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PERSONALIZED MEDICINE

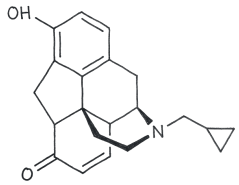
CLINICAL MONOGRAPH · METABOLIC & WEIGHT

Low-Dose Naltrexone (LDN)

Naltrexone at compounded micro-doses for off-label use

Low-dose naltrexone, or LDN, is a small dose of an older medicine called naltrexone [toljan2018]. The standard naltrexone pill is 50 mg and is used to help people with opioid or alcohol use disorder. LDN is much smaller, usually 1 to 4.5 mg, taken as a compounded capsule once a day, often at bedtime. There is no commercial low-dose pill on the U.S. market, so LDN is always made up to order by a compounding pharmacy.

Doctors prescribe LDN off-label for conditions where the immune system or nerves are overactive, most often fibromyalgia, Crohn's disease, and multiple sclerosis, but also complex regional pain syndrome, certain autoimmune skin conditions, and chronic fatigue states. The evidence is strongest in fibromyalgia and Crohn's, where small randomized trials have shown improvements in pain and disease activity [younger2013; smith2007; smith2011]. Larger trials are still missing, so LDN is best thought of as a reasonable add-on for selected patients rather than a first-line treatment.



EVIDENCE POSTURE | FDA APPROVED | WELL STUDIED | REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Low-dose naltrexone (LDN) is compounded oral naltrexone HCl at 0.5, 4.5 mg once daily, approximately one-tenth the 50 mg FDA-approved oral dose for opioid- and alcohol-use disorder [younger2009]. The mechanistic hypothesis is two-fold [toljan2018, younger2014]. First, transient (~4, 6 hour) competitive blockade of mu-opioid receptors at sub-therapeutic doses produces a compensatory upregulation of endogenous opioid (β-endorphin, met-enkephalin) tone after the antagonist clears, with secondary down-regulation of neuro-inflammatory signaling. Second, naltrexone (and its R-stereoisomer dextro-naltrexone) is a non-stereoselective Toll-like receptor 4 (TLR4) antagonist on microglia and other innate-immune cells [hutchinson2008], an action distinct from opioid receptor binding that attenuates glial pro-inflammatory cytokine release implicated in centrally-mediated chronic pain.

Randomized evidence is most developed in fibromyalgia [younger2013, parkitny2017] and Crohn's disease. A 2013 single-site crossover RCT (n=31) by Younger and colleagues at Stanford reported a 28.8% reduction in fibromyalgia pain with 4.5 mg LDN versus 18.0% with placebo; a 2017 follow-on demonstrated reductions in pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) over 8 weeks of treatment [younger2009]. In adult Crohn's disease, Smith and colleagues at Penn State Children's Hospital reported open-label improvement in CDAI in 2007 [smith2007], then a placebo-controlled RCT in 2011 demonstrating mucosal healing on follow-up endoscopy [smith2011], with a 2013 pediatric pilot [smith2013] supporting tolerability in adolescents; the 2014 Cochrane review [segal2014] characterized the evidence as low-certainty but consistent. Multiple sclerosis evidence comprises two small randomized trials, Sharafaddinzadeh 2010 [sharafaddinzadeh2010] in 96 Iranian adults reported improvement in mental health quality-of-life subdomains, and Cree 2010 [cree2010] in 80 U.S. adults reported improvement in self-reported quality of life on the 8-week crossover.

Single-indication evidence is also reported for complex regional pain syndrome [chopra2013], inflammatory dermatologic conditions [bridgman2018, ekelem2019], systemic sclerosis pruritus [frech2011], chronic non-malignant pain syndromes [trofimovitch2019, patten2018], and myalgic encephalomyelitis/chronic fatigue syndrome [cabanas2019, eatonfitch2022]. A 2015 systematic review of opioid antagonists in autism [roy2015] did not establish efficacy for core autism symptoms at low-dose ranges [younger2009]. Safety is favorable across the published evidence: most-frequent adverse events are vivid dreams, transient sleep disturbance during initiation, and mild gastrointestinal upset [younger2013, toljan2018]. The principal pharmacology-driven caution is concomitant opioid use, LDN will precipitate withdrawal in opioid-dependent patients and will partially blunt opioid analgesia [fda_label_revia].

Why Personalized Low-Dose Naltrexone (LDN)

Low-dose naltrexone is the cleanest example of why compounding exists at all. The FDA reviewed naltrexone at 50 mg orally and 380 mg as a monthly depot, doses chosen to produce near-complete opioid receptor blockade for substance-use disorder. The clinical use case for LDN, transient receptor antagonism plus TLR4 modulation in fibromyalgia, Crohn's disease, and multiple sclerosis, runs at 1.5 to 4.5 mg, roughly one-tenth to one-thirtieth of the approved strength. No manufacturer makes that pill. The trial doses behind LDN were not calibrated for your weight, your sleep architecture, your tolerance for vivid dreams during initiation, or whether your prescriber wants to start you at 0.5 mg and walk up over six weeks. They were calibrated for the average patient in a 31-person crossover at Stanford or an 80-person MS trial in San Francisco.

That entire dose range, 0.5, 1, 1.5, 3, and 4.5 mg, only exists because a compounding pharmacy makes it. The molecule is the same naltrexone hydrochloride the FDA reviewed, weighed out at a fraction of the commercial strength and capsuled to the prescriber's titration plan. A compounder can step a sensitive patient up by 0.5 mg increments instead of jumping to 4.5 mg, can switch to a sublingual troche or transdermal cream when a patient cannot tolerate the oral capsule, and can produce a dye-free, lactose-free preparation for patients with the relevant sensitivities. None of that is available off a manufacturer's shelf because the manufacturer's shelf does not carry this dose at all.

This is the older arrangement: a prescriber who knows the patient writes the order, a licensed pharmacist prepares it for that named patient, and the preparation reflects the clinical decision rather than a marketing SKU. Modern state inspection and pharmacist review keep it honest.

Quick Facts About Low-Dose Naltrexone (LDN)

Category: Opioid receptor antagonist at sub-therapeutic dose

Active ingredient: Naltrexone hydrochloride at compounded micro-doses of 0.5, 1, 1.5, 3, or 4.5 mg, typically one-tenth to one-twentieth of the 50 mg FDA-approved oral strength

FDA-approved branded forms (at 50 mg): ReVia (naltrexone HCl 50 mg oral tablet, FDA-approved 1984 for opioid use disorder; 1995 for alcohol use disorder) and Vivitrol (naltrexone extended-release 380 mg intramuscular suspension, FDA-approved 2006 for alcohol use disorder, 2010 for opioid use disorder)

Compounded dosing range: Oral 0.5, 4.5 mg once daily (typically at bedtime); 4.5 mg is the most-studied dose in fibromyalgia and Crohn's disease trials

Evidence posture: Small randomized trials and pilot studies support a Tier 2 (well-studied) posture for fibromyalgia and Crohn's disease. Other indications (multiple sclerosis, CRPS, autism, inflammatory skin disease) are emerging or case-level. No phase III program supports LDN in any indication.

FDA-approval status: Naltrexone HCl is FDA-approved as a 50 mg oral tablet and a 380 mg intramuscular depot for opioid- and alcohol-use disorders. The low-dose (≤5 mg) preparation is not FDA-approved for any indication, there is no commercial low-dose product on the U.S. market.

Compounded under: 503A, patient-specific prescription only. Because no commercial product exists at the 0.5, 4.5 mg strength range, LDN is inherently a compounded preparation rather than a copy of a manufactured drug.

Important compounding caution: Low-dose naltrexone is not 'essentially a copy' of the manufactured 50 mg tablet, the dose is approximately 10, 100× lower and the therapeutic rationale (transient opioid receptor antagonism, glial TLR4 modulation) is mechanistically distinct from full-dose opioid blockade. The compounded preparation should not be conflated with the FDA-approved 50 mg or 380 mg products.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Low-Dose Naltrexone (LDN) described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.
>
> - **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
> - **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
> - **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
> - **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
> - **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Low-Dose Naltrexone (LDN)?

Naltrexone is a small-molecule competitive antagonist at mu-, kappa-, and (to a lesser extent) delta-opioid receptors. As a drug substance it was synthesized in the 1960s and FDA-approved as a 50 mg oral tablet in 1984 for the treatment of opioid use disorder; the indication was extended to alcohol use disorder in 1995. A long-acting 380 mg intramuscular depot (Vivitrol) was approved in 2006 (alcohol use disorder) and 2010 (opioid use disorder). At those doses naltrexone produces near-complete and sustained opioid receptor blockade [fda_label_revia].

Low-dose naltrexone (LDN) refers to compounded oral preparations at 0.5, 4.5 mg once daily, approximately 1/10th to 1/100th the dose used for substance-use disorder. There is no commercial low-dose naltrexone product approved by the FDA [fda_label_revia; fda_label_vivitrol]. LDN is therefore inherently a compounded preparation, typically dispensed as oral capsules at 0.5, 1, 1.5, 3, or 4.5 mg strengths, occasionally as troches or transdermal cream where the prescriber documents an oral-route limitation [toljan2018, brown2009].

The clinical rationale for LDN was developed by Bernard Bihari and colleagues beginning in the mid-1980s, originally in the context of HIV/AIDS-era immune dysregulation, and was subsequently extended to autoimmune, inflammatory, and chronic pain conditions [toljan2018, younger2014, brown2009] [fda_label_revia]. Modern off-label use is heaviest in fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome, with case-level reports across a broader autoimmune and inflammatory disease catalog.

How Low-Dose Naltrexone (LDN) Works

Two distinct mechanisms are proposed for low-dose naltrexone, and both are likely operative. The first is transient mu-opioid receptor antagonism with rebound up-regulation of endogenous opioid tone. At 4.5 mg orally, naltrexone occupies central mu-opioid receptors for approximately 4, 6 hours before clearing; the brief blockade is hypothesized to trigger a compensatory increase in endogenous opioid ligand (β-endorphin, met-enkephalin) production and in receptor density that persists after the drug has cleared, producing a net pro-analgesic, anti-inflammatory state [younger2014, toljan2018] [parkitny2017].

The second mechanism is non-stereoselective antagonism of Toll-like receptor 4 (TLR4) on microglia and other innate-immune cells [hutchinson2008]. Hutchinson and colleagues demonstrated in 2008 that both naloxone and naltrexone (and their non-opioid-binding R-isomers) reverse neuropathic pain in rodent models through a mechanism that does not require opioid receptor binding, and traced the effect to direct antagonism of TLR4-mediated glial cell activation. Because activated microglia release pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) implicated in centrally-mediated chronic pain and autoimmune symptomatology, TLR4 antagonism provides a mechanistic basis for LDN's reported effects on

fibromyalgia, multiple sclerosis, and inflammatory bowel disease that is independent of the opioid receptor pathway [parkitny2017].

Biological Role of Low-Dose Naltrexone (LDN)

Naltrexone occupies endogenous opioid receptor systems that, at physiological tone, modulate pain, mood, immune function, and visceral homeostasis. The mu-opioid receptor system is engaged by β-endorphin from POMC neurons and by exogenous opioid agonists; the kappa-opioid system is engaged by dynorphin and contributes to dysphoric and aversive states; the delta-opioid system is engaged by enkephalins and contributes to mood-regulatory and analgesic tone. Naltrexone is a competitive antagonist at all three receptors with highest affinity at mu.

Beyond the canonical opioid receptor system, naltrexone (and its R-enantiomer, which does not bind opioid receptors) antagonizes Toll-like receptor 4 (TLR4) on microglia and other innate-immune cells [hutchinson2008]. TLR4 sits at the interface between innate immunity and central pain processing, its activation by endogenous danger-associated molecular patterns or by lipopolysaccharide drives a pro-inflammatory glial transcriptional program that has been implicated in fibromyalgia central sensitization, multiple sclerosis disease activity, and neuropathic pain states. The dual mechanism (transient opioid antagonism plus TLR4 glial modulation) is the leading current account of why low-dose naltrexone has clinical signal across an otherwise heterogeneous catalog of conditions [younger2014, toljan2018, parkitny2017].

Detailed Mechanism of Low-Dose Naltrexone (LDN)

Naltrexone is a competitive antagonist at mu-, kappa-, and delta-opioid receptors with highest affinity at mu. Oral bioavailability of the parent compound is approximately 5, 40% due to extensive first-pass metabolism to 6-β-naltrexol, an active metabolite with longer half-life that contributes to clinical effect. Plasma half-life of the parent is approximately 4 hours; the metabolite extends pharmacodynamic effect to approximately 10, 12 hours [fda_label_revia]. At the 50 mg dose used for substance-use disorder, central mu-opioid receptor occupancy is essentially complete throughout the dosing interval. At 4.5 mg, occupancy is partial and short-lived, supporting the 'transient blockade' rationale for LDN.

The endogenous opioid rebound hypothesis was articulated by Bihari and colleagues in the 1980s and reviewed in the modern era by Younger and Mackey (2014) and Toljan and Vrooman (2018) [younger2014, toljan2018]. Mechanistically, brief mu-opioid antagonism is proposed to relieve negative feedback inhibition on enkephalinergic and beta-endorphin neurons in the periaqueductal gray, hypothalamus, and dorsal horn, leading to a compensatory increase in endogenous opioid peptide synthesis and receptor sensitivity. Once the antagonist clears, the upregulated system is hypothesized to produce a net analgesic,

anti-inflammatory state. Direct human pharmacodynamic measurements of this rebound effect remain limited.

The TLR4 mechanism is independent of opioid receptor binding. Hutchinson and colleagues (2008) demonstrated that the R-enantiomers of naloxone and naltrexone, which do not bind opioid receptors, reverse neuropathic pain hypersensitivity in rodent models, and that this effect is abolished in TLR4-knockout animals [hutchinson2008]. TLR4 is expressed on microglia, astrocytes, and peripheral macrophages; its activation drives a pro-inflammatory transcriptional program including IL-1β, IL-6, and TNF-α. Antagonism of TLR4 by low-dose naltrexone is proposed to dampen the central neuroinflammatory state underlying fibromyalgia central sensitization, multiple sclerosis disease activity, and inflammatory bowel disease symptomatology. The Parkitny and Younger (2017) demonstration that 8 weeks of LDN reduced serum IL-1β, IL-6, and TNF-α in women with fibromyalgia [parkitny2017] provides indirect human pharmacodynamic support for the TLR4 mechanism.

A third hypothesis, relevant specifically to Crohn's disease, is direct enteric mucosal healing through opioid growth factor (OGF, -enkephalin) and the OGF-receptor (OGFr) axis [smith2011; smith2013]. Brief mu-antagonism with low-dose naltrexone is proposed to alter OGF tone in intestinal epithelium, supporting mucosal repair. This rationale, developed in the Smith laboratory at Penn State, motivated the placebo-controlled trial design [smith2011] that demonstrated endoscopic mucosal healing as a secondary endpoint.

Low-Dose Naltrexone (LDN) Research History

Bernard Bihari, a New York City neurologist, originated the low-dose naltrexone clinical concept in the mid-1980s in the context of HIV/AIDS-era investigation of immune-modulating agents [toljan2018, brown2009]. Early Bihari case-series work in HIV and in autoimmune conditions remained largely outside the peer-reviewed literature, but established the empiric 1.5, 4.5 mg once-nightly oral dosing schedule that has been carried into every subsequent randomized trial. Brown and Panksepp (2009) [brown2009] consolidated the early clinical rationale into the Medical Hypotheses literature.

The first contemporary randomized fibromyalgia evidence was published by Younger and Mackey (2009) at Stanford [younger2009], an open-label, single-site pilot in 10 women that established feasibility, tolerability, and a substantial within-subject pain-score signal. The follow-on randomized, double-blind, placebo-controlled crossover trial [younger2013] [younger2013] reported a 28.8% reduction in fibromyalgia pain on 4.5 mg LDN versus 18.0% on placebo and demonstrated greater symptom-day responder rates with LDN. The Younger review (Clin Rheumatol 2014) [younger2014] consolidated the mechanism and clinical evidence as it stood at the time. Parkitny and Younger (2017) [parkitny2017] extended the fibromyalgia work mechanistically by demonstrating reductions in serum IL-1β, IL-6, and TNF-α after 8 weeks of LDN treatment.

Crohn's disease evidence was developed by the Smith group at Penn State Children's Hospital. Smith et al. (2007, Am J Gastroenterol) [smith2007] reported an open-label pilot in 17 adults with active Crohn's

disease showing reductions in CDAI on 4.5 mg LDN. The randomized, double-blind, placebo-controlled adult trial [smith2011] [smith2011] demonstrated 78% clinical response and 33% endoscopic mucosal healing on LDN versus 28% and 8% on placebo respectively. A 2013 pediatric pilot in adolescents [smith2013] established tolerability and a within-subject CDAI signal in younger patients. The 2014 Cochrane review (Segal et al.) [segal2014] characterized the body of evidence as low-certainty but consistent across small RCTs.

Multiple sclerosis evidence comprises two small randomized trials. Sharafaddinzadeh et al. (2010, Mult Scler) [sharafaddinzadeh2010] randomized 96 Iranian adults with relapsing-remitting or secondary-progressive MS to 4.5 mg LDN or placebo for 17 weeks and reported significant improvement in the mental health domain of MSQOL-54. Cree et al. (2010, Ann Neurol) [cree2010] randomized 80 U.S. adults with MS in a single-center crossover and reported improvement in self-reported quality of life on LDN. Raknes and Småbrekke (2017) [raknes2017, raknesIBD2018] performed observational pharmacoepidemiology in Norway following a 2013 surge in LDN prescribing, documenting reduced use of co-medications including immunomodulators in MS prescribers.

The fibromyalgia evidence base broadened substantially between 2020 and 2024. Bruun-Plesner and colleagues at the University of Southern Denmark conducted a dose-response investigation in 2020 [bruunPlesner2020], examining 1.0, 2.0, 3.0, 4.0, 4.5, and 6.0 mg dosing in 25 women with fibromyalgia and identifying 3.88 mg as the modal effective dose. Their group then ran the largest LDN-fibromyalgia randomized trial to date, Due Bruun et al. (2024, Lancet Rheumatology) [dueBruun2024], comparing naltrexone 6 mg once daily to placebo in 99 women over 12 weeks; the trial's primary outcome (between-group difference in pain on a 0, 10 NRS at week 12) did not reach statistical significance, although the LDN arm showed a numerically larger improvement and significantly better memory-domain scores on the FIQR. The Driver and D'Souza (2023) [driver2023] enterprise-wide retrospective analysis at Mayo Clinic, 14 years, 115 LDN-treated patients across fibromyalgia and other chronic pain conditions, reported a 65% symptomatic improvement rate and identified body-pain extent and prior opioid exposure as predictors of discontinuation. Partridge et al. (2023) [partridge2023] systematic literature review and Vatvani et al. (2024) [vatvani2024] systematic review with meta-analysis and trial-sequential analysis both concluded that the fibromyalgia LDN evidence direction is consistent with benefit but that available trials are underpowered to confirm a robust effect, and called for further multi-center RCTs.

Crohn's disease evidence was extended by the Lie et al. (2018, J Transl Med) [lie2018] observational cohort in the Netherlands, an IBD-patient audit that reported clinical benefit and tolerability in adults with active Crohn's disease and ulcerative colitis treated with 4.5 mg LDN at the Erasmus MC IBD center. Parker et al. (2018) [parker2018] published the Cochrane systematic review update on LDN for induction of remission in Crohn's disease, replacing the 2014 Segal review with expanded analysis but reaching a similar low-certainty-but-consistent conclusion across the small-trial corpus.

Multiple sclerosis evidence was extended by Gironi et al. (2008, Mult Scler) [gironi2008], a 40-patient pilot trial of LDN in primary progressive MS, the first prospective LDN-MS trial and a precursor to the Sharafaddinzadeh and Cree randomized work, which reported tolerability and modest signal on quality-of-

life and spasticity outcomes over 6 months. Complex regional pain syndrome evidence was consolidated by Soin et al. (2021, Pain Physician) [soin2021] in a systematic literature review that supplemented the Chopra and Cooper case series with additional small-case reports.

Single-indication studies are reported across complex regional pain syndrome [chopra2013, soin2021], psoriasis vulgaris [bridgman2018], systemic sclerosis pruritus [frech2011], Hailey-Hailey disease [albers2017], and inflammatory dermatologic conditions more broadly [ekelem2019]. Albers et al. (2017, JAMA Dermatol) [albers2017] reported sustained clearance of recalcitrant Hailey-Hailey lesions in three patients treated with 3.0, 4.5 mg LDN, the first peer-reviewed evidence in this rare autosomal-dominant acantholytic disease, and the Ekelem 2019 systematic review consolidates the broader dermatologic case-level literature. Roy et al. (2015) [roy2015] systematically reviewed opioid antagonists including low-dose naltrexone in autism spectrum conditions and concluded the evidence did not support efficacy at the core-symptom level. Trofimovitch and Baumrucker (2019) [trofimovitch2019] consolidated the LDN evidence for chronic non-malignant pain in a palliative care pharmacology update. Patten et al. (2018) [patten2018] reviewed safety and efficacy across fibromyalgia, MS, and Crohn's. Cabanas et al. (2019) [cabanas2019] and (2021) [cabanas2021] and Eaton-Fitch et al. (2022) [eatonfitch2022] reported mechanistic and pilot clinical evidence for LDN in myalgic encephalomyelitis/chronic fatigue syndrome via a TRPM3 ion channel restoration mechanism in natural killer cells; Bolton et al. (2020) [bolton2020] independently published a case-level chronic fatigue syndrome response to 4.5 mg LDN. The post-acute-COVID literature emerged with O'Kelly et al. (2022) [okelly2022], a 38-patient interventional pre-post study of 1.0, 4.5 mg LDN over 2 months that demonstrated improvement in WHO long-COVID symptom-score domains, followed by Bonilla et al. (2023) [bonilla2023], a 59-patient Stanford retrospective cohort that reported symptom improvement in fatigue, post-exertional malaise, and pain-domain scores over 2 months of LDN. Toljan and Vrooman (2018) [toljan2018] and the Leiber and Parker (2025, Cureus) scoping review [leiber2025] provide the most recent comprehensive utilization syntheses across the full indication catalog.

Low-Dose Naltrexone (LDN) Timeline

1984 • FDA approves naltrexone HCl 50 mg oral tablet (ReVia) for opioid use disorder [fda_label_revia]

Mid-1980s Bernard Bihari develops the low-dose (≤4.5 mg) clinical concept in HIV/AIDS-era immune-modulation work in New York City; case-series-level evidence accumulates outside the peer-reviewed literature [toljan2018; brown2009]

1995 • FDA extends naltrexone HCl 50 mg oral indication to alcohol use disorder [fda_label_revia]

2006 • FDA approves naltrexone extended-release injectable suspension 380 mg (Vivitrol) for alcohol use disorder [fda_label_vivitrol]

2007 • Smith et al [smith2007]. (Am J Gastroenterol) publish first open-label pilot of LDN 4.5 mg in adults with active Crohn's disease, reduction in CDAI in 17 patients

2008 • Hutchinson et al [hutchinson2008]. (Eur J Neurosci) demonstrate non-stereoselective reversal of neuropathic pain by naloxone and naltrexone via Toll-like receptor 4 antagonism on microglia, mechanistic foundation independent of opioid receptor binding

2009 • Younger and Mackey (Pain Med) publish open-label fibromyalgia pilot at Stanford, 10 women, single-blind crossover, ~30% reduction in fibromyalgia symptom score on 4.5 mg LDN [younger2009]

2009 • Brown and Panksepp (Med Hypotheses) consolidate LDN clinical rationale across disease-prevention and quality-of-life applications [brown2009]

2010 • FDA expands Vivitrol indication to opioid use disorder [fda_label_vivitrol]

2010 • Sharafaddinzadeh et al [sharafaddinzadeh2010]. (Mult Scler) publish RCT of 4.5 mg LDN in 96 Iranian adults with multiple sclerosis, improvement in MSQOL-54 mental health domain at 17 weeks

2010 • Cree et al [cree2010]. (Ann Neurol) publish 8-week crossover RCT of LDN in 80 U.S. adults with MS, improvement in self-reported quality of life

2011 • Smith et al [smith2011]. (Dig Dis Sci) publish randomized double-blind placebo-controlled adult Crohn's trial of 4.5 mg LDN, 78% clinical response and 33% endoscopic mucosal healing vs 28% and 8% on placebo

2011 • Frech et al [frech2011]. (Int J Rheumatol) report case series of LDN for pruritus in systemic sclerosis

2013 • Younger et al [younger2013]. (Arthritis Rheum) publish randomized double-blind placebo-controlled crossover trial of 4.5 mg LDN in 31 women with fibromyalgia, 28.8% reduction in pain on LDN vs 18.0% placebo; greater responder rates

2013 • Smith et al [smith2013]. (J Clin Gastroenterol) publish open-label pediatric Crohn's pilot in 12 adolescents, tolerability established and CDAI reduction observed

2013 • Chopra and Cooper (J Neuroimmune Pharmacol) report case series of LDN in complex regional pain syndrome, symptom and function improvement in 2 patients [chopra2013]

2014 • Segal et al [segal2014]. (Cochrane Database Syst Rev) review LDN for induction of remission in Crohn's disease, low-certainty evidence of benefit across the small-RCT corpus

2014 • Younger et al [younger2014]. (Clin Rheumatol) publish comprehensive review of LDN as a novel anti-inflammatory for chronic pain, consolidates mechanism (opioid rebound plus TLR4 glial modulation) and clinical evidence

2015 • Roy et al [roy2015]. (J Intellect Disabil Res) publish systematic review of opioid antagonists in autism spectrum conditions, no consistent evidence for core symptom efficacy at LDN-range doses

2017 • Parkitny and Younger (Biomedicines) demonstrate reduction in serum IL-1β, IL-6, and TNF-α after 8 weeks of LDN in women with fibromyalgia, human pharmacodynamic support for the TLR4/glial mechanism [parkitny2017]

2017 • Raknes and Småbrekke (Pharmacoepidemiol Drug Saf) document an unprecedented surge in LDN prescribing in Norway after national media coverage, patient and prescriber characteristics and dispense patterns [raknes2017]

2017 • Raknes and Småbrekke (PLoS One), quasi-experimental analysis of medication-use change among new LDN users with multiple sclerosis, demonstrating reduced co-medication use [raknesIBD2018]

2018 • Toljan and Vrooman (Med Sci) publish comprehensive review of LDN therapeutic utilization across autoimmune, inflammatory, and chronic pain conditions [toljan2018]

2018 • Patten et al [patten2018]. (Pharmacotherapy) review safety and efficacy of LDN in chronic pain and inflammation across multiple sclerosis, fibromyalgia, and Crohn's disease

2018 • Bridgman and Bruce-Brand (JAAD Case Rep) report psoriasis vulgaris response to LDN in a single-patient case [bridgman2018]

2019 • Ekelem et al [ekelem2019]. (JAMA Dermatol) systematic review of LDN in chronic inflammatory dermatologic conditions, small-study evidence for Hailey-Hailey disease, lichen planopilaris, and psoriasis

2019 • Trofimovitch and Baumrucker (Am J Hosp Palliat Care) consolidate LDN evidence for chronic non-malignant pain in a palliative-care pharmacology update [trofimovitch2019]

2019 • Cabanas et al [cabanas2019]. (Front Immunol) demonstrate that naltrexone restores impaired TRPM3 ion channel function in natural killer cells from ME/CFS patients, mechanistic basis for an emerging chronic-fatigue-syndrome indication

2022 • Eaton-Fitch et al [eatonfitch2022]. (J Transl Med) extend the TRPM3/NK-cell pharmacodynamic finding in ME/CFS

2008 • Gironi et al [gironi2008]. (Mult Scler) publish 40-patient pilot trial of LDN in primary progressive multiple sclerosis, first prospective LDN-MS trial; tolerability and modest QoL signal over 6 months

2017 • Albers et al [albers2017]. (JAMA Dermatol) report sustained clearance of recalcitrant Hailey-Hailey disease in three patients on 3.0, 4.5 mg LDN, first peer-reviewed dermatologic case series in this autosomal-dominant acantholytic disease

2018 • Lie et al [lie2018]. (J Transl Med) publish observational cohort of LDN in inflammatory bowel disease at the Erasmus MC IBD center, clinical benefit and tolerability in active Crohn's disease and ulcerative colitis

2018 • Parker et al [parker2018]. (Cochrane Database Syst Rev) publish updated Cochrane systematic review of LDN for induction of remission in Crohn's disease, replacing the 2014 Segal review with expanded analysis

2020 • Bruun-Plesner et al [bruunPlesner2020]. (Pain Med) publish dose-response investigation of LDN in fibromyalgia across 1.0, 6.0 mg; identifies 3.88 mg as the modal effective dose in 25 women

2020 • Bolton et al [bolton2020]. (BMJ Case Rep) publish case-level evidence of 4.5 mg LDN response in chronic fatigue syndrome

2021 • Cabanas et al [cabanas2021]. (Front Immunol) consolidate the TRPM3/NK-cell mechanism and clinical rationale for LDN in ME/CFS

2021 • Soin et al [soin2021]. (Pain Physician) publish systematic literature review of LDN in complex regional pain syndrome, consolidating case-series evidence

2022 • O'Kelly et al [okelly2022]. (Brain Behav Immun Health) publish 38-patient interventional pre-post study of 1.0, 4.5 mg LDN in long COVID over 2 months, improvement in WHO long-COVID symptom-score domains

2023 • Driver and D'Souza (Biomedicines) publish 14-year enterprise-wide Mayo Clinic retrospective analysis of LDN in 115 patients across fibromyalgia and other chronic pain, 65% symptomatic improvement rate; identifies predictors of treatment success and discontinuation [driver2023]

2023 • Bonilla et al [bonilla2023]. (Int Immunopharmacol) report 59-patient Stanford retrospective cohort of LDN for post-acute sequelae of COVID-19, improvement in fatigue, post-exertional malaise, and pain-domain scores over 2 months

2023 • Partridge et al [partridge2023]. (Heliyon) publish systematic literature review of LDN clinical efficacy in fibromyalgia and putative pathophysiological mechanisms

2024 • Due Bruun et al [dueBruun2024]. (Lancet Rheumatol) publish 99-women randomized placebo-controlled trial of naltrexone 6 mg in fibromyalgia, primary pain outcome did not reach significance; significant FIQR memory-domain improvement on LDN

2024 • Vatvani et al [vatvani2024]. (Korean J Pain) publish systematic review and meta-analysis of LDN in fibromyalgia with trial-sequential analysis, consistent direction of effect; trial-sequential analysis indicates further RCTs are needed for definitive conclusion

2025 • Leiber and Parker (Cureus) publish scoping review of LDN therapeutic uses and efficacy across the full indication catalog [leiber2025]

Clinical Contexts for Low-Dose Naltrexone (LDN)

Opioid use disorder (full-dose naltrexone, FDA-approved) FDA APPROVED

FDA-approved at 50 mg orally (ReVia) and 380 mg intramuscularly (Vivitrol). This is the molecule's labeled indication, not the low-dose use described elsewhere in this brief.

Naltrexone HCl 50 mg orally once daily and naltrexone extended-release injectable suspension 380 mg every 4 weeks are FDA-approved for the prevention of relapse to opioid dependence after opioid detoxification [fda_label_revia, fda_label_vivitrol]. The labeled mechanism is complete and sustained mu-opioid receptor blockade. This use is mechanistically and clinically distinct from compounded low-dose naltrexone at 0.5, 4.5 mg, which is the focus of the remainder of this brief.

Branded product: ReVia (naltrexone HCl 50 mg tablet) and Vivitrol (naltrexone XR 380 mg IM suspension)

Alcohol use disorder (full-dose naltrexone, FDA-approved) FDA APPROVED

FDA-approved at 50 mg orally and 380 mg intramuscularly.

Naltrexone HCl 50 mg orally and Vivitrol 380 mg IM are FDA-approved for the treatment of alcohol use disorder. As with opioid use disorder, this indication is at full dose and is mechanistically distinct from compounded LDN [fda_label_revia, fda_label_vivitrol].

Branded product: ReVia and Vivitrol

Fibromyalgia (off-label, low-dose) WELL STUDIED

Studied in multiple small randomized trials across Stanford and Denmark; well-studied for this compound at LDN doses, with a 2024 multi-center randomized trial available.

Two single-site Stanford trials [younger2009, younger2013] established the modern LDN fibromyalgia evidence base. The open-label pilot (n=10) reported a ~30% within-subject reduction in fibromyalgia symptom score on 4.5 mg LDN. The 2013 randomized double-blind placebo-controlled crossover trial (n=31) reported a 28.8% reduction in fibromyalgia pain on LDN versus 18.0% on placebo, with greater responder rates at the LDN-stable period. Parkitny and Younger (2017) [parkitny2017] extended these data mechanistically with a demonstration of reduced serum IL-1β, IL-6, and TNF-α over 8 weeks [younger2014]. The Bruun-Plesner et al. (2020) [bruunPlesner2020] dose-response investigation in 25 women identified 3.88 mg as the modal effective dose across 1.0, 6.0 mg, and the Due Bruun et al. (2024, Lancet Rheumatol) [dueBruun2024] 99-women randomized placebo-controlled trial of naltrexone 6 mg over 12 weeks did not meet its primary pain-outcome endpoint, although the LDN arm showed a numerically larger improvement and a significant memory-domain benefit on the FIQR. The Driver and D'Souza (2023) [driver2023] 14-year enterprise-wide Mayo Clinic retrospective in 115 patients reported a 65% symptomatic improvement rate. The Vatvani et al. (2024) [vatvani2024] meta-analysis and Partridge et al. (2023) [partridge2023] systematic review both characterize the evidence direction as consistent with benefit but underpowered; trial-sequential analysis indicates further RCTs are required for definitive conclusion. The Patten 2018 [patten2018] and Toljan-Vrooman 2018 [toljan2018] and Leiber-Parker 2025 [leiber2025] reviews consolidate fibromyalgia as the strongest single-indication signal for LDN in the chronic-pain literature.

Crohn's disease (off-label, low-dose) WELL STUDIED

Studied in small randomized trials at Penn State Children's Hospital with subsequent Dutch observational replication; well-studied for this compound at LDN doses, with updated Cochrane synthesis.

The Smith laboratory at Penn State Children's Hospital developed the Crohn's disease evidence base across three trials [smith2007, smith2011, smith2013]. The 2007 open-label adult pilot in 17 patients reported a reduction in CDAI on 4.5 mg LDN. The 2011 randomized double-blind placebo-controlled trial (n=40) reported 78% clinical response and 33% endoscopic mucosal healing on LDN versus 28% and 8% on placebo. The 2013 pediatric pilot (n=12 adolescents) established tolerability and within-subject CDAI signal in younger patients. Lie et al. (2018, J Transl Med) [lie2018] published an observational cohort of adult IBD patients (Crohn's disease and ulcerative colitis) treated with 4.5 mg LDN at the Erasmus MC IBD center in the Netherlands, reporting tolerability and clinical benefit. The 2014 Cochrane review by Segal et al. [segal2014] and the 2018 update by Parker et al. [parker2018] both characterize the body of evidence as low-certainty but consistent across the small-RCT corpus, supporting a Tier 2 (well-studied for the compound) posture.

Multiple sclerosis (off-label, low-dose) EMERGING

Studied in three small randomized trials; emerging-to-well-studied for this compound at LDN doses.

Three randomized or prospective trials provide the contemporary MS evidence. Gironi et al. (2008, Mult Scler) [gironi2008] conducted a 40-patient pilot trial in primary progressive MS, the first prospective LDN-MS trial, reporting tolerability and modest signal on quality-of-life and spasticity outcomes over 6 months. Sharafaddinzadeh et al. (2010) [sharafaddinzadeh2010] randomized 96 Iranian adults with relapsing-remitting or secondary-progressive MS to 4.5 mg LDN or placebo for 17 weeks and reported significant improvement in the MSQOL-54 mental health domain. Cree et al. (2010) [cree2010] randomized 80 U.S. adults with MS in an 8-week crossover and reported improvement in self-reported quality of life on LDN. None of these trials demonstrated effect on disability progression or relapse rate, and all are small and single-center. Pharmacoepidemiology in Norway after a 2013 LDN prescribing surge [raknes2017, raknesIBD2018] suggests reduced co-medication use in new LDN-prescribed MS patients but is observational and unrandomized [patten2018].

Complex regional pain syndrome (off-label, low-dose) EMERGING

Case-series evidence with a systematic literature review available.

Chopra and Cooper (2013) [chopra2013] reported sustained symptom and functional improvement in two patients with longstanding CRPS treated with 4.5 mg LDN. Soin et al. (2021, Pain Physician) [soin2021] systematically reviewed the LDN-CRPS literature and identified additional small-case reports supporting the Chopra and Cooper findings; randomized trial evidence is absent. Mechanistic rationale rests on the TLR4/glial-modulation account of LDN action [hutchinson2008, younger2014].

Inflammatory dermatologic conditions (psoriasis, Hailey-Hailey, lichen planopilaris) EMERGING

Case-level and small-series evidence; systematic review available.

Albers et al. (2017, JAMA Dermatol) [albers2017] reported sustained clearance of recalcitrant Hailey-Hailey disease lesions in three patients on 3.0, 4.5 mg LDN, the first peer-reviewed evidence in this rare autosomal-dominant acantholytic disease. Bridgman and Bruce-Brand (2018) [bridgman2018] reported psoriasis vulgaris response in a single patient. The Ekelem et al. (2019) systematic review [ekelem2019] in JAMA Dermatology consolidates LDN evidence across Hailey-Hailey disease, lichen planopilaris, psoriasis, and other chronic inflammatory dermatologic conditions, with most evidence at case-series level. Frech et al. (2011) [frech2011] reported LDN benefit for pruritus in systemic sclerosis.

Myalgic encephalomyelitis / chronic fatigue syndrome (off-label, low-dose) EMERGING

Mechanistic and case-level evidence.

Cabanas et al. (2019) [cabanas2019] demonstrated that naltrexone restores impaired TRPM3 ion channel function in natural killer cells from ME/CFS patients, providing a mechanistic basis for the off-label use that had accumulated in clinical practice. Cabanas et al. (2021) [cabanas2021] and Eaton-Fitch et al. (2022) [eatonfitch2022] extended the TRPM3/NK-cell pharmacodynamic findings in a larger ME/CFS cohort and consolidated the mechanistic rationale. Bolton et al. (2020, BMJ Case Rep) [bolton2020] independently reported case-level chronic fatigue syndrome response to 4.5 mg LDN. Randomized symptom-outcome trials are not yet published.

Chronic non-malignant pain (general off-label use) EMERGING

Reviewed across palliative-care and chronic-pain pharmacology updates.

Trofimovitch and Baumrucker (2019) [trofimovitch2019] reviewed LDN as a possible nonopioid modality for chronic non-malignant pain syndromes across the published evidence. Younger (2014) [younger2014] characterized LDN as a novel anti-inflammatory treatment for chronic pain. Patten et al. (2018) [patten2018] consolidated efficacy and safety across the major indications. Single-arm and case-series evidence in chronic pain has accumulated across small studies but no well-powered multi-indication chronic-pain RCT has been completed.

Autism spectrum conditions PRECLINICAL

Systematic review concludes the evidence does not support efficacy at the core-symptom level.

Roy et al. (2015) [roy2015] systematically reviewed opioid antagonists including low-dose naltrexone for core symptoms of autism spectrum conditions in children and concluded that the evidence does not support efficacy. This indication is included here for completeness of the off-label literature but is not a Tier 2 posture and should not be prescribed against the published systematic review.

Hailey-Hailey disease (off-label, low-dose) EMERGING

Single-center case series; emerging evidence for this rare autosomal-dominant acantholytic disorder.

Albers et al. (2017, JAMA Dermatol) [albers2017] reported sustained clearance of recalcitrant Hailey-Hailey disease lesions in three patients on 3.0, 4.5 mg LDN at the Emory University Department of Dermatology, the first peer-reviewed evidence in this rare autosomal-dominant acantholytic disease, where conventional therapies (topical corticosteroids, topical calcineurin inhibitors, surgical intervention) are commonly inadequate. The Ekelem et al. (2019) systematic review [ekelem2019] consolidated this evidence with subsequent case-level reports. No randomized trial in Hailey-Hailey disease has been conducted.

Post-acute sequelae of COVID-19 / long COVID (off-label, low-dose) EMERGING

Two small open-label / observational cohorts; emerging evidence.

O'Kelly et al. (2022, Brain Behav Immun Health) [okelly2022] published a 38-patient interventional pre-post study of 1.0, 4.5 mg LDN over 2 months in long COVID at the Mater Misericordiae University Hospital long-COVID clinic in Dublin, reporting improvement in WHO long-COVID symptom-score domains including recovery from acute illness, mobility, daily activities, energy, pain, sleep, and concentration. Bonilla et al. (2023, Int Immunopharmacol) [bonilla2023] reported a 59-patient Stanford retrospective cohort with improvement in fatigue, post-exertional malaise, and pain-domain scores over 2 months of LDN. Both studies are uncontrolled and short-duration. The mechanistic rationale rests on overlap between post-COVID symptomatology and the proposed TLR4/glial-modulation and TRPM3-restoration accounts of LDN in fibromyalgia and ME/CFS [hutchinson2008, cabanas2019, cabanas2021]. Randomized placebo-controlled trials are pending.

Off-Label Uses of Low-Dose Naltrexone (LDN)

Fibromyalgia WELL STUDIED

Off-label; supported by small Stanford and Danish RCTs, dose-response and meta-analytic synthesis, and a mechanistic cytokine demonstration.

Younger et al. (2013) randomized crossover trial in 31 women reported 28.8% pain reduction on LDN vs 18.0% on placebo [younger2013]. Parkitny and Younger (2017) demonstrated reductions in serum IL-1β, IL-6, and TNF-α over 8 weeks [parkitny2017]. Bruun-Plesner 2020 dose-response found 3.88 mg as the modal effective dose across 1.0, 6.0 mg [bruunPlesner2020]. Due Bruun 2024 99-women RCT of naltrexone 6 mg did not meet its primary pain endpoint but showed numerically larger LDN improvement and a significant FIQR memory-domain benefit [dueBruun2024] [younger2009; younger2014]. Driver 2023 Mayo Clinic retrospective in 115 patients reported 65% symptomatic improvement [driver2023]. Vatvani 2024 meta-analysis and Partridge 2023 systematic review characterize the evidence direction as consistent with benefit but underpowered [vatvani2024, partridge2023].

Crohn's disease WELL STUDIED

Off-label; supported by Penn State RCTs (adult and pediatric) and a Cochrane systematic review.

Smith et al [smith2007]. randomized adult trial reported 78% clinical response and 33% mucosal healing on LDN [smith2011]. Pediatric pilot established tolerability [smith2013]. Cochrane review characterized evidence as low-certainty but consistent [segal2014].

Multiple sclerosis EMERGING

Off-label; supported by two small randomized trials and observational pharmacoepidemiology.

Sharafaddinzadeh 2010 and Cree 2010 both reported improvement in self-reported quality of life on LDN; neither demonstrated effect on disability progression [sharafaddinzadeh2010, cree2010]. Norwegian pharmacoepidemiology supports broader real-world signal but is observational [raknes2017, raknesIBD2018].

Complex regional pain syndrome (CRPS) EMERGING

Off-label; case-series-level evidence.

Chopra and Cooper (2013) report sustained CRPS symptom and functional improvement with 4.5 mg LDN [chopra2013].

Inflammatory dermatologic disease (psoriasis, Hailey-Hailey, lichen planopilaris, systemic sclerosis pruritus) EMERGING

Off-label; small-series and systematic-review evidence.

JAMA Dermatology systematic review consolidates LDN evidence across multiple chronic inflammatory dermatologic indications [ekelem2019]. Individual case-report evidence in psoriasis [bridgman2018] and systemic sclerosis pruritus [frech2011].

Myalgic encephalomyelitis / chronic fatigue syndrome EMERGING

Off-label; mechanistic and case-level evidence.

Naltrexone restores impaired TRPM3 ion channel function in NK cells from ME/CFS patients [cabanas2019, cabanas2021, eatonfitch2022]. Bolton et al. (2020) report case-level response to 4.5 mg LDN [bolton2020]. Randomized symptom-outcome trials are not yet published.

Hailey-Hailey disease EMERGING

Off-label; case-series evidence in a rare autosomal-dominant acantholytic disorder.

Albers et al. (2017, JAMA Dermatol) reported sustained clearance of recalcitrant Hailey-Hailey lesions in three patients on 3.0, 4.5 mg LDN [albers2017]; the Ekelem 2019 systematic review consolidates this with subsequent case-level reports [ekelem2019]. No randomized trial in Hailey-Hailey disease has been conducted.

Post-acute sequelae of COVID-19 / long COVID EMERGING

Off-label; two small open-label / observational cohorts.

O'Kelly et al. (2022, n=38) [okelly2022] and Bonilla et al. (2023, n=59) [bonilla2023] reported improvement in long-COVID symptom-score domains (fatigue, post-exertional malaise, pain, sleep, concentration) over 2 months of LDN. Both studies are uncontrolled; randomized placebo-controlled trials are pending.

FDA-Approved Uses of Low-Dose Naltrexone (LDN)

Brand	Indication	Year	Route
ReVia (and authorized generic naltrexone HCl tablet)	Treatment of alcohol use disorder; blockade of the effects of exogenously administered opioids in detoxified opioid-use-disorder patients	1984	Oral, 50 mg once daily
Vivitrol	Treatment of alcohol use disorder; prevention of relapse to opioid dependence following opioid detoxification	2006	Intramuscular extended-release suspension, 380 mg once every 4 weeks

Naltrexone hydrochloride is FDA-approved as a 50 mg oral tablet (ReVia and authorized generics) and as a 380 mg intramuscular extended-release suspension (Vivitrol). The 50 mg oral product was approved in 1984 for opioid use disorder and extended to alcohol use disorder in 1995. Vivitrol was approved in 2006 for alcohol use disorder and in 2010 for prevention of relapse to opioid dependence. Both labels carry warnings regarding precipitated opioid withdrawal in opioid-dependent patients and hepatotoxicity at supratherapeutic doses, and require documented opioid-free interval before initiation in opioid-use-disorder patients [fda_label_revia, fda_label_vivitrol].

Low-dose naltrexone (typically 0.5, 4.5 mg orally) is not FDA-approved for any indication. No commercial low-dose product exists on the U.S. market. The 50 mg manufactured tablet cannot be split or dispensed at the low-dose-range strengths without compounding; LDN is therefore inherently a 503A patient-specific compounded preparation.

Compounded Low-Dose Naltrexone (LDN) (503A)

Low-dose naltrexone is inherently a compounded preparation [younger2013; parkitny2017; smith2013]. The FDA-approved manufactured naltrexone products, ReVia 50 mg tablet and Vivitrol 380 mg intramuscular suspension, are not available at the 0.5, 4.5 mg strength range used clinically as LDN, and the 50 mg tablet is not formulated for accurate split-dosing to those strengths. Pharmacies that prepare LDN do so under 503A on patient-specific prescriptions, using naltrexone HCl active pharmaceutical

ingredient and a compatible diluent in oral capsules, occasionally as troches or transdermal cream where the prescriber documents an oral-route limitation [toljan2018, brown2009] [smith2011].

Because no commercial low-dose product exists, LDN is not 'essentially a copy' of an FDA-approved drug in the sense intended by section 503A and FDA's 2018 essentially-a-copy guidance [fda_essentially_a_copy]. The compounded preparation is mechanistically distinct from the FDA-approved 50 mg or 380 mg use cases: at 0.5, 4.5 mg, the mu-opioid receptor occupancy is partial and transient (~4, 6 hours), the therapeutic rationale is the proposed endogenous opioid rebound and TLR4 glial modulation rather than complete and sustained opioid receptor blockade, and the labeled indication (substance-use disorder) does not apply. The dose ratio between approved and compounded products is approximately 10, 100× [segal2014].

The compounded LDN evidence base was generated using compounded preparations or pharmacy-prepared liquid dilutions from the start, there is no manufactured comparator at this dose range. Compounded LDN preparations are therefore the standard of evidence as well as the standard of clinical practice in this dose range. Quality considerations particular to compounded LDN include: accuracy of low-strength formulation (sub-milligram dosing demands careful API weighing and capsule blending), excipient profile (avoidance of fillers to which the patient is sensitive), and consistency across refills [sharafaddinzadeh2010; cree2010].

RonanRx prepares LDN under 503A only on patient-specific prescriptions. The pharmacist confirms the prescribed indication is consistent with the published off-label literature, confirms the dose is within the studied 0.5, 4.5 mg range, and confirms the patient is not concurrently on opioid analgesia for pain (which would be blunted by LDN) or in opioid-use-disorder maintenance (where LDN would precipitate withdrawal) [fda_label_revia, toljan2018].

Low-Dose Naltrexone (LDN) Formulations and Routes

Form	Concentration	Description
Compounded oral capsule	0.5, 1, 1.5, 3, or 4.5 mg per capsule	Naltrexone HCl active pharmaceutical ingredient compounded with a compatible filler (e.g., microcrystalline cellulose, avoiding lactose or calcium carbonate where these are part of the rationale for the compound) into size-3 or size-4 gelatin or hypromellose capsules. 4.5 mg is the most-studied single strength across the fibromyalgia, Crohn's disease, and multiple sclerosis trials [younger2013, smith2011, sharafaddinzadeh2010]. Lower strengths (0.5, 3 mg) are used for dose titration during initiation or for patients sensitive to higher doses.
Compounded oral troche / sublingual	0.5, 4.5 mg per troche	Alternative dosage form for patients with swallowing limitations. Pharmacokinetics differ from capsule presentation due to partial sublingual absorption and bypass of first-pass metabolism

Form	Concentration	Description
		[toljan2018]. Not the formulation used in the published randomized trials.
Compounded transdermal cream	Custom	Less common formulation; offered where the prescriber documents an oral-route contraindication. Bioavailability and PK have not been characterized in the LDN-trial literature.
Manufactured naltrexone HCl 50 mg tablet (reference product, not LDN)	50 mg	ReVia and authorized generics; FDA-approved for opioid- and alcohol-use disorder. Cannot be split or used at LDN doses without compounding [fda_label_revia].
Manufactured naltrexone XR 380 mg IM suspension (reference product, not LDN)	380 mg/vial	Vivitrol; FDA-approved for alcohol- and opioid-use disorder. Not used at LDN doses [fda_label_vivitrol].

Routes used in published literature: oral, sublingual, transdermal, troche.

Low-Dose Naltrexone (LDN) Dosing

Route	Population	Range	Duration	Study type
Oral	Adults, fibromyalgia	1.5 mg once nightly for 1, 2 weeks, increase to 3 mg once nightly for 1, 2 weeks, then 4.5 mg once nightly as maintenance	Initial trial of 8, 12 weeks before judging response; continued indefinitely if response is sustained	Randomized double-blind placebo-controlled crossover trial; open-label pilot
Oral	Adults, Crohn's disease	4.5 mg once nightly (the dose used in the Smith trials)	12 weeks to clinical response, with continuation in responders	Randomized double-blind placebo-controlled trial; open-label pilot
Oral	Pediatric, Crohn's disease	0.1 mg/kg once nightly (capped at 4.5 mg) in the Smith 2013 pediatric pilot	8 weeks in the published trial	Open-label pediatric pilot
Oral	Adults, multiple sclerosis	4.5 mg once nightly (Sharafaddinzadeh 2010 used 4.5 mg for 17 weeks; Cree	8, 17 weeks in the published trials; continued indefinitely in clinical practice	Two small randomized trials

Route	Population	Range	Duration	Study type
		2010 used 4.5 mg in an 8-week crossover)	where benefit is documented	
Oral	Adults, other off-label indications (CRPS, inflammatory dermatologic disease, ME/CFS, chronic pain)	1.5, 4.5 mg once nightly, typically titrated as for fibromyalgia	Typically 8, 12 week trial before judging response	Case series and small open-label studies

The standard LDN dose across the published randomized trials is 4.5 mg once nightly orally. Most prescribers titrate from 1.5 mg for 1, 2 weeks, to 3 mg for 1, 2 weeks, to a 4.5 mg maintenance dose to minimize the initial sleep-disturbance and vivid-dream adverse events that occur on initiation [younger2013, toljan2018, patten2018]. Once-nightly dosing is preferred because the proposed transient opioid receptor blockade is hypothesized to be most clinically useful during the overnight period; daytime dosing is described in the literature but is the exception.

Doses above 4.5 mg are sometimes prescribed in clinical practice but are outside the studied range. Doses below 1.5 mg are sometimes used for highly sensitive patients (e.g., starting at 0.5 mg) but have not been independently characterized in the randomized trials. The pediatric Crohn's disease pilot [smith2013] used a weight-based 0.1 mg/kg dose capped at 4.5 mg.

Critical prescriber-level considerations: (1) LDN will precipitate opioid withdrawal in opioid-dependent patients, and (2) LDN will partially blunt the analgesic effect of opioid agonists. Patients on chronic opioid analgesia (including buprenorphine-containing products) or in opioid-use-disorder maintenance should not receive LDN. The pharmacist's review confirms absence of these contraindications at every dispense [fda_label_revia, toljan2018].

Low-Dose Naltrexone (LDN) Safety

Low-dose naltrexone has a favorable safety profile across the published evidence. The most-frequent adverse events in the randomized fibromyalgia and Crohn's trials are vivid or unusual dreams, transient sleep disturbance during initiation, and mild gastrointestinal upset [2][6][4]. These effects are typically self-limited or resolved by dose reduction. In the Younger 2013 fibromyalgia trial [2], adverse events did not differ meaningfully between LDN and placebo periods. The Toljan-Vrooman 2018 review [17] and Patten 2018 review [18] consolidate safety across the broader off-label evidence and characterize LDN as well-tolerated at the 1, 4.5 mg dose range.

The pharmacology-driven safety considerations relate to concomitant opioid exposure rather than to LDN itself. LDN will precipitate withdrawal in opioid-dependent patients, this is a class effect of opioid receptor antagonists [25][26] and applies at the low-dose range as well as the FDA-approved 50 mg or 380 mg doses,

though with smaller magnitude. LDN will partially blunt the analgesic effect of opioid agonists, including buprenorphine-containing products and tramadol. Patients on chronic opioid analgesia or in opioid-use-disorder maintenance should not be initiated on LDN.

Hepatotoxicity warnings carried on the FDA-approved 50 mg and 380 mg products were derived from studies at supratherapeutic (300 mg/day) doses [25]. At LDN doses, hepatic adverse events have not been reported in the randomized trial corpus, and baseline-and-follow-up liver function monitoring is not routinely required, though prescribers commonly check liver enzymes at baseline. The Younger 2014 review [3] and Toljan-Vrooman 2018 review [17] both characterize hepatic safety at LDN doses as a non-issue in the published evidence.

Special situations: emergency analgesia in a patient on LDN may require higher-than-usual opioid doses to overcome the partial receptor blockade, patients should carry a wallet card or medical alert documenting LDN use. Surgical anesthesia planning should account for LDN; the typical recommendation is to discontinue LDN 24, 48 hours before scheduled surgery requiring opioid analgesia.

Contraindications

LDN is contraindicated in: current opioid dependence (precipitated withdrawal); patients receiving chronic opioid analgesia where opioid effect cannot be safely blunted; patients on buprenorphine-containing products (precipitated withdrawal); known hypersensitivity to naltrexone or any compounded excipient [2526][17].

LDN should be used with caution in: acute hepatitis or liver failure (despite the absence of LDN-dose hepatotoxicity in the randomized literature, the FDA-approved labels carry hepatotoxicity warnings at supratherapeutic doses and prescribers reasonably avoid LDN in active liver injury); pregnancy and lactation (no controlled human safety data at LDN doses; full-dose naltrexone is FDA Pregnancy Category C); and patients with anticipated need for opioid analgesia (planned surgery, oncology pain management).

Drug interactions

The dominant interaction is with opioid receptor agonists. LDN partially blocks mu-opioid receptors during its dosing interval (~4, 6 hours after a 4.5 mg dose) and will: (1) precipitate withdrawal in opioid-dependent patients, (2) blunt the analgesic effect of full mu-agonists (morphine, oxycodone, hydrocodone, fentanyl) given concurrently, and (3) precipitate withdrawal in patients on buprenorphine-containing products [2526]. Tramadol's mu-agonist component is similarly affected.

Naltrexone is metabolized primarily by dihydrodiol dehydrogenase (a non-CYP enzyme) to 6-β-naltrexol, the active metabolite. CYP450-mediated drug interactions are not a clinically significant concern at LDN doses [2517]. No specific drug-drug interactions outside the opioid class have been highlighted in the LDN trial literature.

Adverse events

Across the published randomized trials and review literature, the most commonly reported adverse events with LDN are: vivid or unusual dreams (10, 37% across trials, typically diminishing after the first 1, 2 weeks), insomnia or transient sleep disturbance during initiation (5, 20%), mild gastrointestinal upset (5, 15%), and headache (5, 10%). Adverse-event-driven discontinuation in the randomized trials has been low (<10%) and not different from placebo arms [9].

The Cree 2010 MS trial [10] reported a similar adverse-event rate between LDN and placebo periods in the crossover design. The Smith 2011 Crohn's trial [6] reported a comparable adverse-event rate between LDN and placebo arms with no serious adverse events attributed to study drug. The Younger 2013 fibromyalgia trial [2] reported no significant difference in adverse events between the LDN and placebo treatment periods [4]. The Patten 2018 review [18] and Toljan-Vrooman 2018 review [17] consolidate the overall AE profile as mild and self-limited at the studied doses.

Rare events reported in case-level literature include mood changes (rarely worsened depression, more often improved mood as a co-effect of pain reduction), and very rare reports of transaminase elevation; the 2017 Norwegian pharmacoepidemiology analysis [23] did not identify a population-level adverse-event signal in approximately 11,000 LDN prescription episodes [19].

Monitoring Low-Dose Naltrexone (LDN) Therapy

Baseline assessment: review of current and anticipated opioid use (including buprenorphine-containing products, tramadol, and opioid-containing cough preparations), confirmation of indication consistent with published off-label literature, and review of baseline pain or disease-activity scores against which response can be judged [younger2013]. Many prescribers obtain baseline liver enzymes despite the absence of LDN-dose hepatotoxicity in the trial literature; this is reasonable but not strictly required by the published evidence [fda_label_revia, toljan2018].

On therapy: re-assessment of symptoms at 8, 12 weeks against the baseline (the duration over which the randomized fibromyalgia and Crohn's trials demonstrated treatment effect) [younger2013; smith2011]. Patients who do not respond at 12 weeks at the 4.5 mg dose are unlikely to respond with continued dosing and may be candidates for discontinuation or alternative therapy. Patients who respond should be reassessed periodically and continued indefinitely while clinically beneficial. Dose adjustment for adverse events is typically downward to 3 mg or 1.5 mg with re-titration as tolerated.

Low-Dose Naltrexone (LDN) in Special Populations

Low-Dose Naltrexone (LDN) Evidence Quality

The LDN evidence base is heterogeneous and small-trial-dominated. The strongest signals are in fibromyalgia (Stanford [younger2009, younger2013], Danish [bruunPlesner2020, dueBruun2024], and Mayo Clinic real-world [driver2023] data, plus a mechanistic cytokine demonstration [parkitny2017] and meta-analytic synthesis [vatvani2024, partridge2023]) and Crohn's disease (three Penn State trials [smith2007, smith2011, smith2013], a Dutch observational cohort [lie2018], plus two Cochrane reviews [segal2014, parker2018]). Multiple sclerosis evidence comprises three small randomized or prospective trials [gironi2008, sharafaddinzadeh2010, cree2010] plus observational pharmacoepidemiology [raknes2017, raknesIBD2018]. Other indications (CRPS [chopra2013, soin2021], Hailey-Hailey disease [albers2017], other inflammatory skin disease [bridgman2018, ekelem2019, frech2011], ME/CFS, long COVID [okelly2022, bonilla2023], chronic non-malignant pain) rest on case series, systematic reviews of case-level evidence, or small open-label work. No multi-center phase III trial has been completed in any LDN indication; the Due Bruun 2024 trial [dueBruun2024] is the largest LDN RCT to date and did not reach its primary endpoint, although it showed favorable secondary signals.

Effect sizes in the randomized trials are clinically meaningful where reported, a 28.8% vs 18.0% pain reduction in fibromyalgia [younger2013], 78% vs 28% clinical response in Crohn's disease [smith2011], improvement in MSQOL-54 mental health domain in MS [sharafaddinzadeh2010], but the trials are small (n=31, 40, 96 respectively) and single-center. The Due Bruun 2024 trial (n=99) [dueBruun2024], although the largest LDN-fibromyalgia RCT to date, did not reach its primary pain endpoint at 6 mg over 12 weeks, complicating the simple narrative that LDN is unambiguously efficacious in fibromyalgia [trofimovitch2019]. The Vatvani 2024 meta-analysis with trial-sequential analysis [vatvani2024] characterizes the pooled evidence as consistent in direction but underpowered for definitive conclusion. The Cochrane reviews [segal2014, parker2018] explicitly characterize the Crohn's evidence as low-certainty, and the Patten 2018 [patten2018], Toljan-Vrooman 2018 [toljan2018], and Leiber-Parker 2025 [leiber2025] reviews all note that the consistent direction of effect across small trials must be confirmed in larger, multi-center studies before LDN can be recommended as first-line therapy in any indication.

Mechanistic plausibility is on stronger footing. The transient-opioid-blockade rationale articulated by Bihari and consolidated by Younger and Toljan [younger2014, toljan2018] is biologically coherent and consistent with the modest, short-duration receptor occupancy expected at 4.5 mg doses. The TLR4 glial mechanism [hutchinson2008] provides an opioid-receptor-independent pathway that is supported by the Parkitny 2017 cytokine demonstration [parkitny2017] in humans and the rodent neuropathic pain work in the Hutchinson laboratory. The TRPM3-restoration mechanism in NK cells [cabanas2019, cabanas2021, eatonfitch2022] provides a third candidate mechanism specifically relevant to ME/CFS and possibly to

overlapping post-acute COVID symptomatology. The combination of mechanistic plausibility with consistent (if small) randomized signals supports the Tier 2 (well-studied for the compound) posture in fibromyalgia and Crohn's disease and an emerging-evidence posture for MS, CRPS, dermatologic disease, ME/CFS, and long COVID. The 2024 Due Bruun null primary endpoint [dueBruun2024] is the most important counter-signal in the literature and is appropriately reflected in this brief's posture: LDN is reasonable as a Tier 2 option for selected fibromyalgia patients but cannot be characterized as definitively proven [bolton2020].

Major Low-Dose Naltrexone (LDN) Clinical Studies

Study	Design	Participants	Duration	Finding
Younger and Mackey (2009, Pain Med), fibromyalgia pilot	Open-label, single-blind, single-site within-subject crossover pilot trial of 4.5 mg LDN at Stanford	10	14 weeks (4 weeks baseline, 8 weeks treatment, 2 weeks washout)	Approximately 30% within-subject reduction in fibromyalgia symptom score on 4.5 mg LDN compared with baseline; established feasibility and tolerability for the subsequent randomized trial [younger2009]
Younger et al. (2013, Arthritis Rheum), fibromyalgia RCT	Randomized, double-blind, placebo-controlled, single-site crossover trial of 4.5 mg LDN vs placebo	31	12 weeks active treatment per period	28.8% reduction in fibromyalgia pain on 4.5 mg LDN vs 18.0% on placebo; greater responder rate (≥30% pain reduction) on LDN; no significant difference in adverse events between periods [younger2013]
Parkitny and Younger (2017, Biomedicines), fibromyalgia cytokine PD	Open-label, within-subject assessment of serum pro-inflammatory cytokines before and after 8 weeks of 4.5 mg LDN	8	8 weeks	Significant reductions in serum IL-1β, IL-6, and TNF-α after 8 weeks of LDN; provides human pharmacodynamic substrate for the TLR4/glial mechanism [parkitny2017]
Younger et al. (2014, Clin Rheumatol), LDN anti-inflammatory review	Narrative review of LDN mechanism and clinical evidence in chronic pain and autoimmune conditions	—	—	Consolidates the opioid-rebound and TLR4-glial mechanisms with the contemporary clinical evidence; characterizes LDN as a novel anti-inflammatory modality

Study	Design	Participants	Duration	Finding
				with the strongest signals in fibromyalgia and Crohn's disease [younger2014]
Smith et al. (2007, Am J Gastroenterol), Crohn's open-label pilot	Open-label, single-site pilot trial of 4.5 mg LDN in adults with active Crohn's disease	17	12 weeks	Significant within-subject reduction in CDAI on 4.5 mg LDN; 67% remission at week 4 and 89% at week 12; established the dose and duration for the subsequent randomized trial [smith2007]
Smith et al. (2011, Dig Dis Sci), Crohn's adult RCT	Randomized, double-blind, placebo-controlled, single-site trial of 4.5 mg LDN vs placebo with endoscopic confirmation of mucosal healing	40	12 weeks	78% clinical response (≥70-point CDAI reduction) and 33% endoscopic mucosal healing on LDN vs 28% and 8% on placebo; key randomized evidence supporting Tier 2 posture for Crohn's disease [smith2011]
Smith et al. (2013, J Clin Gastroenterol), Pediatric Crohn's pilot	Open-label pediatric pilot trial of 0.1 mg/kg LDN (capped at 4.5 mg) in adolescents with moderate-to-severe Crohn's disease	12	8 weeks	Reduction in pediatric CDAI on LDN with acceptable tolerability; established a pediatric dosing scaffold extending the adult evidence [smith2013]
Segal et al. (2014, Cochrane Database Syst Rev), Crohn's Cochrane review	Cochrane systematic review and meta-analysis of LDN for induction of remission in Crohn's disease	—	—	Two RCTs (n=46 children plus the adult Smith 2011 RCT) showed a higher rate of clinical response and endoscopic improvement with LDN compared with placebo; the body of evidence was characterized as low-certainty owing to small trial size and single-center conduct, but consistent in direction of effect [segal2014]
Sharafaddinzadeh et al. (2010, Mult Scler),	Randomized, double-blind, placebo-controlled, single-	96	17 weeks	Significant improvement in the mental health domain of MSQOL-54 on LDN; no

Study	Design	Participants	Duration	Finding
Multiple sclerosis RCT	center trial of 4.5 mg LDN vs placebo in Iranian adults with relapsing-remitting or secondary-progressive multiple sclerosis			demonstrated effect on disability progression or relapse rate [sharafaddinzadeh2010]
Cree et al. (2010, Ann Neurol), Multiple sclerosis crossover RCT	Randomized, double-blind, placebo-controlled, single-center crossover trial of 4.5 mg LDN vs placebo in U.S. adults with multiple sclerosis	80	8 weeks per period	Improvement in self-reported quality of life on LDN; no demonstrated effect on disability progression; favorable tolerability with no severe adverse events [cree2010]
Hutchinson et al. (2008, Eur J Neurosci), TLR4 mechanism	Preclinical mechanistic study in rodent neuropathic pain models with stereoselective and non-stereoselective opioid antagonists, including TLR4-knockout animals	—	—	Both naloxone and naltrexone, and their R-enantiomers, which do not bind opioid receptors, reverse neuropathic pain hypersensitivity through TLR4 antagonism on microglia; established the opioid-receptor-independent mechanism that underpins much of the LDN clinical rationale [hutchinson2008]
Chopra and Cooper (2013, J Neuroimmune Pharmacol), CRPS case series	Case series of LDN in complex regional pain syndrome	2	—	Sustained symptom and functional improvement on 4.5 mg LDN in two patients with longstanding CRPS; first published evidence supporting LDN in CRPS [chopra2013]
Roy et al. (2015, J Intellect Disabil Res), Autism systematic review	Systematic review of opioid antagonists (including low-dose naltrexone) for core symptoms of autism spectrum conditions in children	—	—	Available evidence does not support efficacy of opioid antagonists for core autism symptoms; concluded that LDN should not be recommended on the basis of the published trial

Study	Design	Participants	Duration	Finding
				corpus for this indication [roy2015]
Bridgman and Bruce-Brand (2018, JAAD Case Rep), Psoriasis case	Single-patient case report of LDN in psoriasis vulgaris	1	—	Sustained clearance of psoriasis vulgaris on 4.5 mg LDN; first published case-level evidence in psoriasis [bridgman2018]
Ekelem et al. (2019, JAMA Dermatol), Dermatologic systematic review	Systematic review of LDN in chronic inflammatory dermatologic conditions	—	—	Reviewed available evidence across Hailey-Hailey disease, lichen planopilaris, psoriasis, and other chronic inflammatory dermatologic conditions; most evidence at case-series level, with consistent direction of effect supporting further controlled study [ekelem2019]
Frech et al. (2011, Int J Rheumatol), Systemic sclerosis pruritus	Open-label case series of LDN for pruritus in systemic sclerosis	3	—	Improvement in pruritus with 4.5 mg LDN in three patients with systemic sclerosis [frech2011]
Toljan and Vrooman (2018, Med Sci), Comprehensive therapeutic-utilization review	Narrative review of LDN therapeutic utilization across autoimmune, inflammatory, and chronic pain conditions	—	—	Consolidates mechanism (transient opioid antagonism plus TLR4/glial modulation) and clinical evidence; characterizes LDN as a low-risk modality with the strongest evidence in fibromyalgia and Crohn's disease and emerging evidence across multiple sclerosis, CRPS, inflammatory dermatologic disease, and chronic non-malignant pain [toljan2018]
Patten et al. (2018, Pharmacotherapy), Safety and efficacy review	Narrative review of LDN safety and efficacy in multiple sclerosis, fibromyalgia, and Crohn's disease	—	—	Characterizes LDN as well-tolerated at 1, 4.5 mg with mild and self-limited adverse events; reviews efficacy signals across the three major indications with consistent direction of effect

Study	Design	Participants	Duration	Finding
				across small randomized and open-label studies [patten2018]
Trofimovitch and Baumrucker (2019, Am J Hosp Palliat Care), Palliative care update	Pharmacology update reviewing LDN as a nonopioid modality for chronic non-malignant pain	—	—	Synthesizes the LDN chronic-pain evidence base for palliative care and chronic-pain practitioners; recommends LDN as a reasonable option in selected chronic non-malignant pain patients given the favorable safety profile [trofimovitch2019]
Brown and Panksepp (2009, Med Hypotheses), Clinical-rationale review	Narrative review consolidating the LDN clinical-rationale literature for disease prevention and quality-of-life applications	—	—	Establishes the contemporary framing of LDN as an immune-modulating, low-side-effect option across a heterogeneous indication catalog; supports continued randomized evaluation [brown2009]
Raknes and Småbrekke (2017, Pharmacoepidemiol Drug Saf), Norway prescribing surge	Drug utilization analysis of LDN prescribing in Norway following a 2013 national-media-driven surge in prescriptions	11247	2013, 2014 dispensing window	Documented an unprecedented surge in LDN prescribing with patient and prescriber characteristics consistent with autoimmune and chronic pain indications; provides observational real-world signal at population scale [raknes2017]
Raknes and Småbrekke (2017, PLoS One), MS medication-use change	Quasi-experimental analysis of co-medication use among new LDN users with multiple sclerosis in Norwegian prescription registry	—	—	Reduced use of co-medications (including immunomodulators and analgesics) among new LDN-prescribed MS patients; observational and not causal but consistent with the small-RCT signals [raknesIBD2018]
Cabanas et al. (2019, Front Immunol), ME/CFS TRPM3 mechanism	Translational electrophysiology study of TRPM3 ion channel function in	—	—	Demonstrates that naltrexone restores impaired TRPM3 channel function in NK cells from ME/CFS patients;

Study	Design	Participants	Duration	Finding
	natural killer cells from ME/CFS patients vs healthy controls			provides mechanistic basis for the off-label use that had accumulated in clinical practice [cabanas2019]
Eaton-Fitch et al. (2022, J Transl Med), ME/CFS TRPM3 confirmation	Translational electrophysiology study extending the TRPM3/NK-cell pharmacodynamic finding in a larger ME/CFS cohort	—	—	Confirms impaired TRPM3-dependent calcium influx in ME/CFS NK cells and restoration by naltrexone; supports continued investigation of LDN in this indication [eatonfitch2022]
Bruun-Plesner et al. (2020, Pain Med), Fibromyalgia dose-response	Open-label dose-response investigation of LDN across 1.0, 2.0, 3.0, 4.0, 4.5, and 6.0 mg in women with fibromyalgia	25	Up to 22 weeks per participant across escalating-dose periods	Identified 3.88 mg as the modal effective dose with substantial inter-individual variability; informs the rationale for individualized titration rather than a fixed 4.5 mg target [bruunPlesner2020]
Due Bruun et al. (2024, Lancet Rheumatol), Fibromyalgia RCT (FINAL trial)	Randomized, double-blind, placebo-controlled, single-center parallel-group trial of naltrexone 6 mg once daily vs placebo in women with fibromyalgia	99	12 weeks	Primary endpoint (between-group difference in 0, 10 NRS pain at week 12) did not reach statistical significance, although the LDN arm showed a numerically larger improvement and a significant FIQR memory-domain benefit; largest LDN-fibromyalgia RCT to date and the first to use the Danish Sygehus Sønderjylland 6 mg formulation [dueBruun2024]
Driver and D'Souza (2023, Biomedicines), Mayo Clinic 14-year retrospective	Enterprise-wide retrospective analysis of LDN-treated patients across fibromyalgia and other chronic pain conditions at Mayo Clinic	115	14 years (2008, 2022)	65% symptomatic improvement rate on LDN; identified body-pain extent and prior opioid exposure as predictors of treatment discontinuation; largest real-world LDN dataset in chronic pain to date [driver2023]
		—	—	

Study	Design	Participants	Duration	Finding
Vatvani et al. (2024, Korean J Pain), Fibromyalgia meta-analysis	Systematic review and meta-analysis of randomized controlled trials of LDN in fibromyalgia, with trial-sequential analysis			Direction of effect consistent with benefit across pooled trials; trial-sequential analysis indicates further RCTs are required for definitive conclusion on efficacy; characterizes safety profile as favorable across the pooled corpus [vatvani2024]
Lie et al. (2018, J Transl Med), Erasmus MC IBD cohort	Observational cohort of LDN 4.5 mg in adult patients with active Crohn's disease and ulcerative colitis at the Erasmus MC IBD center, Netherlands	—	—	Reported tolerability and clinical benefit in IBD patients, extending the Smith laboratory Crohn's evidence into a European observational cohort [lie2018]
Parker et al. (2018, Cochrane Database Syst Rev), Updated Crohn's Cochrane review	Updated Cochrane systematic review and meta-analysis of LDN for induction of remission in Crohn's disease, replacing the 2014 Segal review	—	—	Two RCTs in adults and one pediatric trial showed a higher rate of clinical response and endoscopic improvement with LDN compared with placebo; body of evidence remained low-certainty owing to small trial size [parker2018]
Gironi et al. (2008, Mult Scler), Primary progressive MS pilot	Prospective single-arm pilot trial of 4.5 mg LDN in primary progressive multiple sclerosis	40	6 months	Tolerability and modest signal on quality-of-life and spasticity outcomes; first prospective LDN-MS trial and precursor to the Sharafaddinzadeh and Cree randomized work [gironi2008]
Soin et al. (2021, Pain Physician), CRPS systematic review	Systematic literature review of LDN for chronic regional pain syndrome	—	—	Identified case-series and small-case-report evidence supporting the Chopra and Cooper findings; no randomized trial evidence; recommended controlled investigation given consistent direction of small-case response [soin2021]

Study	Design	Participants	Duration	Finding
Albers et al. (2017, JAMA Dermatol), Hailey-Hailey case series	Case series of LDN in recalcitrant Hailey-Hailey disease at the Emory University Department of Dermatology	3	—	Sustained clearance of recalcitrant Hailey-Hailey lesions in three patients on 3.0, 4.5 mg LDN; first peer-reviewed evidence in this rare autosomal-dominant acantholytic disease [albers2017]
O'Kelly et al. (2022, Brain Behav Immun Health), Long COVID open-label	Single-arm interventional pre-post study of 1.0, 4.5 mg LDN over 2 months in long COVID at the Mater Misericordiae long-COVID clinic, Dublin	38	8 weeks	Significant improvement in WHO long-COVID symptom-score domains including recovery from acute illness, mobility, daily activities, energy, pain, sleep, and concentration; first prospective LDN-long-COVID dataset [okelly2022]
Bonilla et al. (2023, Int Immunopharmacol), Stanford long COVID retrospective	Retrospective cohort of LDN-treated long-COVID patients at Stanford	59	2 months mean follow-up	Improvement in fatigue, post-exertional malaise, and pain-domain scores over 2 months of LDN; uncontrolled but consistent with the O'Kelly findings [bonilla2023]

Low-Dose Naltrexone (LDN) Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Naltrexone is well absorbed after oral administration with extensive first-pass metabolism. The foundational human pharmacokinetic characterization is Verebey et al. (1976, Clin Pharmacol Ther) [verebey1976] in opioid-dependent volunteers receiving 50, 200 mg oral doses, which established the disposition profile that is carried into modern LDN dosing. Oral bioavailability of the parent compound is approximately 5, 40%; the principal active metabolite is 6-β-naltrexol, formed by dihydrodiol dehydrogenase. Plasma half-life of the parent is approximately 4 hours and of 6-β-naltrexol approximately 12 hours [fda_label_revia, verebey1976]. Time to maximum plasma concentration after an oral dose is approximately 1 hour. Naltrexone and its metabolite are eliminated primarily via the kidneys. LDN-specific human pharmacokinetic data at the 0.5, 4.5 mg dose range are sparse, most published PK characterization is at the 50, 200 mg FDA-approved dose range, and LDN-dose disposition is inferred by linear extrapolation.

At the 4.5 mg LDN dose, plasma concentrations are correspondingly lower than at the 50 mg FDA-approved dose, and central mu-opioid receptor occupancy is partial and short-lived (~4, 6 hours). This brief, partial occupancy is the pharmacokinetic substrate for the proposed transient-blockade-and-rebound mechanism articulated by Younger (2014) and Toljan-Vrooman (2018) [younger2014, toljan2018]. Compounded preparations may show modest formulation-specific differences in absorption rate and bioavailability that have not been independently characterized in PK studies.

Pharmacodynamics

Pharmacodynamic effects of LDN that have been characterized in human studies include reduction in serum pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) over 8 weeks of treatment [parkitny2017], improvement in patient-reported pain and symptom-day scores in fibromyalgia [younger2009, younger2013], reduction in CDAI and endoscopic mucosal-healing rate in Crohn's disease [smith2011, smith2013], and restoration of TRPM3 ion channel function in NK cells in ME/CFS [cabanas2019, eatonfitch2022]. The TLR4 antagonist activity demonstrated preclinically by Hutchinson et al. (2008) [hutchinson2008] is the proposed mechanistic substrate for the cytokine and pain-modulation effects.

Direct human in vivo PD characterization of the proposed endogenous-opioid rebound (β-endorphin, met-enkephalin, OGF dynamics) remains limited. Most of the human PD evidence for LDN is captured at the clinical-endpoint level rather than at the biochemical-target level.

↓↑ Comparing Low-Dose Naltrexone (LDN) Formulations

There is no manufactured low-dose naltrexone product on the U.S [younger2013; sharafaddinzadeh2010; cree2010]. market. The FDA-approved naltrexone products are ReVia (50 mg oral tablet) and Vivitrol (380 mg IM extended-release suspension), both used at full mu-opioid-blockade doses for substance-use disorder, mechanistically and clinically distinct from LDN [fda_label_revia, fda_label_vivitrol] [smith2011].

Compounded LDN preparations vary in capsule shell, filler, and overage tolerance per the compounding pharmacy. The randomized trials used pharmacy-prepared 4.5 mg oral preparations; cross-pharmacy bioequivalence has not been independently characterized [younger2013]. Patients who respond to LDN at one pharmacy and lose response on switching pharmacies should consider whether the formulation has changed.

🌡 Low-Dose Naltrexone (LDN) Storage and Handling

Compounded LDN oral capsules are stored at controlled room temperature (20, 25°C) in tight, light-resistant containers, with beyond-use date assigned per USP General Chapter <795> for nonsterile

compounded preparations [usp_795]. The manufactured naltrexone 50 mg tablet is also stored at room temperature.

Cold-chain handling is not required for LDN oral capsules.

Low-Dose Naltrexone (LDN) Compounding & Operations

503A compounding

Low-dose naltrexone is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares LDN oral capsules per USP General Chapter <795> for nonsterile pharmaceutical compounding, with documented active ingredient sourcing, weight-verification at sub-milligram strengths, content-uniformity verification per the pharmacy's quality-management system, and full lot traceability [usp_795] [fda503a]. Because the most-studied LDN doses (0.5, 4.5 mg) are an order of magnitude below the smallest commercially manufactured naltrexone strength, sub-milligram weighing accuracy is the principal quality-control consideration; pharmacies typically use trituration with a compatible filler (microcrystalline cellulose or similar) followed by capsule blending to achieve consistent dose-per-capsule.

Beyond-use dating, ingredient identity verification, and content-uniformity assessment follow USP <795> requirements [fda503a]. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing.

Because no FDA-approved low-dose naltrexone product exists, LDN is not 'essentially a copy' of an approved drug in the sense intended by section 503A's essentially-a-copy restriction [fda_essentially_a_copy] [fda503a]. The compounded preparation is the only way to access naltrexone at the studied LDN dose range.

Pharmacist review

Each prescription for compounded LDN undergoes pharmacist review prior to dispensing. The review confirms: a prescribed indication consistent with the published off-label literature (fibromyalgia, Crohn's disease, multiple sclerosis, complex regional pain syndrome, inflammatory dermatologic disease, ME/CFS, chronic non-malignant pain); a prescribed dose within the studied 0.5, 4.5 mg range; and the absence of concomitant opioid analgesia (full mu-agonists, buprenorphine-containing products, tramadol with mu-agonist component) or opioid-use-disorder maintenance therapy that would be incompatible with LDN [fda_label_revia, toljan2018] [younger2013; smith2011].

RonanRx does not fill prescriptions for LDN at doses substantially above 4.5 mg (which approach the manufactured 50 mg use case and lose the LDN-specific therapeutic rationale), and confirms with prescribers when the indication or dose falls outside the studied evidence base. The pharmacist also confirms patient understanding of: the off-label nature of LDN use; the absence of an FDA-approved low-

dose product; the once-nightly dosing schedule and titration; the requirement to disclose LDN use before any surgical procedure or initiation of opioid analgesia; and the absence of demonstrated benefit for autism spectrum core symptoms [roy2015] [younger2013].

Quality and traceability

Active pharmaceutical ingredient (naltrexone HCl) is sourced from FDA-registered facilities with documented certificates of analysis. Each compounded LDN batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, content-uniformity verification, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

LDN oral capsules are not a cold-chain product. Standard controlled room-temperature storage applies. Shipping is performed at ambient temperature with no special temperature handling required.

Frequently Asked Questions About Low-Dose Naltrexone (LDN)

What is low-dose naltrexone (LDN)?

LDN is a compounded preparation of naltrexone hydrochloride at 0.5, 4.5 mg once daily, about one-tenth the FDA-approved 50 mg oral dose used for opioid- and alcohol-use disorder [fda_label_revia]. There is no commercial low-dose product on the U.S [toljan2018]. market, so LDN is always prepared by a compounding pharmacy on a patient-specific prescription.

Is LDN FDA-approved?

No. The FDA-approved naltrexone products are ReVia (50 mg oral tablet) and Vivitrol (380 mg intramuscular extended-release suspension), both for substance-use disorder [fda_label_revia; fda_label_vivitrol]. LDN at 0.5, 4.5 mg is not FDA-approved for any indication. It is prescribed off-label on the basis of the published clinical literature.

What is LDN used for?

Off-label prescribing is most common for fibromyalgia, Crohn's disease, and multiple sclerosis, where small randomized trials support a Tier 2 (well-studied) posture [younger2013; smith2011; sharafaddinzadeh2010]. LDN is also used in complex regional pain syndrome, inflammatory dermatologic conditions, myalgic encephalomyelitis/chronic fatigue syndrome, and chronic non-malignant pain, where the evidence is at the case-series or systematic-review level [toljan2018] [patten2018].

How does LDN work?

Two mechanisms are proposed and both are likely operative. First, brief partial blockade of mu-opioid receptors during the ~4, 6-hour dosing interval is hypothesized to trigger a compensatory increase in endogenous opioid (β-endorphin, met-enkephalin) tone after the drug clears [parkitny2017]. Second, naltrexone antagonizes Toll-like receptor 4 on microglia, dampening glial pro-inflammatory cytokine release, a mechanism independent of opioid receptors that is supported by the Parkitny 2017 demonstration of reduced serum IL-1β, IL-6, and TNF-α after 8 weeks of LDN [younger2014; toljan2018; hutchinson2008].

What is the standard LDN dose?

4.5 mg once nightly is the dose used in the randomized fibromyalgia and Crohn's disease trials [younger2013; smith2011]. Most prescribers titrate from 1.5 mg for 1, 2 weeks, to 3 mg for 1, 2 weeks, to a 4.5 mg maintenance dose to minimize initiation-related sleep disturbance and vivid dreams [toljan2018].

What are the side effects?

Most common are vivid or unusual dreams, transient sleep disturbance during initiation, mild gastrointestinal upset, and headache. These typically diminish over the first 1, 2 weeks [patten2018]. Adverse-event discontinuation rates in the randomized trials have been low and not different from placebo arms [younger2013; smith2011; toljan2018].

Can I take LDN with pain medication?

Not with opioid pain medications. LDN blocks mu-opioid receptors during its dosing interval and will blunt the effect of opioid analgesics (morphine, oxycodone, hydrocodone, fentanyl, tramadol) and precipitate withdrawal in patients on buprenorphine-containing products or in opioid-use-disorder maintenance. Non-opioid analgesics (acetaminophen, NSAIDs, gabapentinoids, antidepressant-class analgesics) are compatible with LDN [fda_label_revia; toljan2018].

Is LDN safe in pregnancy or breastfeeding?

There are no controlled human safety data for LDN in pregnancy. The full-dose product is FDA Pregnancy Category C. Standard clinical practice is to discontinue LDN before a planned pregnancy or as soon as pregnancy is confirmed unless the clinical indication is severe. Lactation data are limited; the manufactured-product label notes excretion in breast milk at full doses [fda_label_revia; toljan2018].

Why isn't LDN available as a commercial product?

Naltrexone went off patent decades ago, and no manufacturer has pursued FDA approval for the low-dose indication [toljan2018; younger2014]. The randomized evidence base, while consistent in direction across small trials, has not been brought through a multi-center phase III program that would support a new

manufactured product. Compounded LDN is therefore the standard of clinical practice in this dose range, as well as the standard of evidence [segal2014].

Does RonanRx sell LDN directly to patients?

No. Compounded LDN requires a patient-specific prescription written by a licensed prescriber for an identified patient with a documented clinical indication, plus pharmacist review before dispensing. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Low-Dose Naltrexone (LDN)

Compounded Low-Dose Naltrexone (LDN) is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Low-Dose Naltrexone (LDN), sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)