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LOW-DOSE NALTREXONE (LDN) IN THE MANAGEMENT OF CHRONIC PAIN AND INFLAMMATION OF MULTIPLE SCLEROSIS, FIBROMYALGIA, CROHN'S DISEASE, AND OTHER CHRONIC PAIN DISORDERS

Chronic inflammatory diseases are complex to treat and have an impact on a large number of patients. Since the 1990s, opioid prescriptions have been increasing in prevalence in chronic inflammatory and neuropathic conditions. However, most opioids are considered less effective or have unproven efficacy in chronic conditions such as multiple sclerosis, fibromyalgia, and Crohn's disease. Due to the difficulty of treating these diseases and their great impact on quality of life, patients often seek complementary or functional medicine options to obtain relief from symptoms. Naltrexone is a mu-opioid receptor antagonist indicated by the U.S. FDA for opioid and alcohol dependence. It is hypothesized that lower than standard doses of naltrexone inhibit cellular proliferation of T and B cells and block Toll-like receptor 4, resulting in an analgesic and anti-inflammatory effect. Low-dose naltrexone (LDN) has been used off-label for treatment of pain and inflammation and evidence supports the safety and tolerability of LDN in multiple sclerosis, Crohn's disease, fibromyalgia, and other diseases.

Fibromyalgia is not considered a classic inflammatory disease, but rather a disorder of the central nervous system that has a neuroimmune component. The effect of LDN as an immune-modulator may be beneficial for treating fibromyalgia, and pilot studies have started to evaluate its impact. One single-blind crossover study looked at the serum cytokine levels of eight women over the course of 10 weeks. After 8 weeks of LDN therapy, a variety of proinflammatory markers were reduced, especially those associated with nociception and allodynia. The participants reported significantly less pain and symptoms associated with their fibromyalgia, and no moderate or major adverse effects were reported.

A recent pilot study found LDN produced a significant improvement in daily pain, stress, and fatigue associated with fibromyalgia. The study only included 12 participants, who all followed the same treatment schedule. Severity of symptoms was tracked using a visual analog scale, and the patients also underwent mechanical, thermal, and cold pain assessments every 2 weeks.

A notable effect of LDN in fibromyalgia has been increased pain tolerance. One case report involved a patient with fibromyalgia on a daily LDN dose of 6 mg undergoing a cold pressor test (CPT) to determine pain tolerance every few weeks along with self-reporting the patient's quality of life and general pain. After 18 weeks of LDN therapy, the patient's CPT time increased 10-fold. An additional small double-blinded crossover study of 31 participants showed a significant reduction in daily pain as compared to placebo and baseline pain. The participants reported not only reduction in daily pain but also significantly increased quality of life and mood.

The use of LDN as a potential anticancer agent has been researched for some time. The mechanism is presumed to be due to inhibition of cellular proliferation that occurs with intermittent blockade of OGFr.

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LOW-DOSE NALTREXONE FOR REFRACTORY PAINFUL DIABETIC NEUROPATHY

Naltrexone is a long-acting, potent, competitive opioid antagonist approved for the treatment of alcohol and opioid dependence at a dose of 50 mg/day. Naltrexone in doses of 1 mg to 5 mg daily, typically referred to as low-dose naltrexone (LDN), has been reported to treat chronic pain and autoimmune disorders. Pilot trials of LDN in Crohn's disease, multiple sclerosis, cancer-related pain, and fibromyalgia have recently been conducted with success. Hota et al. reported a case in which LDN was used for the treatment of diabetic neuropathic pain refractory to most available therapy. In April 2012, a 76-year-old male with a 30-year history of type-2 diabetes and 7 years of diabetic neuropathic symptoms presented in the endocrinology clinic with complaints of burning pain in both legs below the mid-calf level. The first time he sought treatment for neuropathic pain, he received amitriptyline, pregabalin, duloxetine, lamotrigine, and nonsteroidal anti-inflammatory drugs (NSAIDs) in varying doses and combinations. All drugs and combinations were tried for at least 1–2 months. Subsequently, he underwent a lumbar paravertebral nerve block (L2-L4) which produced near complete pain relief, but the pain reappeared in a few weeks. He also received injectable vitamin B complex and vitamin D in therapeutic doses without any benefit. Touch perception was decreased bilaterally below the knees and with hyperalgesia, but no allodynia. The temperature sensation was normal in both legs. His neuropathy symptom score was 9 out of 9. The deep tendon reflexes were absent in both ankles. The patient had adequate glycemic control (HbA1c, 6.4%) and was on metformin, pioglitazone, and insulin with good compliance. Workup for other causes of neuropathy was non-contributory. MRI of lumbar spine showed degenerative changes without any neural involvement. Based upon earlier reports, Oral LDN was prescribed in increasing dosages (1, 2, and 4 mg at bedtime for 2 weeks each). With the 2 mg dose, the patient reported a partial improvement in the burning pain. The 4 mg dose for 2

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weeks produced much greater pain relief. He rated his pain to be 5% on VAS as compared to 90% before therapy. On examination, there was no hyperalgesia, but the sensory loss was not improved. Following naltrexone therapy, initially he experienced mild diarrhea, nausea, and somnolence, which subsided spontaneously in a few days without any intervention. At every follow up the patient was satisfied with LDN (4 mg at bedtime) and was continuing the same dose until October 2014 (last follow up) without experiencing any significant side effects. The proposed mechanisms of pain relief with LDN include opioid receptor blockade causing compensatory release of endogenous opioids, and antagonism of Toll-like receptor-4 on microglia.

Pain Med. 2016 Apr;17(4):790-1.

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