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Thank you for entrusting in the compounding services at Madison Medical Compounding Pharmacy to help meet the unique medication needs of your patients. We are excited to share our monthly newsletter with you and look forward to working with you. Please don't hesitate to let us know how we can assist you and your practice.

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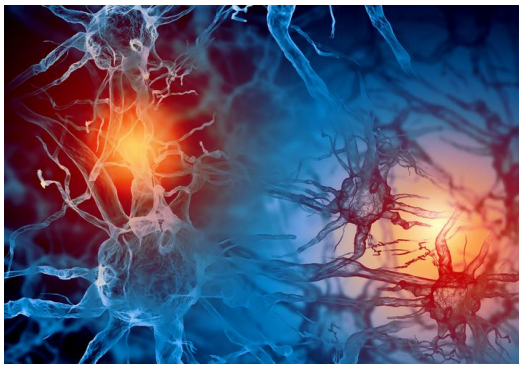
Management of Chronic Pain and Inflammation of Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders with Low-Dose Naltrexone (LDN)



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.

Pharmacotherapy. 2018 Mar;38(3):382-389.

Compounded Topical Analgesics for the Management of Chronic Neuropathic Pain

Due to the increase in opioid use, pain physicians have been turning to new and improved solutions to tackle chronic, refractory pain syndromes. Topical analgesics are emerging as a valued solution.

Neuropathic pain (NP) is defined by the International Association of the Study of Pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". NP can present alone or in any combination with other types of pain and affects 6–8% of the population. NP can originate from focal lesions in the peripheral nervous system such as postherpetic neuralgia (PHN) or post-traumatic neuralgia, or from general lesions such as painful diabetic neuropathy, HIV-neuropathy, etc. Additionally, lesions to the CNS and other complex disorders (spinal cord injuries, stroke, complex-regional pain syndrome, etc.) can cause NP. NP can be described as burning, tingling, electric-like, or a shooting sensation, with a combination of sensory loss and the paradoxical presentation of hypersensitivity in the painful area. The mechanism of NP includes peripheral sensitization, central sensitization in the dorsal horn of the spinal cord as well as changes in cortical and subcortical regions.

Topical versus Transdermal

Transdermal delivery of medication is accomplished through percutaneous absorption, and systemic therapeutic drug levels can be achieved, comparable to those of oral medication. Often, transdermal medications can be administered distally from the painful area. Transdermal drug delivery has advantages because it avoids first-pass hepatic metabolism which occurs with oral drugs, and the need for frequent painful injections associated with parenteral therapy.

Topical medication targets soft tissues and peripheral nerves underlying the site of application and exerts its action at the site of application by penetrating the skin through passive diffusion. Therefore, topical medication does not produce systemic side effects or drug-drug interactions. One of the main targets for topical analgesics are keratinocytes. This network of skin cells includes a number of receptors, neurotransmitters, and neuropeptides,

which play a significant role in the development of NP.

Topical analgesics may be safer and are easier to use as compared to systemic drugs. Due to the complex nature of NP conditions, topical analgesic therapy should be employed as part of a multidrug approach. Elderly patients are a target group that can benefit from topical analgesics. The American Geriatrics Society recommends the use of topical analgesics for NP. The elderly population undergoes a reduction in the fat-to-muscle ratios which makes the use of opioids less optimal. Additionally, reduction in the renal and hepatic metabolism and various comorbidities managed with multidrug therapy supports the use of topical versus systemic medication for safety concerns. However, there are some limitations to the use of topical agents in the management of NP. Topical analgesics can be used on a limited skin area due to increased risk of toxicity, and for that reason, they cannot be used in conditions with skin integrity disruption or large affected areas.

Many studies have been conducted on the efficacy of topical ketamine cream, clonidine gel, topical gabapentin, topical baclofen, and topical phenytoin for peripheral neuropathic pain, either alone or in combination with other formulations.

Practice Notes:

- In order for a topical analgesic to pass through the stratum corneum of the epidermis, it has to possess both hydrophilic and hydrophobic elements.
- The choice of base determines the extent of absorption of a topically applied medication.
- Ketamine acts as an inhibitor on voltage-gated Na+ and K+ ion channels.
- Topically applied ketamine exerts its peripheral antinociceptive effect by the activation of neuronal nitric oxide synthase.
- Clonidine is lipophilic, which aids in easy skin penetration and it has a half-life of approximately 8 hours, thus requiring three-times daily topical application.
- Phenytoin 10% cream, a nonselective voltage-gated Na channel stabilizer, GABA-a receptor agonist, showed promising results in allodynia reduction.
- Topical gabapentin 10% cream reduced allodynia and hyperalgesia in chronic sciatic constriction nerve injury in rats.
- GABA-b receptors are located in cutaneous layers on nerve endings and keratinocytes.

Pain Manag. 2017 Nov;7(6):537-558.