LDN 2026 Prescriber Guide

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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 2026, LDN is now understood to be a powerful adjunctive therapy to support anti-inflammation and immunomodulation. It is most commonly used for Chronic Fatigue, CFS/ ME, chronic viral conditions (including COVID, Long -COVID/Post-Acute Sequelae of COVID-19 (PASC) and other post-viral syndromes), mast cell activation syndrome (MCAS), Dysautonomia, Hypermobility Spectrum Disorder (HSD)/Hypermobile Ehlers-Danlos Syndrome (hEDS), autoimmune diseases (including Multiple Sclerosis), recurrent miscarriage/ infertility, endometriosis, and various cancers. Many autoimmune diseases respond well to LDN.

This is a wide range of conditions, 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. Pleiotropic agents such as LDN can shift the epigenetic trajectory of every receptor in the body. However, we must temper our expectations. LDN is meant to be used in combination with other agents (drugs, botanicals, supplements etc) for potential synergy. This takes time and is highly bio-individual. In addition, LDN is a hormetic drug. Hormesis is the concept of paradoxical responses to different dosages of the same drug.

The first thing to understand is that Naltrexone – the drug in LDN – comes in a 50:50 (racemic) mixture of 2 different shapes (called isomers). 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, and also attenuates TLR 2/4. For clinicians interested in reading more about the pharmacology behind this, there is a published resource available here: https://www.ldnresearchtrust.org/ldn-book

Mechanisms of Action (MOAs)

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 lower than the “high-low dose” LDN range of 12mg, though many patients’ optimal dose ranges between 0.5mg-4.5mg. Some individuals have had positive clinical effects at signifcantly lower doses.

Summary of MOAs

- Toll-Like Receptor-4 (TLR4) inhibition reduces neuroinflammation

- Endorphin rebound effect after transient opioid receptor blockade
- Microglial suppression in the CNS
- Opioid growth factor (OGF)–OGF receptor (OGFr) axis modulation affecting cell proliferation
- Ion channel restoration (TRPM3) in immune cells (recent Long-COVID research)

Historically, LDN was shown by Shen and Crane (1988) to have a bi-modal effect mediated by the mu-opioid receptor. This hormetic response showed that small doses of opioids could paradoxically cause pain, which could be blocked by low dose naloxone. Larger doses of naloxone would eliminate the pro-analgesic effects of lower doses. As per Dr. Marcus and his colleagues, LDN affects mu-opioid receptor signaling at pico and nano-doses. This seems to be mediated through binding with filamin-A, a cytoplasmic scaffolding protein. This LDN-filamin-A complex is presented to a G-protein coupled receptor on mu-opioid receptors. There is a complex system of switching, whereby LDN can bind to two sites and thereby change the shape of Filamin A and can either cause analgesia or elimination of that effect.[1]

Side Effects

Many patients who start LDN do not experience any severe side effects. 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. Autoimmune thyroid disease patients may need medication dosage adjustments. 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 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. Another possible side effect is headaches, likely secondary to the effects in the CNS requiring adjustment.

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 nearly any strength, from Ultra Low Dose Naltrexone at 0.1 microgram, to standard 0.5mg, 1mg, 1.5mg. 3mg and 4.5mg 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 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[2, 3]. 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.[4, 5] 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]

Furthermote, in the 2025 study *Real-World Effectiveness and Tolerability of Low Dose Naltrexone to Treat Chronic Pain: A Retrospective Cohort Study,* of 93 chronic pain patients, 53.8% reported improvement in symptoms (most commonly pain and fatigue), with no serious adverse effects reported.[13]

A 2024 observational analysis to determine the range of effective naltrexone daily dosing in 41 patients with chronic musculoskeletal pain revealed that the determination of the maximally effective dosing varied over a wide range, with statistically significant improvement in Brief Pain Invetory (BPI). The authors concluded that the maximally effective dose of low-dose naltrexone for the treatment of chronic pain is idiosyncratic, suggesting the need for 1) dosage titration to establish a maximally effective dose and 2) the possibility of re-introduction of low-dose naltrexone to patients who had failed initial trials on a fixed dose of naltrexone.[1]

All studies have confirmed the safety of the drug and there is enough positive evidence to merit greater investigation.

The COVID-19 pandemic made necessary the allocation of new and repurposed therapeutics to treat patients suffering from acute and chronic effects of viral infection. LDN can be used to treat the pyramid of pathologies caused by CoV-2 Spike and Envelope proteins. Studies utilizing LDN for the management of Long-COVID continue. 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] In 2025, new mechanistic/ translational research showed that:

- Long-COVID patients showed **TRPM3 channel dysfunction** in natural killer (NK) cells.
- Treatment with LDN (3–4.5 mg/day) **restored TRPM3 function and calcium signaling**.[12]

Key references:

1. Marcus NJ, Robbins L, Araki A, Gracely EJ, Theoharides TC. "Effective Doses of Low-Dose Naltrexone for Chronic Pain – An Observational Study". J Pain Res. 2024 Mar 21;17:1273-1284. doi: 10.2147/JPR.S451183. PMID: 38532991; PMCID: PMC10964028.

2. Rahn KA, McLaughlin PJ, Zagon IS., "Prevention and Diminished Expression of Experimental Autoimmune Encephalomyelitis by Low Dose Naltrexone (LDN) or Opioid Growth Factor (OGF) for an Extended Period: Therapeutic Implications for Multiple Sclerosis", Brain Res, 2011 Mar 24;1381:243-53. https:// www. sciencedirect.com/science/article/abs/ pii/ S0006899311000977

3. Donahue RN, McLaughlin PJ,Zagon,IS, "The Opioid Growth Factor (OGF) and Low Dose Naltrexone (LDN) Suppress Human Ovarian Cancer Progression In Mice", Gynecol Oncol, 2011 Aug;122(2):382-8, https:// pubmed.ncbi.nlm.nih.gov/21531450/

4. Smith JP et al., "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease", Am J Gastroenterol, 2007 Apr;102(4):820-8, https:// pubmed.ncbi.nlm.nih. gov/17222320/

5. Smith JP et al., "Therapy with the Opioid Antagonist Naltrexone Promotes Mucosal Healing in Active Crohn's Disease: A Randomized Placebo-Controlled Trial", Dig Dis Sci, 2011 Jul;56(7):2088-97, https://pubmed.ncbi. nlm.nih.gov/21380937/

6. Younger J, Mackey S, "Fibromyalgia Symptoms are Reduced by Low-Dose Naltrexone: A Pilot Study", Pain Med, 2009 May -Jun;10(4):663-72. https://pubmed. ncbi.nlm.nih.gov/19453963/

7. Gironi M et al, "A Pilot Trial of Low-Dose Naltrexone in Primary Progressive Multiple Sclerosis", Mult Scler, 2008 Sep;14(8):1076- 83. https://journals.sagepub.com/ doi/10.1177/1352458508095828

8. Cree BA et al., "Pilot Trial of LowDose Naltrexone and Quality of Life in Multiple Sclerosis", Ann Neurol, 2010 Aug;68(2):145-50, https://pubmed.ncbi.nlm.nih. gov/20695007/

9. Sharafaddinzadeh N et al., "The Effect of Low-Dose Naltrexone on Quality of Life Of Patients with Multiple Sclerosis: A Randomized Placebo-Controlled Trial", Mult Scler, 2010 Aug;16 (8):964- 9, https://journals.sagepub.com/ doi/10.1177/1352458510366857

10. Gilhooly T, "Low-Dose Naltrexone as a Treatment for Multiple Sclerosis", British Journal of Neuroscience Nursing, Vol. 5, no. 11, 27 Sep, 2013, pp 494, https://www. magonlinelibrary.com/doi/abs/10.12968/ bjnn.2009.5.11.45142

11. O'Kelly B et al., "Safety and Efficacy of Low Dose Naltrexone in a Long Covid Cohort; An Interventional Pre-Post Study", Brain Behav Immun Health, 2022 Oct;24:100485, https:// pubmed.ncbi.nlm. nih.gov/35814187/

12. Sasso, Etianne Martini, Natalie Eaton-Fitch, Peter Smith, Katsuhiko Muraki, and Sonya Marshall-Gradisnik. "Low-Dose Naltrexone Restored TRPM3 Ion Channel Function in Natural Killer Cells from Long COVID Patients." Frontiers in Molecular Biosciences 12 (May 19, 2025): Article 1582967.

13. Aalto, H., S. Paul, and V. McEwen. "Real-World Effectiveness and Tolerability of Low Dose Naltrexone to Treat Chronic Pain: A Retrospective Cohort Study of One Pain Physician's Practice." Journal of Pain Research 18 (December 10, 2025): 6637–49.

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