LOW–DOSE NALTREXONE FOR LONG COVID

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Abstract

In August 2024, the number of people impacted by Long COVID (LC) was estimated to be about 400 million globally (Al-Aly et al., 2024). Currently, there are no FDA–approved treatments for LC. Many of the centres treating LC have noticed the similarity to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in some patients. Low–dose naltrexone (LDN) is a drug that has recently shown potential in treating ME/CFS. In this integrative review, ten articles were selected for analysis to investigate whether LDN could be a viable treatment for LC. Although the studies conducted on LDN and LC are small, non–randomized, and unblinded, a few interesting themes emerged from this analysis that could guide future studies and treatment decisions. LDN seems to be most effective for individuals with a LC phenotype that mimics ME/CFS, as, of all the symptoms of LC, it was found to be most effective for fatigue and pain. In the future, pre–screening tools will likely be developed to identify patients most likely to respond to LDN. Two double–blind randomized controlled trials (RCTs) are currently underway that will be published next year, yielding a higher degree of evidence and certainty around LDN for LC. In the meantime, initial findings support consideration of LDN for patients with LC whose primary complaints are fatigue or pain.

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Glossary

Term:	Definition
Hormesis	a biphasic dose response to an environmental agent that has beneficial effects at low doses and inhibitory or harmful effects at high doses.
Long COVID	The lingering syndrome affecting multi–organ systems that may follow an acute infection of the SARS–CoV–2 Virus. In some instances, this disease state persists for years after initial infection.
Phenotype	The observable characteristics of a disease. Used to sub-categorize different "symptom clusters" in Long COVID.
Seroconversion	The development of specific antibodies in the blood serum due to infection or immunization, including vaccination.
Titrate	The process of slowly adjusting the medication dosage to minimize side effects.

Acronyms:

LC	Long COVID
LDN	Low–dose naltrexone – naltrexone is used in amounts much lower than classical dosing. No exact range is specified, but it generally averages less than 10 milligrams/day.
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
NK cell	Natural killer cell, an immune cell that kills diseased and dysfunctional cells.
PASC	Post–acute sequelae of SARS–CoV–2 infection, another term for Long COVID
PCC	Post–COVID-19 Condition, one common medical term for Long COVID
PESE	symptoms such as disabling fatigue or exhaustion, difficulty thinking, pain, exercise intolerance, and other symptoms that are made worse by exertion

POTS	Postural orthostatic tachycardia syndrome – a disorder of the autonomic nervous system characterized by inappropriate changes in heart rate when transitioning from sitting to standing.
RCT	Randomized controlled trial
TLR4	a protein embedded in the cell wall of glial cells, which is a key activator of the innate immune response and plays a central role in the fight against bacterial infections.
TRPM3	Transient receptor potential cation channel subfamily M member 3 – In natural Killer cells (a type of immune cell), this allows calcium into the cell. The impairment of the TRPM3 protein seen in CFS results in the dysfunction of NK cells.

Low Dose Naltrexone for Long COVID

The ongoing COVID-19 global pandemic is unprecedented and continues to impact every aspect of society. Although in many ways life has returned to the pre–pandemic "normal," the long–term impacts of COVID-19 infection are still being quantified. Most people by now are aware of the effects of an acute COVID-19 infection; less well known, however, is the fact that some individuals who clear the initial acute coronavirus infection are left with persistent manifestations, affecting multiple organ systems (Greenhalgh et al., 2024). The long–term impact of acute COVID-19 infection is variably referred to as long COVID (LC), post–acute sequelae of SARS–CoV–2 infection (PASC) (Collins, 2021), or post–COVID-19 condition (PCC) (Centers for Disease Control and Prevention [CDC], 2022; Collins, 2021). A primary concern with LC is the difficulties faced when quantifying exact case counts, which will be discussed in greater detail below.

For several reasons, LC lacks a standardized treatment plan (Ozanic et al., 2025). In the early days of the pandemic, clinicians working at LC clinics would identify similarities between PCC and other post–viral conditions and trial established treatments for the conditions they resemble (Hurt et al., 2024). Some drugs have also been proposed as treatments based on the presumed pathophysiological underpinnings of the condition (Bonilla, Peluso, et al., 2023). The WHO (2025) and the U.S. Centers for Disease Control (2024) list more than 200 possible symptoms associated with PCC. Symptomatically speaking, some *phenotypes* (or subtypes) of LC share many similarities to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which has led to the implementation of established ME/CFS treatments being considered for LC (Davis et al., 2023a). Although to date, no randomized controlled trials (RCTs) have been conducted on it, one drug that has gained attention recently in the treatment of CFS and other

autoimmune conditions is low–dose naltrexone (LDN) (Polo et al., 2019; Cabanas et al., 2021; Steenhuysen, 2022). This integrative review aimed to collect, analyze, and synthesize the evidence surrounding the efficacy of LDN in people living with PCC.

Background

Scale of COVID-19

Quantifying precisely how many people have had a COVID-19 infection is challenging. Although the statistics from the World Health Organization (WHO, 2025) suggest the total global case count to be approximately 780 million, in fact, this number could be dramatically higher as these WHO figures rely on confirmed cases and do not account for asymptomatic infections or instances where individuals did not meet diagnostic criteria for COVID-19. According to Alvarez et al. (2023), ascertaining a definitive number is difficult for a few reasons. These include issues with the testing process (i.e., factors that influence a person's decision to seek or not seek testing, and errors made with the administration of tests), limited access to testing centres or self–tests, and delays in processing and reporting tests. Variation in data collection methods is also problematic, leading to inconsistent data. Badker et al. (2021) found that another factor that contributes to the difficulty in accurately estimating cases of both COVID-19 and LC is an inconsistent case definition. In addition to this, there is the confounding factor of asymptomatic infections (Bergeri et al., 2022) and variability in individual seroconversion (McConnell et al., 2021). Blood testing for COVID-19 antibodies has demonstrated that some individuals who never had symptoms of a COVID-19 infection have antibodies (or have *seroconverted*) (Banu et al., 2023). In some cases, the opposite may happen; when tested later, a person who tested positive for an acute COVID-19 infection does not have antibodies for COVID-19 (Toh et al., 2022).

To address the issue of asymptomatic infection, some areas have conducted blood tests for COVID-19 antibodies to attain a more accurate understanding of the incidence of COVID-19. However, even here, there is a large variability in seroconversion depending on region. Another issue with assessing COVID-19 incidence through seroconversion is that some people who have had confirmed COVID-19 infection will not seroconvert at all (Toh et al., 2022). To assess the true incidence of COVID-19 infections, some jurisdictions have conducted wastewater analysis for viral RNA. In Peel, Ontario, wastewater showed the incidence of infection to likely be 6–18 times higher than the rates found with laboratory testing (Cheng et al., n.d.). In short, no consensus exists on the precise incidence of COVID-19.

Long COVID

The persistent illness that can follow a COVID-19 infection goes by many names. The term Long COVID was coined by patients. These individuals were also the first to identify this condition and advocate to bring awareness (Callard & Perego, 2021). For these reasons, the term Long COVID (or LC) will be preferentially used in this review; however, when directly quoting or paraphrasing other sources, the original terms will be preserved.

Controversy abounds in the world of LC, with multiple theories about what causes it, how best to identify it, and how to treat it, with widely disparate estimates of prevalence. This general lack of agreement is due to the relative novelty of LC, and it is hoped that as more is studied and discovered about LC, a growing consensus will emerge (WHO, 2025). The lack of agreement can also be attributed to the highly variable way LC presents itself. The existence of diverse clinical phenotypes of LC is generally agreed upon if the phenotypes themselves are described in various ways by different researchers. Another area of confusion with LC is how to diagnose it. No biomarkers have been established for diagnosing or monitoring LC (Erlandson et

al., 2024). As a result, LC remains an entirely clinical diagnosis. This presents diagnostic challenges as there is no agreement on definitive diagnostic criteria (Tan & Koh, 2023). The establishment of biomarkers is imperative as they assist clinicians with the diagnosis and monitoring of the treatment of LC (Davis et al., 2023). Much research is being done in this area; Putrino from Mount Sinai and Iwasaki from the Yale School of Medicine (n.d.) are two leading researchers in this area.

These challenges in ascertaining an accurate instance of acute COVID-19 also contribute to the difficulty in estimating the exact number of people affected by LC. There are also additional factors that make it difficult to assess the frequency of LC. These include the absence of definitive diagnostic tests or criteria and the wide variability in symptom onset and duration (Davis et al., 2023). Due to these factors, estimates of the incidence of LC vary widely. For example, one study in California found that, depending on which definition was used, LC rates after COVID-19 infection ranged from 4.9% to 30.9% (Pry et al., 2024).

Another aspect of LC that remains uncertain is the pathophysiological underpinnings of the syndrome. Fumagalli et al. (2022) identified several risk factors for developing LC, including overall frailty, age, female gender, and pre–existing Chronic Obstructive Pulmonary Disease. Similar factors were also identified in a retrospective cohort analysis of over 270,000 by Taquet et al. (2021). Song and Giuriato (2023) also found that female gender, older age, and specific pre–existing medical comorbidities were risk factors for developing LC. Al–Aly et al. (2024) found that with each additional infection with acute COVID-19, an individual's risk of developing LC increased.

Although objective measures for diagnosing and tracking the progression of LC have not yet been determined, some lab values that have been considered for assessment include

creatinine, C–reactive protein (CRP), D–dimer, ferritin, interleukin–6 (IL–6), IL–10, interferon–gamma (IFN–γ), lactate dehydrogenase (LDH), leukocytes or white blood, lymphocytes, monocytes, neutrophils, neutrophil–lymphocyte ratio, N–terminal prohormone of brain natriuretic peptide (NT–Pro–BNP), platelets, troponin, TNF–alpha (TNF–α), and fibrinogen. (Yong et al., 2023). Determining biomarkers for LC would greatly assist with diagnosis and tracking treatment efficacy.

Despite the increasing understanding of who gets LC, there remains no standardized treatment for people living with this condition (WHO, 2025; Bonilla et al., 2023a) The challenges of conducting trials in this population (Munblit, Nicholson et al., 2022) mean that the existing recommendations are often based on low or very low–quality evidence. Most current recommendations aim to treat symptoms rather than address underlying pathological pathways (Bonilla et al., 2023a). The Canadian Guidelines for Post-COVID-19 Condition (CAN–PCC, 2025) only have 22 clinical recommendations for LC. These include Metformin, Antihistamines, and Beta–Blockers, all of which have a low or very low quality of evidence and focus on alleviating the symptoms rather than the underlying pathology of LC. It is postulated that LDN might reverse the underlying pathology of LC, rather than simply masking the symptoms (Steenhuysen, 2022), which is one reason it may be helpful in ways that existing treatments, such as antihistamines, are not. The relevant pharmacology will be expanded upon below. The WHO Clinical Management of COVID-19: Living Guideline (WHO, 2023) focuses mainly on various physical or behavioural therapies and does not have any recommendations for pharmaceutical approaches. In The Journal of Infection and Chemotherapy, Seo et al. (2024) published a set of recommendations for treating LC that focus on addressing individual symptoms with existing therapies, particularly cognitive behavioral therapy and physical therapy. However, the

guidelines offer limited discussion of pharmacological options, which may be more appropriate for patients with severe fatigue.

Due to symptom severity, some people with LC may find physical or cognitive behavioural therapies impossible due to their debilitating fatigue (DeMars et al., 2023). Those who experience high levels of fatigue are not good candidates for physical or cognitive behavioural therapies due to the severity of their symptomatology. For example, those with post–exertional symptom exacerbation (PESE) may not be candidates for physiotherapy (Long COVID Physio, 2024). CAN–PCC (2025) recommends limiting exercise–based interventions in people with PESE to *only* within the context of research settings. The WHO (2023) also discusses that the use of physical rehabilitation is not appropriate for some people with LC who have overwhelming PESE. Appelman et al. (2024) demonstrated that the PESE in LC patients appears to result from mitochondrial dysfunction, and they stress that exercise should be limited and paced in individuals experiencing fatigue. This leaves a subset of LC sufferers with minimal treatment options. In cases such as these, where therapy is not possible, pharmacological options could be of great benefit. Standardized, evidence–based recommendations for pharmaceutical treatment are urgently needed as LC continues to impact a growing number of people worldwide.

LC symptom clusters

It has been suggested that classifying all LC presentations into one homogenous category is problematic, given the disparate ways LC can present (Pfaff et al., 2022; Soriano et al., 2022; Munblit, O'Hara et al., 2022). Currently, the WHO's International Classification of Diseases (ICD), the global standard for naming and classifying diseases, only has *one* code for LC (WHO, 2019). Pfaff et al. (2022) advocate for the ICD codes to be expanded to include different phenotypes of LC, arguing that this will enable more precise targeting of clinical studies to well–

defined cohorts. This, in turn, should support the creation of more effective, precise treatment and clinical decision support and assist in accurately estimating the incidence of LC.

The precise number of LC phenotypes and how to classify them remain a topic of debate. RECOVER (Researching COVID-19 to Enhance Recovery) is a comprehensive research initiative launched by the U.S. National Institutes of Health (NIH) to understand, diagnose, treat, and prevent LC. In their analysis of 13,647 participants, the RECOVER initiative identified 52 symptoms of LC and noted that these all occurred in every subtype category. They also identified five subtypes of LC based on the primary symptom (Geng et al., 2025). These five categories are subtype 1 – change in taste or smell; subtype 2 – chronic cough; subtype 3 – brain fog; subtype 4 – palpitations; and subtype 5 – post–exertional soreness, dizziness, and gastrointestinal symptoms. Among their 1796 participants, Gentilotti et al. (2023) identified four LC subtypes: 1– chronic fatigue–like syndrome, subtype 2 – respiratory syndrome, subtype 3 – chronic pain syndrome, and subtype 4 – neurosensorial syndrome. Epsi et al. (2024) also categorize LC phenotypes based on symptomatology. They describe these symptom clusters as a *fatigue/difficulty thinking* cluster, a *difficulty breathing/exercise intolerance* cluster, and a *sensory* cluster. Conversely, Gerritzen et al. (2023) divide LC phenotypes into three categories based on overall number rather than type of symptoms (phenotype one comprised participants with a lower–than–average number of symptoms, phenotype 2 with an average number of symptoms, and phenotype 3 with a higher–than–average number of symptoms). Another way in which LC could be categorized is by the time of symptom onset after initial infection. Song and Giuriato (2023) found that, although most diagnoses of LC were made within the first 1–2 months after the initial COVID-19 diagnosis, there is a second peak of diagnoses that occurs around one year after the initial COVID-19 infection. It is not known if this later presenting LC

is fundamentally different from other presentations of LC. However, it may be important in the differentiation of discrete phenotypes. There is much work that remains to be done in this area. Even among those who see the value in subcategorizing LC, there is no clear consensus on what these phenotypes should be or how they should be qualified.

Some have even argued that LC is not, in fact, a discrete entity; instead, it is simply a variation of what is sometimes known as Post–ICU syndrome. Hodgson et al. (2022) found that six months out, there was no significant difference in new disability between COVID-19 and non–COVID–19 patients who had been mechanically ventilated. However, Ma et al. (2023) note that LC also presents in patients whose initial COVID-19 infection was mild, which suggests that it is a discrete condition. This lack of consensus on classifying LC makes it challenging to study and treat, and as the number of individuals impacted continues to grow, this becomes an increasingly significant problem.

Issues surrounding LC research

Several issues have been identified that make LC challenging to research. Five years into the pandemic, the pathophysiology of LC remains an enigma. Theories abound, but no consensus exists on what causes the over 200 symptoms associated with LC, or whether a single unifying cause exists. A comprehensive review of the pathophysiology of LC found many theories on this matter (Castanares–Zapatero et al., 2022). Some theories on the pathophysiological causes of LC are immune dysregulation (Proal et al., 2023), procoagulatory effects (Pretorius et al., 2021), endothelial and microcirculatory disturbances (Varga et al., 2020), spike protein persistence (Swank et al., 2023), coinfections (Peluso et al., 2023), viral reactivations, and microbiome disturbance (Zuo et al., 2020) as well as metabolic effects (Khunti et al., 2021) and inflammatory effects (Wijeratne & Crewther, 2020).

Another research issue is that, since LC is so new, the scales used to assess related symptomatology, such as fatigue, have not yet been validated (Thomas et al., 2024). In some cases, scales used in other conditions, such as ME/CFS, are being repurposed for LC, but these still need to be clinically evaluated and validated. Wong et al. (2023) argue that Patient Reported Outcome Measures (PROM) are an important part of determining the phenotypes of LC. As a result, in the future, the scale or tool used to assess symptoms could help determine a patient's treatment plan. A 2024 scoping review (Thomas et al.) recommended using either the Functional Status Scale (FSS) (Krupp et al., 1989), Fatigue Assessment Scale (FAS) (Michielsen et al., 2004), or the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (Webster et al., 2003) for assessing LC–related fatigue. A 2023 meta–analysis of fatigue in LC (Poole–Wright et al., 2024) noted the difficulty in comparing data from different studies when different fatigue tools were used. They also advocate that the researchers studying LC use fatigue scales validated in other conditions with fatigue as a significant symptom, such as ME/CFS or SLE. Additionally, Campos et al. (2022) recommend including an objective measure of fatigue in outcome measurements.

Often, Likert scales are used to rate symptoms. Although considered a standard approach, this use of Likert scaling is not without issue. The Likert scale was developed nearly a century ago by Rensis Likert (1932) to measure the degree to which a person agrees or disagrees with a statement. This method is not without controversy for several reasons; one of them being that it "cannot be assumed that the difference between responses is equidistant even though the numbers assigned to those responses are" (Sullivan & Artino, 2013, p. 1). Standardized, validated tools should be used to assess symptoms such as fatigue. Simple single–dimensional scales such as the Likert scale should be avoided (Behrangrad & Yoosefinejad, 2021).

Long COVID in Primary Care

The exact burden of LC in primary care in Canada has not been well–established, but in December 2023, 2.1 million people were estimated to be living with long–term symptoms of a COVID-19 infection (Statistics Canada, 2023). Unfortunately, these numbers are expected to increase; the Government of Canada (2023) found that LC rates in adults were around 14% after one COVID-19 infection. However, this rate climbed to nearly 38% after three or more infections. According to the government of British Columbia (BC), the number of nurse practitioners working in primary care in BC increased by 11.3% from December 2022 to December 2023 (BC Gov, 2024). As NPs increasingly provide primary care, and LC is becoming increasingly prevalent in this setting, it can be expected that the treatment of LC will become increasingly performed by NPs, making this review particularly relevant to NP practice.

History and mechanism of action of Naltrexone

In recent years, naltrexone, classically used in the treatment of opioid addiction and alcohol use disorder, has been repurposed as an off–label treatment for a variety of autoimmune, chronic pain, and inflammatory disorders (Toljan & Vrooman, 2018). When it was first developed in 1963, naltrexone was originally used for its opioid antagonist properties. It was approved for opiate use disorder by the FDA in 1984 and for alcohol use disorder in 1994 (Milhorn, 2017). In 1984, physician Dr Bernard Bihari, who was working in the field of addiction, began exploring naltrexone for its potential immunomodulating properties. Most information about this discovery of LDN is in the form of an interview, published posthumously in the non-peer-reviewed journal *Alternative Therapies in Health and Medicine* (Bihari, 2013). In this interview, Dr. Bihari discusses how, when he learned that people with HIV had significantly lower levels of endorphins than those without, he

postulated that naltrexone, in low doses, may be able to increase the body's production of endorphins by transiently blocking endorphin receptors. He then made the connection between the blockade and the resulting upregulation of endorphin receptors he saw in his trials with heroin users and the potential to treat the newly discovered HIV infection. Unfortunately, none of Dr. Bihari's work in this area has been published in peer–reviewed journals, and he could not continue his research in this vein due to a lack of funding. However, through presentations to physicians and word of mouth communication within the HIV/AIDS community, the use of LDN slowly became more well–known and accepted. What initially was used to boost endorphin levels in people with HIV, in more recent years, has been investigated for its anti-inflammatory and immunoregulatory properties in many diseases involving immune dysfunction.

The grassroots history of the development of LDN is reflected in the current situation, with word of mouth substantially contributing to its uptake (Raknes & Småbrekke, 2017). Following the release of a popular documentary on LDN, Norway saw a significant increase in LDN prescriptions. In 2012, there were only 14 people in Norway using LDN; in 2013, following the airing of the aforementioned documentary on LDN in multiple sclerosis, LDN prescriptions in Norway rose to more than 11,000 (Raknes & Småbrekke, 2017).

LDN is also being investigated for use in chronic pain, which is controversial and remains off–label due to a lack of large, high–quality RCTs demonstrating efficacy. Despite this, naltrexone use has continued to increase, driven in part by the abundant anecdotal evidence and word of mouth in online chronic pain and autoimmune community spaces (Raknes & Småbrekke, 2017). An example of this is the popular Facebook group LDN Research Trust (n.d.), which has over 61,000 members from around the globe.

In its FDA–approved role, naltrexone is used in doses of 50–100 mg/day for alcohol use disorder. At this dose, it acts primarily by blocking the mu–opioid receptor, responsible for releasing dopamine in the nucleus accumbens of the user's brain, hence the positive mental state, or *high feeling* accompanying this dopamine release (Swift, 1999). It has a suite of proposed effects in much lower doses, ranging from 1–5 mg/day. Although much is known about the mechanism of action of naltrexone at classical dosing, the precise mechanism of action of LDN remains unproven (Toljan & Vrooman, 2018). This is likely due to Naltrexone lacking FDA approval for dosages other than 50–100 mg and settings other than addiction medicine (US Food and Drug Administration, 2013), so studies looking at the pharmacology of naltrexone in lower doses are lacking. It also may be because LDN works on multiple pathways in the body.

Despite the lack of high–quality pharmacological information on LDN, there are several theories as to why it might be helpful in chronic pain, cancer, and autoimmune conditions. One mechanism behind LDN's efficacy in chronic pain, which has been known since the 1980s, is the temporary blockade of opioid receptors. This blockade results in the body's compensatory production of endorphins (Kosten et al., 1986), which helps improve pain level. It is also proposed that naltrexone in low doses exerts a paradoxical effect that leads to a reduced affinity for the μ–opioid receptor and an increased affinity for the toll–like receptor 4 (TLR4) (Toljan & Brooman, 2018). TLR4s are found in the cell membranes of microglial cells, the most prominent immune cells of the CNS. In 2013, Stevens et al. found that both opioids, such as fentanyl and morphine, and opioid antagonists (in this case, naloxone) interact with TLR4s and so impact inflammation and the immune system. However, this study was conducted *in vitro*, so caution must be used when applying these results to the *in vivo* setting.

Cabanas et al. (2019) recently discovered another mechanism of action of LDN: its impact on regulating the function of natural killer (NK) cells. They found that naltrexone restores function in dysfunctional NK cells in ME/CFS patients.

LDN is also being considered for psychiatric reasons beyond addiction medicine. A proof of concept trial (Mischoulon et al., 2017) showed that LDN might benefit patients with major depressive disorder who are experiencing breakthrough symptoms while on other antidepressants. This is far from definitive proof of its efficacy, but it does show that it may hold promise as an adjunctive treatment for depression. Unfortunately, perhaps due to some of the issues discussed below, LDN has not been further studied for depression; however, a small retrospective survey study found that LDN reduced anxiety in people with multiple sclerosis (MS) during the COVID-19 pandemic (McLaughlin et al., 2022). The results of both studies suggest that LDN may eventually be found to have beneficial effects on psychiatric conditions such as anxiety and depression. In some instances, mental health concerns, such as anxiety and depression, are dominant symptoms of LC in some phenotypes (Bautista–Rodriguez et al., 2023). In these cases, LDN may be found to be a viable treatment. 2–4.5

Dosing and Duration of LDN

Due to the lack of extensive studies, it is challenging to determine the optimal dose of LDN. Dr. Bihari (2013) conducted a small study, which was never published, looking at dose size and timing to raise endorphins most effectively. He found that doses between 1.75 and 5 mg in one nightly dose were the best for most individuals. However, he acknowledged that this was a small study and that there was significant variation amongst individuals, so he encouraged future research into this area as the sample size of his studies were too small to be generalizable to the population at large. Due to a lack of high–quality evidence and the fact that LDN use is

exclusively off–label, the most effective dosing remains unproven. One resource for suggestions on LDN dosing is the LDN Research Trust, a non–profit charity focused on funding research and disseminating information on LDN. The LDN Research Trust recommends starting at a low dose and slowly titrating to avoid or minimize side effects (LDN Research Trust, 2024). The schedule they recommend (based on the analysis of the existing literature and the combined anecdotal experience of their pharmacists and prescribers) is 0.5– 1 mg daily for 14 days, increasing by 0.5 to 1 mg every 2 weeks until 4.5mg or the highest tolerated dose. In this manner, side effects can be minimized. This is like the dosing schedule found most effective by Marcus et al. (2024) in their observational study on the best dosing of LDN for chronic pain. Marcus et al. (2024) also observed that LDN seems to operate in a hormetic manner, meaning there is an optimal dosing range where the drug is most effective and that increasing or decreasing beyond this range does not translate into a better effect; which was also what Bihari found in his early studies in the 1980's (Bihari, 2013).

The dosing of LDN for chronic pain is generally 2–4.5 mg/day (Rassi–Mariani et al., 2024). In fibromyalgia, the doses that have been studied range from 0.1–9 mg/day, with most sources using 4.5 mg/day (Yang et al., 2023). Dosing for most conditions is not well–established due to a lack of high–quality RCTs, but the usual dose is around 4.5 mg/day for a diverse range of conditions, including multiple sclerosis, Crohn's disease, cancer, Hailey–Hailey disease, and complex regional pain syndrome (Toljan & Vrooman, 2018).

Another consideration when looking at the efficacy of LDN is the duration of therapy needed to see optimal effects. There is also a lack of high–quality evidence, and much of the information is anecdotal. The LDN research trust (n.d.) speaks to this, and their physician, Dr Yusuf Saleeby, recommends that patients trial LDN for at least three months before drawing any

conclusions about efficacy. Another factor to consider with duration is that if LDN is titrated slowly, it can lead to the optimal dose not being reached for several weeks, so the duration of therapy should be adjusted to accommodate this. Furthermore, one author (Marcus et al., 2024) found that some patients in their study had previously trialled LDN and found it ineffective. However, when they used a gradual titration schedule, rather than starting at a relatively higher dose of ~4.5 mg/day, many of the patients who in the past had not responded to LDN ended up finding it effective. This finding led Leiber and Parker (2025) to make the following recommendation: "previous studies ruling out LDN as an effective treatment for certain disease states might warrant re-evaluation if titration was not utilized" (Leiber & Parker, 2025, p. 12)

Safety considerations

Naltrexone has a well–established safety profile and has been in use at doses of 50–100 mg since the mid–1980s without any recorded serious adverse effects. For years, however, there was a black box warning on the label for hepatotoxicity. The U.S. Food and Drug Administration (FDA, 2013) removed this in 2013 because it was based on liver damage seen at doses of 300 mg or higher, and there are no known cases of hepatic failure resulting from naltrexone. Furthermore, although dosing for LDN varies, it is generally in the neighbourhood of one–sixtieth of the dose shown to potentially induce hepatic injury. Because of this much lower dose, it is thought that LDN is unlikely to provoke hepatic injury in an uncompromised patient. Despite the lack of significant adverse events associated with naltrexone use, minor adverse events are relatively common. However, they do not appear to occur more than in placebo groups (Bolton et al., 2019). The established safety of LDN makes it a good candidate for investigating for novel uses.

Side effects and interactions

Common side effects of LDN are mild and include vivid dreams, insomnia, nausea, and headache (Leiber & Parker, 2025). These are relatively rare and usually tolerable. These side effects are often transient, disappear with time, and can be minimized with appropriate titration.

A significant potential interaction to consider with Naltrexone is that it can precipitate opiate withdrawal and therefore should be avoided in people who are on opiate medications (U.S. National Library of Medicine, 2021). Naltrexone may also interact with the anti-psychotic thioridazine and alcohol misuse treatment disulfiram. There are no known interactions with herbs or vitamins. The American Society of Addiction Medicine (2013) also notes that the above interactions are for Naltrexone at FDA–approved dosing; it is not known if naltrexone at lower doses also carries the same risks.

Potential issues regarding naltrexone research

Despite many small–scale studies on a myriad of autoimmune and pain conditions, to date, there have been few high–quality randomized controlled trials on LDN. One contributing factor may be that the patent on naltrexone has long since expired; indeed, in its oral form, naltrexone is only available as a generic (Seabright, 2023). It is well known that as the patent expires on a drug, the market price of the drug decreases significantly (Vondeling et al., 2018). Without financial reward, private pharmaceutical corporations have limited incentives to study generics such as naltrexone in novel therapeutic indications.

This situation has led to alternative funding sources, such as publicly funded studies. In 2010, a pilot study on LDN in MS was funded entirely by private contributions from MS patients (Cree et al., 2010). Other studies have been funded by patient advocacy groups such as the LDN Research Trust (Puttick, 2007). Studies of this type raise several concerns, particularly related to

the ethics surrounding the potential exploitation of people who are already facing hardship due to their illness. Additionally, if the patients funding the study are permitted to direct its design, this raises potential validity issues. Wenner et al. (2015) summarize the many potential issues raised by publicly funded trials (PFT), stating that

> "The reconfiguration of research relationships seen in PFTs is prone to inefficiencies, market–unproven, ineffective, and perhaps even dangerous interventions to patients desperate for a cure" (Wenner et al., 2015, p. 1).

Methodology

Study Design

This is an integrative review of low–dose naltrexone in Long COVID. Whittemore and Knafl's (2005) methodology guided this integrative review. The research question was formatted as a PIO question (Population, Intervention, Outcome) based on the model developed by Richardson et al. (1995). The research question was "How does low–dose naltrexone impact people living with Long COVID?"

Search Strategy

The databases selected were CINAHL and MEDLINE, as I expected this to capture the most pertinent literature. In addition, a Google Scholar search was completed to ensure that all relevant literature was included for analysis. Although this review focuses on low–dose naltrexone, to cast a wide net and ensure that all significant literature was identified, the search included "naltrexone" rather than "low–dose naltrexone." The initial search included "COVID-19" as a unique term, but it was evident that this yielded many articles that were not specifically about LC. The MeSH terms settled upon for the final search included the keywords "naltrexone" and "Long COVID" or "chronic COVID-19" or "post COVID-19" or "long haul COVID-19" or "post COVID-19".

Inclusion and Exclusion Criteria

All articles were screened initially with a title review, then a review of the abstract, and finally, a full–text review. Studies that were not published in English were excluded, as were those that were not full–text. The inclusion criteria were that studies must focus on LC, not acute COVID-19. Additionally, the dose of naltrexone discussed must be in the "low–dose" range, not the higher dosage typically used in addiction medicine.

Search Results

The search was conducted on February 8, 2025, and yielded 17 results, 12 from MEDLINE and five from CINAHL. After duplicates were removed, there were 15 results. Please see Appendix A for a PRISMA Flow Diagram of the selection process. Of the 15 articles, one was excluded for not being in English, two for not being full text, and the remaining 12 were selected for abstract review. Of these, four were excluded for not focusing on LC. This left eight selected for review. At this point, Google Scholar was searched with the exact keywords, and the first 30 results were reviewed for inclusion. Of these, two were selected for inclusion. The total number of articles selected for analysis was 10.

Analysis

The study design was critically appraised using the Critical Appraisal Skills Program (CASP) checklists, including the cohort, RCT, and cross–sectional study checklists (Critical Appraisal Skills Program, 2024). The content of each study was then noted in a matrix to compare similarities and identify themes. This matrix was based on the model suggested by Toronto and Remington (2020). See Appendix B.

Findings

This section describes the characteristics of the selected studies, followed by an analysis of four themes which emerged in the studies: a) symptoms/phenotypes assessed and those most improved by LDN, b) delivery methods (titration schedule, dose, duration), c) side effects and safety, and d) outcome measures tracked (scales used and objective measures). An additional theme that will be discussed is the findings of the laboratory study. All ten articles selected for review found that LDN improves symptoms associated with LC.

Study Characteristics

The date ranges of the studies were from 2022 to 2024. Although, thus far, no randomized controlled trials have been conducted on LDN for LC, the selected articles represent a diverse range of methodologies. Two of the articles are retrospective cohort reviews (Tamariz et al., 2024; Bonilla et al., 2023b), one is an interventional pre–post study (O'Kelly et al., 2022), one is a cross–sectional study (Hurt et al., 2024), and one is an observational study (Isman et al., 2024). In addition, there is one lab study (Sasso et al., 2024), a "mini–review" (Dietz & Brondstater, 2024), and a scoping review (Livieratos et al., 2024), as well as one study protocol (Naik et al., 2024) and one case study (Petracek et al., 2023).

Unsurprisingly, given the international nature of the COVID-19 pandemic, the selected articles originate from around the globe. Five are from the USA (Dietz & Brondstater, 2024; Hurt et al., 2024; Isman et al., 2024; Petracek et al., 2023; Tamariz et al., 2024). Of the remainder, one originates in the Netherlands (Bonilla et al., 2023b), one from Canada (Naik et al., 2024), one from Greece (Livieratos et al., 2024), one from Australia (Sasso et al., 2024), and lastly, one from Ireland (O'Kelly et al., 2022).

Apart from the lab study (Sasso et al., 2024), all but one (Isman et al., 2024) of the assessed studies occurred at a LC clinic. Isman et al. (2024) do not specify the study setting. During the analysis of the articles, a few key themes emerged, which will be discussed in further detail below. The first theme that will be expanded upon involves the tracked and treated symptoms in these studies.

Theme One: Symptoms and Phenotypes Most Improved by LDN

Across the studies assessed in this review, one of the most explored areas was which symptoms LDN was most effective for and whether some phenotypes may respond better to LDN. The articles in this review reflect the general lack of consensus about which symptoms define LC. Overall, fatigue was the most common symptom that was assessed. This was monitored across all the studies in the review (Bonilla et al., 2023b; Hurt et al., 2024; Isman et al., 2024; O'Kelly et al., 2022; Petracek et al., 2023; Tamariz et al., 2024) as well as in the two reviews (Dietz & Brondstater, 2024; Livieratos et al., 2024). Sleep disturbances were also commonly assessed. Different studies focused on different aspects of sleep. Bonilla et al. (2023b) looked at unrefreshing sleep and abnormal sleep patterns, Hurt et al. (2024) assessed insomnia, and O'Kelly et al. (2022) focused on the nonspecific term "sleep disturbances". Pain was investigated by Hurt et al. (2024), Isman et al. (2024), O'Kelly et al. (2022), and Tamariz et al. (2024). Interestingly, shortness of breath was only explicitly stated as being tracked in two cases (Hurt et al., 2024; O'Kelly et al., 2022).

Symptoms most improved by LDN

Several studies noted that LDN seemed more effective for some symptoms than others. Bonilla et al. (2023b), O'Kelly et al. (2022), and Tamariz et al. (2024) reported that LDN was most effective for pain. Both Bonilla et al. (2023b) and O'Kelly et al. (2022) assessed pain using

the same scale, the Visual Analog Scale (VAS). However, Tamariz et al. (2024) do not specify how pain was assessed. Many studies also found fatigue to be one of the symptoms most improved by LDN; these included Bonilla et al. (2023b), Tamariz et al. (2024), Isman et al. (2024), and Petracek et al. (2023). Interestingly, Isman et al. (2024) note that in their study of 36 participants aged 29–69 years, fatigue seemed to be more improved in females than males; however, they also note this may be due to the much lower number of males enrolled (11 vs 25 females) and so improvement in fatigue did not reach statistical significance amongst male participants.

Bonilla et al. (2023b) also noted an overall lower number of symptoms after LDN and an overall improvement in the general functionality of participants, which was echoed by Petracek et al. (2023). Overall, fatigue was the symptom that LDN seemed to help most among the LC symptomatology profile. In addition, several studies (Bonilla et al., 2023b; Hurt et al., 2024; Petracek et al., 2023) noted different phenotypes within their studies, including ME/CFS–like, POTS–like, and fibromyalgia-like symptom clusters.

Theme Two: Variation in Delivery Methods (Schedule, Dose, and Duration)

Another area of variation was how LDN was administered, in terms of dosing, duration, and different titration schedules. The range of LDN doses in this review reflects the general lack of standardization. This will be discussed in further detail below.

Dose Range

Bonilla et al. (2023b) and Tamariz et al. (2024) used an individualized dosing schedule and did not find a correlation between dose and response. Isman et al. (2024) and Petracek et al. (2023) used the standard 4.5 mg/day dose. In the cross–sectional survey by Hurt et al. (2024), the doses are not specified, but they do refer to the dosing of naltrexone as being *low.*

Time of Day

Isman et al. (2024) were the only authors to specify the time of day the LDN was administered. They instructed participants to take LDN at bedtime, which aligns with Dr. Bihari's suggestions (as interviewed in Alternative Therapies in Health and Medicine, 2013), who found nighttime dosing was the best for boosting endorphin production. Unfortunately, other authors did not address the time of day LDN was taken.

Titration

Three studies (Bonilla et al., 2023b; Isman et al., 2024; Tamariz et al., 2024) used a gradual titration schedule. Isman et al. (2024) up-titrated rapidly to achieve a therapeutic dose quickly. In contrast, O'Kelly et al. (2022) did one month of LDN therapy at 1 mg, followed by one month of LDN at 2 mg. Hurt et al. (2024) do not mention if the LDN was titrated, as their survey was focused on identifying potential therapeutic candidates for LC for future trials, rather than determining optimal dosing strategies.

Duration

In terms of duration of therapy, given the study designs (retrospective or surveys), there is a wide range of duration of LDN therapy. For example, in their retrospective review, Bonilla et al. (2023b) found the duration of LDN use was 77–255 days. The study by Isman et al. (2024) lasted for 12 weeks. O'Kelly et al. (2022) administered 2 months of LDN. The patient in the case study by Petracek et al. (2023) had been on LDN for 16 months at the time of publishing. The participants in the study by Tamariz et al. (2024) were on LDN for at least 4 weeks, some longer, but the exact amount of time is not specified.

To summarize, the range of LDN doses (0.5–6 mg/day) was generally in keeping with that used in other conditions. The duration of therapy ranged from 77 days to 16 months. Appropriate titration was used in some, but not all, studies.

Theme three: Adverse effects

A third key theme that emerged across the studies was the absence of severe adverse effects. The interventional pre–post study by O'Kelly et al. (2022) was, in part, designed to assess the safety of LDN in a PCC cohort. They found no side effects in 94.7% of participants, which is in keeping with the known safety profile of naltrexone. The side effects mentioned in their study were mild, with one participant reporting diarrhea and another fatigue. Three studies (Bonilla, Tian, et al., 2023; Hurt et al., 2024; Tamariz et al., 2024) do not mention any adverse effects. It is unclear whether this reflects an absence of adverse effects or a lack of reporting. In keeping with previous LDN studies, Isman et al. (2024) found that side effects were "mild" and more common at the beginning of treatment and could generally be managed by decreasing drug dosage. Four of 36 participants withdrew from this study due to adverse effects, three of whom left in the first few weeks. Isman et al. (2024) note that, generally, LDN is up-titrated gradually to minimize adverse events. In contrast, in this study, they titrated rapidly to achieve a therapeutic dose sooner, which may have increased the rates or severity of side effects.

Theme four: Outcome Measures Tracked (scales and objective measures)

Various scales were used across these studies; only one incorporated objective data. Many scales were used in the studies in this review. For example, fatigue alone was assessed with several different scales. Bonilla et al. (2023b) and O'Kelly et al. (2022) used the Fatigue Severity Scale (FSS). Tamariz et al. (2024) used the FACIT–fatigue scale, and Petracek et al. (2023) used the Multidimensional Fatigue Inventory (MFI). Isman et al. (2024) use the SF–

36 symptom scale and a modified Chalder scale, which includes Likert scaling rather than the typical binary scale seen in the Chalder scale. Many studies (Bonilla, Tian, et al., 2023; Hurt et al., 2024; O'Kelly et al., 2022) used Likert scaling of individual symptoms to rate change in these symptoms. Bonilla et al. (2023b) also used a modified FSS scale for assessing fatigue.

Objective measures

Only Tamariz et al. (2024) included any biomarkers in their study. They looked at CRP and morning cortisol and found a non–statistically significant normalization in both these levels in participants who had taken LDN. Although they screened participants for a few biomarkers on intake, O'Kelly et al. (2022) did so only to rule out other conditions, rather than track therapy.

Theme Five: Laboratory Evidence

One of the articles (Sasso et al., 2024) took a mechanistic approach, exploring naltrexone's potential effects on LC in a laboratory setting. The authors aim to investigate two primary outcomes with their study: 1) whether the TRPM3 ion channels in LC patients were impaired similarly to ME/CFS patients, and 2) to investigate the effects of naltrexone on TRPM3 ion channel activity in LC patients. They confirmed impaired TRPM3 channel function in both ME/CFS and LC patients, and that TRPM3 currents were significantly restored in naltrexone-treated natural killer cells.

Study Design and Reporting Limitations

There were several limitations shared among the articles assessed in this review. Firstly, none of the included studies were high–quality RCTs. All the studies lacked randomization, blinding, and a control arm. In one study (Isman et al., 2024), participants received two interventions simultaneously (both NAD+ and LDN),

Furthermore, most studies did not provide the LDN for their patients. In all but one case (Isman et al., 2024), the participants were given scripts and retrieved the LDN from a pharmacy of their choice. In the Bonilla et al. (2023b) study, many participants did not complete the follow–up questionnaire. Only 59/207 patients participated in the follow–up questionnaire, which is a very low number.

Another limitation is the number of studies that did not track or report adverse events. Three studies did not make any mention of adverse events at all (Bonilla et al., 2023b; Hurt et al., 2024; Tamariz et al., 2024), and it is impossible to say if this is because there were none or simply that they were not tracked. Despite the limitations, the studies share some interesting themes that could help guide future investigations.

Discussion

Interpretation of key findings

In this review on LDN for LC, several studies identified fatigue as the symptom for which LDN appears to be most effective. Other symptoms that positively impacted included pain and a variety of sleep disturbances. As a result, in future studies and clinical practice, the use of LDN for LC should focus on the ME/CFS phenotype. This hypothesis is supported by the lab study conducted by Sasso et al. (2024), who identified that the CFS phenotype of LC involved Transient Receptor Potential Melastatin 3 (TRPM3) ion channel dysfunction affecting natural killer (NK) cells which is known to also impact NK cells in ME/CFS (Löhn & Wirth, 2024). Sasso et al. confirmed the presence of impaired TRPM3 ion channel function in NK cells from people with LC. They also demonstrated *in vitro* that faulty TRPM3 currents were significantly restored in naltrexone–treated NK cells from LC patients. This may explain why the evidence in this review indicates it is most effective in improving the ME/CFS phenotype. This finding also

fits with the limited evidence on the efficacy of LDN in various conditions involving fatigue, such as ME/CFS(Cabanas et al., 2021) or fibromyalgia(Yang et al., 2023).

In clinical practice, distinct phenotypes have not yet been defined or added to the ICD, which complicates clinical categorization. In the meantime, initial evidence suggests that LDN is most useful for fatigue, pain, and sleep disturbances, so clinicians could discuss the potential use of LDN with patients who present with these as primary symptoms. Despite the lack of high–quality RCTs, given the promising initial evidence in conjunction with LDN's well–established safety profile, some patients may consider it worthwhile to trial LDN. In this case, clinicians should support this choice. This is in keeping with the recommendations made by CAN–PCC (2025), who state in their guideline on LDN:

> "In light of very limited direct evidence for the potential benefits or harms of low–dose naltrexone among people with post COVID-19 condition, some people with post COVID-19 condition may still decide to trial low–dose naltrexone if they place a relatively higher value on some desirable outcomes and a relatively lower value on the undesirable outcomes (such as adverse effects), especially if they live in a jurisdiction where low–dose naltrexone treatment is feasible."

The CAN–PCC intends to revisit its guidelines on LDN in 2026 or sooner if more evidence becomes available.

Measurement challenges and recommendations

The diverse range of self–reported outcome measures, which use different scales, makes it hard to compare results between studies. Additionally, the studies that use an unvalidated scale risk casting their findings into question. Many studies used Likert scaling to rate symptoms, which, although considered a standard approach, is not without issue as discussed above. One

study used an FSS, which aligns with recommendations on studying fatigue in LC. (Thomas et al., 2024). The FSS scale was explicitly designed by Klok et al. (2020) to track functional status in LC over time and support research. Therefore, its use by Bonilla et al. (2023b) is methodologically justifiable.

Assessing fatigue is difficult, as there are many facets to what constitutes fatigue. Fatigue can impact all aspects of a person's life, so the best assessment instrument for an accurate picture of this would be a multidimensional tool. It has also been suggested that studies on LC fatigue should include an objective measure of fatigability as well as subjective assessments of fatigue (Campos et al., 2022). Due to the lack of objective serum measurements, an objective fatigability measure, such as a grip test, walking test, or a variety of cognitive tests, could increase the credibility of future studies.

The Potential Role of Objective Measures of LC

Another factor that could enhance the credibility of future studies on LC would be the use of objective lab values. As mentioned earlier, there are currently no standardized tests to diagnose or track LC. Therefore, these studies' lack of objective measures is unsurprising. In the meantime, using an objective measure of fatigability could add validity to studies conducted in this area.

Although standardized testing for lab markers has not been established, Yong et al. (2023) report that CRP, D–dimer, LDH, and leukocyte levels have been found to be elevated in people with LC compared to their counterparts who recovered completely from their COVID-19 infection. Much work remains to be done in this area. However, future studies that look at LC should consider adding these objective lab values to further support the results obtained in their subjective symptom analyses. Only one study in this review tracked any lab tests, and this

showed that the participants who took LDN had a non–significant reduction in CRP and an increase (normalization) in cortisol (Tamariz et al., 2024).

Also, in future studies, serum testing could be performed to identify who will likely be a responder or non–responder to LDN. A study in fibromyalgia found that the people who responded best to LDN were those whose baseline erythrocyte sedimentation rate was higher. (Younger et al., 2009). Ideally, in the future, objective measures such as this will be identified in people living with LC so treatments can be tailored to their specific phenotypes.

As these objective measurements are discovered, they need to be included in future research into LC. Though measuring subjective symptoms such as fatigue is important, looking at biomarkers can give a clear sense of whether a treatment is improving the underlying pathology and not simply the symptoms. If the end goal is to cure, objective measures must be identified and included in future studies.

Dosing and Duration Considerations for Future LDN Trials

Another factor that should be considered in future studies using LDN is the duration of therapy. Many patients report that the full effect of LDN may not be felt for up to several months (LDN Research Trust, 2023). This suggests that any studies evaluating the efficacy of LDN should ideally run for at least several months to assess its impact adequately.

The lack of adequate titration, coupled with the short duration of therapy in many of the reviewed studies, limits the ability to assess the efficacy of LDN. Based on preliminary evidence from its use in other conditions and anecdotal evidence from the LDN research trust (2024), LDN may require a gradual titration and a longer duration of treatment to ensure full therapeutic effect. Therefore, it is possible that some participants who may have responded to LDN under

ideal conditions did not experience its benefits within the timeframes and the titration schedules used. Future trials should consider these factors and incorporate them into the study design.

The dosages of LDN seen in this review (1–6 mg daily) were in line with what is generally used in other autoimmune or pain conditions. (Rupp et al., 2023; Vatvani et al., 2024). Most commonly, patients were prescribed the same dose for the duration of the study. As previously outlined, the LDN Research Trust (2024) recommends a slow titration schedule to minimize adverse events, starting at 0.5–1 mg daily and increasing every two weeks until reaching a target dose.

Although many of the reviewed studies used gradual titration, all of them did so in a faster manner than is recommended by the LDN trust. Future studies should take this into account when deciding how to dose. Like many drugs, if patients are started on an adequate dose from the beginning, side effects are more likely (Caffrey & Borrelli, 2020). To minimize these risks, LDN should be up–titrated gradually, in line with the recommendations of the LDN Research Trust.

Another consideration with LDN is the duration of treatment needed to see results. Although there is a dearth of high–quality evidence discussing the time frame in which the effects of LDN are optimally felt, there is an abundance of anecdotal information surrounding this topic. As a slow-titration process delays reaching the therapeutic dose and experiencing full effects, ideally, any future studies on LDN would consider this, and to get an accurate idea of efficacy, trial LDN for an extended period before reassessing. Aitcheson et al. (2023) recommend trialling LDN for at least 3 months before making any assumptions about its efficacy.

Despite the funding challenges associated with the study of generic drugs, a few ongoing trials are looking at LDN for LC. The NALCOVID-19 study in Australia will include 56 LC patients and be a double–blinded RCT (Marshall–Gradisnik, 2024–2025), currently in the recruitment phase. The University of British Columbia also has a study underway of 160 participants for LDN in LC (Nacul, 2024–2025). The duration of treatment will be 16 weeks, and the LDN dose will be 4.5 mg a day, which aligns with the recommendations regarding dosing and duration of LDN. The study also incorporates a gradual titration schedule, which includes an increase of 1 mg per week to a ceiling dose of 4.5 mg/day or the highest tolerated dose. In addition to self–reported ratings of fatigue and other symptoms, the researchers also plan to track several blood measures and objective measures of fatigability. This study will be a double–blind RCT, and its high–quality study design should provide more robust data regarding LDN and LC. This trial is expected to conclude in August 2025.

Clinical and Research Implications

One important consideration regarding the clinical use of the LC phenotype is its potential to facilitate applying for long–term disability (LTD). According to Littlejohn Barristers (n.d.), having a medical diagnosis can improve the likelihood of LTD approval. As discussed above, for some individuals with LC, particularly those whose symptoms persist for an extended period, returning to work might not be possible. In cases where a phenotype mimics a more established condition, such as ME/CFS or POTS, using this as the diagnosis may facilitate an LTD application more effectively than the more ambiguous diagnosis of LC. This clustering of patients into phenotypical categories was justified by Hurt et al. (2024), who state:

> For example, if LC patients meet the criteria for these complex chronic illnesses, we would diagnose them as LC–induced ME/CFS if we determine COVID-19 to be the inducing factor. … In addition to guiding treatment choices with some modicum of success, this approach has helped when LC patients file for medical disability (p.8)

Limitations of the Reviewed Studies

There were many limitations found in the articles looked at in this review. The most obvious is the study design, which introduced a strong possibility of a placebo effect. Many studies were single–arm, lacking a control group. (Bonilla et al., 2023b; Hurt et al., 2024; Isman et al., 2024; O'Kelly et al., 2022; Petracek et al., 2023; Tamariz et al., 2024). None of the studies used proper double–blinding, so in most cases, participants were aware they were taking LDN, which might have influenced self–reported outcome measures. Bonilla et al. (2023b) also noted that many participants did not complete the follow–up questionnaire, which may have skewed the results towards participants with positive experiences with LDN. Another factor contributing to the potential for a placebo effect was that, in many cases, they independently sourced their own LDN, raising concerns of variation in drug formulation (i.e., different fillers) and blinding. This also led to offloading the cost onto the trial participant. In one case (Isman et al., 2024) LDN was given along with NAD+, which made it impossible to say which effects, either positive or negative, were due to which intervention. The authors originally intended this to be an RCT but changed the study design to a single–arm study due to low enrolment levels.

Another possible sign of a placebo effect is that some authors (e.g., Bonilla et al., 2023b) observed no dose–response effect, which may suggest that improvements could have been partly due to a placebo effect. Despite these flaws in study design, the fact that all the studies report improvement in symptoms does suggest LDN may have therapeutic potential in the treatment of LC. However, these findings must be interpreted cautiously until more rigorous RCTs are completed.

Another potential issue is the possibility that participants may not have had LC, for example, in the study by Isman et al., (2024) the range of time from a positive COVID-19 test to

the initiation of therapy was 27–624 days, meaning that at least one study participant (the one with 27 days since the positive COVID-19 test) may not have met the diagnostic threshold for Long COVID. It may have instead been experiencing a longer course of acute COVID-19 infection.

In one case, the study was funded by a private anti–aging company called AgelessRx. This could introduce bias, as the company markets and sells LDN on their website (AgelessRx, n.d.)

Limitations in this review

There are a few potential limitations in this review. Firstly, due to the many names for LC, it is possible that not all relevant literature was identified and analysed due to inadequate search terms. This possibility was minimized by several MeSH terms (LC, PCC, PASC) and supplementing database searches using a Google Scholar search, which uses a search algorithm different from that of medical databases, to ensure all relevant literature was captured.

A second potential limitation is that the author herself is an advocate of LDN and uses it personally to manage health issues, so, despite all attempts to maintain neutrality, there is still a possibility of interpretive bias. Thirdly, by excluding non–English articles, it is possible that some relevant information was missed. Although only one non–English study was found in the search, it is still possible that this linguistic limitation could have led to a less comprehensive review.

Future Directions for Research

The information presented in this review suggests three key areas that should be prioritized for future research. Firstly, there is a critical need for standardized subcategories of LC, based on phenotypes, to be identified and codified. This would facilitate future research and assist with establishing standardized treatments for these phenotypes. Secondly, these

phenotypes should be added to the International Classification of Diseases (ICD) for the same reasons and for more accurate epidemiological tracking. Thirdly, increased funding is needed to support trials for generic drugs such as naltrexone. With limited profitability, pharmaceutical corporations are unlikely to conduct these trials, making public and non–profit funding sources essential to conducting these studies.

Conclusion

This integrative review examined the impact of LDN on LC. CINAHL, MEDLINE, and Google Scholar were searched, and a total of ten articles met the inclusion criteria and were analyzed to answer the research question, "How does low–dose naltrexone impact people living with Long COVID?"

During the analysis, several themes emerged that could be used to guide future research into this area. Key themes included the potential that LDN was effective for specific symptoms or phenotypes of LC (specifically fatigue, pain, and sleep disturbances), a general lack of significant adverse events, and inconsistency between dosage/duration recommendations and those seen in the studies. Until the results of ongoing RCTs are published, it is difficult to make definitive recommendations regarding the use of LDN for LC. However, given the encouraging preliminary findings, the lack of FDA–approved treatments for LC, and the well–known safety profile of naltrexone, it may be reasonable for the primary care provider to consider initiating a trial of LDN in LC patients whose primary complaint is fatigue or pain. Once the ongoing trials by Nacul et al. and Marshall–Gradisnik et al. are completed and published, a clearer picture of the impact of LDN on LC should emerge.

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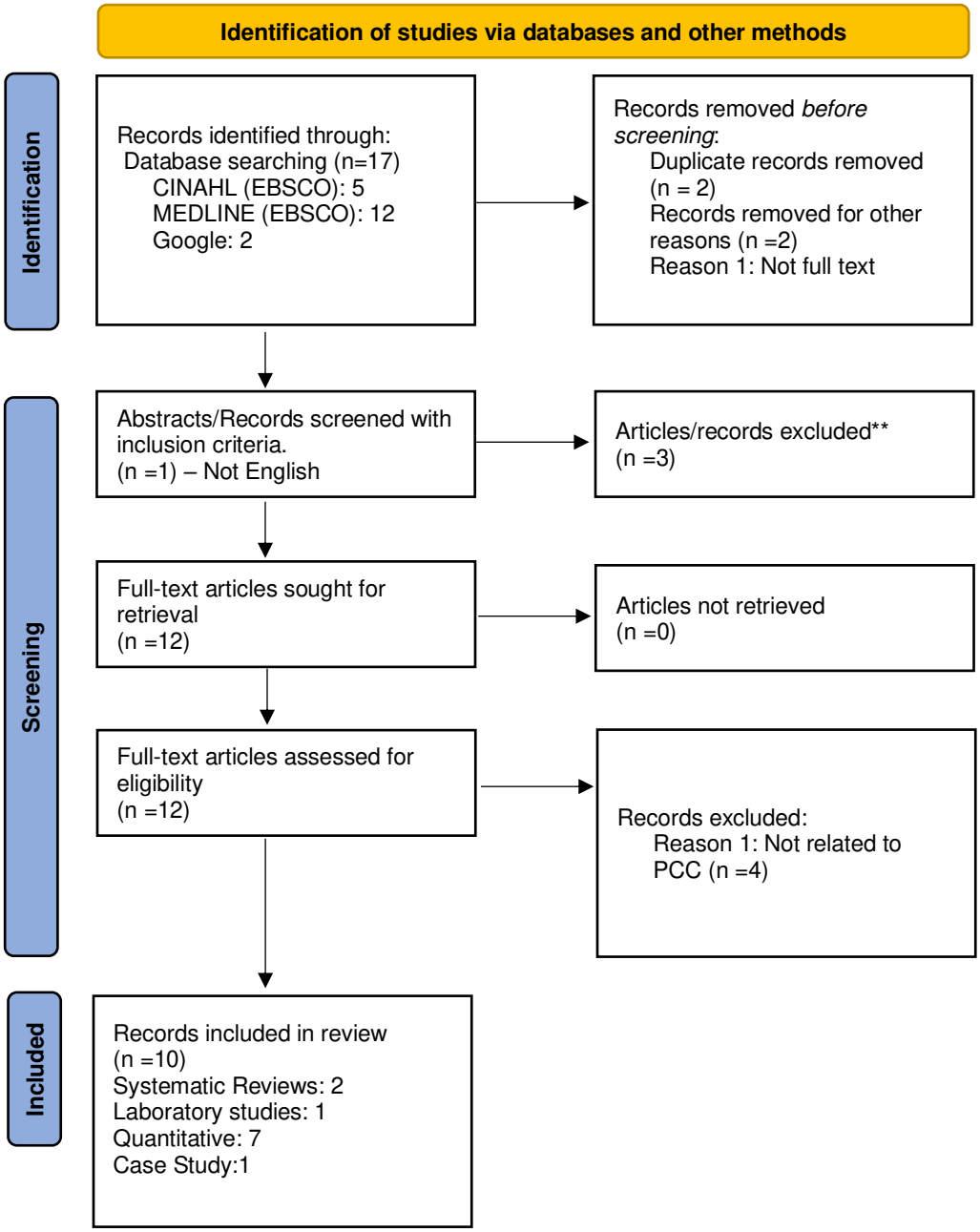
Appendix A: Prisma Flow Diagram



PRISMA 2020 flow diagram adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71

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For more information, visit: http://www.prisma–statement.org/

Appendix B: Data Extraction Matrix

Author etc.	Titration schedule	Dosage and time of day	Dose-dependent effects	Duration of therapy	Side effects	Symptoms tracked and most improved	Scales and biomarkers	Setting
Bonilla et al. (2023)	Individualized dose–titration ranging from 0.5 mg daily to 6.0 mg daily	0.5–6 mg daily	Effects are not dose-dependent	77–255 days	Not discussed	29 symptoms tracked. Fatigue, post-exertional malaise, sleep issues most improved	Likert scale, Post COVID-19 Functional Status Scale	Stanford PASC clinic
Dietz & Brondstater (2024)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Fatigue, chest pain, palpitations, brain fog, sleep disturbances	Not mentioned	Based on Isman, Bonilla, and O'Kelly
Hurt et al. (2024)	Not mentioned	Not mentioned	Not specified	None mentioned	None	Fatigue, brain fog, shortness of breath, muscle pain,	Likert scaling of symptoms	Long COVID clinic

						headache, etc.		
Isman et al. (2024)	Slow titration over 9 days	4.5 mg at bedtime (some up to 6 mg/day)	Not directly assessed	12 weeks	Nausea, fatigue, dizziness, low mood	Persistent fatigue	SF-36 and modified Chalder scale	Ageless Rx clinic
Livieratos et al. (2024)	Reported from other studies	0.5–6 mg/day	Not original data	Not original data	Not original data	Alternative therapies for LC discussed	Not original data	Literature review
Naik et al. (2024)	Week 1–4 titration up to 4.5 mg/day	4.5 mg/day or max tolerated dose	Planned gradual titration	16 weeks (12 weeks at full dose)	Monitored	Primarily fatigue and biomarkers	Fatigue Severity Scale (FSS)	BC-wide, centered on BC Women and Children's Hospital
O'Kelly et al. (2022)	1 mg for 1 month, 2 mg for 1 month	1–2 mg/day	Not discussed	2 months	2/38 withdrew due to side effects	Wide symptom tracking including fatigue, brain fog, sleep issues	Likert scale for symptoms	Mater Misericordiae University Hospital, Dublin
Petracek et al. (2023)	Not specified	4.5 mg	Not discussed	16+ months	None reported	Helped ME/CFS and fibromyalgia symptoms	Patient opinion	Single case study

Sasso et al. (2024).	Not applicable (lab study)	Not applicable	Not applicable	Not applicable	Not applicable	TRPM3 ion channel function studied	Lab outcomes	Lab study
Tamariz et al. (2024)	Not specified	1.5–4.5 mg/day	Not discussed	Minimum 1 month	Not tracked	Fatigue, pain, brain fog, dyspnea	CRP and cortisol biomarkers	VA Medical Center, Miami