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

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Abstract

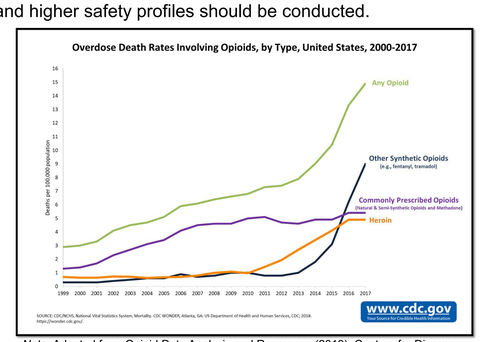
The United States has experienced a dramatic increase in opioid abuse and overdoses, leading to a national epidemic. Contributing to this epidemic is the use of opioid therapy for complex chronic inflammatory and neuropathic conditions that remain difficult to treat. Many traditional treatments are ineffective 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 potential for LDN to improve pain symptoms and quality of life in fibromyalgia patients, 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, minimal side effects, 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.

Introduction

- Increased narcotic use has led to a dramatic rise in opioid abuse and accidental opioid overdoses in the United States
- Chronic inflammatory and neuropathic conditions such as Crohn's disease and fibromyalgia are complex disorders that remain difficult to treat
- Providers utilize opioids in these disorders when all other pharmaceuticals have failed
- To combat this issue, the search for alternative treatment options continues with a focus on alternative treatments with fewer adverse effects
- LDN has unique analgesic and immunomodulatory properties and a low side effect profile

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.



Note. Adapted from Opioid Data Analysis and Resources (2019). Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/drugoverdose/images/data/OpioidDeathsByTypeUS.PNG

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?

Literature Review

Analgesic and Immunomodulatory Properties of LDN

- Mouse models suggest the dysregulation of the opioid growth factor (OGF) and opioid growth factor receptor (OGFr) may contribute to a variety of diseases, including Crohn's disease and fibromyalgia (Patten et al., 2018).
- OGF-OGFr dysregulation leads to decreased natural production of OGF or the inability of OGF to bind to the OGFr due to altered receptor sensitivity (Patten et al., 2018).
- LDN competitively binds to OGFr preventing OGF binding for a short duration, leading to an intermittent blockade of the receptor (Patten et al., 2018).
- The intermittent blockade triggers a compensatory mechanism that upregulates production of OGF and increases OGFr receptor sensitivity (Patten et al., 2018).

Safety Profile of LDN

- Bolton et al. (2019) demonstrated LDN had no increased risk of serious adverse events when compared with placebo.
  - Results were consistent across trials with varying duration, dosages, and conditions.

LDN for Treatment in Crohn's Disease vs. Placebo

- Smith et al. (2011) conducted a prospective double-blind, randomized controlled trial.
  - 88% had a 70-point decrease in CDAI scores compared to 40% decline in the placebo group (p-value=0.009) (Smith et al., 2011).
- A pilot study of 14 pediatric participants with moderate to severe Crohn's disease demonstrated promising results.
  - PCDAI scores significantly improved (p-value=0.005) when comparing pretreatment and post-treatment scores (Smith et al., 2013).

LDN as Adjunct Therapy in Crohn's Disease

- Smith et al. (2007) investigated the use of LDN as adjunct therapy in active Crohn's disease in a prospective cohort study comprised of 17 patients.
  - 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 (Smith et al., 2007).

LDN for Treatment in Fibromyalgia vs. Placebo

- 10-week pilot, single-blind crossover trial with eight female fibromyalgia patients by Parkitny & Younger (2017).
  - Results statistically significant reduction (p-value < 0.016) in plasma concentrations of multiple cytokines when compared to baseline including IL-1, IL-2, IL-4, TNF-alpha, and TNF-beta.
  - 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).
- 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.
  - 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).
  - LDN group was associated with improved life satisfaction (p-value 0.045) and mood (p-value 0.039).

LDN as Adjunct Therapy in Fibromyalgia

- LDN as 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.
  - Results were unremarkable, both groups showed significantly lower mechanical pain sensitivity and improvement in pain thresholds during the LDN administration trial.
- 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.
  - LDN reduced 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).

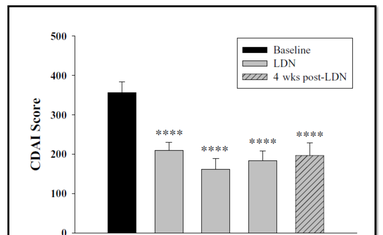


Figure 1. Mean Crohn's disease activity index (CDAI) scores ± SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy and 4 wk after discontinuation of LDN therapy (wk 16). ****Significantly different from baseline at $P < 0.0001$.

Note. Adapted from "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease" by J. P. Smith et al., 2007, *The American Journal of Gastroenterology*, *102*(4), 820–828.

Discussion

LDN's Analgesic Properties and Safety Profile

- Current research supports analgesic properties of LDN via its intermittent blockade of opioid receptors which produce a compensatory increase in endogenous opioids, which contributes to its analgesic and immunomodulatory properties.
- Studies also demonstrate LDN to be a safe pharmaceutical option due to its low side effect profile.

LDN use in Crohn's Disease

- Smith et al. (2011) showed LDN could improve mucosal healing and increase remission rates without significant adverse effects compared to placebo. The potential of LDN to decrease or even eliminate the need for therapies such as corticosteroids, in Crohn's disease is an exciting possibility.
- However, current studies have small sample sizes, requiring results to be interpreted with caution
- Though the data is limited, 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.

LDN use in Fibromyalgia

- It continues to remain unclear if LDN is an effective treatment option for fibromyalgia.
- Studies from Younger et al. (2013) and Parkitny and Younger (2017) both demonstrated that LDN reduced pain and improve quality of life in fibromyalgia patients. However, these studies were small and only included female participants.
- Though it can be argued that because the majority of individuals diagnosed with fibromyalgia are of the female gender, the results can be applied to a large portion of the fibromyalgia population making the results worthwhile.

Applicability to Clinical Practice

- Aid medical professionals in making evidence-based decisions regarding treatment options for patients suffering from Crohn's disease and fibromyalgia
- Inform providers of new and upcoming potential treatment options for patients with these complex chronic diseases
- Encourage providers to do a proper and thorough risk and benefits assessment of all treatment options prior to treatment initiation
- Provide information regarding alternative treatment options to opioid therapy in chronic disease to prevent worsening of current opioid epidemic

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