A "Holy Grail" of Medicine?

The search for the "holy grail" of medicine, a unique compound that improves the quality of care, better patient outcomes, and experience while lowering healthcare costs, is the dream of every pharmaceutical CEO. Add to that the imprimatur of a major medical society, say statins and cardiology, or government, Covid vaccines, and "mandates," and we have the makings of a multibillion-dollar entity that *may* serve humanity along with the shareholders of said company.

"Holy grails" come and go. Some, like ledipasvir/sofosbuvir (Harvoni), live up to their hype, curing hepatitis C in 94-97% of cases. [(1)] Others, CETP inhibitors that boosted HDL, "good cholesterol" while lowering LDL "bad cholesterol," for example, were studied for more than ten years, costing upwards of two billion dollars in research, and failed to provide any benefit whatsoever. [(2)] an entity that could affect many ailments, particularly in the "mysterious" and challenging to treat rheumatoid and \ autoimmune category? What if the said entity was proven effective, easy to obtain, inexpensive, had a nearly non-existent side effect profile, acting as an aid, and sometimes substitutes for expensive and toxic biologics? What if the same said entity was hiding in plain sight, largely unknown in the medical community as it is "unpatentable" due to its reformulation from an older drug?

The said entity, of course, the subject of this paper, is "low-dose" naltrexone.

The story of low-dose naltrexone begins the darkest days of the AIDS crisis. A terrifying "plague" was devastating the immune systems of a subsegment of the population. Later found to be a virus, it manifested itself as a bewildering array of previously rare, difficult to treat, and opportunistic infections.

Those of us on the frontlines, myself included, found ourselves scrambling to learn what we could about, for example, *pneumocystis carinii pneumonia, Kaposi's Sarcoma, and cytomegalovirus meningitis.* Our diagnostic and treatment regimens for these "orphan" diseases were generally ineffective and came too late for our patients. There were no HIV antivirals.

Desperate times call for desperate and sometimes brilliant measures. In 1985, New York City physician Bernard Bihari discovered that AIDS patients had less than 33% of the expected levels of endorphins. [(3)] Secreted by the pituitary gland, endorphins act on opiate receptors resulting in pain reduction and pleasure enhancement. [(4)]

Low endorphin levels weaken the immune system. [(5)] So, Dr. Bihari, a Harvard-trained researcher, reasoned, raising endorphin levels would strengthen a patients' natural defenses.

Sometimes the unseen hand of an unknown entity acts as a guiding angel. Some might call it luck. Others deemed it a happy accident. Or, whatever took place before his discovery, was necessary to get to the right place at the right time.

In any event, Dr. Bernard Bihari's interest before the AIDS crisis was addiction medicine. In 1984, his attention was on a newly released FDA-approved competitive opioid receptor antagonist, naltrexone, dosed at 50 and 100 mg. to treat alcohol and opioid dependence.

100 mg of naltrexone provides at 24 hours after dosing, 96% blockade of the opioid receptors, 86.5% at 48 hours, and 46.6% at 72 hours. [(6)] Repeat dosage of 100 mg. of naltrexone results in the binding to and blockade of the pleasure-promoting μ(mu)-, (delta)-and (epsilon)-opioid receptors[endorphins] found on cell membranes and lowers endorphin levels. [(7)]

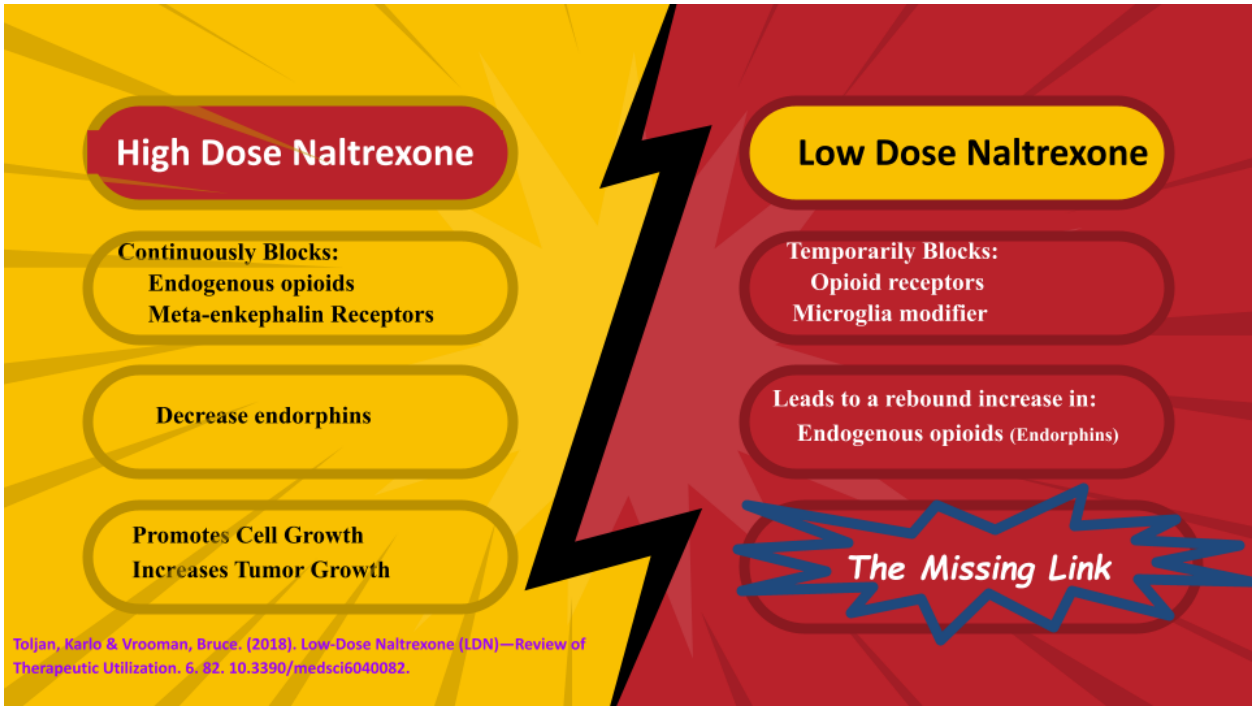
What happens with a rise in endorphins? By temporarily blocking opioid receptors, the body reacts to the clearing of the opioid receptors after a four-hour to the six-hour impediment that endorphins rebound, boosting endorphin production by as much as 200-300 % from baseline. [(8)]

Dr. Bihari's study published in 1986 sought to determine the outcome of administering low-dose naltrexone on a group of HIV patients. At nine months into the placebo-controlled trial, the treatment group's survival rate and rate of opportunistic infections greatly exceeded the non-treated cohort by 92 to 67%. [(9)]

The "gold standard" at the time for tracking HIV infection progress was in CD4 counts. Low dose naltrexone halted the progressive decline of CD4 cells but did not increase them. [(10)] Hence, it never caught on as a mainstream HIV treatment.

So if raising endorphins but not CD4 counts are LDN's mechanism of action, how do we account for the impressive list of maladies low dose naltrexone effects? [(11)]

There is something in the make-up of low-dose naltrexone that is very different from its' high-dose parent? [12]



Recall from the archives of yesteryear Certs Breath Mint. Certs were a candy mint and a breath mint. "Two, two mints in one." (And it contained retsyn, whatever that was.)

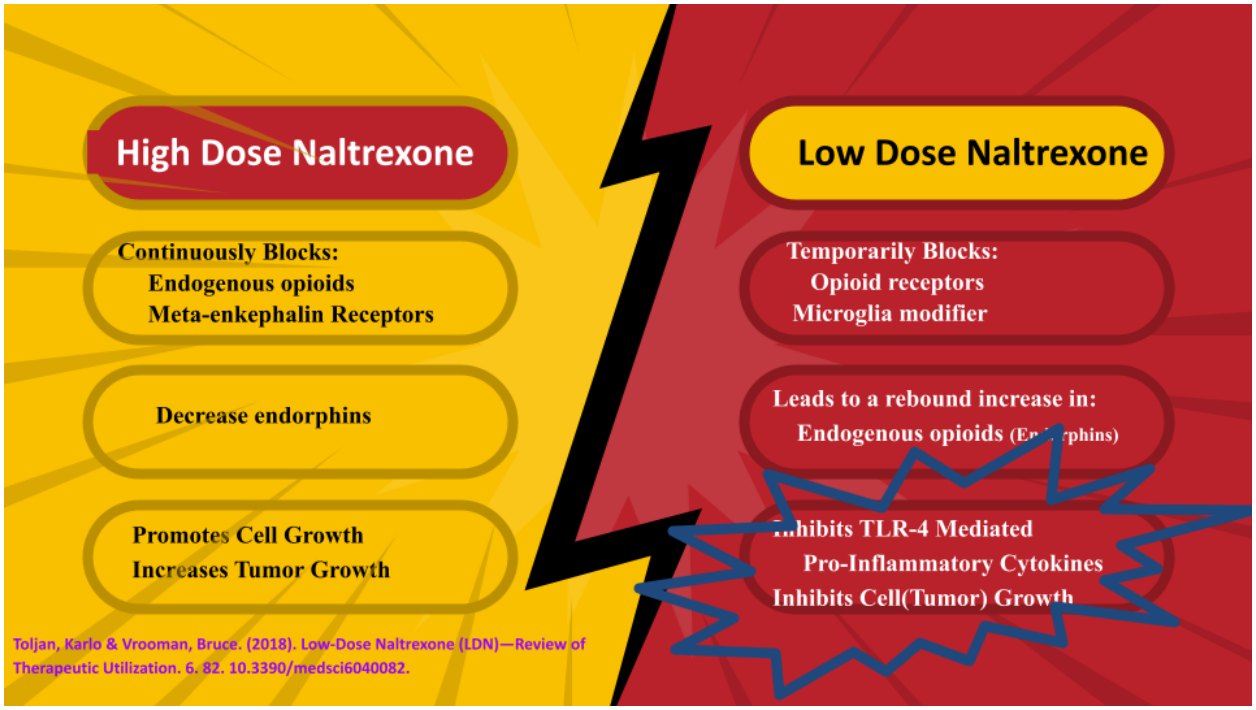
Low dose naltrexone a 50:50 mixture of dose-dependent L *(Levo)* and D (*Dextro*) isomers, is "two" drugs in one. The *Levo* portion of naltrexone blocks opioid receptors, creating the rebound-induced endorphin increase discussed above. [13]

The *Dextro* naltrexone isomer antagonizes inflammatory proteins, specifically "Toll-Like Receptors (TLF) generated in the presence of noxious stimuli. [14] Toll-Like Receptor occur in many inflammatory states and varieties, labeled 1 through 10.

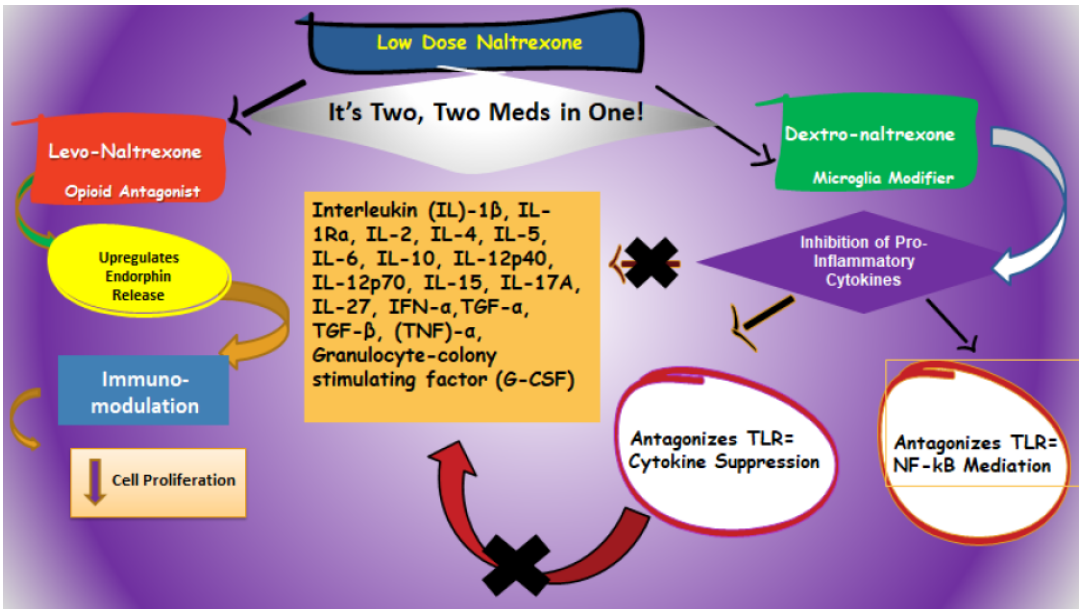
The *Dextro,* right-handed portion of low dose naltrexone, antagonizes TLR 4 proteins resulting in a significant reduction in the inflammatory cytokines TNF-a, ROS, and NF-kB1. [15] This immune regulatory effect is not seen in high dose (50-300 mg) naltrexone.

Found in the central nervous system's immune cells, the microglia, house inflammatory-inducing TLR 4 proteins. Activation of the microglia produces inflammatory & excitatory transmitters, and if chronic leads to neurotoxicity. [16]

"The Missing Link" that makes low-dose naltrexone so powerful is the immune-modulating effects on pro-inflammatory cytokines.



"Levo" low dose naltrexone thus increases endorphins, while "dextro" low dose naltrexone decreases inflammatory cytokines. [17]



A Brief Time Out. Two (Slightly) Off-Topic, but Interesting Observations:

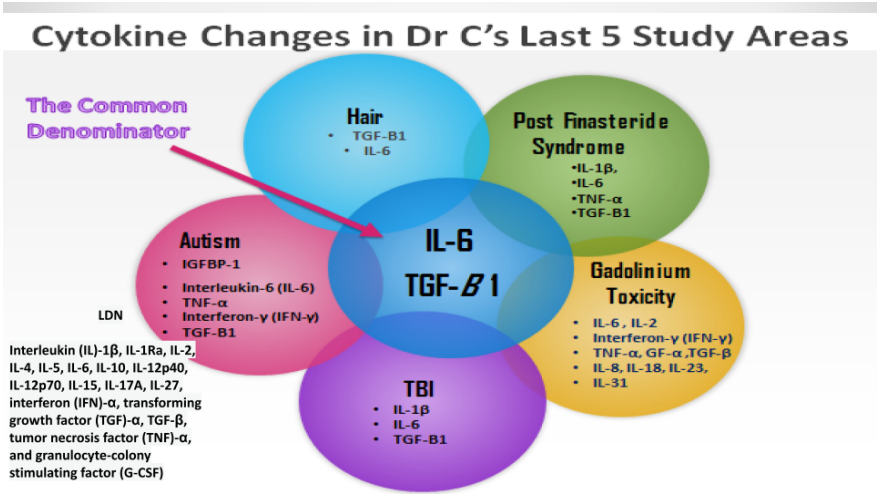
In 1991 I attended and graduated from the UCLA School of Medicine's Medical Acupuncture for Physician's program. Like any other medical intervention, some techniques are beneficial, others not so much. The mechanism of action of acupuncture as a body of knowledge is always a contentious issue, especially amongst the "learned" crowd who think they know everything. (Small wonder that during my time in Kenya, the Westerners and those who "followed the science" suffered the most from malaria. The native population who stuck with their traditional tribal remedies were much less afflicted. Go figure.

Return with me to the American Academy of Medical Acupuncture's annual symposium in St. Louis, Missouri, circa 2015. Dr. William Clearfield delivered a paper on the inflammatory cytokine and chemokine changes induced by acupuncture therapy.

1. Acupuncture downregulates proinflammatory markers: [18-19]
   a. *Cytokines*: IL-1b, IL-2, IL-6, IL-12, Il 17, IFN-g, and TNF-a
   b. *Neuropeptides*: Substance P, Neurokinin A, VIP, Bradykinin, and Calcitonin Gene-Related Peptide

2. Acupuncture upregulates anti-inflammatory cytokines IL-4 and IL-10.

And for good measure, here are the cytokine changes in a few of the projects I've lectured on from 2019 through 2021:



Now Back to Our Regularly Scheduled Program

A Deep Dive into Selected Conditions Treated by Low Dose Naltrexone

Psoriasis

Psoriasis is a chronic skin condition caused by keratinocyte hyperproliferation resulting in flaking, inflammation, and thick, white, silvery, or red patches of skin. [20]

Psoriasis is associated with an increased risk of atherosclerotic vascular disease, coronary artery disease, and cerebrovascular accidents. Psoriatic patients, on average, have a 5-year shortening of life expectancy. They should be screened periodically as at risk for coronary and cerebrovascular disease. [21]

Cytokines elevated in psoriatic conditions include TNF-alpha, IL-12/23, IL-17, IL-22, IL-23, GM-CSF, and the Janus kinases. [22] LDN was found safe and effective in psoriatic sitting. [23]

The mechanism of low-dose naltrexone in the psoriatic setting includes both its effect on opioid receptor rebound beta-endorphins and the reduction of proinflammatory cytokines.

The discovery of opioid-like growth factors (OGF) and opioid growth factor receptors (OGF-R) in immune cells leads to the third mechanism of action for LDN.[24] Opioid growth factors, Met(5)-enkephalin, is the model we use, act as pain modulators and immune and cell function modulators. Opioid growth factor receptors exhibit antibacterial, anti-fungal, antiviral, anti-neoplastic, and anti-inflammatory properties by decreasing IFN-Gamma and TNF-alpha. [25-26]

A five-year retrospective study involving the use of low-dose naltrexone reported an additional 57% reduction in symptoms versus "conventional" therapies. [27]

Dosing LDN in Psoriasis

Basic Protocol [28]

- **1.5 mg @ bedtime x 14 nights then:**
- **3.0 mg @ bedtime x 14 nights then:**
- **4.5 mg @ bedtime x 14 nights then:**

- **Reassess after six months. If relief is inadequate, decrease LDN to 3.0 mg, then increase by 0.5 mg every 2-4 months until a maximum of 4.5 mg.**

With Anxiety and/or Depression

- **0.5 mg @ bedrtime x 14 nights then:**
- **0.5 mg in am and @ bedtime x 14 nights then:,actingand**
- **0.5 mg in AM, 1 mg in PM then**
- **1 mg in am, 1 mg in PM**

With Skin Issues

★ ***Increase dose by 0.5 mg 2x/day every two months up to a maximum of 4.5 mg***

Topical Solutions for Eczema, Itch, Psoriasis[29-30]

- **Naltrexone HCl 0.5%/Diphenhydramine HCl, 2%/Vitamin D3 5000 IU/Gm**
- **Naltrexone HCl 1%, Tranilast 1%/Cyanocobalamin 0.07% Topical Cream**
- **Naltrexone HCl 1%/Melatonin 2.5%/Tranilast 1% Topical Cream**
- **Naltrexone HCl 1%/Pramoxine HCl 1% Topical Gel**
- **Naltrexone HCL 1% in Xematop Cream**

Autoimmune Thyroid Disease

Thyroid abnormalities originate from two main entities; innate (heredity) and acquired (something happened somewhere). Up until the mid-1960s, thyroid disease was mainly a hand-me-down family trait. With the rise of eight thousand + and still rising chemicals, drugs, food alterations, you name it; our immune systems haven't kept up. Autoimmunity, especially thyroid autoimmunity, is on a relentless rise.

Hypothyroidism, a result of thyroglobulin-specific T cell-mediated thyroid tissue destruction, is known as *Hashimoto's Thyroiditis.* [31] Excessive production of thyroid hormone-induced, i.e., *Graves Disease,* is hyperthyroidism, occurring via thyrotropin receptor-specific stimulatory autoantibodies. [32]

The reported incidence of autoimmune hypothyroidism varies between 2.2/100 000/year (males) and 498.4/100 000/year (females). For autoimmune hyperthyroidism, incidences range from 0.70/100 000/year (Black males) to 99/100 000/year (Caucasian females). [33]

"Conventional" wisdom dictates that autoimmune thyroid disease is an inherited condition and that, other than "normalizing" thyroid function with levothyroxine, T4, we physicians can do nothing about it. Patients asking "experts" and their primary care practitioners about diet, Vitamin D, and anti-inflammatory agents, for the most part, are told, "none of that matters. Live with it."

I have been called a "shaman," which I thought meant medicine man and healer. Still, in this case, the author, a board-certified endocrinologist, meant definition number eight "a dweller of the dark arts."

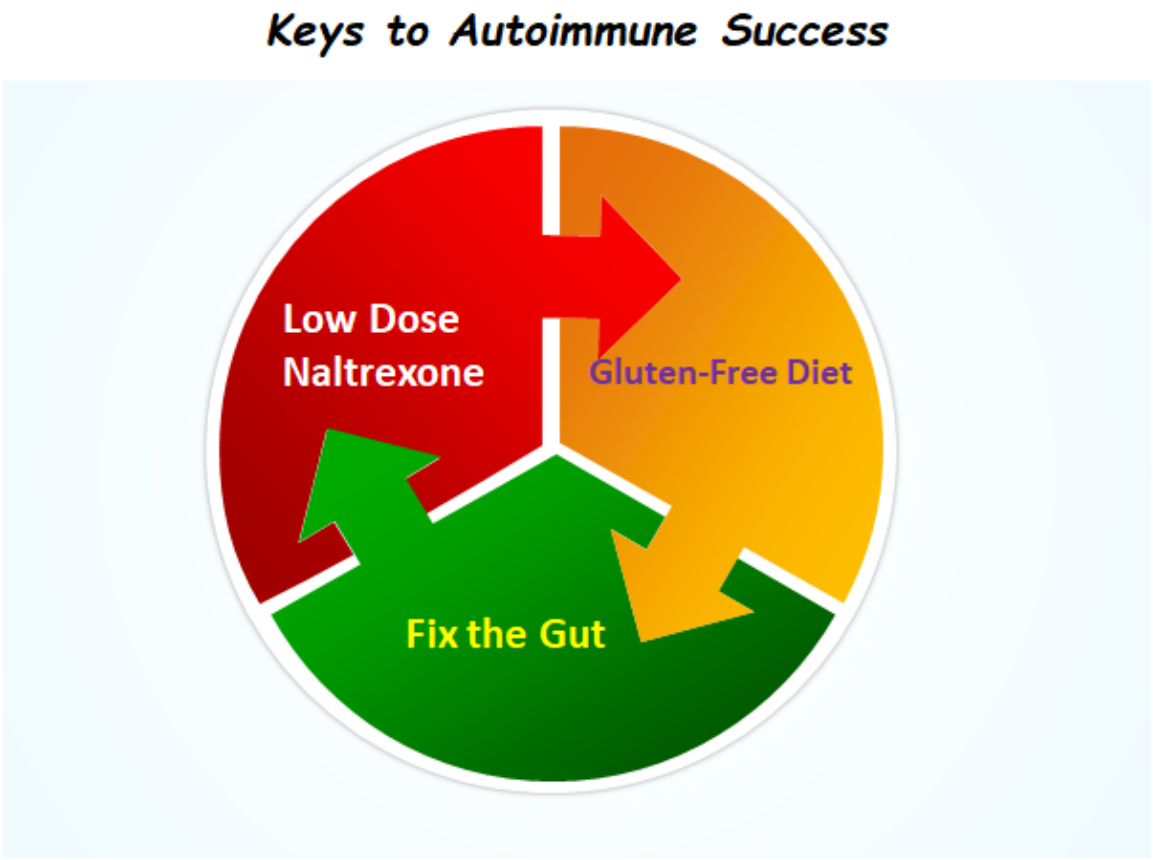
> Ms. nas Hashimotos. She also probably has untreated OSA, which is likely the driver of her sympto complex. Overall, I feel Dr. Clearfield is a shaman, preying on the placebo effect and some modest clinica side effects from drugs like T3 to "help" patients. In my opinion, its a shame he is a DO and he disgraces degree.

A VA doctor called me a "concierge doctor who orders beaucoup tests and does things like injecting patients' genitals. Just ridiculous stuff."

Guilty on both counts. In the latter case, we offer platelet-rich plasma as part of our adult anti-aging program.

As to the former, I emulate one of my mentors, Dr. Pam Smith, who offers a bit of a short-cut

when dealing with autoimmune issues: [34]

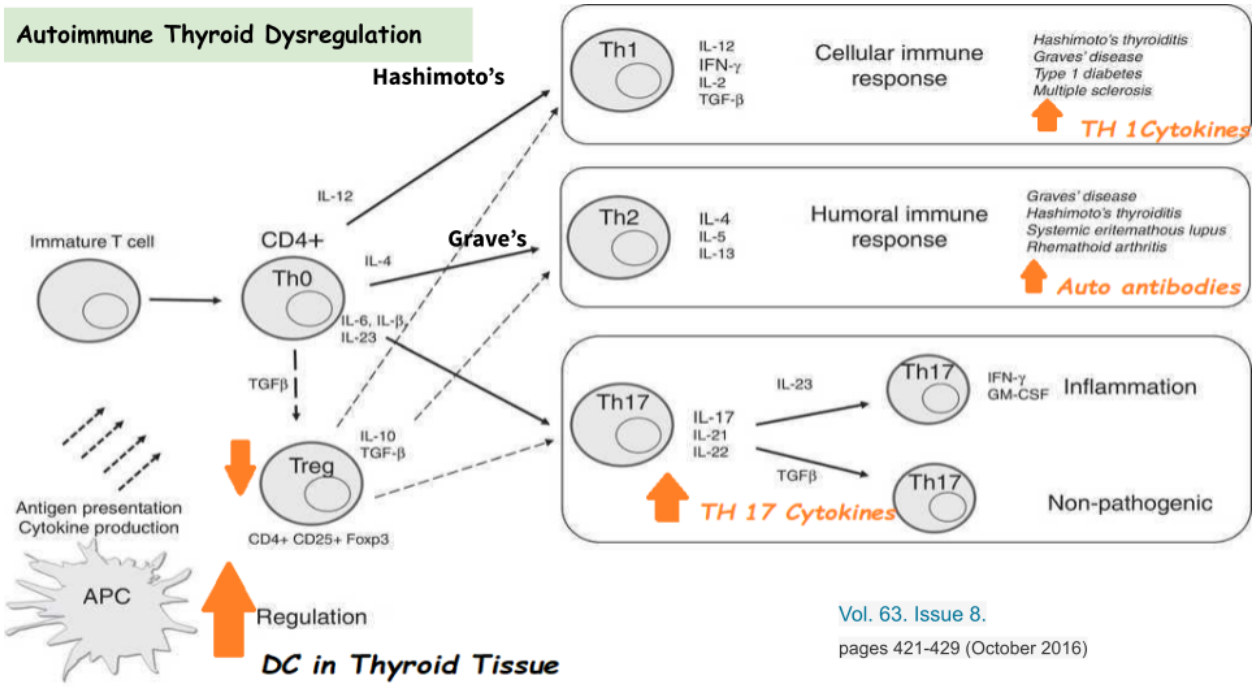


Low dose naltrexone's effect on thyroid antibodies includes (1) a two to three (2-3) fold increase in endorphin activity and increased number of endorphin receptors, (2) a reduction of pro-inflammatory cytokines and increase of anti-inflammatory cytokines, and (3) regulation of OGF/OGFr axis. [35]

We monitor thyroid function every six to eight weeks, at least initially, as LDN improves T4 to T3 conversion. It is not uncommon for thyroid activity to improve, rendering the patient hyperthyroid without adjustments.

Cytokines active in Hashimoto's thyroiditis (autoimmune hypothyroidism) include IL-2 IL-12, IFN-gamma, and TGF-beta. Cytokines of note in Graves' Disease (autoimmune hyperthyroidism) are IL4, IL-5, and IL-13. Inflammatory cytokines triggering thyroid disease involve IL-17, IL-21, IL-22, IFN-gamma and GM-CSF. [36]

A five-year study resulted *in* pain reduction in 57% of patients, improved energy in 55% of patients, and improved mood in 41%. [37]



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pages 421-429 (October 2016)

Dosing LDN in Hashimoto's Thyroiditis

Loading Dose: 0.5-1.0 mg @ bedtime.

Follow-up: Increase by 1 mg. every 1-2 weeks to a maximum of 3 mg.

a. *Some literature recommends dosing to 4.5 mg. In my experience of > 500 Hashi patients, 2.0-2.5 mg is the usual tolerated dose.*
b. If sensitive to LDN, use the liquid form.
c. Compound LDN in 0.1 mg intervals

Crohn's Disease

Crohn's disease is a transmural, relapsing inflammatory, ulcerating condition afflicting the digestive tract. It arises via the abnormal actions of lymphocytes which alter vascular permeability setting off a cytokine storm. [38] Opioid signaling, long known to affect secretion and motility in the gut, is also implicated in the inflammatory cascade of Crohn's disease.

Cytokines engaged in Crohn's disease are:

1. TNF-α, IL-1β
2. IL-10 (anti-inflammatory), IL-12 [39]

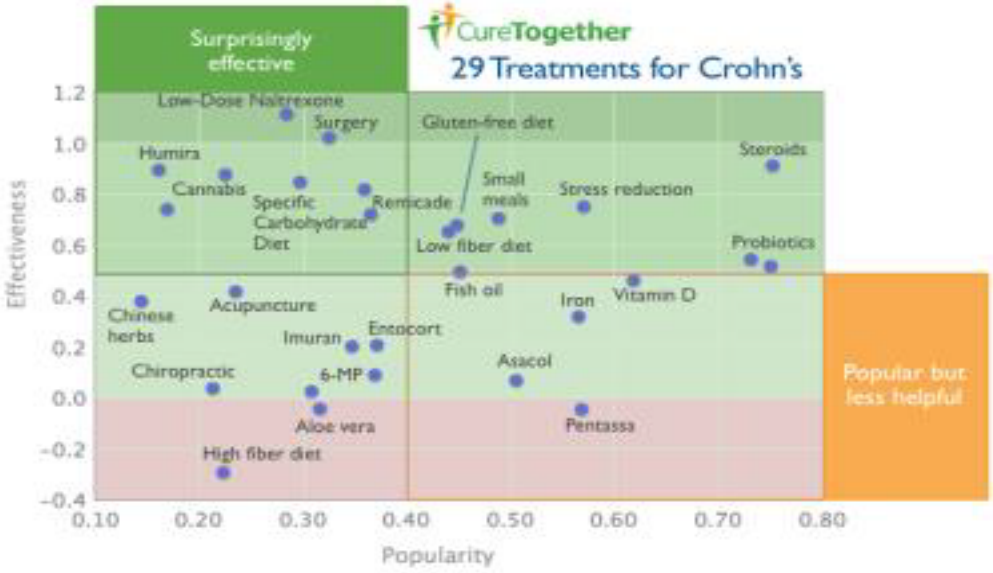
67% of treatment-resistant Crohn's patients in a 2007 study were in remission within 90 days after being administered a bedtime dose of 4.5 mg of low-dose naltrexone. [40] Participants reported

improved quality of life scores within four weeks when given the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ).

A forty (40) patient follow-up randomized, double-blind placebo-controlled study of patients given either 4.5-mg naltrexone or placebo, with the providers and patients masked, resulted in a 70-point decline in Crohn's Disease Activity Index score (CDAI). [41] A secondary outcome revealed a >200% increase in mucosal healing based upon colonoscopy appearance and histology versus placebo. At twelve weeks, 78% of the LDN patients revealed some endoscopic response versus 28% in the placebo group. [42]

LDN is cost-effective (15-30$/mo as of this writing) versus "standards" therapies such as aminosalicylates (Asacol; Pentasa generics $985-1200$/mo) or infliximab ($5683/mo). [43-44]

CureTogether, a medical survey company, now part of 23 and Me, reported that low-dose naltrexone was rated the most effective of twenty most common therapies. Dead last? "The conventional medications mentioned in the previous paragraph. [45]



Dosing of LDN in Crohn's Disease

Follow the "Basic Protocol" as in psoriasis. [46]

The dose can be 0.1 mg/kg up to 4.5 mg daily.

- 1.5 mg @ bedtime x 14 nights then:
- 3.0 mg @ bedtime x 14 nights then:
- 4.5 mg @ bedtime x 14 nights.
- If tolerated, use 4.5 mg dose for maintenance.

Fibromyalgia

Fibromyalgia is a diffuse musculoskeletal pain & sensitivity to pressure at specific trigger points without a diagnosable cause. In other words, "I hurt, I don't know why, and nothing fixes it."

Signs and symptoms of fibromyalgia include fatigue, sleep disturbances, and harmful effects on thinking, concentration, and memory. It affects 2–8% of the general population, primarily women. [47] Conventional medical treatments are notoriously ineffective.

Cytokines involved include *TNF-α, IL-6, and IL-8.* [48]

Although the exact etiology of fibromyalgia has yet to be determined, one mechanism of action is an abnormal number of nerve cell discharges. Thus the FDA's approval of *Pregabalin (Lyrica)*. Also indicated as an anticonvulsant for diabetic peripheral neuropathic pain (DPNP) and post-herpetic neuralgia (PHN), *Pregabalin's* effectiveness is a bit hit or miss.

A perusal of review websites finds *Pregabalin's* effectiveness rating somewhere between 3.0 and 3.5 on a 5 point scale. Some patients rave about, for many others, there is little to no benefit. [49]

Side effects include dizziness, sleepiness, including a feeling of being "hungover," blurred vision, dry mouth, swelling of the hands, feet, mouth, or throat, chest tightness, weight gain, loss of concentration and memory, sudden mood changes, unusual thoughts or behavior such as extreme happiness or depression, suicidal thoughts, bleeding, bruising, or weakness. [50]

Low-dose naltrexone affects the microglia, the first line of defense in the central nervous system. Activated by cell death, inflammation, and infection, microglia increase pro-inflammatory cytokines, excitatory amino acids, and nitric oxide (NO). These neuroinflammatory proteins stimulate NF-Kappa beta to produce more proinflammatory cytokines to act on neurons to create pain, fatigue, and other S/S of fibromyalgia. LDN suppresses microglial activation.

Twelve women with fibromyalgia, average age 44, took part in a placebo-controlled single-blind crossover study. Exclusions included RF>20 IU/mL, ANA>1:80, and ESR>60.

Recording parameters included a subjective VAS 0-100, "How severe are your fibromyalgia symptoms been today?" Also reviewed were average daily pain, highest pain, fatigue, sadness, stress, sleep quality, ability to think/ remember, GI symptoms & headache frequency, and severity diary.

Objective findings included an ashi (tender) point exam, thermal and cold pain perception, and erythrocyte sedimentation rate (ESR) inflammatory marker.

50 % of patients perceived their fibromyalgia as "improved or much improved." Only 10% of patients stated there was little to no change. [51]

A follow-up study by the same investigators enrolled 31 women with fibromyalgia in a randomized, double-blind, placebo-controlled, crossover trial.

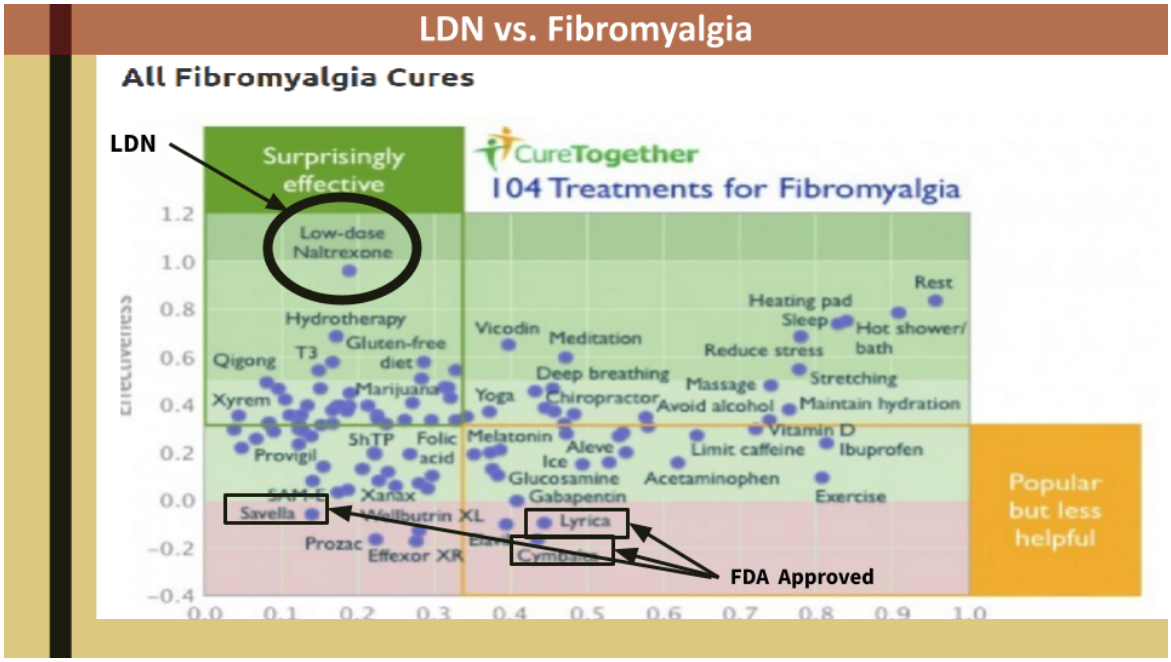
Materials used included an algometer (point tenderness finder), the Fibromyalgia Impact Questionnaire (FIQ), and the Beck Depression Index (BDI-II). The treatment arm had 4.5 mg of naltrexone for 22 weeks. [52]

Study results indicated a 28.8% reduction of pain with LDN versus a reported 18.0% reduction in the placebo group. (P= 0.016). General satisfaction with life (P= 0.045) and mood improved (P= 0.039), but neither fatigue nor sleep got better. 32% of patients met the criteria for a significant reduction in pain plus a significant reduction in either fatigue or sleep problems vs. 11% placebo (P= 0.05)

Side effects were similar to placebo.

Just as we saw in the "CureTogether" graphic concerning Crohn's Disease, low dose naltrexone was deemed the most effective therapy by those with fibromyalgia. And again, at the bottom of the list are harsh, toxic pharmaceuticals. [53]

Follow the "Basic" dosing regimen of LDN in Fibromyalgia.



Multiple Sclerosis

Multiple sclerosis is a chronic inflammatory disease involving demyelination of the central nervous system. [54-55]

The mechanism of action in multiple sclerosis from an inflammatory standpoint is (1) OGF-OGFr axis dysregulation with evidence of (2) a decrease in OGF before the onset of clinical disease and (3) microglial activation. [56]

Cytokines involved in multiple sclerosis include Th1 induced *TNF-α, IFN-g, IL-2,* TH-17 induced

IL-1, IL-17, IL-22, and reductions in anti-inflammatory cytokines IL-4 and IL-10. [57]

Low dose naltrexone in the setting of multiple sclerosis restores levels of OGF, reduces inducible nitric oxide synthase activity, decreases IFN-Gamma and TNF-alpha levels, inhibits glutamate transporters, and reduces apoptosis of oligodendrocytes. [58-59]

LDN's anti-inflammatory effect causes a "die-off" of infectious disease materials, termed the Jarisch-Herxheimer (J-H) reaction. This J-H affair is due to the release of apoptotic microorganism particles released within the body**.** The prescriber must warn the M.S. patient that the symptoms of M.S., due to this die-off, are often perceived as worsening before lessening. They should be informed of this phenomenon and reassured It would clear within eight weeks of use. [60]

60 (of 80) patients completed eight weeks of a 4.5 mg LDN nightly regimen with self-reported quality of life questionnaires. LDN was well tolerated and exhibited no serious adverse events.

Findings included a 3.3-point improvement on the Mental Component of the SF-36 General Health Survey (p = 0.04), a 6-point improvement on the Mental Health Inventory, a 1.6-point improvement on the Pain Effects Scale (p =.04), and a 2.4-point improvement on the Perceived Deficits Questionnaire (p = 0.05) [61]

Another six months multicenter trial of 40 patients with Multiple Sclerosis looked at effects on spasticity, pain, fatigue, depression, and quality of life.

Beta-endorphins (BE) and beta-endorphin concentration increased, resulting in a significant reduction of spasticity. [62]

M.S. Patients, like their autoimmune thyroid brethren, are often sensitive to low-dose naltrexone.

Dosing LDN in Multiple Sclerosis

Similar to Hashimoto's Thyroiditis

Loading Dose: 0.5-1.0 mg @ bedtime.

Follow up: Increase by 1 mg. every 1-2 weeks to a maximum of 3 mg.

- ★ If sensitive to LDN, use the liquid form.
- ★ Compound LDN in 0.1 mg intervals.

Cancer

Opioid growth factors (OGF) are essential regulators in the onset and progression of various human cancers. OGF binds to the OGF receptor (OGFr) to delay the interface of the cell cycle by modulating cyclin-dependent kinase inhibitory pathways. Increasing OGF-OGFr activity in cancer cells by exogenous OGF depresses cell proliferation. [63]

OGF suppresses cancer growth in hepatocellular and follicular thyroid carcinoma cell lines. [64-66]

The opioid growth factor (OGF;[Met(5)]-enkephalin) and its receptor (OGFr) mediate the action of LDN on cell proliferation. LDN produces rebound OGF activity and inhibits cell proliferation in vivo. [67]

In vitro and in vivo experiments have shown increases in IL-2, WBCs, NK cell activity, interferon, more significant destruction of opportunistic organisms, and cancer cells. [68]

LDN (0.1 mg/kg) reduced neuroblastoma tumor incidence in mice by 66%, decreased tumor development by 98%, and increased survival by 36%. [69]

Short-term LDN combined with taxol or cisplatin administered to mice with ovarian tumors revealed that LDN + cisplatin, but not taxol, mice had less tumorigenesis and angiogenesis. LDN alleviated weight loss associated with cisplatin toxicity. [70]

A review of case reports of several pancreatic cancer patients treated with IV lipoic acid + LDN reported all signs of cancer, including liver metastases. [71]

A prospective phase II trial of 24 advanced pancreatic cancer patients who failed chemotherapy were treated with 250 µg/kg OGF IV. There was a three-fold increase in median survival time vs. untreated patients with tumor sizes stabilizing or shrinking in 62% of patients. [72]

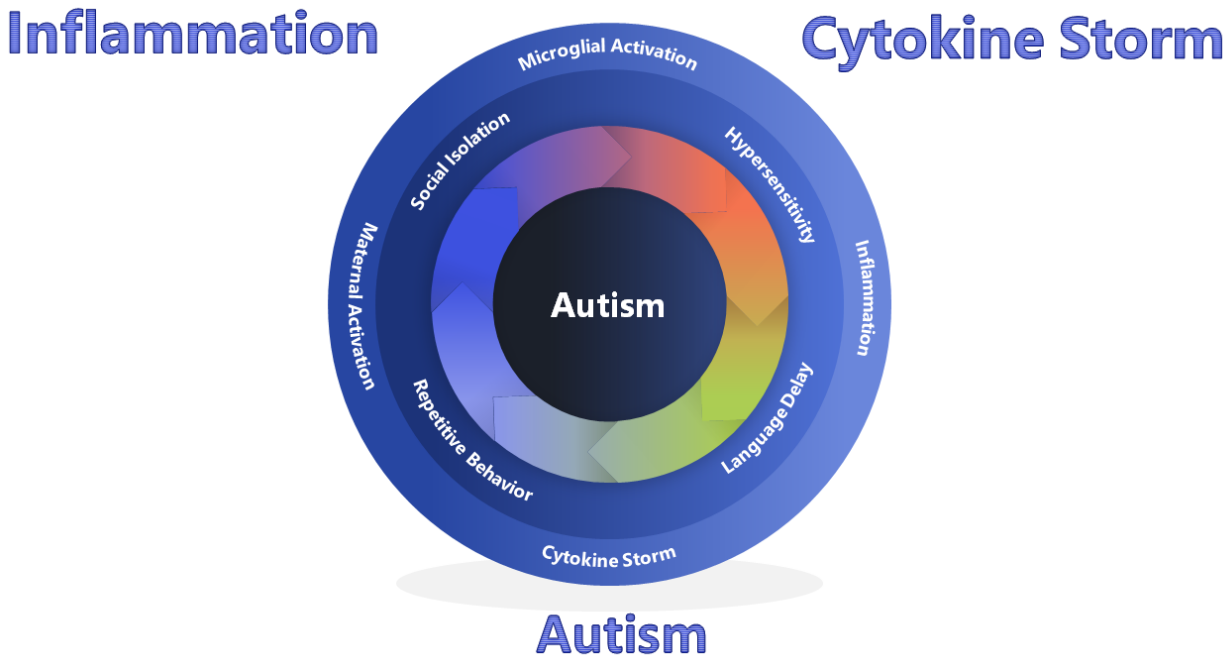
Cytokine involvement in cancer: [73]

Cytokine	Cancer Type	Chemokine	Cancer Type
IL-1	**Prostate** **Endometrium, Vulva**	**TNF**	**Prostate** **Endometrium, Vulva** **Lymphoma**
IL-2	**Lymphoma** **Endometrium, Vulva**	**FGF**	**Breast, Vulva** **Lung** **Bladder**
IL-6	**Breast, Endometrium, Vulva** **Lung, Glioblastoma** **Lymphoma**	**TGF**	**Endometrium**
IL-10	**Lymphoma**		

General Dosing LDN in Cancer [74]

- ➔ 1.5 MG @ bedtime x 7 nights, then
- ➔ Increase weekly to a maximum dose of 4.5 mg
- ➔ Upon remission: 4.5 mg x 7 nights, then alternate three days on, three days off.
- ➔ Note: LDN interferes with the action of the chemotherapy. Stop LDN two (2) days before until two (2) days after chemo.

The Autistic Spectrum



Affecting upwards of 1.7% of children born in the United States in 2018, a 15 percent increase from two years prior, autism spectrum disorders (ASD**)** represents a significant, increasingly prevalent collection of neurodevelopmental disorders. [(75-76)]

A combination of maternal activation, microglial activation, inflammation, and vulnerability to cytokine storms accounts for most of the issues noted in the autistic child.

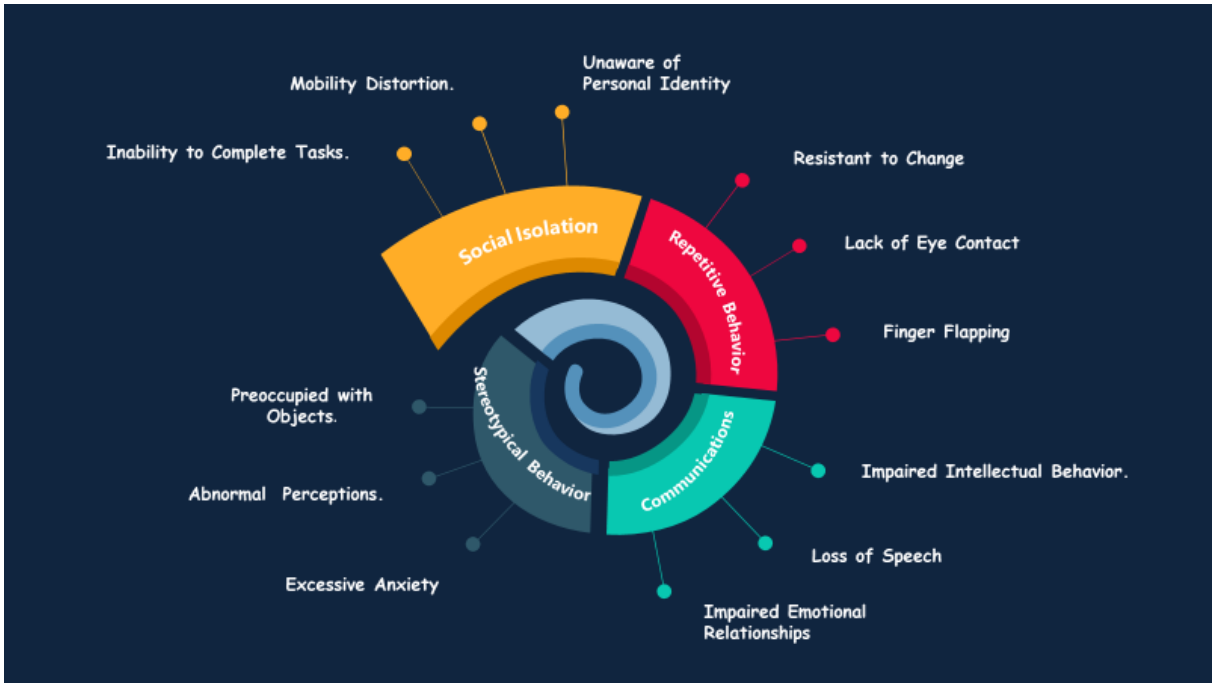
ASD children exhibit difficulties in communication, abnormal repetitive and stereotypical behaviors such as hand or finger flapping, poorly functional routines, and parts of objects. [(77)]

These patients show delayed language skills, including an inability to initiate or sustain a conversation, repeated use of idiosyncratic language, lack of age-appropriate imaginative play, a failure to develop peer relationships, joyful experiences, emotional and social reciprocity, and a for solitary activities. [(78)]

Summary of Key Features of Autism [(79)]

- Gross and sustained impairment of emotional relationships with people
- Apparent unawareness of own personal identity
- Pathological preoccupation with particular objects
- Sustained resistance to change in the environment
- Abnormal perceptual experience
- Acute, excessive, and seemingly illogical anxiety

- Loss, or never acquired speech
- Distortion in motility patterns
- Inability to complete tasks
- Background of severe retardation in which islets of ordinary, near-normal, or exceptional intellectual function or skill may appear



Low dose naltrexone shifts TH-1 proinflammatory cytokines to (TH-2) anti-inflammatory proteins. Low dose naltrexone downgrades IL-1, IL-6, and TNF alpha.

LDN improves self-injurious behavior, social withdrawal, communication skills, stereotypy, hyperactivity, agitation, attention deficits, and eye contact. [80]

A limited eighteen (18) patient study of children ages 3 through 8 showed improved fidgeting and hyperactivity with little effect on learning. [81]

In a double-blind, placebo-controlled crossover study, 13 children 3-8 year8-year-olds showed improvement in restlessness, communication skills, and hyperactivity. [82]

Dosing of LDN in the Autistic Spectrum [83-84]

- Dose: 0.1 mg/kg
- Mix the compound as a liquid or transdermal cream 1 mg/ml
- Increase by 0.1 mL q 3-7 days up to a maximum dose of 1 mg/kg
- Max dose: 4.5 mg (orally)
- Transdermal application: 3 mg applied between 9 PM and 12 Pm
- Children > 40 kg Adult dosing

Weight Gain

Obesity leads to a state of thyroid resistance, a decrease in the conversion of T4 to T3, and an increase in insulin resistance. Obesity leads to increased leptin which in turn increases appetite.

Low-dose naltrexone suppresses the pleasure centers making it an attractive remedy for binge eating, appetite reduction, and sugar and carbohydrate cravings blocker.

LDN normalizes metabolism, reduces resting energy expenditures, positively impacts insulin resistance, and improves the sleep cycle.

LDN, in combination with the atypical antidepressant bupropion, increases serotonin and dopamine production leading to mood elevation, decreased stress, and a reduction in emotional eating. [85]

LDN increases, and thyroid hormone production results in increased energy and exercise tolerance. [86]

Consider adding low dose naltrexone as a weight loss adjunct for the following patients: [87]

1. Autoimmune disorders including hypothyroidism and Hashimoto's Thyroiditis
2. Sleep disorders and REM sleep disorders
3. Chronic pain (avoid taking this medication if you are on narcotics)
4. Known inflammatory conditions
5. Low resting energy expenditure, or slow/low metabolism, or chronic fatigue, fibromyalgia issues.
6. Patients with ravenous appetites and a mismatch between energy consumption and appetite
7. Patients with hormone imbalances like Insulin and Leptin resistance

The cytokines involved in obesity are ***IL-1, TNFα, and IL-6.*** [88]

Dosing of LDN for Weight Loss

- Naltrexone 8 mg/Bupropion 90 mg: Combination FDA approved compound. Titrate up to 4/d (32 mg naltrexone/360 mg bupropion)
- Naltrexone 4.5 mg + liraglutide (Saxema 3.0 mg or Victoza 1.5 mg) [89]
- High dose Naltrexone (50-100 mg)-Decreases cravings and pleasure associated with food intake.
- Off-label-Extended Release Naltrexone (Vivitrol) 380 mg IM monthly
- Extended-Release Implant 400-4 gms

Traumatic Brain Injury

According to the CDC, there are 1.7 million traumatic brain injuries suffered annually in the U.S. alone. 52,000 die, 275,000 are hospitalized, there are approximately 1.365 million ER visits, and at any time, up to 10 million undiagnosed or underdiagnosed head injury victims. [90]

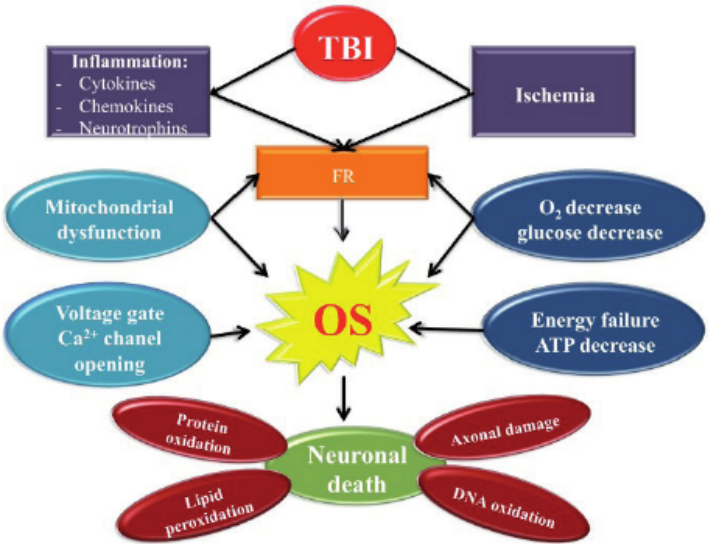
Traumatic brain injury is a traumatically induced structural or physiological disruption of brain function due to an external force. To be classified as a "traumatic brain" injury, the patient must experience specific symptoms including new-onset or worsening of loss of or a decreased level of consciousness, loss of memory for events immediately before or after the injury (posttraumatic amnesia), or an altered mental state at the time of the injury.

Other qualifying s/s include confusion, disorientation, slowed thinking, and neurological deficits (e.g., weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, and aphasia) not be transient or an Intracranial lesion. [91]

Recovery from TBI occurs in two phases. Phase I includes assessment of all mechanical, biochemical, radiation-induced traumas causing mechanical injury to the brain. *Phase II* deals with limiting progressive brain damage leading to psychological and cognitive impairments due to the secondary sequelae of inflammation.

Phase I interventions include the "ABC's" of emergency care, airway, breathing, cardiac and cognitive function, along with *antihypertensives* to prevent exacerbation of intracerebral hemorrhage in hypertensive encephalopathy, *diuretics*, *anticonvulsants,* ***antipyretics, hemorrhage, or clotting*** a***ntidotes,*** vitamin K/FFP, or protamine, *antacid* prophylaxis for Cushing's gastric ulcer, *glucocorticoids* to reduce head/neck pain and reduce cerebral edema, *anti-anxiety agents, anti-depressants* to treat symptoms of depression, *antipsychotics* to target psychotic symptoms of combativeness, hostility, hallucinations, and sleep disorders, *muscle relaxants, sedatives, and stimulants.*

Phase II pathology involves oxidative stress on the brain and its structures due to hypoxia, ischemia, and cerebral edema. Oxidative stress disrupts the blood-brain barrier, the brain's natural protection against inflammatory and infectious insults leading to necrosis, apoptosis, neuronal cavitation, and destruction of brain tissue. [92]



Traditional management of traumatic brain injury all but ignores the metabolic issues associated with traumatic brain injury. Instead, researchers hunt for the "Holy" Grail, the drug or pharmaceutical "cure" for the signs and symptoms of TBI. "Success" is a mere 10% of clinical symptoms. To date, all pharmaceutical efforts searching for "the go-to drug for TBI" have failed. Moreover, might the "missing link" be hiding all along in plain sight?

48.3% of all documented TBI patients in a 30-year follow-up study suffer from a Type I Axis psychological disorder. [93] 26.7% exhibit major depression, 11.7% substance abuse disorders, and 8.3 % deal with phobias, panic disorders, and paranoia.

Axis II psychopathology associated with TBI includes borderline personality disorders (34%), obsessive-compulsive disorders (27%), avoidant personality (26%), and antisocial personality (26%). [94]

Of the nearly 80% of TBI victims diagnosed with chronic, long-term depression, up to 30% of those patients are "resistant" to treatment. Treatment-resistant depression requires 5 of these 9 criteria for diagnosis: [95]

The ten most common long term symptoms of TBI include: [96]

1. Fatigue (100% of patients)
2. Excessive sleepiness +/- disturbed sleep patterns.
3. Inattention with difficulty concentrating
4. Impaired memory
5. Faulty judgment with slowed thinking.
6. Depression w/wo anxiety and panic attacks
7. Irritability with emotional outbursts of Anger
8. Diminished libido
9. Difficulty switching between two tasks.
10. Alcohol Abuse w/wo drugs.

We've covered our take on the "missing link," hormone insufficiencies and deficiencies, in traumatic brain healing, here and here.

The gut-brain axis and maintenance of a stable microbiome form the rationale for considering low-dose naltrexone in the context of TBI.

After a brain injury, the tight junctions connecting the mucosal epithelial cells of the small intestine become dysfunctional, allowing large macromolecule antigens to enter the bloodstream. This "leaky gut" triggers the immune system to perform over (and at times under), leading to autoimmunity or an immunocompromised state. [97]

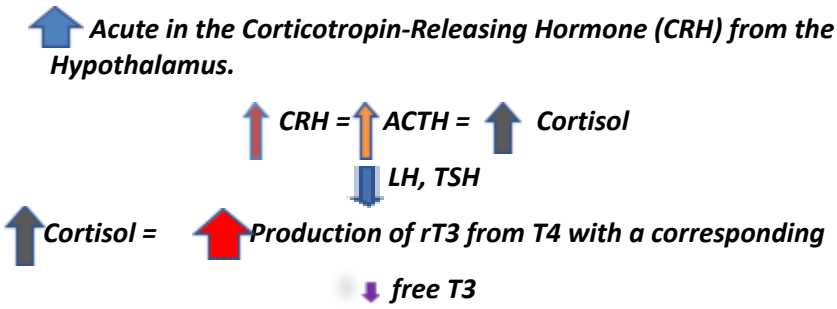
Simultaneously, the hypothalamic-pituitary-adrenal (HPA) axis is activated, as evidenced by increased plasma cortisol levels within 1-2 days of a mild to moderate injury. (Severe TBI = suppression of the HPA axis). The brain reacts by acutely increasing Corticotropin-Releasing Hormone (CRH) from the hypothalamus. Elevated CRH stimulates the anterior pituitary to produce ACTH in excess, which results in a significant rise of cortisol in 40% of TBI patients within twenty-four hours of the incident. [98]

Cortisol seizes control of the entire anterior pituitary. It relegates LH and TSH, the sex and thyroid generating hormones, to the periphery, reducing the patient's downstream production of testosterone, estrogen and progesterone, and thyroid production.

Reverse T3, an inert form of T3, is a nonusable T3patient's generated mainly via excess cortisol in the bloodstream. Reverse T3 diminishes the viable portion of the thyroid hormone, free T3.

Cortisol stimulates dopamine activity, which increases prolactin inhibiting factor resulting in anxiety and panic attacks. [99]

TBI =



Chronically elevated cortisol levels release inflammatory cells desensitizing thyroid receptors to thyroid hormone. Like a person with diabetes who does not respond to insulin, excess cortisol in the bloodstream leads to "thyroid resistance." Laboratory studies may indicate our brains detect adequate thyroid hormone on board, yet free T3, the hormone delivering the thyroid's "fuel," isn't getting to its end organ.

Elevated cortisol levels increase estrogen in the bloodstream. Estrogen increases thyroid-binding globulin, tying up T3 and T4, reducing the thyroid progenitors to convert to free T3.

Elevated cortisol levels indicate a state of chronic inflammation, "leaky gut syndrome," and latent infections, precursors to the autoimmune disease spectrum.

The microglia, the central nervous system's first line of defense, migrates to the injury site, engulfing and eliminating cellular and molecular debris. Activation of the microglia releases pro-inflammatory cytokines, reactive oxygen and nitrogen species, and the excitatory neurotransmitter glutamate. [100]

Excess glutamate results in panic attacks, anxiety, poor concentration, obsessive-compulsive tendencies, depression, sugar, carbohydrate, alcohol, and MSG cravings. [101]

As noted on page 4, *(dextro)* low-dose naltrexone antagonizes TLR 4 proteins resulting in a significant reduction in the inflammatory cytokines TNF-a, ROS, and NF-kB1. [15] LDN's downregulating effect on TLR-4 reduces inflammatory cytokines, modulates the microglia, increases, thus providing a layer of neuroprotection. [102]

Because it crosses the blood-brain barrier, LDN is an adjunct remedy for neuroinflammation and neuro-autoimmunity. However, in TBI, we find that it is not a standalone but one of several agents needed for symptom remission. [103]

Adding hyperbaric oxygen therapy (HBOT) to low-dose naltrexone reduces apoptosis (programmed cell death), is a potent inhibitor of inflammatory cytokines, increases the production of growth factors, and elevates antioxidant levels. [104]

Dose of Low Dose Naltrexone in Traumatic Brain Injury

- **Start: 1.0 mg @ bedtime x 14 nights then:**
- **Increase by: 0.5-1.0 mg @ bedtime x 14 nights until maximum dose of 4.5 mg or**
  - **Highest dose tolerated at 3.0 mg or above.**
  - **If agitated or severely depressed can break dose in to quarters/administer 4 x/d**
    - **Dose = 1.125 mg 4x/d**
- **1 mg in am, 1 mg in PM**

Gynecologic Issues

Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is a predictable cluster of symptoms that include hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. [105] Affecting 4-10% of the women in the U.S., PCOS is the most common endocrine disorder in women of reproductive age.

Symptoms are predictable from the hormone abnormalities that arise from the baseline abnormalities and include amenorrhea, menorrhagia, hirsutism, acne, insulin resistance, metabolic syndrome, weight issues, alopecia, high blood pressure, and infertility.

Laboratory markers that shift due to polycystic ovarian syndrome include: [106]

Elevated	Diminished
c- Reactive Protein Homocysteine PAI-1 Insulin, Insulin Resistance Testosterone, Androstendione, DHEA Estradiol, Estrone, Total Estrogens Cortisol Prolactin (25% of pts) LH/FSH ratio (>/1 from average in 81% of pts.) Lipid profile BP IGF-1 Anti-Mullerian hormone (AMH) (>6 = PCOS)	Thyroid (fT3) SHBG Adiponectin Progesterone

Dosing of Naltrexone in Polycystic Ovary Syndrome

- **High dose (50 mg/d) Naltrexone** has a favorable effect on the clinical and endocrine-metabolic disturbances of obese PCOS women. (6 mo. study) [107]

- ➢ Body mass index decreased 12.9%
- ➢ Plasma levels of free T, androstenedione, dehydroepiandrosterone sulfate and cortisol significantly decreased
- ➢ The fasting glucose-to-insulin ratio improved in women with insulin resistance
- ➢ Menstrual cycle improved in 80% of PCOS women:
  - The mean cycle length was 40-360 days before treatment.
  - The mean cycle length was 25 and 120 days after three months of treatment.
  - The mean cycle length was 28-120 days after six months of treatment.

❖ **Low-Dose Naltrexone** [108]

- ➢ Start at 0.5-1.0 mg @ bedtime x 14 nights
- ➢ Increase every 14 days until the maximum dose of 4.5 mg or the highest amount tolerated at 3.0 mg or above.
- ➢ If agitated or severely depressed, can break the dose into quarters and administer four x/d
  - Dose = 1.125 mg 4x/d
- ➢ Gynecology Dosage
  - Start at 2.25 mg @ bedtime. If tolerated;
  - Increase by 2.25 mg weekly until a maximum of 9 mg.

Side Effects

Patients with clinically low endorphin levels, poor mood, fatigue, PMS, painful periods, endometriosis, sleep disturbances, anxiety, or an autoimmune issue respond, generally, favorably. Side effects, typically insomnia, vivid dreams, and nausea, usually subside within two weeks.

When administered low-dose naltrexone, Eu-endorphin patients become overstimulated and experience the side mentioned above effects, along with a dry mouth and persistent headache indicating endorphin overload. Our remedy is to lower the dosage of LDN or stop it altogether. [109]

Side effects are most prominent in capsule form. [110] We recommend administration of LDN via a compounded tablet or transdermal cream.

LDN and Opioids

Adding low-dose naltrexone to an opioid-dependent patient increases the risk of induced withdrawal, headaches, or nausea. [111] If opioids are needed, discontinue LDN two days before until two days after opioid administration.

Long-term opioid users are at risk for severe and life-threatening reactions if started on LDN. The patient must have a seven-day washout of their opioid of choice before beginning LDN.

Ultra-low dose naltrexone, 1-20 mcg, is recommended for opioid weaning. The plan is to decrease opioid dosage by 10 % per month (weekly if on opioids less than three months). ULDN in microdoses, usually 1 mcg twice daily to start and increasing by 10 % monthly.

Fibromyalgia patients are likely to respond to ultra-low doses of naltrexone. Our goal is to find the LDN sweet spot, where we benefit from LDN's endorphin response without disrupting the analgesic and anxiolytic effects of opioids. [112]

Dosing Protocols

Basic Protocol [28]

- **1.5 mg @ bedtime x 14 nights then:**
- **3.0 mg @ bedtime x 14 nights then:**
- **4.5 mg @ bedtime x 14 nights then:**

- **Reassess after six months. If relief is inadequate, decrease LDN to 3.0 mg, then increase by 0.5 mg every 2-4 months until a maximum of 4.5 mg.**

With Anxiety and/or Depression

- **0.5 mg @ bedtime x 14 nights then:**
- **0.5 mg in am and @ bedtime x 14 nights then:**
- **0.5 mg in AM, 1 mg in PM then**
- **1 mg in am, 1 mg in PM**

With Skin Issues

- ***Increase dose by 0.5 mg 2x/day every two months up to a maximum of 4.5 mg***

Topical Solutions for Eczema, Itch, Psoriasis[29-30]

- **Naltrexone HCl 0.5%/Diphenhydramine HCl, 2%/Vitamin D3 5000 IU/Gm**
- **Naltrexone HCl 1%, Tranilast 1%/Cyanocobalamin 0.07% Topical Cream**
- **Naltrexone HCl 1%/Melatonin 2.5%/Tranilast 1% Topical Cream**
- **Naltrexone HCl 1%/Pramoxine HCl 1% Topical Gel**
- **Naltrexone HCL 1% in Xematop Cream**

Hashimoto's Thyroiditis

Loading Dose: 0.5-1.0 mg @ bedtime.

Follow-up: Increase by 1 mg. every 1-2 weeks to a maximum of 3 mg.

d. *Some literature recommends dosing to 4.5 mg. In my experience of > 500 Hashi patients, 2.0-2.5 mg is the usual tolerated dose.*

e. If sensitive to LDN, use the liquid form.
f. Increase or decrease LDN in 0.1 mg intervals as tolerated

Clinical Pearl: Thyroid function normalizes with LDN use. Monitor and decrease thyroid supplementation as indicated.

Dosing LDN in Multiple Sclerosis

Similar to Hashimoto's Thyroiditis

Loading Dose: 0.5-1.0 mg @ bedtime.

Follow up: Increase by 1 mg. every 1-2 weeks to a maximum of 3 mg.

★ If sensitive to LDN, use the liquid form.
★ Increase or decrease LDN in 0.1 mg intervals as tolerated

Rule of Thumb for LDN Dosing in Cancer

➔ 1.5 MG @ bedtime x 7 nights, then
➔ Increase weekly to a maximum dose of 4.5 mg
➔ Upon remission: 4.5 mg x 7 nights, then alternate three days on, three days off.

Dosing of LDN in the Autistic Spectrum [83-84]

➢ Dose: 0.1 mg/kg
➢ Mix the compound as a liquid or transdermal cream 1 mg/ml
➢ Increase by 0.1 mL q 3-7 days up to a maximum dose of 1 mg/kg
➢ Max dose: 4.5 mg (orally)
➢ Transdermal application: 3 mg applied between 9 PM and 12 Pm
➢ Children > 40 kg Adult dosing

Dosing of LDN for Weight Loss

- Naltrexone 8 mg/Bupropion 90 mg: Combination FDA approved compound. Titrate up to 4/d (32 mg naltrexone/360 mg bupropion)
- Naltrexone 4.5 mg + liraglutide (Saxema 3.0 mg or Victoza 1.5 mg) [89]
- High dose Naltrexone (50-100 mg)-Decreases cravings and pleasure associated with food intake.
- Off-label-Extended Release Naltrexone (Vivitrol) 380 mg IM monthly
- Extended-Release Implant 400-4 gms

Dose of Low Dose Naltrexone in Traumatic Brain Injury

❖ Start: 1.0 mg @ bedtime x 14 nights then:
❖ Increase by: 0.5-1.0 mg @ bedtime x 14 nights until maximum dose of 4.5 mg or

- ➢ Highest dose tolerated at 3.0 mg or above.
- ➢ If agitated or severely depressed can break dose in to quarters/administer 4 x/d
  - ■ Dose = 1.125 mg 4x/d

❖ 1 mg in am, 1 mg in PM

Dosing of Naltrexone in Polycystic Ovary Syndrome

❖ **High dose (50 mg/d) Naltrexone** has a favorable effect on the clinical and endocrine-metabolic disturbances of obese PCOS women. (6 mo. study) [107]

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- ➢ Menstrual cycle improved in 80% of PCOS women:
  - ■ Mean cycle length was 40-360 days before treatment.
  - ■ Mean cycle length was 25 and 120 days after three months of treatment
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❖ **Low-Dose Naltrexone** [108]

- ➢ Start at 0.5-1.0 mg @ bedtime x 14 nights
- ➢ Increase every 14 days until the maximum dose of 4.5 mg or
- ➢ The highest amount tolerated at 3.0 mg or above.
- ➢ If agitated or severely depressed, can break the dose into quarters and administer four x/d
  - ■ Dose = 1.125 mg 4x/d
- ➢ Gynecology Dosage
  - ■ Start at 2.25 mg @ bedtime. If tolerated;
  - ■ Increase by 2.25 mg weekly until a maximum of 9 mg.

Pediatric LDN Dosages

★ *Compound:* Naltrexone liquid or topical 1 mg/ml
★ *Start* 0.1 mg (0.1 ml)
★ *Increase* by 0.1 mL q3-7 days up to a maximum dose of 1 mg/kg
★ Max dose 4.5 mg
★ Children > 40 kg Adult dosing

Low Dose Naltrexone Pearls

Allergies

Dose 2-3 x /d 1 mg to maximum of 2.75 mg

Cancer Chemotherapy

LDN interferes with the action of chemotherapy. Stop LDN two (2) days before until two (2) days after chemo.

Chronic Fatigue Syndrome

Dose twice daily 1.5 mg (2x/d) to 4.5 mg (2x/d-technically not "low dose naltrexone.")

Chronic Infectious Diseases

Candida, EBV, Herpes 1 and 2, H. pylori, Yersinia (gastroenteritis), Lyme Disease can result in Herxheimer's reactions can occur as immune function improves.

Hashimoto's Thyroiditis

Thyroid function normalizes with LDN use. Thyroid supplementation doses must be monitored and decreased as indicated every 8-12 weeks to prevent "overdosing."

Gyn Issues

Start: 2.25 mg x 1 week then:
Increase: by 2.25 mg weekly to a maximum of 9 mg.

Mood DIsorders

Dose up to 4.5 mg 1-4 x/d (Tab is 1.125 mg)

LDN-Drug Interactions

Alcohol-No LDN for 6 hours
Antibiotics-Caution with tetracycline and aminoglycosides
Biologics-Compatible
Ketamine-Monitor airway, mental status
Opioids-Risk Of withdrawal
Contraindicated in sustained-release opioids or high doses
Prednisone-OK if < 20 mg equivalent prednisolone
Tramadol-No LDN for 6 hours after taking tramadol

LDN Contraindications

Anti-rejection (transplant patient)
Anti-TNF factor
Programmed Death ligand-1; PD-1 inhibitors

Anticancer vaccines

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