Low Dose Naltrexone (LDN) – a review of evidence

Naltrexone was synthesized in 1963 as an orally active competitive opioid receptor antagonist[1]. Naltrexone is structurally and functionally similar to the opioid antagonist naloxone, but it has greater oral bioavailability and a longer biologic half-life[2]. 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[3].

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[3 4]. 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[3], and the treatment approach was reported to be used clinically since the mid-1980s[5]. Basic science work examining the use of opioid antagonists for treating disease states did not start to appear until the late 1980s[6], and the first published LDN trial in humans was presented in 2007[7]. 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-inflammatories and does not seem to be an inflammatory disorder in the classic sense[8], inflammatory processes may still be involved[9]. Two separate, small clinical trials showed that LDN may be an effective treatment for FM[10 11].

A greater amount of scientific support for LDN efficacy relates to its use in Crohn's disease (CD)[4 7 12]. 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)[4 7 12]. 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[4 7].

Naltrexone has also shown some promise in improving disease severity in multiple sclerosis[13]. There is some evidence of reduced spasticity and improved mental health, but many clinical endpoints fail to show difference from placebo, and one study[14] 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)[15 16], a disease that often shows evidence of both local and low-level systemic inflammation[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[18]. Another case report of LDN use in chronic back pain also showed a significant loss of pain and return to work[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[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 hydroxycitirate[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[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[23]. There are several studies which have found potential benefit for children with autism[24-28].

Research suggests that low- and high-dose naltrexone have quite different impacts on physiology[29]. LDN induces a small and transient opioid blockade which prompts the body to compensate by upregulating both endogenous opioids and opioid receptors[30] and corresponds with the opioid upregulation effect of temporary naltrexone or naloxone[31 32]. LDN may also attenuate inflammatory responses by blocking receptors on immune cells, including microglia[33], thereby reducing pro-inflammatory cytokines and superoxides[34]; and LDN may be neuroprotective by modulating mitochondrial apoptosis[35]. A potential mechanism of LDN activity in cancer involves the modulation of the native OGF–OGFr regulatory network[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[38]. The most common side effect is the reporting of more vivid dreams, which is seen in approximately 37 % of the participants[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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