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REVIEW

# Low-Dose Naltrexone: What is the Evidence? A Narrative Review

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## ABSTRACT

Naltrexone is prescribed off-label at low doses, typically 0.5–6.0 mg, for a variety of therapeutic indications. This review evaluates the clinical evidence for low-dose naltrexone (LDN). A literature search was conducted in February 2026 across PubMed, Embase and CINAHL for studies published from 1989 to 2026. Title and abstract searches for "low dose naltrexone" identified peer-reviewed English-language studies using doses of ≤ 12.5 mg in humans. A total of 105 studies were reviewed, including 15 randomised controlled trials (RCTs) in chronic pain, autoimmune and neuroimmune disorders, gastrointestinal disease, dermatological conditions, post-infectious syndromes, mental health and oncology. Across these fields, early positive findings from uncontrolled studies were rarely replicated in placebo-controlled trials. Most available evidence consists of case reports and small feasibility studies that are prone to publication bias and rely heavily on subjective outcomes. LDN is generally safe, inexpensive and well tolerated, with most studies using a daily dose of 4.5 mg. Although these features contribute to its appeal, current evidence does not support routine clinical use. LDN may have a pragmatic role in treatment-resistant cases where standard therapies have failed, provided its experimental status and uncertain efficacy are clearly explained. Larger, well-designed RCTs with objective endpoints, along with *N*-of-1 approaches to identify potential responders, are needed to clarify its true clinical value.

**Keywords:** Fibromyalgia; Off-label prescribing; Opioid receptor antagonist; Pain management

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**Key Summary Points**

Low-dose naltrexone (LDN) has gained popularity as an off-label therapy across a diverse range of therapeutic areas due to its proposed mechanisms of action, yet the quality of the evidence base remains unclear.

LDN has been investigated in 105 studies, including 15 randomised controlled trials (RCTs), across chronic pain, autoimmune, neuroimmune, gastrointestinal, dermatological, post-infectious, mental health and oncology settings.

Positive findings from early uncontrolled studies are rarely confirmed in placebo-controlled trials.

The evidence base is dominated by small, low-quality studies that rely on subjective outcomes and are vulnerable to publication bias.

LDN is generally safe, inexpensive and well tolerated at typical doses, but current data do not justify routine clinical use.

It may be considered in treatment-resistant situations, but its experimental status and uncertain efficacy should be made clear, and more rigorous RCTs and *N*-of-1 studies are needed to determine its true value.

## INTRODUCTION

Naltrexone is an opioid receptor antagonist first approved by the Food and Drug Administration in 1984 for use in opioid use disorder at oral doses of 50–100 mg and subsequently extended in 1994 to encompass alcohol use disorder [1, 2]. At these conventional doses, naltrexone functions as a non-selective competitive antagonist of mu (μ), kappa (κ) and delta (δ) opioid receptors, with a higher affinity for the μ-opioid receptor over κ and δ [1, 3–5]. Opioid receptors exhibit stereoselectivity, preferring the levo-isomer of opioid ligands [6]. As such, levo-naltrexone serves as the primary opioid receptor antagonist. By blocking opioid receptors, naltrexone prevents both the euphoric effects of exogeneous opioids and the rewarding effects of endogenous opioid release, thereby reducing cravings through modulation of mesolimbic dopaminergic pathways [1].

Low-dose naltrexone (LDN), typically administered at doses of 0.5–6 mg/day, emerged in the 1980s through off-label use in the treatment of patients with HIV/AIDS [7]. Unlike conventional naltrexone, LDN exhibits hormesis, a biphasic dose response that exerts distinct pharmacodynamic effects extending beyond opioid receptor antagonism [8]. This dose-dependent behaviour has positioned LDN as a potential treatment across a diverse range of conditions, with proposed therapeutic applications in pain management, gastroenterology, immunology, dermatology, mental health and oncology.

Clinical research into LDN has largely outpaced mechanistic research. Nonetheless, three distinct mechanistic pathways have been proposed to underlie LDN's therapeutic effects, each representing a departure from the pharmacological profile of conventional naltrexone: (1) Toll-like Receptor 4 (TLR4) antagonism of microglial cells, disrupting pro-inflammatory signalling cascades and producing anti-inflammatory and immunomodulatory effects [9]. Notably, the TLR4-MD-2 interaction with naltrexone is non-stereoselective, theoretically allowing dextro-naltrexone to selectively inhibit TLR4 without interfering with endogenous opioid signalling, thereby providing anti-inflammatory effects independent of opioid receptor modulation [10]; (2) transient intermittent opioid receptor blockade lasting 6–8 h triggering compensatory upregulation of endogenous opioid peptides and receptor expression, potentially enhancing immune modulation [11]; (3) temporary antagonism of the Opioid Growth Factor Receptor (OGFr) resulting in compensatory receptor upregulation of OGF and OGFr, inhibiting cellular proliferation through enhanced OGF–OGFr signalling [12]. Importantly, these mechanisms remain largely theoretical and speculative, with limited high-quality clinical evidence demonstrating their therapeutic relevance in human disease.

Despite its purported versatility and growing interest among patients, researchers and prescribers [13, 14], LDN remains an off-label treatment with supply limited primarily to compounding pharmacies under prescriber discretion. Lower-dose regimens such as very-low-dose naltrexone (VLDN; 0.1-0.5 mg) and ultra-low-dose naltrexone (ULDN; <1 µg) have attracted interest, but the mechanistic evidence base remains limited. No specific mechanisms have been demonstrated for VLDN, and some of the key mechanistic studies for ULDN have been retracted due to concerns about the integrity and reliability of data presented [15, 16]. Claims about distinct mechanisms of action at these very-low and ultra-low doses should therefore be interpreted in light of these considerations.

This review seeks to clarify what the current evidence reveals about the therapeutic applications and clinical value of LDN, while also identifying critical gaps in the existing literature. Ultimately, it aims to support evidence-based practice in the provision of patient care.

## METHODS

A comprehensive literature search was conducted in August 2025, with a final update performed in February 2026 using PubMed, Embase and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. The search included studies published from 1989 to February 2026. The term "low dose naltrexone" was used, in title and abstract searches, to identify peer-reviewed English-language publications exploring the off-label therapeutic utilisation of naltrexone at doses of ≤ 12.5 mg in humans. Of 324 records identified, 122 duplicates were removed and 97 studies excluded, leaving 105 studies for full review. To ensure a comprehensive evaluation of the available literature, no additional exclusion criteria were applied. This article is a review of the published literature and does not involve the collection or analysis of primary data from human participants.

## RESULTS

Of the 105 studies reviewed, 15 were randomised controlled trials (RCTs) spanning seven therapeutic areas. The remaining evidence consisted primarily of case reports, small case series and observational or retrospective studies. Once-daily dosing was most common, and a daily dose of 4.5 mg was the most frequently reported, often achieved through gradual titration. The strongest controlled evidence was found in chronic pain, although early positive findings have not been reproduced in larger, more recent trials. Small RCTs in autoimmune and gastrointestinal disorders show possible benefit, although findings remain inconsistent. All other therapeutic areas, including neuroimmune, dermatological, post infectious, mental health, oncological and other investigational uses, are supported predominantly by uncontrolled or anecdotal evidence. The few placebo-controlled trials conducted in these areas have not demonstrated clear clinical benefit. Across all indications, LDN appears well tolerated, with adverse effects that are mild, transient and most often limited to insomnia, vivid dreams, nausea and dizziness. As studies vary widely in quality and design, findings are presented descriptively by indication, with evaluation reserved for the discussion.

### Pain and Central Sensitisation Disorders

The majority of RCTs conducted to investigate the clinical effect of LDN have involved participants experiencing chronic pain conditions. There were nine trials that included a comparator in the design: eight RCTs and one non-randomised crossover study, which together enrolled 430 participants (Table 1). Across these trials, LDN (typically 4.5 mg/day) demonstrated a favourable safety profile but variable efficacy. Early controlled trials in fibromyalgia reported clinically meaningful pain reductions and mood improvements [17, 18]. However, despite early promise, these findings have not translated to more recent, larger fibromyalgia RCTs, which demonstrate no superiority of LDN over placebo [19–21]. LDN has shown comparable analgesic

**Table 1** Clinical trials investigating low-dose naltrexone (LDN) in chronic pain conditions that include comparison with a control, grouped by study population

| Population (*n*) | Design | LDN intervention | Comparator | Concurrent therapy | Key findings | Authors (Year) |
|---|---|---|---|---|---|---|
| Fibromyalgia (*n* = 10) | Non-randomised, single-blind, fixed-sequence crossover | 4.5 mg/day 8 weeks | Placebo | Stable concomitant medications permitted; opioids excluded | Statistically significant reduction in pain ratings vs. placebo phase; mild insomnia reported | Younger & Mackey (2009) [17] |
| Fibromyalgia (*n* = 31) | Randomised, double-blind, crossover | 4.5 mg/day 12 weeks | Placebo | Stable concomitant medications permitted | Statistically significant pain reduction vs. placebo; improved mood and life satisfaction; no serious adverse events | Younger et al. (2013) [18] |
| Fibromyalgia (*n* = 86) | Randomised, double-blind, four-arm parallel | 4.5 mg/day 26 days ± tDCS | Placebo + tDCS and Placebo + tDCS sham | Stable concomitant medications permitted | Statistically significant within-group mood outcome improvements with LDN + tDCS; LDN alone not statistically superior; well tolerated | Paula et al. (2023) [19] |
| Fibromyalgia (*n* = 52) | Randomised, double-blind, crossover | 4.5 mg/day 21 days | Placebo | Stable concomitant medications permitted | No statistically significant differences in pain or functional outcomes vs. placebo | Bested et al. (2023) [20] |

**Table 1** continued

| Population (*n*) | Design | LDN intervention | Comparator | Concurrent therapy | Key findings | Authors (Year) |
|---|---|---|---|---|---|---|
| Fibromyalgia (*n* = 99) | Randomised, double-blind, parallel | 6 mg/day 12 weeks | Placebo | Rescue analgesia permitted | No statistically significant superiority for primary pain outcome vs. placebo; similar adverse-event rates | Due Bruun et al. (2024) [21] |
| Painful diabetic neuropathy (*n* = 67) | Randomised, double-blind, crossover | 2–4 mg/day 6 weeks | Amitriptyline 10–50 mg/day | Monotherapy | No statistically significant differences in analgesic efficacy vs. amitriptyline; fewer adverse effects | Srinivasan et al. (2021) [22] |
| Osteoarthritis inflammatory arthritis (*n* = 29) | Randomised, double-blind, crossover | 4.5 mg/day 8 weeks | Placebo | Stable concomitant medications permitted | No statistically significant differences in pain interference or severity vs. placebo; adverse effects mild and comparable | Beaudette-Zlatanova et al. (2023) [23] |
| HIV-associated pain (*n* = 11) | Randomised, double-blind, parallel | 4.5 mg/day 8 weeks | Nalmefene 16 mg/day | Adjunct to stable antiretroviral therapy | LDN feasible and tolerable; nalmefene arm discontinued due to intolerance | Bendiks et al. (2023) [24] |
| HIV + alcohol-use disorder with pain (*n* = 45) | Randomised, double-blind, three-arm parallel | 4.5 mg/day 8 weeks | Gabapentin ≤ 1800 mg/day and placebo | Adjunct to stable antiretroviral therapy | No statistically significant difference in pain outcome vs. gabapentin or placebo; well tolerated | Tsui et al. (2024) [25] |

*tDCS* transcranial direct current stimulation

efficacy and superior tolerability to amitriptyline in painful diabetic neuropathy but no statistically significant therapeutic benefit in osteoarthritis or inflammatory arthritis compared to placebo [22, 23]. Trials in HIV-associated pain have shown no superiority of LDN over gabapentin or placebo but tolerability and safety were demonstrated in a single feasibility study [24, 25]. Overall, the evidence from controlled trials (Table 1) underscores the need for larger, rigorously designed studies to clarify the genuine therapeutic value of LDN.

Retrospective chart reviews of cohorts prescribed LDN have reported improvements across various chronic pain populations. One study matched patients treated with LDN (4.5 mg/day) for at least 2 months ($n=36$) with usual-care controls ($n=42$), and found that they experienced substantially greater reductions in pain intensity, with larger improvements observed in the neuropathic subgroup [26]. Other studies report only on patients who were recorded to have taken LDN. In a refractory chronic fibromyalgia pain cohort ($n=65$) treated with LDN (typically 4.5 mg/day, adjusted for tolerance) significant improvements at 3 and 6 months were reported [27]. For patients with localised neuropathic corneal pain ($n=30$), long-term LDN (4.5 mg/day) reduced neuropathic corneal pain by approximately 49% and improved quality-of-life measures [28]. Likewise, treatment with LDN (titrated up to 4.5 mg twice daily) improved pain tolerance for a cohort of patients ($n=76$) with opioid-induced hyperalgesia or fibromyalgia [29].

Retrospective studies may also highlight the presence of both responders and non-responders within populations. In a tertiary pain clinic cohort, 70 patients took LDN (1–5 mg/day), of whom 64% reported at least some pain relief, with responders being more likely to have neuropathic pain or complex regional pain syndrome than other conditions such as spondylosis [30]. However, by the end of the review time, only 31.6% of patients were still taking LDN, and lack of efficacy was a more common reason than side effects as the reason for discontinuation. Similarly, two chart reviews of veterans prescribed LDN for pain ($n=136$ and $n=41$) reported reductions in numeric pain scores over several months of therapy with typical LDN doses of 3.8–4.5 mg/day [31, 32]. Only mild adverse effects were reported, most commonly sleep disturbances, gastrointestinal upset and drowsiness; but the most common reason for ceasing LDN was lack of efficacy [31, 32]. Cohort average pain intensity and functional disability scores improved from baseline. A chronic pain cohort with indications for treatment across 12 diagnostic categories ($n=93$) who all received LDN (1.5–4.5 mg/day), recorded subjective improvement in pain in 53.8% of patients [33]; the remainder reported a lack of efficacy. For a mixed chronic pain cohort ($n=68$), 65% of patients perceived some reduction in pain symptoms associated with LDN (most commonly titration up to 4.5 mg/day); however, 37% discontinuation was reported [34]. A separate cohort ($n=31$) showed a small but statistically significant improvement in composite PEG scores following LDN treatment (< 10 mg/day). In this study, 87% of patients discontinued their LDN treatment, most of these being due to lack or loss of benefit [35].

Case reports and small case series involving a total of approximately 65 patients describe subjective and sometimes substantial improvement across diverse pain conditions following LDN use at doses of 1–4.5 mg per day. Across fibromyalgia and other central sensitisation disorders, individual reports describe pain and fatigue reductions of approximately 30–60%, with additional reports of marked symptom relief and functional gains in musculoskeletal and lower back pain [36–41]. One study treated a group of patients with fibromyalgia ($n=25$) with LDN (3–4.5 mg/day) for 3 months and reported that half of them experienced an average 41% improvement in symptom severity (FIQ-R) scores alongside reported reductions in pain and anxiety [42]. Individual case reports describe symptom improvement in burning mouth syndrome, vulvodynia and gadolinium deposition disease [43–46]. Sustained or near-complete remission has also been reported in individual cases of trigeminal neuropathic pain, complex regional pain syndrome, treatment-resistant back pain and chronic migraine in multiple sclerosis, with progressive improvement observed over time

in a small retrospective neuropathic-pain case series ($n=14$) [37, 47–51].

Across all trials, studies and reports relating to LDN for pain, the most reported dose is 4.5 mg/day. A single-blinded sequential dose–response trial ($n=25$) involving doses changing across a 3-week period confirmed this dose. It was estimated that clinically meaningful symptom improvement in fibromyalgia occurred at LDN doses of approximately 3.9–5.4 mg/day ($ED_{50}$–$ED_{95}$) [52]. However, an observational dose-finding study in patients with chronic musculoskeletal pain ($n=41$) demonstrated that the maximally effective dose varied widely between individuals (range 0.1–5.6 mg/day), and recognised the value of titration up to the patient's effective dose wherever possible [8].

### Auto-Immune Disorders

Evidence for LDN in multiple sclerosis is limited, with mixed findings across symptomatic and quality-of-life outcomes. Two studies incorporated comparison with placebo (Table 2). In a double-blind, placebo-controlled, crossover RCT ($n=60$), LDN (4.5 mg/day) significantly improved mental health-related quality-of-life indices [SF-36 (mental component), MHI] as well as pain and perceived cognitive function (PES, PDQ) [53]. However, there was no improvement in fatigue or physical function [MFIS, SF-36 (physical component)]. In contrast, a larger double-blind, placebo-controlled crossover RCT ($n=96$) found that LDN (4.5 mg/day) produced no consistent benefits across quality-of-life domains (MSQoL-54) [54].

In primary progressive multiple sclerosis, a 6-month open-label phase II study ($n=40$) showed that LDN (titrated from 2 to 4 mg/day) significantly reduced spasticity symptoms [55]. However, pain increased during treatment and no significant changes were observed in fatigue or depression. Furthermore, a retrospective review of patients with relapsing–remitting multiple sclerosis ($n=54$) found no significant differences in laboratory parameters, magnetic resonance imaging findings and 25-foot walk times between patients treated with LDN (3–4 mg/day) alone and those receiving LDN in combination with the immunomodulator, glatiramer acetate [56].

In patients with Sjögren's syndrome, case reports of three individuals treated with LDN (1–8.5 mg/day) describe marked improvements in musculoskeletal pain, fatigue and inflammatory markers. However, their symptoms of dry eyes and dry mouth did not improve [57, 58].

### Gastrointestinal Disorders

Crohn's disease has received the greatest research focus among gastrointestinal disorders, with limited, small, single-centre studies suggesting that LDN may confer potential benefit. The most rigorous evidence comes from a paediatric double-blind RCT ($n=12$; Table 2), where 8 weeks of LDN (0.1 mg/kg, maximum 4.5 mg/day) was associated with significant within-subject improvements in disease activity (Paediatric Crohn's Disease Activity Index) and quality-of-life domains compared to placebo [59]. These findings are consistent with a case report from a prior paediatric patient with duodenal Crohn's disease showing complete mucosal healing after 3 months of LDN (4.5 mg/day) use [60]. Similar outcomes were observed in adults using the same dose, with an open-label study ($n=17$) reporting a clinical response (Crohn's Disease Activity Index) in 89% and remission in 67% of participants over the 12-week treatment period and follow-up [61]. Improvements in quality-of-life scores were also reported alongside mild adverse effects, most commonly sleep disturbance.

There may be potential broader benefit across inflammatory bowel diseases (IBD). In an open-label cohort of patients with therapy-refractory Crohn's disease or ulcerative colitis ($n=47$), treatment with LDN (4.5 mg/day) was associated with clinical improvement in 74.5% of participants, with 25.5% maintaining a response for at least 3 months and only mild adverse effects reported [62]. Additional insights come from a retrospective survey of patients with IBD, irritable bowel syndrome, or chronic constipation ($n=121$), who had been prescribed LDN (2.5–4.5 mg/day) [63]. The survey reported symptomatic improvement in several diagnostic

**Table 2** Clinical trials investigating low-dose naltrexone in non-pain conditions that include comparison with a control, grouped by study population

| Population (*n*) | Design | LDN intervention | Comparator | Concurrent therapy | Key findings | Authors (Year) |
|---|---|---|---|---|---|---|
| Multiple sclerosis (*n* = 60) | Randomised, double-blind, crossover | 4.5 mg/day 8 weeks | Placebo | None specified | Statistically significant improvement in mental health quality of life measures vs. placebo; well tolerated | Cree et al. (2010) [53] |
| Multiple sclerosis (*n* = 96) | Randomised, double-blind, crossover | 4.5 mg/day 8 weeks | Placebo | Stable concomitant medications permitted; disease-modifying drugs excluded | No statistically significant differences in quality of life outcomes vs. placebo; safe and well tolerated | Sharafaddinzadeh et al. (2010) [54] |
| Crohn's disease (*n* = 12) | Randomised, double-blind | 0.1 mg/kg/day 8 weeks | Placebo | None specified | Statistically significant reduction in disease activity vs. placebo, improvement in quality of life; well tolerated | Smith et al. (2013) [59] |
| Gulf War illness (*n* = 37) | Randomised, double-blind, crossover | 4.5 mg/day 3 months | Placebo | None specified | Greater improvement observed in a subset of patients across fatigue, cognition and quality of life measures vs. placebo | Brewer et al. (2018) [64] |
| Lichen planopilaris (*n* = 34) | Randomised, triple-blind | 3 mg/day 6 months | Placebo | Topical clobetasol | No statistically significant differences in disease severity vs. placebo; well tolerated | Lajevardi et al. (2022) [73] |

**Table 2** continued

| Population (*n*) | Design | LDN intervention | Comparator | Concurrent therapy | Key findings | Authors (Year) |
|---|---|---|---|---|---|---|
| Major depressive disorder (*n* = 12) | Randomised, double blind | 1 mg twice daily 3 weeks | Placebo | Stable antidepressants | Statistically significant improvement in depressive symptom scores but not depression severity vs. placebo | Mischoulon et al. (2017) [103] |
| High-grade glioma (*n* = 110) | Randomised, double-blind | 4.5 mg/day 16 weeks | Placebo | Concurrent chemoradiotherapy | No statistically significant differences in quality of life or fatigue outcomes vs. placebo | Peters et al. (2022) [106] |

groups, particularly IBS-SIBO and chronic constipation. Among respondents, 61% reported adverse effects, of which 32.4% were short-lived with 27% discontinuing treatment.

### Neuroimmune Disorders

A double-blind, placebo-controlled crossover RCT (*n* = 37) in Gulf War Illness found that 38% of participants receiving LDN (4.5 mg/day) during a 3-month treatment were classified as responders on the Clinical Global Impression Scale [64]. LDN responders demonstrated significantly better scores in emotional functioning and greater improvements in energy and fatigue measures compared with non-responders (Table 2).

Research into LDN in epilepsy is limited to case notes about paediatric patients (*n* = 5) who received LDN (1–5 mg/day) adjunctive to their existing anti-epileptic medications [65]. After 3 months of treatment, marked seizure reduction was observed, with three patients reported to be seizure-free. Improvements in electroencephalograms were also noted in the three cases that underwent repeat assessments.

### Post-infectious Disorders

In recent years, there has been interest in the potential use of LDN in disorders relating to post-COVID-19 conditions. In an interventional pre-post study (*n* = 52), 2 months of LDN (1–3 mg/day) was associated with significant improvements in self-reported recovery, activities of daily living, energy, pain, concentration and sleep, while mood improvement approached but did not reach significance [66]. In a retrospective analysis of a Veterans Affairs post-COVID clinic cohort, records for patients taking LDN (1.5–4.5 mg/day) were compared with patients receiving physical therapy (*n* = 50). LDN was linked to an approximate five-fold higher likelihood of documented improvement in at least one symptom (fatigue, pain, brain fog or dyspnoea) [67]. A retrospective review of another post-COVID clinic cohort (*n* = 59) reported that individualised dosing up to 6 mg/day was associated with reduced symptom

burden and improved functional status [68]. Consistent with these findings, a large survey of patients post-COVID found that, of those taking LDN ($n=77$), 58% rated it as helpful [69]. Combination approaches also show potential, with an open-label study ($n=36$) combining LDN (4.5 mg/day) with weekly $NAD^+$ iontophoresis achieving significant improvement in fatigue and quality-of-life scores, with 52% of participants classified as responders after 12 weeks [70].

In a retrospective review of 218 patients with chronic fatigue syndrome (CFS) treated with LDN (3–4.5 mg/day) for a mean of 1.7 years, 73.9% reported some degree of symptomatic improvement, most commonly in vigilance, physical performance or cognitive function [71]. Non-response was reported by 18.3% of patients, 13.8% discontinued treatment because of lack of effect and 4.6% discontinued due to adverse effects such as insomnia, nausea or dizziness [71]. Similarly, a small case series ($n=3$) reported variable responses with LDN (4–12 mg/day) treatment in CFS, ranging from life-changing improvement to partial symptomatic improvement [72].

### Dermatological Disorders

There has been some preliminary work in the treatment of lichen planopilaris (LPP) using LDN. The only identified RCT ($n=34$; Table 2) in patients with this chronic inflammatory condition of the scalp, found that LDN (3 mg/day) in addition to topical clobetasol did not improve overall LPP severity compared to placebo combined with topical clobetasol across 6 months of use [73]. In subsequent studies involving mixed cohorts of frontal fibrosing alopecia and LPP, a prospective open-label study ($n=26$) found that LDN (3 mg/day), when added to stable anti-inflammatory regimens, was associated with a significant reduction in erythema at 12 months compared with baseline [74]. Symptoms of pruritus, burning and pain showed no significant change. Similarly, a retrospective case series ($n=20$) reported symptomatic improvement in some patients and stability in around two-thirds of participants using LDN (2.5–4.5 mg/day), although several patients were using concurrent treatments [75]. A smaller case series ($n=4$) and an additional single case report also describe reductions in pruritus and inflammation and dramatic hair regrowth in a scarring alopecic patch with adjunctive LDN (3 mg/day) and platelet-rich plasma [76, 77].

Hailey–Hailey disease (HHD), a rare hereditary skin condition, has been the subject of several case reports and case series across 27 patients using LDN. Smaller reports typically used 1.5–6.25 mg/day, occasionally up to 9 mg/day (3 mg three times daily), with initial improvements often observed within the first several weeks (1–6 weeks) and relapse frequently noted after withdrawal [78–84]. Additional cases describe clearance of vulvar HHD at 5 months, improvement of symptoms with LDN in combination with magnesium chloride and benefit in patients refractory to multiple therapies [85–87]. While many accounts highlight dramatic patient improvements, the largest case series ($n=14$) found that most patients showed no improvement or only transient benefit followed by relapse, with only two patients demonstrating a sustained response [87]. Adverse effects were uncommon and mild, consisting mainly of vivid dreams, nausea and dizziness [78, 84, 85, 87].

In a cohort of patients with psoriasis ($n=71$), LDN (6 mg/day) was well tolerated and was associated with reductions in psoriasis severity, percentage surface area affected (Psoriasis Area and Severity Index) and improvements in quality-of-life scores (Dermatology Life Quality Index) over 3 months [88]. Similarly, a case series ($n=15$) reported that LDN (4.5 mg/day) led to improvement in over half of the patients, while one-third remained unchanged and only mild adverse events noted [89]. Three case reports further suggest potential efficacy in plaque and in guttate and erythrodermic psoriasis, with substantial improvement or remission reported within months of LDN (4.5 mg/day) use and only minor adverse effects such as localised skin dryness noted in one case [90–92].

In Darier disease, a defect in skin keratinisation, a case series ($n=6$) reported variable

responses to LDN (5 mg/day) combined with magnesium (200 mg/day), with near-remission observed in mild to moderate disease but worsening or lack of sustained benefit in severe cases [93]. A separate case report described substantial clinical improvement following LDN titrated up to 12.5 mg/day, with relapse on dose reduction, renewed response upon dose escalation, and no adverse effects reported [94]. A subsequent case report described near-complete clearance of severe, refractory Darier disease after 3 months of combined LDN (4.5 mg/day) and oral isotretinoin, with no adverse effects reported [95].

LDN (1.5–5 mg/day) has been explored in several other dermatological disorders, with variable outcomes. Improvements have been reported in cases of nail lichen planus (LDN 3 mg/day monotherapy), systemic sclerosis-associated pruritus, dermatomyositis and amyopathic dermatomyositis, usually following inadequate response to conventional immunosuppressants [96–99]. Additional single-patient reports also describe antipruritic benefit in excoriated prurigo and, following dupilumab failure, in epidermolysis bullosa pruriginosa [100, 101]. A more recent case also demonstrated marked improvement of excoriation (skin-picking) disorder with LDN (4.5 mg/day), where cessation of therapy led to symptom relapse and reinitiation restored improvement, suggesting a possible behavioural and neuroimmune contribution [102].

## Mental Health Applications

Evidence for LDN in mental health conditions is limited but generally positive. In a proof-of-concept RCT ($n = 12$; Table 2) involving patients with major depressive disorder receiving dopaminergic antidepressants, 3 weeks of LDN (1 mg twice daily) significantly improved mood scale (MADRS) scores compared to placebo, although no significant effect was observed in the primary measure of overall depression severity (HAM-D-17) [103]. Similarly, a survey of individuals with MS taking LDN, either alone or alongside oral disease-modifying therapies ($n = 14$), had significantly lower anxiety and depression scores (HADS-A and HADS-D) compared with those on disease-modifying therapy alone ($n = 32$) [104]. A case report also describes remission of fibromyalgia-associated severe depression following addition of LDN (titration to 4.5 mg twice daily) though changes to other medications and psychotherapy also occurred so attribution of the improvement to LDN is unclear [105].

## Oncological Utilisations

The only identified RCT in patients with cancer, conducted in high-grade glioma ($n = 110$; Table 2), evaluated LDN (4.5 mg/day) for 16 weeks alongside concurrent radiation and temozolomide, finding no significant differences from placebo in fatigue or quality-of-life scores and comparable adverse event rates between groups [106]. Beyond this trial, evidence is limited to case reports in which LDN is adjunct to metabolic or cytotoxic agents. In a prospective case series ($n = 10$) of patients with advanced chemo-resistant cancers, a regimen of intravenous α-lipoic acid, hydroxycitrate and LDN (5 mg/day) produced mixed outcomes, including disease stabilisation or radiological responses in selected cases, with nausea and vomiting reported as dose-limiting toxicities [107]. Additional case reports describe prolonged survival in pancreatic adenocarcinoma treated with combined intravenous α-lipoic acid and LDN (3–4.5 mg/day), complete radiological remission attributed primarily to LDN (3 mg) in a follicular lymphoma case report and no evidence of recurrent disease on follow-up imaging in a non-small-cell lung cancer case following LDN (4.5 mg/day) initiation post-resection and completion of radiation [108–111]. A patient paediatric hepatoblastoma given LDN (0.5 mg/day) and opioid growth factor also remained disease-free for close to 10 years following resection [112].

### Other Investigational Uses

LDN has also been considered for use as an emerging therapy across a diverse spectrum of conditions. The benefit of LDN (1–4.5 mg/day) has been described in case reports in uremic pruritus secondary to end-stage kidney disease, sarcoidosis, stiff-person syndrome, postural orthostatic tachycardia syndrome (POTS) and POTS with mast cell activation syndrome, the latter alongside intravenous immunoglobulin and antibiotics [113–117]. A single case report has also described improved bone mineral density in osteopenia using a combination therapy including LDN [118]. Additionally, a survey ($n$=41) in amyotrophic lateral sclerosis found that those who used LDN ($n$=8) had higher physical quality-of-life scores (RAND-12 PCS) compared to respondents who did not take LDN [119].

In the context of reproductive health, a prospective controlled trial was conducted in women with immunological infertility and recurrent implantation failure ($n$=350) [120]. Critically, the study reporting did not meet CONSORT guidelines [121], so methodology details such as randomisation and allocation concealment are unclear. Yet, it is reported that LDN (4.5 mg/day) given prior to and during the first 12 weeks of pregnancy was associated with significant improvements in endometrial thickness, mature follicle numbers, higher pregnancy implantation and pregnancy rates compared to individuals who did not receive LDN [120]. While miscarriage rates were lower than the control group, the difference was not statistically significant. This is the first time that LDN has been proposed as a therapeutic option in this setting. There is no prior published evidence to support the rationale for its use in this context.

## DISCUSSION

The evidence base for LDN is broad but lacks methodological strength. Of the 105 studies reviewed, only 15 were RCTs, which spanned seven conditions and recruited between 10 and 99 participants. The remaining literature is predominantly comprised of case reports, cohort studies and retrospective surveys. These lower-quality designs frequently report favourable outcomes, while negative or inconclusive findings are rarely published, leaving the field highly vulnerable to publication bias. Consequently, perceptions of LDN's efficacy are likely inflated by selective reporting, with early enthusiasm often contradicted by more rigorous study designs [122]. At present, no indication has sufficient high-quality evidence to support routine clinical use of LDN.

LDN is generally well tolerated, with reported adverse effects typically mild and transient, including vivid dreams, insomnia, nausea, dizziness and mild gastrointestinal upset [17, 18, 22, 67, 68]. Its favourable safety profile likely contributes to widespread off-label use, particularly among patients who have not responded to or cannot tolerate standard therapies. Studies specifically examining the safety of LDN are sparse, and the literature does not currently address its use in high-risk groups. This is an area worth further investigation, given the concerns reported with conventional naltrexone doses (50 mg) in pregnancy and people with hepatic and renal impairment, and the absence of evidence on whether these risks extend to low doses [1]. A dose of 4.5 mg once daily achieved through gradual titration is most common, though doses up to 6–9 mg/day have been reported in dermatological cases. Nonetheless, dosing generally falls within a narrow range, suggesting emerging consensus in clinical practice. However, this remains empirically derived rather than evidence-based and condition-specific dose–response studies may, therefore, be valuable.

Across indications, a consistent pattern emerges whereby early uncontrolled or open-label studies frequently report substantial improvements, yet these findings are rarely reproduced in larger or placebo-controlled trials. This is most clearly demonstrated in chronic pain, where initial crossover studies in fibromyalgia suggested clinically meaningful benefit [17, 18]. However, larger, subsequent RCTs showed no superiority over placebo [19–21]. Similar discrepancies are evident across autoimmune, neuroimmune, gastrointestinal, dermatological,

post-infectious, mental health and other investigational conditions, where extensive anecdotal reporting contrasts with limited and inconsistent controlled evidence. The most reliable data therefore suggest that, if LDN has therapeutic effects, it is likely modest, inconsistent and patient specific.

Several factors likely contribute to the gap between anecdotal reports and controlled findings. Many trials have small sample sizes and are short in duration. They also rely heavily on subjective patient-reported outcomes, which are particularly vulnerable to placebo effects in conditions with fluctuating symptoms or strong patient expectations. Differences in how conditions are defined and diagnosed can also make it challenging to identify which patients may benefit from treatment. The concurrent use of other therapies makes it difficult to attribute improvements specifically to LDN. This co-administration confounds attribution of any observed effect, and such uncertainty can only be clarified in controlled settings. Notably, several studies report enhanced outcomes when LDN is combined with other interventions, including intravenous $NAD^+$ in long COVID [70], magnesium chloride in Hailey–Hailey disease [86], oral isotretinoin in Darier disease [95] and metabolic agents in oncology [107]. Differences in outcome measures may further limit comparability across studies, and inconsistencies in compounded formulations may introduce additional uncertainty. Together, these factors make it challenging to determine the extent to which observed improvements can be attributed to LDN.

Although case reports are susceptible to selective reporting, they do document genuine individual responses. These accounts indicate that LDN may offer meaningful benefit to some individuals, even when this is not consistently replicated in RCTs. This raises the possibility that LDN functions as an individualised therapy with variable and unpredictable responses rather than a uniformly effective treatment. Despite being considered the highest-quality study design, conventional parallel-group RCTs may therefore be poorly suited to detecting benefit in small responder subgroups. In this context, *N*-of-1 RCTs offer a promising alternative, preserving randomisation and blinding, while directly quantifying within-patient treatment effects [123, 124]. Aggregation of data from a series of *N*-of-1 trials is possible with appropriate statistical techniques. Such designs are particularly suited to identifying which individual patients may benefit from LDN and therefore warrant consideration in future research to determine genuine therapeutic value beyond population-level averages.

Ultimately, LDN is a safe, low-cost therapy with promise in early-phase and uncontrolled studies, particularly in neuropathic pain and Crohn's disease. However, current evidence remains insufficient to support routine clinical use outside treatment-resistant cases. Given its favourable safety profile, LDN may still be considered in patients who do not respond to or cannot tolerate established first-line therapies. Future research should focus on adequately powered, placebo-controlled trials with objective endpoints in the most promising indications, alongside *N*-of-1 methodologies to identify which patients derive benefit and refine treatment selection. Until such evidence emerges, LDN should be considered a low-risk experimental therapy with insufficiently validated clinical benefit. Nonetheless, the use of LDN may be a genuinely reasonable option in treatment-resistant cases.

Interpreting these findings also requires consideration of limitations inherent to this review. The scope was restricted to off-label use of LDN in humans, which excluded ex vivo mechanistic or exploratory work. Variation in terminology across the literature may also have resulted in some eligible studies not being captured. The review relied on English-language sources, introducing the possibility of missing non-English reports. These constraints reflect the defined scope of the review and indicate areas where future research could further strengthen and extend the evidence base.

## CONCLUSION

LDN has attracted substantial clinical interest, yet the current evidence remains limited in both quality and consistency. Across therapeutic areas, early positive findings from uncontrolled studies are seldom replicated in

placebo-controlled trials, and no indication has sufficient high-quality evidence to support routine clinical use. LDN is generally safe, inexpensive and well tolerated, which may justify cautious use in treatment-refractory cases where established therapies have failed. Future research should prioritise adequately powered, placebo-controlled trials with objective endpoints, alongside *N*-of-1 methodologies capable of identifying responder subgroups. Until such evidence emerges, LDN should be regarded as a low-risk but unproven therapy with uncertain generalisability beyond individual case-level responses. The current evidence base supports cautious, individualised use of LDN while underscoring the need for rigorous trials to determine its true therapeutic value.

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### *Declarations*

***Conflict of Interest.*** Amina HK Gouda, Nicholas EC Aitcheson and Kathryn J Steadman declare no personal, financial, commercial or academic conflicts of interest and have no disclosures.

***Ethical Approval.*** This article is a review of the published literature and does not involve the collection or analysis of primary data from human participants. As such, approval from a human research ethics committee was not required.



## REFERENCES

1. Singh D, Saadabadi A. Naltrexone. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2025 Jan; cited 2026 Feb 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534811/.

2. Substance Abuse and Mental Health Services Administration; Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice. Treatment improvement protocol (TIP) series 49. Rockville (MD): US Department of Health and Human Services; 2009.

3. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci U S A. 1993;90:5391–3.

4. Goldstein A, Naidu A. Multiple opioid receptors: ligand selectivity profiles and binding site signatures. Mol Pharmacol. 1989;36:265–72.

5. Pasternak GW. Pharmacological mechanisms of opioid analgesics. Clin Neuropharmacol. 1993;16:1–18.

6. Dunwiddie TV, Perez-Reyes E, Rice KC, Palmer MR. Stereoselectivity of opiate antagonists in rat hippocampus and neocortex: responses to (+) and (−) isomers of naloxone. Neuroscience. 1982;7:1691–702.

7. Bihari B. Efficacy of low dose naltrexone as an immune stabilizing agent for the treatment of HIV/AIDS. AIDS Patient Care STDS. 1995;9:3.

8. Marcus NJ, Robbins L, Araki A, Gracely EJ, Theoharides TC. Effective doses of low-dose naltrexone for chronic pain—an observational study. J Pain Res. 2024;17:1273–84.

9. Wang X, Zhang Y, Peng Y, et al. Pharmacological characterization of the opioid inactive isomers (+)-naltrexone and (+)-naloxone as antagonists of toll-like receptor 4. Br J Pharmacol. 2016;173:856–69.

10. Zhang X, Cui F, Chen H, et al. Dissecting the innate immune recognition of opioid inactive isomer (+)-naltrexone derived toll-like receptor 4 (TLR4) antagonists. J Chem Inf Model. 2018;58:816–25.

11. Zagon IS, McLaughlin PJ. Intermittent blockade of OGFr and treatment of autoimmune disorders. Exp Biol Med (Maywood). 2018;243:1323–30.

12. Donahue RN, McLaughlin PJ, Zagon IS. Low-dose naltrexone targets the opioid growth factor-opioid growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from a tissue culture model. Exp Biol Med (Maywood). 2011;236:1036–50.

13. Leiber KK, Parker RW. Therapeutic uses and efficacy of low-dose naltrexone: a scoping review. Cureus. 2025;17:e81086.

14. Aitcheson N, Lin Z, Tynan K. Low-dose naltrexone in the treatment of fibromyalgia: a systematic review and narrative synthesis. Aust J Gen Pract. 2023;52:189–95.

15. Wang HY, Frankfurt M, Burns LH. High-affinity naloxone binding to filamin A prevents Mu opioid receptor-Gs coupling underlying opioid tolerance and dependence. PLoS ONE. 2008;3:e1554.

16. Wang HY, Burns LH. Naloxone's pentapeptide binding site on filamin A blocks Mu opioid receptor-Gs coupling and CREB activation of acute morphine. PLoS ONE. 2009;4:e4282.

17. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med. 2009;10:663–72.

18. Younger J, Noor N, McCue R, MacKey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum. 2013;65:529–38.

19. Paula TMHD, Castro MS, Medeiros LF, et al. Association of low-dose naltrexone and transcranial direct current stimulation in fibromyalgia: a randomized, double-blinded, parallel clinical trial. Braz J Anesthesiol. 2023;73:409–17.

20. Bested K, Jensen LM, Andresen T, et al. Low-dose naltrexone for treatment of pain in patients with fibromyalgia: a randomized, double-blind, placebo-controlled, crossover study. Pain Rep. 2023;8:e1080.

21. Due Bruun K, Christensen R, Amris K, et al. Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trial. Lancet Rheumatol. 2024;6:e31–9.

22. Srinivasan A, Dutta P, Bansal D, Chakrabarti A, Bhansali AK, Hota D. Efficacy and safety of low-dose naltrexone in painful diabetic neuropathy: a randomized, double-blind, active-control, crossover clinical trial. J Diabetes. 2021;13:770–8.

23. Beaudette-Zlatanova B, Lew RA, Otis JD, et al. Pilot study of low-dose naltrexone for the treatment of chronic pain due to arthritis: a randomized, double-blind, placebo-controlled, crossover clinical trial. Clin Ther. 2023;45:468–77.

24. Bendiks S, Cheng DM, Blokhina E, et al. Pilot study of tolerability and safety of opioid receptor antagonists as novel therapies for chronic pain among persons living with HIV with past year heavy drinking: a randomized controlled trial. AIDS Care. 2023;35:1191–200.

25. Tsui JI, Rossi SL, Cheng DM, et al. Pilot RCT comparing low-dose naltrexone, gabapentin and placebo to reduce pain among people with HIV with alcohol problems. PLoS ONE. 2024;19:e0297948.

26. Martin SJ, McAnally HB, Okediji P, Rogosnitzky M. Low-dose naltrexone, an opioid-receptor antagonist, is a broad-spectrum analgesic: a retrospective cohort study. Pain Manag. 2022;12:699–709.

27. Roehmer C, Deshpande K, Khan S, Navlani R, Chu A. Low-dose naltrexone for treatment of refractory chronic pain. J Pain Manag. 2022;15:119–23.

28. Dieckmann G, Ozmen MC, Cox SM, Engert RC, Hamrah P. Low-dose naltrexone is effective and well-tolerated for modulating symptoms in patients with neuropathic corneal pain. Ocul Surf. 2021;20:33–8.

29. Jackson D, Singh S, Zhang-James Y, Faraone S, Johnson B. The effects of low dose naltrexone on opioid induced hyperalgesia and fibromyalgia. Front Psychiatry. 2021;12:593842.

30. McKenzie-Brown AM, Singh V, Boorman DW, Ibanez KR, Agwu E. Low-dose naltrexone (LDN) for chronic pain at a single institution: a case series. J Pain Res. 2023;16:1993–8.

31. Pogue J, Johnson D, Burch A. A utilization review of patients that respond to low-dose naltrexone (LDN) for chronic pain at a single institution. J Pain Palliat Care Pharmacother. 2024;38:406–13.

32. Spargo A, Gonser L, Faley B. Evaluation of low-dose naltrexone for chronic pain management. J Pain Palliat Care Pharmacother. 2025;39:319–22.

33. Aalto H, Paul S, McEwen V. Real-world effectiveness and tolerability of low dose naltrexone to treat chronic pain: a retrospective cohort study of one pain physician's practice. J Pain Res. 2025;18:6637–49.

34. Driver CN, D'Souza RS. Efficacy of low-dose naltrexone and predictors of treatment success or discontinuation in fibromyalgia and other chronic pain conditions: a fourteen-year, enterprise-wide retrospective analysis. Biomedicines. 2023;11:1087.

35. Irwin MN, Cooke DA, Berland D, Marshall VD, Smith MA. Efficacy and safety of low dose naltrexone for chronic pain. J Pain Palliat Care Pharmacother. 2024;38:13–9.

36. Ramanathan S, Panksepp J, Johnson B. Is fibromyalgia an endocrine/endorphin deficit disorder? Is low dose naltrexone a new treatment option? Psychosomatics. 2012;53:591–4.

37. Chopra P, Cooper MS. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). J Neuroimmune Pharmacol. 2013;8:470–6.

38. Hota D, Srinivasan A, Dutta P, Bhansali A, Chakrabarti A. Off-label, low-dose naltrexone for refractory painful diabetic neuropathy. Pain Med. 2016;17:790–1.

39. Carolfi K, Nickasch BL. What do primary care providers and nurses need to know about managing chronic pain? Pain Manag Nurs. 2021;22:455–8.

40. de Carvalho JF. Low-dose naltrexone as first option for fibromyalgia patients: a case series. Isr Med Assoc J. 2024;26:441–2.

41. Moser U. Low-dose naltrexone for severe fibromyalgia syndrome: a report of a case with two-year follow-up. Cureus. 2025;17:e83824.

42. Metyas S, Chen CL, Yeter K, Solyman J, Arkfeld DG. Low dose naltrexone in the treatment of fibromyalgia. Curr Rheumatol Rev. 2018;14:177–80.

43. Neuman DL, Chadwick AL. Utilization of low-dose naltrexone for burning mouth syndrome: a case report. A A Pract. 2021;15:e01475.

44. Sangalli L, Miller CS. Low-dose naltrexone for treatment of burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol. 2023;135:e83–8.

45. Sullender RT, Silverstein RG, Goodwin DM, McClurg AB, Carey ET. Low-dose naltrexone as a treatment for vulvodynia: a case series. Case Rep Womens Health. 2025;45:e00677.

46. Ruhoy I, Koran LM. Low-dose naltrexone and pain relief in gadolinium deposition disease: a case series. Interv Pain Manag Rep. 2022;6:99–102.

47. Soin A. Management of pediatric complex regional pain syndrome with low-dose naltrexone. Pain Med Case Rep. 2021;5:109–13.

48. Ghai B, Bansal D, Hota D, Shah CS. Off-label, low-dose naltrexone for refractory chronic low back pain. Pain Med. 2014;15:883–4.

49. Codino H, Hardin A. Low dose naltrexone in conjunction with the Wahls protocol to reduce the frequency of chronic migraines in a patient with multiple sclerosis: a case study. Integr Med. 2021;20:30–4.

50. Lee MT, Eckmann MS. Retrospective analysis of naltrexone for persistent neuropathic pain case series. Pain Med Case Rep. 2023;7:377–83.

51. Ananthan S, Heir G, Korczeniewska O. Use of low-dose naltrexone in the management of posttraumatic trigeminal neuropathic pain: a retrospective case series. Quintessence Int. 2025;56:682–90.

52. Bruun-Plesner K, Blichfeldt-Eckhardt MR, Vaegter HB, Lauridsen JT, Amris K, Toft P. Low-dose naltrexone for the treatment of fibromyalgia: investigation of dose-response relationships. Pain Med. 2020;21:2253–61.

53. Cree BAC, Kornyeyeva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. Ann Neurol. 2010;68:145–50.

54. Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, Majdinasab N, Shalbafan B. The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. Mult Scler. 2010;16:964–9.

55. Gironi M, Martinelli-Boneschi F, Sacerdote P, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. Mult Scler. 2008;14:1076–83.

56. Ludwig MD, Turel AP, Zagon IS, McLaughlin PJ. Long-term treatment with low dose naltrexone maintains stable health in patients with multiple sclerosis. Mult Scler J Exp Transl Clin. 2016;2:1–11.

57. Zashin S. Sjogren's syndrome: clinical benefits of low-dose naltrexone therapy. Cureus. 2019;11:e4225.

58. Zashin S. Sjogren's syndrome and clinical benefits of low-dose naltrexone therapy: additional case reports. Cureus. 2020;12:e8948.

59. Smith JP, Field D, Bingaman SI, Evans R, Mauger DT. Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study. J Clin Gastroenterol. 2013;47:339–45.

60. Shannon A, Alkhouri N, Mayacy S, Kaplan B, Mahajan L. Low-dose naltrexone for treatment of duodenal Crohn's disease in a pediatric patient. Inflamm Bowel Dis. 2010;16:1457.

61. Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol. 2007;102:820–8.

62. Lie MRKL, van der Giessen J, Fuhler GM, et al. Low dose naltrexone for induction of remission in inflammatory bowel disease patients. J Transl Med. 2018;16:55.

63. Ploesser J, Weinstock LB, Thomas E. Low dose naltrexone: side effects and efficacy in gastrointestinal disorders. Int J Pharm Compd. 2010;14:171–3.

64. Brewer KL, Mainhart A, Meggs WJ. Double-blinded placebo-controlled cross-over pilot trial of naltrexone to treat Gulf War Illness. Fatigue. 2018;6:132–40.

65. Abokrysha N, Kishk N, Nawito A, Mounir N. Effect of low-dose naltrexone on Egyptian children with intractable epilepsy: a case series study. Neurol India. 2021;69:1781–4.

66. O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G, Lambert JS. Safety and efficacy of low dose naltrexone in a long COVID cohort; an interventional pre-post study. Brain Behav Immun Health. 2022;24:100485.

67. Tamariz L, Bast E, Klimas N, Palacio A. Low-dose naltrexone improves post-COVID-19 condition symptoms. Clin Ther. 2024;46:e101–6.

68. Bonilla H, Tian L, Marconi VC, et al. Low-dose naltrexone use for the management of post-acute sequelae of COVID-19. Int Immunopharmacol. 2023;124:110966.

69. Hurt RT, Yadav S, Schroeder DR, et al. Longitudinal progression of patients with long COVID treated in a post-COVID clinic: a cross-sectional survey. J Prim Care Community Health. 2024;15:1–11.

70. Isman A, Nyquist A, Strecker B, et al. Low-dose naltrexone and NAD+ for the treatment of patients with persistent fatigue symptoms after COVID-19. Brain Behav Immun Health. 2024;36:100733.

71. Polo O, Pesonen P, Tuominen E. Low-dose naltrexone in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Fatigue Biomed Health Behav. 2019;7:207–17.

72. Bolton MJ, Chapman BP, Van Marwijk H. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Rep. 2020;13:e232502.

73. Lajevardi V, Salarvand F, Ghiasi M, Nasimi M, Taraz M. The efficacy and safety of oral low dose naltrexone versus placebo in the patients with lichen planopilaris: a randomized controlled clinical trial. J Dermatol Treat. 2022;33:769–73.

74. Hamel RK, Chen L, O'Connell C, Mann C. Oral low-dose naltrexone in the treatment of frontal fibrosing alopecia and lichen planopilaris: an uncontrolled open-label prospective study. Cureus. 2023;15:e34169.

75. Yossef SM, English JC. Attenuation of disease process following treatment with low-dose naltrexone in patients with frontal fibrosing alopecia and lichen planopilaris: a retrospective study. J Am Acad Dermatol. 2024;91:141–2.

76. Strazzulla LC, Avila L, Sicco KL, Shapiro J. Novel treatment using low-dose naltrexone for lichen planopilaris. J Drugs Dermatol. 2017;16:1140–2.

77. Klein EJ, Karim M, Kim R, Sicco KL, Shapiro J. Reversible hair loss in lichen planopilaris: regrowth with low-dose naltrexone and platelet-rich plasma. J Drugs Dermatol. 2022;21:671.

78. Albers LN, Arbiser JL, Feldman RJ. Treatment of Hailey-Hailey disease with low-dose naltrexone. JAMA Dermatol. 2017;153:1018–20.

79. Campbell V, McGrath C, Corry A. Low-dose naltrexone: a novel treatment for Hailey–Hailey disease. Br J Dermatol. 2018;178:1196–8.

80. Garayar Cantero M, Canseco Martín M, Aguado García Á, Ruiz-Sánchez D, Valtueña J, Manchado López P. Use of low-dose naltrexone in the treatment of severe Hailey–Hailey disease: one case report. Dermatol Ther. 2019;32:e12892.

81. Ibrahim O, Hogan SR, Vij A, Fernandez AP. Low-dose naltrexone treatment of familial benign pemphigus (Hailey–Hailey disease). JAMA Dermatol. 2017;153:1015–7.

82. Andrea C, Breton AL, Kanitakis J. Dermpath & clinic: Hailey Hailey disease treated with low-dose naltrexone. Eur J Dermatol. 2021;31:675–6.

83. Kollman N, Bass J. Generalized familial benign chronic pemphigus (Hailey–Hailey disease) treated successfully with low-dose naltrexone. JAAD Case Rep. 2018;4:725–7.

84. Michael M, Benjamin MW, Shannon CT. Recalcitrant Hailey-Hailey disease successfully treated with low-dose naltrexone. J Clin Aesthet Dermatol. 2020;13:19–21.

85. Sousa Gomes M, Araújo Pereira J, Trocado V, Prata JP, Teixeira V, Pinheiro P. Vulvar Hailey–Hailey disease treated with low-dose naltrexone: case report and literature review. Arch Gynecol Obstet. 2020;302:1081–6.

86. Lim D, Belisle A, Davar S. Improvement in Hailey–Hailey disease with a combination of low-dose naltrexone and oral magnesium chloride: a case report. SAGE Open Med Case Rep. 2020;8:1–3.

87. Riquelme-Mc Loughlin C, Riera-Monroig J, Morgado-Carrasco D, et al. Low-dose naltrexone therapy in benign chronic pemphigus (Hailey–Hailey disease): a case series. J Am Acad Dermatol. 2019;81:644–6.

88. Khan S, Ghafoor R, Kaleem S. Efficacy of low dose naltrexone in psoriasis. J Coll Physicians Surg Pak. 2020;30:579–83.

89. Weinstock LB, Cottel J, Aldridge L, Egeberg A. Low-dose naltrexone therapy for psoriasis. Int J Pharm Compd. 2020;24:94–6.

90. Bridgman AC, Kirchhof MG. Treatment of psoriasis vulgaris using low-dose naltrexone. JAAD Case Rep. 2018;4:827–9.

91. Muller G, Grieshaber R, Talley JF, Riepl M, Fellows D. Compounded low-dose naltrexone for the treatment of guttate psoriasis: a case report. Int J Pharm Compd. 2018;22:270–8.

92. Beltran Monasterio EP. Low-dose naltrexone: an alternative treatment for erythrodermic psoriasis. Cureus. 2019;11:e3943.

93. Boehmer D, Eyerich K, Darsow U, Biedermann T, Zink A. Variable response to low-dose naltrexone in patients with Darier disease: a case series. J Eur Acad Dermatol Venereol. 2019;33:950–3.

94. Smith-Pellegrin DL, Rivera-Vega MR, Cazarín-Barrientos JR, Melgarejo-Gómez A, Messina-Baas OM, Cuevas-Covarrubias S. Naltrexone, a therapeutic alternative in Darier disease. Rev Med Hosp Gen Mex. 2021;84:177–80.

95. Costa T, Rebelo C, Marques Pinto G, Duarte B. Combination of naltrexone and isotretinoin for the treatment of Darier disease. Cureus. 2023;15:e33321.

96. Bray ER, Morrison BW. Low-dose naltrexone use in biopsy-proven lichen planus of the nails. JAMA Dermatol. 2024;160:1334–7.

97. Frech T, Novak K, Revelo MP, et al. Low-dose naltrexone for pruritus in systemic sclerosis. Int J Rheumatol. 2011;2011:804296.

98. Manudhane AP, Schrom KP, Ezaldein HH, Armile JA. Low-dose naltrexone: a unique treatment for amyopathic dermatomyositis. Dermatol Online J. 2019;25:13030/qt89b75552.

99. Tran T, Chen A, Worswick S. Successful treatment of dermatomyositis with low-dose naltrexone. Dermatol Ther. 2018;31:e12720.

100. Timoney L, Bunker CB. Prurigo excoriée treated with low dose naltrexone. BMJ Case Rep. 2021;14:e243773.

101. LaMonica LC, Lang-Houser M, Bresler SC, Mervak JE. Low-dose naltrexone as treatment for epidermolysis bullosa pruriginosa-associated refractory pruritus. JAAD Case Rep. 2023;38:82–5.

102. Varghese K, Yan X, Cao F. Low-dose naltrexone for excoriation disorder. Cureus. 2024;16:e55336.

103. Mischoulon D, Hylek L, Yeung AS, et al. Randomized, proof-of-concept trial of low dose naltrexone for patients with breakthrough symptoms of major depressive disorder on antidepressants. J Affect Disord. 2017;208:6–14.

104. McLaughlin PJ, Odom LB, Arnett PA, Orehek S, Thomas GA, Zagon IS. Low-dose naltrexone

reduced anxiety in persons with multiple sclerosis during the COVID-19 pandemic. Int Immunopharmacol. 2022;113:109438.

105. Siembida J, Johnson B. Depression in fibromyalgia patients may require low-dose naltrexone to respond: a case report. Cureus. 2022;14:e22677.

106. Peters KB, Affronti ML, Woodring S, et al. Effects of low-dose naltrexone on quality of life in high-grade glioma patients: a placebo-controlled, double-blind randomized trial. Support Care Cancer. 2022;30:3463–71.

107. Schwartz L, Buhler L, Icard P, Lincet H, Steyaert JM. Metabolic treatment of cancer: intermediate results of a prospective case series. Anticancer Res. 2014;34:973–80.

108. Berkson BM, Rubin DM, Berkson AJ. The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic/low-dose naltrexone protocol. Integr Cancer Ther. 2006;5:83–9.

109. Berkson BM, Rubin DM, Berkson AJ. Reversal of signs and symptoms of a B-cell lymphoma in a patient using only low-dose naltrexone. Integr Cancer Ther. 2007;6:293–6.

110. Berkson BM, Rubin DM, Berkson AJ. Revisiting the ALA/N (alpha-lipoic acid/low-dose naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases. Integr Cancer Ther. 2009;8:416–22.

111. Miskoff JA, Chaudhri M. Low dose naltrexone and lung cancer: a case report and discussion. Cureus. 2018;10:e2924.

112. Rogosnitzky M, Finegold MJ, McLaughlin PJ, Zagon IS. Opioid growth factor (OGF) for hepatoblastoma: a novel non-toxic treatment. Investig New Drugs. 2013;31:1066–70.

113. Stallkamp Tidd SJ, Cantrell C, Greene BD, Wilson R. Low-dose naltrexone use in postural orthostatic tachycardia syndrome: a case series. Cureus. 2023;15:e43426.

114. Weinstock LB, Brook JB, Myers TL, Goodman B. Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment. BMJ Case Rep. 2018;2018:bcr2017221405.

115. Rungkitwattanakul D, Brooks M, Adesina S, et al. Extemporaneous preparation and effectiveness of low-dose naltrexone for the treatment of uremic pruritus: a literature review and case report. Pharmacy (Basel). 2025;13:160.

116. Weinstock LB, Myers TL, Shetty A. Low-dose naltrexone for the treatment of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2017;34:184–7.

117. Zappaterra M, Shouse E, Levine RL. Low-dose naltrexone reduces symptoms in stiff-person syndrome. Med Hypotheses. 2020;137:109546.

118. Britton A, Harinath G, Morgan S, Zalzala S. Unexpected increase in bone mineral density with rapamycin and low-dose naltrexone: a case report of a 52-year-old woman with osteopenia. Cureus. 2025;17:e77435.

119. Skulstad Johanson GA, Tysnes OB, Bjerknes TL. Use of off-label drugs and nutrition supplements among patients with amyotrophic lateral sclerosis in Norway. Neurol Res Int. 2022;2022:1789946.

120. Raffeq ZN, Hammo AHZSY. The effect of low-dose naltrexone on immunological infertility in women with recurrent implantation failure. Reprod Health Woman. 2025;85:152–9.

121. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. Lancet. 2025;405:1633–40.

122. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. BMC Res Notes. 2014;7:264.

123. McDonald S, Nikles J. N-of-1 trials in healthcare. Healthcare (Basel). 2021;9:330.

124. Scuffham PA, Nikles J, Mitchell GK, et al. Using N-of-1 trials to improve patient management and save costs. J Gen Intern Med. 2010;25:906–13.