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Low-Dose Naltrexone for Treatment in Crohn's Disease and Fibromyalgia

Hannah Rachel Tkach
University of North Dakota, tkach.hannah@und.edu

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by

Hannah Rachel Tkach, PA-S

Bachelor of Science in Health Professions, University of Minnesota Rochester, 2016

Contributing Author: Julie Solberg, MSPA

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Abstract

The United States has experienced a dramatic increase in opioid abuse and overdoses, leading to a national epidemic. Contributing to this epidemic is the use of opioid therapy for complex chronic inflammatory and neuropathic conditions that remain difficult to treat. Many traditional treatments are ineffective or have intolerable side effects, forcing providers to utilize opioid therapy as a last resort. Recently, there is increased interest in the use of partial opioid antagonist naltrexone to treat Crohn's disease and fibromyalgia. Previous research suggests the potential for naltrexone to provide analgesic effects when administered in low doses via its unique interaction with opioid receptors located throughout the body. A literature review was performed using a comprehensive electronic search of scientific databases, applying search criteria that included the mesh term naltrexone and keywords Crohn's disease and fibromyalgia. Preliminary research on the use of low-dose naltrexone (LDN) in fibromyalgia demonstrates mixed results. Some studies show the potential for LDN to improve pain symptoms and quality of life, while others exhibit statistically insignificant results. Current research on LDN use in Crohn's disease demonstrates that it can improve pain, mucosal healing, and quality of life without adverse effects. The high safety profile and effectiveness of LDN seen in preliminary studies support the need for larger, randomized controlled trials to investigate LDN's efficacy in the treatment of Crohn's disease and fibromyalgia.

Keywords: Naltrexone, Crohn's disease, fibromyalgia, analgesia, immunomodulatory, treatment, adjunct, therapy

Introduction

Chronic inflammatory and neuropathic conditions such as Crohn's disease and fibromyalgia are complex disorders that remain difficult to treat. Crohn's disease is an autoimmune disease of the gastrointestinal tract which causes abdominal pain, diarrhea, and transmural mucosal inflammation. Fibromyalgia causes widespread musculoskeletal pain, fatigue, and sleep disturbances. Many traditional treatment options for these conditions including systemic corticosteroids, immunosuppressants, and antidepressants are ineffective or have substantial side effects, leaving patients with chronic pain and a poor quality of life. The utilization of chronic opioid therapy to treat these disorders has contributed to an increase in abuse. Despite research demonstrating poor effectiveness, providers utilize opioids when all other pharmaceutical options have failed. Increased narcotic use has led to a dramatic rise in opioid abuse and accidental opioid overdoses in the United States. Studies have reported that addiction in opioid-treated chronic pain patients in the United States is as high as 26%, and others demonstrate it as high as 33% (Kay et al., 2017). This increasing problem has led to significant interest throughout the medical community in finding alternative treatment options for these complex conditions.

Currently, the search for alternative treatment options focuses primarily on treatments with fewer adverse effects. Recently, there has been increasing interest in the use of the opioid antagonist, naltrexone, to treat these conditions due to its analgesic properties and low side effect profile. Past use of naltrexone was limited to patients with opioid use disorders or alcohol use disorders, with typically daily dosing of 50 mg. However, preliminary research suggests that when administered in low doses (1.5 mg to 4.5 mg daily), naltrexone can inhibit pro-inflammatory pathways through interaction with the opioid receptors which are present

throughout the entire body. It also shows immunomodulatory properties by suppressing certain immune cell function. More importantly, early research has demonstrated LDN to be extremely safe with a very low side-effect profile. The unique mechanism of action of LDN in combination with its low side-effect profile suggests it has the potential to be an effective treatment option for patients suffering from chronic pain and autoimmune conditions. The purpose of this literature review is to determine if low-dose naltrexone (LDN) is a viable and safe treatment option or adjunct treatment for these chronic diseases.

Statement of the Problem

Increased use of opioid therapy to treat chronic pain in autoimmune and neuropathic conditions has contributed to a dramatic increase in opioid abuse and overdoses in the United States. Further research investigating alternative treatment options with less adverse effects and higher safety profiles should be conducted.

Research Question

Is low-dose naltrexone an effective and safe treatment for patients with Crohn's disease or fibromyalgia compared to placebo or traditional treatment options alone?

Research Methods

A literature review was performed using electronic search databases; PubMed, Embase, CINHAL, Scopus, and Cochrane Library. Search criteria included the mesh term naltrexone and keywords fibromyalgia and Crohn's disease. Each keyword was paired separately with the mesh term and used to define a set of literature discussing therapeutic uses of low-dose naltrexone in Crohn's disease or fibromyalgia. The initial search time frame of 10 years demonstrated limited data so it was expanded to articles published within the past 12 years. The literature review yielded a total of 629 articles. Exclusion criteria included periodicals, editorials, and articles

published before 2007. Inclusion criteria included randomized controlled trials, peer-reviewed journal articles, case reports, pilot studies, and systematic reviews. These articles were reviewed and assessed for pertinence to the desired topic, quality research methods, duplicate articles, and obvious bias. The criteria above yielded a total of twenty studies, which are discussed below.

The introductory section provides a description of the current opioid epidemic and justification for further investigation into the use of opioid antagonist, LDN, for patients suffering from the chronic pain diseases, Crohn's disease and fibromyalgia. The relevant themes of the literature review include the analgesic properties of LDN, safety and financial feasibility of LDN, efficacy of LDN as monotherapy or adjunct therapy in Crohn's disease, and efficacy of LDN as monotherapy or adjunct therapy in fibromyalgia.

Analgesic Properties of Low-Dose Naltrexone

The analgesic and immunomodulatory properties of LDN have been noted throughout the last decade, however, the exact mechanism remained unknown. Hypotheses to explain LDN's analgesic and cellular proliferative properties are discussed in a recent review article by Patten, Schultz, and Berlau (2018). A specific growth factor termed opioid growth factor (OGF) and its corresponding receptor (OGFr) are linked to the inhibition of cellular proliferation. It has been suggested by research using mouse models, that dysregulation of this OGF-OGFr axis is the cause of a variety of disease states, including Crohn's disease and fibromyalgia (Patten et al., 2018). This dysregulation leads to the decreased natural production of OGF, or the inability of OGF to bind to the OGFr, due to altered receptor sensitivity. LDN competitively binds to OGFr preventing OGF binding for a short duration due to low dosages, leading to an intermittent blockade of the receptor. The intermittent blockade also triggers a compensatory mechanism that upregulates the production of OGF and increases OGFr receptor sensitivity (Patten et al., 2018).

After naltrexone metabolization, the blockade resolves but the rebound effect of the compensatory mechanisms remains, allowing proper functioning of the OGF-OGFr axis and analgesic effects (Patten et al., 2018).

In another review article published in *International Immunopharmacology* Li, You, Griffin, Feng, and Shan (2018) describe how groups of opioid receptors are distributed throughout a variety of systems in the body including nerve cells in the brain, spinal cord, and the digestive tract. OGFr plays a major role in cellular proliferation while also being expressed on immune cells (Li et al., 2018). LDN's ability to interact and intermittently block these receptors causes a compensatory upregulation of endogenous opioids as well as increased OGFr sensitivity. Preliminary research suggests this as the primary mechanism by which LDN promotes proper function of the OGF-OGFr axis in these conditions (Li et al., 2018). The above review also suggests that it is LDN's interaction with the OGF-OGFr axis contributes to its analgesic properties and provides a potential mechanism for how it may provide symptomatic improvement in Crohn's disease and fibromyalgia.

Additional research has been done on LDN's immunomodulatory properties by Donahue, McLaughlin, and Zagon (2011). A tissue culture model of LDN and short-term, continuous opioid receptor blockade in a human ovarian cancer cell were studied. It was noted that the duration of the opioid receptor blockade affects cell proliferation response. Additionally, the OGF and its receptor (OGFr) played a role in cell proliferation response and that naltrexone upregulated both OGF and OGFr leading to a decrease in cellular proliferation (Donahue, McLaughlin & Zagon, 2011). The study suggested that if Crohn's disease is secondary to an exaggerated proliferation of T and B cells, that the upregulation of the OGF and OGFr axis seen

upon LDN administration can decrease immune cell proliferation and promote proper cellular proliferation function (Donahue, McLaughlin & Zagon, 2011).

These properties have further been investigated in animal studies. Yi, Guo, Hu, Wang, Zhang, Griffin, and Shan (2016) investigated the immunomodulatory properties of LDN in mice. More specifically, they investigated the effect that LDN had on the function and phenotype of the immune cell, macrophages. Macrophages harvested from six to eight week old mice were obtained and analyzed for changes in key surface markers. Study results indicated that LDN can upregulate or downregulate the expression of multiple surface markers on macrophages, confirming the immunomodulatory properties of LDN.

In 2007, Berkson, Rubin, and Berkson published a case report of a 61-year-old male diagnosed with B-cell lymphoma who was treated with LDN. The patient refused chemotherapy and was therefore started on LDN (3 mg daily) due to its low side effect profile. One week post treatment initiation, the patient reported improved pain symptoms. Follow-up CT/PET imaging revealed significant improvement in abnormal foci in the neck, axillae, and groin (Berkson et al., 2007). At the patient's one year follow-up, he was symptom free. This case report suggests LDN has the potential of exhibiting specific analgesic and immunomodulatory properties. Limitations of this case report are due to its design which prevents generalization of results, increase risk of publication bias, and inability to establish a causal relationship between the disease remission and the treatment described.

The exact mechanism by which naltrexone interacts with cellular signaling and proliferation is still not fully understood, however; potential mechanisms have been studied and suggest it is the interaction with the OGF-OGFr axis that contributes to the immunomodulatory effects. This interaction can result in a compensatory increase in endogenous opioids leading to

an improved pain response, in addition to depression of cellular proliferation and allowing for proper immune cell function and proliferation.

Safety and Financial Feasibility of Low-Dose Naltrexone

The high safety profile of naltrexone contributes to the great interest in its use for a variety of chronic diseases. Bolton et al. (2019) conducted a systematic review and meta-analysis to investigate the safety profile of oral naltrexone. The review included placebo-controlled randomized trials greater than 4-weeks duration and included 89 randomized controlled trials with a total of 11,194 participants. Bolton et al. (2019) demonstrated no increased risk of serious adverse events when compared with placebo. The review also showed that this finding was consistent across trials with varying duration, dosages, and conditions. Mild side effects such as nausea, vomiting, and dizziness were potentially more common for naltrexone compared to placebo; however, the reporting of adverse effects was poor so only 21 studies contributed to the analysis (Bolton et al., 2019).

Two major strengths of the review above included the large number of studies included and the large sample size. Another strength of this study was the inclusion criteria of trials greater than 4-weeks duration, allowing the assessment of the long-term safety profile of oral naltrexone. Many of the studies included in the systematic review were greater than 12 weeks and 18 of the studies being included were between 16-25 weeks duration. One weakness was that only three out of the 89 studies included participants who were taking oral naltrexone for inflammatory disorders and did not specifically investigate the use of LDN but oral naltrexone in a variety of different dosages. Despite this weakness, the large population size and proper methodology of this study suggest that LDN has a high safety profile.

With the increased interest in LDN for chronic disease, it is necessary to assess the pharmaceutical stability of LDN. To acquire naltrexone in low doses, it must be compounded. Therefore, it is necessary to investigate the utility of pharmaceutical compounding of LDN and the limited data available to assess the long-term stability of naltrexone in this form. Cote, Ross, Fortner, and Rao (2018) investigated this using a scientific experiment assessing the stability of 1.5mg LDN capsules compounded in batches of 100. High-performance liquid chromatography was used to determine naltrexone concentration of these capsules after specific time periods to assess long-term stability (Cote et al., 2018). Samples were analyzed at a variety of periods, including 240, 270, 300, 330, and 360 days. Results demonstrated that the LDN capsules remained within 90-110% of the labeled potency throughout the 360-day study period (Cote et al., 2018).

The scientific study above demonstrated that compounded LDN is a practical pharmaceutical option for pharmacies to prepare and store for extended periods, which can help reduce product-associated waste. Decreasing waste reduces the cost of the medication, which may further encourage patient compliance. Also, it can improve patient compliance by decreasing the number of visits required for patient refills because larger doses can be dispensed for extended intervals. One limitation of the experiment above is that it did not include a wide range of LDN dosages assessed for stability, it included only one dosage. However, the results above still suggest that compounded LDN has the potential to be a low-cost, convenient and safe pharmaceutical therapy.

Efficacy of Low-Dose Naltrexone for Treatment of Crohn's Disease Compared to Placebo

Animal studies have been conducted investigating LDN use in inflammatory bowel disease. Tawfik et al. (2016) conducted an experimental study involving the treatment of adult

albino male rats with experimentally induced enteritis with sulfasalazine, LDN, or both in combination. Assessment of intestinal inflammation was done using the disease activity index score (DAI), stool analysis, venous blood samples measuring TNF-alpha and serum CRP measurements, and microscopic examination of the small intestine postmortem (Tawfik et al., 2016).

Results demonstrated a significant reduction in TNF-alpha and serum CRP levels in groups treated with sulfasalazine, naltrexone, and the combination groups compared to placebo with naltrexone group seeing the largest improvement. DAI scores, intestinal inflammation, ulcers, and edema upon macroscopic appearance and histopathological examination were also significantly reduced in the groups with the greatest results seen in the group treated with naltrexone alone. The results of this experimental study are consistent with other experimental studies that suggest the potential benefits of opioid receptor antagonism in this type of gastrointestinal disease. The case-controlled animal study above contained proper statistical analysis and adequate sample size, with results demonstrating LDN's anti-inflammatory properties to be beneficial in inflammatory bowel disease.

There is also clinical research investigating the use of LDN for the treatment of Crohn's disease compared to placebo. Smith et al. (2011) conducted a prospective double-blind, randomized controlled trial to investigate the safety and efficacy of LDN, 4.5 mg daily oral administration, to improve mucosal healing in active Crohn's disease in 40 adult participants. The primary outcome measure was change in the baseline of participants' Crohn's Disease Activity Index score (CDAI) and Crohn's disease endoscopy index severity score (CDEIS) which were used to assess secondary outcomes. Results demonstrated that 88% had a 70-point decrease in CDAI scores compared to 40% decline in the placebo group, with a p-value of 0.009

(Smith et al., 2011). In addition, 78% of participants in the LDN group showed a 5-point decline in CDEIS scores, compared to 33% in the placebo group (Smith et al., 2011).

The strengths of this study include study design and the power of the study. The prospective double-blind and randomized design of this study decreases the likelihood of bias skewing study results. The power of the study was high, 86%, indicating a high probability that results will obtain a statistically significant effect. It also included both male and female participants allowing the results to be more easily applied to the general population.

Study limitations included a small sample size and the continuation of the participants' current medications; however, these medications were stable prior to study enrollment and were maintained at the same dose throughout the entire duration of the study. The results of this study with its well-designed methodology and randomization, though limited due to small sample size, suggest consideration of further investigation with larger sample size. Finally, important to note that the author and principal investigator in the study above holds a patent for the use of LDN in inflammatory bowel disease, which increases the risk for bias, specifically detection bias. Therefore, study design must be evaluated thoroughly and results must be interpreted cautiously.

There is great interest and need for safe treatment options for Crohn's disease, especially in the pediatric population. A case report by Shannon et al. (2010) of a 14-year-old female diagnosed with Crohn's disease demonstrated encouraging results. The patient underwent esophagogastroduodenoscopy (EGD) and biopsy to confirm duodenal Crohn's disease and was started on 4.5 mg of naltrexone after failing treatment with prednisone, azathioprine, empiric treatment for H. pylori, and acid-suppressive therapy (Shannon, Alkhouri, Mayacy, Kaplan, & Mahajan, 2010). The patient experienced significant improvement within four weeks of treatment and repeat EGD after three months following LDN initiation demonstrated complete

mucosal healing and normal biopsies (Shannon et al., 2010). No severe adverse effects were reported in the above case report.

Though the above results were from a single case report, it suggests the potential of LDN to improve mucosal healing and pain caused by Crohn's disease without severe adverse effects in the pediatric population. It suggests that LDN is potentially a safe and effective treatment option for pediatric patients with inflammatory bowel disease (IBD) and warrants further investigation.

Smith, Field, Bingaman, Evans, and Mauger (2013) conducted a pilot study of 14 pediatric participants with moderate to severe Crohn's disease and showed similar results to the case report discussed above. The mean age for the participants was 12.3 years, and the study enrolled children ages 8-17 years old (Smith et al., 2013). The participants were randomized to a placebo group or received naltrexone 0.1 mg/kg orally for 8 weeks which was then followed by open-label treatment with eight additional weeks of naltrexone therapy (Smith et al., 2013). Safety and toxicity were assessed using blood chemistries, physical examinations, and the Pediatric Crohn's Disease Activity Index (PCDAI) along with Impact III survey which were used to assess clinical activity and quality of life respectively.

Results of the study were promising with no reports of serious adverse events in any participants and no laboratory abnormalities detected. The frequency of minor side effects was low and there was no difference in the incidence reported between the naltrexone group and the placebo group. PCDAI scores significantly improved ($p=0.005$) when comparing pretreatment and post-treatment scores, but group size was small and differences comparing the naltrexone group and the placebo group were not statistically significant (Smith et al., 2013). However, only the naltrexone treated participants had PCDAI scores less than 30 after the first eight weeks of

the study. At study completion, 25% of participants achieved clinical remission and 67% had a significant response to therapy (Smith et al., 2013).

Limitations of the study above include a small sample size which reduced the power of the study, the use of a subjective scoring system to assess results, and study duration. Based on the cross-over design of the study, all participants knew that they would receive the drug at some point in the study. An advantage of this was that it allowed the sample size of participants who received the active drug to be increased, however, it also increased the risk of the placebo effect. In addition, a subjective scoring tool, the PCDAI score, rather than the gold standard for determination of remission via endoscopic evaluation, was used to evaluate for mucosal healing. Another limitation included the duration of the study, which was only eight weeks. It has been suggested that the physiological effects of naltrexone may require longer periods of use, such as 12 weeks, which means potential results could have been missed due to short study duration. The pilot study above is a quality study; however, a larger trial is needed to come to definite conclusions.

Efficacy of Low-Dose Naltrexone as Adjunct Therapy in the Treatment of Crohn's Disease

The limited pharmaceutical interactions of LDN suggests it has potential as an adjunct therapy in Crohn's disease. A retrospective case series conducted by Nathoo and Glover (2015) included 56 participants (84% female and mean age of 45) with inflammatory bowel disease (IBD) treated with LDN (4.5 mg or 9 mg) as adjunct therapy. Clinical response was based on short inflammatory bowel disease questionnaire (SIBDQ) score, cessation of abdominal pain and/or diarrhea, or decrease in Harvey Bradshaw Index (HBI). Concomitant treatments included systemic corticosteroids, immunomodulators, and anti-TNF agents. Clinical response was seen in

54% of the participants, and 71% of the participants on systemic steroids were able to taper their dosage while on LDN therapy (Nathoo & Glover, 2015).

The case series demonstrates the potential of LDN to be used as adjunct therapy in the treatment of IBD. The adverse effects reported in this case series were minimal and included insomnia, headache, and nausea. Thus, the potential for LDN as an adjunct therapy to decrease the dosing or overall need for additional treatment modalities in IBD patients is a promising finding.

Similar results were seen in an empirical interventional before-and-after study conducted by Raknes, Simonsen, and Smabrekke (2018) which assessed the impact of LDN on corticosteroid use in IBD patients with a subgroup looking specifically at participants with Crohn's disease. It included 256 persistent LDN users, classified as participants who had at least one LDN prescription recorded in the Norwegian Prescription Database (NorPD). The study analyzed users' prescriptions two years prior to LDN initiation and two years after. Results showed a reduction in the use of intestinal corticosteroids, immunosuppressants, and anti-inflammatory agents (Raknes et al., 2018). In the subgroup of patients with Crohn's disease with one dispensed prescription for LDN, there was a 32% relative reduction in the number of intestinal corticosteroid users however, it was not statistically significant (p-value 0.965). In the subgroup of Crohn's patients with four or more prescriptions of LDN dispensed in the two years, the number of users of intestinal corticosteroids was reduced by 44%, again not showing statistical significance (p-value 0.266) (Raknes et al., 2018).

Limitations of this study include the study design, which is not randomized and does not include a control group that did not receive LDN. Without a control group, it is difficult to avoid bias, specifically selective bias. The inclusion of IBD patients who utilized LDN prescriptions

may represent those who were more willing to use alternative treatment methods, rather than the general IBD patient population. This could have been avoided with the use of a control group. Strengths include the study's long duration of four years and the large sample size.

One potential explanation for the findings of the study above is that LDN therapy can decrease the need for pharmaceutical therapy in patients with Crohn's disease, specifically intestinal corticosteroids. The significant reduction in drug use following initiation of LDN therapy suggests an interesting hypothesis. However, this observation lacks statistical significance, randomized data, and would require further research.

Smith et al. (2007) also investigated the use of LDN as an adjunct therapy in active Crohn's disease in a prospective cohort study comprised of 17 patients with Crohn's Disease Activity Index (CDAI) score of 220-450. Patients were given a daily dosage was 4.5 mg of oral naltrexone. Infliximab was not allowed for the duration of the 12-week study, however, adjunct Crohn's treatments with stable doses for four weeks prior to study onset were allowed. Inflammatory bowel disease questionnaire (IBDQ), the short form quality of life survey, and CDAI scores were used to assess patient response prior to initiation and at four-week intervals. CDAI scores decreased by 49% from baseline in the 12th week of LDN therapy with a statistically significant decrease after four weeks of completing therapy (p-value 0.01) (Smith et al., 2007). The number of bowel movements and pain assessment portions of the CDAI score were evaluated separately which showed a statistically significant improvement from baseline (Smith et al., 2007). Also, 89% of patients showed a response to therapy and 67% achieved remission (p-value < 0.001). Both IBDQ and quality of life survey demonstrated significant improvement in quality of life on LDN therapy.

The cohort study above shows promising results of LDN as an adjunct therapy in active Crohn's disease. The statistical method used to adjust collected data included the Bonferroni method, which allows overall confidence coefficients to be maintained to prevent data from inaccurately appearing statistically significant. However, limitations included a small sample size of 17 participants and an unequal gender distribution, with only three participants being male. Also, it was an open-label study, so participants knew what drug was being administered which has the potential to skew results via the placebo effect, particularly in the case of subjective assessments of each participant completing quality of life questionnaires. Though the above pilot study was small, it demonstrated proper methodology with statistically significant results which warrant further research.

Efficacy of Low-Dose Naltrexone for Treatment of Fibromyalgia Compared to Placebo

Fibromyalgia is another complex chronic condition that is still not completely understood and one that remains difficult to treat. It consists of chronic widespread pain, tender points throughout the body, fatigue, mood changes, and sleep disturbances all with unknown origin. The ability of LDN to interact and produce a rebound analgesic effect involving the OGF-OGFr axis suggests potential benefits in this complex condition. There is limited research on its use, however in 2012 Ramanathan, Panksepp, and Johnson released results of a case report that utilized LDN in a male patient with newly diagnosed fibromyalgia. The patient's symptoms were significantly impacting his quality of life and included trouble concentrating, insomnia, gastrointestinal symptoms, and significant tender points. The patient was treated with doses of LDN beginning at 1 mg and titrated up to 4.5 mg for the six-month duration of the study (Ramanathan, Panksepp & Johnson, 2012).

Results included a significant reduction in subjective pain, rating it seven out of 10 before initiation of LDN and four out of 10 post-initiation. The patient also had a significant increase in pain tolerance as demonstrated by the Cold Pressor Test (CPT) with his tolerance increasing from seven to 46 seconds post-initiation of LDN. The patient reported minimal side effects and an increase in overall quality of life, the patient was even able to begin previous employment again. (Ramanathan et al., 2012).

Limitations of this case report include its study design, which prevents results from being generalized across an entire patient population. Additionally, the only objective measurement in this report was the use of CPT and the testing was not blinded. The other methods of evaluation in this case report were subjective self-reporting to the primary physician, which increased the risk of bias. It was also not stated directly in the case report if the patient was on any additional therapy in conjunction with the LDN, which leaves ambiguity when evaluating the patient's response to treatment. This case reports suggested the potential for LDN to benefit fibromyalgia patients by improving their pain tolerance and overall quality of life. However, further research is required with controlled, blinded trials to further understand the efficacy of LDN in fibromyalgia symptom management.

Since the previously discussed case report, additional research on LDN use in fibromyalgia has been conducted. Younger, Noor, McCue, and Mackay (2013) continued to investigate the use of LDN in 31 females with fibromyalgia pain in a small, randomized, double-blind, placebo-controlled crossover trial that was an extension study of previous clinical trials. Participants were given 4.5 mg of oral naltrexone daily and their pain levels were assessed daily using an intensive longitudinal design. Results indicated a significantly greater reduction of baseline pain in those taking LDN compared to placebo with a 28.8% reduction versus 18.0%

reduction in daily pain levels respectively (Younger et al., 2013). In addition, the LDN group was associated with improved life satisfaction (p-value 0.045) and mood (p-value 0.039). The criteria for a beneficial response was considered a significant reduction in pain plus a significant reduction in fatigue or sleep problems. In the fibromyalgia group, 32% of participants met the criteria for response compared to 11% in the placebo group. Though the results of this study suggest LDN has a beneficial impact on fibromyalgia pain, the small sample size and lack of diversity in patient gender cause hesitance when applying results to the general population.

More recently, a 10-week pilot, single-blind crossover trial was conducted by Parkitny and Younger (2017) to evaluate the immunologic effects of 4.5 mg of oral LDN daily in eight female fibromyalgia patients with an average age of 46 years. The trial consisted of a two-week baseline phase and an eight-week LDN administration phase. Blood samples were collected twice weekly and symptoms were assessed twice daily using a 0-100 visual analog scale (Parkitny & Younger, 2017). Trial results showed a statistically significant reduction (p-value < 0.016) in plasma concentrations of multiple cytokines when compared to baseline levels including IL-1, IL-2, IL-4, TNF-alpha, and TNF-beta. In addition, there was a statistically significant reduction (p-value < 0.017) of fibromyalgia-associated pain symptoms and overall symptoms compared to baseline, 15% and 18%, respectively (Parkitny & Younger, 2017).

Weaknesses of this study included the small sample size, lack of gender diversity, lack of a control group, and short study duration. The small sample size makes it difficult to generalize these results to a larger population of fibromyalgia patients particularly in the male gender since the study did not include any male participants. The lack of a control group prevents conclusive results regarding the immunological changes observed to be contributed exclusively to naltrexone. Finally, the short duration of the study meant the maximal effects of LDN could not

be evaluated. The weaknesses highlighted could be improved and more conclusive results could be made by conducting larger, placebo-controlled trials that include male participants.

Efficacy of Low-Dose Naltrexone as Adjunct Therapy in the Treatment of Fibromyalgia

Research has also been conducted to investigate the use of LDN as an adjunct therapy in fibromyalgia patients. Younger, Zautra, and Cummins (2009) conducted a study that included 10 females with fibromyalgia and 10 healthy controls matched for gender, age, and income. All participants attended two laboratory sessions on separate days to receive LDN in one session and placebo in another. All participants could continue current medications during study participation, these medications included antidepressants, anti-inflammatories, muscle relaxants, and sleep-aid medications. Each administration session was randomized, double-blinded, and the participants were tested for pain sensitivity, mood measurement, and opioid withdrawal. Study results were unremarkable with both the healthy and the fibromyalgia group showing improvement in pain thresholds during the LDN administration trial. Both groups also showed significantly lower mechanical pain sensitivity during the LDN administration trial. The findings of this small study suggest that LDN does not improve pain sensitivity or mood in fibromyalgia patients.

Despite the discouraging results of the previous study, later that same year Younger and Mackey (2009) conducted a single-blind, placebo-controlled, crossover trial of 10 female fibromyalgia patients to investigate the use of 4.5 mg of LDN daily to improve fibromyalgia symptoms. The study lasted 14 weeks, which included a two-week baseline phase, placebo phase, washout phase, and an eight-week drug administration phase. All participants received both LDN and placebo to act as their own control. Daily symptom measurements, laboratory studies, and pain/sensitivity thresholds were collected. Results were promising with LDN

reducing symptoms in the entire cohort, a 30% symptoms reduction seen in the LDN administration (p-value < 0.0005) when compared to placebo (p-value = 0.003). (Younger & Mackey, 2009). Statistically significant improvement was also seen in fatigue (p-value = 0.008) and stress level (p-value = 0.003). Improvement in mechanical and heat pain thresholds was also seen during LDN administration (Younger & Mackey, 2009).

Limitations of this study include its single-blind design and small sample size. Also, the combined data showed that symptomatic improvement began to decline during the placebo phase of the study, questioning whether results seen during the administration phase should be contributed to LDN administration or a continuation of the placebo effect. A follow-up double-blind study would be ideal to substantiate results. Despite the limitations described above, this pilot study suggests a link between LDN use and the improvement of fibromyalgia symptoms.

Metyas, Chen, Yeter, Solyman, and Arkfeld (2018) conducted a prospective, open-label study that investigated LDN as adjunct therapy in 25 fibromyalgia patients (24 females and one male). All participants continued prior medications if on stable dosages for months before initiation of LDN, those on opioid therapy were excluded. Participants were started on 2.5 mg daily and titrated up to 4.5 mg daily as tolerated. The primary outcome was an improvement in the Revised Fibromyalgia Impact Questionnaire (FIQR) which assessed the impact of fibromyalgia symptoms on daily life. Results demonstrated a 19.5% improvement in the FIQR score, with half of the participants showing an average improvement of 41% after 90 days of therapy (Metyas et al., 2018). The only side effect reported during the study was diarrhea.

There are some limitations to the study discussed above, including the small sample size and the lack of a control or placebo group. It was an open-label study which means participants' subjective improvement could have been due to the placebo effect. Many of the participants were

on different dosages of LDN according to what they could tolerate, causing an unclear picture of the LDN dose required to provide a therapeutic effect. With many participants on additional medical therapy, it is difficult to assess whether the response was due to synergistic effects or due to LDN alone. This is a preliminary study that showed similar results as previous studies which suggest possible benefits of LDN as an adjunct therapy in fibromyalgia patients.

Discussion

Based on the literature review above, LDN possesses unique analgesic and immunomodulatory properties. The most likely explanation for this was first described by Donahue et al. (2011) which suggested LDN could interact with the OGF-OGFr axis that played a role in cellular proliferation. Patten et al. (2018) also supported this hypothesis and went further to explain the rebound effect of LDN when administered in lower-than-normal dosages. The intermittent blockade caused by the small dosages led to a compensatory increase in endogenous opioid production and reduced cellular proliferation of T and B cells. Furthermore, Patten et al. (2018) suggested that the dysregulation of the OGF-OGFr axis seen in Crohn's and fibromyalgia can be improved by LDN's increase in endogenous opioid production, leading to an improved pain response (Patten et al., 2018).

Animal studies conducted by Yi et al. (2016) showed LDN also interacts with the immune system, influencing surface marker expression on macrophages. Additional animal studies demonstrate immunomodulatory properties, such as an increased threshold for T-cell activation and depression of cellular proliferation (Donahue, McLaughlin & Zagon, 2011). Though these studies were small and animal-based, the results suggest that LDN has unique properties that could be used to benefit patients suffering from autoimmune and chronic pain conditions. Current trends support this theory with a growing number of providers now

prescribing LDN in autoimmune and chronic pain conditions to increase endogenous opioid production, to improve pain, and decrease the need for opioid therapy.

The reviewed studies also show that LDN is a safe pharmaceutical therapy that has a low side effect profile. This is supported by the systemic review by Bolton et al. (2019) which had a large sample size and only included randomized controlled trials. It demonstrated no increased risk of serious adverse events when compared to placebo. This is also supported by the study conducted by Smith et al. (2011) which demonstrated no adverse effects in the control group receiving LDN compared to placebo. However, there are limited studies available that confirm the safety of LDN when used for extended periods (i.e. decades), as would be necessary for use in these chronic conditions. Thus, the safety of long-term use of LDN for Crohn's disease or fibromyalgia remains unknown.

Assessing LDN's financial feasibility and pharmaceutical stability are other important factors when considering its use in chronic conditions. The unique immunomodulatory properties of LDN are seen specifically in low dosages, thus the need for compounding of the medication through specific compounding pharmacies. The cost of production and stability of the compounded medication are important factors that contribute to patient compliance and cost. The scientific study by Cote et al. (2018) showed that LDN capsules remained at the labeled potency even after 360 days. The extended stability allows for reduced pharmaceutical waste, leading to lower pharmaceutical costs. It also gives patients the ability to fill larger quantities at once, increasing patient convenience and compliance. This study demonstrates that LDN is a financially feasible pharmaceutical option for pharmacies and has the potential to be a low-cost, convenient pharmaceutical therapy.

Efficacy of Low-Dose Naltrexone in Crohn's Disease

Current treatment options available for Crohn's disease have many intolerable side effects. Chronic systemic corticosteroid use leaves patients at risk for osteoporosis, hypertension, diabetes, weight gain, cataracts, and many other conditions. Immunosuppressants, such as TNF blockers, leave the patient at risk for opportunistic infections such as tuberculosis, influenza, and lymphomas. It is the low side-effect profile of LDN and the unique analgesic effects that may explain the significant interest in it as a potential treatment option. In addition, its minimal pharmaceutical interactions and its potential to decrease the need for additional pharmaceutical therapy contribute to the increased interest. This may also explain why some providers are beginning to prescribe it off-label for this complex disease, even with the limited data supporting its use.

When used alone, studies demonstrate LDN has the potential to be an effective treatment option in Crohn's disease. Studies by Parker et al. (2018) and Smith et al. (2011) showed LDN could improve mucosal healing and increase remission rates without significant adverse effects compared to placebo. Studies investigating the use of LDN as an adjunct therapy in Crohn's disease have yielded similar results. Results from Nathoo and Glover's (2015) retrospective study and Smith et al. (2017) cohort study demonstrated LDN's ability to improve quality of life and abdominal pain in Crohn's disease when used as adjunct therapy. The studies also demonstrated the potential of LDN to allow titration or cessation of higher-risk therapies, such as corticosteroids, which is also an exciting possibility. However, these studies had small sample sizes that limit the ability to draw casual associations and apply results to the general population. Therefore, results must be interpreted with caution.

The limitation of small sample size also applies to the current studies conducted in the pediatric Crohn's population. The case report published by Shannon et al. (2010), and the pediatric pilot study conducted by Smith et al. (2013) all share the major limitation of a small sample size. However, the results are promising with patients showing symptomatic improvement with no report of serious adverse effects. This finding is especially significant in the pediatric population where treatment of Crohn's begins earlier in life, causing more significant growth consequences and increased risk of long-term disability.

Currently, there are very limited treatment options for pediatric patients with Crohn's disease. Corticosteroids, such as prednisone, are used to manage acute flares; however, these can have detrimental side effects especially in the pediatric population when used long-term. Furthermore, immunosuppressants, such as TNF-alpha blockers, can cause severe immunosuppression and leave children susceptible to a variety of communicable diseases. Though the data is limited and the studies are small, LDN's ability to improve symptoms of Crohn's disease in both the adult and pediatric population, along with its low side-effect profile, warrant further investigation.

Efficacy of Low-Dose Naltrexone in Fibromyalgia

Fibromyalgia is another complex, chronic disease that remains difficult to treat. It is a condition that is not only difficult to treat but also difficult to diagnose. Currently, the clinical assessment tools for symptom severity in fibromyalgia entail subjective assessments of pain, symptom severity, and overall quality of life making it difficult to quantitatively assess. Fibromyalgia also remains a difficult condition to treat because of poor symptomatic response with traditional treatment methods. Current treatment methods include nonprescription pain relievers, tricyclic antidepressants, and physical or occupational therapy.

Based on current research, it continues to remain unclear if LDN is an effective treatment option for fibromyalgia patients. Studies from Younger et al. (2013) and Parkitny and Younger (2017) both demonstrated that LDN reduced pain and improved quality of life in fibromyalgia patients. However, these studies were small and only included female participants. Though it can be argued that because most individuals diagnosed with fibromyalgia are of the female gender, the results can still be applied to the larger fibromyalgia population making the results worthwhile. The use of subjective clinical assessment tools in these studies increases the chance of the placebo effect contributing to the participants' symptomatic improvement rather than the LDN administration itself. Study findings suggest the need for research on more quantitative means to assess and monitor fibromyalgia symptoms, as well as research to determine the efficacy of LDN for fibromyalgia treatment compared to placebo.

Research investigating LDN as an adjunct therapy in fibromyalgia showed mixed results. Initial studies by Younger, Zautra, and Cummins (2009) demonstrated unremarkable results with no significant difference in pain thresholds between the control group and the LDN groups during LDN administration. In contrast, another study performed by Younger and Mackey (2009) later that same year demonstrated a 30% reduction of fibromyalgia symptoms in the entire cohort of participants. Currently, most available research regarding LDN use in fibromyalgia involves the same principal investigator or group of researchers. This increases the chance of bias and may bring into question the validity of research, despite the apparent proper methodology of the studies. These conflicting results make it difficult to draw concrete, evidence-based conclusions regarding the efficacy of LDN use in fibromyalgia.

Current research investigating LDN and its use in Crohn's disease and fibromyalgia has included small randomized-controlled trials, retrospective single-blind cross-over studies, open-

label studies, or case reports. Preliminary results demonstrate LDN to be safe with a very low side effect profile. Research regarding its mechanism suggests that it is LDN's specific analgesic and immunomodulatory properties that contribute to symptomatic improvement in these chronic conditions. In terms of effectiveness, results suggest a possible link between LDN and decreased inflammatory markers, pain, and mucosal healing in Crohn's disease. Regarding fibromyalgia, results are mixed with some studies suggesting the potential for LDN to improve pain symptoms and quality of life. Further research is required to evaluate its efficacy in both chronic conditions.

Applicability to Clinical Practice

The information collected and presented in this literature review will aid medical providers in making evidence-based decisions regarding the safest and most effective treatment options for patients suffering from Crohn's disease and fibromyalgia. Both conditions are complex chronic diseases that significantly impact a patient's quality of life. Many current treatment options for these conditions come with significant adverse effects that can become increasingly intolerable. This results in cessation of therapy, chronic pain, and a poor quality of life. The current opioid epidemic in the United States demonstrates that the increased use of opioid therapy to treat these chronic conditions is having determinantal consequences. Opioid addiction and unintentional overdoses have dramatically increased within the past decade and the quality of life for individuals with these chronic pain conditions remains poor.

This unfortunate circumstance presents the need for medical providers to consider alternative therapies with fewer adverse effects and a higher safety profile. A review of current research suggests that providers should be aware and potentially consider the alternative therapy, LDN, before initiation of opioid therapy. However, providers must understand and effectively communicate to their patients that there is limited research on the use of LDN for both Crohn's

disease and fibromyalgia. Providers must educate and assist patients with assessing the benefits and risks of all available treatment options. Providers must also determine if they are comfortable prescribing a therapy that has limited research regarding its use, even if that research demonstrates that LDN has minimal adverse effects and promising results. Many providers may instead choose to wait until larger clinical trials are conducted. Current research suggests that LDN offers a potentially effective, inexpensive, and safe treatment option for patients with Crohn's disease and fibromyalgia. This research substantiates the need for larger, randomized controlled trials to prove its efficacy in these complex conditions which require extensive medical management.

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