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Low Dose Naltrexone in Dermatology

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ABSTRACT

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.[1-5] Recently, off label LDN has been shown to improve dermatologic conditions such as systemic sclerosis, Hailey-Hailey Disease, lichen planopilaris, and guttate psoriasis.[6-9] In this article, we examine the existing evidence for use of LDN in skin disease and discuss its potential application in the treatment of atopic dermatitis (AD).

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INTRODUCTION

The concept of low-dose naltrexone (LDN) has been successfully studied as an immunomodulatory and anti-inflammatory therapy in a wide range of conditions. These include Crohn's disease, fibromyalgia, major depressive disorder, cancer, chronic regional pain syndrome, Charcot-Marie-Tooth, and multiple sclerosis.[1-5] LDN is an attractive treatment option because its side effects are generally mild (including vivid dreams, nightmares, headaches, and anxiety),[6] it has a low abuse potential,[4] and it is cost-effective at approximately $35 per month.[6]

Recently, off label LDN has been shown to improve dermatologic conditions such as systemic sclerosis, Hailey-Hailey Disease, lichen planopilaris, and guttate psoriasis.[6-9] In this article, we examine the existing evidence for use of LDN in skin disease and discuss its potential application in the treatment of atopic dermatitis (AD).

What is Low Dose Naltrexone?

Naltrexone was synthesized in 1963 as an orally active competitive opioid receptor antagonist.[10] Naltrexone is structurally and functionally similar to the opioid antagonist naloxone, but it has greater oral bioavailability and a longer biologic half-life of 4 hours.[11] It is now well known that naltrexone actually exerts its effects on humans via at least two distinct receptor mechanisms. The first effect is a directly antagonistic effect on mu-opioid receptors. The second is via antagonism of the Toll-like receptor 4 (TLR4)-mediated proinflammatory pathway in macrophages and microglia.[3,5,12] Notably, sustained mu-opioid receptor blockade by naltrexone has been shown to lead to inflammation and proliferation of immune cells.[3]

Naltrexone was first approved by FDA in 1984 for the treatment of opioid addiction. The typical daily dosage for opioid addiction is 50-100 mg daily, and 50 mg tablets are available commercially.[4] This typical daily dosage has been referred to as "high dose naltrexone" (HDN) in literature.[3] Low-dose naltrexone (LDN) refers to daily dosages of naltrexone that are approximately 1/10th of the typical opioid addiction treatment dosage. Common LDN doses range from 1-4.5 mg daily.[5]

The mechanism of LDN is thought to be distinct from high-dose naltrexone (HDN). Proposed mechanisms include: 1. Blockade of the opioid growth factor receptor (OGFR) axis, which normally stimulates B and T cell proliferation; and, 2. Stimulation of beta-endorphin and enkephalin release, which has anti-inflammatory effects on T and B cells.[6,13] 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.[3]

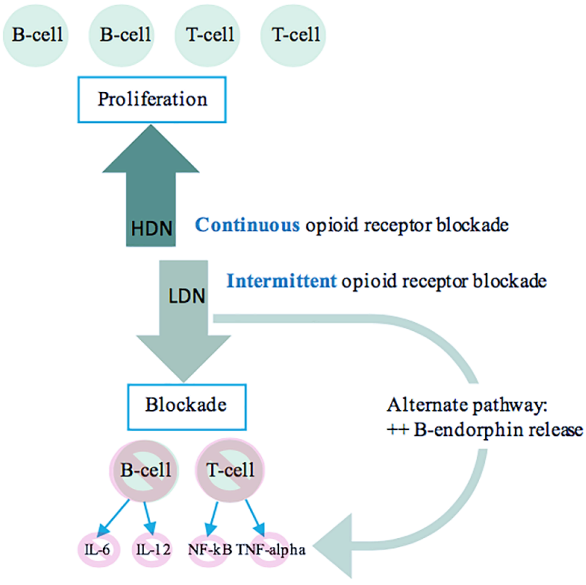
Remarkably, this implies that naltrexone can both be anti-inflammatory as well as pro-inflammatory depending on its duration of action, squarely placing the drug in the "immunomodulatory" category.[3] HDN has a longer duration of action, and thus continuously blocks the OGFR axis leading to increased cellular proliferation and inflammation. LDN, on the other hand, has a shorter duration of action which results in an intermittent blockade of the OFGR axis, leading to a compensatory mechanism that upregulates production of OGF receptors and endogenous opioids. This strengthens the inhibitory effects of the OGFR axis on cellular proliferation and inflammation. The OFGR axis and its unique responses to sustained and intermittent blockade may potentially explain the paradoxical dose-associated effects

of naltrexone.[3,14] This concept has served as the basis of various trials of LDN therapy in cancer and autoimmune disease.

In 2007, a prospective open-label trial of LDN in pediatric Crohn's disease was published showing good efficacy and safety.[1] The study showed that of patients treated with LDN, 25% went into remission and 67% had improved to mild disease activity at 16 weeks. Systemic and social quality of life improved with LDN treatment (p=0.035). Importantly, all children tolerated LDN without any severe adverse side effects at 8, 16 and 20 weeks of the study. The most common side effect was sleep disturbance, occurring in 7 of the 17 subjects. Five subjects changed the timing of LDN from the evening to morning due to insomnia. In no instance was a dose reduction necessary for sleep disturbances. A follow-up randomized-controlled study of LDN in 14 pediatric Crohn's patients yielded similar results.[15]

Since the first successful application of LDN in Crohn's disease, its use has been studied in other chronic inflammatory conditions with promising results. These include fibromyalgia, major depressive disorder, cancer, chronic pain, Charcot-Marie-Tooth and multiple sclerosis.[1-5] It has recently been suggested that LDN's efficacy in these conditions may be due to the blockade of the OFGR axis leading to downstream regulation of T-lymphocyte proliferation and a decrease in proinflammatory cytokines IL-6, IL-12, tumor necrosis factor-α, and nuclear factor NF-κB ultimately leading to clinical improvement.[16] Activation of pro-apoptotic mechanisms may also play a role in halting pathogenesis.[3] This overall immunomodulatory function of LDN is thought to contribute to resolution of pain, pruritus, and inflammation in the aforementioned conditions.

FIGURE 1. Effects of HDN and LDN on immune function.



The Evidence in Skin

In light of several studies showing the immunoregulatory functions of LDN, it is possible to imagine its application within dermatology. To date, only several case reports and case series have been published suggesting the efficacy of LDN in skin conditions. One of the first articles demonstrating the potential of LDN in systemic sclerosis was published in 2011.[7] In a 3-patient case series, treatment with LDN was shown to significantly improve pruritus. At 2 month follow-up, the mean improvement in pruritus symptoms was a decrease of 6.7 points on a 10-point scale. Two of the three patients reported a score of 0 for pruritus, and no adverse side effects were reported. These findings suggest that LDN may be an effective, well-tolerated treatment for the pruritic component of systemic sclerosis. Interestingly, LDN did not improve the physical lesions of systemic sclerosis.[7]

However, there are articles that support LDN's potential for clearing certain types of skin lesions. In 2017, two case studies simultaneously reported that patients with Hailey-Hailey disease (HHD), a genetic blistering condition, achieved improvement of lesions with LDN therapy.[8,17] In one of the reports, patients noted improvement of their lesions at 1-2 weeks and clinical resolution at 2 months.[8] Lesions flared when stopping LDN and cleared within a few days on re-challenge. A 2018 case report of a patient with HHD started on LDN reports similar findings.[13] It has been suggested that (in addition to influencing opioid receptors and the TLR signaling pathway) the possible mechanism for this successful treatment may involve improved keratinocyte differentiation and wound healing.[3]

LDN has also been trialed in cases of lichen planopilaris (LPP).[6] A case of series of 4 patients with LLP, including one with the frontal fibrosing variant, showed that adding LDN to the treatment regimen led to improvements in subjective pruritus, inflammation, and alopecia at one month follow-up. A limitation of this case series is that all patients were on concomitant therapy with topical, intralesional, and/or systemic therapies at the start of therapy. However, the fact that addition of LDN to these regimens led to notable improvements in both pruritus and physical findings such as extent of alopecia and scalp inflammation is encouraging.

Most recently, a case report showing improvement of guttate psoriasis with compounded LDN has been published.[9] The patient had previously been on apremilast and topicals with 50-60% improvement of psoriatic lesions, but had discontinued all therapies due to high cost. After starting on compounded LDN (4.5 mg), the patient experienced an 80% improvement at 2 months and 80-90% improvement at 12 months. The authors reported that several lesions recurred briefly; however, their appearance and symptoms were mild. Thus, the patient has elected to continue LDN therapy. The only reported side effect was xerosis at the site of the lesions. The above reports are summarized in Table 1.

LDN in Atopic Dermatitis

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disorders, affecting up to 20% of children and 10% of adults in the industrialized world.[18] While the pathogenesis of AD is not fully understood, it is currently theorized that AD arises due a disruption in the epidermal barrier leading to: 1. increased permeability of the epidermis, 2. pathological inflammation in the skin, and 3. percutaneous sensitization to allergens.[3] Thus, many treatment strategies seek to target specific aspects of the skin barrier or cutaneous inflammation.

Given the well-established role of both immune dysfunction and pruritus in of 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.[19] Topically administered naltrexone has been shown to cause upregulation of the μ-opioid receptor and provide better relief of pruritic symptoms relative to placebo.[20] A trial of a topical formulation of 1% naltrexone in 40 patients with severe atopic dermatitis revealed a 29% improvement in pruritus after just 2 weeks of use. The formulation containing naltrexone required a median of 46 minutes to reduce the itch symptoms to 50%, while the placebo required 74 minutes. Punch biopsies were performed in 11 of the patients before and after the application of the cream and histopathological examination revealed increased staining of epidermal mu-opioid receptors after 2 weeks of naltrexone application.[20] This suggests that a naltrexone-mediated upregulation of opioid receptors in the epidermis may be responsible for the decrease in pruritus. A recent study tested the efficacy of absorption of a LDN cream and found that it may be an effective formulation for the sustained transdermal delivery of LDN.[21] This means that a potentially effective preparation for transdermal delivery of LDN could be tested in AD.

Oral LDN has not been studied in AD, but oral HDN has been trialed. Several single-arm trials, case series, and case reports have reported variable responses to HDN.[22] In a case series of 4 patients, only 1 patient achieved full remission of pruritus on 50 mg naltrexone.[23] A follow-up study in 16 patients showed antipruritic effect in 50% of patients, further suggesting a mixed response to HDN.[24] Trials of a structurally and functionally similar opioid derivative, nalmefene, have shown that lowering the dose to 20 mg and 10 mg leads to resolution of pruritus in 35% and 60% of patients, respectively.[25] These studies lead us to the following questions: Could an even lower dose of naltrexone i.e. LDN lead to even better outcomes? And, could LDN clear AD lesions?

The role of LDN in halting AD pathogenesis and potential applications to clinical disease has not been studied. It is now know that atopic dermatitis is a predominantly T-cell-driven disease,[26] and changes in the T-cell populations and the associated cytokines during the acute and chronic phases of AD can cause variations in disease presentations and treatment responses. In theory, LDN's blockade of the OGFR axis and/or stimulation of beta-endorphins and enkephalins could serve to blunt T-cell over-proliferation and production of inflammatory cytokines.[3] However, such speculation requires further scientific research to elucidate a potential mechanism of action and potential clinical efficacy.

One final caveat has been posed in literature: Does low-dose naltrexone decrease the pleasure derived from scratching (thus terminating the itch-scratch cycle) or the pruritus itself?[27] Could it be a combination of both? Again, further studies are needed to shed light on this notion.

TABLE 1.

Summary of LDN Trials in Dermatologic Conditions			
Condition	**Reference**	**Study Type**	**Outcome**
Guttate Psoriasis	Muller *et al* (2018) [9]	Case report	80% improvement at 2 months 80-90% improvement at 12 months
Hailey-Hailey	Ibrahim *et al* (2017) [17]	Case series (3 patients)	>80% improvement at 2 and 3 months
Hailey-Hailey	Albers *et al* (2017) [8]	Case series (3 patients)	Clinical resolution of lesions at 2 months
Lichen planopilaris	Strazzulla *et al* (2017) [6]	Case series (4 patients)	Decreased pruritus and disease progression at 1 and 4 month follow-up
Systemic Sclerosis	Frech *et al* (2011) [7]	Case series (3 patients)	Decrease in pruritus by a mean of 6.7 points on a 10-point-faces scale. Note: two of the three patients scored 0/10 at 2 months.

CONCLUSION

Despite LDN's increasing prevalence of off-label use and growing scientific interest, there are still many unanswered questions. Some animal and in vitro studies support the use of LDN, but its clinical efficacy as an analgesic and anti-inflammatory has been tested only in a small number of chronic conditions such as multiple sclerosis, fibromyalgia, Crohn's disease, and Charcot-Marie-Tooth.[5] Within dermatology, the supporting literature for LDN is limited to only a few case series; few replications of the findings have been performed. As a result, the overall quality of the evidence thus far is insufficient to allow any definitive conclusions as to the efficacy of LDN in anti-inflammation or disease modification.

More studies are needed to elucidate the role of LDN as a therapeutic agent in dermatologic conditions. Given that oral and topical naltrexone has been shown to improve pruritus in patients with AD, this is certainly an exciting question and challenge.[22] The question of LDN's efficacy in clearing skin lesions also remains unanswered. Until more evidence becomes available, we must continue engaging in balanced dialogues with our patients to weigh the risks and benefits of off-label treatments such as LDN.

DISCLOSURE

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