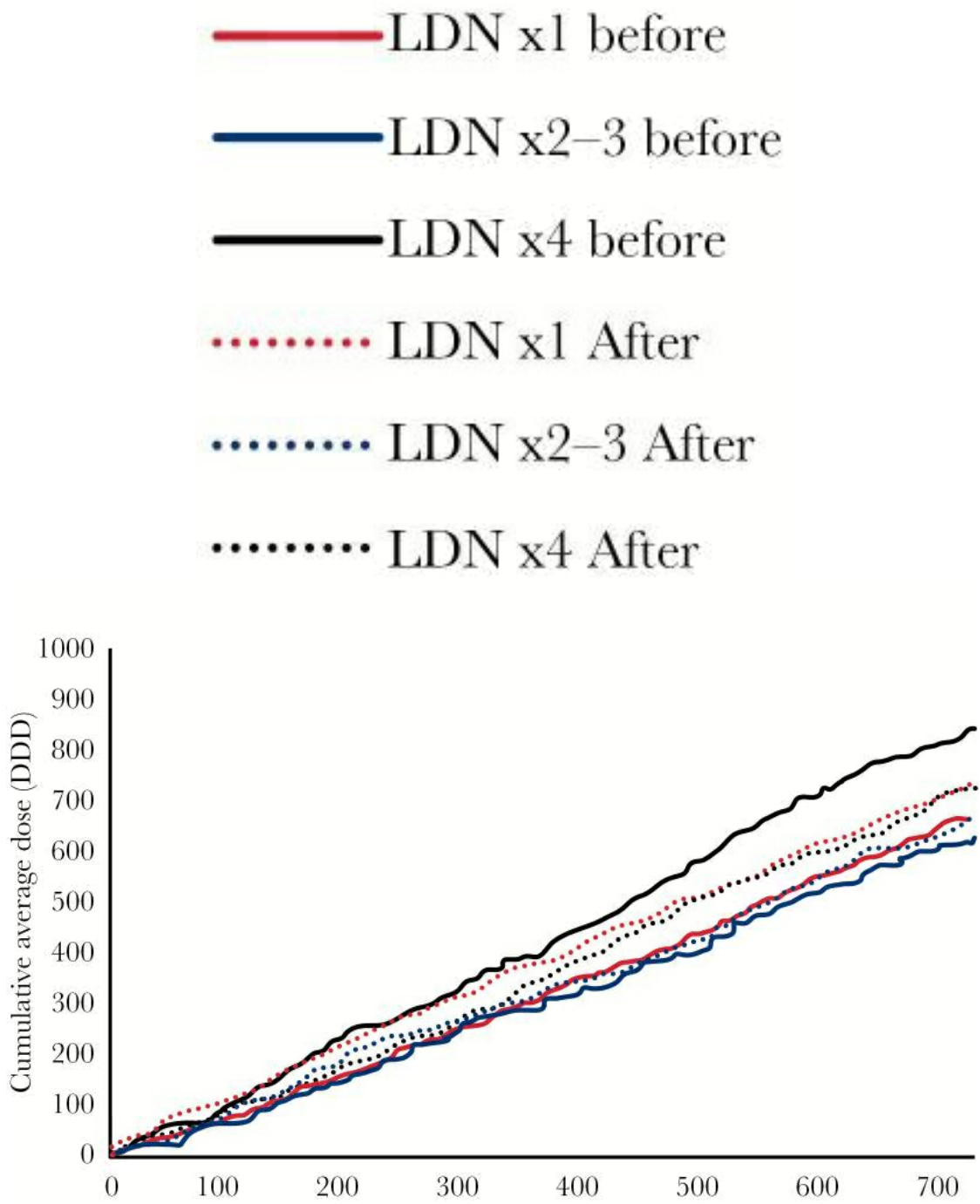
582 patients had IBD, 137 patients had CD and 178 patients had UC

Methods

- They performed a quasi-experimental before-and-after study following a sudden increase in LDN use in the Norwegian population in 2013 (index date)
- IBD patients were identified from among all the patients who had at least one LDN prescription recorded in the Norwegian Prescription Database in 2013
- Drug dispensing 2 years before and after the first LDN prescription was compared
- Included patients who received prescriptions for medications that are almost exclusively used by IBD patients
  - Mesalazine, olsalazine, balsalazine, intestinal corticosteroids

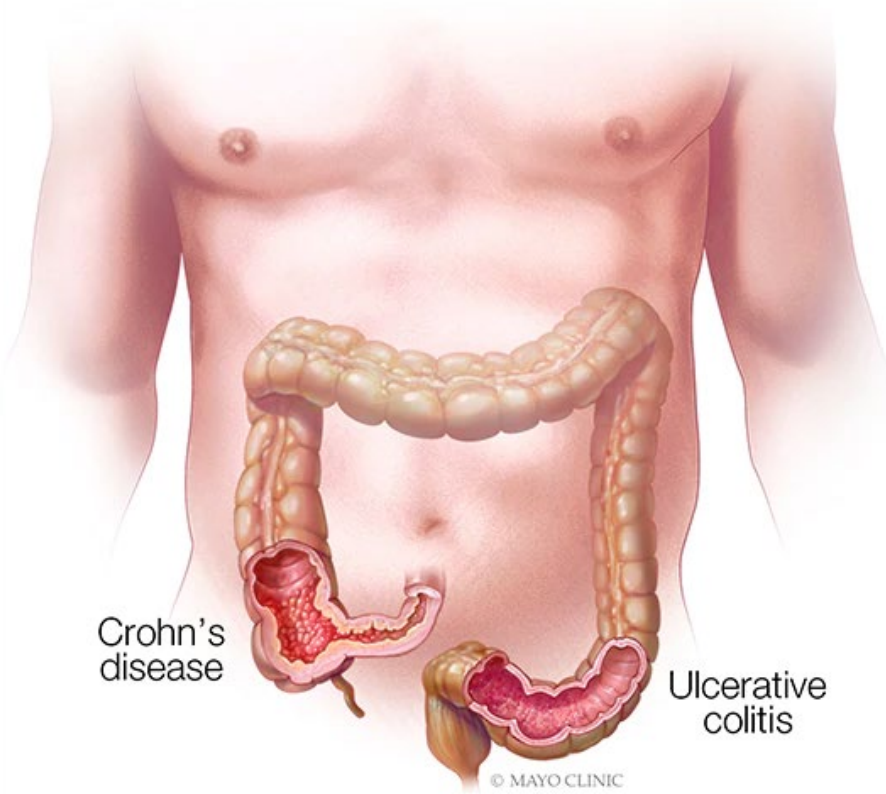
Results for CD Subpopulation

- The use of all drugs being studied among identified CD patients was consistently higher throughout the 2 years before index date compared with after in patients who became persistent users of LDN [LDN x 4+]



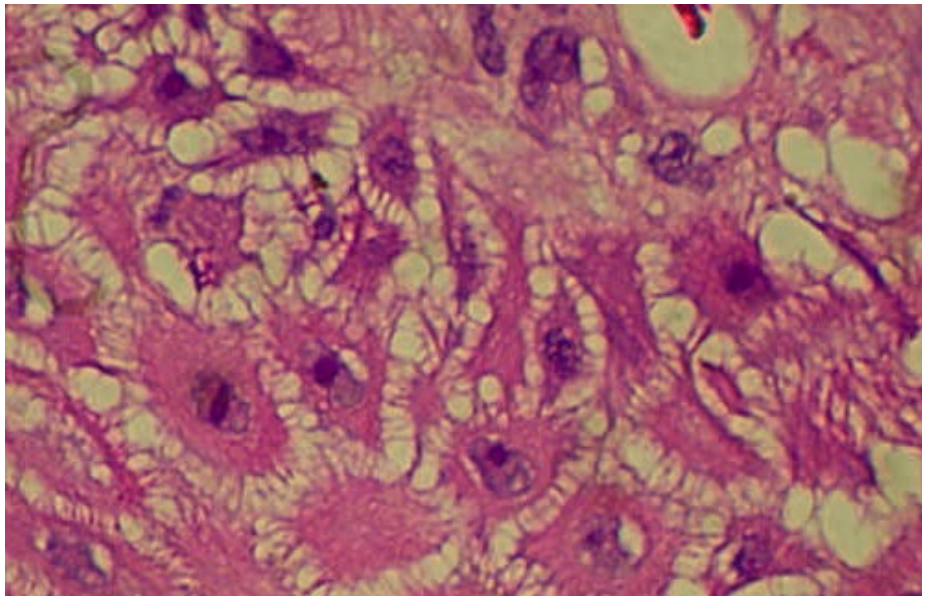
LDN for Crohn's Disease

- Is it a panacea?
- Does it work for every patient it is tried on?
  - No, but enough to make it worth trying.



Dermal Inflammation

- Naltrexone blocks toll-like receptor 4 (TLR4), which is found on keratinocytes, macrophages and microglia
- Macrophages release inflammatory cytokines such as TNFα and IL-6
- Low-dose naltrexone can suppress levels of these inflammatory markers
    - Lee B, Elston DM. The uses of naltrexone in dermatologic conditions [published online December 21, 2018]. J Am Acad Dermatol. 2019;80:1746-1752.



LDN in Dermatologic Conditions

- Dermatology is encountering increasing rates of autoimmune disease manifesting in primary skin conditions that are difficult to treat without a risk of immunosuppression
- From over 1,000 articles published from 1971 to April 2018, 22 were deemed to be appropriate for inclusion in this review for a qualitative synthesis
- There were 7 articles on low-dose naltrexone, 1 on topical naltrexone, and 14 on high-dose naltrexone use in dermatology
    - JAMA Dermatol. 2019 Feb 1;155(2):229-236. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. Ekelem C, et al.

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LDN in Dermatologic Conditions

- In high, low, and topical doses, naltrexone was effective in treating pruritus attributable to atopic dermatitis, prurigo nodularis, cholestasis, burn injury, systemic sclerosis, Hailey-Hailey disease, and lichen planopilaris
- High-dose naltrexone was ineffective in treating flushing and uremic pruritus most likely because of the lack of opioid involvement in the pathophysiologic mechanisms of these conditions
    - JAMA Dermatol. 2019 Feb 1;155(2):229-236. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. Ekelem C, et al.

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LDN in Dermatologic Conditions

- The findings suggest that low-dose naltrexone is safe and effective… both low- and high-dose naltrexone successfully treat pruritus attributable to various pathologic conditions; however, more adverse effects occurred in those taking high doses
- Low-dose naltrexone has the potential for the treatment of chronic inflammatory skin conditions
    - JAMA Dermatol. 2019 Feb 1;155(2):229-236. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. Ekelem C, et al.

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LDN in Dermatology

- In low doses, “naltrexone demonstrates immunomodulatory action i.e. modulates toll-like receptors signaling, decreases release of proinflammatory cytokines (tumor necrosis factor, interleukin-6, interleukin-12)”
- The efficacy of standard and low doses of naltrexone in a variety of dermatological disorders has been reported. These include diseases such as … psoriasis. Optimistic preliminary findings, low cost of therapy and good tolerance make naltrexone a promising alternative therapy or adjunct drug in dermatology.
    - Curr Drug Targets. 2019 Mar 18. The use of naltrexone in dermatology. Current evidence and future directions. Sikora M, et al.

Topical vs Topical with Permeation Enhancement (Transdermal)

- While NTX was delivered through the skin, the pharmacokinetics of delivery varied from oral prompt release capsules
- Then manufactured 50 mg oral tablet exhibits rapid absorption and almost complete (roughly 96%)
- Due to extensive first-pass metabolism in the liver, however, only 5—40% of the drug reaches the systemic circulation unchanged

  - Monograph Naltrexone. Clinical Pharmacology [Internet]. Tampa (FL): Elsevier. insert current year of copyright- [9/19/2020]. Available from: http://www.clinicalpharmacology.com

Topical vs Topical with Permeation Enhancement (Transdermal)

- The cream formulation exhibited steady state release of NTX over 24 h after an initial lag time of 2.74 hours and it was concluded that the cream may be an effective formulation for the sustained transdermal delivery of LDN

  - Pharm Dev Technol. 2015;20(6):694-701. Ex vivo studies for the passive transdermal delivery of low-dose naltrexone from a cream; detection of naltrexone and its active metabolite, 6β-naltrexol, using a novel LC Q-ToF MS assay. Dodou K, et al.

Topical vs Topical with Permeation Enhancement (Transdermal)

- But do we want a 24-hour sustained delivery?
- Would the opioid blockade and subsequent endorphin rebound effect change with a 24-hour delivery?
- However, 24-hour delivery may be beneficial for other mechanisms for pain or dermatological applications where it is desirable for TLR4 driven inflammation to be attenuated
    - Eur J Neurosci. 2008 Jul;28(1):20-9. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Hutchinson MR, et al.
    - J Am Acad Dermatol. 2019 Jun;80(6):1746-1752. The uses of naltrexone in dermatologic conditions. Brigette Lee, Dirk M Elston

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Eczema

- Eczema is the name for a group of conditions that cause the skin to become red, itchy and inflamed
- From the Greek: ‘to boil over’
- Pruritic papulovesicular dermatitis characterized by erythema, edema and a serous exudate in the epidermis, an inflammatory infiltrate in the dermis, oozing and vesiculation, and crusting and scaling; and later by lichenification, thickening, signs of excoriations and altered pigmentation.
- Over 30 million Americans have some form of eczema

https://nationaleczema.org/eczema/

Types of Eczema – According to the AAD

- There are several different types of eczema that you should know about:
  - Atopic dermatitis
  - Contact dermatitis
  - Dyshidrotic eczema
  - Neurodermatitis
  - Nummular eczema
  - Stasis dermatitis

https://www.aad.org/public/diseases/eczema

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https://www.aad.org/public/diseases/eczema

Atopic Dermatitis

- Atopic dermatitis is a chronic inflammatory skin disease that is characterized by intense itch and acute, subacute, or chronic eczematous skin lesions
- The disease course can be chronic or relapsing-remitting
- Lesions typically present with an age-related morphology and distribution
    - Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70:338–351.

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Atopic Dermatitis

- The prevalence of atopic dermatitis is high, affecting up to 13% of children continuing later into life and thus affects 4% to 10% of adults in the United States
- Approximately 50% of individuals having symptoms within the first year of life and 95% of patients are under the age of 5 years at onset
- The burden of atopic dermatitis on the quality of life (QOL) of patients and their families is substantial, encompassing physical and psychological well-being, social functioning and economic costs
    - Am Health Drug Benefits. 2019 Apr;12(2):83-93. The Challenge of Managing Atopic Dermatitis in the United States. Feldman SR, et al.

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Atopic Dermatitis

- Infantile atopic dermatitis is generally acute, with lesions on the face and extensor surfaces of the limbs.
- From age 1–2 and older, polymorphous manifestations with various skin lesion types are seen, particularly in flexural folds.
- Adolescents and adults often present with lichenified and excoriated plaques at flexures, wrists, ankles, and eyelids, and adults might only have chronic hand eczema or prurigo-like lesions.

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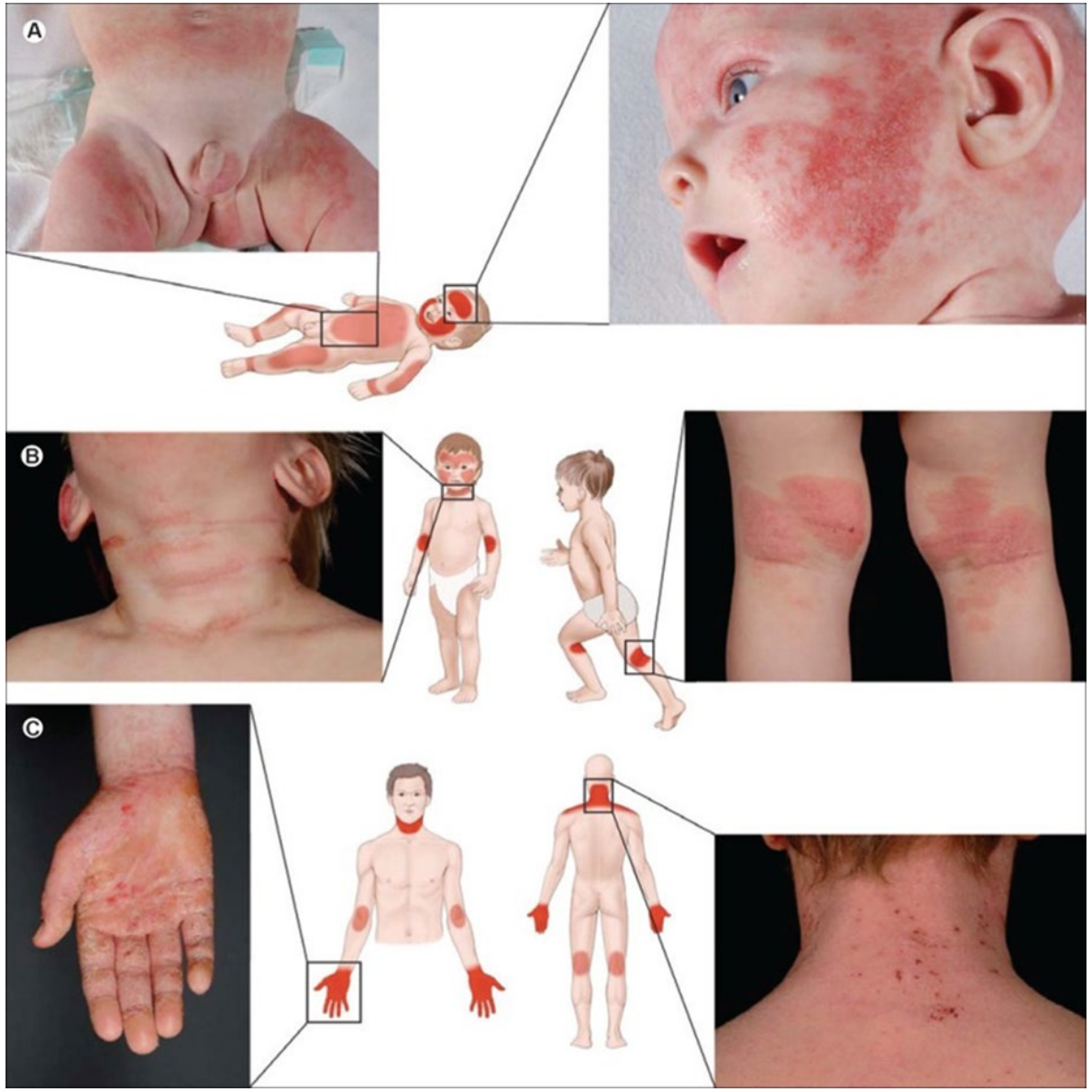
Atopic Dermatitis (AD)

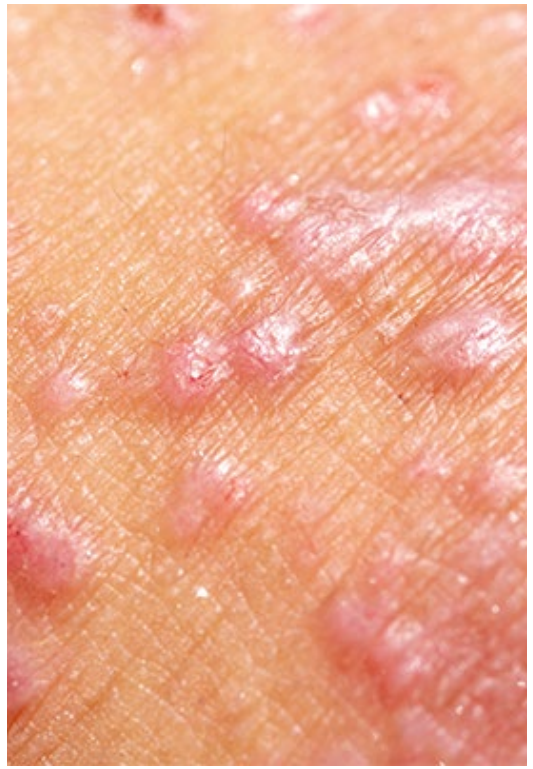
- External limbs/face (infants)
- Flexural folds (1-2yr)
- Chronic hand eczema or prurigo-like lesions (adolescents and adults)



- Am Health Drug Benefits. 2019 Apr;12(2):83-93.
  The Challenge of Managing Atopic Dermatitis in the United States.
  Feldman SR, et al.

Naltrexone Topical Options

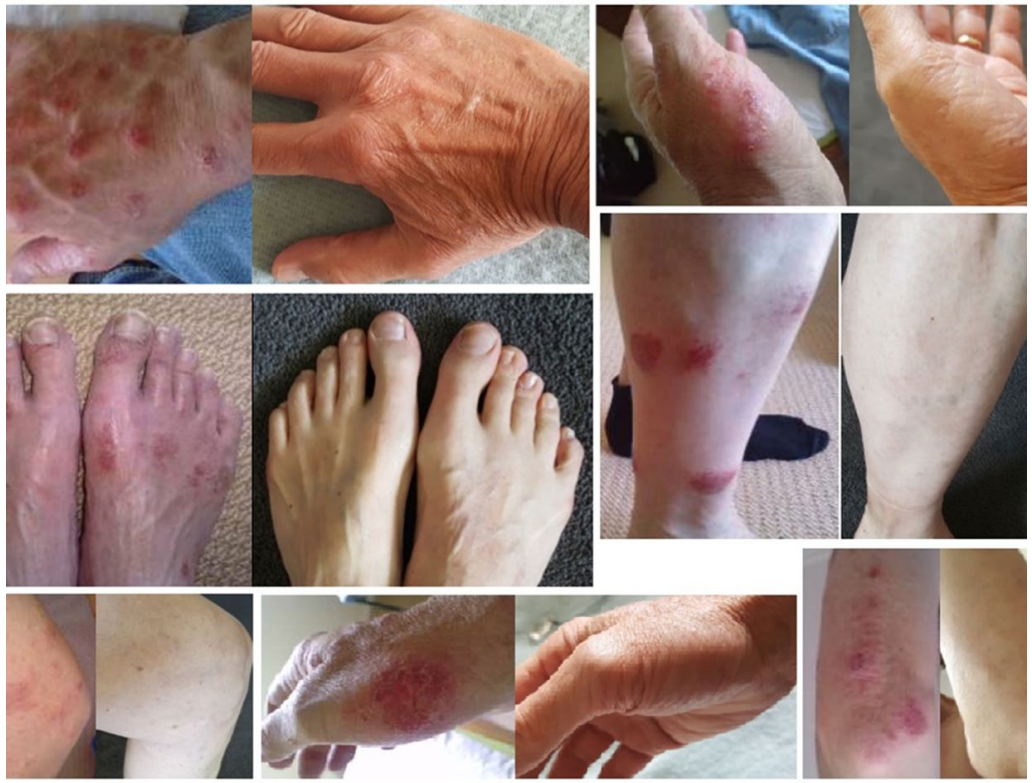
- PCCA Formula #11934 - Naltrexone HCl 1% Topical Cream (XemaTop™) (BUD Study)
- PCCA Formula #13568 - Tacrolimus 0.1%/ Naltrexone 0.5% Topical Gel (WO6® Anhydrous)
- PCCA Formula #11940 - Naltrexone HCl 0.5%/Diphenhydramine HCl 2%/Vitamin D3 5000 IU/Gm Topical Cream (XemaTop™)
- PCCA Formula #12946 - Azelastine HCl 0.175%/Ketotifen 0.05%/Naltrexone HCl 0.5% Topical Cream (VersaBase®)



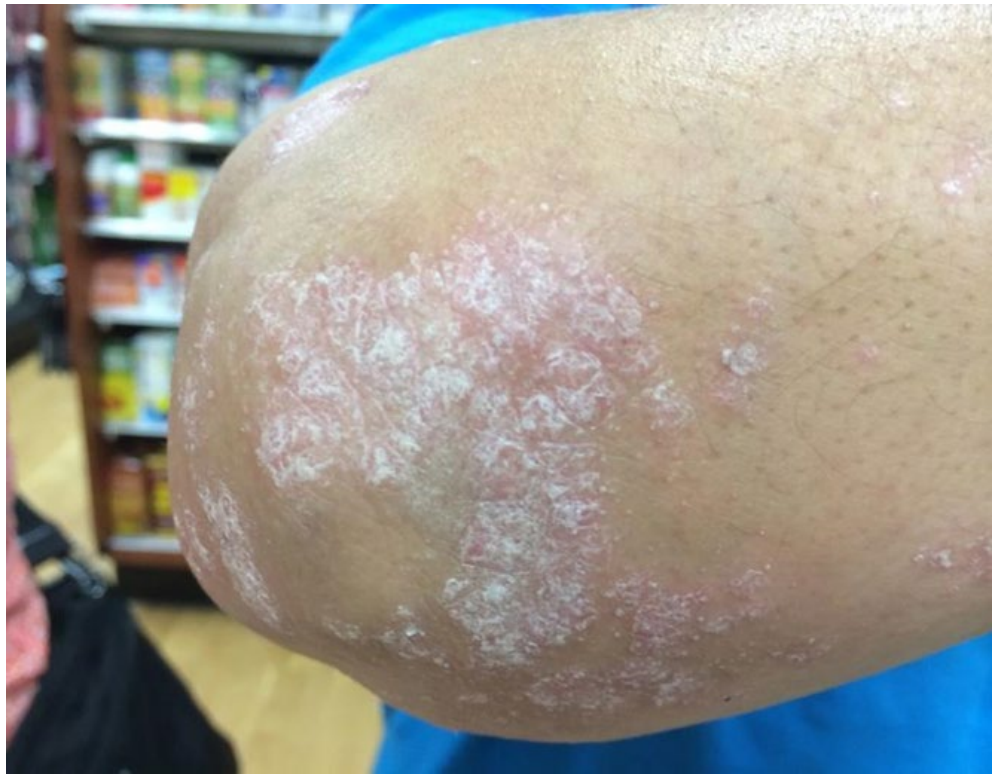
J Am Acad Dermatol. 2007 Jun;56(6):979-88. Epub 2007 Feb 22.
Treatment of pruritus with topically applied opiate receptor antagonist.
Bigliardi PL, Stammer H, Jost G, Rufli T, Büchner S, Bigliardi-Qi M.

Oral Low-Dose Naltrexone (LDN)

- Atopic dermatitis case from the www.ldnscience.org website
- “I experienced severe eczema all over my body for 12 years. It was a total change in my ability to actually live my life. I currently take 4.0 mg.”



Plaque Psoriasis

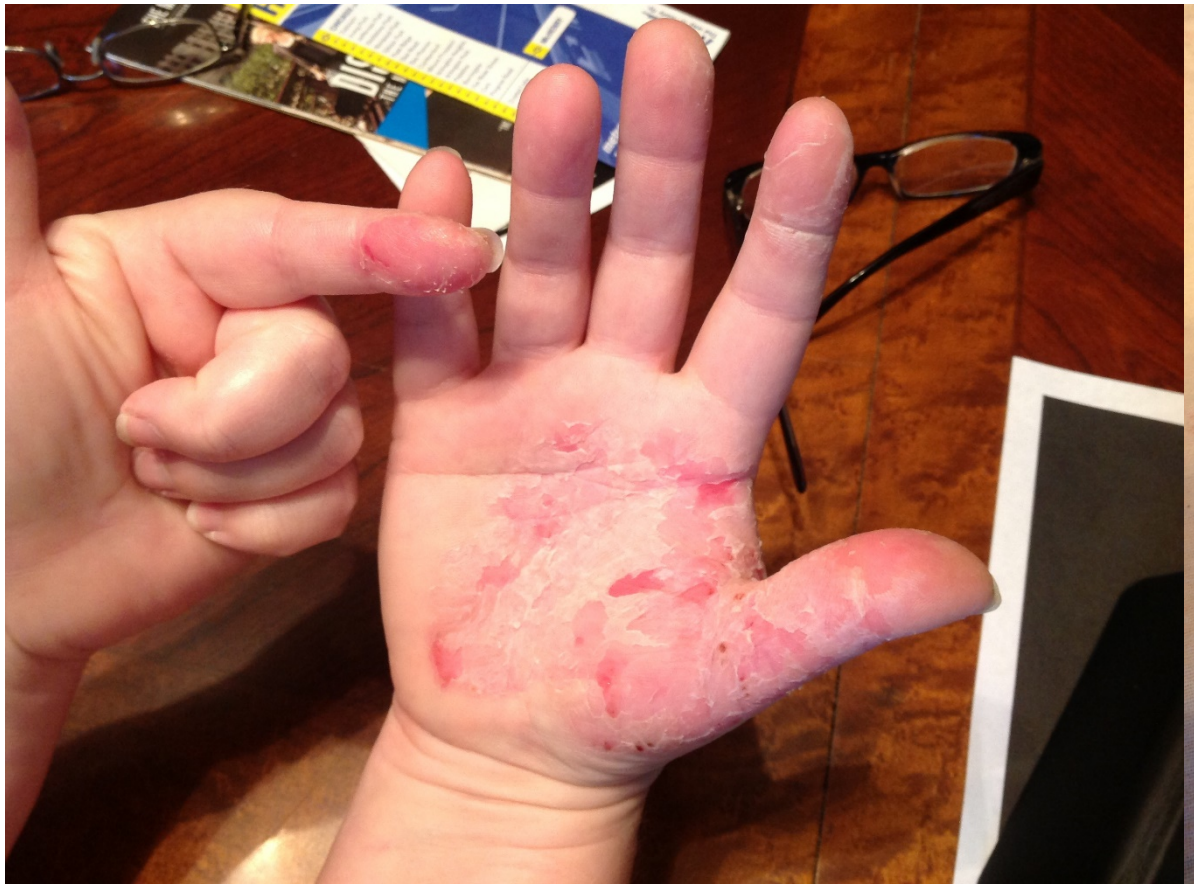


- Lifelong autoimmune disease characterized by patches of abnormal skin that are typically red, itchy and scaly
- Is genetically transmitted but environmentally triggered
- Inflammatory skin disease affecting all major human populations with the greatest prevalence of 2-3% in those of northern European ancestry

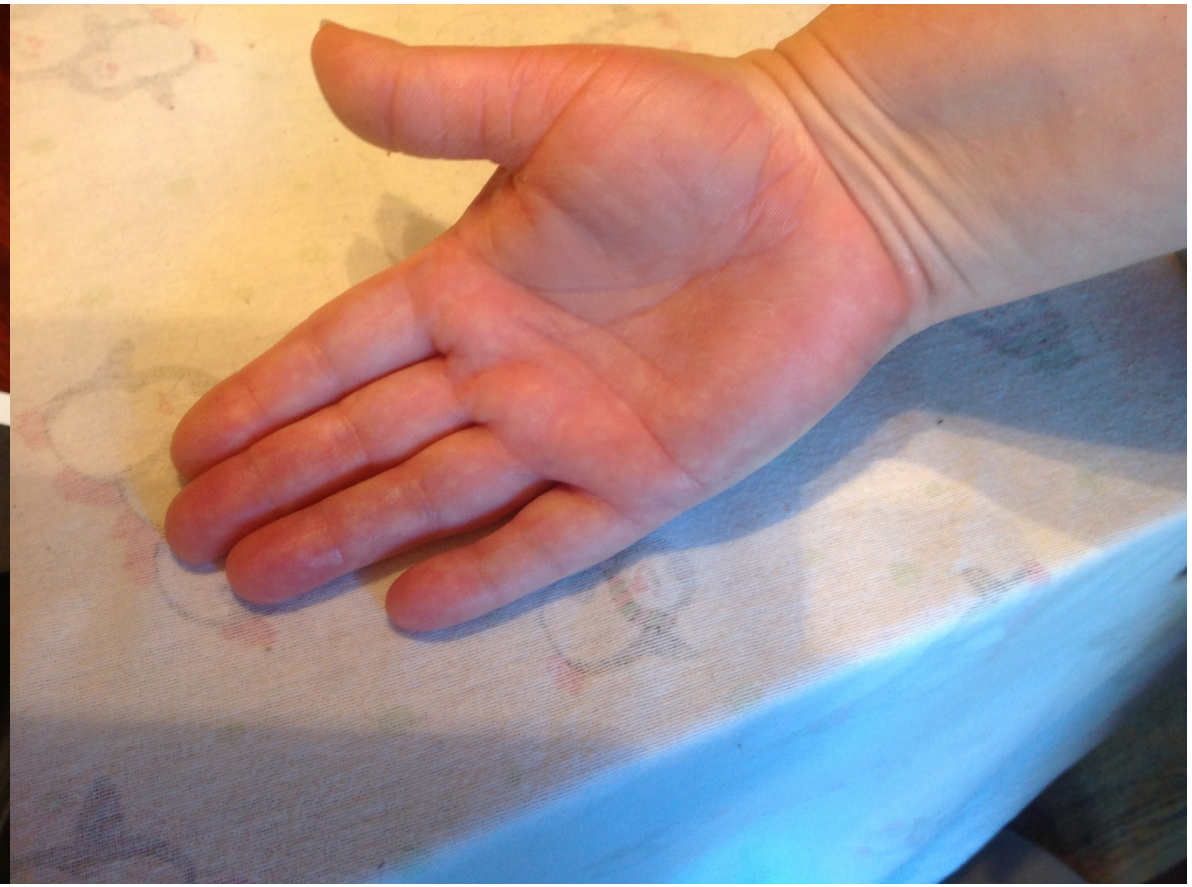
Compounding Options

- PCCA Formula #11788 - Zinc Pyrithione 0.2%/Clobetasol Propionate 0.05%/Cyanocobalamin 0.07% Topical Cream (XemaTop™) (BUD Study)
- PCCA Formula #13100 - Carbamazepine 2%/Zinc Pyrithione 0.2%/Cyanocobalamin 0.07% Topical Cream (XemaTop™)
- PCCA Formula #13568 - Tacrolimus 0.1%/Naltrexone HCl 0.5% Topical Gel (WO6® Anhydrous)
- PCCA Formula #11940 - Naltrexone HCl 0.5%/Diphenhydramine HCl 2%/Vitamin D3 5000 IU/Gm Topical Cream (XemaTop™)

Psoriasis Case (Photo Courtesy of Kevin Hoey)



Before

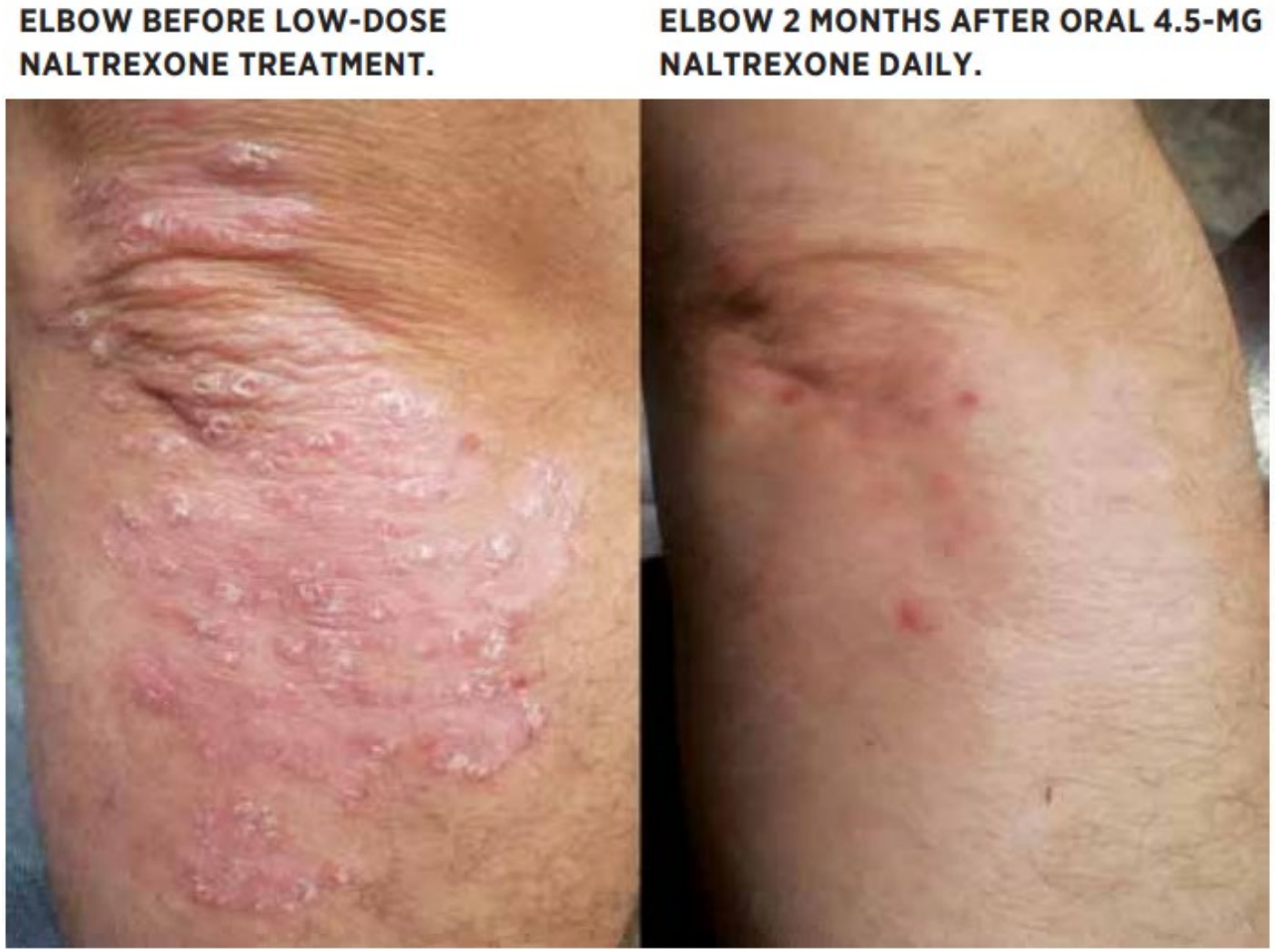


After

Ten weeks of LDN therapy

Psoriasis

- Marked improvement was seen by 53% of the 15 patients. Low-dose naltrexone regulates lymphocyte responses, reduces cytokine production, and likely reduces mast cell activity. Low-dose naltrexone is safe, inexpensive, and appears be effective in this open-label study.
  - Int J Pharm Compd. Mar-Apr 2020;24(2):94-96. Low-dose Naltrexone Therapy for Psoriasis. Leonard B Weinstock, Jill Cottel, Lindsey Aldridge, Alexander Egeberg



TLR Receptors and Vaginal Tissue

- TLR-dependent stimulation of Female Genital Tract (FGT) epithelial cells *in vitro* induces secretion of IL-1α, IL-1β, IL-6, IL-8 and TNF-α, and cyclooxygenase 2 (COX-2), an inducible enzyme associated with mucosal inflammation
  - Front Immunol. 2014 Aug 12;5:386. TLR-Dependent Human Mucosal Epithelial Cell Responses to Microbial Pathogens. Ryan McClure, Paola Massari

Vaginal Issues

- Vulvodynia/vestibulodynia – chronic neuropathic inflammatory condition of complicated origin, often following a vaginal yeast infection or BV where the innate immune response is not downregulated properly
- Lichen sclerosus – T-cell mediated autoimmune disease

Vaginal Naltrexone

- Topical for vulvodynia/vestibulodynia
  - PCCA Formula #13862 - Naltrexone HCl 1%/Baclofen 2% Topical/Vaginal (Ellage™ Anhydrous)
  - PCCA Formula #13319 - Naltrexone HCl 0.5% Vaginal Gel (MucoLox™/VersaBase®)
  - PCCA Formula #13860 - Naltrexone HCl 0.5% Topical/Vaginal (Ellage™ Anhydrous)
- Vaginal lichen sclerosus
  - PCCA Formula #13319 - Naltrexone HCl 0.5% Vaginal Gel (MucoLox™/VersaBase®)
  - PCCA Formula #13934 - Naltrexone HCl 0.5%/Ketotifen 0.05%/Tacrolimus 0.03% Topical/Vaginal (Ellage™ Anhydrous)

Dosing Dilemmas

- Big issue is that a lot of practitioners are stuck in the Bihari protocol and less than 50% of patients get results with that standard titration protocol
  - We need to realize that it's not as simple as we thought…
- It is very frustrating because it can be a miracle for some and other's, nothing… 70% of the practitioners get frustrated and don't alter their approach and stop and say, "Well I tried LDN, but it didn't work for a lot of my patients."
- It's not a race to 4.5…

We Can’t Be Myopic

- We should take dosing schedules a step further
- Every patient is unique
- There is no one regimen that works for every patient
- We need to start closer monitoring and analyze the dosage to see where benefits occur, not just remission of the main problem but any benefit!
- If benefits decline as we increase the dosage, then we need to reduce it back to that dosage that gave the best result
  - If we don’t track results, how will we know what worked or didn’t?

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What Are the Dangers?

- Other than idiosyncratic anaphylaxis, you can do little harm with LDN
  - What do you have to lose in trying this therapy?
- The side effects of low dose are minimal and probably almost impossible to discern with ultra low dose
- If you mess up, start over
  - Do-overs are allowed!
  - Be flexible, start over, go slow (try 0.25 mg increments)

Mulligans for Everybody!

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Depression in Autoimmune

- Up to 50% of patients with autoimmune diseases show an impairment of health-related quality of life and exhibit depression-like symptoms
- The immune system not only leads to inflammation in affected organs, but also mediates behavior abnormalities including fatigue and depression-like symptoms

  - Curr Top Behav Neurosci. 2017;31:139-154. Depression in Autoimmune Diseases. Pryce CR, Fontana A.

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LDN

- You can use LDN for any chronic pain condition, but it is not a pain medication that covers pain up
- It **is a disease modification agent**
- The benefit of this modification can be decreased symptoms which can include inflammation and pain
- It not only can improve those symptoms but some of the comorbidities like depression and anxiety

Dosing 2.0

Hybrid Dosing – to Treat Comorbidities

- What if you have someone with fibromyalgia and depression or anxiety?
  - Depression (or other psych issues) can be titrated with daytime dosing and fibromyalgia with bedtime dosing.
- Given the extremely short half life of LDN (4 hours) the am and pm doses can be treated as completely independent doses with different purposes behind them. This is different compared to the concept of "splitting" the dose as is often the case with other medications to treat one condition.
- Morning dose (0.5 to 1 mg) for mood, evening dose for the disease state. Titrate up in 0.5 mg increments or less.

Your Pharmacy Partner

- Patient interaction
  - Patient counseling
  - Handling patient questions
  - Dose response and dosage titration recommendations
  - Patient follow-up

Under-Promise and Over-Deliver
Results May Vary!

- We need to give our patients a reasonable expectation as to how long LDN therapy will take before they start to see results
- How long?
  - Crohn's: titrate up to 4.5 mg and may take 3 months at maintenance dose
  - Dermatologic problems can take a long time (6 months)
  - Hashimoto's thyroiditis, about 2 weeks for initial response
  - Usually takes about a month for autoimmune, fibromyalgia, general pain (LDN is usually subtle in its effects)
  - Mental health 1-2 weeks response most of the time (morning dose)
- Dietary changes with gut repair protocol usually required

PCCA®

Quality of Naltrexone

The PCCA Standard™

Our commitment to going beyond what is required.

Sourcing Chemicals

We set the bar high because we want you to have a reliable supply of chemicals that consistently meet The PCCA Standard, above and beyond USP specifications. Because your pharmacy and patients matter to us, and because **the best clinical outcomes start with the best ingredients.**

To ensure that we find the best active pharmaceutical ingredient (API) manufacturer every time, we developed **PCCA API Manufacturer Qualification Program.**

1 Manufacturer Assessment

At the heart of our API Manufacturer Qualification Program is our extensive **API Manufacturer Qualification Assessment**, which considers **over 40 important factors** within the manufacturer's quality management system, manufacturing and materials management systems, and distribution system.

2 Sample Testing

Even if a manufacturer passes our API Manufacturer Qualification Assessment, we also obtain a sample of the chemical we plan to buy from them and test it in our Quality Control lab like we do with every other chemical we receive.

3 PCCA Formula Testing

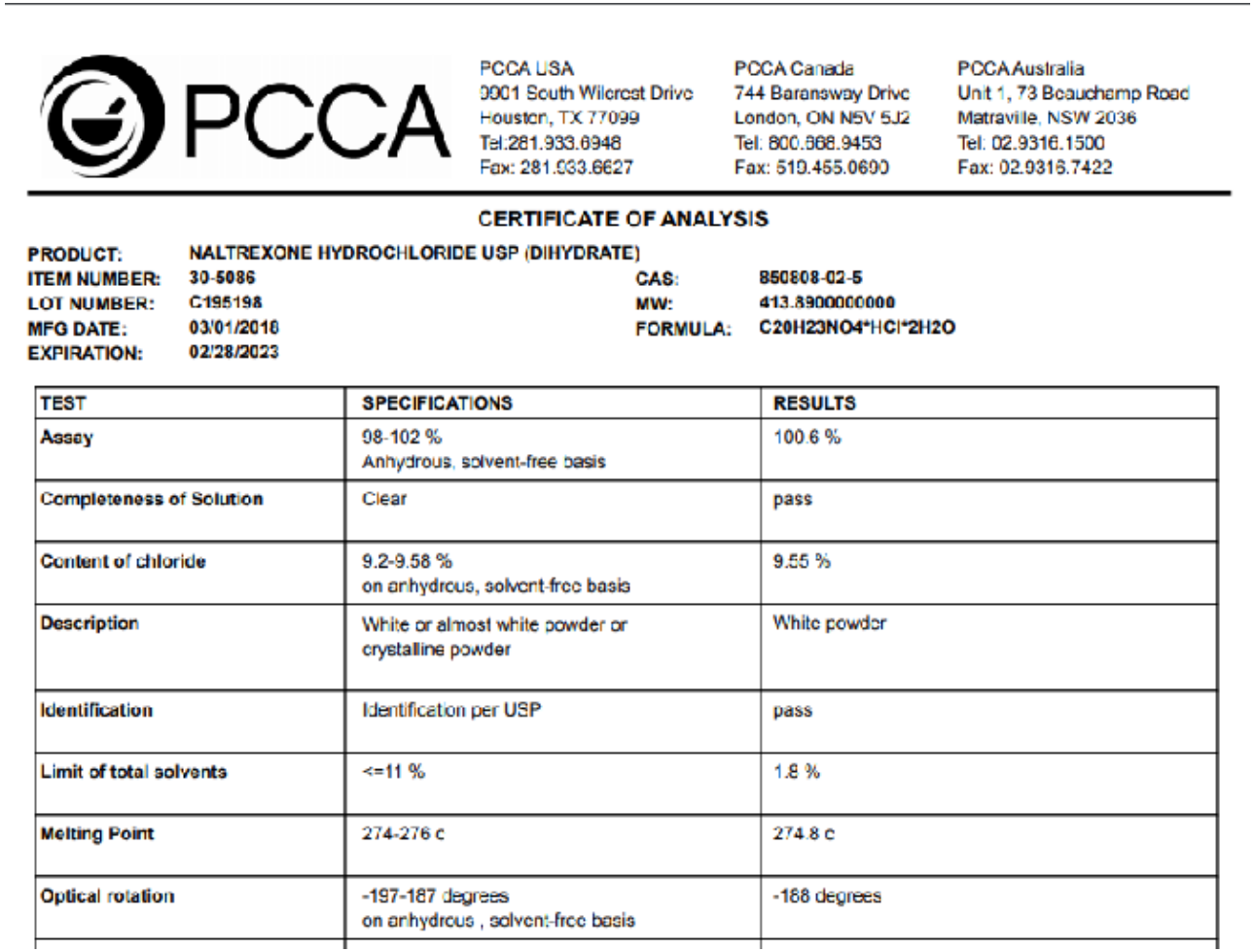
We also verify the chemical with our Formulation Development department, and they conduct further testing to ensure that the chemical works in our formulas when necessary. Because we won't create formulations for our members with products that we don't stand behind.

4 Manufacturer Reassessment

Not only do we extensively assess API manufacturers and their products before we approve them as a source, we then re-assess the manufacturer every two years. We also verify their licenses initially and annually thereafter with the appropriate regulatory agencies.

Not Organic Chemistry

- Accuracy
- Precision
- Reproducible
- Clinical outcomes for your patients



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Matraville, NSW 2036
Tel: 02.9316.1500
Fax: 02.9316.7422

CERTIFICATE OF ANALYSIS

PRODUCT: NALTREXONE HYDROCHLORIDE USP (DIHYDRATE)
ITEM NUMBER: 30-5086
LOT NUMBER: C195198
MFG DATE: 03/01/2018
EXPIRATION: 02/28/2023
CAS: 850808-02-5
MW: 413.8900000000
FORMULA: C20H23NO4*HCl*2H2O

TEST	SPECIFICATIONS	RESULTS
Assay	98-102 % Anhydrous, solvent-free basis	100.6 %
Completeness of Solution	Clear	pass
Content of chloride	9.2-9.58 % on anhydrous, solvent-free basis	9.55 %
Description	White or almost white powder or crystalline powder	White powder
Identification	Identification per USP	pass
Limit of total solvents	<=11 %	1.8 %
Melting Point	274-276 c	274.8 c
Optical rotation	-197-187 degrees on anhydrous , solvent-free basis	-188 degrees

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Submit your questions to the pharmacy via private Chat.

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COMPOUNDING
PHARMACY

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