

The Lowdown on Low-Dose Naltrexone

Nadine Shabeeb, MD, MPH



RESIDENT PEARL

- Low-dose naltrexone is an alternative anti-inflammatory treatment to consider in patients with inflammatory skin diseases, with a minimal side-effect profile.

Low-dose naltrexone (LDN) has become a hot topic in many fields of medicine, including dermatology. It has gained popularity as an alternative, off-label treatment that works by targeting inflammation. Patients may ask you about LDN as a treatment option for a variety of inflammatory skin conditions, specifically in comparison to more traditional systemic treatments. It is important for dermatologists to know what LDN is, how it works, how to prescribe it, and what side effects should be monitored.

Cutis. 2020;105:E17-E18.

Low-dose naltrexone (LDN) has shown efficacy in off-label treatment of a variety of inflammatory diseases ranging from Crohn disease to multiple sclerosis.¹ There are limited data about the use of LDN in dermatology, but reports regarding how it works as an anti-inflammatory agent have been published.^{1,2}

Naltrexone is an opioid receptor antagonist that originally was approved by the US Food and Drug Administration to treat addiction to alcohol, opiates, and heroin.² The dose of naltrexone to treat addiction ranges from 50 to 100 mg/d, and at these levels the effects of opioids are blocked for 24 hours; however, the dosing for LDN is much lower, ranging from 1.5 to 4.5 mg/d.³ At this low dose, naltrexone partially binds to various opioid

receptors, leading to a temporary blockade.⁴ One of the downstream effects of this opioid receptor blockade is a paradoxical increase in endogenous endorphins.³

In addition to opioid blockage, lower doses of naltrexone have anti-inflammatory effects by inhibiting nonopioid receptors. Naltrexone blocks toll-like receptor 4, which is found on keratinocytes and also on macrophages such as microglia.⁵ These macrophages also contain inflammatory compounds such as tumor necrosis factor α and IL-6. Low-dose naltrexone can suppress levels of these inflammatory markers. It is important to note that these anti-inflammatory effects have not been observed at the standard higher doses of naltrexone.¹

When to Use

Low-dose naltrexone is a treatment option for inflammatory dermatologic conditions. A recent review of the literature outlined the use of LDN in a variety of inflammatory skin conditions. Improvement was noted in patients with Hailey-Hailey disease, lichen planopilaris, and various types of pruritus (ie, aquagenic, cholestatic, uremic, atopic dermatitis related).³ A case report of LDN successfully treating a patient with psoriasis also has been published.⁶ We often use LDN at the University of Wisconsin (Madison, Wisconsin) to treat patients with psoriasis. Ekelem et al³ also discussed patients with skin conditions that either had no response or worsened with naltrexone treatment, including various types of pruritus (ie, uremic, mycosis fungoides related, other causes of pruritus). Importantly, in the majority of cases without an improved response, the dose used was 50 mg/d.³ Higher doses of naltrexone are not known to have anti-inflammatory effects.

Low-dose naltrexone can be considered as a treatment option in patients with contraindications to other

From the Department of Dermatology, University of Wisconsin Hospital and Clinics, Madison.

The author reports no conflict of interest.

Correspondence: Nadine Shabeeb, MD, MPH, One S Park, 7th Floor, Madison, WI 53715 (nshabeeb@uwhealth.org).

systemic anti-inflammatory treatments; for example, patients with a history of malignancy may prefer to avoid treatment with biologic agents. Low-dose naltrexone also can be considered as a treatment option in patients who are uncomfortable with the side-effect profiles of other systemic anti-inflammatory treatments, such as the risk for leukemias and lymphomas associated with biologic agents, the risk for liver toxicity with methotrexate, or the risk for hyperlipidemia with acitretin.

How to Monitor

The following monitoring information is adapted from the practice of Apple Bodemer, MD, a board-certified dermatologist at the University of Wisconsin (Madison, Wisconsin) who also is fellowship trained in integrative medicine.

There is a paucity of published data about LDN dosing for inflammatory skin diseases. However, prescribers should be aware that LDN can alter thyroid hormone levels, especially in patients with autoimmune thyroid disease. If a thyroid-stimulating hormone (TSH) level within reference range has not been noted in the last year, consider screening with a TSH test and also assessing for a personal or family history of thyroid disease. If the TSH level is within reference range, there generally is no need to monitor while treating with LDN. Consider checking TSH levels every 4 months in patients with thyroid disease while they are on LDN therapy and be sure to educate them about symptoms of hyperthyroidism.

Side Effects

Low-dose naltrexone has a minimal side-effect profile with self-limited side effects that often resolve within approximately 1 week. One of the most commonly reported side effects is sleep disturbance with vivid dreams, which has been reported in 37% of participants.¹ If your patients experience this side effect, you can reassure them that it improves with time. You also can switch to morning dosing to try and alleviate sleep disturbances at night. Another possible side effect is

gastrointestinal tract upset. Importantly, there is no known abuse potential for LDN.¹ To stop LDN, patients should be stable for 6 to 12 months, and there is no need to wean them off it.

Cost and Availability

Because use of LDN in dermatology is considered off label and it is not approved by the US Food and Drug Administration to treat any medical conditions, it must be prescribed through a compounding pharmacy, usually without insurance coverage. The monthly cost is approximately \$30 depending on the pharmacy (unpublished data), which may be cost prohibitive for patients, so it is important to counsel them about price before starting treatment.

Final Thoughts

Low-dose naltrexone is an alternative treatment option that can be considered in patients with inflammatory skin diseases. It has a favorable side-effect profile, especially compared to other systemic anti-inflammatory agents; however, additional studies are needed to learn more about its safety and efficacy. If patients ask you about LDN, the information provided here can guide you with how it works and how to prescribe it.

REFERENCES

1. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol*. 2014;33:451-459.
2. Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses*. 2009;72:333-337.
3. Ekelem C, Juhasz M, Khera P, et al. Utility of naltrexone treatment for chronic inflammatory dermatologic conditions: a systematic review. *JAMA Dermatol*. 2019;155:229-236.
4. Bihari B. Efficacy of low dose naltrexone as an immune stabilizing agent for the treatment of HIV/AIDS. *AIDS Patient Care*. 1995;9:3.
5. Lee B, Elston DM. The uses of naltrexone in dermatologic conditions [published online December 21, 2018]. *J Am Acad Dermatol*. 2019;80:1746-1752.
6. Bridgman AC, Kirchhof MG. Treatment of psoriasis vulgaris using low-dose naltrexone. *JAAD Case Rep*. 2018;4:827-829.