THE SCIENCE BEHIND LOW DOSE NALTREXONE

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Low dose naltrexone (LDN) has been demonstrated to reduce symptom severity in conditions such as fibromyalgia, Crohn's disease, multiple sclerosis and complex regional pain syndrome. Evidence indicates that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action on microglial cells.

Mechanism of Action

Naltrexone exerts its effects on humans via at least two distinct receptor mechanisms. In addition to the antagonist effect on mu-, delta- and kappa-opioid receptors, naltrexone simultaneously has an antagonist effect on non-opioid receptors (Toll-like receptor 4 or TLR4) that are found on macrophages such as microglia {1}. It is via the non-opioid antagonist path that LDN is thought to exert its anti-inflammatory effects. Microglia are central nervous system immune cells that are activated by a wide range of triggers {2}. Once activated, microglia produce inflammatory and excitatory factors that can cause symptoms such as pain sensitivity, fatigue, cognitive impairment, sleep disorders, mood disorders, and general malaise {3}. When chronically activated, the resulting proinflammatory cascade may become neurotoxic, causing several deleterious effects {4}. Given the wide variety of inflammatory factors produced by activated microglia (e.g., proinflammatory cytokines, substance P, nitric oxide, and excitatory amino acids) {5}, a range of symptoms and medical outcomes could share the pathophysiological mechanism of central inflammation. Conditions such as fibromyalgia may involve chronic glial cell activation and subsequent production of proinflammatory factors. The hypothesis is indirectly and partially supported by the high degree of symptom overlap between fibromyalgia and cytokine-induced sickness behaviors.

Both naltrexone and naloxone have been demonstrated to exert neuroprotective and analgesic effects {6}. The neuroprotective action appears to result when microglia activation in the brain and spinal column is inhibited {7}. By suppressing microglia activation, the opioid antagonists reduce the production of reactive oxygen species and other potentially neuroexcitatory and neurotoxic chemicals {8}. The anti-inflammatory effect of opioid antagonists may also extend to the periphery, as evidenced by suppressed TNF-alpha, IL-6, MCP-1, and other inflammatory agents in peripheral macrophages {9}.

The hypothesis that naltrexone operates via glial cells to exert its beneficial actions is supported by work with dextro-naltrexone. Dextro-naltrexone is a stereoisomer of naltrexone which is active at microglia receptors, but has no activity on opioid receptors {10}. Dextro-naltrexone possesses analgesic and neuroprotective properties {11}. Therefore, the analgesic, anti-inflammatory, and neuroprotective effects of naltrexone do not appear to be dependent on opioid receptors.

Other targets have been proposed for naltrexone's mechanism of action, including astrocytes {12} and NADPH oxidase 2 {13}. Another hypothesis states that inducing a small and transient opioid blockade will prompt the body to compensate by upregulating both endogenous opioids and opioid receptors {40}. This "opioid rebound" effect could result in enhanced endogenous analgesia and repression of critical immune factors {14}.

Both the TLR4 and opioid receptor mechanisms may play a role in LDN action, as the hypotheses are not mutually exclusive.

Clinical Trials with LDN

I. **Fibromyalgia**

a. **Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study**
Younger J & Mackey S. Pain Med 2009 May-Jun; 10(4):663-72.
Single-blind crossover study, ten women, fibromyalgia diagnosis, naltrexone 4.5 mg qd. LDN reduced fibromyalgia symptoms in entire cohort, with a > 30% reduction of symptoms over placebo. Mechanical and heat pain thresholds were improved by the drug. Baseline erythrocyte sedimentation rate predicted over 80% of the variance in drug response. Participants with higher sedimentation rates (indicating general inflammatory processes) had the greatest reduction of symptoms in response to LDN.

b. **Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels**

c. *Younger J, Noor N, Mackey S. Arthritis Rheum 2013 Feb; 65(2):529-38.*
Thirty-one women, fibromyalgia diagnosis, naltrexone 4.5 mg qd. Significant reduction in baseline pain over placebo (28.8% reduction versus 18.0%). General satisfaction with life and improved mood were also seen with the drug. Thirty-two percent of participants met criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep problems) during LDN therapy, versus an 11% response rate during placebo therapy.

II. **Crohn's Disease**

a. **Low-dose naltrexone therapy improves active Crohn's disease**
Smith JP, Stock H, Mauger D, et al. Am J Gastroenterol 2007 Apr;102(4):820-8.
Seventeen patients, open-label, 12 weeks, naltrexone 4.5 mg qd. Histologically and endoscopically confirmed active Crohn's disease activity index (CDAI) score of 220-450. Infliximab not allowed. Other therapy for Crohn's disease continued at same dose. CDAI scores decreased significantly with LDN, and remained lower than baseline 4 weeks after completing therapy. Eighty-nine percent of patients exhibited a response to therapy and 67% achieved a remission.

b. **Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial.**
Smith JP, Bingaman SI, et al. Dig Dis Sci 2011 Jul;56(7):2088-97.
Forty subjects, 12 weeks, naltrexone 4.5 mg qd. Active Crohn's disease. Primary outcome was proportion of subjects with a 70-point decline in Crohn's Disease Activity Index Score (CDAI). Eighty-eight percent of subjects treated with LDN had at least a 70-point decline in CDAI scores compared with 40% of placebo-treated subjects. After 12 weeks, 78% of subjects treated with LDN exhibited an endoscopic response as indicated by a 5-point decline in the Crohn's disease endoscopy index severity score (CDEIS) from baseline compared to 28% response in placebo-treated controls, and 33% achieved remission with a CDEIS score < 6, whereas only 8% of those on placebo showed the same change.

III. **Irritable Bowel Syndrome**

a. **Low-dose naltrexone for the treatment of irritable bowel syndrome: a pilot study**
Kariv R, Tiomny E, et al. Dig Dis Sci 2006 Dec;51(12):2128-33.
Forty two patients, 4 weeks, open-label, naltrexone 0.5 mg qd. Global assessment improved in 76% of patients; and the weekly number of pain-free days increased from 0.5 to 1.25.

IV. Complex Regional Pain Syndrome

a. **Treatment of complex regional pain syndrome (CPRS) using low dose naltrexone (LDN)**
Chopra p & Cooper MS. J Neuroimmune Pharmacol 2013 Jun;8(3):470-6.
Two patients, open label, naltrexone 4.5 mg qd. Conventional CPRS pharmacotherapy had failed to suppress their recalcitrant CRPS symptoms. Prominent CRPS symptoms remitted in these two patients, including dystonic spasms and fixed dystonia (respectively), following treatment with LDN.

V. Multiple Sclerosis

a. **Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis**
Cree BA, Kornyeyeva E, Goodin DS. Ann Neurol 2010 Aug;68(2):145-50.
Eighty subjects with clinically definite MS, 8 weeks, double-blind, placebo-controlled, crossover study evaluating efficacy of LDN on self-reported quality of life. LDN was associated with significant improvement on the following mental health quality of life measures; 3.3-point improvement on the Mental Component Summary score of the Short Form-36 General Health Survey, a 6-point improvement on the Mental Health Inventory, a 1.6-point improvement on the Pain Effects Scale, and a 2.4-point improvement on the Perceived Deficits Questionnaire.

Conclusions

The totality of the basic and clinical research to date suggest that LDN is a promising treatment approach for conditions thought to involve inflammatory processes. The literature suggests that other inflammatory conditions such as rheumatoid arthritis, polymyalgia rheumatica, and lupus may benefit from LDN.
As conventional anti-inflammatories have poor blood-brain barrier permeability, centrally active immune modulators have become an area of interest.
Clinical trials listed on clinicaltrials.gov that are currently ongoing or recently completed include the use of LDN for glioma, fibromyalgia, metastatic melanoma, pervasive developmental disorder, multiple sclerosis, HIV, major depressive disorder and osteoarthritis.

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