

# LDN Prescriber Information

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 2021, LDN is most commonly being used for Chronic Fatigue, Multiple Sclerosis,

CFS/ME, chronic viral conditions, mast cell activation syndrome (MCAS), autoimmune thyroid 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.

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.

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

- Antagonises “TLR,” suppressing cytokine modulated immune system
- Antagonises 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 higher doses.

### **Ultra Low Dose Naltrexone (ULDN):**

Used for opiate medication weaning, enhancement of opiate analgesia

Ultra low-dose naltrexone or naloxone (ULDN) is dosed in the 1µg (microgram) range. The mechanism of action of ULDN with respect to opioid weaning is its bimodal cellular response to opiates via G protein signaling cascades – both an inhibitory G-coupled protein response and

induction of a more subtle stimulatory response.

A randomized controlled, blinded trial of 719 patients with chronic low back pain were treated concomitantly with 80 mg/day or less of oxycodone and 2 or 4 µg Naltrexone daily. The final analysis of 360 patients concluded that 2 µg Naltrexone daily showed the least opiate-related adverse effects, including constipation, somnolence, and pruritus, in addition to the fewest withdrawal symptoms following active treatment and weaning. <sup>1</sup>

Dr Ginevra Liptan, a Fibromyalgia specialist and internist, puts it best: “The key is finding the dosage sweet spot where LDN is able to calm the glial cells, but not knock the opiates off their receptors”. One concern is that opioid-induced tolerance may be secondary to increased irritation of glial cells in the central nervous system. By reducing glial cell sensitivity, opioid effectiveness can be restored and enhanced. <sup>2</sup>

ULDN may, in fact, act as a reset button for the opioid response pathway, much like rebooting a frozen computer.

### **Opiate Weaning Considerations:**

The recommended dose of Ultra-Low Dose Naltrexone (ULDN) is 1 µg twice daily. The general recommendation for opiate weaning is to taper by 10% monthly if a patient has been taking opiate medications longer than a year. A more aggressive weaning may be considered for a relatively opiate naïve patient (use not longer than weeks to months), such as decreasing by 10% weekly or more – as quickly as 5 weeks overall. This is a general approach and must be individualized to each patient. This must be done with a multidisciplinary approach utilizing primary care, pain management and other specialists to determine the appropriate treatment plan and closely monitor for adverse effects and need for greater support.

### **Side Effects**

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

As mentioned earlier, symptoms may become worse initially – 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, sometimes lasting 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 the dose by 50% for 7 days, before increasing it again is a good idea.

Some patients, very rarely, experience gastrointestinal 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 may find the liquid 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 the 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, it 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. 3, 4 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. 5, 6 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 randomised controlled trial. The pilot study showed significant improvement in symptoms of pain in these patients. 7

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<sup>8</sup> and two on quality of life. 9, 10 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. 11 All studies have confirmed the safety of the drug, and there is enough positive evidence to merit greater investigation.

Disclaimer: The information is designed as a guide, each patient is unique as is their treatment plan.

## Which Diseases Are Being Treated With LDN

This list is not exhaustive and patients are directed to the LDN Research Trust website for more information [www.ldnresearchtrust.org/](http://www.ldnresearchtrust.org/) conditions

- Autoimmune Hepatitis
- Inflammatory Bowel Disease (Crohn's/Ulcerative Colitis)
- Multiple Sclerosis
- CFS/ME
- Lyme Disease
- Chronic Viral Infections
- Mast Cell Activation Syndrome (MCAS)
- Hashimoto's Thyroiditis
- Grave's Disease
- Chronic Regional Pain Syndrome
- Parkinson's Disease
- Diabetes Type I
- Vitiligo
- Scleroderma
- Psoriasis
- Anxiety and Depression
- PCOS
- Melanoma
- Nerve Pain (Neuropathic conditions)
- Glioblastoma
- Esophageal and Oral Cancers
- Non-Small Cell Cancer
- Breast Cancer
- Multiple Myeloma
- Lymphoma
- Ovarian Cancer

Renal Cell Cancer  
 Colorectal Cancer  
 Duodenal and Stomach Cancer  
 Uterine Cancer  
 Hepatic Cancer  
 PTSD  
 PMDD  
 Fibromyalgia

Infertility (based on the research by Dr Phil Boyle, who is the Director of the NaProFertility Clinic in Dublin, Ireland and the President of the International Institute for Restorative Reproductive Medicine)

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