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Efficacy of Low Dose Naltrexone on Pain Reduction in Chronic Pain Syndromes: A Meta Analysis

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Abstract

Chronic pain is a multifaceted debilitating experience often associated with significant physical and emotional burden. Low dose naltrexone (LDN) has gained attention in recent years for its potential utility in the management of fibromyalgia, irritable bowel syndrome, multiple sclerosis, and painful diabetic neuropathy. LDN's analgesic effects have been associated with its ability to increase the production of endorphins while reducing the production of tumor necrosis factor-alpha, interleukin-6, reactive oxygen species and nitric oxide. This meta-analysis aims to systematically review and synthesize the available evidence on efficacy of LDN as an analgesic in pain syndromes, with a focus on chronic (neuro) inflammatory diseases. The goal is to provide clinicians with a more comprehensive estimate of the effectiveness of LDN as a non-opioid option for managing chronic pain and guide future research in the area. Thirteen randomized control trials, published from 1990 to 2022, were selected for the analysis that satisfied inclusion criteria. The overall effects in these studies were calculated using the standardized mean difference (SMD) between the LDN and placebo groups. We found an overall SMD of −10.77 (95% CI: −13.96 to −7.58) with a p-value of 0.002. This indicated that the LDN group experienced a statistically significant reduction in pain compared to placebo. This meta-analysis provides evidence for the potential efficacy of low dose naltrexone in reducing pain and enhancing analgesia in various pain syndromes. LDN may be a useful treatment option for patients suffering from chronic pain, particularly with fibromyalgia, multiple sclerosis, or diabetic neuropathy. However, further research is needed to confirm the efficacy and safety of low dose naltrexone for chronic pain conditions, especially with larger sample sizes, standardized dosing regimens and treatment durations.

Keywords

Pain Management, LDN, Pain, Anesthesiology, Neurology, Low Dose Naltrexone, Chronic Pain

1. Introduction

Pain is a complex and often debilitating experience that can have a significant impact on an individual's quality of life. Chronic pain, which is defined as pain that persists for more than 12 weeks, affects approximately 20% of the adult population worldwide and is associated with significant physical, emotional, and financial burdens [1]. Conventional treatments for chronic pain often include the use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and other analgesics. However, these medications can be associated with significant side effects and may not always provide adequate relief for some patients [2]. Low-dose naltrexone (LDN) is a medication that has gained increasing attention in recent years for its potential utility in the management of chronic pain. Naltrexone was developed in the early 1960s as an opioid antagonist and is currently FDA approved for the indication of opioid use disorder and alcoholism. When used to combat these conditions, it is prescribed in doses of 50 mg/day - 100 mg/day. In low doses, particularly 1 mg/day - 5 mg/day, naltrexone has been found to have anti-inflammatory and immunomodulatory effects, which may explain its efficacy in the treatment of chronic pain [3]. LDN has been shown to increase the production of endorphins, which are natural painkillers in the body. It also reduces the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thereby reducing inflammation and pain [4].

Low dose naltrexone (LDN) has been utilized in chronic (neuro)inflammatory diseases such as fibromyalgia, irritable bowel syndrome, painful diabetic neuropathy, and multiple sclerosis in attempts to study its efficacy. Fibromyalgia is characterized by widespread musculoskeletal pain, hyperalgesia, fatigue, sleep disturbance, and cognitive disruption. Irritable bowel syndrome and painful diabetic neuropathy are also widespread chronic pain conditions for which effective treatment modalities are limited [5]. Additionally, the neuroinflammatory disorder of multiple sclerosis has limited options for oral analgesia to target pain management. Although, chronic opioids are sometimes used to manage pain in these conditions, many patients and physicians are reluctant to rely on them. Currently, there are only a few non-opioid options which can effectively alleviate symptoms [1].

LDN's analgesic effects may be attributed to its immunomodulatory properties. In animal studies, LDN has demonstrated a capacity to decrease pro-inflammatory cytokines while increasing anti-inflammatory cytokines release. Furthermore, LDN has been found to reduce the production of reactive oxygen spe-

cies and nitric oxide, both implicated in the development and persistence of chronic pain. Its efficacy in chronic pain management may extend to enhancing the analgesic effects of other medications. For instance, studies have revealed LDN's ability to augment the pain-relieving properties of opioids, leading to lower opioid dosages and diminished side effects. Moreover, LDN has demonstrated the capability to enhance the analgesic effects of non-opioid medications like gabapentin, particularly in individuals with neuropathic pain [6]. Generally well-tolerated, LDN presents minimal side effects, including transient symptoms such as insomnia, vivid dreams, headaches, and gastrointestinal discomfort, typically resolving within a few days of treatment initiation [7]. It is important to note that LDN is contraindicated in patients with acute hepatitis or liver failure [8]. Despite its potential benefits, LDN has limitations as it currently lacks approval from the United States Food and Drug Administration (FDA) for the treatment of chronic pain, limiting its availability and insurance coverage.

The aim of this meta-analysis is to systematically review and synthesize the available evidence on the utility and efficacy of low dose naltrexone (LDN) in reducing pain and enhancing analgesia in various chronic pain disease processes. Specifically, the meta-analysis aims to evaluate the effectiveness of LDN in improving pain outcomes in chronic neuroinflammatory diseases such as fibromyalgia, irritable bowel syndrome, painful diabetic neuropathy, and multiple sclerosis. The meta-analysis also examined the safety and tolerability of LDN treatment in these populations and identifies any potential sources of heterogeneity or inconsistency in the results across studies. This meta-analysis is to provide clinicians (and patients) with a more comprehensive and accurate estimate of the effectiveness of LDN as a non-opioid option for managing chronic pain and guide future research direction in this area.

2. Materials and Methods

2.1. Search Strategy

A search was conducted by performing an electronic search through MEDLINE, Embase, Cochrane Library and PubMed using the Cochrane Handbook for Systematic Reviews and Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards, which were adhered to during the conduction of this meta-analysis [9]. A twenty-year time cap was placed on the studies that would be considered during the search, with concentration on studies published between 1990 and 2022. This deliberation was made to get a closer perspective on the most recent and currently applicable naltrexone treatment regimens for pain management. The search made use of identifying keywords coupled with Medical Subject Headings (MeSH). MeSH and the keywords were then expanded by incorporating Boolean operators, truncation techniques, and field tags to create preliminary queries for the initial search. These queries were then cumulated through building blocks technique to create a single com-

prehensive search query. The keywords and MeSH terms used during these search queries included "low dose naltrexone", "chronic pain syndrome", "fibromyalgia", and "multiple sclerosis". All the identified research studies were published materials in different journals. Studies were screened and selected according to following inclusion and exclusion criteria.

2.2. Inclusion Criteria

- Studies must be published in English.
- Studies must be peer-reviewed.
- Studies must be conducted on human subjects.
- Studies must be original research articles or randomized controlled trials.
- Studies must have been conducted on adults aged 18 years or older.
- Studies must have investigated the use of low dose naltrexone on pain management.
- Studies must have included a comparison group that received a placebo or other pain management modality.
- Studies must have reported quantitative data on pain intensity or other pain-related outcomes.

2.3. Exclusion Criteria

- Studies that are not original research articles or randomized controlled trials.
- Studies that are not conducted on human subjects.
- Studies that are published in languages other than English.
- Studies that do not investigate the use of low dose naltrexone on pain management.
- Studies that do not include a comparison group or use a non-placebo comparator.
- Studies that do not report quantitative data on pain intensity or other pain related outcomes.
- Studies that do not report sufficient data to calculate effect sizes.

2.4. Data Extraction

Data was extracted manually by two investigators working independently. The data extraction process excluded ineligible studies if they did not completely fit the inclusion criteria, met one or more exclusion criteria, or where shows to be repeat studies in the search process. Extracted data was inputted into a standardized statistical analysis machine. Analysis was concentrated on the primary and secondary outcomes of the studies. Data was collected with study characteristics and the research's intended outcomes. Other research outcomes of interest that could inform the analysis of the results were also collected. These included the population age ranges, conditions studied, interventions, study designs, sample sizes, durations. The two collected data sets were then cross-checked to ensure accuracy and remove any existing discrepancies.

2.5. Statistical Analysis and Data Synthesis

The statistical analysis process was conducted on Review Manager version 5.4 (RevMan 5.4) using the standard methods of the Cochrane Neonatal Review Group. The effectiveness of the treatment effects was estimated as mean difference (MD) and risk ratio (RR) for the dichotomous outcomes. A 95% confidence interval (CI) was used to assess the continuous outcomes. Generated forest plots were assessed to inspect the included studies for heterogeneity. An I2 statistic quantified the heterogeneity value. Standard methods of the Cochrane Neonatal Review Group were used to report on heterogeneity as follows: a value below 25% indicated no heterogeneity, a value between 25% and 49% indicates low heterogeneity, a value between 50% and 74% indicates moderate heterogeneity, and anything above 75% was considered high heterogeneity. Publication bias was assessed using funnel plots. Statistical significance was set at $p < 0.05$ for all analyses.

2.6. Quality Assessment

The Cochrane risk-of-bias tool was adapted for the outcome measures in this review, highlighting eight areas of trial conduct and reporting. Each domain's bias risk was analyzed and the first three were additionally assessed for concerns about applicability. Bias risk and applicability were rated as "low", "high", or "unclear" respectively.

3. Results

3.1. Electronic Search Results

3275 studies were found using the basic search method. After removal of duplicates, the remaining studies were checked for abstracts and titles. This led to an additional 3251 items being removed as they contained irrelevant references that did not fully encompass the use of low dose naltrexone's utility in pain score reduction. The full texts of the remaining 24 papers were examined thoroughly. As 11 studies did not match the eligibility requirements, they were further excluded. Finally, this meta-analysis contained 13 studies that satisfied all inclusion criteria. **Figure 1** displays the search approach and study selection.

3.2. Study Characteristics

The main characteristics of the studies are presented in **Table 1**. Many of the studies were carried out in the United States of America (n = 8), two studies were conducted in Iran, one from Italy, one from Sweden and another from India. Srinivasan *et al.* (2021) conducted a study with 38 participants suffering from painful diabetic neuropathy. The study found that low dose naltrexone reduced pain severity and improved quality of life for these patients [10]. Younger *et al.* (2013) reported about populations suffering from fibromyalgia; the study found that low dose naltrexone reduced pain severity and improved mood for these patients [11]. Cree *et al.* (2010) conducted a study in the United States with

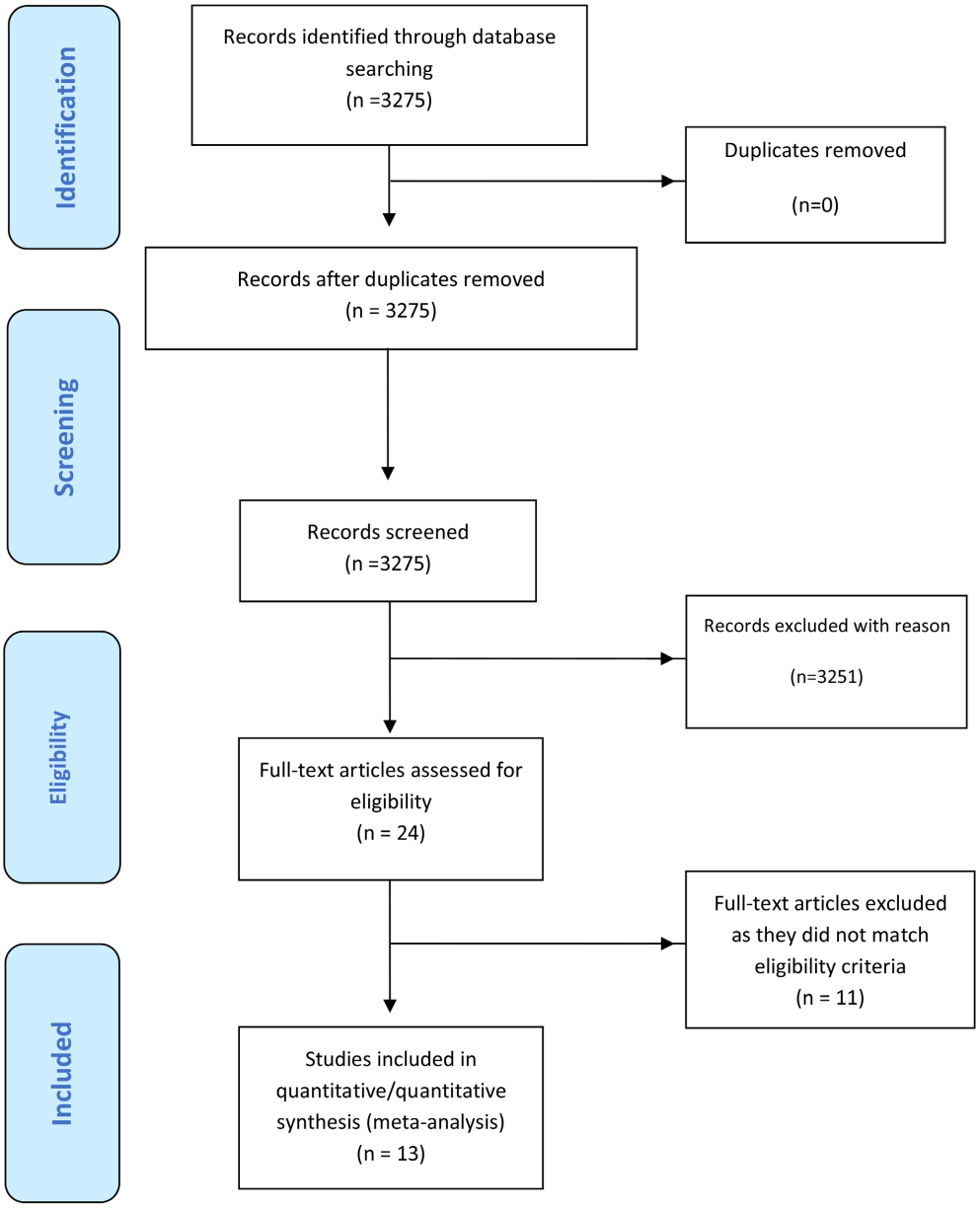

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Figure 1. PRISMA flow chart.

40 participants suffering from multiple sclerosis. The study found that low dose naltrexone did not have a significant effect on disease activity or quality of life in this population [12]. Sharafaddinzadeh *et al.* (2010) also included 96 participants suffering from multiple sclerosis. The study found that low dose naltrexone reduced disease activity and improved quality of life for these patients [13]. Specifics of the remaining nine studies, including chronic condition studied, duration of treatment and subsequent outcomes measured are detailed in **Table 1**.

Table 1. Characteristics of included studies.

Study ID	Condition	Intervention	Study Design	Sample Size	Age Range	Gender	Duration	Outcome Measures
Srinivasan *et al.* (2021)	Painful diabetic neuropathy	low dose naltrexone	Randomized, double-blind, active-control, crossover	67	30 - 70	16 M, 20 F	16 weeks	Pain scores
Pontén *et al.* (2020)	Pain conditioning	naltrexone	Double-blind, placebo-controlled experimental trial	24	18 - 50	14 M, 10 F	2 days	Pain ratings
Bruun *et al.* (2020)	Fibromyalgia	low dose naltrexone	Single-blinded clinical trial	27	18 - 60	27 F	3 weeks	PGI-I score, Pain scores
Metyas *et al.* (2018)	Fibromyalgia	low dose naltrexone	Prospective pilot study	25	34 - 62	24 F, 1 M	8 weeks	Pain scores, quality of life
Younger *et al.* (2013)	Fibromyalgia	low dose naltrexone	Randomized, double-blind, placebo-controlled, counterbalanced, crossover	31	18 - 70	2 M, 29 F	16 weeks	Pain scores
Cree *et al.* (2010)	Multiple sclerosis	low dose naltrexone	Randomized, double-blind, placebo-controlled	80	18 - 75	30 M, 50 F	6 months	Quality of life
Sharafaddin zadeh *et al.* (2010)	Multiple sclerosis	low dose naltrexone	Randomized, double-blind, placebo-controlled	40	20 - 50	22 M, 18 F	2 months	Quality of life
Younger *et al.* (2009)	Fibromyalgia	low dose naltrexone	Pilot study	10	30 - 54	10 F	8 weeks	Pain scores, quality of life
Hamann and Sloan (2007)	Chronic pain	low dose naltrexone	Randomized, double-blind, prospective pilot	20	23 - 65	16 M, 4 F	12 weeks	Pain scores
Kariv *et al.* (2006)	Irritable bowel syndrome	low dose naltrexone	Pilot study	11	18 - 60	7 M, 4 F	12 weeks	Quality of life
Dieckmann *et al.* (2022)	Neuropathic corneal pain	low dose naltrexone	Retrospective cohort	29	60 - 65	29 M/F	4 - 12 weeks	Pain scores
Gironi *et al.* (2008)	Primary progressive multiple sclerosis	low dose naltrexone	Pilot study	40	25 - 50	24 M, 16 F	6 months	Quality of life
Webster *et al.* (2005)	Low back pain	Oxytrex	Randomized, double-blind, placebo-controlled	40	20 - 60	20 M, 20 F	4 weeks	Pain scores, physical dependence

The use of low dose naltrexone as a single therapy or in combination with other pain management modalities appears to be promising in reducing patient pain burden in fibromyalgia, multiple sclerosis, and diabetic neuropathy pain syndromes. The mean scores for pain reduction in the low dose naltrexone group ranged from 3.5 to 48.6, with standard deviations ranging from 2.6 to 23.1. In comparison, the mean scores for the placebo group ranged from 4 to

55.9, with standard deviations ranging from 15.4 to 29.8. Several studies reported statistically significant differences between the low dose naltrexone group and the placebo group. For example, Cree *et al.* (2010) reported a mean pain reduction of 35 in the low dose naltrexone group compared to 51 in the placebo group, with a p-value of <0.001 [12]. Similarly, Dieckmann *et al.* (2021) reported a mean pain reduction of 34 in the low dose naltrexone group compared to 40 in the placebo group, with a p-value of 0.047 [14]. However, it is important to note that some studies did not report statistically significant differences between the low dose naltrexone group and the placebo group. For instance, Hamann *et al.* (2007) reported a mean pain reduction of 4.8 in the low dose naltrexone group compared to 9.6 in the placebo group, with a p-value of 0.07 [15]. The study was conducted in the United States with 20 participants suffering from chronic pain. It found that low dose naltrexone reduced pain severity and improved quality of life for these patients, but due to the small sample size used, it was not able to reach traditional levels of statistical significance. It is important to note that although the thirteen studies used in the meta-analysis were measuring low-dose naltrexone's effect on pain reduction, these observations were made while studying different chronic pain conditions with variability in the sample sizes, dosing regimens and pain scores.

The overall effect in these studies were calculated using the standardized mean difference (SMD) between the LDN and placebo groups. It showed an overall SMD of −10.77 (95% CI: −13.96 to −7.58) with a p-value of 0.002, **Figure 2**. This indicated that the LDN group experienced a statistically significant reduction in pain compared to placebo, as a negative SMD favors the naltrexone group compared to the placebo group. A positive SMD would favor the placebo group, but in our meta-analysis, the placebo group had smaller reductions in pain compared to the experimental group. The effect size is moderate and statistically

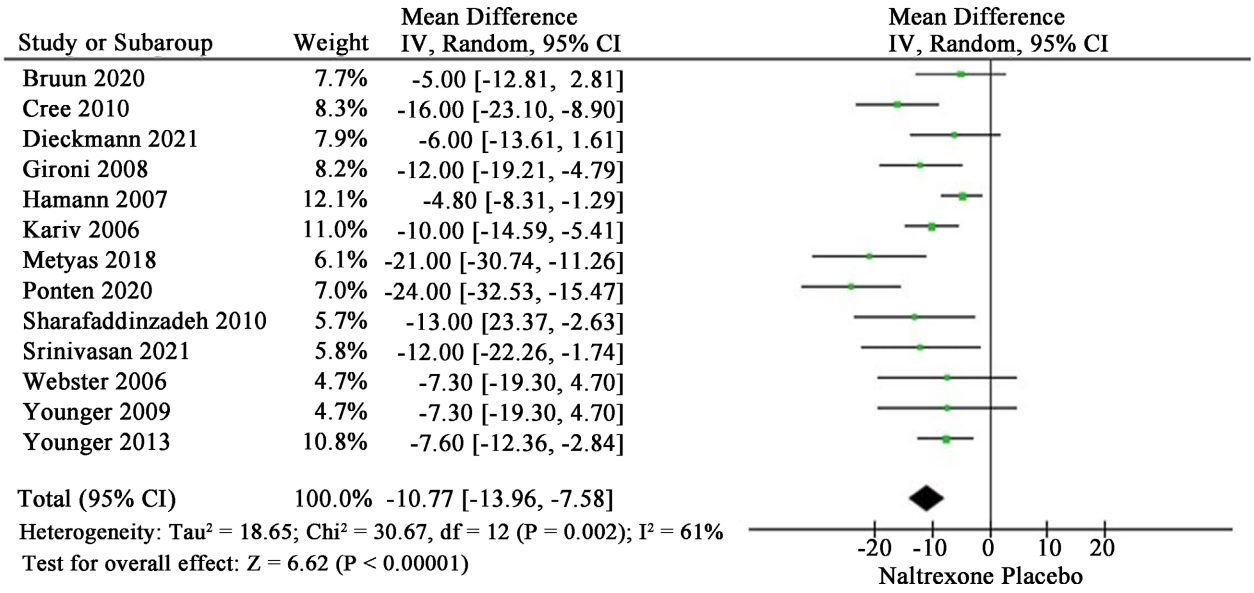

Figure 2. Mean difference.

significant (p = 0.002), indicating that low dose naltrexone may be effective in reducing pain in these conditions. There was no evidence of funnel plot asymmetry to indicate publication bias for the included studies. The funnel plot for the main analysis is included as Figure 3.

4. Discussion

The presented meta-analysis aimed to evaluate the utility and efficacy of low dose naltrexone in the reduction of pain and enhancement of analgesia in various chronic pain disease processes. The results of this meta-analysis suggest that low dose naltrexone may be an effective and well-tolerated treatment option for reducing pain in patients with fibromyalgia, multiple sclerosis, and diabetic neuropathy pain syndromes. The analysis of the data from the thirteen studies included revealed that low dose naltrexone was associated with a significant reduction in pain scores compared to placebo. This finding is consistent with previous research indicating the potential of low dose naltrexone as a treatment for chronic pain conditions [16] [17] [18]. The results acquired through this study reveal that low dose naltrexone, an opioid antagonist, may be a successful agent in enhancing analgesia in patients with chronic pain conditions. However, it is important to note that the sample sizes of the included studies were small and there were variations in dosing regimens and treatment durations across studies [19]. These limitations may affect the generalizability of the findings. Therefore, further research is needed to confirm the efficacy and safety of low dose naltrexone for chronic pain conditions. Another limitation of this meta-analysis was the heterogeneity in the type of chronic pain conditions included. Although fibromyalgia, multiple sclerosis, and diabetic neuropathy pain syndromes were the most studied conditions, there were also studies investigating the efficacy of low dose naltrexone in other conditions such as irritable bowel syndrome. Therefore,

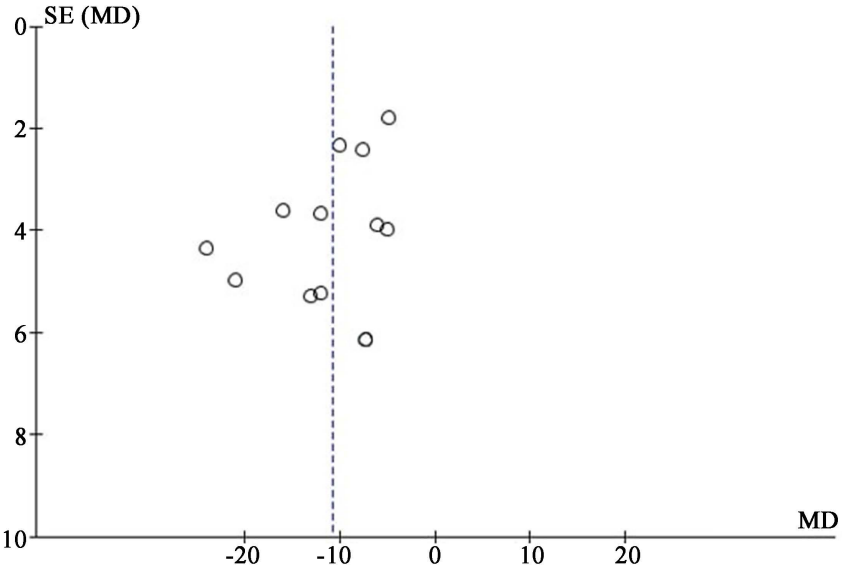

Figure 3. Scatter plot of mean differences.

the generalizability of the findings to other chronic pain conditions may be limited.

This meta-analysis provides evidence for the potential efficacy of low dose naltrexone in reducing pain and enhancing analgesia in various pain syndromes. LDN may be a useful treatment option for patients suffering from chronic pain, particularly with fibromyalgia, multiple sclerosis and diabetic neuropathy. However, further research is needed to confirm the efficacy and safety of low dose naltrexone for chronic pain conditions, especially with larger sample sizes, standardized dosing regimens and treatment durations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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