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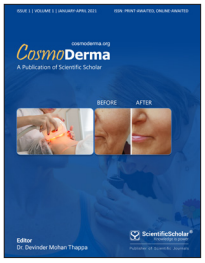

Resident Forum

Low-dose naltrexone in dermatology: A brief review

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INTRODUCTION

Naltrexone is a competitive μ-opioid receptor antagonist.[1] It was primarily used for alcohol and opioid abuse disorder, but many studies reported anti-inflammatory and immunosuppressive action, leading to its widespread usage in various dermatological and non-dermatological conditions.[2,3] Major depressive disorder, chronic regional pain syndrome, fibromyalgia, multiple sclerosis, Charcot-Marie-Tooth, Crohn's disease, and cancer are some of the non-dermatological conditions where naltrexone has been used successfully.[4-7] Low-dose naltrexone (LDN), which is approximately 1/10th the dose used for opioid and alcohol abuse, has shown beneficial effects in various cutaneous disorders such as excoriation disorder, alopecia areata, Hailey–Hailey disease, Darier's disease, trichotillomania, lichen planopilaris, and frontal fibrosing alopecia.[8-13] The use of LDN is encouraged primarily due to its low abuse potential, mild adverse effects, and cost efficacy.[3] This article will briefly review the various off-label indications of LDN in dermatology, its dosage, efficacy, and adverse effects profile.

METHODOLOGY

I conducted an advanced search in PubMed, Scopus, and Embase with the search terms "low dose naltrexone" and "dermatology." My search included original research articles, case reports, and review articles. The primary goal was to determine studies focusing on the drug mechanism, safety, clinical efficacy, adverse events, dosage, and indications of LDN in various dermatological conditions that were included in this article. A total of 44 articles were reviewed that were published between 2017 and December 2024. We reviewed all the articles to exclude duplicate studies, non-original articles, and articles not focusing on the relevant subject. The articles published in languages other than English were also excluded.

MECHANISM OF ACTION

Naltrexone in conventional dosage (50–100 mg daily) blocks the μ-opioid receptor and acts as an antagonist to toll-like receptor 4, thus blocking the pro-inflammatory pathway in macrophages and microglia.[14] However, LDN has several other mechanisms of action:

1. Blocks the opioid growth factor receptor axis, which normally stimulates B and T-cell proliferation[15]
2. Stimulates β-endorphin and enkephalin release, which has anti-inflammatory effects on B and T cells[3]
3. LDN causes a temporary blockage of opioid receptors, which leads to a homeostatic increase in endogenous opioids with increased opioid receptor binding, resulting in reduced inflammation.[16]

USAGE IN DERMATOLOGICAL DISORDERS

There is a case report of the successful use of LDN at 4.5 mg every 6 hours for excoriation disorder, showing excellent improvement after 3 months of therapy.[8] Another author reported a significant reduction in itch and resolution of lesions in a prurigo nodularis patient where LDN at a dosage of 3 mg once daily was prescribed.[17] A study reported reduced erythema and scaling after daily 3 mg LDN in patients with lichen planopilaris and frontal fibrosing alopecia. However, no significant improvement was noticed in pruritus and burning/pain.[12] Sousa Gomes *et al*. report successful use of 3 mg LDN for treating Hailey–Hailey disease after 5 months of therapy without any serious adverse events.[10] Another study reported 80–90% improvement in the extent of disease with 1.5–3 mg LDN after 3 months of therapy.[18]

In a case series, 3 mg LDN was used for treating biopsy-proven nail lichen planus, where a 35% reduction in nail lichen planus severity index was observed among 4/7 patients, and no adverse events were reported.[19] Another case series reports variable response of 5 mg LDN in the treatment of Darier's disease.[20] The study reported complete resolution in mild–moderate cases, while severe cases showed worsening after initial improvement during therapy. There is an interesting case report of treating guttate psoriasis in a 75-year-old male patient with compounded oral LDN by Muller *et al*.[21] Dryness around the lesions on arms and legs was the only reported adverse effect. Another author reported successful use of 4.5 mg LDN in the treatment of chronic plaque psoriasis with a reduction in psoriasis area severity index (PASI) from 7.2 to 0.9 after 6 months of therapy.[22] In addition, no adverse events were noted. In another case, LDN (4.5 mg daily) was successfully used for the treatment of erythrodermic psoriasis.[23] The authors reported significant improvement in flare-ups and disease remission during 6-month follow-up therapy.

In a case report, the authors have successfully used LDN at a 3 mg dosage for treating a case of epidermolysis bullosa pruriginosa refractory to dupilumab therapy.[24] LDN was continued for 5 months with a significant reduction in pruritus and burning over the legs and thinning of the lichenified plaques. In a separate case report, Tran *et al*. reported successful use of LDN (5 mg daily) for persistent pruritus in two cases of dermatomyositis.[25] The drug was continued for 9–12 months without any flare-up and minimal adverse events. Tortelly *et al*. proposed LDN as an alternative for the treatment of scalp dysesthesia or trichodynia in symptomatic alopecia cases where there is no specific therapeutic guideline to date.[26] For compounding, a simple ingredient such as orange juice can be used to reduce the total cost.[27] Table 1 highlights the various studies that used LDN in different skin conditions with the level of evidence and strength of recommendation for its use.[28-31]

Table 1: Highlights of the various studies that used LDN in various skin conditions with level of evidence and strength of recommendation.

Dermatosis	Study	Type of study	Level of study	Strength or recommendation
Excoriation disorder	Varghese *et al*.,[8] 2024	Case report	Level 5	Weak
Frontal fibrosing alopecia and lichen planopilaris	Hamel *et al*.,[12] 2023	Pseudo-randomized control trials	Level 3a	Strong
Lichen planopilaris	Lajevardi *et al*.,[28] 2022	Randomized clinical trial	Level 2a	Strong
Vulvar Hailey-Hailey disease	Sousa Gomes *et al*.,[10] 2020	Case report	Level 5	Weak
Psoriasis	Khan *et al*.,[29] 2020	Pseudo-randomized control trials	Level 3a	Strong
Nail Lichen Planus	Bray and Morrison,[19] 2024	Case series	Level 4	Weak
Darier disease	Boehmer *et al*.,[20] 2019	Case series	Level 4	Weak
Prurigo nodularis	Timoney and Bunker,[17] 2021	Case report	Level 4	Weak
Hailey-Hailey disease	Ibrahim *et al*.,[18] 2017	Case series	Level 4	Weak
Hailey-Hailey disease	Riquelme-Mc Loughlin *et al*.,[30] 2019	Case series	Level 4	Weak
Erythrodermic psoriasis	Beltran Monasterio,[23] 2019	Case report	Level 5	Weak
Guttate psoriasis	Muller *et al*.,[21] 2018	Case report	Level 5	Weak
Epidermolysis bullosa pruriginosa	LaMonica *et al*.,[24] 2023	Case report	Level 5	Weak
Dermatomyositis	Tran *et al*.,[25] 2018	Case report	Level 5	Weak
Segmental Darier's disease	Pastukhova and LaBerge,[31] 2023	Case report	Level 5	Weak

LDN: Low-dose naltrexone

ADVERSE EFFECTS

LDN generally has a milder side-effect profile. Vivid dreams, nightmares, anxiety, and headaches are some of the common side effects reported.[3] Some rare adverse events reported are sleep disturbance, insomnia, hyperhidrosis, dry mouth, metallic taste, tongue swelling, and vertigo.[12]

LIMITATION OF THE STUDY

Studies published in languages other than English were excluded, which could be a potential limitation of this article.

CONCLUSION

LDN has shown early, promising results in the treatment of various inflammatory skin conditions. Its low abuse potential, minimal adverse effect profile, and low price make this drug a promising agent. In India, LDN is currently not available. Naltrexone 50 mg tablets are easily available, costing 70–80 rupees per tablet. These 50 mg tablets can be compounded in the hospital pharmacy as per our requirement to prepare LDN ranging from 3 to 5 mg/day. Hence, approximately 3 tablets costing 200–220 rupees will be sufficient for the preparation of a 1-month medication, which is significantly lower than most of the currently available immunosuppressive and biological agents in the market. For patients belonging to the lower-middle class, LDN can be a good alternative. However, the lack of a well-equipped pharmacy for drug compounding will pose a challenge until LDN is available in the market. Furthermore, the current evidence of LDN in various inflammatory conditions is based on low-level evidence (case reports/series), which requires further validation with randomized controlled trials, especially in the Indian population.

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