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REVIEW

The Safety and Efficacy of Low-Dose Naltrexone in Patients with Fibromyalgia: A Systematic Review

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Abstract: Fibromyalgia (FM) is a chronic pain sensitivity syndrome characterized by diffuse musculoskeletal pain and many other systemic manifestations. Low-dose naltrexone (LDN) has been increasingly used as an off-label treatment option in FM. However, current evidence on the safety and efficacy of LDN in patients with FM is not well known. To systematically assess the current evidence on the safety and efficacy of LDN use in the treatment of FM. A comprehensive bibliographic search was conducted on EBM Reviews – Cochrane Central Register of Controlled Trials, EBM Reviews – Cochrane Database of Systematic, Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions and Scopus databases in September 2022. Inclusion criteria were articles that were published in English, focusing on clinical trials involving LDN for the treatment of FM. Two reviewers independently screened and extracted the data. A qualitative analysis was used due to the high methodological heterogeneity between studies. The electronic search produced 805 articles. After applying the inclusion criteria, 9 articles (one RCT, two case reports, two case series, and four pilot trials) were selected for evaluation. LDN intervention protocols, study designs, and follow-up periods were different among the included studies. Overall, LDN was found to be effective in the symptomatic management of FM, and of the 78% of included studies that evaluated for safety, no severe adverse events were reported. Proving the efficacy and safety of low-dose naltrexone is a future possibility based on current study data, but the level of scientific evidence is limited. Future well-designed trials with large sample sizes are required.

Keywords: fibromyalgia, naltrexone, low-dose naltrexone, chronic pain, review

Introduction

Fibromyalgia (FM) is a chronic, centralized, pain sensitivity syndrome, mainly characterized by widespread musculoskeletal pain, fatigue, nonrestorative sleep, mood issues, deconditioning, and cognitive impairments.[1] The prevalence of FM is approximately 2–8% worldwide with a higher prevalence for women.[2] Age, sex, family history, and certain conditions/factors (rheumatoid arthritis, systematic lupus erythematous, repetitive injuries, stressful or traumatic events, and preceding infections) are associated risk factors for the development of FM.[3] Individuals with FM report a wide range of somatic and psychological symptoms, which contribute to significant symptom burden and functional impairment. The annual associated direct costs, per patient, range from $ 1750 to $ 35,920 in the USA.[4]

The underlying mechanisms for FM continue to be investigated, with a greater focus on the pathophysiological process known as central sensitization.[5] Central sensitization involves the amplification of both central and peripheral pain and sensory processing in the ascending and descending sensory pathways, due to a variety of antecedent triggers (including pain, infection, inflammation, or prolonged stressors).[6,7] Recent research has focused on the underlying trigger of neuroinflammation as a potential contributor to the development of central sensitization in the setting of FM. Increased blood–brain barrier permeability is an important feature of neuroinflammation, which results in increased leukocyte relocation into the central nervous system. Recent immunological evidence indicates that inflammation-

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driven pathways play an important role in the pathogenesis of FM.[8] Immune cells such as macrophages, glial cells, monocytes, mast cells, and neutrophils as mediators of inflammation, may have a role in the development of an inflammatory substrate in FM.[9]

Despite FM being highly prevalent, the treatment remains controversial. Current FM management consists of both pharmacological and non-pharmacological treatment approaches in accordance with recommendations from institutions such as the American College of Rheumatology and the European League Against Rheumatisms. Various medications have been used to treat FM, though only three (duloxetine, milnacipran, and pregabalin) are approved specifically for this purpose by the US Food and Drug Administration (FDA). However, the current first-line prescribed agents were shown to have limited use due to side effects, small benefits over placebo, and failure of improvements in patients' fatigue or quality of life.[10] Thus, the need for continued research into other medication options that can be safe and efficacious in patients with FM.

Low-dose naltrexone (LDN) was initially introduced into clinical practice in the 1980s by Dr. Bernard Bihari, demonstrating the effectiveness of LDN in a dose range of 1.5 mg to 3 mg, as an alternative option, for a wide range of autoimmune disorders.[11] Over the ensuing decades, there has been increasing attention and use of LDN as an adjunct treatment modality for FM.[12,13] As a result, there has been a noticeable rise in available literature evidence from a variety of investigative sources purporting the benefits of LDN in FM management.

Recently, Hatfield et al[14] performed a systematic review evaluating the efficacy of LDN in patients with chronic pain conditions, such as chronic pelvic pain, complex regional pain syndrome, FM, and interstitial cystitis. This review consisted of six articles (published from 2009 to 2019) with ninety-six FM participants. Overall, LDN reduced FM-associated pain and improved quality of life. In a subsequent systemic review, Kim et al[15] assessed the clinical use of LDN in patients with chronic pain (FM, complex regional pain syndrome, inflammatory bowel disease, multiple sclerosis, chronic back pain, and osteoarthritis). Results demonstrated symptomatic improvement with LDN usage.

The above systematic reviews hypothesized the underlying benefits of LDN were due to the analgesic, anti-inflammatory (especially at the level of microglial cells), endogenous opioid system modulatory, and neuroimmune modulatory roles of LDN in chronic pain conditions.[14,15] In contrast, the current FDA-approved medications (duloxetine, milnacipran, and pregabalin) have no effect on the endogenous opioid system.[16]

Until now, there has been no dedicated systematic review solely focusing on the efficacy of LDN in patients with FM. Furthermore, the potential safety of LDN use in FM has never been systematically assessed or reported. Given these gaps in the existing literature, the present systematic review aims to comprehensively identify, appraise, and summarize studies evaluating the efficacy and safety of LDN in patients with FM.

Methods

This study was performed at Mayo Clinic (Rochester, MN) in September 2022, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic electronic literature search was conducted identifying all peer-reviewed, English-language articles in the databases of EBM Reviews – Cochrane Central Register of Controlled Trials, EBM Reviews – Cochrane Database of Systematic Reviews, Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions and Scopus to collect data regarding LDN for FM. Initial publications were screened and the eligible full texts were evaluated based on eligibility criteria, followed by a manual search of the selected full-text references. Only articles focusing on LDN use in FM were included. Review articles, commentary, note, medical hypothesis articles, letters to the editor, study protocol, cellular or animal-level studies were excluded. Study characteristics and demographics were systematically extracted from each article and summarized in a Microsoft Excel file with the following information: author name(s), publication year, study type, population, sample size, age, gender, intervention, outcome, and adverse events (AEs). This qualitative review relied on summary data for analysis. Data screening and selection were performed by two reviewers independently; any disagreement was resolved through meetings and discussions.

Results

Study Selection

The initial literature search yielded 805 citations. A total of 4 additional studies were identified through searching of websites and reference reviews. After 4 duplicates were removed, a total of 805 records remained for review of titles and abstracts. Next, 94 conference abstracts, 32 study registrations, 8 trials with insufficient data, and other irrelevant records were further removed. Of the remaining citations, 613 studies were excluded for not including LDN or FM. The remaining 15 full-text articles were assessed for eligibility, and 6 of these studies were excluded due to various reasons. Overall, 9 studies were included for the qualitative analysis. The screening process of the systematic review is presented with the PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

This systematic review included one randomized controlled trial (RCT), four pilot non-RCTs, two case reports, and two case series. Characteristics of the included studies are summarized (Table 1). All studies were published between 2009 and 2022, with eight studies being conducted in the USA[16–22,24] and one in Denmark.[23] Trial participants consisted mainly of women, age ranging between 14 and 89 years, and trial sample sizes ranging from 1 to 37. In total, 431 study participants were included among all of the included studies, with 159 individuals with FM. Participants in seven of the nine studies were diagnosed according to the 1990 ACR diagnostic criteria,[16–19,21,22,24] one study used the 2010 ACR criteria,[20] and one study used a combination of 1990 and 2011 ACR criteria.[23]

All the pilot trials and a case report assessed the efficacy of LDN in patients with FM. Two other case series examined the use of LDN in opioid-induced hyperalgesia and FM. The remaining case report analyzed the application of LDN in FM patients with depression. Overall, the included studies reported numerous beneficial outcomes for LDN in FM symptom management. The included studies presented a diversity of outcome variables related to FM management,

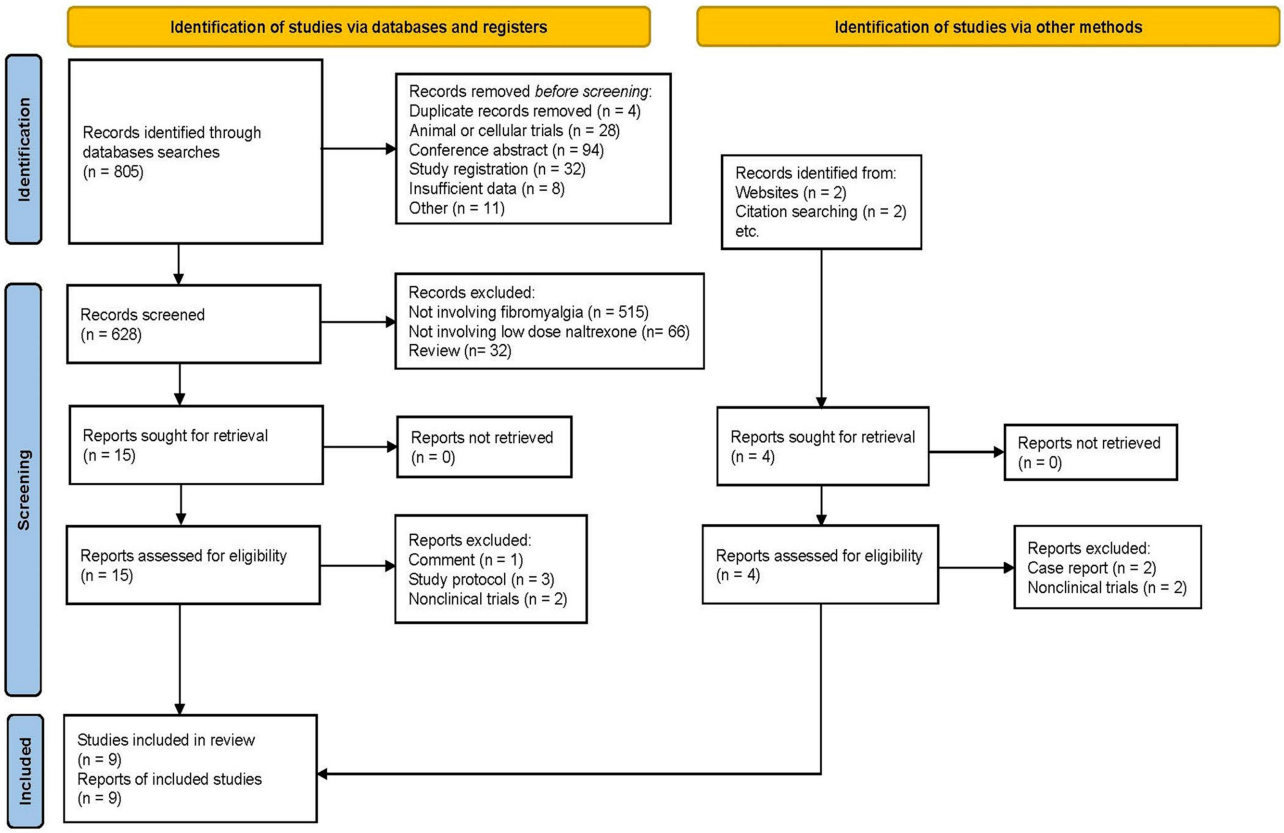

Figure 1 Selection of included studies.

Table 1 Characteristics of Included Studies

Author	Country	Study Design	Condition	N	Gender	Age	Criteria
Younger 2009[17]	USA	Placebo-controlled, single-blind, crossover, pilot study	Fibromyalgia	10	Female	22–55	ACR 1990
Ramanathan 2012[18]	USA	Case report	Fibromyalgia	1	Male	37	ACR 1990
Younger 2013[19]	USA	Randomized placebo-controlled crossover double-blind study	Fibromyalgia	31	Female	23–65	ACR 1990
Parkitny 2017[20]	USA	Single-blind, crossover study	Fibromyalgia	8	Female	31–63	ACR 2010
Metyas 2018[21]	USA	Two small prospective pilot open label studies	Fibromyalgia	25	24 Female +1male	30–75	ACR 1990
Oaks 2018[22]	USA	Case series	Opioid-Induced Hyperalgesia and Fibromyalgia	254(217 OIH & 37 FM)	152 Female & 102 Male	14–89	ACR 1990
Bruun-Plesner 2020[23]	Denmark	Prospective dose–response study	Fibromyalgia	25	Female	27–59	ACR 1990 and ACR 2011
Jackson 2021[24]	USA	Case series	Opioid Induced Hyperalgesia and Fibromyalgia	76(55 OIH, and 21 FM)	19 Female +2 Male	37–50	ACR 1990
Siembida 2022[16]	USA	Case report	Depression in Fibromyalgia	1	Male	60	ACR 1990

Note: ACR, American College of Rheumatology; OIH, opioid-induced hyperalgesia; FM, fibromyalgia.

which can be generally divided into the following seven domains: pain intensity (pain, FIQR, VAS, NRS, FPS), sleep quality (ISI), quantitative sensory testing (CPT), psychological variables (HAM-D score), wellness (Daily Self-Reported FM Symptom Report, quality of life, IMMPACT, Symptom Data Survey, Patient Global Impression of Improvement Scale), and other (plasma markers of inflammation). The duration of study intervention ranged from 3 weeks to 14 months. All studies compared outcomes at the end of the study intervention duration, while six trials also performed follow-up assessments, ranging from 1 week to 15 months post-intervention.

In terms of safety, two studies did not report relevant safety data,[22,24] while the other seven (78%) narratively reported safety information regarding LDN use.[16–21,23] Siembida[16] and Parkitny et al[20] reported no side effects related to LDN. Younger and Ramanathan et al reported transient insomnia, vivid dreams, and headache which could be minimized by dose reduction.[17–19] Metyas et al[21] reported diarrhea. Bruun-Plesner et al[23] reported no serious AEs occurred during the trial, but mild and tolerable side effects included fatigue, depression, nausea, abdominal pain, and headache.

The high heterogeneity (study design, intervention, outcome measure, and follow-up) across the included trials did not allow for a meta-analysis. Study characteristics of included trials are summarized in Table 1 and Table 2.

Table 2 Efficacy of Low-Dose Naltrexone Treatment

Author	LDN Intervention	Notable Outcomes	Mechanism	AE
Younger 2009[17]	8 weeks (Baseline 2 weeks, placebo 2 weeks, 4.5 mg naltrexone hydrochloride capsule 1 hour before bedtime 8 weeks, and washout 2 weeks.)	Daily self-reported FM symptom report Quantitative sensory testing Basic individual responder analyses	Inhibit the activity of microglia and reverse central and peripheral inflammation.	Minor and transient insomnia and vivid dreams.
Ramanathan 2012[18]	13 months (4.5mg naltrexone for 2 weeks, and then stopped for the next 2 weeks. Restarted at week 4 for the next 14 weeks. Then restarted back on 4.5 mg at week 20. Reduced to 3.0 mg at week 23, and further reduced to 2 mg at week 27, switched back to 3 mg after 1 month and for the last 6 months.)	CPT Pain (0–10) Quality of life	Improve endogenous endorphin function.	Transient insomnia and vivid dreams.

(*Continued*)

Table 2 (Continued).

Author	LDN Intervention	Notable Outcomes	Mechanism	AE
Younger 2013[19]	12 weeks (baseline2 weeks, placebo 4 weeks, 4.5 mg of oral naltrexone daily for 12 weeks and follow up 4 weeks.)	VAS IMMPACT	Inhibit the activity of microglia and improve endogenous endorphin function.	Vivid dreams and headache could be minimized by reducing the dosage to 3.0 mg/day.
Parkitny 2017[20]	10 weeks (2 weeks baseline+ 4.5 mg oral dose, at least one hour before going to bed at night or 3 mg if experienced unpleasant AEs at the standard dose for 8 weeks. Follow up 8 weeks.)	Symptom data survey Plasma markers of inflammation	Reduces inflammation in FM.	No AE related to LDN.
Metyas 2018[21]	90 days (1.5mg daily, up titrating to 4.5mg daily as tolerated.)	Revised Fibromyalgia Impact Questionnaire (FIQR)	Inhibit the activity of microglia, reduce the production of neuroexcitatory and neurotoxic chemicals.	Diarrhea.
Oaks 2018[22]	14 months (Patients on opioids: 1w after buprenorphine administration, began at 0.1 mg/day and building up gradually to 4.5 mg/day. More recently immediately after buprenorphine and given it twice a day; Patients not on opioids: immediately after buprenorphine began at 0.1 mg twice a day. Follow-up 10.1±3.7 weeks.)	CPT FPS	Improve endogenous endorphin function.	N/A.
Bruun-Plesner 2020[23]	3 weeks (0.75–6 mg for 3 weeks with the dosing interval 0.75 mg for two weeks. Follow up 1 week.)	PGI-I ISI FIQR NRS	Improve opioid signaling and anti-inflammatory effect.	Common but mild and tolerable fatigue, depression, nausea, abdominal pain, and headache.
Jackson 2021[24]	Averaged 7 weeks (Patients on opioids: After 8mg sublingual buprenorphine LDN, 0.1mg twice per day to 4.5mg twice a day. Patients not on opioids: started LDN 0.1mg twice per day to 4.5mg twice a day. Follow up averaged 7 weeks.)	CPT FPS	Improve endogenous endorphin function.	N/A.
Siembida 2022[16]	10 weeks (0.1 mg twice a day and is gradually increased over 11 days to a maximum of 4.5 mg twice a day thereafter. Follow up 15 months.)	HAM-D score CPT FPS	Inhibit the activity of microglia and improve endogenous endorphin function.	No side effects.

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; ESR, Erythrocyte Sedimentation Rate; CPT, Cold Pressor Test; VAS, Visual Analogue Scale; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; FIQR, Revised Fibromyalgia Impact Questionnaire; FPS, FACES Pain Scale; PGI-I, Patient Global Impression of Improvement Scale; ISI, Insomnia Severity Index; NRS, Numeric Rating Scale; HAM-D, Hamilton Rating Scale for Depression.

Discussion

This is the first systematic review to solely assess and summarize the current body of evidence for the use of LDN in the management of FM. Overall, LDN therapy appears to be a safe and effective option in the treatment of FM.

The included studies differed in study design, LDN intervention strategies, sample sizes, patient demographics, and outcome measures. Studies also utilized various versions of the ACR diagnostic criteria as part of study inclusion. Given all these variabilities, a direct comparison of the effect of LDN across all studies is not feasible and thus no meta-analysis could be performed.

Naltrexone is a medication approved by the FDA for the treatment of alcohol use disorder and opioid dependence, with typical daily dosages ranging between 50 and 100 mg.[25] At these doses, naltrexone can significantly block activity at mu-, delta-, and kappa-opioid receptors.[26] Beta-endorphin activity at mu-opioid receptors is associated with endogenous analgesic processes.[27] Naltrexone simultaneously has an antagonist effect on non-opioid receptors (Toll-like receptor 4 or TLR4) that are found on microglia.[28] Microglia are central nervous system immune cells that are activated by a wide range of triggers. Once activated, microglia produces inflammatory and excitatory factors that can cause sickness behaviors such as fatigue, pain sensitivity, sleep disruption, cognitive changes, mood disorders, and general malaise.[29] At low doses, LDN appears to have paradoxical analgesic and anti-inflammatory systemic effects. Study findings in this review revealed LDN was proposed to exert its effects via at least two hypothesized mechanisms: 1) improving endogenous endorphin function[16,18,19,22–24] and 2) neuroprotective and anti-inflammatory effects by suppressing microglia activation.[16,17,19–21,23]

The efficacy of LDN in treatment of FM has been demonstrated, though there is no consensus on a specific dose, frequency, or duration. Among the included studies, LDN doses varied from 0.1mg to 9mg daily, with 4.5mg once daily as the most common option. Two studies used 4.5mg daily,[17,19] and the other seven used varying titrating doses as needed.[16,18,20–24] Six studies used once daily dosing,[17–21,23] two studies used twice daily dosing,[16,24] while the remaining study used once daily dosing first, followed by twice daily.[22] Of note, in a single-blinded prospective dose–response prospective clinical trial, Bruun-Plesner et al[23] assessed the dose–response relationship of LDN in the treatment of 25 patients with FM. The tested LDN doses ranged from 0.75 to 6 mg. They estimated the effective dose in ED50 of 3.88 mg and ED95 of 5.40 mg on ten common FM symptoms. As such, they concluded that a daily dose of 4.5 mg seemed to be most appropriate for the management of FM.

Study Strengths and Limitations

This review has several strengths. It is the first review to systematically assess the safety and efficacy of LDN in patients with FM patients. This review followed a rigorous protocol, and all citations were reviewed in duplicates independently. This review included a broad range of study settings, outcomes, and patient populations. In addition, the overall findings of the present review are in accordance with previous studies that recommended LDN as a promising intervention for chronic pain management.[14] The present review will further improve and provide meaningful information about the potential role of LDN in the symptomatic management of patients with FM.

The study results must also be viewed with caution due to several limitations in relation to the included studies. First, the predominant study design of included trials were non-RCTs. Apart from the single included RCT, there were two case reports, two case series, and four pilot trials in this review. Second, though there has been increasing interest in LDN as a potential pharmacological intervention in FM, the overall body of evidence remains small, which can be attributed to the low number of published studies and small sample sizes. Third, the heterogeneity of the study designs, intervention parameters, and outcome measures across the included studies prevented the feasibility of performing a meta-analysis or direct comparison between studies; as a result, this limits the ability to draw a firm conclusion regarding the safety and efficacy of LDN in FM. Finally, only studies published in English were included. It is possible that other studies in languages other than English were not considered, which could potentially impact the conclusions of this review.

Conclusion

LDN appears to be a safe and efficacious treatment option in patients with FM. The current clinical data supporting its use are preliminary; interventional parameters such as dosage, frequency, duration, and outcomes still need to be refined. Well-designed, large-scale studies are needed before LDN can be widely recommended in the management of FM.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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