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Low-dose naltrexone in treating fibromyalgia and major depressive disorder

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Low-dose naltrexone (LDN) can modulate CNS microglial cells and is being used as an experimental treatment to reduce inflammatory autoimmune processes in a number of diseases, including fibromyalgia. Additionally, LDN has been shown to demonstrate antidepressant effects by enhancing dopaminergic signaling. This mechanism suggests LDN as a possible concurrent treatment of both fibromyalgia and associated major depressive disorder. Fibromyalgia is considered a chronic disorder of central nervous system pain regulation. It is an inflammatory rheumatic disease that presents as widespread musculoskeletal pain and stiffness. Fibromyalgia does not have clear pathogenesis and consequently does not have a targeted treatment. Chronic pain and major depressive disorder are often diagnosed simultaneously; 40-60% of chronic pain patients also have depression and require concurrent treatment. There is no direct cause-andeffect relationship between chronic pain and depression; however, two illness share many biochemical, physical and cognitive symptoms. J.B. is a 32-year-old Caucasian female with a past psychiatric history of major depressive disorder, generalized anxiety disorder and panic attacks and medical history of fibromyalgia diagnosed in 2010. Patient has recurring depressive episodes with multiple etiologies including problems with her family and work and postpartum. However, many of the depressive episodes concurred with painful symptoms of her fibromyalgia and dictated by the pain level.Patien ,fibromyalgia and major depressive disorder did not respond to duloxetine. There was significant symptomatic relief of both chronic pain and depression with the initiation of 6mg naltrexone. The patient reported improvements in mood, energy, and concentration from suboptimal level. We discuss the indications of this case and the future possibility of using LDN as a treatment option for patients with concurrent fibromyalgia and major depressive disorder.

Naltrexone hydrochloride is a potential novel treatment for chronic pain. The drug is a competitive antagonist of opioid receptors, and has been used clinically for over 30 years to treat opioid addiction. More recently, naltrexone (and its shorter acting cousin, naloxone) has also been found to attenuate the production of proinflammatory cytokines and neurotoxic superoxides via suppressive effects on central nervous system microglia cells . The reduction of proinflammatory cytokines can be achieved with ultra low doses, and can reduce thermal hyperalgesia in a rat model.The effect is not due to opioid receptor activity, as the opioid nonactive isomers dextro-naloxone and dextro-naltrexone also exhibit neuroprotective benefits; it is instead potentially mediated by activity on toll-like receptor 4 . Naltrexone has also been proposed to exert neuroprotective effects via modulation of mitochondrial apoptotic pathways.

Despite a solid base of basic science evidence suggesting a neuroprotective role for naltrexone, human studies are rare. One study found that naltrexone strongly attenuated the side effects associated with interferon-alpha treatment in cancer patients. More recently, the drug has been used in dosages ranging from 3 mg to 4.5 mg per day to treat chronic pain and autoimmune disorders. Naltrexone used in this dosage range is typically referred to as low-dose naltrexone (LDN). Pilot trials for LDN in Crohn's disease and multiple sclerosis have recently been conducted. Beneficial effects were reported in these trials; however, both were open label.

According to the previous study A crossover design was used to minimize the statistical demand for large sample sizes. A single-blind approach was used over the more typical open-label approach for an initial, signal-detecting study. Each participant received both LDN and placebo, thereby acting as their own control. Participants were not told when they would receive the placebo capsules. All participants provided informed consent, and all procedures were approved by the Institutional Review Board at Stanford University School of Medicine.

Average daily tolerability during the drug condition was 96.3% (compared with 89.7% during placebo).Two individuals in the study reported more vivid dreams. One individual reported transient nausea and insomnia for the first few nights of capsules. No other symptoms were reported. All side effects were reported as mild, and no change in dosage or dosing schedule was required.

the first to examine the effectiveness of LDN in reducing the symptoms of fibromyalgia. Overall symptom severity was significantly reduced in the drug condition, as contrasted to baseline and placebo conditions. In the entire group of participants, LDN reduced fibromyalgia symptoms by 30.2% over and above placebo. Specific symptoms, including average pain, highest pain, fatigue, and stress, were also significantly impacted by the drug. The observed effects were accompanied by a very low incidence of side effects, suggesting LDN may be an effective and well-tolerated treatment option for individuals with fibromyalgia

There are a few methodological limitations in this study that are associated with the exploratory nature of the project. First, as an initial signal-detecting study, a single-blind design was used. While this approach provides more scientific control than an open-label design, the results will need to be confirmed in a double-blind study. Second, placebo was administered before LDN in all participants, which could have led to confounding

order effects. Third, while a rich dataset was obtained on participants, the subject size was small, and generalization to a larger population needs to be established. Fourth, the pooled data from responders and nonresponders show a slow decline of symptom reporting over the placebo period and continuing into the drug period. The slope of the line (Figure 1A) could suggest that the lower symptom reports given during the drug period were just a continuation of the placebo effect. Future studies may distinguish drug effects from placebo with longer conditions, and by utilizing crossover or parallel group research designs. Fifth, the lack of a difference between washout and the drug condition suggests that effects of the drug were sustained after cessation of capsules. The complete clinical picture of LDN for fibromyalgia will therefore be made clearer by utilizing a longer washout or follow-up period. Sixth, subsequent trials may use a validated scale for the primary outcome measure, rather than the single-item fibromyalgia severity measure employed in this study. Seventh, more exploration of dose-response relationships are needed.