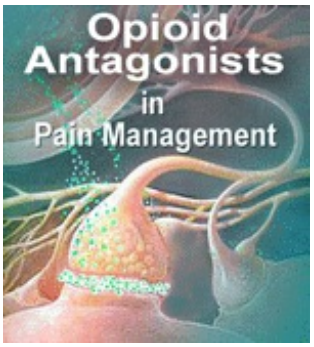
More Evidence That Naltrexone Aids Fibromyalgia



The difficult-to-treat chronic pain disorder fibromyalgia syndrome (FMS) is characterized by diffuse musculoskeletal pain, fatigue, sleep disturbance, and cognitive impairments. Significant numbers of patients with FMS do not respond adequately to drugs currently approved for the disorder by the U.S. FDA: pregabalin (Lyrica®), milnacipran (Savella®), and duloxetine (Cymbalta®). Naltrexone — an orally administered opioid-receptor antagonist sometimes used to treat alcohol or opioid dependence — is hypothesized to aid FMS by enhancing endogenous endorphin function and suppressing centrally-acting proinflammatory cytokines, thereby helping to attenuate pain and other symptoms.

At the 2013 Annual meeting of the American College of Rheumatology (ACR), Samy Metyas, MD and colleagues presented a prospective, open-label, single-center, uncontrolled pilot study involving 25 patients (24 female) diagnosed with FMS by ACR criteria [Metyas et al. 2013]. Subjects were started on low-dose oral naltrexone, 3 mg, at night, with titration up to a maximum 4.5 mg nightly. Primary outcome was measured on the Revised Fibromyalgia Impact Questionnaire (FIQR) at month 3, and adverse reactions were also recorded.

Participants were allowed to continue on their FDA-approved medications for FMS, and 18 of the 25 did so; the other 7 (32%) were on naltrexone monotherapy during the study. Twenty-two patients completed the 3-month study, with 2 discontinuing because they considered naltrexone ineffective and 1 drop-out was due to diarrhea.

Overall, study participants improved their FIQR scores by an average of 19.5%; however, half of the 22 study completers displayed a more robust response, with an average 41% improvement. (*Data specifically for the 7 patients on naltrexone monotherapy were not separately noted.*) Furthermore, patients reported decreases in pain, anxiety, and sleep disturbances from baseline. The researchers conclude that treatment of FMS with low-dose naltrexone may be effective, highly tolerable, and inexpensive; although, further controlled trials are needed.

COMMENTARY:

This study by Metyas et al. is one of relatively few that have explored low-dose naltrexone, or LDN, for fibromyalgia. And, while the results were promisingly favorable, the small size of the trial, possible confounding by concurrent medications, and lack of a control group raise significant questions about the validity and reliability of results.

A prior *Pain-Topics UPDATES* article [here], by guest author Dmitry M. Arbuck, MD, discussed clinical applications of naltrexone for various pain and psychiatric disorders. However, his expert commentary was based on clinical experience in a single practice, rather than broader-ranging research evidence, and LDN naltrexone in the 2-to-6 mg/day range was not noted to be effective for FMS and other painful conditions.

In a separate *UPDATE* article [here], we described a pilot study by Jarred Younger, PhD and colleagues at Stanford University demonstrating that daily LDN (4.5 mg/day) reduced symptom severity in 10 women with FMS [Younger et al. 2009]. In a followup to that study, Younger et al. [2012] conducted a 22-week double-blind, placebo-controlled, crossover-design study of LDN 4.5 mg/day that enrolled 30 women with FMS.

Pain was reduced significantly more by LDN (49%) than placebo (27%; P=0.006). In addition to the roughly half of patients who reported feeling very much or much improved with LDN, an additional quarter reported smaller improvement; however, there was no impact on fatigue or sleep quality. Participants rated LDN equally as tolerable

as placebo and the only side effects reported more often with LDN than placebo were vivid dreams (37% versus 13%) and mild headache (16% versus 3%).

While the latter trial by Younger et al. [2012] was adequately powered to detect a large effect of LDN for pain relief, our own statistical evaluation of the data revealed only a small-to-medium effect size. Still, the results seemed encouraging; although, it should be noted that patients treated with LDN — eg, at the 4.5 mg naltrexone dose used in the studies by Metyas et al. and by Younger et al. — cannot simultaneously be administered opioid analgesics for pain, as it could block opioid effects and/or precipitate withdrawal in persons already maintained on opioids.

All 3 clinical studies of LDN for FMS noted above were published as conference presentation abstracts, so the data and results should be considered as preliminary. In fact, the most disappointing aspect of LDN for fibromyalgia is that studies to date have been too few and generally on an anecdotal scale (ie, too small) to provide high-quality evidence of definitive outcomes.

Naltrexone, as well as naloxone — the other opioid antagonist of interest and most commonly used to reverse opioid overdose (eg, Narcan®) — are both generic, economically priced drugs; so, they have not yet attracted the necessary funding from industry to launch large, randomized, controlled clinical trials for pain management. Applications of these agents in pain management are “off label” and the smaller doses needed must be specially compounded.

Overall, a growing body of evidence suggests potential benefits of opioid antagonists — particularly low- or ultralow doses of naloxone or naltrexone — as adjunctive therapy for providing effective and safe pain management. In addition to FMS, low-dose naltrexone has been successfully tested by itself as monotherapy for the management of several other pain-related conditions, including Crohn’s disease, irritable bowel syndrome, and neuropathy. At ultralow doses — 1-8 microgram (mcg) — opioid antagonists may reduce tolerance to and physiologic dependency on opioid analgesics, and lessen certain opioid side effects.

In 2009, we developed peer-reviewed, evidence-based reports describing naloxone and naltrexone pharmacology and the theoretical foundations of opioid antagonists in pain management. The reports also included summaries of 17 studies available at the time that investigated opioid-antagonist therapy for pain in adult humans. These papers have been archived and are accessible as follows:

> ***Opioid Antagonists, Naloxone & Naltrexone — Aids for Pain Management***
> *An Overview of Clinical Evidence. [16-pages; **PDF Here**]*
>
> ***Opioid Antagonists in Pain Management [Journal Article]***
> *From: Practical Pain Management, 2009(April);9(3):10-21. [11-pages; **PDF Here**]*

As the 2 reports describe, available evidence has suggested a number of applications that may be of interest to pain-management practitioners and their adult patients:

1. Brief detoxification via IV naloxone for difficult cases of opioid-unresponsive intractable pain, opioid tolerance, or suspected opioid-induced hyperalgesia.
2. Ultralow-dose (microgram amounts) oral naloxone combined with various opioid agonists for managing acute postoperative pain.
3. Adjuvant ultralow-dose naloxone (continuous IV infusion) combined with patient controlled analgesia (PCA) postoperatively.
4. Ultralow-dose naltrexone (oral) or naloxone (intrathecal) as a component of intrathecal opioid analgesia for difficult cases of intractable pain.

5. Ultralow-dose naltrexone combined with opioid agonists to provide an opioid-sparing effect, offering equivalent pain relief at lower opioid doses.

6. Oral ultralow-dose naloxone or naltrexone combined with oral opioid analgesics to help prevent or reverse opioid-induced constipation and potentially ameliorate other opioid side effects.

7. Ultralow-dose naltrexone to help facilitate more comfortable opioid-agonist tapering.

8. Low-dose (3.0-4.5 milligram) naltrexone monotherapy may aid Crohn's disease, fibromyalgia, and short-term for irritable bowel syndrome.

These are only some of the possibilities, since further research is needed to better understand the capabilities and safety of opioid antagonists for treating pain conditions of various types. Meanwhile, healthcare providers interested in using low- or ultralow-dose naloxone or naltrexone would need to cautiously prescribe these agents off-label for compounding at properly equipped pharmacies.

REFERENCES:

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> Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Medicine. 2009;10, 663-672 [article here].

> Younger J, McCue R, Noor N, et al. Low-dose naltrexone reduces the symptoms of fibromyalgia: A double-blind and placebo-controlled crossover study. In posters and abstracts, AAPM Annual Meeting, Palm Springs, CA; Feb 23-26, 2012; Abstract 251 [available here].

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