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NEWS, VIEWS, AND REVIEWS

An Update on the Off-Label Uses of Low-Dose Naltrexone in Dermatology

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INTRODUCTION

Naltrexone is an FDA-approved opioid receptor antagonist for the treatment of opioid and alcohol use disorder at standard doses of 50 to 100 milligrams (mg) daily. Low-dose naltrexone (LDN), 1 to 5 mg daily, functions differently than standard doses by only binding to receptors for 4 to 6 hours. This temporary blockade is believed to paradoxically increase endogenous opioids, including opioid growth factor, and opioid receptors, potentiating their anti-inflammatory effects on T and B cells.[1] Naltrexone also inhibits toll-like receptor 4, decreasing the release of pro-inflammatory cytokines.[2]

The efficacy of off-label LDN in treating various dermatologic conditions including Hailey-Hailey disease (HHD), lichen planopilaris (LPP), psoriasis, dermatomyositis (DM), and scleroderma has been demonstrated in recent years throughout the literature.[1,2,3,4] Here, we summarize new data on dermatologic applications of LDN that have emerged over the past 5 years. This includes additional evidence for previously reported uses and new applications: Darier disease (DD), epidermolysis bullosa pruriginosa (EBP), and skin-picking disorder (SPD).

Hailey-Hailey Disease

HHD was 1 of the first dermatologic conditions for which LDN's efficacy was demonstrated. While previous literature was limited to case reports and small case series, 2 larger case series have since been published.[2,3,4] One included 14 patients started on naltrexone between 1.5 and 6 mg, with 2 patients exhibiting sustained improvement, 6 initially improving then relapsing, and 6 without improvement.[5] Notably, 4 patients without improvement were increased to naltrexone doses between 12 and 50 mg, which is above the threshold that confers the unique biological properties of LDN.[6] In a subsequent 8-patient case series, 7 patients experienced sustained clinical improvement with LDN.[7] Additionally, several newer case reports demonstrate the efficacy of LDN in recalcitrant HHD.[6,8,9] Altogether, the data suggests that LDN should be considered as a treatment option for HHD especially in intractable cases.

Lichen Planopilaris

LDN's efficacy in LPP was first demonstrated through a 4-person case series showing improvements in scalp inflammation and pruritus, however, the study was limited by 3 patients concurrently starting pioglitazone, which also has known efficacy in this setting.[2] Larger studies have since been published, including an open-label study following 26 patients treated with LDN for 12 months. Here, investigators observed reduced scale over time, but the only significant mean difference between baseline and 12 months was decreased scalp erythema (P<0.001).[10] Another study retrospectively reviewed 52 patients with classic LPP or frontal fibrosing alopecia (FFA) treated with LDN, 2.5 to 4.5 mg daily, while continuing baseline topical therapies. A significant proportion of patients experienced decreased perifollicular erythema (classic LPP: P=0.0233; FFA: P=0.0015).[11] To date, the highest-level study was a randomized controlled trial (CT) of 34 patients assigned to receive topical clobetasol and LDN or topical clobetasol and placebo for 3 months. Improvement in scalp erythema was significantly greater in the LDN group (P=0.033), but there was no significant difference in LPP activity index score between groups.[12] Overall, there is conflicting evidence for LDN's efficacy in LPP, but there may be a role for LDN as an adjunctive therapy, particularly in LPP with prominent erythema.

Psoriasis

While evidence for LDN in psoriasis was initially limited to case reports, there is now a prospective, non-randomized CT including 71 patients started on naltrexone 6 mg daily. After 3 months, there was a 4.96-point reduction in mean psoriasis area and severity index score (P<0.001) and 3.9-point reduction in body surface area (P<0.001).[13] This data builds on pre-existing evidence of LDN's efficacy in 3 case reports of psoriasis vulgaris, guttate psoriasis, and erythrodermic psoriasis.[4,14] Some side effects including headache, insomnia, and anxiety were observed, but all resolved after 3 LDN doses. There are already many highly effective treatments for psoriasis, however, given LDN's low cost and safety, it should be considered in cases where insurance coverage, for other treatments, is a barrier.

Dermatomyositis and Scleroderma

Efficacy of LDN in DM and scleroderma was initially established through a small case series of each condition, both demonstrating significant improvements in pruritus.[1,4] Since then, only 1 new case report of LDN in amyopathic DM has been published. This patient was unresponsive to several treatments and presented with extensive skin involvement and generalized pruritus while on hydroxychloroquine. One month after initiating naltrexone 1.5 mg daily, the patient's scalp pruritus and burning sensation resolved and their facial erythema and cutaneous lesions started to clear. Improvement persisted even after stopping hydroxychloroquine.[15]

New Dermatologic Applications of LDN

Darier Disease

DD and HHD are both caused by mutations of genes encoding Ca^{2+}-ATPase pumps, prompting an investigation of LDN in DD. In this case series, 6 patients were started on naltrexone 5 mg daily for twelve weeks. Four patients who had severe disease experienced worsening (2 of which had stopped their systemic retinoid 1 day before initiating LDN), and 2 patients with mild-to-moderate disease experienced clearance (1 of which was simultaneously on a systemic retinoid).[16] A subsequent case report described a patient with active DD who was started on naltrexone 4.5 mg while taking isotretinoin. After 3 months, the patient experienced near complete clearance of lesions and no adverse effects.[17] Based on the limited data, there may be potential for LDN in mild-to-moderate DD or when combined with a systemic retinoid.

Epidermolysis Bullosa Pruriginosa

There is 1 case report of a patient with extensive EBP, affecting the bilateral legs, successfully responding to LDN. Following a lack of response to dupilumab and refusal to start a JAK inhibitor due to potential side effects, the patient was prescribed naltrexone 3 mg daily. After 3 months, she reported notable reductions in pruritus and burning, as well as thinning of plaques.[18]

Skin-Picking Disorder

There are 2 reported cases of LDN's efficacy in SPDs, a spectrum of psychiatric disorders characterized by compulsive skin manipulation. The first patient had a 25-year history of recalcitrant acne excoriée and prurigo excoriée, but within a few weeks of initiating naltrexone 3 mg daily, the patient was itch-free.[19] The second patient with SPD was prescribed naltrexone 4.5 mg daily for fibromyalgia-associated pain. However, at her 3-month follow-up, she reported reduced compulsion to itch, healing of prior lesions, and fewer new lesions.[20]

CONCLUSION

LDN is a compelling therapy due to its low cost, safety, and efficacy in numerous inflammatory dermatologic conditions, especially in several treatment recalcitrant cases. Furthermore, the dermatologic applications of LDN continue to grow with conversations surrounding its potential role in other alopecias, such as alopecia areata.[21] Larger, controlled, and comparative studies to first-line treatments are still needed. Nonetheless, given LDN's widespread efficacy thus far, dermatologists should keep LDN in their toolkits when managing the conditions described in this review and continue to cautiously explore new applications.

DISCLOSURE

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