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Pain Relief Without Opioids? Revisiting Naltrexone in Low Doses for Chronic Pain

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Abstract

Introduction and purpose: Chronic pain remains a major clinical challenge, often resistant to conventional therapies and significantly impairing quality of life. As the opioid crisis persists and standard treatments prove insufficient, many patients turn to off-label alternatives. One such candidate is low-dose naltrexone (LDN) – an opioid receptor antagonist traditionally used in addiction therapy, now gaining attention for its unexpected role in pain management. Evidence suggests that LDN may exert anti-inflammatory and immunomodulatory effects beyond opioid receptor antagonism. This review aims to summarize the current understanding

of LDN's clinical use in managing chronic pain, with a focus on conditions such as fibromyalgia (FM), complex regional pain syndrome (CRPS), multiple sclerosis (MS), inflammatory bowel diseases (particularly Crohn's disease), diabetic neuropathy, and chronic low back pain.
Methods: A literature review was conducted using PubMed and Google Scholar, with keywords: "low dose naltrexone," "LDN," "chronic pain," "fibromyalgia," "multiple sclerosis," "inflammatory bowel disease," "CRPS," "diabetic neuropathy," and "low back pain."
Brief description and state of knowledge: At doses of 1–5 mg, LDN transiently blocks opioid receptors, enhancing endorphin release, while also modulating microglial activity. This dual mechanism reduces central sensitization and the release of pro-inflammatory cytokines, contributing to pain relief.
Conclusion: Though still underrecognized in conventional medicine, LDN shows promise as a safe, low-cost, and potentially paradigm-shifting adjunct in chronic pain management. Its impact on pain, fatigue, mood, and quality of life across multiple conditions merits further high-quality research to validate its role and optimize dosing.

Keywords

low dose naltrexone, LDN, fibromyalgia, multiple sclerosis, low back pain, CRPS, inflammatory bowel disease, diabetic neuropathy, chronic pain

Introduction

Naltrexone is a long-lasting, well-known opioid receptor antagonist authorized to treat alcoholism and opioid dependence [1]. It was approved by the FDA in the 1980s, firstly to treat opioid addiction. Its mechanism of action involves targeting opioid receptors. Naltrexone binds to μ-opioid receptors with the highest affinity while exhibiting lower affinity for κ and δ-opioid receptors [2]. It has been proven to reduce the euphoric effects of opioids, and it remains an essential component in the treatment of opioid dependency at usual dosages of 50–100 mg [3]. Furthermore, naltrexone lowers the risk of relapse and aids in the fight against alcohol abuse by lessening the enjoyment that comes with drinking [4].

Naltrexone at low doses, on the other hand, is a quite distinct treatment approach that utilizes the drug in reduced daily doses- often 10 times lower or more (typically ranging from 1 mg to 5 mg) compared to those approved by the Food and Drug Administration (FDA). It seems that its mechanism of action is beyond the opioid receptor antagonism and may involve neuro-inflammatory modulation. The interest in naltrexone has grown widely since the 1980s. Currently, as an off-label therapy, LDN has shown potential for the treatment of various conditions, including Crohn's disease, multiple sclerosis, CRPS, and fibromyalgia [5]. Chronic pain associated with these diseases is undoubtedly difficult to treat and is linked with negative outcomes such as a decreased quality of life. Although the pathophysiology of chronic pain is complex, central sensitization can be identified as its important cause [6]. This neurophysiological process increases the sensitivity of neurons in the central nervous system (CNS) in response to nociceptive stimuli. Aberrant microglia activity may contribute to atypical pain processing. Central sensitization is often characterized by hyperalgesia, allodynia, prolonged pain perception, and increased neural response [7]. Treatment options available for patients with chronic pain are limited and include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), opioids, antidepressants, and behavioral therapy. However, the benefits of these treatments may not be long-lasting, which leads patients to seek off-label methods to alleviate pain. LDN has recently emerged as a potential option for targeting chronic pain disorders. This review aims to summarize the potential of low-dose- naltrexone (LDN) in treating chronic pain conditions with particular emphasis on fibromyalgia, CRPS, multiple sclerosis, crohn's disease, diabetic neuropathy and low back pain.

Mechanism of action

_Naltrexone has an active metabolite that reversibly and competitively inhibits μ-opioid receptors with the highest affinity while also affecting δ- and κ-opioid receptors, albeit with lower affinity. Its mechanism of action is not only limited to blocking opioid receptors but also serves as an example of hormesis. Hormesis is a phenomenon where the same substance exhibits a biphasic mechanism of action. In the case of naltrexone, at standard doses, it functions as an antagonist used to treat opioid or alcohol addiction. Conversely, at low doses (ranging from 1-5 mg), it paradoxically acts as an agonist, exhibiting weak stimulation of opioid receptors [8][9][10]. Numerous studies indicate that low-dose naltrexone modulates glial cells and has a neuroprotective effect. Microglia are immune cells of the central nervous system (CNS) that become activated due to various stressors. Upon activation, they release inflammatory and excitatory molecules, triggering a pro-inflammatory cascade that can lead to

neurotoxic effects. The pathophysiology of central sensitization is often linked to the described process. Naltrexone reduces glial cell activation by interacting with the Toll-like receptor 4 (TLR4 receptor). By interfering with TLR signaling, it reduces the production of pro-inflammatory cytokines-IL-6, tumor necrosis factor-alpha (TNF-α) and nitric oxide (NO)[5][11][12][13]. This modulation of glial cells suggests that LDN reduces inflammation around the nociceptive neural pathways. Therefore, the drug is believed to attenuate the initiation of central sensitization and a wide range of associated symptoms, including increased pain sensitivity, fatigue, cognitive decline, and sleep and mood disturbances[14]. Moreover, LDN has long been believed to increase endorphin levels by promoting receptor upregulation [15]. Recent studies suggest that LDN binds briefly and intermittently to opioid receptors (OGFr). This transient binding increases endogenous opioids like β-endorphins and the expression of μ and δ receptors. Unlike high doses of naltrexone, which cause constant OGFr blockade and increased cellular proliferation, LDN activates compensatory mechanisms. It is suggested that LDN inhibits opioid growth factor (OGF) binding by intermittently blocking OGFr. This leads to increased production of OGF and OGFr as a rebound effect and restores the OGF-OGFR axis to balance. Therefore, LDN might inhibit cell proliferation and modulate immune response[5].

CRPS

_CRPS is a neuropathic pain syndrome, which usually occurs after an injury or trauma. Physiological mechanisms, which have been proposed for its development include inflammatory cascades, vasomotor dysfunction, and central nervous system dysfunction[16]. Central nervous system sensitization in CRPS is caused by the activation of glial cells, resulting in an increased release of pro-inflammatory cytokines[13]. Thus LDN can be a promising therapy in this condition.

_A case study by McKenzie Brown et al. focused on the use of LDN for chronic pain management at a single institution. The purpose was to compare, which groups of patients with various chronic pain disorders would benefit the most from LDN. The charts of 137 patients who visited the Pain Treatment Center between 2014 and 2021 were reviewed. Participants received gradually increased doses of LDN ranging from 1-4,5 mg daily. It was found that 75% of the 12 patients diagnosed with CRPS reported pain reduction. Two patients reported significant improvement, with pain relief exceeding 50%, while seven reported a reduction of less than 50%. To sum up the study, patients with neuropathic pain or diagnosed with CRPS

were more likely to respond to naltrexone and to experience pain relief than patients with spondylosis. No serious side effects were noted during the study [17].

Chopra et al. presented case reports involving patients with CRPS who benefited from LDN. The first study described two patients with long-standing CRPS who reported significant pain relief after using LDN. A 48-year-old veteran developed CRPS after an injury. Despite various treatments, his symptoms persisted and worsened, affecting his upper limbs and chest. Prior to LDN therapy, the patient presented with patchy allodynia in the medial and dorsal part of the right foot, widespread dysesthesia in the lower leg below the knee, and bilateral dysesthesia in the upper limbs. He started low-dose naltrexone (4.5 mg daily), and within two months, his dystonic spasms resolved, pain intensity decreased (NRS 8–10 to 5–6), physical activity and sleep improved, and he could even walk without a cane. Pain distribution remained unchanged, but no side effects were noted. Another documented case involved a 12-year-old female with Ehlers-Danlos Syndrome (EDS) hypermobility type 1 and multiple comorbidities and CRPS. Before LDN therapy, her main symptoms included allodynia on the dorsum of the right and left foot, dysesthesia in the right leg, and sensitivity to touch and temperature. Symptoms were also present in the left lower extremity and both upper extremities. She also had fixed dystonia in the lower right leg and ankle, with plantar flexus and varus deformity. The patient rated her pain at 8-10 on the NRS scale. Initially, the patient was given 3 mg of LDN a day alongside 10 mg of sublingual ketamine. After 4 weeks, the dose of LDN was increased to 4,5 mg. The patient reported a reduction in allodynia, sensitivity to the touch and temperature changes. Pain levels on the NRS scale also decreased to 3-5/10 after 2 of LDN therapy. Despite undergoing numerous invasive procedures, due to EDS, she did not experience a spread of CRPS. The therapy was continued for 18 months and no side effects were reported [18].

Another case report from 2016 presented a 56-year-old woman with long-lasting CRPS, ED syndrome, Irritable Bowel Syndrome, and other comorbidities. The patient with severe pain, discoloration, and edema of the right leg reported that signs of CRPS resolved completely after treatment with 4,5 mg LDN daily for 9 months [19].

The third case report described a 17-year-old patient with CRPS, which was resistant to standard treatment, including clonidine, nortriptyline, and gabapentin. She suffered from CRPS on her left- lower extremity along with extreme pain that made it impossible for her to walk in regular shoes. Before starting LDN treatment, she rated the pain as 7/10 on the NRS scale. After

beginning a daily dose of 1.5 mg LDN, the patient reported significant pain relief, with her pain level decreasing to 1/10 on the NRS scale by the end of the 4-week treatment [20].

Fibromyalgia

Fibromyalgia is among the most common rheumatological conditions, affecting 2-3% of the global population. This complex syndrome is not only characterised by chronic widespread musculoskeletal pain (CWP) but also sleep disturbances, fatigue, autonomic dysfunction, hypersensitivity, cognitive issues, and psychiatric manifestations [21]. The pain, often linked to neuropathic, can be debilitating for many patients [22]. While the exact pain mechanisms in fibromyalgia remain unclear, they are thought to involve a combination of central and peripheral pathways [23][24]. In patients with FM, microglial activation leads to chronic neuroinflammatory responses with pro-nociceptive cytokine profiles, which confirms that treatment using LDN, could have a positive effect on FM symptoms [25]. Furthermore, treatment options, including SNRIs, often show limited efficacy and are frequently discontinued due to unfortunate side effects [26].

A recent systematic review and meta-analysis were conducted to assess the effectiveness and safety of low-dose naltrexone (LDN) in the treatment of fibromyalgia. By pooling data from four randomized controlled trials involving 214 participants, the analysis revealed a reduction in pain scores for patients receiving LDN compared to placebo. LDN also led to a statistically significant improvement in pressure pain thresholds. However, no significant differences were found in the Fibromyalgia Impact Questionnaire-Revised scores or physical component summary scores. These results suggest that LDN may offer meaningful relief from pain and improve pain sensitivity in fibromyalgia. Additionally, no serious side effects were reported. LDN was associated with a slightly higher incidence of vivid dreams and nausea. It did not show any significant difference regarding serious adverse events, headaches, diarrhea, or dizziness. However, its impact on broader disease outcomes and physical function requires additional research [27].

A single-blind clinical trial was conducted to evaluate the dose-response relationship in the treatment of fibromyalgia with LDN. Out of 27 women involved in the study, 11 responded positively to the treatment (reduction in pain of at least 30% and improvement on the Patient Global Impression of Improvement (PGI) scale were observed). The most significant improvements concerned „tenderness", while only a small percentage of responders reported

pain relief. Side effects were primarily gastrointestinal symptoms (abdominal pain, diarrhea), and two participants withdrew due to adverse effects. Overall, the standard LDN dose of 4.5 mg daily appeared to be appropriate [28].

Siembda et al. presented a case report of a patient with refractory depression and chronic widespread pain successfully treated with LDN. Initially, the patient's cold pressor test (CPT) time was only 21 seconds. Treatment included LDN with a minor increase in trazodone dose, and psychotherapy. Following this approach, the patient's CPT time showed an increase to 26 seconds. Remarkably, remission of both depression and pain was achieved within 10 weeks of starting LDN therapy, leading to improved quality of life [29].

Jackson et al. conducted an open-label case series examining the impact of chronic opioid treatment on pain tolerance (measured by the cold pressor test, CPT) and the efficacy of low-dose naltrexone (LDN) as an alternative treatment for hyperalgesia and fibromyalgia. The study included 55 patients with opioid-induced hyperalgesia (OIH) and fibromyalgia (FM). Pain tolerance in patients with FM doubled. No side effects were reported. However, the limitation of the study was the lack of a control group [30].

As suggested by a small pilot study, LDN may improve quality of life and offer pain relief. In a single-blind placebo-controlled crossover trial, ten women diagnosed with fibromyalgia participated. The design of the study included two weeks of placebo, followed by eight weeks of 4.5 mg naltrexone, with a subsequent 2-week washout period. Among the six patients who completed the study, a 30% reduction in symptoms, including pain, fatigue, and stress, was observed. In addition, laboratory assessments reported increased thresholds for mechanical and heat pain. Notably, a higher initial erythrocyte sedimentation rate was identified as a key predictor of a positive response to the drug. There were no serious side effects reported. Two patients noticed vivid dreams, one participant reported insomnia and nausea at the beginning of the treatment. All of the symptoms were classified as mild and did not require a change in dosage [31]. A follow-up, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial, indicates that low-dose naltrexone has a clinically beneficial effect on pain in fibromyalgia. The participants were receiving either low-dose naltrexone or placebo for 12 weeks. The results showed that participants treated with 4,5 mg of LDN daily experienced a significant reduction in pain compared to placebo (28,8% vs. 18,0%; p=0,016). Moreover, LDN was associated with improvement in general life satisfaction (p=0.045) and mood (p=0,039).

Similarly to the previous study, no serious side effects were reported. The most common ones were vivid dreams, which were observed more frequently (37% vs. 13% for placebo) [32].

A 10-week, single-blind, crossover pilot study conducted in 2017 aimed to evaluate if LDN therapy reduces pro-inflammatory cytokine levels. The study involved eight patients, with symptom severity of 62 out of 100. A broad range of cytokines, associated with the promotion of nociception, hyperalgesia, and allodynia, were mentioned. These include TNF-α, IL-1β, IL-2, IL-6, IL-15, and IL-17 [33][34]. Significant reductions in various pro-inflammatory cytokines were observed. Additionally, a 15% decrease in pain associated with fibromyalgia and an 18% reduction in overall symptoms were reported [35].

LDN may be a promising treatment option as demonstrated by another case study. A 37-year-old patient with fibromyalgia, experiencing symptoms like burning sensations, recurrent pain, muscle stiffness, extreme fatigue after minor activity, and insomnia, was treated with LDN. After 27 weeks of treatment, the participant reported a reduction in generalized pain, measured on a scale of 1 to 10. At week 4, the pain level was rated as 6/10, decreasing to 4/10 by week 8. Later visits showed pain levels fluctuating between 1 and 4/10. Additionally, improvements in sleep quality, physical endurance, mood, and overall quality of life were noted. A significant increase in Cold Pressor Test (CPT) was reported, rising from 7 seconds at baseline to 50 seconds by week 8 of using LDN. After 27 weeks, the patient remained stable on LDN for at least six months, experiencing no side effects [36].

Multiple sclerosis

LDN demonstrated a positive effect on reducing the symptoms of Multiple Sclerosis (MS), an autoimmune disease of the central nervous system. The disease remains inadequately defined, though astrocyte inflammation, demyelination, axonal damage and neurodegeneration play a crucial role in its pathogenesis [37].

A retrospective study of 215 patients with an average MS duration of 10 years, treated with 3,5 mg LDN daily, demonstrated its beneficial potential. Significant reduction in fatigue, improvement in disease severity and relief of symptoms were noted by 60% of patients. Seventy-five percent reported increased quality of life while on LDN. Minor adverse events were documented, including insomnia (6%) and nightmares (5%), whereas 77% of the participants recalled no serious side effects [38]. Similar conclusions can be drawn from a multi-center, open-label pilot study. In this case, 40 patients with primary progressive multiple

sclerosis (PPMS) treated with LDN reported a significant decrease in spasticity over the course of 6 months. Only minor adverse events were noted and disappeared completely after the end of the treatment [39].

A retrospective analysis found that LDN is a safe option, compatible with standard MS medication. The study outlined two patient cohorts,- one treated only with LDN and thea second with LDN as an adjuvant alongside standard FDA-approved disease-modifying medication-Copaxone. No significant differences in terms of magnetic resonance imaging (MRI) markers for inflammation or disease aggravation, serum inflammatory markers, and walking tests were observed. This leads to the conclusion that LDA alone or as an adjuvant could be a well-tolerated therapy option for MS. However, the authors claim further research is needed to validate its efficacy [40].

A case report of a 62-year-old woman receiving 4.5 mg of LDN per day showed decreased intensity, duration, and frequency of recurrent migraine headaches. Her quality of life improved notably as a result of the LDN therapy[41].

According to another study, LDN may help to address immune system imbalances. The authors looked into how LDN affected the levels of serum enkephalin (OGF/PENK) in MS patients. In this study, MS patients exhibited reduced serum levels of OGF, which plays a role in suppressing immune cell activity. The findings indicated that LDN, either alone or combined with glatiramer acetate, was effective in restoring enkephalin levels and could potentially improve patients' quality of life [42].

Finally, two randomized placebo-controlled trials were also carried out to assess the efficacy of LDN on the quality of life of individuals with multiple sclerosis. While the 17-week trial of 96 patients did not present a satisfactory outcome showing no statistical difference in quality of life and only change in health perception, the second 8-week study showed notable improvement in mental health indicators [43][44].

Inflammatory Bowel Diseases

Inflammatory Bowel Diseases (IBD) are believed to be a result of a combination of genetic and environmental factors. Immune dysregulation toward mucosal antigens or bacteria is crucial in their pathogenesis. Chronic pain is a common symptom, which often persists even during remission due to central and peripheral sensitization mechanisms. Research suggests that pain

is present even in up to 70% of patients affected by IBD. Multiple studies describe the role of naltrexone in the treatment of inflammatory bowel diseases, stating that LDN may alleviate symptoms in patients with active IBD by modifying glial cells and targeting mu-opioid receptors [45].

One of the earliest open-label pilot prospective trials confirmed LDN's effectiveness in reducing symptoms and improving the quality of life in patients with active Crohn's disease. In this study, 17 patients treated with 4.5 mg LDN for 12 weeks participated. Crohn's Disease Activity Index- CDAI scores decreased notably in the LDN group. Clinical remission was achieved in 67% of patients, and 89% showed a clinical response. LDN was well tolerated, and there were no laboratory abnormalities observed during the study. Minor side effects, including sleep disturbances, occurred in 7 patients [46].

Another prospective study investigating LDN as a promising treatment in refractory IBD, led to similar conclusions. Of 17 patients treated with 4.5 mg naltrexone daily for 12 weeks, 74.5% achieved clinical improvement, whereas 25.5% observed sustained clinical remission. Interestingly, naltrexone improved epithelial barrier and wound healing in patients with IBD. Minor adverse events, such as vivid dreams, drowsiness and headache were noted during the study (n=4, 2 and 1 respectively) [47].

A 2018 systematic review of two randomized placebo-controlled trials focused on the efficacy and safety of LDN as a possible medication to induce remission in patients with active Crohn's disease. [46][48]. Among 46 participants 12 children were included. A clinical response (a decrease in Crohn's Disease Activity Index- CDAI by ≥70) was observed in 83% of patients treated with LDN compared to 38% in the placebo group. In the pediatric group, 25% of participants treated with LDN achieved clinical remission (PCDAI < 10), compared to no patients in the placebo group. Moreover, seventy-two per cent of LDN patients achieved an endoscopic response compared to 25% of patients receiving placebo. However, there was no statistically significant difference in the endoscopic assessment comparing the LDN and the placebo group. Mild side effects such as sleep disturbances, fatigue, and headaches were not common [49].

A retrospective chart review involving 121 patients with various diagnoses, including IBD, evaluated the safety and efficacy of LDN, using a retrospective survey, given to the patients following their visit to the gastroenterological clinic. For an average of 16.8 weeks, participants with IBD were prescribed LDN at 4,5 mg daily. Survey results showed that, among 8 IBD patients, two noticed significant, one moderate, one mild, and four showed no change in symptom severity. Notably, before receiving LDN treatment, two of the four subjects whose

symptoms remained unchanged were already in remission Side effects were reported by 61,2 % of patients (74 of 121) and included neurological (vivid dreams, insomnia, headaches) and gastrointestinal (abdominal pain, diarrhea) complaints. Although unwanted symptoms resolved with extended use, 20 of the 74 patients discontinued LDN therapy. Unfortunately, the study's retrospective design and unsatisfactory survey-response rate (58,7%) limit definitive conclusions [50].

Shannon et. al. presented a 14-year-old patient who suffered from Crohn's disease and developed serious complications, such as muscle rigidity and muscle pain after standard therapy with prednisone and azathioprine. Subsequently, she was prescribed 4,5 mg LDN daily and, after 4 weeks of treatment, observed a notable decrease in symptoms. An esophagogastroduodenoscopy (EGD) performed after three months of therapy showed normal biopsies results and complete mucosal recovery of the duodenum in comparison to the pre-treatment image, which showed a flare of Crohn's disease in this area [51].

Diabetic neuropathy

LDN has also shown benefits in the treatment of patients with diabetic neuropathy. A randomized, double-blind, active-control, crossover clinical trial compared the safety and efficacy of LDN and amitriptyline. Sixty-seven patients were initially assigned to receive either 2 mg naltrexone or 10 mg amitriptyline daily. Based on the change in VAS score, efficacy was evaluated- if it did not improve by more than 20%, the doses were escalated up to a maximum of 4 mg LDN and 50 mg amitriptyline. After 6 weeks and a 2-week preliminary phase, patients crossed over, and the trial was conducted again. The study found both medications to have equivalent efficacy. However, LDN demonstrated a superior safety profile. The most frequently reported side effects were daytime drowsiness in the amitriptyline group (18 cases) and mild abdominal discomfort accompanied by diarrhea (3 cases) in the naltrexone group [52].

Hota et al. presented a case report of a patient with type-2 diabetes, diagnosed with diabetic neuropathy, that was refractory to most available therapy. After a marked improvement with 2 mg of naltrexone daily, the dose was increased to 4mg. The patient experienced significant pain relief without any side effects [53.]

Low back pain

Low back pain can be another chronic pain-related condition responding to LDN, due to its underlying pathophysiology, which includes central sensitization and neural glial modulation

[54]. Ghai et al. described a 35-year-old patient with nonspecific axial low back pain, which was not responsive to conservative treatment. Initially, he rated his pain severity on the VAS score as 10 out of 10, and his Modified Oswestry Disability Questionnaire (MODQ) score was 70%. After all commonly used pain-modulating strategies failed to alleviate the symptoms, the therapy with 2mg naltrexone started. The dose was increased to 4 mg. Four weeks after starting LDN, his pain severity VAS score decreased to 3.5, and his MODQ score dropped to 35.5%. He did not observe any adverse events [55].

Another study, which presented a combination of oxycodone and ultra-low-dose naltrexone (ULDN), showed that naltrexone in even very low doses provides therapeutic benefits. In this randomized controlled trial, 719 patients with chronic back pain were assigned to a placebo, oxycodone, or oxycodone with a two-two-mcg ULDN group. The combination of oxycodone and 2mcg ULDN resulted in fewer adverse events, such as constipation or drowsiness, compared to oxycodone only. Additionally, patients who received naltrexone used 12% fewer opioids, and the twice-daily combination was as effective as oxycodone administered four times daily. However, the study results should be interpreted cautiously, due to a notable dropout rate [56].

Discussion

Chronic pain-related diseases present a therapeutic challenge. Many standard medications are not well-received by patients due to the high risk of side effects. In an era where opioids are the last resort for treating chronic pain, alternative therapeutic options, such as low-dose naltrexone, should be taken into account. Although LDN has not yet been approved for the treatment of any chronic pain-related diseases and is considered an off-label therapy, available studies suggest its efficacy. LDN's effectiveness has been documented in multiple case reports and several randomized controlled trials (RCTs), which have primarily focused on conditions like IBD and FM. However, most presented studies depend on subjective measures such as quality of life and self-reported pain, and there is limited evidence based on objective data.

Chronic pain, common in the discussed conditions, is often linked to central sensitization. The pathophysiology of this phenomenon is due to abnormalities within the CNS and the dysfunction of glial cells. LDN modulates glial cells, interrupting the production of pro-

inflammatory cytokines, which confirm its potential in treating described chronic pain conditions [57].

Beyond pain reduction, improvements in spasticity, quality of life, sleep, and mood have frequently been reported following LDN therapy. In reviewed studies, low-dose naltrexone showed minimal side effects. If any adverse events occurred, they were generally mild or low intensity. Sleep disruptions, such as vivid dreams, nightmares, gastrointestinal issues (diarrhea), and headaches, were most frequently reported. Frequently, the symptoms subsided after prolonged use of LDN. Very few patients discontinued LDN due to side effects. In the trials, dosing regimens typically began with a lower dose, which was gradually increased depending on the occurrence of side effects or severity of pain. Therefore, it is unclear if the patients' improvement of symptoms were brought on by the particular dosage or the amount of time that had passed since they began taking LDN. Future studies should examine how patients react to various dosages and when initial changes are observed. Furthermore, clinical research could also look into alternative delivery methods of naltrexone, such as topical, intrathecal, sublingual, and submucosal.

Conclusion

Positive research results and the increasing number of conditions in which LDN is used as an off-label therapy, as presented in this literature review, highlight LDN as a potentially valuable and relatively safe pharmacologic option for managing chronic pain conditions. However, further high-quality, randomized, long-term studies on different populations are needed. If the efficacy and safety of LDN are confirmed, LDN could be a breakthrough therapy due to its low cost, availability, and safety profile.

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All authors declare that they have no conflicts of interest.

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