

# Treating chronic pain with low dose naltrexone and ultralow dose naltrexone: a review paper.

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## Abstract

Naltrexone is an opioid receptor antagonist with FDA approval for treating opioid addiction since 1984. While typical dose for treating opioid addiction with naltrexone is between 50 mg to 150 mg, the use of low dose naltrexone (LDN) with doses ranging from 1.5 mg to 4.5 mg per day has been growing in popularity. The most common use of LDN has been treating autoimmune disorders; consequently, there have been clinical trials investigating the effectiveness of LDN for clinical conditions such as multiple sclerosis, systemic sclerosis, and Crohn's disease. More recently, exploring the role low dose naltrexone and ultra-low dose naltrexone (microgram dosing of naltrexone) for chronic pain have been described in the literature. It has been proposed that LDN halts inflammatory cascades via glial cell inactivation. In addition, the role of microgram dosing of naltrexone has shown promise as a means to increase analgesia and decrease tolerance to opioid medications. This review evaluates the existing evidence for using LDN for treating pain and its microgram dosing in the potentiation of opioid medication while reducing side effects.

**Keywords:** Naltrexone, chronic pain, low dose, autoimmune, hormesis, therapeutic, crohn's disease.

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## History of Naltrexone

Naltrexone is an opioid receptor antagonist created by Endo Laboratories in 1963 [1]. In 1984, the FDA approved the use of naltrexone for treating opioid addiction [2]. Intramuscular injection formulation of naltrexone was approved by the FDA in 2006 for alcohol dependence and in 2010 for opioid dependence. The typical dose for treating opioid addiction with naltrexone is between 50 mg to 150 mg [3].

In contrast, low dose naltrexone (LDN) therapy utilizes much lower doses of naltrexone, usually ranging between 1.5 mg to 4.5 mg per day. Furthermore, microgram dosing of low dose naltrexone, referred to as ultralow dose naltrexone (ULDN), has been described in the literature.

### **Characterization of naltrexone: pharmacodynamics, mechanism of action, and pharmacokinetics**

Naltrexone functions as a competitive antagonist for mu, kappa, and delta opioid receptors. Naltrexone selectively binds to the mu-opioid receptor as opposed to the kappa opioid (about 1:10) and to delta opioid receptors (about 1:100) [4].

Naltrexone is metabolized in the liver to 6beta-naltrexol, a competitive peripheral opioid antagonist, with about half the affinity of naltrexone. However, the plasma half-life of 6beta-naltrexol is 13 hours whereas the plasma half-life of naltrexone is only 4 hours [5].

### **Current use of LDN therapy in the practice of medicine**

Clinical use of the low dose naltrexone was pioneered by Dr. Bernard Bihari [6] in the 1980s who observed the regulation of immune function with use of low dose naltrexone in clinical practice. Bihari initially used LDN in those with human immunodeficiency virus (HIV) and later, in those with cancer

[6]. Today, LDN is most recognized in for the management of autoimmune conditions. Accordingly, clinical trials are beginning to emerge. The effectiveness of LDN in the treatment of autoimmune conditions such as Crohn's disease, multiple sclerosis, and systemic sclerosis are under active investigation [7-9].

In 2014, the FDA approved Contrave, a weight loss medication, which contains 8 mg of naltrexone combined with 80 mg of bupropion in extended-release tablets. Combining bupropion and low dose naltrexone is believed to synergistically activate proopiomelanocortin (POMC) neurons in the hypothalamus. The latter results in the loss of appetite and increased energy output [10]. While this application is not directly related to treating pain, it demonstrates how low dose naltrexone may differ from pharmacological doses of the drug.

### **Theoretical basis of using ultralow dose naltrexone for pain: hormesis v. mu-opioid receptor-antagonist interaction.**

The theory of hormesis may best explain the mechanistic actions of Ultralow Dose Naltrexone. Hormesis, is a phenomenon in which, lower doses of a given antagonist may act, conversely, as a weak agonist. The action is biphasic; i.e., when an antagonist is given at a low dose, weak stimulation takes place whereas the same antagonist, given at a high dose, results in inhibition [11]. The initial low dose of a drug may cause a temporary disruption in homeostasis. This is followed by an adaptive and compensatory stimulation [12].

The Naltrexone-mu receptor complex may provide another mechanistic explanation as to how LDN may work. Co-authors, Crain and Shen [13], published the results of in vitro and in vivo studies evaluating the effects of morphine plus naltrexone

on nociceptive types of dorsal-root ganglionic neurons [13]. These studies demonstrated that ultra-low doses of naltrexone enhanced morphine's anti-nociceptive actions and reduced opioid tolerance and dependence. It is believed that ultra-low dose naltrexone may function to inhibit activated opioid receptors thereby resulting in recovery of these receptors to their original resting state. While this may explain how LDN enhances the anti-nociceptive activities of morphine, there is still much unknown about the exact mechanism of low dose naltrexone.

#### ***Oxycodone/Ultra-low dose naltrexone: oxytrex-investigational medication***

Oxytrex is an investigational medication that combines ultra-low dose naltrexone (1 µg) with a therapeutic dose of oxycodone [14]. Chindalore et al. [15] sought to evaluate this medication and published the results of a randomized double-blind, placebo-controlled trial of 360 patients. All patients had moderate to severe chronic pain caused by osteoarthritis of the knee or hip [15]. The patients were randomly divided into the following four groups:

- Group 1: Placebo
- Group 2: Oxycodone QID (Oxycodone 40 mg/day)
- Group 3: Oxytrex QID (Oxycodone 40 mg/day+naltrexone 4 µg/day)
- Group 4: Oxytrex BID (Oxycodone 40 mg/day+naltrexone 2 µg/day)

Each group was treated for 3 weeks using the above doses. The results of the study revealed that Group 4 (Oxytrex BID group) reported a 39% reduction in pain, which was significantly greater than placebo group ( $P<0.001$ ), Oxycodone QID group ( $P=0.006$ ) and Oxytrex QID group ( $P=0.003$ ). The authors concluded that Oxytrex BID produced the best pain relief and that adding ultra-low dose naltrexone to oxycodone enhanced and prolonged analgesic effects.

In 2006, Webster et al. [16] conducted a randomized controlled trial on 716 patients with chronic low back pain. The patients were divided into four groups as listed below [16]:

- Group 1: Placebo
- Group 2: Oxycodone QID (Oxycodone 80 mg/day)
- Group 3: Oxytrex QID (Oxycodone 80 mg/day+naltrexone 4 µg/day)
- Group 4: Oxytrex BID (Oxycodone 80 mg/day+naltrexone 2 µg/day)

Each group was treated for 12 weeks. Group 4 (Oxytrex BID group) reported a 55% decrease in physical dependence than patients on oxycodone ( $P=0.01$ ) in addition to decreased constipation (44%,  $P=0.01$ ), and somnolence (33%,  $P=0.03$ ) while experiencing comparable analgesic effects. The authors concluded that Oxytrex minimized physical dependence while providing effective analgesia.

While Oxytrex is referred to as an agonist/antagonist combination, the description is not entirely accurate as the regular dose of naltrexone starts at 50 mg. Since Oxytrex

contains 1 microgram of naltrexone and contains therapeutic doses of Oxycodone, it is more accurately described as an agonist/ultra-low dose antagonist medication.

Unfortunately, the manufactures of Oxytrex, Pain Therapeutics, subsequently abandoned the development of Oxytrex and have returned the intellectual property rights for Oxytrex to Albert Einstein College of Medicine [17]. Therefore, ultra-low dose naltrexone is not available through conventional pharmacies at this time. In the U.S., licensed medical practitioners may prescribe ultra-low dose naltrexone through specific compounding pharmacies.

In theory and conclusion, ultra-low dose naltrexone has the potential to augment the pain relief mechanisms of opioid medications while reducing potential side effects from narcotic medication.

#### ***Morphine/Low dose naltrexone: embeda, using LDN for abuse deterrent purposes***

In 2014, the FDA approved the use of Embeda as an abuse deterrent. Embeda contains 20 mg of morphine and 0.8 mg sequestered naltrexone [17]. Sequestered naltrexone is intended to remain contained within an indigestible inner core when the product is swallowed whole. However, crushing the pill negates this property, releasing naltrexone and results in an antagonist action of naltrexone i.e., serving to block the effects of morphine. This design is expected to reduce abuse potential as crushing the pills and ingesting the powder through oral and intranasal routes would inhibit the desired euphoria. Unfortunately, there are cases of people crushing Embeda and ingesting the powder. The latter also results in narcotic withdrawal symptoms.

Embeda does not qualify as an example of LDN for pain control. However, the Embeda experience provides two helpful observations. First, it lends support to the dosing of ultra-low dose naltrexone in microgram ranges when used with existing opioid medications [18]. Second, it lends support to the current practice of avoiding LDN use when a patient is on narcotic medications to avoid potential narcotic withdrawal symptoms.

#### ***Using LDN for chronic pain***

While LDN is best known and used clinically for immune modulation, there is increasing interest in the use of LDN for treating chronic pain syndromes.

#### ***Mechanism of LDN for Treating Pain***

In 2012, Ramanathan et al. [19] published an article that questioned the connection between fibromyalgia and an endorphin deficit [19]. The authors note that fibromyalgia appears to be a complex syndrome that includes, in addition to pain, additional symptoms of sleep deficits, daytime fatigue, and altered cognition/mood [20]. Ramanathan et al. [19] proposed that LDN may be a viable treatment option [20]. LDN is long thought to increase endorphins through receptor up-regulation and increased production of endorphins due to negative feedback [21].

Recently, an alternate 2014 study questions if LDN acts more as an anti-inflammatory molecule, one which targets toll-like receptor 4 (TLR4) found within the microglia [22]. Microglia, once activated, produce inflammatory factors that result

in sensitivity to pain, fatigue, cognitive impairment, sleep impairment, and mood disorders. As a TLR4 antagonist, LDN is thought to reduce the inflammatory state in the CNS, thereby resulting in decreased pain and increased opioid analgesia. Subsequently, naltrexone and naloxone have been studied, in vivo, for the reversal of neuropathic pain via TLR4 [23].

When coupled with acupuncture, authors observed that ultra-low dose naltrexone appears to have a synergistic effect. Hesselink and Kopsky [24] described this synergistic effect in article titled “enhancing acupuncture by low dose naltrexone” [24]. The evidence of co-sharing the pain relief pathway via acupuncture and naltrexone is evidenced by many early studies of acupuncture. Essentially, the acupuncture response was blocked by naltrexone [25].

### ***The use of LDN in the treatment of Fibromyalgia***

To date, there is no consensus as to the pathophysiological mechanism of fibromyalgia. The disease is not responsive to anti-inflammatories and it is therefore not considered a disorder of inflammation, in the classical sense [26]. It is thought that conditions such as fibromyalgia may involve chronic glial cell activation with subsequent production of pro-inflammatory mediators [27]. Per mechanism of action as proposed per previous studies, as noted above, LDN may offer promise in the treatment/symptom amelioration in those afflicted with fibromyalgia (FM).

In 2009, Younger et al. [28] completed the first clinical trial evaluating the use of LDN in the treatment of FM [28]. Trial design was that of a single-blind, cross-over study with duration of 14 weeks. Ten women diagnosed with fibromyalgia were included in the study. LDN was dosed at 4.5mg, at night, 1 hour prior to bedtime, for a total of 8 weeks. LDN administration was preceded by a baseline (2 weeks) and use of placebo (2 weeks) and proceeded by a washout period (2 weeks). Outcome measures were achieved via daily, self-reported fibromyalgia symptom severity in addition to 2 week sensory testing protocols, which obtained mechanical, hot, and cold pain thresholds and the use of the fibromyalgia impact questionnaire (FIQ). The use of LDN resulted in a 30% reduction in fibromyalgia symptom severity ( $p=0.0005$ ) as well as significant decrease in pain ( $p=0.001$ ), fatigue ( $p=0.008$ ), and stress ( $p=0.003$ ).

Due to the promising results and also limitations of the 2009 study, namely its single blind design, short duration, and small sample size, the authors completed a second clinical trial in 2013 [29]. Unlike the first, this was a randomized, double-blind, placebo controlled, counterbalanced, crossover study. The sample size was only slightly larger with a total participation of thirty-one women diagnosed with fibromyalgia. Similar to the first, dosing of LDN was that same at 4.5 mg, at night, 1 hour prior to bedtime. Protocol duration was 22 weeks per participant. Use of LDN or placebo was preceded by a baseline period (2 weeks) and follow-up period (4 weeks). In an effort to minimize attrition, placebo was given for 4 weeks while LDN was administered for 12. There was no washout period. Outcome measurements included daily pain severity (primary outcome) with life satisfaction, mood sleep quality, and fatigue secondary outcomes. The use of LDN resulted in a 32% response rate, which was defined as a reduction of pain plus

fatigue or sleep problems as opposed to placebo response at 11%. Pain reduction was most significant with LDN treatment ( $p=0.016$ ). In addition, patient’s general satisfaction with life was significantly increased as opposed to placebo ( $p=0.045$ ) as was mood ( $p=0.039$ ). Unlike the initial study, the authors did not find an effect of low dose naltrexone on fatigue.

Both the 2009 and 2013 trials by Younger et al. [22] collected baseline labs on all patients. These labs included erythrocyte sedimentation rate (ESR). When both study groups were aggregated, it was noted that fibromyalgia patients with greater ESR at baseline had a greater response rate to the use of LDN for pain ( $p=0.0001$ ) [22]. There was no such association with placebo administration. This suggests that the effects of LDN may include the reduction of inflammation. However, its reach into the amelioration of fibromyalgia is likely more expansive as fibromyalgia is more likely a central immune disorder associated with an amplification of pain. (Unfortunately, the authors did not measure ESR at the conclusion of both trials.) More studies are certainly needed to correlate LDN with ESR levels. Its application may positively impact conditions characterized by high ESR.

### ***LDN and complex regional pain syndrome- a case report***

Complex Regional Pain Syndrome is of a similar presentation to fibromyalgia although is unique in its intensity and duration. Although fibromyalgia can come and go into remission for weeks or months, CRPS does not typically wax and wane [30]. The associated pain is of grave intensity as compared to the pain of fibromyalgia. There are three, primary proposed physiological causes in the development of CRPS; these include inflammatory cascades, vasomotor dysfunction and central nervous system pathology [30]. Like fibromyalgia no consensus as to a pathophysiological mechanism exists.

While there are no clinical trials to date on the use of LDN for the treatment of CRPS, a 2013 case study describes its positive impact on a young 17-year-old female with the diagnosis of intractable CRPS [31]. The patient presented with a chief complaint of left lower extremity pain rated at an 8/10 (10 being most) on a pain visual analogue scale (VAS). Despite varied administration of gabapentin, ibuprofen, nortriptyline, transdermal clonidine, and trazadone, pain continued with minimal change. LDN was eventually administered at 1.5 mg alongside trazadone. At four weeks the patient rated her pain on the VAS at 1/10. The patient remained at a dose of 1.5mg LDN with good tolerance. It is thought that the application of LDN for CRPS may result similarly to fibromyalgia, in modulation of CNS immune activation and decreased inflammation.

### **Discussion**

While the original clinical use of LDN by Dr. Bihari focused on HIV patients and cancer patients, to date LDN is primarily used in the treatment of autoimmune conditions. The latter is supported by emerging evidence. In addition, LDN has been incorporated into FDA approved medications such as Embeda and Contrave, demonstrating its diverse therapeutic mechanisms.

As noted per given studies, it is proposed that LDN may best act as a glial cell antagonist thereby preventing their activation and subsequent inflammatory cascades. This mechanism may

explain why and how LDN may function to not only treat autoimmune conditions but also mitigate pain response. The latter is best exhibited per the two summarized clinical trials which demonstrated the positive effect of LDN in the treatment of fibromyalgia. However, these studies should be considered foundational research that sets the stage for multi-center randomized controlled trials.

The use of ULDN appears to be more complex as efforts to develop Oxytrex have failed; Oxytrex combined one microgram of naltrexone combined with therapeutic dose of oxycodone. While compounding of 1 microgram of naltrexone is theoretically possible, a commercial assay to verify the dose is not easily available at this time in the U.S.

## Conclusion

LDN may offer an innovative, safe, and affordable way to treat pain conditions. Its actions are diverse and therefore, it may offer broad therapeutic potential in many conditions. As of now, it may be best suited in conditions associated with immune deregulation however, its use in inflammation, and aberrant pain response deserve further research. In so doing, the best utilization of LDN in the treatment of chronic pain will emerge and the very nature of these conditions further elucidated.

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