LDN 2024 Prescriber Guide

Naltrexone is a class of drug known as an opiate antagonist. Its normal use is in treating addiction to opiate drugs such as heroin or morphine, or to treat acute overdose. The dose used for this purpose is usually between 50 mg (moderate dose naltrexone) and 300mg (high dose naltrexone) daily, or acute dosing.

Low-dose Naltrexone (LDN) has been used in the treatment of autoimmune diseases in the USA since 1985. Despite the fact that the drug is used at a very low dose, the occurrence of significant introductory or long-term side effects cannot be excluded.

This method was devised and subsequently developed by the late Dr. Bernard Bihari, a Neurologist from New York, USA who passed away on May 16th 2010. Dr. Bihari was qualified in Internal Medicine, Psychiatry and Neurology, and we hope to honor him by continuing with his pioneering work.

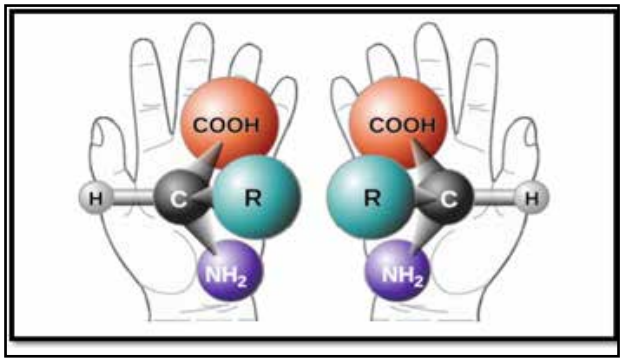
How Naltrexone Works

As of 2024, LDN is most commonly being used for Chronic Fatigue, Multiple Sclerosis, CFS/ME, chronic viral conditions (including COVID, Long-Covid and other post-viral syndromes), mast cell activation syndrome (MCAS), autoimmune diseases and various cancers. Many autoimmune diseases respond well to LDN.

This is a wide range of diseases and many clinicians will find it difficult to understand how one drug can have a positive effect on all these pathologies. Naltrexone is an example of a drug that exhibits pleiotropy — there are many effects of this compound other than those for which the agent was specifically developed.

The first thing to understand is that Naltrexone – the drug in LDN – comes in a 50:50 mixture of 2 different shapes (called isomers). It has been recently discovered that one particular shape binds to immune cells, whilst the other shape binds to opioid receptors.

Although consisting of exactly the same components, the two isomers appear to have different biological activity.



The LEVO (left-handed) version of naltrexone blocks opiate receptors.

The DEXTRO (right-handed) version blocks receptors on immune cells. These include "Toll Like Receptors" (TLRs), which are heavily involved in immunity. LDN is an antagonist of TLR-4.

For clinicians interested in reading more about the pharmacology behind this, there is a published resource available here:

https://www.ldnresearchtrust.org/ldn-book

Summary of Mechanism of Action

Levo-Naltrexone is an antagonist for the opiate/endorphin receptors

- This causes increased endorphin release
- Increased endorphins modulate the immune response
- This reduces the speed of unwanted cells growing
- No contraindication with vaccinations or viral infections, used to enhance immune modulatory response

Dextro-Naltrexone is an antagonist for at least one, if not more immune cells

- Antagonizes "TLR," suppressing cytokine modulated immune system
- Antagonizes TLR-mediated production of NF-kB – reducing inflammation, potentially downregulating oncogenes

Taking Naltrexone in larger doses of 50-300mg seems to negate the immunomodulatory effect by overwhelming the receptors, so for the effect to work, the dose must be in the range of 0.5mg, usually maxing at 4.5mg in clinical experience, though some individuals have had positive clinical effects at lower doses.

Side Effects

Many patients who start LDN do not experience any severe side effects.

Your symptoms may initially become worse – in MS, this can be characterized by increased fatigue, or increased spasticity. In CFS/ME, this can be the onset of apparent flu-like symptoms.

LDN can cause sleep disturbances if taken at nighttime – this is most likely because of the increase in endorphin release. These disturbances can take the form of vivid dreams, or insomnia.

In various studies (and anecdotal accounts), the number of T-Lymphocytes has been shown to dramatically increase when a patient starts on LDN. This may account for some of the benefits patients feel when they are being treated for an autoimmune disease, or cancer. This has not been directly evidenced in multiple sclerosis.

Clinical experience shows that in less than ten percent of cases treated, increased introductory symptoms may be more severe or more prolonged than usual, lasting sometimes for several weeks. Rarely, symptoms may persist for two or three months before the appropriate beneficial response is achieved.

If side effects are troublesome, then reducing your dose by 50% for 7 days, before increasing it again, is a good idea.

Some patients, very rarely, experience gastro-intestinal side effects, such as nausea and or constipation/diarrhea. The reason for this is currently unknown, but may be due to the presence of large numbers of delta-opiate receptors in the intestines. Patients experiencing this side effect can request LDN Sublingual Drops, which transfer the LDN directly into the bloodstream – avoiding the GI tract.

Types of LDN:

Liquid

Oral Liquid Formulation at 1mg/1ml is the most commonly used type of LDN. It is taken daily, and dosed using a baby oral syringe. It does not contain very high amounts of lactose or any other excipient known to cause hypersensitivity. The base is similar to children's cough syrup – so is quite palatable, and some pharmacies compound it in sterile water for the most sensitive patients. Because there are so few preservatives, it should be stored in the fridge.

Capsules

For patients who the liquid would be impractical, there are capsules available in 3mg and 4.5mg strengths, and other strengths as required. These have up to 12 months stability data and can be stored anywhere. They contain a variety of customizable fillers and are instant release formulation.

Sublingual Drops

Sublingual drops are designed for patients who

are having problems taking the medication orally, or for people who want to guarantee the fastest delivery of the drug into their bloodstream. A number of drops are placed under the tongue from a dropper bottle and dose is increased and decreased by the number of drops taken. There are basically no excipients in this product, trace lactose and a small amount of glycerol.

Cream

LDN Cream is available for application to the skin. This is helpful for children, or for patients allergic to colorants or any excipients in all other forms of LDN. It is more expensive and lasts for 28 days only.

Intrinsic Toxicity of the Drug:

Naltrexone, in full doses of 50-300mg, has been shown to transiently increase liver enzymes. Patients being prescribed Naltrexone for addictions must have liver function tests performed before initiating therapy.

This is not necessary with LDN – as the dose is much smaller, however, patients with advanced liver failure should consult their GP before considering treatment.

Patients with renal or liver failure should only start treatment after a consultation with their own GP or specialist, and should be monitored during the treatment initiation period. It is normal for people with poor renal or liver function to experience a transient elevation – but this usually resolves after a few weeks.

Contraindications and Special Precautions:

LDN is compatible with most other therapies. It does not directly interact with steroids, however, can negate the effect of opiate based painkillers. Patients should give their doctor a full drug history before starting therapy.

Patients who are taking multiple medications and/or herbal medicines – especially those with cancer or advanced disease, should take careful advice from a qualified doctor or pharmacist before initiating LDN.

Key clinical studies

Low Dose Naltrexone has been the subject of much debate but actually very few clinical trials. Ian Zagon from Penn State University has been studying LDN for over 20 years and conducted many pre-clinical studies investigating LDN in cancer and in the animal model of MS (1,2). He has also been involved in two clinical studies into Crohn's disease with his colleague Professor Jill Smith from Penn State. These demonstrated a significant improvement in symptoms and in bowel mucosal appearance with LDN treatment (3,4). In the RCT, LDN patients were twice as likely to have a 70-point decline in the Crohn's Disease Activity Index. 78% of the LDN group achieved an endoscopic response compared to 28% with placebo.

Jarred Younger from Stanford University has studied LDN in Fibromyalgia, firstly in a small pilot study and more recently in a yet to be published randomized controlled trial. The pilot study showed significant improvement in symptoms of pain in these patients (5).

Multiple Sclerosis is one of the areas where LDN has been used the most frequently. There are three published studies, one in primary progressive MS (6) and two on quality of life (7,8). The results of two studies were positive with improved quality of life in one and reduced spasm in the PPMS study. The third showed no significant difference between the treatment and placebo groups but found the treatment to be safe. A review of the available studies into LDN and MS was published in 2009 (9). All studies have confirmed the safety of the drug and there is enough positive evidence to merit greater investigation.

The COVID-19 pandemic has made necessary the allocation of new and old therapeutics to treat patients suffering from acute and chronic effects of viral infection. Studies utilizing LDN for the management of Long-COVID are ongoing. Given that nearly 40% of patients have symptoms persist 12 weeks after infection, and no standard therapies have been shown to have benefit, there is a critical global patient need. In one single center study, the safety of LDN in post COVID-19 syndrome was studied. 1mg was given for one

month, followed by 2mg in the second month. Fifty-two patients participated, thirty-eight of which took the LDN and two stopped due to poor tolerance (diarrhea, fatigue). Improvement was seen in 6 out of 7 parameters measured, including recovery from COVID-19, limitation in activities of daily living, energy levels, pain levels, levels of concentration and sleep disturbance (all highly significant), and improvement in mood approached but was not significant (10).

Key references:

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