Low Dose Naltrexone (LDN) – a review of evidence

Naltrexone was synthesized in 1963 as an orally active competitive opioid receptor antagonist. Naltrexone is structurally and functionally similar to the opioid antagonist naloxone, but it has greater oral bioavailability and a longer biologic half-life. Naltrexone HCl was approved by FDA in 1984 for the treatment of opioid addiction. The typical daily dosage for opioid addiction is 50.0–100.0 mg daily, and 50.0-mg tablets are available commercially. A more complete review of the early history of naltrexone can be found elsewhere.

LDN refers to daily dosages of naltrexone that are approximately 1/10th of the typical opioid addiction treatment dosage. In most published research, the daily dosage is 4.5 mg, though the dosage can vary a few milligrams below or above that common value. At the low dosage level, naltrexone exhibits paradoxical properties, including analgesia and anti-inflammatory actions, which have not been reported at larger dosages. LDN was reported to have interesting physiological properties (primarily enhancement of endogenous opioid production) in the 1980s, and the treatment approach was reported to be used clinically since the mid-1980s. Basic science work examining the use of opioid antagonists for treating disease states did not start to appear until the late 1980s, and the first published LDN trial in humans was presented in 2007. Since that time, LDN has been studied in a small number of labs and has been slowly gaining attention as a possible treatment for some chronic medical conditions.

LDN has been tested experimentally in a small number of chronic pain conditions. One such condition is fibromyalgia (FM). Although FM does not respond to common anti-inflammatory agents and does not seem to be an inflammatory disorder in the classic sense, inflammatory processes may still be involved. Two separate, small clinical trials showed that LDN may be an effective treatment for FM.

A greater amount of scientific support for LDN efficacy relates to its use in Crohn’s disease (CD). LDN has been reported to reduce not only self-reported pain in that condition but also objective markers of inflammation and disease severity (including the severity scores from endoscopic evaluation). The response rate of LDN in Crohn’s disease may be even higher than that seen in fibromyalgia, with over 80% of the study participants exhibiting significant improvement.

Naltrexone has also shown some promise in improving disease severity in multiple sclerosis. There is some evidence of reduced spasticity and improved mental health, but many clinical endpoints fail to show difference from placebo, and one study did not find improvements in any of the clinical endpoints.
Limited case-study evidence suggests that LDN may also be effective in controlling symptoms of complex regional pain syndrome (CRPS)\textsuperscript{15,16}, a disease that often shows evidence of both local and low-level systemic inflammation\textsuperscript{17}. A case report of a patient with severe diabetic painful neuropathy which was refractory to conventional management showed a marked improvement with LDN treatment which persisted over the 2 year follow up\textsuperscript{18}. Another case report of LDN use in chronic back pain also showed a significant loss of pain and return to work\textsuperscript{19}.

There may be a role for LDN in cancer treatment. Bihari has reported a small case series of significant PSA reduction in prostate cancer patients commenced on LDN\textsuperscript{20}. Another case series of 12 patients with brain tumours showed a marked increase in remission and longevity with the use of LDN, combined with lipoic acid and hydroxycitrate\textsuperscript{21}. LDN has been shown to have a selective impact on genes involved with cell cycle regulation and immune modulation, and cancer cells pre-treated with LDN were more sensitive to the cytotoxic effects of a number of common chemotherapy agents\textsuperscript{22}.

Other uses of LDN include possible benefit in depression and a randomized, proof-of-concept trial of LDN for patients with breakthrough symptoms of major depressive disorder on antidepressants showed a moderate positive response\textsuperscript{23}. There are several studies which have found potential benefit for children with autism\textsuperscript{24-28}.

Research suggests that low- and high-dose naltrexone have quite different impacts on physiology\textsuperscript{29}. LDN induces a small and transient opioid blockade which prompts the body to compensate by upregulating both endogenous opioids and opioid receptors\textsuperscript{30} and corresponds with the opioid upregulation effect of temporary naltrexone or naloxone\textsuperscript{31,32}. LDN may also attenuate inflammatory responses by blocking receptors on immune cells, including microglia\textsuperscript{33}, thereby reducing pro-inflammatory cytokines and superoxides\textsuperscript{34}; and LDN may be neuroprotective by modulating mitochondrial apoptosis\textsuperscript{35}. A potential mechanism of LDN activity in cancer involves the modulation of the native OGF–OGFr regulatory network\textsuperscript{6,36,37}.

LDN has a low reported incidence of adverse side effects and no known toxicity issues with chronic use or withdrawal symptoms when LDN treatment is stopped\textsuperscript{38}. The most common side effect is the reporting of more vivid dreams, which is seen in approximately 37% of the participants\textsuperscript{38}. Even though naltrexone has a long history of safe use with a wide range of dosages, more research is needed about the long-term safety of the drug when used chronically in low dosages.

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References


