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Systematic Review

Does Low-Dose Oral Naltrexone Alleviate Symptoms of Long COVID? A Systematic Review and Meta-Analysis

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Abstract

Long COVID, a condition marked by persistent symptoms following COVID-19 infection, poses significant challenges in regard to clinical management. While emerging pharmacological treatments have demonstrated limited benefits in isolated studies, clinical experience and the literature suggest that low-dose naltrexone (LDN) may be a promising therapeutic option. Therefore, in this systematic review, we aim to synthesise findings from the available literature and evaluate the overall safety and efficacy of LDN as a potential treatment for long COVID. A literature search was conducted using a combination of key terms—'COVID', 'COVID-19', 'SARS-COV-2', and 'Naltrexone'— and the following databases: MEDLINE, Web of Science (Clavirate), Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Cumulative Index in Nursing and Allied Health Literature (CINAHL). The methodology is available on the PROSPERO database (CRD42025630362). Screening identified five eligible articles. Four studies were included, but only two provided comparable data suitable for meta-analysis. Meta-analysis demonstrated statistically significant improvements in fatigue, brain fog, and headaches. Preliminary evidence suggests LDN has potential benefits in the treatment of long COVID, particularly with respect to fatigue, brain fog, and headaches, but more robust studies, such as randomised controlled trials, are urgently needed to confirm LDN's safety and efficacy.

Keywords: COVID-19; long COVID; naltrexone

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1. Introduction

The World Health Organisation (WHO) defines long COVID as a condition characterised by the persistence or development of symptoms 3 months after an initial COVID-19 infection, though varying definitions exist [1,2]. Common symptoms include fatigue and cognitive dysfunction; however, the symptoms can be highly variable, with over 200 manifestations reported [1]. It has been estimated that 10–20% of people previously affected by acute COVID-19 infection will develop prolonged symptoms suggestive of long COVID [1]. The impact of long COVID is considerable, not only affecting individuals but also placing strain on the economy and broader healthcare systems globally [3,4]. An international study involving 11,860 participants across 17 countries conducted by Pazukhina et al. [3] highlighted a high prevalence of prolonged cardiorespiratory, gastrointestinal, and neurocognitive disturbances, all of which significantly impair quality of life. A modelling study conducted by Costantino et al. [4] estimated that long COVID resulted in an approximate loss of AUD 9.6 billion in Australia in 2022, along with a projected loss of

102.4 million working hours. Moreover, increased demands for medical treatment have further stressed healthcare capacity, resulting in inefficiencies and negative impacts on broader healthcare accessibility [4]. Supporting this is an Israelian cohort study involving 642,686 participants conducted by Sagy et al. [5], who demonstrated that prolonged recovery from COVID-19 incurred significantly greater costs due to an increased need for medical attention—likely resulting in reallocation of healthcare resources and negatively affecting healthcare accessibility.

The pathogenesis of long COVID is yet to be elucidated; however, several mechanisms have been hypothesized [6]. These include immune dysregulation, cellular mitochondrial dysfunction, microbiota dysbiosis, endothelial dysfunction, viral persistence, and abnormalities in neuronal signalling leading to chronic inflammation and cell damage [6]. A considerable amount of effort has been focused on reducing the incidence and severity of initial acute COVID-19 infections, with the belief that this may minimise or reduce the severity of long COVID [7,8]. Consequently, pharmacotherapeutic options for long COVID are limited and aimed at symptom control [7,8]. Many pharmacotherapy-based long-COVID studies are limited to small-scale observational analyses [8]. While various drugs have been trialled, they have demonstrated limited efficacy and are associated with adverse effects, making them only suitable for select patients [8]. The lack of clarity regarding the pathogenic mechanisms driving the diverse manifestations of long COVID has likely hindered the development and testing of effective therapeutics for both acute and long COVID [9].

Low-dose naltrexone (LDN), defined in this review as daily oral doses of 0.5–6 mg/day, has been proposed as a potential therapeutic agent for treating long COVID [10,11]. Doses of 1–5 mg/day have been shown to exert effects beyond opioid receptor antagonism [12–14]. In vitro studies demonstrated that the compound antagonised Toll-like receptor 4 (TLR4) on macrophages, reducing the production of pro-inflammatory and nociception-inducing cytokines, resulting in anti-inflammatory and analgesic effects [12–14]. Unlike standard-dose naltrexone (i.e., 50 mg/day), which induces a sustained opioid receptor blockade, naltrexone at low doses results in a transient and partial receptor blockade, which is postulated to upregulate endogenous opioid pathways associated with neuropsychological benefits [15].

In addition, Sasso et al. identified a shared pharmacological target of LDN in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID [16,17]. These findings suggest that dysfunction of transient receptor potential melastatin 3 (TRPM3) channels in natural killer cells reduces GABA production, leading to unopposed neuroexcitation, contributing to hypervigilance, increased stress, and skeletal muscle pathophysiology [16,18].

These effects are thought to contribute to the utility of LDN in alleviating long-COVID symptoms, as evidenced by a small number of clinical studies [10,11,19].

The objective of this systematic review is to evaluate the effectiveness of LDN in the treatment of long COVID. Specifically, the review aims to assess the impact of LDN on the incidence and severity of common long-term COVID manifestations, including fatigue, headache, sleep disturbances, cognitive impairment (brain fog), and dizziness/lightheadedness, while also assessing its safety profile.

2. Materials and Methods

2.1. Search Strategy and Study Selection

A search of MEDLINE, Web of Science (Clavirate), Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Cumulative Index in Nursing and Allied Health Literature (CINAHL) was conducted independently by two reviewers, A.D. and

A.D.K.N. A.D. performed literature searches from November to December 2024, while A.D.K.N. conducted searches from December 2024 to January 2025. A combination of the following key terms was used in the searches: 'COVID', 'COVID-19', 'SARS-COV-2', and 'Naltrexone'. The database search strategy is provided in Supplementary Table S1, and it is also available on the PROSPERO database (CRD42025630362).

The literature search identified 629 articles. Both reviewers independently and manually screened the articles using selection criteria (Table 1). Differences in outcomes were resolved through discussion. After screening, four articles were retrieved—they are provided in Table 2. Upon full-text review, two articles were included for meta-analysis. Two articles were excluded from the meta-analysis due to limited methodology and unclear descriptions of LDN use in participants. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) guidelines upon registration on the PROSPERO database. A summary of the search strategy is shown in the PRISMA flow diagram below (Figure 1).

Table 1. Selection criteria.

Inclusion Criteria	Exclusion Criteria
Patients 18 years of age or above with documented (clinical or biochemical) evidence of COVID-19 infection Persistent symptoms attributed to previous COVID-19 infection for 28 days or more Use of oral LDN	Patients under 18 years of age Patients currently infected with COVID-19

LDN, low-dose naltrexone (defined as 0.5–6 mg once daily).

Table 2. Summary of studies evaluating the effect of low-dose naltrexone on long-COVID symptoms.

Authors	Design and Sample Size	Oral LDN Dose and Follow-Up Periods	Outcomes
O'Kelly et al., 2022 [10] *	Prospective interventional pre–post cohort study, $n = 36$	1–3 mg/day, 2–3 months	Significant improvement in perception of recovery, limitations in activities of daily living, energy levels, intensity, pain/discomfort, concentration difficulties, and sleep disturbances. Statistically significant incidence reduction in chest pain/tightness, arthralgia, coughing, low mood, and personality changes ($p < 0.05$). Subjects ($n = 2$) dropped out due to gastrointestinal upset and fatigue.
Bonilla et al., 2023 [11] *	Retrospective cohort study, $n = 59$	0.5–6 mg/day, 31–540 days	Significant reduction in the intensity of fatigue, sleep disturbances, and post-exertional malaise ($p < 0.05$). No statistical differences in symptom incidence and intensity between subjects with long COVID symptoms < 365 days versus ≥ 365 days.
Tamariz et al., 2024 [19]	Retrospective cohort study, $n = 24$	1.5–4.5 mg/day, unknown	Statistically significant improvement in dyspnoea, brain fog, pain, fatigue provided as hazard ratios ($p < 0.05$).
Isman et al., 2024 [20]	Interventional single-arm study, $n = 31$	1.125 mg/day (days 0–4), 2.25 mg/day (days 5–8), 4.5 mg/day (day 9 onwards)	Statistically significant improvement in responses to total short-form 36 questionnaire and Chalder Fatigue Scale.

* Articles included in meta-analysis.

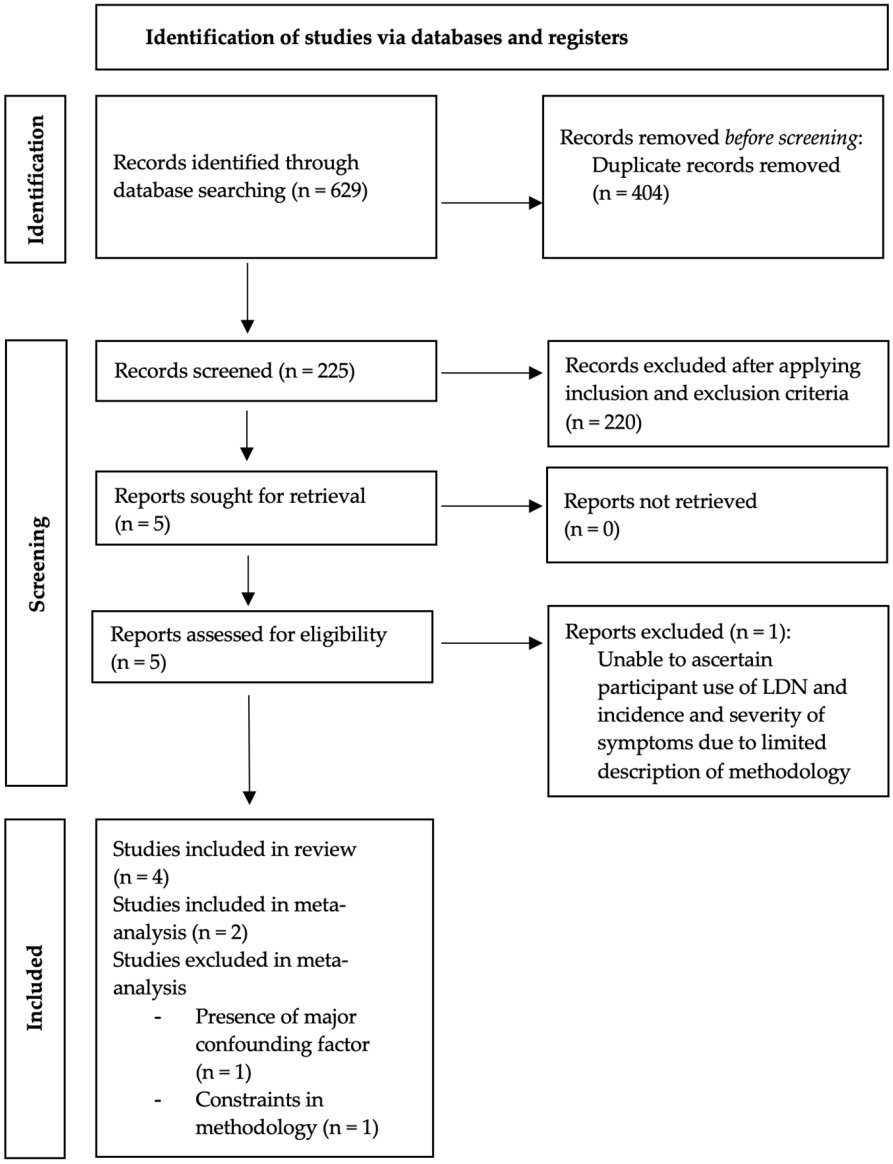


Figure 1. PRISMA flow diagram of included and excluded studies. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

2.2. Risk-of-Bias Assessment

We employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the quality of evidence [21]. This approach evaluates five domains—risk of bias, imprecision, inconsistency, indirectness, and publication bias [21]. Each domain was independently evaluated by the authors, and the quality of evidence of each article was then classified as very low, low, moderate, or high [21]. The GRADE approach helped the authors select articles during the screening process, and an agreement was reached before analysis of results.

2.3. Data Synthesis and Analysis

We calculated the relative risk and 95% confidence intervals of individual and combined studies using Minitab Statistical Software v22.2.0. We performed a small meta-analysis of selected studies to summarise the effects of LDN on long-COVID symptoms—fatigue, headache, sleep disturbances, cognitive impairment (brain fog), and dizziness/light-headedness. Participants with reduced severity of symptoms (as evidenced by the Likert scale on questionnaires) or absence of symptoms after using LDN were con-

sidered positive responders to LDN. Participants with symptoms or no change in severity (assessed via the Likert scale) after the use of LDN were considered non-responders to LDN. Heterogeneity analysis was completed using MetaAnalysisOnline (metaanalysisonline.com (accessed on 25 November 2025)). Articles with ambiguous data were excluded from the meta-analysis. The incidence of adverse effects was also obtained from individual studies.

3. Results

After screening, we found that four articles met the review criteria—one interventional single-arm study, one prospective cohort study, and two retrospective cohort studies. After applying the GRADE approach, we excluded two articles from the meta-analysis, as they were unsuitable for comparison. The study by Tamariz et al. [19] provided hazard ratios for the combined effects of LDN on four symptoms (dyspnoea, brain fog, pain, and fatigue), and hence we were unable to analyse the effects of LDN on individual symptoms. The study by Isman et al. [20] involved concurrent use of transdermal nicotinamide adenine dinucleotide (NAD+) patches alongside LDN, introducing a significant confounding factor that precluded analysis of the effects of LDN monotherapy on long-COVID symptoms. The authors' analysis of the selected articles subjected to the GRADE approach is provided in Supplementary Table S2.

3.1. Meta-Analysis

A meta-analysis of the severity and incidence of symptoms—fatigue, headache, sleep disturbances, cognitive impairment (brain fog), and dizziness/light-headedness—after LDN use was completed. The articles selected for meta-analysis are indicated in Table 2. A statistically significant improvement in sleep disturbances was demonstrated by O'Kelly et al. [10], whereas Bonilla et al. [11] found statistically significant improvements in fatigue, brain fog, headache, and sleep disturbances. Analysis of both studies combined showed promising effects of LDN on fatigue, brain fog, headache, and sleep disturbances—reflective of the initial findings reported by Bonilla et al. [11]. A summary of the data is shown in Figure 2.

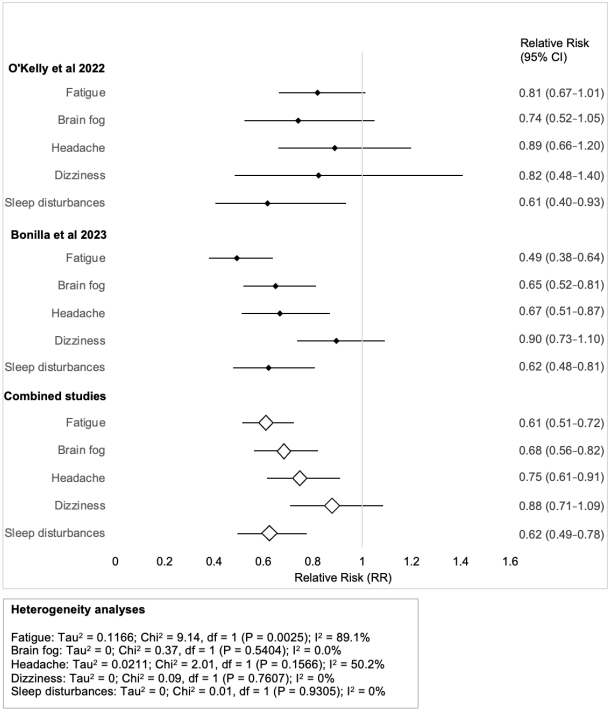


Figure 2. Frequency or reduction in severity of long-COVID symptoms in subjects treated with low-dose naltrexone. Black diamonds refer to the relative risk of individual studies and white diamonds refer to the relative risk of combined studies [10,11].

3.2. Adverse Effects

In an interventional cohort study conducted by O'Kelly et al. [10] involving 38 participants, 2 individuals withdrew due to adverse effects, namely, diarrhoea, fatigue, and difficulty sleeping [10]. A retrospective cohort study of 59 participants conducted by Bonilla et al. [11] demonstrated the following adverse effects after the use of LDN—headache in 6 participants, fatigue in 1 participant, brain fog in 3 participants, sleep disturbances in 8 participants, and light-headedness in 5 participants. The cumulative frequency of reported adverse effects documented by O'Kelly et al. [10] and Bonilla et al. [11] is provided in Table 3. Adverse effects were also documented by Isman et al. [20]; however, due to concurrent use of NAD^+ patches, these findings should be interpreted with caution. We do, however, acknowledge the presence of commonly reported adverse effects of LDN in this study, including insomnia, gastrointestinal disturbances, and headache. Adverse effects were not reported by Tamariz et al. [19].

Table 3. Cumulative frequency of adverse effects.

Adverse Effects	Frequency
Headache	10%
Sleep disturbances	9%
Light-headedness	8.5%
Gastrointestinal disturbances	5%
Brain fog	5%
Fatigue	2.5%

4. Discussion

Implications of Systematic Review

The findings of this review suggest that LDN may help alleviate fatigue, brain fog, headache, and sleep disturbances associated with long COVID. These results highlight the potential therapeutic effects of LDN on conditions with overlapping symptomatology, notably myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM) [12].

Aitcheson et al.'s [12] systematic review of 21 studies examining the effects of LDN on fibromyalgia symptoms supported LDN's efficacy with reported benefits regarding fatigue, sleep disturbances, and cognitive function. Furthermore, a single-blinded randomised controlled trial of 25 participants conducted by Brunn-Plesner et al. [22] identified the ED_{50} and ED_{95} (effective doses for 50% and 95% of participants, respectively) of LDN for FM symptoms as 3.88 mg/day and 5.40 mg/day, respectively. These findings are consistent with the studies evaluated by Aitcheson et al. [12], wherein most clinical trials utilised doses of 4.5 mg/day. LDN was also reported to be well-tolerated, with a low incidence of adverse effects and mild adverse profile severity, including abdominal pain, diarrhoea, nausea, and constipation [12].

A retrospective analysis of the medical records of 218 ME/CFS patients who received LDN (3–4.5 mg/day) over a mean follow-up period of 1.7 years conducted by Polo et al. [23] showed improvement in alertness (51.4%), physical function (23.9%), and cognitive function (21.1%). The incidence of adverse effects was higher than expected, with 15.3% of participants reporting insomnia and nausea, 6.9% reporting dizziness, 6.4% reporting gastrointestinal symptoms, 5.4% reporting headaches, and 5% reporting sleepiness [23]. However, these adverse effects were reported during the initial phase of treatment, while long-term adverse effects were essentially absent [23].

LDN appears to be a promising treatment for long COVID, offering improvements to fatigue, brain fog, headache, and sleep disturbances and a favourable side-effect profile.

While the effect sizes in this review were modest, clinically appreciable outcomes were still anticipated. Positive outcomes have also been reported in other studies evaluating syndromes with overlapping symptoms, such as ME/CFS and FM, where pathophysiological mechanisms remain unclear [12,22,23]. Furthermore, a prospective cohort study of 46 participants conducted by McLaughlin et al. [24] demonstrated that LDN may exert anxiolytic and antidepressant effects in patients with multiple sclerosis, indicating potential neuropsychiatric effects of LDN in addition to its physical benefits. Given the positive findings regarding the use of LDN in the treatment of long COVID, these results may be applicable to conditions of overlapping symptomatology and diagnostic criteria, such as ME/CFS and FM—in alignment with the statement made by Aitcheson et al. [12].

5. Limitations

5.1. Systematic Review Design

The inclusion criteria for long COVID constitute a key limitation of this review. We decided not to adopt the WHO's definition of long COVID—a chronic condition characterized by the continuation or development of new symptoms 3 months after an initial COVID-19 infection [1]. Rather, we have defined it as persistent symptoms attributed to a previous COVID-19 infection that last 28 days or more, as few studies are in accordance with the WHO's definition. As a result, the findings of this review may not be strictly applicable to participants with the WHO's definition of long COVID.

We amalgamated the incidence of symptoms among participants, as reported by O'Kelly et al. [10], and the severity of symptom reduction, as reported by Bonilla et al. [11], to define a positive response to LDN for the meta-analysis. Hence, we cannot qualitatively evaluate the magnitude of LDN's effects on participants. One suggested approach to addressing this limitation is to employ randomised controlled trials (RCTs) with Likert scales to assess improvement and/or complete alleviation of symptoms.

Finally, we chose to exclude the study by Hurt et al. [25] due to limitations in methodology. Although a large number of participants were recruited in this study (n = 568), the authors could not correlate the use of LDN with symptom improvement, and participants who used LDN were simply asked to rate their experience. The exclusion of Hurt et al.'s study [25] resulted in a smaller overall sample size of the cohort used for meta-analysis.

5.2. Small Sample Size and Lack of Control Groups

Although we included most of the available literature, this study is limited by the small sample size for the analysed studies, which reduces the statistical power and generalisability of the findings. In addition, the lack of control groups in all studies meant evidence of symptom improvement with LDN use cannot be solely attributed to the drug and could instead be secondary to the placebo effect or natural recovery from the disease. Furthermore, confounding factors such as concurrent use of other medications (including opioids), the presence of co-morbidities (such as gastrointestinal conditions affecting absorption of LDN), and engagement in other therapies (such as physical therapy) were not controlled for. Consequently, it is challenging to isolate the specific effects of LDN on alleviating long-COVID symptoms.

5.3. Dose–Response Relationship and Onset of Symptom Improvement

In the study by O'Kelly et al. [10], participants were started on 1 mg/day of LDN. Doses were titrated monthly to a maximum of 3 mg/day. We propose that the narrow dosing range in this study was inadequate for completely capturing the therapeutic effects of LDN, as the literature has suggested doses of 1–5 mg/day to be beneficial [12–14]. In contrast, the study by Bonilla et al. [11] explored doses of up to 6 mg/day; however,

the expected linear dose–response relationship could not be obtained, with some participants experiencing less symptom improvement on higher doses compared to those on lower doses.

Another significant limitation was the lack of thorough exploration relating to symptom improvement following LDN administration [10,11,19,20]. The methodologies used in the reviewed studies lacked frequent participant assessments conducted to track the severity of symptoms after commencement of LDN. The short follow-up period of approximately 2 months employed by O'Kelly et al. [10] was inadequate for determining the onset of symptom improvement. Given that the half-lives of oral naltrexone and its metabolite, 6β-naltrexone, are approximately 4 and 132 h, respectively, steady-state concentrations are typically achieved within 2–3 days, reflecting the time required for LDN to accumulate in the body [26]. Moreover, Younger et al. [13] found that a minimum of two months is needed to obtain an estimate of efficacy, suggesting that the follow-up period in the study by O'Kelly et al. [10] was insufficient. While the follow-up period in the study by Bonilla et al. [11] was greater (>365 days for some participants), infrequent assessments hindered the approximation of symptom improvement.

Evaluation of studies using the Bradford–Hill criteria highlights limitations in establishing a dose–response relationship [27]. While some criteria were met, including plausibility, wherein proposed mechanisms align with potential therapeutic roles and coherence, as the findings complement established biological principles, several key criteria were not met. These include strength, as the association between LDN and symptom improvement was weak; consistency, due to the variability in the findings across studies; and biological gradient, given the lack of a clear correlation between symptom improvement and increasing doses. Further research is required to address these limitations to clarify the dose-response relationship.

5.4. Future Research

The preliminary research on the effects of LDN on the treatment of long COVID is encouraging, with LDN also demonstrating physical benefits for syndromes with overlapping symptoms, such as ME/CFS and FM. Conflicting evidence on neurocognitive improvements was also reported in studies on long COVID [10,20]. Notably, a study by McLaughlin et al. [24] demonstrated substantial improvement in symptoms of depression and anxiety when LDN was given to patients with multiple sclerosis.

The studies evaluated in this review were constrained by small sample sizes, failure to control for confounding factors, and a lack of control groups—all of which reduce the reliability of observed effects. This review exemplifies the need for large-scale studies, particularly RCTs, which will enable exploration of dose–response relationships and identify the therapeutic onset of action and the number needed to treat and enhance the external validity of findings. Two upcoming RCTs—the British Columbia study [28] and the Griffith study [29], both of which are in the recruitment stages—will be critical for addressing the gaps in the existing literature. Additionally, the authors believe that in vitro studies investigating potential additional mechanisms of LDN could catalyse future research. Supporting this idea is a 2022 review by Shehaby et al. [30] exploring mechanisms of LDN that are not widely known, including stimulation of anti-inflammatory cytokine transforming growth factor-beta (TGF-β) and downregulation of pro-inflammatory cytokine interleukin-17 (IL-17)—hypothesized to mitigate in vivo cellular damage and alleviate the effects of long COVID.

6. Conclusions

This review provides good preliminary evidence of the potential impact of a simple intervention with a favourable risk–benefit profile while also highlighting the need for

clinicians and researchers to implement objective outcome measures, such as the use of validated questionnaires in assessing symptom severity. By delineating the limitations of the current literature, this review serves as a foundation for future research and emphasizes the need for more rigorous research, especially in the form of RCTs. By synthesizing the available data, this review provides clinicians and researchers with insight into the potential role of LDN in the treatment of long COVID.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/covid5120198/s1. Table S1: Search strategy, Table S2: Grading of Recommendations Assessment, Development and Evaluation (GRADE) of selected studies.

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