Long COVID Guiding Council
Convened by the Minnesota Department of Health
Long COVID Program in partnership with Stratis Health

Update from the Field: Low Dose Naltrexone for Treatment of Long COVID

A Series on Long COVID

Introduction

This update focuses on the efficacy of Low Dose Naltrexone (LDN) for treatment of long COVID.

Experts in Long COVID have taken interest in LDN based on positive reported experiences by patients along with a relevant mechanism of action. Naltrexone is thought to work as a partial opioid agonist resulting in compensatory release of endogenous opioids via receptor blockade. Naltrexone may suppress cytokines and other pro-inflammatory factors acting on microglia, astrocytes and which are known to promote nociception, allodynia, and hyperalgesia. Furthermore, transient receptor potential melastatin 3 (TRMP3) restoration via LDN has been suggested as a mechanism for regulating abnormal natural killer cell function. Based on the neuroinflammatory mechanisms of Long COVID, LDN therefore presents an opportunity for potential management in at least a subgroup of patients. It is also being explored in related conditions such as myalgic encephalomyelitis and autoimmune conditions such as inflammatory bowel disease.[1,2]

A literature search through July 2024 yielded five published observational studies on the use of LDN to treat long COVID. (see end of document for description of literature search). There is one ongoing registered randomized-control clinical trial comparing LDN to a placebo among individuals experiencing post-COVID fatigue symptoms.[3]

Notable Findings

- The current published literature is promising but limited due to study design biases and small sample sizes.
- Low-Dose Naltrexone appears to be safe and for some patients and may be effective at relieving long COVID symptoms. However, more rigorous studies, including randomized controlled trials, are needed to provide conclusive evidence of the beneficial effects of LDN.
    - Note: Low-dose naltrexone is commonly prescribed in doses ranging from 1 mg - 4.5 mg, but can be used in even lower doses for people with sensitivities. Both capsule and liquid formulations are available." For more detail on prescribing practices, see reference guide at: LDN Research Trust - The Low Dose Naltrexone Charity (https://ldnresearchtrust.org/2024_LDN_Guides).

Literature Considerations

- Four studies were cross-sectional or cohort observational studies. One study was a pre-post LDN intervention study. These study designs are vulnerable to confounding, participant selection bias, response bias, and without a control group the placebo effect cannot be ruled out.

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[1] Cabanas, H., Muraki, K., Eaton-Fitch, N., Staines, D. R., & Marshall-Gradisnik, S. (2021). Potential Therapeutic Benefit of Low Dose Naltrexone in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Role of Transient Receptor Potential Melastatin 3 Ion Channels in Pathophysiology and Treatment. *Frontiers in immunology*, *12*, 687806. https://doi.org/10.3389/fimmu.2021.687806

[2] Paulides, E., Lie, M. R. K. L., & van der Woude, C. J. (2022). Low-dose naltrexone for the induction of remission in patients with mild to moderate Crohn's disease: protocol for the randomized, double-blinded, placebo-controlled, multicentre LDN Crohn study. *BMJ open*, *12*(4), e058358. https://doi.org/10.1136/bmjopen-2021-058358

[3] ClinicalTrials.gov. (2022, June 24). Low-dose Naltrexone for Post-COVID Fatigue Syndrome (NCT05430152). U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT05430152

- The participants in these studies were actively seeking treatment for their long COVID symptoms, causing a potential for selection bias in favor of more severe long COVID cases.
- In two studies (Isman, 2024; Tamariz, 2023), LDN was combined with another treatment, confounding our ability to attribute outcomes to LDN alone.
- The study sample sizes were small, ranging from 24-77, which makes their findings more susceptible to selection bias.
- Long COVID is more commonly diagnosed in females, and this is reflected in the study populations. In Isman (2024), significant improvements in pain were detected only in women which may reflect differences in the underlying etiology of SARS-CoV-2 effects in women compared to men.

Summary of Literature for Use of Low Dose Naltrexone

Study	Population	Outcomes
Bonilla 2023 **Pre-Post Retrospective Cohort**	Patients with a previous positive SARS-CoV-2 test and symptoms persisting for ≥28 days post-infection and receiving LDN 59 patients • Median age: 45 • 67.8% female • Median duration of symptoms from initial infection to LDN use: 361 days Severity of symptoms at baseline: • 1.7% symptomatic without limitations • 35.6% symptomatic with reduced daily activity • 50.8% symptomatic with a struggle to perform daily activities • 11.9% incapacitated and bedridden Median severity responses for the 7 most common symptoms: • "Very severe": fatigue, brain fog, post-exertional malaise, and unrefreshing sleep • "Severe": Abnormal sleep pattern • "Moderate": light-headedness	Post-COVID-19 Functional Status Scale (FSS) • Improvement in FSS and in severity of fatigue, post-exertional malaise, unrefreshing sleep, abnormal sleep pattern. Modest improvement in seven symptoms: headache, fatigue, brain fog, unrefreshing sleep, sleep difficulties, post-exertional malaise, light-headedness: • No correlation between LDN dose and individual scored responses to each of the 7 symptoms. • Sum composite score for 7 symptoms improved in 32 patients (54.2%), worsened in 19 (32.2%). Analysis of comparison group not presented in the results. Limitations: Response bias, selection bias
Hurt 2024 **Cross-Sectional Survey**	Adult patients with symptoms persisting >28 days following COVID-19 infection Of 536 patients, 77 were given LDN For total study population: • Mean age: 52.3 • 63% female • 93% white • 23.2 months since first positive COVID test	Self-reported helpfulness of LDN • 45 participants reported that LDN was helpful (58%).

Study	Population	Outcomes
Isman 2024 **Observational Pilot Study**	Adult patients with positive SARS-CoV-2 test 1-12 months before enrollment reporting moderate-severe fatigue Exclusion criteria: clinically significant renal, cardiovascular, or hepatic impairment; current use of opioid analgesics; current treatment for an opioid use disorder; naltrexone sensitivity; suspected or confirmed pregnancy; currently breastfeeding; known issues with the use of iontophoresis patches; active cancer; enrolled in another trial; currently taking LDN or NAD+ 36 patients given LDN and NAD+ • 69.4% female • Median time between COVID-19 test and first trial dose: 193.5 days	Chalder Fatigue Scale, Short Form 36 survey, adverse events: • Nausea, fatigue, dizziness, and low mood occurred during first weeks of treatment, were managed with dosing schedule adjustments. • Mean quality of life score improved consistently. • Largest benefit seen in mean role limitations due to physical health, mean energy/fatigue, and mean pain scores. Age-specific differences: • ≤39 age group did not experience significant improvements in physical functioning, emotional well-being, or pain levels after 12 weeks of treatment • 39+ age group did not experience a significant improvement in role limitations due to emotional problems and general health Sex differences: • Significant improvements in pain after 2 and 3 months of treatment were detected only in women
O'Kelly 2022 **Low Dose Naltrexone Intervention Pre-Post Study**	Adult patients with symptoms for at least 3 months post-COVID-19 diagnosis, other causes of symptoms excluded 38 patients given LDN • 76.9% female • Median age: 43.5	Questionnaire at recruitment and 2-3 months to assess 7 components of clinical status and adverse effects: • Modest improvement in 6/7 components: perception of overall recovery from COVID-19, limitation in activities of daily living, energy levels, pain, concentration, and sleep disturbance. Largest effect seen in pain. • Two patients stopped LDN due to diarrhea and fatigue (LDN was safe in 94.7% of participants). Limitations: Response bias, selection bias, no comparison group

Study	Population	Outcomes
Tamariz 2023 **Retrospective Cohort Study**	Veterans being seen in a post-COVID-19 clinic 24 patients given LDN combined with physical therapy: • Mean age: 53.8 • 34% female • 44% Black race • 38% Hispanic ethnicity • 44% with hypertension • 56% with diabetes • 40% with PTSD	Reported improvement in at least 1 of the following symptoms 1 month after beginning treatment: fatigue, pain, brain fog, or dyspnea: • 67% reported improvement. • Found interaction between LDN and physical therapy. • Adjusting for age, Charlson Comorbidity Index score, and prior COVID-19 hospitalization, patients taking LDN had 5.04 times the relative hazard of improvement compared to physical therapy alone (p=0.02). Secondary outcome: changes in CRP and morning cortisol • Patients taking LDN had reduced CRP and increased cortisol, but the difference was not statistically significant.

Literature Search Description

The first search was run in April 2024 for literature published between mid-2020 through early April 2024. A repeat search was conducted in July 2024 for any additional literature published between April and June 2024. The searches were run with two broader search engines (EBSCO Discovery Health and PubMed), including randomized controlled trials, systematic reviews/meta-analyses, cohort studies, case studies, and general summary reports. The following search terms were used and included both MeSH terms and subject terms: ("Post-COVID conditions" OR "long COVID" OR "post-acute COVID-19 syndrome" OR "PASC" OR "post-acute sequelae of SARS-CoV-2" OR "Post COVID syndrome" OR "PSC" OR "Post-acute Sequelae of SARS-CoV-2") AND ("Naltrexone" OR "Low Dose Naltrexone" OR "Naltrexone Hydrochloride" OR "LDN" OR "NTX"). The search produced 13 articles of which five were relevant to the question of "relationship of Low Dose Naltrexone treatment for treatment of Long COVID".

Acknowledgments

Thank you to our work group members for their expertise, feedback, and review to review available evidence and develop this update. The work group members included *(in alphabetical order by organization)*:

- Stephanie Grach, MD, MBBS, Mayo Clinic
- Ravindra Ganesh, MD, MBBS, Mayo Clinic
- Bazak Sharon, MD, Independent Consultant

Document produced: November 2024. Updates to this document will be made as new evidence becomes available.

This project is funded through the State of Minnesota.