

LOW-DOSE NALTREXONE (LDN) FACT SHEET

ABOUT LDN

Naltrexone is an opioid antagonist used primarily in the management of alcohol and opioid dependence; the FDA approved Naltrexone in 1984 at 50mg. However, “Accumulating evidence suggests LDN can promote health supporting immune-modulation, which reduces various oncogenic inflammatory autoimmune processes.”¹

The value of Naltrexone as an immune modulator was recognized by Dr. Ian Zagon at the University of Pennsylvania.^{2,3} The late Dr. Bernard Bihari, a Neurophysician from New York, USA (who passed away on May 16th, 2010) began treating his patients in the late 1980s^{4,5}. Since that time, many doctors throughout the United States prescribe LDN for a number of indications including Multiple Sclerosis (MS), Parkinson’s disease, Crohn’s disease, HIV/AIDS, cancer and other autoimmune and inflammatory diseases.

A number of research and clinical trials have been completed and undergone in regards to LDN immunotherapies, with phase I and phase II clinical trials successfully run at a number of universities in the United States and Europe, including Pennsylvania State University Medical School at Hershey; University of Chicago; State University of New York; SUNY Upstate Medical University; London Health Sciences Centre - University Hospital, USA; Alpert Medical School of Brown University; Department of Neurology, San Raffaele Scientific Institute; Division of Rheumatology, St. Louis College of Pharmacy; Department of Internal Medicine, University of Utah; Jondi-Shapoor University of Medical Sciences; Department of Psychiatry & Behavioral Sciences, Duke University Medical Center; and Multiple Sclerosis Center at UCSF⁶. These efforts were pioneered by leading immunologists Dr. Nicholas Plotnikoff, Dr. Ronald Herberman, Dr. Bernard Bihari, Dr. Angus Dalgleish, Dr. Ian S. Zagon, Dr. Jill Smith, Dr. McLaughlin, Dr. Jacqueline McCandless, and Moshe Rogosnitzky, among others.

HOW LDN WORKS

The mechanism of action of naltrexone, in autoimmune diseases and cancer, is still being researched, but there are theories as to the mechanism of action that both explain why LDN works on both autoimmune diseases and cancers, as well as inflammatory disease.

According to Mark J. Donahue’s paper on LDN that uses interviews from Dr. David, Gluck, Dr. Jacquelyn McCandless, Dr. Jarred Younger, and Dr. Ian Zagon:

“LDN is an opioid antagonist that not only blocks the reception of opiates, but also the body’s own endogenous opioids – endorphins. However, because LDN is administered in such a 'low dose' it is believed that LDN only briefly (for 3-4 hours) obstructs the effects of endorphins. Sensing an endorphin deficit, the hypothalamus signals for increased production of endorphins in what is called 'the rebound effect.' The rebound effect results in three things happening:

- Opioid receptor production increases in order to try and capture more endorphins.
- Opioid receptor sensitivity increases, also in order to try and capture more endorphins.
- Production of endorphins is increased in order to compensate for the perceived shortage.

Once LDN is metabolized by the liver and eliminated from the body (after 3-4 hours), the elevated levels of endorphins produced, as a result of the rebound effect, can now interact and bind with the more sensitive and more plentiful opioid receptors. These opioid receptors, are found throughout the body, including virtually every cell of the body's immune system.

The elevated levels of endorphins will usually last around 18-20 hours. During this time the elevated endorphins act by up-regulating vital elements of the body's immune cells. By doing so clinical trials has been shown that elevated levels of

- Down regulating inflammatory cytokines
- Reducing inflammation and oxidative stress
- Facilitating tissue repair and wound healing
- Restoring T-helper/CD4 levels
- Restoring the balance between Th1 & Th2 lymphocytes
- Increasing cytotoxic T cells and natural killer (NK) cells
- Regulating cell growth & inhibiting tumor growth
- Reducing excitotoxicity and microglial activation
- Reducing apoptosis of the myelin-producing oligodendrocytes
- Stimulating mucosal healing (lining of bowel)"⁷

According to Dr. Nancy Sajben in an article she wrote about LDN, she explains it's mechanism as follows:

"In 2008 in the US and UK have shown that naltrexone in addition to binding to the opiate receptor's binds to naltrexone in addition to binding to the opiate receptor's binds to Toll Like Receptors (TLR),. There are 13 TLRs, and so far they have studied naltrexone only in two of them TRL4 and TRL9. That is important because the TLR receptors are part of the innate immune system and effect the inflammatory markers.

The Toll Like Receptors are not like other receptors. They are not these snug little pockets where naltrexone binds. Instead the Toll Like Receptors are like an entire football field, with enormous nooks and crannies where it has many interactions with

many molecules. Now, in 2010, scientists are asking if naloxone or naltrexone is acting at TLR4 or even higher up in the cascade.

The study of immune cell glial interactions is in its infancy. Glial cells are the immune cells in your central nervous system (brain, spinal cord). They are very involved in dysregulation of pain systems, neuroinflammation, and some neurological diseases such as Multiple Sclerosis, Alzheimer's, Parkinson's disease, Autism, ALS, infections of the brain, etc." ⁸

WHAT IS BEING TREATED WITH LDN?

There are a number of conditions where LDN could benefit based on clinical studies and patient data.

PUBLISHED CLINICAL STUDIES

- Crohn's Diseases
- Fibromyalgia
- Melanoma,
- Cervical Cancer
- Ulcerative Colitis
- Chemo Resistant Advanced Carcinoma
- Glioma Patients
- Complex Regional Pain Syndrome
- Gastrointestinal Disorders
- Low-dose naltrexone for disease prevention and quality of life
- Multiple Sclerosis
- HIV/AIDS
- Prostate Cancer
- Autism
- Hepatoblastoma
- Metastatic Breast
- Gulf War Syndrome
- Pruritus in Systemic Sclerosis
- Irritable Bowel Syndrome
- Low Dose Naltrexone (LDN) Immune Monitoring (LDNIM)

For a list of current ongoing LDN studies, please go to the following website:

<https://clinicaltrials.gov/ct2/results?term=low+dose+naltrexone&Search=Search>

PATIENT-REPORTED

- Malaria
- Hepatitis C
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Parkinson's Disease
- Wound Healing
- Malignant Melanoma
- Glioblastoma
- Liver Cancer
- Multiple Myeloma
- Ovarian Cancer
- Epstein-Barr Syndrome
- Lung Cancer
- Bladder Cancer
- Breast Cancer
- Lymphoma (Hodgkin's and Non Hodgkin's) Colon & Rectal Cancer
- Uterine Cancer
- Throat Cancer
- Neuroblastoma
- Renal Cell Carcinoma

SUGGESTED METHOD OF THERAPY:

According to LDNScience.org, a public information project of the MedInsight® Research Institute, co-founded by Moshe Rogosnitzky:

“There is no single dose that will work for every person. Some people find that a daily dose as low as 2 mg is effective, and others have found that they achieve greatest benefit using two doses of 4.5mg each day (12 hours apart). The clinical trials so far have used a single daily dose of 4.5mg and for most users this dose seems to be effective.”⁹

Dr. Terry Grossman, M.D. give the following recommendations regarding dosing in his lecture on LDN:

“SPECIAL CONSIDERATIONS:

- **Hypothyroidism – Hashimoto’s**
 - Thyroid function may normalize and less supplemental thyroid needed
 - Start at lower dose and increase slowly)
- **Underlying chronic infections – candida, EBV, etc**
 - Herxheimer’s reactions may occur as immune function improves
- **Cancer chemotherapy**
 - LDN may interfere with action of chemo
 - Stop LDN 2d before until 2d after chemo

DOSING BASED ON INDICATION:

- **Hashimoto’s:** Typical full dose 3 – 4.5 mg
- **Multiple Sclerosis:** Typical full dose: 3 mg
- **Most other conditions - Crohn’s, Autoimmune disease, Fibromyalgia, Cancer:** full dose: 4.5 mg

Initial Dosing

- Begin at 0.5mg (**Hashimoto’s**), 1mg (**MS**) or 1.5mg (**most other patients**) and increase by same amount q 2 weeks as tolerated
- 0.5, 1 or 1.5 mg -1st 2 weeks
- 1, 2 or 3 mg – 2nd 2 weeks
- 1.5, 3 or 4.5 mg 3rd 2 week

MAINTENANCE

- See patient in follow up 6 weeks after beginning LDN
- If full dose tolerated, consider 3 - 6 month Rx, usually 3 – 4.5 mg

CHILDREN

- Naltrexone liquid or topical 1 mg/mL
- Begin at 0.1 mL (0.1 ml)
- Increase by 0.1 mL q 3-7 days up to maximum dose of 0.1 mg/kg
- Max dose 4.5 mg
- Children > 40 kg Adult dosing¹⁰

LDN SIDE EFFECTS

According to lowdosenaltrexone.org, “patients report sleep problems (vivid dreams or insomnia), which gradually fade away after the first week of treatment. If sleep problems continue, a modification in the dosage usually takes care of the problem.”¹¹

The LDN Trust reports that “some patients, very rarely, experience gastro-intestinal side effects. Nausea and or constipation/diarrhea. The reason for this is currently unknown, but may be due to the presence of large numbers of TLR4 receptors in intestines.”¹²

Lowdosenaltrexone.org also states the following cautionary warnings:

1. Because LDN blocks opioid receptors throughout the body for three or four hours, people using medicine that is an opioid agonist, i.e. narcotic medication — such as Ultram (tramadol), morphine, Percocet, Duragesic patch or codeine-containing medication — should not take LDN until such medicine is completely out of one's system. Patients who have become dependent on daily use of narcotic-containing pain medication may require 10 days to 2 weeks of slowly weaning off of such drugs entirely (while first substituting full doses of non-narcotic pain medications) before being able to begin LDN safely.
2. Those patients who are taking thyroid hormone replacement for a diagnosis of Hashimoto's thyroiditis with *hypothyroidism* ought to begin LDN at the lowest range (1.5mg for an adult). Be aware that LDN may lead to a prompt decrease in the autoimmune disorder, which then may require a rapid reduction in the dose of thyroid hormone replacement in order to avoid symptoms of *hyperthyroidism*.
3. Full-dose naltrexone (50mg) carries a cautionary warning against its use in those with liver disease. This warning was placed because of adverse liver effects that

were found in experiments involving 300mg daily. The 50mg dose does not apparently produce impairment of liver function nor, of course, do the much smaller 3mg and 4.5mg doses.

4. People who have received organ transplants and who therefore are taking immunosuppressive medication on a permanent basis are cautioned against the use of LDN because it may act to counter the effect of those medications.¹¹

For information on Naltrexone, including its side effects, please see

<http://www.drugs.com/pro/naltrexone.html>

PRESCRIPTION AND COMPOUNDING INFORMATION

Immune Therapeutics owns the IP and patented formulations for LDN that they will be using in their upcoming Phase IIb/III clinical trials. As such, Immune Therapeutics has licensed their formulation and compounding rights to KRS Global Biotechnologies, Inc. (“KRS”) - an FDA compliant 503B Outsourcing Facility.

Whereas previous patient fulfillment options have been limited to compound pharmacies with uncertainty as to fill and provenance; the result of this licensing partnership is that KRS is now offering LDN in a **formulated, quality-controlled, tablet**, previously unavailable in the market.

As noted, KRS Global Biotechnology, Inc. (“KRS”) is licensed (#PH23506a) with each individual state boards of pharmacy in 44 states as a non-resident pharmacy, wholesaler, and/or manufacturer as appropriate. KRS works closely with the boards of pharmacy of relevant states to ensure compliance with respective statues and regulations.

KRS is registered, inspected, and has been granted 503B status with the FDA as a Human Outsourcing Facility. Outsourcing facilities registered must adhere to good manufacturing standards; subject themselves to routine inspections by the agency and report adverse events associated with their products. In return, they join a new class of compounding firm known as outsourcing facilities. In addition to filling patient prescriptions, these facilities are also allowed to sell products in bulk to hospitals and physician practices in accordance with specific regulations.

This collaboration between Immune Therapeutics and KRS has focused their attention on the fact that the compounded product being fulfilled today appears to have significant variation in quality and dose control. KRS delivers comprehensive analytical reports to ensure optimal quality assurance (Pharma Quality Assurance) and quality control (Pharma Quality Control) throughout the whole continuum of the production processes. Quality analyses are carried out at all stages of pre-, in- and post-production. In addition to the quality control of KRS, Immune Therapeutics currently initiates random testing by an outside third-party lab prior to clearance.

KRS has available LDN tablets at the following dosages: .5mg; 1mg; 1.5mg; 3mg and 4.5mg.

KRS can be reached at their headquarters location:

791 Park of Commerce Blvd. Suite 600
Boca Raton, Florida 33487
Phone Number: 866-422-6780
Fax Number: 561-9891590
email: waynekrebs@gbtbio.com

KRS has indicated that they are available to discuss LDN and individual patient prescription fulfillment and are available via the above telephone number Monday through Friday, 10am to 6pm EST.

KRS has indicated that those patients seeking to fill an LDN prescription can have physicians fax the prescription to KRS, whereupon a KRS representative will contact the patient to arrange fulfillment and payment details.

DISCLAIMER AND SAFETY INFORMATION

This information is not intended as medical advice. Responsibility for patient care resides with healthcare professionals on the basis of their professional license, experience and knowledge of a patient. In addition, this information (and any accompanying material) is not intended to replace the attention or advice of a physician or other qualified health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other lifestyle change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a physician or other qualified health care professional.

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For the most recent version of this document and access to more published data and studies on LDN, please go to:

<https://tnibio.sharepoint.com/sites/ImmunelInfo>

username: immunepub@immunetherapeutics.com

password: !1970Pubs