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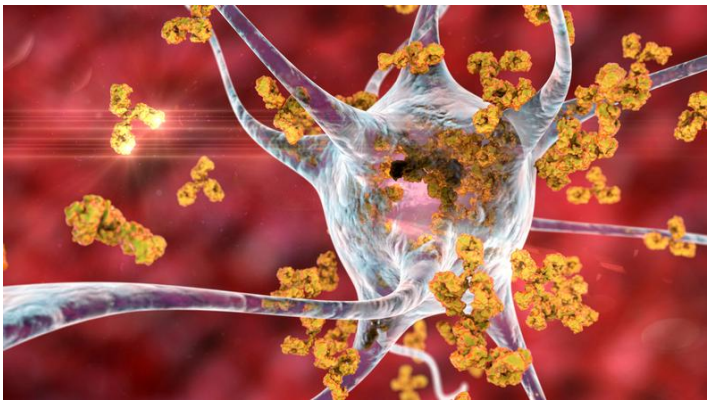
LDN in the Management of Chronic Pain Conditions



A comprehensive literature review was conducted by professionals from the School of Dentistry and College of Pharmacy at the University of Michigan to evaluate the efficacy of Low Dose Naltrexone (LDN) in the management of chronic pain conditions and determine its potential use in orofacial pain management. The primary outcome of all the studies was pain intensity reduction, and secondarily, improvement in quality of life. The authors found that LDN provides an alternative in medical management of chronic pain disorders as a novel anti-inflammatory and immunomodulator. Orofacial pain conditions share characteristics with other chronic pain disorders and LDN can offer additional pain management options.

J Am Dent Assoc. 2020 Dec;151(12):891-902.

Benefits of Low Dose Naltrexone for Opioid Induced Hyperalgesia and Fibromyalgia

While opioids temporarily alleviate pain, chronic opioid use may increase pain, leading to

opioid induced hyperalgesia (OIH). Despite the opioid epidemic, the prescription of opioids for chronic pain continues. The irony is that opioids worsen pain during the course of long-term use. This phenomenon, opioid induced hyperalgesia (OIH), is the “state of nociceptive sensitization caused by exposure to opioids”. OIH leads to a vicious cycle of increasing doses of opioids while increasing pain. Exogenous opioid use leads to alteration and dysfunction of the endogenous opioid system and conditions such as fibromyalgia (FM), a syndrome of diffuse chronic pain that is accentuated at multiple tender points along with other somatic and cognitive symptoms.

Jackson et al. of State University of New York (SUNY) Upstate Medical University, Syracuse, NY studied the effects of chronic opioid use and pain tolerance as measured by the cold pressor test (CPT). A pain service is embedded in the Addiction Medicine Service at SUNY to evaluate pain complaints because many addicted patients also have chronic pain. Participants were 55 patients with OIH and 21 patients with fibromyalgia; all had at least two CPTs. Detoxification included sublingual buprenorphine, followed by treatment with Low Dose Naltrexone (LDN), a pure opioid receptor antagonist that the researchers hypothesized would treat OIH and FM by restoring endogenous opioid tone.

Following buprenorphine administration, LDN was started at 0.1 mg twice a day and titrated with the following schedule:

- 0.2 mg twice a day on day 2
- 0.3 mg twice a day on day 3
- 0.4 mg twice a day on day 4
- 0.5 mg twice a day on day 5
- 1.0 mg twice a day for day 6
- 2.0 mg twice a day for days 7 and 8
- 4.5 twice a day thereafter

This titration occurred more slowly if there was a return of opioid withdrawal symptoms with increased dosing. FM patients not currently on opioids started LDN as soon as their treatment plan was agreed upon. Changes in pain sensitivity were used to assess LDN treatment.

Patients maintained on opioids for chronic pain presented with an average initial CPT of 24 seconds, underscoring their diminished pain tolerance. However, three months of treatment with LDN more than quadrupled OIH patients' pain tolerance; their average of 107 seconds at their last CPT suggests a restoration of their endogenous opioid tone. Indications are that the endogenous opioid system needs time to normalize, perhaps 3 months on average.

FM patients were comprised of 90% women compared to the equal sex distribution in OIH and started with more pain compared to OIH patients (initial CPT of 14 seconds). Their CPT responded more sluggishly over seven weeks to 30 seconds, coinciding with FM patients typically doubling their pain tolerance but not achieving complete resolution.

By constantly using patient feedback, the team at SUNY discovered how to detoxify patients from opioids as an easy outpatient procedure, assess pain tolerance with CPT, and ameliorate OIH with LDN. The detoxification process described above provides an alternative to slow tapering of opioids, and the restoration of endogenous opioid tone by LDN leads to restoration of relatedness. Support persons make comments such as, “I have the woman/man I married back!” Such encouraging results from this pilot data are of interest given the continued use of opioids for chronic pain and the lack of efficacious treatments for FM.

Detoxification, attention to underlying emotional issues, and LDN can make a substantial difference for patients as shown in this case series report. Naltrexone's antagonism at mu, kappa, delta, and orphanin FQ/nociceptin opioid receptors and at opioid growth factor receptor (OGFr) induces a variety of cellular responses at different doses. LDN may influence neuroimmunomodulation by intermittent blockade of opioid growth factor receptor (OGFr). Further investigation via double blind, randomized-controlled trials of LDN is indicated.

Front Psychiatry. 2021; 12: 593842.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7921161/

Low Dose Naltrexone for Chronic Pain

Recent pre-clinical uses and clinical studies further elucidate the use of Low Dose Naltrexone (LDN) in the treatment of chronic pain. LDN has shown promise to reduce symptoms related to chronic pain conditions such as fibromyalgia, inflammatory bowel conditions, and multiple sclerosis. The mechanism of LDN appears to be modulation of neuro-inflammation, specifically, the modulation of the glial cells and release of inflammatory chemicals in the central nervous system.

Curr Pain Headache Rep. 2020 Aug 26;24(10):64.

Low Dose Naltrexone is not commercially available, but our pharmacy can compound LDN by prescription.

Naltrexone Safety

The aim of a systematic review was to extensively evaluate the safety of oral naltrexone by examining the risk of serious adverse events in randomized controlled trials of naltrexone compared to placebo.
Parallel placebo-controlled randomized controlled trials of oral naltrexone at any dose, lasting longer than 4 weeks and published after January 1, 2001 were selected. Any condition or age group was included, excluding only studies in opioid or ex-opioid users.
Eighty-nine randomized controlled trials with 11,194 participants were found.
There was no evidence of increased risk of serious adverse events for naltrexone compared to placebo.

BMC Med. 2019 Jan 15;17(1):10.

Off-label prescribing is a common and legal practice which is justified when scientific evidence suggests the efficacy and safety of a medication for an indication for which it does not have FDA approval. More than one in five outpatient prescriptions written in the U.S. are for off-label therapies. Low dose naltrexone (LDN) is an example of off-label usage of naltrexone.
