

SYSTEMATIC REVIEW



The use of naltrexone in the treatment of chronic pain: a systematic review

Victor Rassi-Mariani^a , Eduardo Silva Reis Barreto^{*,a} , César Romero Antunes Júnior^a , Vinicius Borges Alencar^a , Liliane Elze Falcão Lins-Kusterer^a , Liana Maria Torres de Araujo Azi^a  and Durval Campos Kraychete^a 

^aFederal University of Bahia, Salvador, Bahia, Brazil

ABSTRACT

This study aims to assess the efficacy of low-dose naltrexone (LDN) in treating chronic pain. We conducted a systematic review using the PICO strategy: (P) Patients with chronic pain, (I) Use of oral naltrexone, (C) Placebo or active drug and (O) Pain relief and quality of life. We included articles from PubMed, Scopus, Cochrane CENTRAL and EMBASE databases. Seven randomized clinical trials involving 406 patients were analyzed. The doses ranging from 2 to 4.5 mg once daily across all studies. Various chronic pain conditions were evaluated. The results suggest that low-dose naltrexone is not effective in managing chronic pain and improving the quality of life in patients with diverse chronic pain conditions. However, further research with larger sample sizes and standardized methodologies is necessary.

PLAIN LANGUAGE SUMMARY

This study looks at how well low-dose naltrexone (LDN) works for treating long-lasting pain. We reviewed research where patients with chronic pain were given either LDN or a placebo (a fake treatment). We found eight studies that included a total of 421 patients. The LDN doses used ranged from very small amounts 2–4.5 mg, taken once a day. These studies looked at different types of chronic pain. Our results suggest that LDN cannot help to reduce pain and improve the quality of life for people with chronic pain. However, more research with larger groups of people and consistent methods is needed to confirm these findings.

ARTICLE HISTORY

Received 25 May 2024

Accepted 4 September 2024

KEYWORDS

chronic disease;
fibromyalgia; opioid;
pharmacotherapy; quality
of life

1. Introduction

Chronic pain significantly impacts the quality of life and can lead to various consequences, including depression, physical limitations and social isolation [1–3]. Pharmacological treatments encompass a range of options including simple analgesics, anti-inflammatories, opioids and adjuncts such as antidepressants, anticonvulsants, local anesthetics, alpha-2 agonists, corticosteroids, muscle relaxants, topical analgesics, cannabinoids, among others [4–7]. These pharmacological treatments can be utilized depending on the type of pain experienced by the patient, whether nociceptive, neuropathic or nociplastic [8].

Naltrexone is a long-acting antagonist of μ and κ opioid receptors and has been utilized in the treatment of alcoholism, addiction, opioid abuse and misuse at doses ranging from 20 to 150 mg orally [9]. At low doses, has gained interest as an off-label treatment for various chronic pain disorders due to its cost-effectiveness and favorable safety profile [10]. Despite the extensive discussion about its potential in conditions

like fibromyalgia, the current evidence on its efficacy remains inconclusive [11,12]. Systematic reviews offer several advantages, including synthesizing a large body of evidence, assessing the consistency of findings across studies and providing a comprehensive overview of the efficacy of interventions [13]. These reviews are particularly important in the field of pain management, where treatment options are diverse and often yield variable results.

This study aims to systematically review the existing literature on the efficacy of low-dose naltrexone (LDN) in managing chronic pain, providing a detailed evaluation of its potential benefits, limitations and implications for clinical practice. By doing so, we aim to inform clinical decisions and highlight areas where further research is needed.

2. Materials & methods

This is a systematic literature review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] recommendations, aimed at

CONTACT Eduardo Silva Reis Barreto Tel.: +55 7199109 8611;  eduardosrb@ufba.br

 Supplemental data for this article can be accessed at <https://doi.org/10.1080/17581869.2024.2401769>

© 2024 Informa UK Limited, trading as Taylor & Francis Group

assessing the efficacy of naltrexone in chronic pain relief. The PICO strategy was applied as follows: (P = Patients with chronic pain; I = Use of oral naltrexone; C = Placebo or active drug; O = Pain relief; quality of life). This review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023422502.

2.1. Eligibility criteria

We included full-text randomized clinical trials published until July 2024, in English, and fully available in the PubMed, Scopus, EMBASE and Cochrane CENTRAL databases. Exclusion criteria encompassed articles not available in digital platforms, conference abstracts, case reports, and series, preprints, observational studies and review studies.

2.2. Search strategy

Descriptors related to Naltrexone and chronic pain were employed for the database search strategy. The descriptors used were obtained from the Medical Subject Headings (MeSH), available at www.ncbi.nlm.nih.gov/mesh. Boolean operators and and or were used for term searches on the mentioned platforms, adhering to the inclusion and exclusion criteria for articles. All descriptors used and the complete search strategy for each database are available in the [Supplementary Material](#).

2.3. Selection of studies

Two reviewers (Victor Rassi-Mariani and Eduardo Silva Reis Barreto), who had no access to each others assessments, evaluated the identified article titles, selecting those that met the inclusion criteria. Subsequently, abstracts were reviewed for selection purposes. Articles that passed the initial screening were examined in their entirety to determine inclusion in the systematic review. In situations where discrepancies arose between the two reviewers, a third reviewer (Durval Campos Kraychete), who had exclusive access to the conflicting articles, intervened to resolve differences. Data from the articles were extracted using the Rayyan app [15].

2.4. Data summarization

The data from the articles were extracted into a structured table in Microsoft Excel[®], version 2205. This table captured details concerning the study population size, intervention and control group characteristics, methodology and outcomes assessed in the evaluated articles.

2.5. Quality assessment

The risk of bias assessment was conducted using the Cochrane Risk of Bias tool for randomized trials (RoB 2) [16], evaluated independently by two reviewers (Eduardo Silva Reis Barreto and César Romero Antunes Júnior), with discrepancies resolved through a third reviewer (Durval Campos Kraychete). This tool addresses five specific domains for bias assessment, including randomization, potential deviations in the intervention, absence of data, outcome measurement and result selection. After each reviewer evaluates each domain, risks are categorized as 'low risk', 'high risk' or 'some concerns', indicating an uncertain bias risk, and the overall bias risk of the article is calculated.

3. Results

The search across the databases, applying filters based on pre-established inclusion and exclusion criteria, yielded 723 articles. Following the removal of duplicates, 626 articles remained. Upon scrutinizing the titles and abstracts of these articles, 613 were excluded, leaving 13 for full-text review. Subsequently, seven articles were included in the review [17–23]. The flowchart outlining the study selection process, along with the reasons for exclusion, is presented in [Figure 1](#).

3.1. Characteristics of the studies

All included studies were randomized clinical trials [17–23]. Five of these studies were crossover trials [17–19,21,22]. In total, 406 patients were randomized, of whom 333 received LDN. All studies assessed the oral administration of naltrexone, with doses ranging from 2 to 4.5 mg, administered once a day. In the control group, in addition to the placebo, some studies evaluated the use of gabapentin [23], amitriptyline [19] and transcranial direct current stimulation (tDCS) [20]. The follow-up ranged from 26 days to 7 months. The studies addressed a variety of chronic pain conditions, such as multiple sclerosis [17], Gulf War illness [18], painful diabetic neuropathy [19], chronic arthritis [21], chronic pain in people with HIV [23] and fibromyalgia [20,22]. Further details about the included articles are available in [Tables 1 & 2](#).

3.2. Geographic characteristics

Two studies were conducted in the USA [18,21]. One study was carried out in Iran [17], one in India [19], one in Brazil [20], one in Denmark [22] and one in Russia [23].

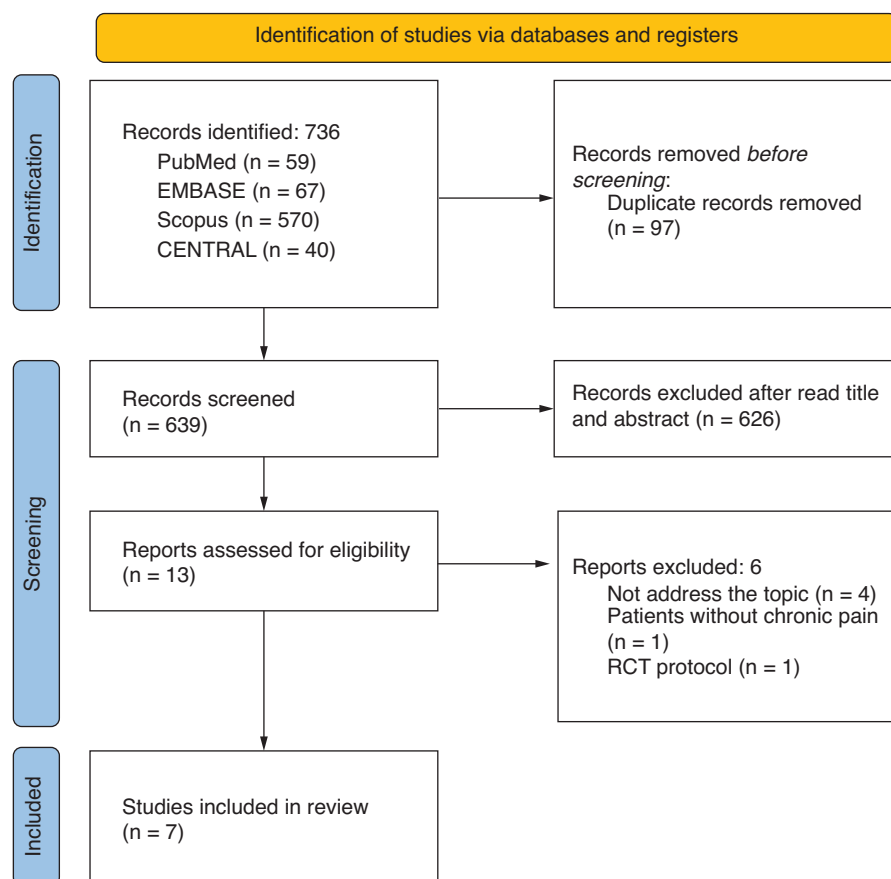


Figure 1. Flowchart of included studies.

3.3. Summarization of the studies

All included studies evaluated pain improvement using oral LDN [18–23]. Furthermore, all studies assessed improvement quality of life and function with the use of oral LDN, utilizing scales such as SF-36 [18], Patient Global Impression of Change [19], Profile of Chronic Pain Scale [20], Fibromyalgia Impact Questionnaire [20,22], Pain Catastrophizing Scale [20,22], Hospital Anxiety and Depression Scale [22], BDI-II [20,21], Brief Pain Inventory [23], MSQoL-54 [17] and Expanded Disability Status Scale (EDSS) [17]

3.3.1. Gulf War illness

In the study conducted by Brewer et al. (2018) [18], a double-blind crossover trial was performed involving 37 patients. Each treatment arm, consisting of 4.5 mg naltrexone and placebo, lasted for 3 months, with a 1-month washout period in between. According to the Clinical Global Impression Scale, 38% of patients (n = 14) showed improvement (responders), with six reporting 'much improvement'. The remaining patients exhibited no change from baseline (n = 18; 49%) or demonstrated minimal worsening (n = 5; 13%) (nonresponders). The

responders exhibited greater improvement, evidenced by decreased scores from baseline, on the VAS for confusion, dizziness and depression compared with nonresponders. Pain assessment via the SF-36 subscale revealed no significant differences between responders and non-responders ($p > 0.05$). However, responders displayed less disability, as indicated by higher scores, in the emotional role limitation subscale of the SF-36 compared with nonresponders (85.2 ± 11.3 vs 46.9 ± 8.4 ; $p = 0.01$).

3.3.2. Painful diabetic neuropathy

In the study by Srinivasan et al. (2021) [19], a double-blind crossover trial was conducted with 67 patients diagnosed with painful diabetic neuropathy. Participants underwent treatment with naltrexone 2 mg, titrated up to 4 mg and amitriptyline 10 mg, titrated up to 25 mg to 50 mg, for 6 weeks in each arm, with a 2-week washout period between them. Approximately 92% of patients used 4 mg of naltrexone, while 67% used 25 mg of amitriptyline. The baseline mean score on the VAS was around 6 for both groups. Both the naltrexone and amitriptyline groups showed a significant decrease in VAS score compared with baseline (naltrexone: -2.67 , 95% CI:

Table 1. Main characteristics of included studies.

Authors/year	Pain condition	Test group	Control group	Experimental intervention	Control intervention	Follow-up time	Time between crossover groups	Mean age (years) ^a	Gender ^c
Sharafaddinzadeh et al. 2010	Multiple sclerosis	96 ^b		Naltrexone 4.5 mg	Placebo	8 weeks ^d	1 week	34.81 ± 9.31	23/73
Brewer et al. 2018	Gulf War illness	37 ^b		Naltrexone 4.5 mg	Placebo	3 months ^d	1 month	51 (43–76)	36/1
Srinivasan et al. 2021	Painful diabetic neuropathy	67 ^b		Naltrexone 2 mg up to 4 mg	Amitriptyline 10 mg, titrated up to 25 to 50 mg	6 weeks ^d	2 weeks	49 ± 4	35/32
Paula et al. 2023	Fibromyalgia	LDN + tDCS: 21	Placebo + tDCS: 22	Naltrexone 4.5 mg + tDCS	Placebo + tDCS	26 days	–	LDN + tDCS: 49.74 ± 1.97 LDN + tDCS sham: 48.09 ± 1.56 Placebo + tDCS: 50.57 ± 2.23 Placebo + tDCS sham: 48.95 ± 2.08 63 ± 10 (37–81)	0/86
Beaudette-Zlatanova et al. 2023	Osteoarthritis, rheumatoid arthritis, spondylarthritis	23 ^b	LDN + tDCS sham: 22	Naltrexone 4.5 mg + tDCS sham	Placebo + tDCS sham	8 weeks ^d	–		19/4
Bested et al. 2023	Fibromyalgia	52 ^b		Naltrexone 4.5 mg	Placebo	3 weeks ^d	2 weeks	50.4 (24–66)	6/46
Tsui et al. 2024	Chronic pain in people with HIV	15	Gabapentin: 15	Naltrexone 4.5 mg	Gabapentin (300 mg up to 1800 mg)	8 weeks	–	LDN: 40 ± 6 Gabapentin: 41 ± 7 Placebo: 41 ± 7	LDN: 9/6 Gabapentin: 10/5 Placebo: 10/5

^aMean ± standard deviation (Range).^bCrossover trial.^c(Male/Female).^dEach group of study.

LDN: Low dose naltrexone; tDCS: Transcranial direct current stimulation.

Table 2. Outcomes of interest and adverse effects of included studies.

Authors/year	Outcomes of interest	Adverse effects
Sharafaddinzadeh et al. 2010	The study evaluated the effects on the quality of life using the MSQoL-54 scale. Baseline mental health scores averaged 56.06 ± 19.18 , physical health scores averaged 52.16 ± 18.21 , and health perception scores averaged 49.01 ± 18.84 . Throughout the 17-week study period, there were minimal fluctuations observed in mental health, physical health and health perception scores ($p > 0.05$).	The most frequent adverse events in our trial were minor (grade I) and did not disrupt daily activities (grade II). They were tolerable and resolved after treatment. Nausea, epigastric pain, mood changes, mild irritability, headache and joint pain were the main recorded adverse events.
Brewer et al. 2018	The CGIS identified improvement in 38% of patients ($n = 14$), with 6 reporting 'much improvement', while the remaining patients showed no change from baseline ($n = 18$; 49%) or experienced minimal worsening ($n = 5$; 13%). Responders identified by the CGIS exhibited less disability (i.e., higher scores) in the SF-36 emotional role limitation subscale compared with nonresponders (85.2 ± 11.3 vs 46.9 ± 8.4 ; $p = 0.01$). However, there were no statistically significant differences between responders and nonresponders in other SF-36 subscales, including the pain subscale ($p > 0.05$).	Only one patient reported a nonserious adverse effect, which was not specified by the authors
Srinivasan et al. 2021	The baseline visual analog scale (VAS) scores were around 6 for both groups. Naltrexone treatment led to a decrease of 2.67 (95% CI: 2.48–2.85) ($p < 0.001$) on the VAS, while amitriptyline treatment resulted in a decrease of 2.50 (95% CI: 2.32–2.68) ($p < 0.001$). The McGill Pain Questionnaire, both naltrexone and amitriptyline treatments showed significant reductions from baseline ($p < 0.001$), with a difference between groups of -0.1 (95% CI: -0.4 to 0.1) ($p = 0.39$).	The naltrexone group experienced daytime somnolence (2 cases), constipation (1 case), diarrhea (3 cases), nausea (1 case), and headache (1 case). In comparison, the amitriptyline group had 36 patients with adverse effects ($p < 0.001$).
Paula et al. 2023	The LDN + tDCS and LDN + tDCS sham groups showed no significant differences at baseline compared with the placebo groups. By day 26, both LDN + tDCS ($p = 0.01$ - baseline) and LDN + tDCS sham ($p = 0.001$ - baseline and day 21) exhibited significant decreases. Overall, LDN-inclusive groups demonstrated improvements in the PCPS after 26 days, particularly in the interference with activities domain.	In terms of LDN adverse effects, there was no significant difference among the groups when analyzing adverse effects such as nausea, blurred vision, headache, sleepiness, difficulty in concentrating and acute mood changes ($p > 0.05$)
Beaudette-Zlatanova et al. 2023	The reduction in pain interference or average pain severity did not differ between LDN and placebo groups ($p = 0.22$). However, two secondary measures showed nominal differences between LDN and placebo: total scores on the painDETECT ($p = 0.02$) and BDI-II ($p = 0.04$), however these findings are likely spurious given the simultaneous testing of many secondary measures	Fatigue (one case), dizziness (two cases), urinary tract infection (one case), swelling of tongue and lips (one case), dermatitis (poison ivy) (one case) and fall with ankle injury (one case) were reported.
Bested et al. 2023	The difference observed in FIQR was minimal at -1.65 (IQR 18.55). Statistical analysis using both the Wilcoxon signed-rank test and the random effects model showed no significant difference between LDN and placebo (ES = 0.15, CI = -6.72 to 2.15, $p = 0.30$)	The adverse effects of naltrexone were similar to those of the placebo group: headache (9), fatigue (9), nausea (8), dizziness (7), stomach ache (3), diarrhea (3), constipation (2), blurry vision (1), worsened sleep (0), improved sleep (1) and more intense pain (2).
Tsui et al. 2024	Pain severity, as measured by the BPI, showed similar baseline scores across all groups: gabapentin (3.1 ± 1.3), naltrexone (3.2 ± 1.4) and Placebo (3.3 ± 1.5). At week 8, the reductions were as follows: gabapentin (-2.12), naltrexone (-0.97) and placebo (-1.85). No significant differences were found against gabapentin ($p = 0.73$) or placebo ($p = 0.55$).	Totalling 13 cases, mostly mild, adverse effects included fatigue (3), diarrhea (1), stomach ache (1), loss of appetite (1), dizziness (1), seizure (1), impediment (1), tremor (1), sleepiness (1), insomnia (1) and hypertension (1).

BPI: Brief pain inventory; CGIC: Clinical global impression of change; CGIS: Clinical Global Impression Scale; CI: Confidence interval; ES: Effect size; FIQR: Fibromyalgia Impact Questionnaire; LDN: Low dose naltrexone; PCPS: Profile of chronic pain scale; tDCS: Transcranial direct current stimulation.

2.48–2.85, $p < 0.001$; amitriptyline: -2.50, 95% CI: 2.32–2.68, $p < 0.001$). There was no statistically significant difference between the groups in terms of change in VAS score (between-group difference: 1.6, 95% CI: -0.9 to 4.2, $p = 0.21$). Similarly, both naltrexone and amitriptyline resulted in a significant decrease in McGill Pain Questionnaire and Likert Pain Scale scores compared with baseline, but there was no statistically significant difference between the groups for these parameters ($p = 0.39$ and 0.59 , respectively). None of the participants experienced worsened sleep, although the group treated with amitriptyline reported improved sleep quality. The Patient Global Impression of Change did not show any significant difference between the two groups ($p = 0.54$).

3.3.3. Fibromyalgia

In the study conducted by Paula et al. (2023) [20], a double-blind clinical trial was performed with 86 patients diagnosed with fibromyalgia, divided into four groups. The follow-up period lasted 26 days. During the first 21 days, patients received either naltrexone or a placebo, and from the 22nd day onwards, they received either tDCS or a sham tDCS until the 26th day. Up until day 21, only the placebo + sham tDCS group showed a significant decrease in VAS scores ($p = 0.011$). By day 26, significant decreases were observed in the LDN + tDCS group (5.10 ± 0.61 , $p = 0.01$ from baseline) and the LDN + sham tDCS group (4.67 ± 0.58 , $p = 0.001$ from baseline and day 21). The Profile of chronic pain scale,

both the LDN + tDCS and LDN + sham tDCS groups achieved better scores by the end of the study. In the tDCS group, improvements were observed across all domains: frequency and intensity ($p = 0.001$), Interference in Activities ($p = 0.014$), and Interference in Emotions ($p = 0.008$). In the LDN + sham tDCS group, improvement was observed only in the Interference in Activities domain ($p = 0.008$) after 21 days. Groups involving placebo did not show improvement. Significant improvements were noted in the Fibromyalgia Impact Questionnaire (FIQR) on day 26 in the LDN + tDCS group ($p = 0.005$), particularly in the function domain, however, baseline scores were heterogeneous. Symptom domain scores were more homogeneous among the groups, with all showing improvement by day 26 ($p < 0.05$). For the Pain Catastrophizing Scale, only the LDN + tDCS and placebo + sham tDCS groups showed reductions in total scores and the Hopelessness domain ($p = 0.027$ and 0.032 , respectively). Baseline scores for the Beck Depression Inventory II (BDI-II) were heterogeneous among the groups.

Another study investigating the effects of naltrexone in patients with fibromyalgia was conducted by Bested et al. (2023) [22]. This double-blind crossover trial involved 52 patients and found no significant differences between the naltrexone 4.5 mg and placebo groups across various outcome measures. Summed pain intensity ratings showed no difference between the groups ($p = 0.24$). Similarly, quantitative sensory testing assessments, including hyperalgesia area ($p = 0.83$), allodynia ($p = 0.65$), and pressure pain threshold ($p = 0.75$), revealed no significant differences between the groups. The study also evaluated the Pain Catastrophizing Scale scores and found no difference between the groups. Baseline and outcome scores for the FIQR were obtained for both the LDN and placebo groups ($n = 50$), with the difference between the two groups being -1.65 (IQR 18.55). The Wilcoxon signed-rank test did not indicate any significant difference between LDN and placebo (effect size = 0.15, CI = -6.72 to 2.15 ; $p = 0.30$). Similarly, the random effects model showed no significant difference between LDN and placebo (conditional mean difference 22.50, $p = 0.34$). Furthermore, the Hospital Anxiety and Depression Scale showed no difference in the depression domain between the groups ($p = 0.32$). However, an improvement was noted in the anxiety domain in the LDN group ($p = 0.04$).

3.3.4. Arthritis

In the double-blind crossover trial conducted by Beaudette-Zlatanova et al. (2023) [21], involving 23 patients diagnosed with osteoarthritis, peripheral spondylarthritis and rheumatoid arthritis, the baseline

VAS score was recorded at 5.9 ± 1.2 . Among the participants, 17 had osteoarthritis (14 knee, 1 hip, 1 knee and hip, 1 knee and shoulder), while six had inflammatory arthritis. The reduction in pain interference or average pain severity did not differ significantly between the use of Naltrexone and placebo ($p = 0.22$). Secondary measures differed nominally between Naltrexone and placebo: painDETECT ($p = 0.02$). However, these findings were likely spurious, given the numerous secondary measures tested simultaneously. Total scores on the BDI-II differed significantly from the baseline and the placebo group ($p = 0.04$). However, it's important to note that numerous secondary measures were tested simultaneously, which may have influenced these findings.

3.3.5. Chronic pain in HIV-positive patients

In the double-blind trial conducted by Tsui et al. (2024) [23], which included 45 HIV-positive alcoholic patients experiencing chronic pain, three groups were assigned: naltrexone 4.5 mg, placebo and gabapentin 300 mg up to 1800 mg. Over the 8-week follow-up period, no clinically important differences in pain measures were observed among the groups. Baseline pain severity scores on the Brief Pain Inventory (BPI) were similar across all groups, with gabapentin at 3.1 ± 1.3 , naltrexone at 3.2 ± 1.4 , and placebo at 3.3 ± 1.5 . By week 8, all groups exhibited reductions in pain severity, with no statistically significant differences observed between gabapentin and either naltrexone ($p = 0.73$) or placebo ($p = 0.55$). No statistically significant differences were found between the groups in cold pressor test measures, including pain threshold and tolerance to cold.

3.3.6. Multiple sclerosis

In the double-blind parallel controlled crossover trial conducted by Sharafaddinzadeh et al. (2010) [17], involving 96 patients with multiple sclerosis, participants were administered either naltrexone 4.5 mg or placebo for 8 weeks in each arm, with a 1-week washout period. The MSQoL-54 scores at baseline showed a mental health score of 56.06 ± 19.18 , physical health score of 52.16 ± 18.21 and health perception score of 49.01 ± 18.84 . At week 8, there were no significant differences observed in these scores between the two groups, with mental health scores at 58.04 ± 20.27 , physical health scores at 50.05 ± 18.98 and health perception scores at 51.46 ± 20 . At week 17, no statistically significant differences were found in these scores between the groups either. The EDSS scores at baseline averaged 3.18 ± 1.87 , with no difference observed between the groups at the end of the study period ($p = 0.92$).

3.4. Adverse effects

The adverse effects were classified as mild or moderate, without significantly interfering with the patients' daily activities. Among the most common symptoms were fatigue (12 cases; 2.96%), headache (ten cases; 2.46%), dizziness (nine cases; 2.21%) and nausea (nine cases; 2.21%). Although two authors did not specify the frequency of adverse effects in the studied population, they highlighted that headache, nausea, epigastric pain and mood changes were reported as more frequent [17,20].

Additionally, stomach ache (four cases), diarrhea (four cases), constipation (three cases) and mild irritability (one case) were observed. Other less common adverse effects include burning sensation on the scalp (one case), insomnia (one case), tremors (one case), daytime somnolence (one case), urinary tract infection (one case), swelling of the tongue and lips (one case), dermatitis (one case) and fall with an ankle injury (one case). In another mentioned study [18], there was a report of a mild adverse effect not specified by the authors. These findings can be seen in Table 2.

3.5. Risk of bias of included studies

The Risk of bias of included studies is summarized in Figures 2 & 3.

3.5.1. Randomization process

All studies were classified as having a low risk of randomization bias due to appropriate randomization procedures [17–23].

3.5.2. Intervention

In six of the included studies, there was a low risk of bias stemming from intervention deviations [17–20,22,23].

However, Beaudette-Zlatanova et al. (2023) [21] were classified with a high risk of bias because the authors failed to recruit a sufficient number of patients as per the pre-calculated sample size, potentially leading to type 1 or type 2 errors in the study interpretation. This also imposed limitations on the generalizability of the results.

3.5.3. Outcome

We classified six articles as having a low risk of bias in outcome measurement, aligning with items three and four of RoB 2 [17,19–23].

However, Brewer et al. (2018) [18] were rated as having a high risk of bias in item three due to the absence of comparison between the naltrexone group and the placebo. Item four was evaluated as having a low risk of bias.

3.5.4. Selective reports

We evaluated five studies as appropriate, categorized as having a low risk of bias [17,19,20,22,23].

However, Brewer et al. (2018) [18] also received a “some concerns” rating for selectively analyzing key outcomes, omitting comparison with the placebo group. Beaudette-Zlatanova et al. (2023) [21] were classified as high risk of bias because they conducted multiple outcome analyses to compensate for the small number of included patients.

4. Discussion

In this review, our objective was to evaluate the use of naltrexone for the treatment of chronic pain. Our article synthesizes existing evidence, providing a comprehensive analysis of 406 patients across diverse clinical conditions with varied pain characteristics.

Naltrexone, traditionally used in high doses for the treatment of opioid dependence, blocks opioid receptors. However, at low doses (4.5 mg or less), it appears to exert a paradoxical effect. According to Patten et al. (2018) [24], LDN can reduce inflammation by inhibiting the activation of microglia, the immune cells of the central nervous system, which, when activated, contribute to neuropathic pain and neuroinflammation. This anti-inflammatory effect is particularly beneficial in chronic pain conditions where inflammation plays a significant role.

Furthermore, Younger et al. (2014) [25] highlight that LDN has the potential to increase the production of endorphins, natural neurotransmitters that relieve pain and improve mood. This finding is particularly relevant for improving the quality of life in patients with fibromyalgia. Toljan and Vrooman (2018) [26], corroborate this hypothesis by reporting a significant increase in endorphin levels following LDN treatment, in patients suffering from chronic pain and autoimmune conditions. Their study demonstrated that LDN's modulation of the opioid growth factor receptor pathway results in elevated endorphin production, contributing to its analgesic and anti-inflammatory effects. However, in a 7-day pilot study by Hamann and Sloan (2007) [27], which evaluated ultra-low doses of naltrexone (10 and 100 μ g) in patients with chronic non-malignant pain, no significant differences were found between the naltrexone and placebo groups. In the studies we reviewed, the LDN doses typically used were around 4.5 mg.

Analysis of pain relief outcomes from the studies reviewed reveals limited evidence for the efficacy of LDN in managing chronic pain. Despite differing methodologies and patient groups, most studies found no significant difference in pain reduction between LDN and placebo or other treatments [17,18,21]. found significant pain

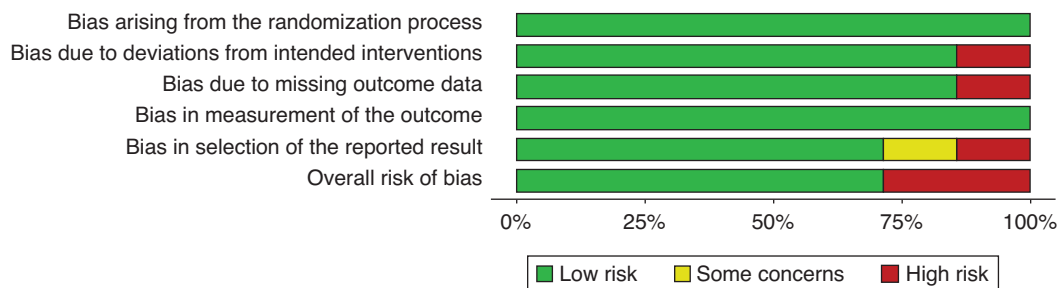


Figure 2. Summary plot of bias analysis.

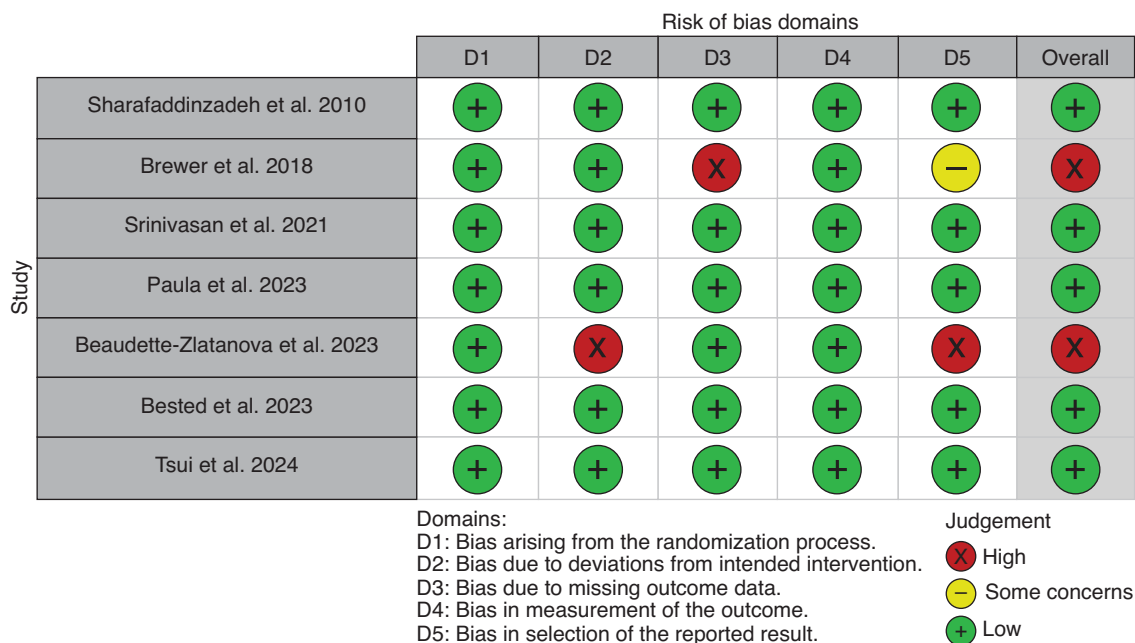


Figure 3. Traffic light plot of bias analysis.

reduction in fibromyalgia patients using a combination of naltrexone and tDCS, suggesting a potential synergistic effect. However, this finding is based on a small sample size, and the observed benefits might be due to tDCS. Moreover, sham-tDCS often showed similar or better results compared with real tDCS, complicating the assessment of its effectiveness. In contrast, Bested et al. (2023) [22] found no significant difference in pain relief between fibromyalgia patients treated with LDN and those receiving a placebo.

In a noninferiority study, Srinivasan et al. (2021) [19] found that both naltrexone and amitriptyline significantly reduced pain in patients with diabetic neuropathy. However, there were no notable differences between the two treatments, suggesting that naltrexone may be as effective as, but not necessarily superior to, traditional pain management options. In contrast, Tsui et al. (2024) [23] observed no significant differences in pain relief between naltrexone, gabapentin, and placebo in HIV-positive patients with chronic pain. These varying

results highlight the need for more focused research to identify specific conditions or patient populations that might benefit most from naltrexone.

Comparing the findings of this review with the existing literature on the use of LDN for other chronic pain conditions, there appears to be consistency in the evidence pointing to varied outcomes. Studies in conditions such as fibromyalgia and neuropathic pain have shown that while some patients report significant pain relief with LDN, overall results often do not demonstrate statistically significant differences compared with placebo [28,29]. A systematic review on LDN use in fibromyalgia reported mixed results, with some trials showing reduced pain intensity and improved quality of life, while others did not find significant benefits [28]. These results suggest that, although LDN has potential as an adjuvant treatment in fibromyalgia, its effectiveness appears to be low, however, the heterogeneity of results and the small group of patients included highlights the need for further investigation.

The impact of LDN on quality of life and function in chronic pain patients varies across different conditions. Studies included in this review, such as those on multiple sclerosis and fibromyalgia, showed mixed results. Sharafaddinzadeh et al. (2010) [17] found no significant improvements in MSQoL-54 scores or the EDSS with LDN treatment, indicating that LDN did not markedly enhance mental or physical health or health perception. Similarly, the EDSS scores remained unchanged, suggesting that LDN had no significant effect on the overall disability status of the patients. Studies on fibromyalgia by Paula et al. (2023) [20] and Bested et al. (2023) [22] reported no significant differences in quality of life or function between LDN and placebo groups, as measured by the Fibromyalgia Impact Questionnaire and the BDI-II. In contrast, Brewer et al. (2018) [18] observed that LDN responders showed less disability and improved emotional role functioning on the SF-36 subscale compared with nonresponders, in patients with Gulf War illness.

The findings from this review are consistent with the broader literature on LDN for chronic pain, highlighting variability in treatment outcomes across different conditions. Systematic reviews on LDN for fibromyalgia have shown varying responses among patients, with some experiencing significant pain relief and improved quality of life, while others do not benefit compared with placebo [30]. Additionally, recent studies address the quality of life in patients with various chronic pain conditions, refractory depression, and COVID-19 associated with chronic fatigue, where the use of LDN could be beneficial [24,31–33]. Chronic pain is often linked with both depression and post-viral conditions like long COVID-19, exacerbating the overall burden on patients. Emerging evidence indicates that LDN may help alleviate depressive symptoms, especially in patients who do not respond well to traditional treatments, many of whom also experience chronic pain [33]. Regarding COVID-19, recent studies are exploring the potential of LDN to improve the quality of life in patients suffering from post-viral fatigue and “long COVID” symptoms, which are frequently accompanied by chronic pain [32].

Adverse effects of LDN in chronic pain conditions are typically mild to moderate, as evidenced by the studies included in this review. This aligns with findings in the broader literature, where LDN is generally well-tolerated. For instance, a review by Patten et al. (2018) [24] on LDN in fibromyalgia patients found that the most common side effects were similar to those reported here, including headache, nausea, and fatigue, with a low incidence of severe adverse effects. Furthermore, a study by Cree et al. (2010) [34] on LDN in multiple sclerosis patients also reported mild adverse effects, predominantly gastroin-

testinal issues and headaches, further supporting the safety profile of LDN.

The minimal adverse effects observed with LDN, when compared with other pharmacological treatments for chronic pain, such as opioids or antidepressants like amitriptyline, which are associated with a higher risk of severe side effects, including sedation, weight gain and potential for dependency [17–23]. This favorable safety profile makes LDN a promising alternative for the long-term management of chronic pain. Additionally, the low rate of significant adverse effects observed in LDN studies may encourage further research and clinical trials to solidify its role in pain management, particularly in patients who are sensitive to conventional medications.

4.1. Study limitations

This study encountered several limitations that warrant acknowledgment. First, the number of included studies was small, each with a limited number of patient population, which impact the generalizability of the findings. The maximum follow-up duration across studies was relatively short (7 months), restricting the evaluation of long-term chronic use of LDN. Furthermore, the substantial heterogeneity among the diseases precluded the conduct of a meta-analysis. Notably, the study by Beaudette-Zlatanova et al. (2023) [21], which focused on patients with inflammatory nociceptive pain, faced significant limitations due to its inclusion of a small number of participants, falling below the required sample size, thus impacting the external validity of the findings.

5. Conclusion

In conclusion, this review indicates that LDN alone is not effective for managing chronic pain. While some studies noted minor improvements in pain, quality of life and functional outcomes, most did not find significant benefits. Adverse effects were mild to moderate, suggesting a favorable safety profile. However, the lack of consistent efficacy warrants caution in recommending LDN for chronic pain. Further well-designed studies are needed to confirm these findings.

Article highlights

- The review encompassed 421 patients across eight randomized clinical trials, addressing various chronic pain conditions such as fibromyalgia, multiple sclerosis, Gulf War Illness, diabetic neuropathy, arthritis and chronic pain in HIV-positive patients.
- Low-dose naltrexone (LDN) doses ranged from 2 to 4.5 mg daily across the studies.
- Results indicated that LDN may effectively reduce chronic pain and improve quality of life in several chronic pain conditions.
- Some studies reported significant pain reduction and quality of life improvements with LDN compared with placebo.

- Other studies found no significant differences between LDN and placebo or other treatments.
- Mild to moderate adverse effects of LDN were reported, including headache and fatigue.
- The studies reviewed had varying methodologies and sample sizes, indicating the need for further research with larger and more standardized trials.
- The review emphasises the potential of LDN as a treatment for chronic pain but highlights the necessity for more consistent and robust evidence.

Financial disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

ORCID

Victor Rassi-Mariani  <https://orcid.org/0009-0007-5732-4988>

Eduardo Silva Reis Barreto  <https://orcid.org/0009-0008-4688-8857>

César Romero Antunes Júnior  <https://orcid.org/0000-0003-1701-5279>

Vinicius Borges Alencar  <https://orcid.org/0009-0009-9655-6479>

Liliane Elze Falcão Lins-Kusterer  <https://orcid.org/0000-0003-3736-0002>

Liana Maria Torres de Araujo Azi  <https://orcid.org/0000-0002-9466-6537>

Durval Campos Kraychete  <https://orcid.org/0000-0001-6561-6584>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

- Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019;160:53–59. doi:10.1097/j.pain.0000000000001365
- **Presents important concepts about pain.**
- Kanematsu J dos S, Atanazio B, Cunha BF, Caetano LP, Arada DMY. Impacto da dor na qualidade de vida do paciente com dor crônica. *Rev Med*. 2022;101:1–8. doi:10.11606/issn.1679-9836.v101i3e-192586
- Barr A, Moore K, Flegge LG, Atsaphanthong E, Kirby KE, Craner JR. Predictors of sexual satisfaction among patients with chronic pain. *Front Pain Res*. 2024;5:1–9. doi:10.3389/fpain.2024.1375546
- Cashin AG, Wand BM, O'Connell NE, et al. Pharmacological treatments for low back pain in adults: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2023;2023:1–51. doi:10.1002/14651858.CD013815.pub2
- **Presents important concepts about pain treatment.**
- Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2018;3:1–91. doi:10.1002/14651858.CD012182.pub2
- Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;8:1–20. doi:10.1002/14651858.CD012539.pub2
- Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017;8:1–54. doi:10.1002/14651858.CD012537.pub2
- Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. 2021;397:2082–2097. doi:10.1016/S0140-6736(21)00393-7
- Zangiabadian M, Golmohammadi S, Nejadghaderi SA, Zahmatkesh MM, Nasiri MJ, Sadeghian M. The effects of naltrexone on retention in treatment and being opioid-free in opioid-dependent people: a systematic review and meta-analysis. *Front Psychiatry*. 2022;13:1–11. doi:10.3389/fpsy.2022.1003257
- Ghai B, Bansal D, Hota D, Shah CS. Off-label, low-dose naltrexone for refractory chronic low back pain. *Pain Med*. 2014;15:883–884. doi:10.1111/pme.12345
- Patten DK, Schultz BG, Berlau DJ. The Safety and efficacy of low-dose naltrexone in the management of chronic pain and inflammation in multiple sclerosis, fibromyalgia, Crohn's disease, and other chronic pain disorders. *Pharmacother J Hum Pharmacol Drug Ther*. 2018;38:382–389. doi:10.1002/phar.2086
- Oaks Z, Stage A, Middleton B, Faraone S, Johnson B. Clinical utility of the cold pressor test: evaluation of pain patients, treatment of opioid-induced hyperalgesia and fibromyalgia with low dose naltrexone. *Discov Med*. 2018;26:197–206.
- Phillips V, Barker E. Systematic reviews: structure, form and content. *J Perioper Pract*. 2021;31:349–353. doi:10.1177/1750458921994693
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Brit Med J*. 2021;n71. doi:10.1136/bmj.n71
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210. doi:10.1186/s13643-016-0384-4
- Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Brit Med J*. 2011;343:d5928–d5928. doi:10.1136/bmj.d5928
- Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, Majdinasab N, Shalbafan B. The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. *Mult Scler J*. 2010;16:964–969. doi:10.1177/1352458510366857

18. Brewer KL, Mainhart A, Meggs WJ. Double-blinded placebo-controlled cross-over pilot trial of naltrexone to treat Gulf War Illness. *Fatigue Biomed Heal Behav*. 2018;6:132–140. doi:[10.1080/21641846.2018.1477034](https://doi.org/10.1080/21641846.2018.1477034)
19. Srinivasan A, Dutta P, Bansal D, Chakrabarti A, Bhansali AK, Hota D. Efficacy and safety of low-dose naltrexone in painful diabetic neuropathy: a randomized, double-blind, active-control, crossover clinical trial. *J Diabetes*. 2021;13:770–778. doi:[10.1111/1753-0407.13202](https://doi.org/10.1111/1753-0407.13202)
20. de Paula TMH, Castro MS, Medeiros LF, et al. Association of low-dose naltrexone and transcranial direct current stimulation in fibromyalgia: a randomized, double-blinded, parallel clinical trial. *Brazilian J Anesthesiol (English Ed)*. 2023;73:409–417. doi:[10.1016/j.bjane.2022.08.003](https://doi.org/10.1016/j.bjane.2022.08.003)
21. Beaudette-Zlatanova B, Lew RA, Otis JD, et al. Pilot study of low-dose naltrexone for the treatment of chronic pain due to arthritis: a randomized, double-blind, placebo-controlled, crossover clinical trial. *Clin Ther*. 2023;45:468–477. doi:[10.1016/j.clinthera.2023.03.013](https://doi.org/10.1016/j.clinthera.2023.03.013)
22. Bested K, Jensen LM, Andresen T, et al. Low-dose naltrexone for treatment of pain in patients with fibromyalgia: a randomized, double-blind, placebo-controlled, crossover study. *Pain Rep*. 2023;8:e1080. doi:[10.1097/PR9.00000000000001080](https://doi.org/10.1097/PR9.00000000000001080)
23. Tsui JI, Rossi SL, Cheng DM, et al. Pilot RCT comparing low-dose naltrexone, gabapentin and placebo to reduce pain among people with HIV with alcohol problems. Nyirenda M, editor. *PLOS ONE*. 2024;19:e0297948. doi:[10.1371/journal.pone.0297948](https://doi.org/10.1371/journal.pone.0297948)
24. Patten DK, Schultz BG, Berlau DJ. The safety and efficacy of low-dose naltrexone in the management of chronic pain and inflammation in multiple sclerosis, fibromyalgia, crohn's disease, and other chronic pain disorders. *Pharmacotherapy*. 2018;38:382–389. doi:[10.1002/phar.2086](https://doi.org/10.1002/phar.2086)
25. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol*. 2014;33:451–459. doi:[10.1007/s10067-014-2517-2](https://doi.org/10.1007/s10067-014-2517-2)
26. Toljan K, Vrooman B. Low-dose naltrexone (LDN)—review of therapeutic utilization. *Med Sci*. 2018;6:82. doi:[10.3390/medsci6040082](https://doi.org/10.3390/medsci6040082)
27. Hamann S, Sloan P. Oral naltrexone to enhance analgesia in patients receiving continuous intrathecal morphine for chronic pain: a randomized, double-blind, prospective pilot study. *J Opioid Manag*. 2007;3:137–144. doi:[10.5055/jom.2007.0051](https://doi.org/10.5055/jom.2007.0051)
28. Aitcheson N, Lin Z, Tynan K. Low-dose naltrexone in the treatment of fibromyalgia: a systematic review and narrative synthesis. *Aust J Gen Pract*. 2023;52:189–195. doi:[10.31128/AJGP-09-22-6564](https://doi.org/10.31128/AJGP-09-22-6564)
- **Review of the use of LDN in fibromyalgia**
29. McKenzie-Brown AM, Boorman DW, Ibanez KR, Agwu E, Singh V. Low-dose naltrexone (LDN) for chronic pain at a single institution: a case series. *J Pain Res*. 2023;16:1993–1998. doi:[10.2147/JPR.S389957](https://doi.org/10.2147/JPR.S389957)
30. Partridge S, Quadt L, Bolton M, et al. A systematic literature review on the clinical efficacy of low dose naltrexone and its effect on putative pathophysiological mechanisms among patients diagnosed with fibromyalgia. *Heliyon*. 2023;9:e15638. doi:[10.1016/j.heliyon.2023.e15638](https://doi.org/10.1016/j.heliyon.2023.e15638)
31. Rupp A, Young E, Chadwick AL. Low-dose naltrexone's utility for non-cancer centralized pain conditions: a scoping review. *Pain Med*. 2023;24:1270–1281. doi:[10.1093/pm/pnad074](https://doi.org/10.1093/pm/pnad074)
32. Isman A, Nyquist A, Strecker B, et al. Low-dose naltrexone and NAD+ for the treatment of patients with persistent fatigue symptoms after COVID-19. *Brain Behav Immun*. 2024;36:100733. doi:[10.1016/j.bbih.2024.100733](https://doi.org/10.1016/j.bbih.2024.100733)
33. Plank JR, Glover SC, Moloney BD, et al. A randomized, double-blind, placebo-controlled, hybrid parallel-arm study of low-dose naltrexone as an adjunctive anti-inflammatory treatment for major depressive disorder. *Trials*. 2022;23:822. doi:[10.1186/s13063-022-06738-3](https://doi.org/10.1186/s13063-022-06738-3)
34. Cree BAC, Kornyeveva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol*. 2010;68:145–150. doi:[10.1002/ana.22006](https://doi.org/10.1002/ana.22006)