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

**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.

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**References**

