LOW DOSE NALTREXONE
(LDN)

Prescriber Reference Guide · The Medicine Shoppe, York PA

Autoimmune · Chronic pain · Neurological · Fatigue syndromes · Non-controlled · $65/month

What Is Low Dose Naltrexone?

Naltrexone is an FDA-approved opioid antagonist used at 50 mg/day for alcohol and opioid use disorder. At a fraction of that dose — typically 1.5 to 4.5 mg — it produces an entirely different set of pharmacological effects that are generating substantial clinical interest across a wide range of chronic conditions.

At low doses, naltrexone produces a brief (4–6 hour) opioid receptor blockade, typically during overnight hours. The body responds by upregulating endogenous opioid production — increasing endorphin and enkephalin levels. Concurrently, LDN appears to modulate microglial activity in the central nervous system, reducing neuroinflammation. These two mechanisms — endorphin upregulation and neuroimmune modulation — are believed to underlie its therapeutic effects across a broad range of inflammatory and autoimmune conditions.

Key Clinical Advantages

- Non-controlled substance — no DEA scheduling, no prescribing restrictions, no prior authorization requirements
- Excellent safety profile — no organ toxicity, no significant drug interactions at LDN doses, no physical dependence
- Broad applicability — single mechanism addresses neuroinflammation underlying multiple chronic conditions
- Low cost — $65/month cash pay; eliminates insurance prior authorization burden common with specialty biologics
- Compounded to exact dose — commercial naltrexone is 50 mg; LDN requires 1.5–4.5 mg capsules unavailable commercially
- Growing evidence base — over 40 clinical trials completed or ongoing across autoimmune, pain, and neurological conditions

Mechanism of Action

Opioid Receptor Upregulation

At standard doses (50 mg), naltrexone produces sustained opioid receptor blockade. At low doses (1.5–4.5 mg), the blockade is brief and reversible — lasting approximately 4–6 hours after bedtime administration. During this window, the body interprets the transient blockade as an opioid deficiency and responds by increasing production of endogenous opioids (beta-endorphins, met-enkephalin). The net result is elevated endorphin tone throughout the following day, with downstream effects on mood, pain threshold, and immune regulation.

Microglial Modulation & Neuroinflammation

LDN exerts significant effects on microglia — the resident immune cells of the central nervous system. Overactivated microglia are increasingly recognized as a driver of neuroinflammation in chronic pain, autoimmune disease, and neurodegenerative conditions. LDN appears to reduce microglial activation via antagonism of toll-

like receptor 4 (TLR4), a receptor that is distinct from the classical opioid receptor pathway. This dual mechanism — classical opioid receptor modulation plus TLR4 antagonism — accounts for LDN's broad efficacy across conditions that share neuroinflammation as a common pathophysiological thread.

Primary Mechanism 1	Transient opioid receptor blockade → endogenous opioid upregulation → elevated beta-endorphin and enkephalin tone
Primary Mechanism 2	TLR4 antagonism → reduced microglial activation → decreased neuroinflammation and central sensitization
Timing	Both mechanisms are most active during the rebound period following the overnight blockade — hence bedtime dosing
Dose-Dependence	Effects are highly dose-dependent; the therapeutic window is narrow — too low produces insufficient blockade; too high produces sustained blockade that blunts the rebound
Onset of Effect	Most patients require 4–12 weeks of consistent use before clinical benefits are apparent; immune modulation is gradual

Clinical Indications & Evidence

LDN has been studied across a wide range of conditions. The evidence base varies by indication — from well-designed RCTs to case series and observational data. The following represents current evidence as of the date of this document; the field is rapidly evolving.

Autoimmune Conditions

Hashimoto's Thyroiditis	Multiple case series and observational studies report reduction in TPO antibody titers, improved TSH stability, and reduced symptom burden. LDN is increasingly used as adjunct to thyroid hormone replacement.
Multiple Sclerosis	Phase 2 RCT (Cree et al.) demonstrated improved quality of life and mental health scores vs. placebo. Observational data from the LDN Research Trust registry supports symptom benefit in a majority of MS patients.
Crohn's Disease	Pilot RCT (Smith et al., Pediatric Crohn's) showed 88% response rate vs. 40% placebo; adult trials show significant reduction in CDAI scores. Mechanism: reduced intestinal inflammation via opioid receptor and TLR4 pathways.
Ulcerative Colitis	Emerging evidence from open-label studies; less robust than Crohn's data but consistent with mechanistic rationale. Ongoing RCTs.
Lupus / RA / Psoriasis	Case series and patient registry data suggest benefit; formal RCT data limited. Frequently used off-label given favorable safety profile.

Chronic Pain Conditions

Fibromyalgia	Landmark pilot RCT (Younger & Mackey, Stanford) demonstrated 30% reduction in pain scores vs. placebo with 4.5 mg LDN. Subsequent replication studies confirm significant pain reduction and improved fatigue.
Complex Regional Pain Syndrome (CRPS)	Case series report significant pain reduction. Mechanistic rationale strong — CRPS involves central sensitization and microglial overactivation, both targeted by LDN.
Chronic Low Back Pain	Observational data and case reports; formal trial data limited. Commonly used in integrative pain practices.
Headache / Migraine	Emerging use; some evidence for reduction in migraine frequency in patients with inflammatory or autoimmune comorbidities.

Fatigue & Systemic Conditions

Long COVID / Post-Viral Fatigue	Growing clinical experience and emerging trial data support LDN for post-COVID fatigue, cognitive symptoms, and pain. Mechanistic fit is strong — Long COVID is characterized by persistent neuroinflammation and microglial activation.
ME/CFS (Chronic Fatigue Syndrome)	Multiple case series and observational studies report meaningful improvement in fatigue, pain, and cognitive function. One of the most prescribed conditions in the LDN community.

Low Dose Naltrexone for Cancer (LDNC)	Preclinical data suggests LDN may have anti-tumor properties via opioid growth factor pathway modulation. Adjunctive use in oncology is investigational; discuss with oncologist.

Dosing, Titration & Administration

Standard Dosing Protocol

LDN is initiated at a low dose and titrated upward over several weeks to allow the body to adjust. Rapid initiation at full dose is associated with higher rates of early side effects (vivid dreams, sleep disturbance) and discontinuation.

Starting Dose	1.5 mg nightly at bedtime for 2 weeks
Titration Step 1	Increase to 3.0 mg nightly if well tolerated after 2 weeks
Titration Step 2	Increase to 4.5 mg nightly after an additional 2–4 weeks
Maintenance	4.5 mg nightly is the most commonly used maintenance dose; some patients respond optimally at 3.0 mg
Timing	Bedtime administration (10 PM – midnight) is strongly recommended to align the rebound period with daytime waking hours
Duration	Clinical benefits typically emerge at 4–12 weeks; a minimum 3-month trial is recommended before assessing response
Reassessment	If no benefit at 4.5 mg after 3 months, consider whether diagnosis is appropriate; some patients respond to lower doses (1.5–3.0 mg)

Important Prescribing Notes

- Opioid medications must be discontinued before initiating LDN — even low doses will precipitate withdrawal in opioid-dependent patients
- Hold LDN for 24 hours before and after any procedure requiring opioid analgesia; resume after opioids are cleared
- Thyroid patients on levothyroxine — some patients experience improved thyroid function with LDN, which may require dose adjustment of their thyroid medication
- Immunosuppressed patients — LDN's immune-modulating effects are generally well-tolerated but discuss with specialist for patients on biologics or high-dose steroids
- Vivid dreams in the first 2–4 weeks are common and typically resolve; counsel patients proactively to prevent unnecessary discontinuation

Formulation & Dispensing

Dosage Form	Oral capsules — compounded at The Medicine Shoppe
Available Strengths	1.5 mg, 3.0 mg, 4.5 mg — custom strengths available on request
Excipients	Compounded without unnecessary dyes or fillers; microcrystalline cellulose used as needed
Important Note	Do NOT use commercially available naltrexone 50 mg tablets split or dissolved — bio-availability and dose accuracy are unreliable; compounded capsules are required for LDN

Quantity	30-day supply standard; 90-day supply available
Pricing	$65/month — cash pay; no insurance processing required
BUD	Per USP compounding standards; labeled on each preparation

Ordering & Contact Information

All LDN preparations require a valid prescription. Patients fill directly at our pharmacy. No prior authorization required — cash pay, simple monthly pricing.

How to Order

- By phone — call (717) 846-0500; ask for the compounding pharmacist; have patient name, DOB, dose, and quantity ready
- By fax — send prescription to (717) 845-8767; specify dose (1.5, 3.0, or 4.5 mg), quantity, and any titration instructions
- E-prescribe — select 'Compound' as medication type; enter 'Naltrexone [dose] mg capsules — Low Dose Naltrexone (LDN)' in the Sig/Comments field

LDN Resources for Prescribers

- LDN Research Trust (ldnresearchtrust.org) — patient registry, trial updates, prescriber resources
- LDN Science (ldnscience.org) — peer-reviewed publications and clinical trial database
- Younger JW et al. — Fibromyalgia trial (Stanford, 2013) — landmark RCT
- Smith JP et al. — Pediatric Crohn's trial — published in American Journal of Gastroenterology
- Cree BAC et al. — Multiple Sclerosis pilot RCT — published in Annals of Neurology

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