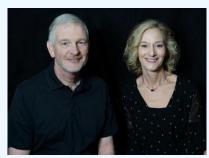


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Sincerely, Jim Andreesen, R.Ph. and Angie Svoboda, Pharm.D. FIACP

Low Dose Naltrexone in Dermatology

"Low-dose naltrexone (LDN) has been successfully studied as an immunomodulatory and anti-inflammatory therapy in a wide range of conditions including Crohn's disease, fibromyalgia, major depressive disorder, cancer, chronic regional pain syndrome, Charcot-Marie-Tooth, and multiple sclerosis. Recently, off label LDN has been shown to improve dermatologic conditions such as systemic sclerosis, Hailey-Hailey Disease, lichen planopilaris, and guttate psoriasis... LDN is an attractive treatment option because its side effects are generally mild



(including vivid dreams, nightmares, headaches, and anxiety), and it has a low abuse potential."

Low-dose naltrexone (LDN) refers to daily dosages of naltrexone that often start at 1 mg/day and is gradually increased to 4.5 mg/day, or approximately 1/10th of the typical opioid addiction treatment dosage. The mechanism of LDN appears to be distinct from traditional "high-dose naltrexone" (HDN). Proposed mechanisms of LDN include blockade of the opioid growth factor receptor (OGFR) axis, which normally stimulates B and T cell proliferation; and stimulation of beta-endorphin and enkephalin release, which has anti-inflammatory effects on T and B cells. "In contrast to high dose naltrexone, which stimulates the immune system, the intermittent activity of LDN is thought to depress immune cell proliferation and activity. Remarkably, this implies that naltrexone can both be anti-inflammatory as well as pro-inflammatory depending on its duration of action, squarely placing the drug in the 'immunomodulatory' category. HDN has a longer duration of action, and thus continuously blocks the OGFR axis leading to increased cellular proliferation and

inflammation. LDN, on the other hand, has a shorter duration of action which... strengthens the inhibitory effects of the OGFR axis on cellular proliferation and inflammation."

"Atopic dermatitis (AD) is one of the most common chronic skin disorders, affecting up to 20% of children and 10% of adults in the industrialized world... Given the well-established role of both immune dysfunction and pruritus in AD, the idea of LDN as a potential treatment is intriguing. Chronic pruritic disorders such as atopic dermatitis demonstrate downregulation of the μ -opioid receptor. Topically administered naltrexone has been shown to cause upregulation of the μ -opioid receptor and provide better relief of pruritic symptoms relative to placebo. A trial of a topical formulation of 1% naltrexone [cream] in 40 patients with severe atopic dermatitis revealed a 29% improvement after just 2 weeks of use."

J Drugs Dermatol. 2019;18(3):235-238.

Low Dose Naltrexone is not commercially available but rather is compounded by prescription.

LDN for Chronic, Nonmalignant Pain Syndromes

Pain can have a devastating effect on the quality of life of patients in palliative medicine. To date, the majority of research has been centered on opioid-based pain management in palliative care. However, opioid and nonopioid medications such as nonsteroidal anti-inflammatory drugs have limitations in clinical use due to the risk of adverse effects; therefore, there is a need for more research directed at finding an alternative approach to chronic pain management that would adequately alleviate pain and enhance quality of life without significant risks of adverse effects that would limit its use.

Naltrexone is a reversible competitive antagonist at μ -opioid and κ -opioid receptors, and was initially approved to treat addiction at standard doses of 50 to 150 mg daily. However, it was discovered that its use in low doses follows alternate pharmacodynamic pathways. Low-dose naltrexone (LDN), in doses of 1 to 5 mg per day, acts as a glial modulator with a neuroprotective effect via inhibition of microglial activation. It binds to Toll-like receptor 4 and acts as an antagonist, therefore inhibiting the downstream cellular signaling pathways that ultimately lead to proinflammatory cytokines, and reducing the inflammatory response. LDN's other mode of action involves transient opioid receptor blockade which upregulates opioid signaling resulting in increased levels of endogenous opioid production, known as opioid rebound effect. Low-dose naltrexone has gained popularity as an off-label treatment for several autoimmune diseases as well as chronic pain disorders including fibromyalgia, complex regional pain syndrome, and diabetic neuropathy. Low dose naltrexone (LDN) may also have utility in improving mood disorders and the potential to enhance the quality of life.

Am J Hosp Palliat Care. 2019 Mar 27. [Epub ahead of print]

Topical Loperamide for Localized Neuropathic Pain

Peripheral nerve damage can result in neuronal hyperexcitability and neuropathic pain. Localized neuropathic pain is confined to a specific area not larger than a letter-size paper. Topical analgesics are increasingly popular for the treatment of localized neuropathic pain because systemic agents for managing neuropathic pain often produce undesirable and intolerable side effects. Medications commonly compounded for topical use include amitriptyline, baclofen, ketamine and lidocaine; however, these agents do not always give the desired analgesic effect in some patients. Kopsky et al. reported for the first time a patient with chronic idiopathic axonal polyneuropathy



and intractable localized neuropathic pain treated successfully with loperamide 5% cream. After application of loperamide 5% cream, the patient reported a complete reduction of pain within 30 minutes, lasting for 2.5 hours. Subsequently, the patient was able to reduce his daily intake of oxycodone, while using topical loperamide for pain relief. Loperamide is an opioid agonist, commonly used to treat diarrhea. As a topical formulation, it is preferable over other opioids due to its low systemic bioavailability and low risk of crossing the blood-brain barrier. Peripheral upregulation and sensitization of opioid receptors at peripheral nerve endings and perhaps at other cell populations in the epidermis might be achieved with topical loperamide.

J Pain Res. 2019 Apr 29;12:1189-1192.

Topical Oral Anesthesia

Topical anesthesia is widely used in dentistry to reduce pain caused by needle insertion and injection of the anesthetic. However, successful anesthesia is not always achieved using the formulations that are currently commercially available. Novel drug delivery systems can help to improve the efficacy of topical agents. Various bases can be used or chemicals can be added to a preparation to enhance permeation or to promote superficial anesthesia. The combination of different chemical and physical methods can be used to optimize topical anesthesia in the oral mucosa.

Expert Opin Drug Deliv. 2017 May;14(5):673-684.

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