Roxanne Radi, MD, MPH; Harriet Huang, MD; Jason Rivera, MD; Corey Lyon, DO
University of Colorado Family Medicine Residency, Denver

Kristen DeSanto, MSLS, MS, RD
University of Colorado Health Sciences Library, Denver

DEPUTY EDITOR
Rick Guthmann, MD, MPH
Advocate Health Care Illinois Masonic Medical Center Program, Chicago

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Q/ Is low-dose naltrexone effective in chronic pain management?

EVIDENCE-BASED ANSWER

A/ **YES.** Low-dose naltrexone is as effective as amitriptyline in the treatment of painful diabetic neuropathy and has a superior safety profile (strength of recommendation [SOR], **B**; single randomized controlled trial [RCT]).

Low-dose naltrexone significantly reduced pain by 32% in inflammatory conditions and 44% in neuropathic conditions (SOR, **B**; single retrospective cohort study).

Doses as low as 5.4 mg were found to reduce pain in 95% of patients with fibromyalgia (SOR, **B**; single prospective dose-response study).

Evidence summary

Naltrexone is comparable to amitriptyline for diabetic neuropathy pain

A 2021 randomized, double-blind, active-comparator, crossover clinical trial conducted in India examined the efficacy of low-dose naltrexone vs standard-of-care amitriptyline in patients (N = 67) with painful diabetic neuropathy. Participants were adults (ages 18 to 75 years) with painful diabetic neuropathy who had been on a stable dose of nonopioid pain medication for at least 1 month.[1]

Patients were randomly assigned to start receiving naltrexone 2 mg (n = 33) or amitriptyline 10 mg (n = 34). They received their starting medication for 6 weeks (with follow-up every 2 weeks), then completed a 2-week washout period, and then switched to the other study medication for 6 weeks (same follow-up schedule). If patients reported < 20% pain reduction on the Visual Analog Scale (VAS; 0-100 scoring system with 0 = no pain and 100 = worst pain) at a follow-up visit, their medication dose was titrated up, to a maximum of 4 mg of naltrexone or 25 to 50 mg of amitriptyline.[1]

The primary outcome of interest was the mean change in VAS pain score following 6 weeks of treatment. There was no statistically different change from baseline VAS pain score between the amitriptyline and naltrexone groups (mean difference [MD] = 1.6; 95% CI, –0.9 to 4.2; $P = 0.21$). These findings were consistent across the secondary endpoints (Likert 5-point pain scale and McGill Pain Questionnaire scores). There was no statistically significant difference in Hamilton Depression Rating Scale scores (13 in the naltrexone group vs 11 in the amitriptyline group; $P = .81$), no reports of decreased sleep quality in either group, and no significant difference in Patients' Global Impression of Change scores at 6-week evaluation.[1]

The naltrexone cohort experienced 8 adverse events (most commonly, mild diarrhea), while the amitriptyline cohort experienced 52 adverse events (most commonly, somnolence) ($P < .001$). The limitations of the study include the lack of a placebo arm and a relatively small sample size.[1]

Greater reduction in pain scores with naltrexone

A 2022 retrospective cohort study evaluated the effectiveness of naltrexone for patients treated at a single outpatient integrative pain management practice in Alaska between 2014 and 2019. The exposure group (n = 36) included patients who had completed at least a 2-month continuous regimen of oral naltrexone 4.5 mg. Controls (n = 42) were selected from the remaining practice population receiving standard care and were primarily matched by diagnosis code, followed

by gender, then age +/– 5 years. Patients were divided into subgroups for inflammatory and neuropathic pain.[2]

The primary outcome measured was the mean change in VAS score or numeric rating score (NRS; both used a 1-10 rating system), which was assessed during a patient's appointment from initiation of treatment to the most recent visit or at the termination of therapy (intervention interquartile range, 12-14 months). There was no statistically significant difference in VAS/NRS between the low-dose naltrexone and control groups at baseline (6.09 vs 6.38; $P = .454$). The low-dose naltrexone group experienced a greater reduction in VAS/NRS pain scores compared to the control group (–37.8% vs –4.3%; $P < .001$).[2]

Compared with control patients in each group, patients in the inflammatory pain subgroup and the neuropathic pain subgroup who received low-dose naltrexone reported reductions in pain scores of 32% ($P < .001$) and 44% ($P = .048$), respectively. There was no statistically significant difference in mean change in VAS/NRS scores between the inflammatory and neuropathic subgroups ($P = .763$). A multivariate linear regression analysis did not identify significant variables other than low-dose naltrexone that correlated with pain improvement. The number needed to treat to observe a ≥ 50% reduction in pain scores was 3.2.[2]

Limitations for this study include its small sample size and open-label design.[2]

Low-dose naltrexone is effective for fibromyalgia pain

A 2020 single-blind prospective dose-response study utilized the up-and-down method to identify effective naltrexone dose for patients in a Danish university hospital pain clinic. Patients were White women ages 18 to 60 years (N = 25) who had a diagnosis of fibromyalgia unresponsive to traditional pharmacologic treatment. All patients received treatment with low-dose naltrexone (ranging from 0.75 mg to 6.0 mg) but were blinded to dose.[3]

Patients were evaluated for improvement in fibromyalgia symptoms using the Patient Global Impression of Improvement (PGI-I) scale—which ranges from 1 (very much improved) to 7 (very much worse), with 4 being "no change"—at baseline and after 2 to 3 weeks of treatment with low-dose naltrexone. A patient was considered a responder if they scored 1 to 3 on the follow-up PGI-I scale or if they experienced a > 30% pain reduction on the VAS. If a patient did not respond to their dose, the next patient began treatment at a dose 0.75 mg higher than the previous patient's ending dose. If a patient did respond to low-dose naltrexone treatment, the next patient's starting dose was 0.75 mg less than the previous patient's. Eleven of 25 patients were considered responders.[3]

The primary outcomes were effective dose for 50% of fibromyalgia patients (3.88 mg; 95% CI, 3.39-4.35) and effective dose for 95% of fibromyalgia patients (5.4 mg; 95% CI, 4.66-6.13). Secondary outcomes were fibromyalgia symptoms as evaluated on the Fibromyalgia Impact Questionnaire Revised. Five of the 11 responders reported a > 30% improvement in tenderness and 8 of the 11 responders reported a > 30% decrease in waking unrefreshed.[3]

Limitations of the study include the short time period of treatment before response was assessed and the decision to use low test doses, which may have hindered detection of effective doses > 6 mg in fibromyalgia.[3]

Editor's takeaway

Low-dose naltrexone, a less-often-used form of pain management, is a welcome option. Studies show some effectiveness in a variety of pain conditions with few adverse effects. The small number of studies, the small sample sizes, and the limited follow-up duration should encourage more investigation into how to best use this intervention. JFP

Studies show that low-dose naltrexone has some effectiveness in a variety of pain conditions—including diabetic neuropathy and fibromyalgia—with few adverse effects.

References

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