The uses of naltrexone in dermatologic conditions

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Background: Naltrexone in standard and reduced doses is efficacious in many inflammatory and acantholytic disorders.

Objective: We summarized the current data of naltrexone that are relevant to dermatologic practice.

Methods: An English language PubMed literature search was performed using the terms naltrexone, low-dose naltrexone, Hailey–Hailey, psoriasis, lichen planopilaris, alopecia, opioid, opioid receptor, treatment, dermatology, monitoring, side effect, skin, pruritus, cutaneous, acantholytic, and Darier.

Results: Opioid receptors are found throughout the skin and affect cell proliferation, migration, and adhesion. μ Opioid receptors have been found in all layers of the epidermis, while δ receptors are concentrated at cell junctions and can reduce desmoglein expression. Typical doses of naltrexone result in continuous binding to receptors. Low doses result in intermittent blockade with increased ligand and receptor expression, potentiating their effect.

Limitations: Our review was restricted to the English language literature.

Conclusion: Naltrexone affects inflammation, cell adhesion, and keratinocyte proliferation and migration. While low-dose naltrexone has demonstrated efficacy in treating patients with Hailey–Hailey disease, further dose-ranging studies are needed. Data suggest that naltrexone could be helpful in the treatment of pruritus and a variety of inflammatory and acantholytic skin diseases that are refractory to other treatments. At higher doses, liver function tests should be monitored on a periodic basis. (J Am Acad Dermatol 2019;80:1746-52.)

Key words: dermatology; Hailey–Hailey disease; lichen planopilaris; low-dose naltrexone; naltrexone; opioid receptor; opioid receptor antagonist; opioids; pruritus; psoriasis; scleroderma.

Naltrexone is a relatively inexpensive long-lasting opioid antagonist that was first synthesized in 1963. To treat opioid addiction, it is usually given orally in 50- to 100-mg doses and binds to "classic" opioid receptors (μ, κ, and δ) as well as the opioid growth factor receptor (OGFr).[1] Low-dose naltrexone (LDN) refers to daily doses between 1 and 5 mg, compounded by a pharmacist.[1] LDN exhibits paradoxical properties with both analgesia and antiinflammatory effects, some of which have not been shown to occur with higher doses.[1] LDN has been used to treat patients with Crohn's disease, fibromyalgia, multiple sclerosis, and chronic pain disorders.[1]

In dermatology, classic doses of naltrexone (50-100 mg) have been used to treat pruritus, and LDN has been reported to be beneficial in the treatment of benign chronic pemphigus (Hailey–Hailey disease).[2-6] However, LDN may also be helpful in a wide variety of cutaneous conditions.[7-11] This review serves to discuss the proposed mechanisms and potential uses for LDN in dermatologic conditions.

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HISTORY

Naltrexone was approved by the US Food and Drug Administration to treat opioid addiction in 1984.[1] Alcohol use disorder was approved as an additional indication in 1994.[12] Compared with naloxone, a chemically similar opioid receptor antagonist, naltrexone has a greater oral bioavailability and a longer half-life.[1] Ultra low-dose naltrexone refers to doses <0.001 mg.[1,13] This dosage has been combined with opioids to increase their analgesic effect.[14] LDN refers to doses in the range of 1 to 5 mg per day.[1,13]

Early evidence for the use of LDN in inflammatory diseases focused on Crohn's disease.[1,15,16] In dermatology, naltrexone at standard doses has been used for the treatment of pruritus.[17] More recently, LDN, although not currently approved by the US Food and Drug Administration for any dermatologic indication, has been reported to be effective in the improvement of the signs and symptoms of familial benign chronic pemphigus (Hailey–Hailey disease), lichen planopilaris, guttate psoriasis, and scleroderma.[2-9]

CAPSULE SUMMARY

- Naltrexone is a long-acting opioid antagonist that is used to treat a wide variety of inflammatory conditions in multiple organ systems.
- Evidence supports the use of low-dose naltrexone in patients with Hailey–Hailey disease.
- Full therapeutic doses may have a role in treating a variety of inflammatory skin disorders.

MECHANISMS OF ACTION

The 3 classic opioid receptors (μ, κ, and δ) are G protein–coupled transmembrane receptors that when activated cause inhibition of adenylyl cyclase activity as well as L- and N-type calcium channels.[18,19] Each receptor has preferred binding to specific endogenous ligands. However, the ligands are not exclusive to each receptor subtype.[18] Endorphins are the main ligand for the μ opioid receptor, while dynorphins are the main ligand for the κ receptor, and enkephalins are the main ligand for the δ receptor.[18]

Opioid receptors are found ubiquitously throughout the body, including in many of the cells that comprise the skin. All 3 classic opioid receptors are found in keratinocytes, fibroblasts, melanocytes, and immune cells in the skin.[20-24] μ Opioid receptors have been found in all layers of the epidermis, most densely concentrated in the basal and suprabasal layers.[25] β Endorphins have been shown to upregulate cytokeratin 16, which is overexpressed in many hyperproliferative skin conditions, such as wounds, psoriasis, and skin cancers.[25] Keratinocytes have been shown to produce β endorphins.[26] The migration of keratinocytes is stimulated by β endorphins, and other research has shown that naltrexone inhibits this movement, suggesting that the μ opioid receptors play an important role in keratinocyte migration.[25] μ Opioid receptors have also been associated with stimulating itch, while κ opioid receptor activation has been shown to suppress itch.[18,24]

δ Opioid receptors preferentially accumulate at cell junctions in keratinocytes.[27] Activation of the δ opioid receptors reduces desmoglein expression.[27] This effect would enable loosening of cell–cell adhesion, initiating the change from a stationary to a migratory keratinocyte.[27] Mice that lack δ opioid receptors exhibit delayed wound healing, suggesting an important relationship between δ opioid receptors, desmosomes, and wound recovery.[27] δ Opioid receptor overexpression causes dysregulation of involucrin, loricrin, and filaggrin, proteins that are important in the stratum corneum,[20] and a topical naltrexone preparation has shown improvement in the resolution of diabetic rat cutaneous wounds.[28] While desmosomal adhesion and migration have important roles in normal skin mechanics and wound healing, they also play a role in the pathogenesis of common skin diseases, creating the opportunity for therapeutic targeting of the receptors.[27]

An additional opioid receptor is the OGFr whose ligand is opioid growth factor (OGF), also known as methionine5-enkephalin.[19] OGFr has been widely conserved among species but bears little structural similarity to the classic opioid receptors.[19,29] OGF and OGFr have been reported in the basal and suprabasal cells of the human epidermis.[30] OGFr is a nuclear-associated protein that when coupled with its ligand translocates to the nucleus and interacts with DNA to inhibit DNA replicative activity.[19,29] This interaction leads to decreased cellular proliferation.[19] Interestingly, imiquimod upregulates OGFr and stimulates the OGF–OGFr axis, which causes inhibition of cell proliferation. This mechanism has been hypothesized to play a role in imiquimod's effect on external and anal warts, basal cell carcinoma, Kaposi sarcoma, actinic keratosis, and chronic hepatitis C virus infection.[31,32]

In contrast to the continuous binding of 50- to 100-mg doses of naltrexone to its receptors, LDN

Abbreviations used:

LDN: low-dose naltrexone
OGF: opioid growth factor
OGFr: opioid growth factor receptor

only binds to the receptors for 4 to 6 hours.[29] This intermittent blockade results in a compensatory increase in endogenous opioids, including β endorphins and OGF as well as an increase in the expression of μ receptors, δ receptors, and OGFr.[13,16,29,33,34] Therefore, instead of inhibiting the opioid receptors, LDN paradoxically increases ligand and receptor expression, potentiating their effect (Fig 1). Therefore, variations in dose titration may result in different cutaneous effects.

Naltrexone also affects nonopioid receptors, such as Toll-like receptor 4, where it acts as an antagonist.[16] Toll-like receptor 4 has been found on keratinocytes and macrophages.[1,35] This binding results in decreased amounts of tumor necrosis factor–α, interleukin-6, and nitric oxide.[16] It is believed that naltrexone exerts its antiinflammatory effects through this mechanism.[1]

SIDE EFFECTS AND MONITORING OF NALTREXONE

The most significant drug interaction with naltrexone is with opioids themselves. Concurrent use may precipitate opioid withdrawal symptoms and decrease opioid effectiveness.[36] Patients should be advised of the risk and the conversation should be documented. Some of the satisfaction from scratching an itch relates to endorphin release, and patients who are being treated for pruritus may exhibit some symptoms of withdrawal early in the course of therapy. Concurrent use of other opioid antagonists, including naldemedine and naloxegol, may result in an increased risk of opioid withdrawal, and administration with lofexidine (an $\alpha 2$ adrenergic agonist) may result in reduced efficacy of oral naltrexone.[36]

Common adverse effects of 50- to 100-mg doses of naltrexone include gastrointestinal (abdominal cramps, abdominal pain, and nausea), musculoskeletal (arthralgias and myalgias), neurologic (difficulty sleeping, headache, and lack of energy), and psychiatric (anxiety and feeling nervous) symptoms.[36] Hepatotoxicity was noted in patients who were treated for alcoholism.[37] However, more recent studies have indicated that naltrexone poses a significantly lower risk than previously thought, even among alcohol- and opioid-dependent patients.[38] It is prudent to obtain baseline liver function tests before initiating naltrexone therapy and repeat these tests 8 to 12 weeks after starting treatment.[39] We prefer to check them quarterly for the first year of therapy, then periodically thereafter.

Patients should be screened for preexisting opioid dependence, recent use of opioids, and signs or symptoms of opioid withdrawal before initiation of naltrexone treatment,[36] and those with risk factors should be evaluated for HIV, hepatitis B virus, and hepatitis C virus infection.[39]

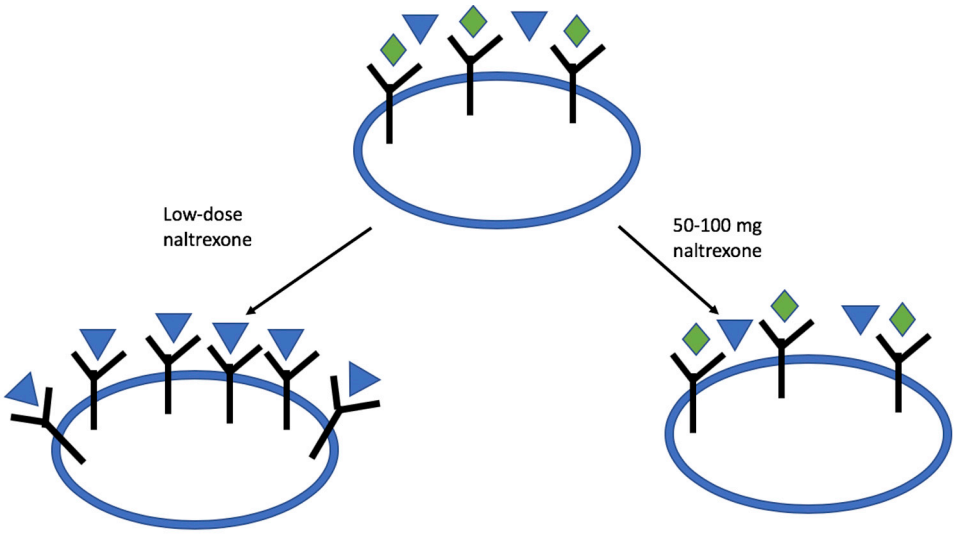

Fig 1. The shorter binding time of low-dose naltrexone results in an increase in endogenous opioids and an increase in the expression of receptors compared with 50- to 100-mg doses that inhibit opioid receptors. The green diamond represents naltrexone, the blue triangle represents endogenous opioids, and the black Y represents the opioid receptor.

Table I. Summary of cases that use low-dose naltrexone to treat patients with Hailey–Hailey disease

Author	No. of patients	Dose, mg	Time to improvement	Side effects
Kollman and Bass[2]	1	1.5-9	Started on 1.5 mg LDN daily with ciprofloxacin for 2 weeks; increased to 1.5 mg twice daily, similar presentation after 1 week; increased to 1.5 mg 3 times/day, less maceration and rash improvement after 1 week; increased to 3 mg 3 times/day for 4 weeks, achieved 95% clearance	No significant side effects
Cao et al[3]	3	4.5-50	Patient 1—4.5 mg, 95% clearance at 18 months Patient 2—12.5 mg for 2 months, complete resolution; stopped for 3 weeks, resulting in a flare; started LDN at 4.5 mg, erosions improved after 1 month Patient 3—50 mg for 1 month, no change; added acitretin 10 mg/day, 30% clearance in 1 month; stopped treatment for 2 weeks, resulting in a flare; started LDN at 4.5 mg, acitretin 25 mg, and systemic and intralesional steroid therapy; eventually, started glycopyrrolate and continued on 4.5 mg LDN, resulting in 30% clearance after 3 months	No significant side effects
Campbell et al[4]	1	4.5	Dermatology Life Quality Index score reduced from 29 to 4 in 7 months	No significant side effects
Ibrahim et al[5]	3	1.5-3	Patient 1—started on 1.5 mg/day, titrated to 3 mg/day within 4 weeks; 80% clearance by 3 months; sustained results after 9 months, mild intermittent flares every 3-4 months Patient 2—started on 1.5 mg/day, titrated to 3 mg/day within 1 month; 80% clearance after 3 months Patient 3—started on 1.5 mg/day, increased dosage to 3 mg/day for flares; 90% clearance after 4 months	No significant side effects
Albers et al[6]	3	3-4.5	Patient 1—started on 3 mg/day, began to heal after 1-2 weeks; increased to 4.5 mg after 6 weeks with complete clearance after several days; discontinued after 3 months, developed erosions; restarted LDN at 4.5 mg, erosions cleared in 1 week; remained clear for 7 months, ran out of medication for 2 weeks, and developed new erosions that healed after restarting LDN Patient 2—LDN 3 mg/day, erosions began to heal after 1-2 weeks; significant improvement after 1 month, increased to 4.5 mg nightly; complete resolution after 4 months; discontinuing LDN resulted in a flare within 4 days, which resolved within a week Patient 3—started LDN 3 mg/day, began to heal after 2-3 days; pruritus increased during the first week then improved; complete clearance after 2 months; discontinued LDN, 2 new erosions appeared within 12 days; erosions healed within 1 week of restarting LDN	Patient 3 reported 1 episode of intense dreams; no changes in complete blood cell count or metabolic panel from baseline to 1 month

LDN, Low-dose naltrexone.

In contrast, there is little evidence of serious effects associated with LDN. Some of the more common side effects include vivid dreams, nightmares, and headaches.[1,9] In 1 study, vivid dreams developed in ≤37% of patients but decreased over time. It should be noted that vivid dreams were also the most common side effect in the placebo group, indicating that there may be an element of suggestion.[1] LDN can be administered as a morning dose to minimize this complaint.[13] In 1 fibromyalgia study, headaches were observed in 16% of patients treated with LDN versus 3% treated with placebo.[40] There is evidence that a dose reduction from 4.5 to 3 mg daily may improve these symptoms.[13]

A retrospective chart review of 54 patients with multiple sclerosis treated with LDN noted no changes in blood values.[16,41] One study examined the use of LDN in patients with Crohn's disease. The primary endpoint measured was a 70-point decline in the Crohn's Disease Activity Index.[42] The Crohn's Disease Activity Index takes into consideration the number of liquid stools, abdominal pain, general well-being, extraintestinal complications, the use of antidiarrheal drugs, abdominal mass, hematocrit, and body weight, and weighs each factor differently to obtain the score.[43] Two of 40 patients in this trial had transient elevation in liver transaminases that resolved over the following month.[42] No significant changes occurred in hemoglobin, white blood cell count, albumin, electrolytes, glucose, or renal profiles.[42] No laboratory evaluations are required for LDN in the absence of signs or symptoms.

DERMATOLOGIC USES OF NALTREXONE

In dermatology, 50- to 100-mg doses of naltrexone have been shown to treat pruritus associated with psoriasis, atopic dermatitis, lichen simplex chronicus, and prurigo nodularis.[17,21] More recently, LDN has been shown to have a role in treating a variety of other dermatologic conditions. Most data come from case reports or small series. In a series of 3 patients with scleroderma, LDN was shown to improve itch symptoms. These patients were treated with 2 to 4.5 mg LDN daily for 2 months, and all showed improvement. No side effects were reported except for insomnia for 2 nights in 1 patient.[7] In another case series, 4 patients with lichen planopilaris, including 1 with frontal-fibrosing alopecia, were treated with 3 mg of naltrexone daily, which caused a reduction in pruritus, clinical evidence of scalp inflammation, and disease progression. All patients had significant improvement within 1 to 2 months of commencing therapy. The longest follow-up was 7 months. No side effects were reported.[8] LDN has also been reported to help treat guttate psoriasis. One patient treated with 4.5 mg LDN daily saw improvement after 4 weeks, manifested as a resolution in the number of lesions as well as the pruritus and weeping. He continued treatment for 12 months and had no side effects except for dry skin.[9] In a different patient with psoriasis vulgaris, 4.5 mg LDN improved her psoriatic lesions after 3 months, with the affected body surface area decreasing from 10% to 1% after 6 months of treatment. In addition, the calculated Psoriasis Area Severity Index score decreased from 7.2 to 0.9 after 6 months of treatment, and pruritic symptoms improved. No side effects were reported.[10] Finally, LDN has demonstrated potential use in the treatment of 2 patients with dermatomyositis. The first patient had clearance of skin lesions after 3 months with intravenous immunoglobulin G, then began 5 mg LDN because of persistent pruritus. After 9 months, his skin remained clear and he experienced no pruritus, hand arthralgia, or severe muscle weakness. The second patient was transitioned from intravenous immunoglobulin G infusions to subcutaneous immunoglobulin and started on 5 mg LDN. After 6 weeks, her pruritus resolved; after >1 year, she had only minimal cutaneous flaring.[11]

The most compelling evidence to date is LDN treatment of patients with Hailey–Hailey disease in doses ranging from 1.5 to 50 mg daily. A summary of the results is shown in Table I. We have had some success in the reduction of signs and symptoms in both Grover disease and Darier disease, which are related conditions that are notoriously refractory to therapy.

In conclusion, the use of naltrexone in dermatology has expanded because the drug is relatively inexpensive, is well tolerated by patients, and has demonstrated potential value in a number of diseases at both low and standard doses. Preliminary evidence suggests it may have a role in the treatment of Hailey–Hailey disease as well as lichen planopilaris, Grover disease, and Darier disease. Variations in dosing can result in either the potentiation or the blockade of opioid receptors, and future studies should focus on pharmacokinetics and dose-response curves.

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