

Low Dose Naltrexone (LDN) in Fibromyalgia - 2026

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Low-dose naltrexone (LDN) remains an off-label, non-standard treatment for fibromyalgia. The evidence base has expanded, but the more recent controlled trials and meta-analyses are conflicting; it is best regarded as a **reasonable experimental/third-line option in selected opioid-free patients**, rather than established fibromyalgia pharmacotherapy.

Aspect	Current evidence / practical role
What is meant by LDN?	Usually 1–6 mg/day of oral naltrexone, substantially below the conventional 50-mg dose used for alcohol/opioid-use disorders. 4.5 mg once daily has been the most commonly studied dose.
Proposed mechanism	Not established. Proposed mechanisms include transient opioid-receptor antagonism with subsequent modulation of endogenous opioid signalling and possible TLR4/microglial/neuroinflammatory modulation . These mechanisms remain substantially more speculative than the established μ -opioid receptor antagonism of naltrexone.
Rationale in fibromyalgia	Fibromyalgia involves altered central nociceptive processing/central sensitisation. LDN has therefore attracted interest as a non-opioid centrally acting treatment, particularly where conventional therapies are ineffective or poorly tolerated.
Early efficacy evidence	Small early studies suggested reductions in pain and global fibromyalgia symptoms. However, these studies generally had small samples, predominantly included women, and had important methodological limitations. Systematic reviews consequently rated the early evidence as low quality.
2023 crossover RCT	In 58 patients, 4.5 mg/day was not significantly better than placebo for FIQR or summed pain-intensity outcomes (FIQR difference -1.65 , $P=0.3$; pain difference -0.33 , $P=0.4$).
2024 larger RCT	A Danish double-blind RCT studied 6 mg/day for 12 weeks in 99 women. LDN was not superior to placebo for the primary pain outcome , an important negative finding given the earlier small positive studies.
2024 meta-analysis	Four RCTs/222 participants suggested a statistically significant improvement in pain versus placebo (MD -0.86 , 95% CI -1.20 to -0.51), but no significant improvement in revised FIQ or pain catastrophising. The limited number and size of trials remain important caveats.
2025 meta-analysis – positive interpretation	Five RCTs produced a pooled improvement in pain (SMD -0.61 , 95% CI -1.14 to -0.08), leading the authors to conclude that LDN may be effective, while explicitly calling for further RCTs.
2025 meta-analysis – more conservative interpretation	A separate review of eight trials found improvement from baseline, but no statistically significant advantage over placebo for pain (SMD -0.50 , 95% CI -1.19 to 0.19) or fibromyalgia symptom severity. Heterogeneity was high.
2026 synthesis	A recent broad LDN review concludes that early encouraging fibromyalgia findings have not been consistently reproduced in the larger/more recent controlled studies . Thus efficacy remains uncertain.
Which symptom is most likely to respond?	If effective, the strongest signal is for pain reduction . Evidence for meaningful improvement in fatigue, sleep, cognition, physical function or overall FIQ/FIQR is considerably less convincing.
Suggested place in therapy	Not first-line . Consider only after diagnosis and important mimics/comorbidities have been addressed and evidence-based non-pharmacological management (graded/individualised physical activity, education, sleep and psychological interventions where appropriate) $\pm$ established pharmacotherapy has been insufficient or poorly tolerated.

Aspect	Current evidence / practical role
Potential candidate	Opioid-free patient with persistent pain despite/intolerance of standard approaches who understands the uncertain evidence and off-label nature of treatment. Its relatively favourable tolerability may make a therapeutic trial attractive when adverse effects limit conventional agents.
Typical practical regimen	There is no validated fibromyalgia regimen . Published practice commonly starts around 1–1.5 mg once daily , titrating according to tolerability toward 4–4.5 mg/day ; trials have generally used ~4.5 mg/day, with the 2024 RCT using 6 mg/day.
Timing of dose	Often given at night, although morning dosing can be considered if insomnia or vivid dreams are troublesome. Evidence does not establish superiority of a particular administration time.
Duration of therapeutic trial	A pragmatic approach is to assess tolerability during titration and then assess pain/function after approximately 8–12 weeks at a therapeutic/tolerated dose . Continuing indefinitely without demonstrable functional or symptomatic benefit is difficult to justify given the uncertain evidence.
Adverse effects	Generally mild. Most consistently reported are vivid dreams/sleep disturbance, nausea, headache and dizziness . The 2025 meta-analysis found vivid dreams significantly increased (RR 2.41, 95% CI 1.77–3.28). Serious adverse events have not emerged as a signal in the small fibromyalgia RCT literature.
Major contraindication / interaction	Concurrent opioid treatment is the key issue . Naltrexone blocks opioid analgesia and can precipitate severe withdrawal in opioid-dependent patients. This includes attention to tramadol and opioid-containing cough/antidiarrhoeal preparations.
Opioid washout	Product information recommends being opioid-free for at least 7–10 days after short-acting opioids before naltrexone; vulnerability to precipitated withdrawal can persist for up to 2 weeks after buprenorphine or methadone .
Planned surgery/acute pain	Particularly important clinically: opioid analgesia may be ineffective while naltrexone is active. Patients likely to require opioid analgesia need an anticipatory perioperative/acute-pain plan.
Hepatic considerations	Naltrexone undergoes hepatic metabolism; review hepatic disease and interacting medications. The hepatic safety concerns associated with conventional-dose naltrexone should be considered even though exposure at LDN doses is substantially lower.
Monitoring	Establish baseline pain, FIQR/function, sleep and patient-defined functional goals rather than judging efficacy solely from subjective global improvement. Medication reconciliation for opioids is essential. LFT assessment is reasonable where there is hepatic disease/risk or other clinical indication.
Overall evidence certainty	Low/very low to low-moderate , depending on outcome and review methodology. Small trials, heterogeneous protocols, crossover designs and inconsistent results limit certainty.
Clinical bottom line	LDN is promising but unproven . There is a pooled signal for analgesia in some meta-analyses, but two relatively recent placebo-controlled trials were negative and another 2025 meta-analysis found no significant placebo-adjusted benefit. It can reasonably be discussed as an off-label therapeutic trial in carefully selected opioid-free patients , with explicit outcome targets and discontinuation if ineffective.

Interpreting the conflicting evidence

The apparent contradiction between the meta-analyses is clinically important. A 2024 meta-analysis of four RCTs and a 2025 meta-analysis of five RCTs generated statistically significant pooled pain effects. Conversely, Ologunowa et al.’s 2025 analysis found that although patients improved after receiving LDN, the **between-group effect versus placebo was not significant**, with substantial heterogeneity.

I would therefore **not interpret the pooled evidence as establishing efficacy**. The negative 4.5-mg crossover RCT and particularly the 99-patient, 12-week 6-mg RCT weaken the earlier efficacy signal. This interpretation is consistent with the 2026 narrative review, which concludes that promising early results have not been reliably reproduced in more recent trials.

References

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Practical summary: I would position LDN as **off-label, opioid-incompatible, relatively well tolerated, but with uncertain efficacy**. If conventional measures have failed, a monitored trial titrating roughly **1–1.5 mg → 4–4.5 mg/day** is defensible provided the patient is opioid-free and there are predefined pain **and functional** response criteria. The current literature does **not** support presenting LDN as an established or guideline-equivalent fibromyalgia therapy.