

Supplementary table S1. Search strategy.

Database	Keywords used	Results by reviewer one (Nov 2024 to Dec 2024)	Results by reviewer two (Dec 2024 to Jan 2025)
MEDLINE	((COVID) OR (COVID-19)) OR (SARS-COV-2)) AND (Naltrexone)	60 studies	60 studies
Embase	COVID or COVID-19 or SARS-COV-2 and Naltrexone	183 studies	192 studies
Scopus	COVID-19 or COVID or SARS-CoV-2 and Naltrexone	60 studies	173 studies
CINAHL	COVID-19 or COVID or SARS-CoV-2 and Naltrexone	33 studies	38 studies
Web of Science (Clavirate)	COVID or COVID-19 or SARS-COV-2 and NALTREXONE	63 studies	63 studies
Cochrane Register of Controlled Trials	COVID or COVID-19 or SARS-COV-2 and Naltrexone	66 studies	103 studies

Supplementary table S2. Grading of Recommendations Assessment, Development and Evaluation (GRADE) of selected studies

Study	Grading of Recommendations Assessment, Development and Evaluation					
	Imprecision	Inconsistency	Indirectness	Risk of bias	Publication bias	Quality of evidence ratings by reviewers
O' Kelly et al 2022 [10]	No concerns, p-values stated for questionnaires and incidence of symptoms	Not applicable as a single study	No concerns – research aims align with results	Minor concerns – lack of placebo group Minimal selection bias - patients were recruited from the “COVID clinic” – a follow-up clinic where patients were previously hospitalized, diagnosed in the emergency department or referrals from general practitioners in the community, rather than patient self-referrals. Confounding factors not controlled for include presence of other medications and medical conditions exacerbating symptoms associated with long COVID.	No concerns	Moderate
Bonilla et al 2023 [11]	No concerns, p-values stated for questionnaires and incidence of symptoms	Not applicable as a single study	No concerns – research aims align with results	Some concerns – high dropout rates may cause participation bias Unable to comment on influence of selection bias - retrospective review of electronic health records from patients of the Stanford post-acute sequelae of COVID-19 (PASC) clinic. This cohort was “referred” to the PASC clinic, however details ascertaining referral process (i.e. self-	No concerns	Moderate

referrals vs clinician-driven referrals) are not provided.

Confounding factors – 43% of patients fit criteria for myalgic encephalomyelitis/chronic fatigue syndrome (overlapping symptoms with long COVID). Majority were also female and obese, making data less generalisable.

Tamariz et al 2024 [15]	Some concerns in relation to LDN and symptom improvement – large hazard ratio	Not applicable as a single study	No concerns – research aims align with results	Major concerns – follow-up dates not provided and use of clinician-driven tools rather than validated tools resulting in potential interviewer bias Unable to comment on influence of selection bias – patients were referred by primary care providers or screened via national Miami Veterans Affairs Healthcare System’s (VAHS) digital prescreening pilot. Details of VAHS prescreening was not provided. Confounding factors – selection of veterans, and concurrent exposure to physical activity (physical therapy group) with low-dose naltrexone.	No concerns	Low
Isman et al 2024 [17]	No concerns, p- values stated for questionnaires and incidence of symptoms	Not applicable as a single study	No concerns regarding research aim and results, however major concerns as	Major concerns – lack of placebo arm and unable to interpret sole effects of LDN due to significant confounding factor; co-existing use of NAD ⁺ patches	No concerns	Very low

concurrent
use of LDN
and NAD⁺
patches
hinders
analysis of
sole effects
of LDN

Major concerns of
selection bias –
participants were patients
with self-reported high-
severity long COVID
symptoms. They were also
actively seeking out
treatment. No secondary
referral system (i.e. from a
primary care practitioner)
was in place.
