LONG COVID TREATMENT PRIORITY SETTING WORKSHOP GUIDE

Australian Government
National Health and Medical Research Council

Medical Research Future Fund

Medical Research Future Fund – Emerging Priorities and Consumer Driven Research Initiative

2023 Post-Acute Sequelae of COVID-19 Grant Stream 4 aim is to establish a multidisciplinary national adaptive platform trial that accelerates assessment and implementation of therapeutic interventions (pharmacological and non-pharmacological) for PASC.

Contents

Guide to the long COVID Priority Setting Workshop 3

What is this workshop for? 3

What time is the workshop and where is it? 3

Who will be there? 3

What will happen? 4

What do I have to do? 4

Do I need to do anything to prepare? 4

How were the evidence summaries prepared? 4

Summary Format 5

What will happen to the top treatments once agreed? 5

Publication notice 5

Overview of evidence for the top 14 treatments 6

Low Dose Naltrexone for long COVID – low level evidence 7

Antivirals for long COVID – moderate level evidence 10

Antihistamines for long COVID – very low level evidence 15

Nicotine/Nicotine patches for long COVID – very low level evidence 17

Metformin for long COVID - no current evidence 20

Vagus Nerve Stimulation for long COVID – low level evidence 22

Guanfacine for long COVID – very low level evidence 24

Colchicine for long COVID - no current evidence 26

Monoclonal antibodies for long COVID– low level evidence 29

Nattokinase for long COVID - no current or upcoming evidence 33

Intravenous immunoglobulins (IVIg) for long COVID – very low level evidence 35

Coenzyme Q10 for long COVID – moderate level evidence 38

Multi-component intervention package for long COVID – high level evidence 43

Exercise training for long COVID - high level of evidence 48

Guide to the long COVID Priority Setting Workshop

What is this workshop for?

The aim of the workshop is to select the most promising treatments for long COVID that should be included in a planned clinical trial.

You will be working with a list of possible treatments compiled from an initial literature review and from a survey we carried out - with people who have long COVID and clinicians who treatment patients long COVID. The workshop is not about answering whether these treatments are effective. Researchers will do that later. The workshop is about deciding what the most important treatments to test in a clinical trial.

Workshop objectives:

1. To give an overview of the priority setting process and work done so far.
2. To reflect on and discuss participants' ranking views of the shortlisted treatments.
3. In small and larger groups to order the short list by priority, noting areas of agreement and disagreement across groups.
4. To agree together the 3-5 most important treatments to be assessed in the clinical trials.

What time is the workshop and where is it?

The workshops will be held online on:

Workshop 1:	9:00-11:00 am Tuesday 11 Feb 2025 **(Brisbane AEST)**
Location:	Online via Zoom (**please join the Zoom room 15 min early**)
Meeting URL:	https://bond.zoom.us/j/99687651399
Meeting ID:	99687651399

Workshop 2:	1:00-3:00 pm Wednesday 12 Feb 2025 (**Brisbane AEST**)
Location:	Online via Zoom (**please join the Zoom room 15 min early**)
Meeting URL:	https://bond.zoom.us/j/96362835986
Meeting ID:	96362835986

Zoom invitation with the link and exact times for your state were sent by email.

Who will be there?

There will be about 25 people at the workshop who will be:

1. People with long COVID or carers of people with long COVID
2. People involved in providing clinical services for patients with long COVID.
3. People involved in research on treatments for long covid who will help support the process

Three facilitators will run the meeting. Their job is to make sure that everyone is included equally, listened to and can have their say. There will be a few people there who will watch the meeting to take notes but won't be taking part in the discussions or ranking.

Short biographies and photos of all the participants are provided at the end of this booklet.

What will happen?

There will be an introduction at the start of the first workshop to explain how it will run and to answer any questions you might have. You will then work in small groups of 6 people to discuss 14 possible treatments. With help from one of the facilitators, you will decide together the order of importance of the treatments. In the second workshop, you will all look at the rankings as one large group and then discuss and agree the order of the top 3-5.

To allow participants some rest and reflection time, there will be short breaks in sessions. The treatments that will be discussed will be shown on screen and will be scored according to participants choices. A researcher will be calculating the scores and creating final ranking list for your group. The facilitators will help you and are there to answer any questions you have.

What do I have to do?

We want you to talk about your opinions and experiences. Everyone at the workshop will have different experience, views and ideas, and they are all valid and important. Everyone will be encouraged to share their views, but also to listen to each other. We want to know your personal views and experiences on which treatments could really make a difference to patients with long COVID if research evaluated them. The workshop facilitators are there to support you and will make sure you have a chance to have your say.

Do I need to do anything to prepare?

There are a few things you can do to prepare for the workshops:

1. **Watch a 12-min video** to get an understanding of the grant, the work we have done so far, and what we aim to achieve in this workshop: **https://youtu.be/CrEYf_WRXQE** This video is not publicly available. You can only view it via the link.
2. **Familiarise yourself with the list of treatments** we will be discussing at the workshop. These have been shortlisted by a ranking process that took place between August 2024 to January 2025 with people who have long COVID or treat patients with long COVID. Please **read the general evidence summary** beforehand and decide which treatments you think are most important to research, and which treatments are less important, in your opinion. Please bring that list to the workshop with you.
3. **Read the short biographies** of all participants including the facilitators to help you acquaint yourself with everyone who will be attending the workshops.

How were the evidence summaries prepared?

In the next section of this booklet, you'll find a few page summaries of the currently available evidence for each of the 14 treatments we are evaluating.

Since June 2024, we have been monitoring monthly updates on research related to long COVID treatments. Our process involved systematically prioritizing the highest-quality evidence available:

- **Systematic reviews** were reviewed first, as they provide the most reliable evidence.
- If no systematic reviews were available, we looked for **randomized controlled trials (RCTs)**.

In cases where neither reviews nor RCTs were available, we considered lower-quality evidence such as:

- Studies with single groups of patients.
- Studies using historical data.
- Case reports involving only a few patients.

Additionally, we searched large international registries of ongoing or planned trials to identify who else is testing these treatments globally. This allows us to track and incorporate future results as they become available.

Case definition

Our eligibility criteria for the included randomised controlled trials were based on the WHO definition where patients had a "continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection" and were designed to cover a wide range of evidence. However, it is important to note that these criteria may not be universally applicable or relevant for all patients across all levels of disease severity.

Summary Format

The first page of each summary is designed for general readership (boxed with grey background) and the information is presented in clear and accessible language. It includes:

- A brief background on the treatment: how the treatment generally works, how it might improve long COVID symptoms.
- Summary of key evidence finding
- Information on its accessibility and feasibility in Australia including cost considerations.
- Any safety concerns.

The subsequent pages (smaller fonts) are for those seeking a deeper understanding and provides more detailed evidence in slightly more technical language.

What will happen to the top treatments once agreed?

The most important treatments will be part of a grant proposal to the Medical Research Future Fund which will be submitted in April 2025. That will include initial treatments recommended for the trial, but also a "wish list" of treatments that might be added to the trial as it proceeds.

Publication notice

This workshop, conducted as part of the long COVID treatment prioritization process, will be documented and written up for publication. All participants will be acknowledged as part of a group authorship on the resulting publication.

Overview of evidence for the top 14 treatments

	Intervention	# SRs	# RCTs	# Other studies	# Clinical trials in progress	Level of Evidence	Effect on long COVID symptoms
1	**Low dose naltrexone**	1 new	0	4 non-randomised pre post study	3	Low	Probably small effect
2	**Antivirals**	0	1		8	Moderate	Probably no effect
3	**Antihistamines**	0	0	1 non-randomised	1	Very low	Unclear
4	**Nicotine**	0	0	1 case series	0	Very low	Unclear
5	**Metformin**	0	0	0	4	None	Unknown
6	**Vagus nerve stimulation**	0	1 pilot	1 non-randomised	1	Low	Probably small effect
7	**Guanfacine**	0	0	1 case series	0	Very low	Unclear
8	**Colchicine**	0	0	0	4	None	Unknown
9	**Monoclonal antibodies**	0	1 pilot	1 case series	3	Low	Probably no effect
10	**Nattokinase**	0	0	0	0	None	Unknown
11	**IVIG**	0	0	3 (1 case series, 2 retrospective case-control)	2	Very Low	Unclear
12	**Coenzyme Q10**	0	2	1	1	Moderate	Probably no effect
13	**Multicomponent intervention package**	0	5	0	Unclear	High	Probably small effects
14	**Person-centred sustainably increasing activity**	0	16	0	Unclear	High	Probably effective

SR – systematic review; RCT – randomised controlled trial

Low Dose Naltrexone for long COVID – low level evidence

Brief background

Naltrexone is a medication often used to treat opioid addiction. Low-dose naltrexone (LDN) is a much smaller amount of the drug- about 10% of the normal dose (around 4.5 mg per day instead of 50 to 100gm). At this low dose, LDN helps reduce inflammation by calming certain cells in the body which have a key role in overall inflammation and nerve pain. It also helps the brain make more natural painkillers. LDN may help with problems like pain, tiredness, stress, inflammation, and an overactive immune response. In addition to long COVID, it is being studied to help other conditions like fibromyalgia, Crohn's disease, and chronic fatigue syndrome (ME/CFS), among others.

Summary of key evidence

There are currently no published randomized controlled trials (RCTs) of LDN for long COVID nor existing systematic reviews. Therefore, this new review looked at all studies where LDN was tested, either alone or added to regular care for treating long COVID. This review found four small single arm studies that compared symptoms before and after treatment with LDN. These four studies found a small improvement in five important symptoms, but the overall evidence is low quality. Three more clinical trials are still ongoing.

Accessibility and Feasibility

Low dose naltrexone (LDN) can be prescribed by a general doctor or a specialist. It is not subsidised by the PBS. It can be compounded for about $35 for a 1-month supply.

Safety profile

LDN has a good safety profile with no blood pathology monitoring required and no drug-drug interactions except for opioids. Whilst becoming established on LDN a significant number of people experience unpleasant and sometimes debilitating side effects in particular headaches, muscle aches and pains and vivid dreams. Starting with a low dose and increasing it slowly can help reduce these side effects.

Detailed evidence profile

Key Study- 1 new systematic review:

Byambasuren, O, Atkins, T, Chakraborty, S, Baptista, S, Glasziou, P. ***Effect of low dose naltrexone for long COVID: a systematic review***. (unpublished)

Summary of methods

We searched PROSPERO and Open Science Framework (OSF) databases to rule out existence of similar reviews then searched PubMed, Embase (Elsevier) and Cochrane Library for published studies, ClinicalTrials.gov and World Health Organization – International Clinical Trials Registry Platform (ICTRP) for registered ongoing studies from inception to 12 Sep 2024. The risk of bias was assessed using an adapted Newcastle-Ottawa scale.

Summary of results

We can see from table 1 below that there were four non-randomised pre and post studies included within the review.

Table 1. Characteristics of included studies

Study ID Location	**Study type, timeframe**	**N**	**Intervention**
Bonilla 2023 USA	Retrospective before-after cohort, 18 May 2021 - 18 Mar 2023	59	individualised LDN dose-titration ranging from 0.5mg/d to 6mg/d (median 2mg/d for median of 143 days)
Isman 2024 USA	Before-after study, 31 Mar 2021 to 22 Dec 2022	36	4.5 mg/d LDN and 1 ml/wk NAD+ was applied using iontophoresis patches (400 mg/mL)
O'Kelly 2022 Ireland	Before-after study, Jun – Nov 2020	36	LDN 1mg/d in first month, 2mg/d in month two (max of 3mg/d)
Tamariz 2024 USA	Retrospective before-after cohort, 2021 to Jan 2023	24	LDN 1.5–4.5 mg/d

A summary of the pooled effect sizes (see figure 1 below) for each outcome demonstrates that the use of LDN is favoured versus those that did not use LDN for all outcomes (fatigue, pain, brain fog, quality of sleep, and daily functioning)

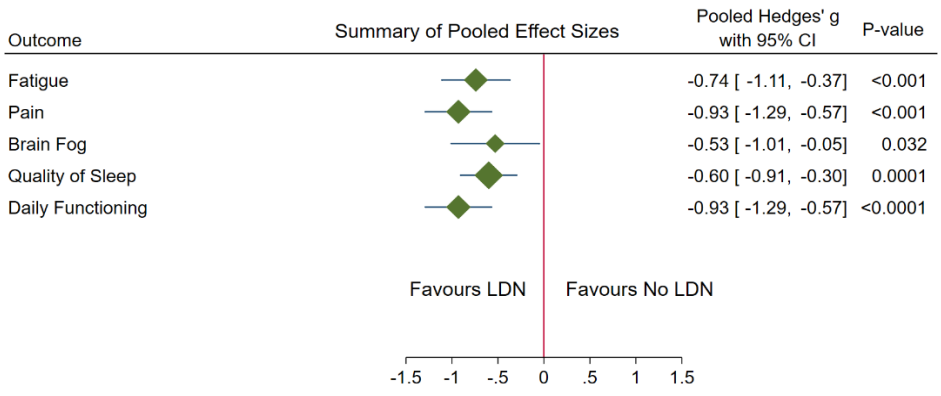

Figure 1. Summary of the pooled effect sizes (Hedges' g) across outcomes.

Risk of bias

All 4 studies were rated either a total of 4 or 5 maximum number of points which indicate a low risk of bias using an adapted Newcastle-Ottawa scale for non-randomized studies. However, these were not randomised studies, so there is inherent risk of confounding bias compared to RCTs, making them overall a lower quality level of evidence.

Conclusion

This small group of pre post studies suggests a possible small beneficial effect for low dose naltrexone on five important symptoms of post-acute syndromes of Covid but constitutes only low-quality evidence. However, this preliminary evidence is probably sufficient to justify a well powered randomised controlled trial. Three clinical trials are currently in progress (see table 2 below). One such trial of randomising 160 patients is underway and due for completion at the end of 2024 (NCT05430152).

Summary of registered and ongoing trials

Table 2. Summary of registered trials currently in progress (n=3)

Study ID (completion date)- Target size	Protocol reference	Intervention & dose	Treatment Duration	Follow-up	Comparator	Primary Outcome
NCT05430152 (original completion date; 2024-12) Status: **Updated to 2025-08-16** "Recruiting"- **N=160**	Naik H, Cooke E, Boulter T, et al. Low-dose naltrexone for post-COVID fatigue syndrome: a study protocol for a double-blind, randomised trial in British Columbia. *BMJ Open*. 2024;14(5):e085272. Published 2024 May 13. doi:10.1136/bmjopen-2024-085272	Low-Dose Naltrexone as a compounded capsule starting at 1 mg/day and increasing up to 4.5 mg/day (by week 4)	16 weeks	16 weeks	Placebo (to look exactly like LDN doses)	Change in Fatigue intensity by 4.7 points over using the Fatigue Severity Scale (FSS)
ACTRN12623001042639 (completion date; 2025-04-01) Status: "Recruiting"- **N=56**	Efficacy of Low Dose Naltrexone for the treatment of symptoms of Post COVID-19 Condition	Naltrexone Hydrochloride at low doses (low dose naltrexone [LDN], 3-6mg/day).	12 weeks	12 weeks	Placebo	DSQ Symptom Inventory Questionnaire (Determine detectable change in symptom presentation and severity)
ACTRN12624001162505 (completion date; 2029-10-14) Status: "Not yet recruiting"- **N=56**	Low Dose Naltrexone for the treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and long COVID Condition	Naltrexone -start at 1.5mg/day and will increase their dose by 1.5mg/day weekly until their maximum dose is reached (target 4-	12 weeks	12 weeks	Placebo	Change in the Transient receptor potential cation channel subfamily M member 3 (TRPM3) function

		6mg/day) for 12 weeks				

Antivirals for long COVID – moderate level evidence

Brief background

Several studies have identified evidence of persistent COVID proteins or genetic material out to 14 months following acute infection. Some studies have correlated symptoms of long COVID with evidence of persistent COVID, leading to the hypothesis that persistent COVID infection is what is driving long COVID.
Nirmatrelvir works by stopping the virus from multiplying, and it's even more effective when combined with a small dose of ritonavir. This combination is sold under the brand name Paxlovid. There is interest in determining if taking Paxlovid for a prolonged period may stop the COVID replication and result in an improvement of symptoms.

Summary of key evidence

The only published randomised controlled trial to test Paxlovid is from the USA and looked at 155 patients. Of these, 102 patients were given Paxlovid (300 mg of nirmatrelvir with 100 mg of ritonavir) twice a day for 15 days, and 53 patients got a placebo with only 100 mg ritonavir. At the end of 15 weeks, there was no difference in how much their symptoms improved.

Accessibility and Feasibility

In Australia, Paxlovid can only be prescribed by a doctor or nurse practitioner, and patients must meet certain requirements to get it through the Pharmaceutical Benefits Scheme (PBS). It is usually for people with mild to moderate COVID-19 (within 5 days of symptoms starting) who are at high risk of getting very sick. Paxlovid is not specifically mentioned for long COVID in the PBS guidelines.
The version used in studies (300 mg of nirmatrelvir) is not available in Australia. Only a lower-dose pack (150 mg of nirmatrelvir with 100 mg of ritonavir, taken twice a day for 5 days) is available, and it costs $1,115.31 if not subsidized.

Safety profile

Overall, it is considered safe, and most side effects are mild. However, Paxlovid can interact with many other medicines, which might cause serious side effects or even be life-

threatening. Because of this, it's very important your doctor knows about all the medications you're taking, including prescription drugs, over-the-counter medicines, vitamins, and herbal supplements. The most common side effect is a strange taste in the mouth, along with diarrhea. Paxlovid can also cause allergic reactions and liver problems. Other possible side effects include headaches, vomiting, stomach pain, nausea, high blood pressure, or just feeling unwell. Paxlovid isn't linked to any other serious side effects besides interactions with other medicines.

Detailed evidence profile

Key study – 1 RCT

Geng LN, Bonilla H, Hedlin H, et al. *Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial.* JAMA Intern Med. 2024

Summary of methods

Geng, 2024 was a 15-week double blinded, placebo-controlled, randomized clinical trial which was conducted from November 2022 to September 2023 at Stanford University in the USA. (table 1) Of the n=155 patients, nearly all (n=153) had received the primary series for COVID-19 vaccination.

Table 1. Summary of Geng, 2024

RCT design	N.	Participants	Intervention	Comparator	Follow-up
Parallel 2-arm	155 (102 intervention, 53 comparator)	aged 18+, wt> 40kg, eFGR>=60 ml/min, history of COVID-19 and at least 2 PASC symptoms for more than 90 days after initial COVID infection	300 mg nirmatrelvir plus 100 mg ritonavir twice daily **for 15 days**	Placebo plus 100mg ritonavir twice daily for 15 days	Up to 15 weeks

Summary of results (see table 2 also)

There was no statistically significant difference in the primary outcome which was the pooled severity of 6 core symptoms at 10 weeks (p=0.90). There were also no statistically significant differences in change from baseline to 10 weeks in the PROMIS individual scores of fatigue (p=0.79), dyspnea (p=0.70), cognitive function (p=0.98), physical function (p=0.66) measures, or other outcomes such as; patient global impression of severity (PGIS) score (p=0.40), patient global impression of change (PGIC) score (p=0.74), summative symptom score (p=0.69), or adverse events.

Risk of bias

Risk of bias was assessed with the Cochrane Collaboration's Risk of Bias tool 2. There were some concerns of bias arising from the randomization process which overall gives this RCT having some concerns of bias (figure 1 below).

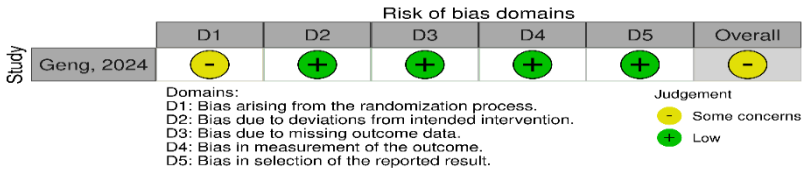

Figure 1. Risk of bias assessed by Cochrane's ROB-2 tool

Table 2. Summary of results from 1 RCT (Geng, 2024)

Outcomes	**Nirmatrelvir +** 100 mg ritonavir **N=102 (%)**	**Placebo**+100 mg ritonavir **N=53 (%)**	**Adjusted mean difference in change scores between groups**[A] (95% CI)	**P-value**	**Comments**
Pooled Core symptom severity during the past 7 days based on Likert scale score (where 0 is none, 1 mild, 2 mod, and 3 severe) 10 weeks post randomisation	Not reported N=99	Not reported N=49	Not reported	0.90	**No detectable difference**
PROMIS[C] Physical function	2.7 (6.6)	1.3 (5.8)	0.57 (-1.96 to 3.10)	0.66	**No detectable difference**
PROMIS[C] Fatigue	−3.9 (7.9)	−4.1 (5.9)	0.38 (-2.40 to 3.15)	0.79	**No detectable difference**
PROMIS[C] Dyspnea	−2.0 (7.9)	−2.4 (6.1)	0.60 (-2.55 to 3.75)	0.70	**No detectable difference**
PROMIS[C] Cognitive function	4.8 (8.2)	5.1 (7.6)	0.03 (-3.21 to 3.28)	0.98	**No detectable difference**
PGIC at 10 weeks	3.4 (1.3)	3.1 (1.0)	0.10 (-0.48 to 0.67)	0.74	**No detectable difference**
PGIS at 10 weeks	4 (1.0)	3.8 (1.1)	0.19 (-0.25 to 0.62)	0.40	**No detectable difference**
Summative symptom score at 10 weeks	7.6 (3.75)	7.7 (4.1)	-0.24 (-1.46 to 0.97)	0.69	**No detectable difference**

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity

[A] Adjusted mean differences from a linear regression (beta coefficients) for PGIC or PGIS can be interpreted as differences in PGIC and PGIS score values between groups, eg, an estimate of 0.3 means that, on average, those on NMV/r reported PGIC/PGIS 0.3 points higher than those on PBO/r. However, for PROMIS measures should be interpreted as differences (in NMV/r vs PBO/r) in change scores (baseline vs wk 10). A higher score value corresponds to reduced severity for PROMIS-physical and cognitive function; greater severity for PROMIS-fatigue and dyspnea; worsening status for PGIC; and greater severity for PGIS. Therefore, improvement from baseline to week 10 corresponds to positive change scores for PROMIS-physical and cognitive function, and negative scores for PROMIS-fatigue and dyspnea

[C] Change from baseline to 10 weeks

Conclusion

The results from the best evidence from only one RCT (Geng, 2024) indicate that antivirals such as nirmatrelvir did not indicate a statistically significant improvement in PASC symptoms. Further RCT studies using longer courses (up to 30 days) of the medication are required for consolidation. In addition, there are many (total n=8) ongoing clinical trials for the treatment of long COVID that consist of Amantadine, and Paxlovid (a combination of Nirmatrelvir and Ritonavir) among others (see table 3 below).

Summary of registered and ongoing trials

There are 8 ongoing trials of antivirals (Table 3), with most being of short- term treatment, except for two trials that use 10 week and 12 weeks of treatment (see last rows of Table).

Table 3. Summary of registered trials currently in progress **(n=8 trials**)

Study ID (completion date) **Target Size**	Drug	Dose	Treatment Duration	Follow-up	Comparator	Outcomes
Amantadine (n=2)						
NCT06055244 (completion date; 2025-05-15) **N=60**	Amantadine	100 mg 2 x per day	unknown	4 months	Placebo	Overall cognitive functioning (self-assessed and objective), anxiety, depression, side-effects
NCT06234462 (completion date; 2025-06-01)- **N=30**	Amantadine + standard of care	100 mg 2 x per day	4 weeks	At 6 weeks	Standard of care= PT, OT, SLP, provider counselling, and/or pharmacologic interventions	Cognitive functioning (R BANS), FAS, Trails A& B, Digit vigilance test (DVT), cognitive subscale of modified fatigue impact scale (MFIS), other secondary outcomes
Nirmatrelvir + Ritonavir (Paxlovid) (n=3)						
NCT05668091 (Completion date-2024-09-08) **N=100**	Nirmatrelvir + Ritonavir (Paxlovid)	Nirmatrelvir 2x150mg tablets 2 x per day + Ritonavir 1x 100mg capsule 2 x per day	15 days	28 days for primary outcome and up to 24 weeks for 2dary outcomes	Placebo + Ritonavir (100 mg twice per day)	Primary- Physical Health summary; depression, physical function, pain interference, fatigue, sleep disturbance, and satisfaction with participation in social roles) (PROMIS-29) Secondary- physical symptoms (Modified GSQ-30), Quality of life (EQ-5D-5L), chronic illness (FACIT), patient opinion of severity (PGIS), and change (PGIC)
NCT05823896 (Completion date; 2024-11-30) **N=219**	Paxlovid (nirmatrelvir + ritonavir)	Oral nirmatrelvir (300 mg + ritonavir (100 mg) 2 x per day	15 days	Up to 90 days	Placebo/ritonavir (100 mg tablet of ritonavir twice per day)	Quality of life (EQ-5D-5L VAS scale), other secondary outcomes such as; hemodynamic response over time (active standing test), Composite Autonomic symptom score (compass31), and other secondary outcomes
NCT05595369 (completion date; 2025-03) NCT05965726-appendix (Paxlovid sub-study) **N=964**	**2 treatment arms;** Paxlovid nirmatrelvir + ritonavir)	**Arm 1**; Paxlovid 25 days (nirmatrelvir 300mg, ritonavir 100mg) bid x 25 days **Arm 2**; Paxlovid 15 days (nirmatrelvir 300mg and ritonavir 100mg) bid x 15 days then ritonavir 100mg bid plus nirmatrelvir matching placebo x 10 days	25 days or 15 days	90 days	Placebo control (ritonavir 100 mg + nirmatrelvir matching placebo for 25 days)	Change in Cognitive function (PROMIS cognitive function-8a), change in autonomic dysfunction (OHQ-orthostatic hypotension questionnaire), Change in exercise intolerance symptoms (DSQ-PEM), Other secondary outcomes such as SAE's
Other (repurposed antivirals) (n=3)						
NCT06316843 (Completion date; 2024-10) **N=59**	**2 treatment arms**; different doses of (Valacyclovir + celcoxib)	**Arm 1**- 1500 mg valacyclovir + 200 mg celecoxib -2 x per day	10 weeks	12 weeks	Placebo (placebo capsules taken 2 times per day)	Fatigue assessed with PROMIS Fatigue 7a instrument

		Arm 2- 750 mg valacyclovir + 200 mg celecoxib-2 x per day				
NCT06161688 (Completion date; 2025-12-31) **N=40**	Ensitrelvir (S-217622)	Oral capsule- 375 mg on day 1, followed by 125 mg daily for 4 additional days	5 days	Baseline, 10 days and up to 60 days post initiation of study drug	Placebo	Primary outcome is change in patient reported outcomes such as physical function, anxiety, depression, fatigue, sleep disturbance, social, and pain (PROMIS-29) Secondary outcomes; patient reported change (PGIC), distance walked in 6 min (6MWT), Global health (VAS)
NCT06511063 (Completion date; 2026-01) **N=90**	**2 trt arms; arm 1** - Truvada (tenofovir disoproxil/emtricitabine **Arm2**- Selzentry	**Group 1** (300 mg tenofovir oral capsule 1 x day **Group 2** (300 mg Selzentry) Oral capsule 2 x per day	90 days	At day 180	Placebo pill (once per day, oral capsule for 90 days)	Health status that contains 5 dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (EuroQol 5-Dimension 5-Level (EQ-5D-5L) Individuals own rating of overall health 0 -worst to 100- best (Visual Analogue Scale-VAS)

Antihistamines for long COVID – very low level evidence

Brief background

Antihistamines are medicines usually used to treat allergies by blocking histamine, a substance in the body that causes allergic reactions. In long COVID, scientists are studying whether antihistamines can help because of the role of mast cells. Mast cells release histamine and other chemicals that might contribute to symptoms of long COVID. By blocking histamine, antihistamines could help reduce some of these symptoms. However, more research is needed to understand how well they work for long COVID.

Summary of key evidence

A non-randomised study tested the effects of a combination of two medications, fexofenadine (180 mg per day) and famotidine (40 mg per day), on long COVID symptoms. The study included 14 patients who took the treatment and 13 patients who did not. After 20 days, 29% of the patients who took the treatment had no long COVID symptoms left, and all the treated patients showed major improvements in symptoms like tiredness, brain fog, stomach issues, and faster heart rate compared to the patients who didn't take the treatment.

Accessibility and Feasibility

Antihistamines are easy to get in Australia without a prescription, and they are usually cheaper than other treatments for long COVID. However, the specific combination and doses used in the study (fexofenadine 180 mg per day and famotidine 40 mg per day) might need a prescription or guidance from a doctor.

Safety profile

Antihistamines are usually safe when used as directed. Common side effects include feeling sleepy, dry mouth, and dizziness. In the study, no major problems were reported from using antihistamines to treat long COVID.

Detailed evidence profile

Key study – 1 non-randomised study

Salvucci F, Codella R, Coppola A, Zacchei I, Grassi G, Anti ML, Nitisoara N, Luzi L, Gazzaruso C. ***Antihistamines improve cardiovascular manifestations and other symptoms of long-COVID attributed to mast cell activation. Front Cardiovasc Med.*** 2023 Jul 17;10:1202696. doi: 10.3389/fcvm.2023.1202696. PMID: 37529714; PMCID: PMC10388239.

Summary of methods

This non-randomised controlled trial included 14 patients (9 female, 5 male; average age 49.5 years) with long COVID symptoms attributed to mast cell activation in the treatment group. A control group of 13 untreated long COVID patients was also included for comparison. The treatment consisted of a combination of fexofenadine (180 mg/day) and famotidine (40 mg/day) for 20 days.

Summary of results

After 20 days of treatment:

- 29% of treated patients experienced complete resolution of long COVID symptoms
- All treated patients showed significant improvement in each of the evaluated symptoms (fatigue, brain fog, abdominal disorders, and increased heart rate)
- The improvement was significantly greater in the treated group compared to the control group
- No significant changes in symptoms were observed in the untreated control group

Conclusion

The small non-randomised study suggests that antihistamines may be effective in treating Long COVID symptoms, particularly those attributed to mast cell activation. However, the quality of evidence is very low due to the study design and small sample size. We believe that larger randomised controlled trials are needed to confirm these findings and establish the efficacy and safety of antihistamines for long COVID treatment. The ongoing STIMULATE-ICP trial (ISRCTN10665760), which includes a nested drug trial testing famotidine and loratadine (**target size 1555**), may provide more robust evidence when completed.

Nicotine/Nicotine patches for long COVID – very low level evidence

Brief background

Nicotine might help with long COVID symptoms because it interacts with certain parts of your body called nicotinic acetylcholine receptors (nAChRs). These receptors help control inflammation, manage energy, and keep the nervous system balanced. However, nicotine can be addictive and cause side effects, especially if too much is taken too quickly.

Summary of key evidence

There is no official proof that nicotine is safe or works for treating long COVID. There are no controlled trials or ongoing studies about it, and no reviews of research. One small study looked at four people who used nicotine patches to treat their long COVID symptoms. Three men and one woman saw improvement in their symptoms, and the benefits lasted for up to 6 months after using the patches (7.5 mg per day) for 7 days. However, the results from just four people are not enough to confirm that nicotine is an effective treatment for long COVID.

Accessibility and Feasibility

Nicotine replacement therapy (NRT) products like patches, gums, and lozenges can be bought at pharmacies without a prescription. Patches are easy to apply, discreet, and release a controlled amount of nicotine over a set period, usually 16–24 hours. They are fairly affordable, with prices ranging from $20–50 for a one- or two-week supply.

Safety profile

Nicotine is very addictive in smoking form but there is some evidence that it is not addictive in patch form. It can cause nausea, vomiting, and headaches at too high doses. New users might also feel dizzy, weak, or have stomach cramps. Taking too much nicotine too quickly can lead to vomiting. Serious side effects are rare.

Detailed evidence profile

Key study- 1 case series

Leitzke M. ***Is the post-COVID-19 syndrome a severe impairment of acetylcholine-orchestrated neuromodulation that responds to nicotine administration?*** Bioelectron Med. 2023 Jan 18;9(1):2. doi: 10.1186/s42234-023-00104-7. PMID: 36650574; PMCID: PMC9845100

Mechanism of action

There are several possible mechanisms of actions for the effectiveness of nicotine for long COVID. The COVID-19 spike glycoprotein (SGP) is thought to bind to not only angiotensin-converting enzyme 2 (ACE2) but also to Nicotinic Acetylcholine receptors (nAChRs) leading to long COVID symptoms.

1. Nicotine may improve the responsiveness of receptors called Nicotinic Acetylcholine receptors (nAChRs) that help neurotransmission and thus help to regulate inflammation, cognitive function, and the nervous system. Nicotinic acetylcholine receptors respond to both acetylcholine and nicotine. Nicotine has a 30-fold higher affinity to the receptor than acetylcholine thereby enhancing neurotransmission. Nicotine may counteract the viral SGP blockade of nACHRs and displace the virus from the binding also leading to an enhancement of neurotransmission.
2. COVID-19 is thought to bind to the receptor and enzyme, angiotensin-converting enzyme 2 (ACE2) using its spike protein which allows it to infect human cells. Nicotine may displace the COVID-19 virus from ACE2, which in turn alleviates the symptoms related to long COVID.

Summary of methods

A study by Leitzke, 2023 described the mechanism of action of nicotine and investigated 4 individual cases. Three males and 1 female who suffered from numerous symptoms of long COVID were instructed to use a nicotine patch of 7.5 mg/24 hours for up to 7 days. All patients were asked to register their symptoms from a scale of 0 to 5 daily starting at 4 days before applying patch. The patients had improved symptoms that remained after 6 months after using nicotine patches (usual dose-7.5 mg/24 h) for up to 7 days.

Summary of results

All four patients had improved symptoms that remained after 6 months after using nicotine patches (usual dose-7.5 mg/24 h) for up to 7 days. Please see table 1 below for details regarding each case.

Table 1. Outline of the 4 case studies from Leitzke, 2023

Age	Sex	Symptoms	Dose (mg of nicotine)	How long	Outcome
19	Male	Weakness, anosmia, and ageusia	7.5 mg/24 h	7 days	Improved symptoms. Symptom-free at 6 months
31	Female	Chronic fatigue, loss of smell and taste, reduced concentration, headache, exercise intolerance	7.5 mg/24 h	6 days	Improved symptoms remained at 6 months
41	Male	Chronic fatigue, dyspnea, anosmia, loss of taste, muscle weakness, difficulty sleeping, headaches	Took 2x recommended dose (15 mg/24 h)	10 hours	Patient suffered AE (intolerable vomiting + diarrhea) discontinued therapy after 10 hours but still had improved symptoms with no recurrence after 6 months.
52	Male	Chronic fatigue, breathlessness, difficulties with concentration and sleeping, mood swings, chest tightness	nicotine patch (7.5 mg/24 h). 2 patches at 7.5 mg/24 h starting on day 3	4 days	Most symptoms decreased and no longer present by day 7 onwards. At 3 months, patient confirmed that he did not have recurrence of any symptoms

Conclusion

The only evidence for the efficacy of nicotine for long COVID comes from only 4 individual cases which did show improved symptoms after using nicotine patches. The results from only four patients are not enough evidence to confirm the efficacy for long COVID. There is currently no other formal evidence to confirm nicotine's safety or efficacy for long COVID. Thus, a formal randomised controlled trial is required. However, no registered or ongoing trials were identified.

Metformin for long COVID - no current evidence

Brief background

Metformin is a medication that is commonly used to treat diabetes. It is also thought to reduce inflammation, which can help lessen the severity of symptoms and complications in people with acute COVID-19. It is also thought that metformin acts as an antiviral by stopping the SARS-Cov-2 virus from multiplying. Metformin may help prevent long COVID if given early to people with COVID-19, but its role in treating people who already have long COVID is still unclear.

Summary of key evidence

Some studies suggest that metformin might help prevent long COVID if taken during the early stages of a COVID-19 infection. However, no major studies have looked at using metformin to treat people who already have long COVID. There are currently four registered trials in progress that are specifically studying the use of metformin for treating long COVID. At present, the efficacy of metformin to treat patients with long COVID is unknown.

Accessibility and Feasibility

Metformin can be prescribed by a doctor for people with diabetes and other indications. The cost is about $20 for a pack of 120, 500 mg modified-release tablets.

Safety profile

Metformin is commonly used to treat diabetes and is generally safe. Most people don’t have side effects, but some might experience diarrhea, nausea, or stomach pain. For people who don’t have diabetes, metformin can cause low blood sugar. It's also not safe to drink alcohol while using metformin. People with liver or kidney disease should use it carefully. It is likely safe to use during pregnancy and breastfeeding, but there aren’t many studies on this.

Detailed evidence profile

Key study - None

Conclusion

There is currently no published study for the use of metformin to treat long COVID. There have only been studies that showed promise in preventing long COVID when given to acute COVID-19 patients. However, there are four clinical trials that are currently in progress looking specifically as a treatment in long COVID patients (see table below). At present, the efficacy of metformin to treat patients with long COVID is unknown.

Summary of registered and ongoing trials

Study ID (completion date), status, **Target size**	Title	Intervention & dose	Treatment Duration	Follow -up	Comparator	Primary Outcome
NCT06147050 (completion date; 2024-12) Status: "Not yet recruiting" **N=16**	Effect of Metformin in reducing fatigue in long COVID in Adolescents (REVIVE)	Metformin- 500 mg dose of extended-release formulation twice daily for a period of 30 days	30 days	90 days	Placebo twice daily	Mean pediatric Quality of life Multidimensional Fatigue Scale (PedsQL-MFS)
NCT06128967 (Completion; 2025-05-18) "Recruiting" **N=1500**	A Multicentre, Adaptive, Randomized, double-blinded, Placebo-controlled study in participants with Long COVID-19: The REVIVE Trial (REVIVE)	Metformin extended-release oral tablet-750 mg	unknown	60 days	Placebo/ Fluvoxamine Maleate-100 MG	Improvement on Fatigue Severity Score Scale (FSS 60 days after randomization.
KCT0009342 (Completion; unknown) Status; "Recruiting" **N=396**	Exploratory double-blind randomized placebo-controlled trial of Metformin and Ursodeoxycholic acid (UDCA) to treat post-acute sequelae of SARS-CoV-2 infection (PASC)	Metformin-500 mg	8 weeks	Up to 6 months	Placebo- 500 mg or Test medication 2- "300mg Urusa ("urusodeoxy cholic acid") or Placebo 300 mg	Change in PASC score symptoms
CTIS2024-511580-28-00 (Completion; 01/10/2026 Status; "Not Recruiting" N="unknown"	RECLAIM: an adaptive platform trial for the evaluation of treatments for post-acute sequelae of SARS-CoV-2 infection (PASC)	Metformin-oral 1500 mg (max dose per day) *part of platform trial with Colchicine	12 weeks	12 weeks	placebo	Patient-reported physical-health related quality of life (HRQoL)

Vagus Nerve Stimulation for long COVID – low level evidence

Brief background

Vagus nerve stimulation (VNS) is a way to send signals to the vagus nerve to help control how the body works. For people with long COVID, scientists are studying VNS because it might help reduce inflammation and balance the nervous system. This could improve some of the symptoms caused by long COVID.

Summary of key evidence

A small pilot randomised trial tested if using a special device at home to stimulate the vagus nerve could help with long COVID symptoms. The study had 13 people with long COVID. Some used the real device (8 people), and others used a fake one that didn't actually work (5 people). They used it for 15 minutes twice a day for two weeks. The people who used the real device felt less tired and showed better mood and thinking skills compared to those who used the fake one. However, the quality of evidence is low due to the small sample size. Large randomized controlled trials are needed to confirm these findings and establish the efficacy and safety of taVNS for long COVID treatment.

Accessibility and Feasibility

The study used a vagus nerve device that people could buy and use at home after learning how to use it properly. This means the treatment could be easy to access and simple for people to do on their own.

Safety profile

The study found that the taVNS treatment was safe and didn't cause any serious problems. Some people felt mild pain or discomfort where the device touched their skin, but this went away after adjusting the device.

Detailed evidence profile

Key study – 1 RCT

Badran B, Huffman S, Dancy M, Austelle C, Bikson M, Kautz S, et al. *A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms*. Bioelectronic medicine. 2022;8:13.

Summary of methods

This pilot randomized controlled trial included 13 participants with long COVID symptoms. Participants were randomized to receive either active taVNS (n=8) or sham stimulation (n=5) for 15 minutes twice daily over two weeks. Symptoms were assessed using standardized questionnaires before and after the treatment period

Summary of results

After 2 weeks of taVNS treatment the active taVNS group showed significant improvements in fatigue, mood, and cognitive symptoms compared to the sham group. Active taVNS participants reported an average of 62% global improvement in long COVID symptoms.

Conclusion

This pilot RCT provides preliminary evidence that taVNS may be effective in treating various long COVID symptoms. However, the quality of evidence is low due to the small sample size. Larger, randomized controlled trials are needed to confirm these findings and establish the efficacy and safety of taVNS for long COVID treatment. There is a randomised controlled trial (NCT 05630040) with an enrolment size of n=40, that was completed in Nov 2024 that may add to the evidence base.

Additional information (non RCTs)

Zheng ZS, Simonian N, Wang J, Rosario ER. *Transcutaneous vagus nerve stimulation improves long COVID symptoms in a female cohort: a pilot study*. Front Neurol. 2024 May 2;15:1393371. doi: 10.3389/fneur.2024.1393371. PMID: 38756213; PMCID: PMC11097097.

Guanfacine for long COVID – very low level evidence

Brief background

Guanfacine is a medication that has been used to treat high blood pressure and ADHD. It works by targeting specific receptors in the brain and can help improve focus and attention. Researchers are exploring its use for long COVID because it may help improve brain function and reduce inflammation in the brain.

Summary of key evidence

There is no direct evidence showing that guanfacine is effective for treating long COVID symptoms. However, a case report looked at 12 people with "brain fog" who had trouble with memory, focus, and decision-making. Eight of them showed improvement in these areas after taking guanfacine (1 mg daily for the first month, increased to 2 mg if tolerated) along with 600 mg of N-acetylcysteine (NAC) daily. Four people stopped the treatment—two for unknown reasons and two due to low blood pressure or dizziness, which are common side effects of guanfacine.

Accessibility and Feasibility

In Australia, guanfacine is only subsidised for children aged 6–17 years to treat ADHD as a second line therapy. It is a schedule 4 medication which means it can be prescribed off label (i.e. for other reasons) without the PBS subsidy. A private script is about $60 for a month supply.

Safety profile

The study showed that four patients stopped treatment. Low blood pressure (hypotension) was noted as a possible side effect. However, guanfacine is an FDA-approved medication that is already used to treat high blood pressure and ADHD.

Detailed evidence profile

Key study – 1 case report

Arman Fesharaki-Zadeh, Naomi Lowe, Amy F.T. Arnsten, ***Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in "Long-COVID19***", Neuroimmunology Reports, Volume 3, 2023, 100154

Summary of methods

This case report described clinical experiences with using Guanfacine + on 12 patients (11 women, 1 man; ages 21-73 years).

Summary of results

Those who continued with treatment reported improvements in working memory, concentration, and executive functions.

Conclusion

This case report presents a hypothesis and rationale for using guanfacine in the treatment of cognitive deficits associated with long COVID. The article is primarily a review and theoretical discussion, drawing on existing knowledge of neurobiology, the effects of COVID-19 on the brain, and the known mechanisms of action of guanfacine. **We emphasise the need for rigorous clinical trials to test the efficacy of Guanfacine in treating long COVID symptoms.** There are currently no clinical trials testing the effectiveness of Guanfacine as a treatment for long COVID.

Additional information:

Kondo T, Higa R, Kuniba M, Shinzato H, Takaesu Y. ***Successful treatment with guanfacine in a long-COVID case manifesting marked cognitive impairment.*** Neuropsychopharmacol Rep. 2024; 44: 585–590.

Colchicine for long COVID - no current evidence

Brief background

Colchicine is an anti-inflammatory medicine that has been used in medicine for a long time. It is mainly used to treat and prevent gout, a condition that causes joint pain and swelling. Colchicine may also help people with long COVID who have inflammation around the heart (called pericarditis) or lungs (called pleuritis), because it helps reduce inflammation. It has been found to be helpful for people with pericarditis.

Summary of key evidence

There are studies, including randomized trials, on colchicine for people with long COVID. However, some studies have been done on people with severe acute COVID-19 in the hospital. These studies found that colchicine had little to no effect on survival or recovery compared to a placebo or standard care. There are a few trials currently in progress that are studying colchicine for long COVID.

Accessibility and Feasibility

In Australia, colchicine is only available with a prescription from a healthcare professional if they think it's needed for your condition. The price can range from ~$10-20 for pack of 30 tablets.

Safety profile

In high doses, colchicine can be very dangerous because the difference between a safe and harmful dose is small. The most common side effect is stomach upsets such as nausea, vomiting, and diarrhea.

Detailed evidence profile

Key study - No current evidence

Conclusion

Currently there are no studies published for the use of colchicine for patients with long COVID. Furthermore, studies have already shown that Colchicine did not show any benefit in those with acute COVID. There are currently four clinical trials (see table below) in patients with long COVID still in progress.

Summary of registered and ongoing trials

Study ID (completion date), status, **Target size**	Reference/Title	Treatment and Dose	Treatment Duration	Follow-up	Comparator	Outcomes
ACTRN12621000637842 Status: not yet recruiting and expected date of last collection 6/02/2023 **N=1000**	A multi-centre trial of colchicine vs control to improve clinical outcomes in adults with long-SARS-CoV-2 (COVID-19) or ARDS https://anzctr.org.au/ACTRN12621000637842.aspx University of Sydney	Colchicine 0.5 mg tablet twice per day given orally	6 months	6 months	Standard of care	COVID-19 WHO score, Dyspnoea management questionnaire-30
ISRCTN10665760 Expected date of completion December 2024 **N=1555**	Forshaw D, Wall EC, Prescott G, Dehbi HM, Green A, Attree E, Hismeh L, Strain WD, Crooks MG, Watkins C, Robson C, Banerjee R, Lorgelly P, Heightman M, Banerjee A; STIMULATE-ICP trial team. STIMULATE-ICP: A pragmatic, multi-centre, cluster randomised trial of an integrated care pathway with a nested, Phase III, open label, adaptive platform randomised drug trial in individuals with long COVID: A structured protocol. PLoS One. 2023 Feb 15;18(2):e0272472. doi: 10.1371/journal.pone.0272472. PMID: 36791116; PMCID: PMC9931100	Colchicine 500 mcg taken twice daily by mouth *part of platform trial	12 weeks	Up to 24 weeks	Control (no drug)	Fatigue assessment scale at 12 weeks and 24 weeks
CTRI/2021/11/038234 status unknown **N=350**	Thankachen SS, Devasenapathy N, Bassi A, et al. Colchicine to reduce coronavirus disease-19-related inflammation and cardiovascular complications in high-risk patients post-acute infection with SARS-COV-2-a study protocol for a randomized controlled trial. *Trials*. 2024;25(1):378. Published 2024 Jun 12. doi:10.1186/s13063-024-08205-7	Colchicine 0.5 mg once daily (< 70kg) or twice daily (>=70kg)	26 weeks	52 weeks after randomisation	Matched placebo for 26 weeks	Distance walked in 6 minutes at 52 weeks from baseline
CTIS2024-511580-28-00 (Completion date; 01/10/2026) Status; "Not Recruiting" N="unknown"	RECLAIM: an adaptive platform trial for the evaluation of treatments for post-acute sequelae of SARS-CoV-2 infection (PASC) *part of platform trial with Metformin	Colchicine (up to 1 mg /day	12 weeks	12 weeks	Placebo	Patient-reported physical-health related quality of life (HRQoL)

Monoclonal antibodies for long COVID– low level evidence

Brief background

Monoclonal antibodies (mAbs) are lab-made proteins that work like the immune system to fight viruses and bacteria. They are usually given through an IV, but some can be injected. Monoclonal antibodies are approved for treating severe acute COVID-19, but they are not yet approved for long COVID. Some scientists think leftover bits of the virus may stay in the body in people with long COVID, and monoclonal antibodies might help remove these. One monoclonal antibody, called "leronlimab," blocks a specific receptor called CCR5, which reduces inflammation and boosts the immune system. Other types of monoclonal antibodies may also be helpful for treating long COVID in the future.

Summary of key evidence

Only one small RCT has tested how well monoclonal antibodies work as a treatment for long COVID. In this RCT (Gaylis, 2022), 55 people with long COVID got weekly injections of either leronlimab or a placebo for 8 weeks. The group treated with leronlimab showed more improvement in their symptoms than the placebo group, but the results were not strong enough to be considered statistically significant. Currently, three more RCTs are underway to test if monoclonal antibodies are effective for treating long COVID.

Accessibility and Feasibility

In Australia, it may be hard to access monoclonal antibodies to treat long COVID. Some monoclonal antibodies are approved for treating severe cases of acute COVID-19 in hospitals, but they are not approved for long COVID yet. This makes them difficult to access and likely very expensive. Emicizumab products can be accessed through the National Blood Authority (NBA) if patients meet certain medical requirements, but the cost to buy them privately is unknown. Monoclonal antibodies are generally very expensive.

Safety profile

Monoclonal antibodies have been safely used to treat many diseases in the short term. Most people don't have any side effects, but some may have mild ones like headaches or feeling sick to their stomach (nausea). However, monoclonal antibody infusions can sometimes cause immune system reactions, such as severe allergic reactions (anaphylaxis), infections, or autoimmune issues. Scientists are still studying their long-term safety.

Detailed evidence profile

Key study - 1 RCT

Gaylis NB, Ritter A, Kelly SA, Pourhassan NZ, Tiwary M, Sacha JB, et al. ***Reduced Cell Surface Levels of C-C Chemokine Receptor 5 and Immunosuppression in Long Coronavirus Disease 2019 Syndrome***. Clin Infect Dis. 2022;75(7):1232-4.

Summary of methods

An exploratory RCT by Gaylis 2022 was an 8-week randomized controlled trial which was conducted in the USA (table 1 below). 55 participants were randomised to receive weekly subcutaneous 700mg of leronlimab or placebo for 8 weeks. Changes in 24 common symptoms were compared in participants receiving either leronlimab or placebo. All symptoms were scored as 0-4 or 0-3 and then a total was given for each person based on 24 symptoms. The primary outcome was the change in symptom severity from baseline compared at 8 weeks. Exploratory outcomes included changes in peripheral blood leukocyte CCR5 cell surface levels, immune cell phenotypes, and plasma cytokines.

Table 1. Summary of 1 RCT (Gaylis, 2022)

Study, year, location	RCT design	N	Participants	Intervention	Comparator	follow up
Gaylis, 2022	Parallel	55 (leronlimab group=28, placebo group=27)	18+, history of COVID-19 and have long COVID (>12 weeks post covid)	Weekly subcutaneous 700mg of leronlimab for 8 weeks	Subcutaneous saline Placebo for 8 weeks	Up to week 8

PCC=Post COVID-19 condition

Summary of results

The mean symptom score change for the leronlimab treatment group was an improvement of -16 (95%CI; -21.5 to -12.5) whereas for the placebo group it was only -12 (95% CI -16.6 to -7.4) (a negative number change indicates improvement). However, after adjusting for pre-specified covariates, the adjusted mean difference was -1.0 (and not found to be statistically significant). Although, cell surface CCR5 levels showed significant increases ($p<0.0001$) in the leronlimab vs placebo group. Leronlimab treatment was also associated with increases in key adaptive immune cell populations.

Risk of Bias

The risk of bias was assessed by the Cochrane ROB-2 for parallel trials. It was found that the RCT had some concerns with potential bias arising from both the randomization process and bias due to deviations from intended interventions. Overall Gaylis, 2022 had some concerns of risk of bias.

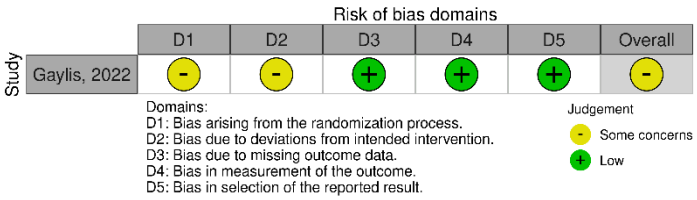

Fig 1. ROB-2 for Gaylis, 2022

Summary of other evidence -(1 case series)

[Scheppke KA, Pepe PE, Jui J, et al. **Remission of severe forms of long COVID following monoclonal antibody (MCA) infusions: A report of signal index cases and call for targeted research**. *Am J Emerg Med*. 2024;75:122-127. doi:10.1016/j.ajem.2023.09.051]

The case series (Scheppke, 2024) followed 3 cases of 2 women (age 60 and 43) and 1 man (age 63) whereby each subject had a complete remission of their persistent symptoms within a week of monoclonal antibody infusions (casirivimab/imdevimab-"Regeneron") and this was sustained after a follow-up of 2 years. All three patients recovered from their symptoms even though they all had different past histories, sex, age, and illness duration.

Conclusion

The results from only one pilot RCT indicate that overall, monoclonal antibodies did not indicate a statistically significant improvement in long COVID symptoms. However, it did seem to show that leronlimab stabilizes CCR5 expression, although the exact mechanism is not yet known. Further research is required into the role of CCR5 in long COVID. Additionally, findings from one prospective case series (Scheppke, 2024) found that 3 subjects experienced symptom remission within 7 days after receiving casirivimab/imdevimab infusions**. Overall, there is not enough evidence to suggest that monoclonal antibody treatment is effective in treating the symptoms of long COVID**. There are a few clinical trials currently in progress that may add to the evidence base (see table 3 below).

Summary of registered and ongoing trials

Table 3. Summary of registered trials in progress **(n=3 clinical trials in progress and 2 other studies**)							
Study ID (completion date), Status, **Target size**	Title	Intervention	Dose	Treatment Duration	Follow-up	Comparator	Primary Outcomes
NCT05877508 (completion date; 2025-07-31) Status: "Active, no recruiting" **N=36**	Anti-SARS-CoV-2 Monoclonal Antibodies for Long COVID (COVID-19) (outSMART-LC)	AER002	1200 mg administered once by IV (intravenous infusion)	once	Up to 1 year	Placebo infusion by IV	Change in Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Physical Health Summary Score from Baseline and Day 90
ISRCTN46454974 (Completion; Dec 2025) "Recruiting" **N=152**	A research trial to find out if tocilizumab helps adults with Long Covid feel better	tocilizumab	162 mg Subcutaneous injection (body weight <100 kg 162 mg fortnightly/body weight ≥100 kg 162 mg weekly for 12 weeks)	12 weeks	12 weeks	Subcutaneous placebo for 12 weeks	Health-related quality of life
NCT05926505 (completion date; 2025-08) Status: "Recruiting" **N=182**	Safety and Efficacy of Anakinra Treatment for Patients with Post Acute Covid Syndrome (PRECISION)(*crossover trial)	Anakinra	Anakinra 149 MG/ML Prefilled Syringe [Kineret] Anakinra is injected subcutaneously as 100 mg once daily for 4 weeks.	4 weeks	Up to 2 years	Placebo- Placebo is injected subcutaneously once daily for 4 weeks.	Score of PACS progression reversal
Other ongoing/incomplete studies:							
Retrospective case-control							
NCT05013723 (completion date; 2025-07-31) Status: "Active, no recruiting" **N=260**	Impact of Monoclonal Antibody Treatment on Post-Acute COVID-19 Syndrome (MAbPACs)	Patients who received casirivimab-imdevimab antibody infusion (Regeneron)	unknown	unknown	Between day 60 and day 90 from date of positive test	Matched control group who did not receive MAb, matched on diagnosis date, age, gender and Utah COVID-19 Risk Score	Post-acute COVID-19 symptom score (out of 60)
Observational cohort cross-sectional							
NCT05508295 (completion date; 2024-01-31) Status: "Recruiting" **N=300**	Long COVID-19 and MAB study	COVID positive case with mAb treatment	unknown	unknown	Up to 6 months follow-up	COVID positive case having not received mAb treatment Control= "COVID negative cases"	modified comprehensive PRO instrument based on PROMIS

Nattokinase for long COVID - no current or upcoming evidence

Brief background

Nattokinase is an enzyme made by bacteria during the process of fermenting soybeans to create a Japanese food called “Natto.” It is a natural blood thinner that can dissolve blood clots and has been studied as a treatment for heart and cardiovascular diseases. Some researchers believe nattokinase might break down the SARS-CoV-2 spike protein, and one study showed this happening in a lab setting, but not inside the human body. Claims that nattokinase supplements can “detox” the body from the SARS-CoV-2 spike protein are not supported by evidence. Most research on nattokinase has been done in labs, not in people.

Summary of key evidence

There haven’t been any studies on nattokinase for long COVID patients. There are also no clinical trials currently planned, ongoing, or recently completed.

Accessibility and Feasibility

Nattokinase supplements are easily available over the counter online and in pharmacies. They are available in 50 to 100 mg capsules and are relatively inexpensive (30 capsules (100 mg each) cost about $20).

Safety profile

Nattokinase is considered to be safe however, caution is advised if blood thinners are also being taken because it could increase the risk of bleeding too much. It is also not recommended for pregnant or breastfeeding women because there isn't enough research on its safety.

Detailed evidence profile

Key study - No current evidence

Conclusion

Nattokinase is a easily available supplement produced from a traditional Japanese food called “Natto”. There have been no studies on Nattokinase for long COVID. Furthermore, no future studies have been initiated. At this stage it is likely that more evidence will be needed supporting the efficacy of Nattokinase as a treatment for long COVID before it can be considered as a suitable candidate treatment.

References

Tanikawa T, Kiba Y, Yu J, et al. Degradative Effect of Nattokinase on Spike Protein of SARS-CoV-2. *Molecules*. 2022;27(17):5405. Published 2022 Aug 24. doi:10.3390/molecules27175405

Kim J.Y., Gum S.N., Paik J.K., Lim H.H., Kim K.C., Ogasawara K., Inoue K., Park S., Jang Y., Lee J.H. Effects of nattokinase on blood pressure: A randomized, controlled trial. Hypertens. Res. 2008;31:1583–1588. doi: 10.1291/hypres.31.1583.

Weng Y, Yao J, Sparks S, Wang KY. Nattokinase: An Oral Antithrombotic Agent for the Prevention of Cardiovascular Disease. Int J Mol Sci. 2017 Feb 28;18(3):523. doi: 10.3390/ijms18030523. PMID: 28264497; PMCID: PMC5372539.

Intravenous immunoglobulins (IVIg) for long COVID – very low level evidence

Brief Background

Intravenous immunoglobulins (IVIg) are a mixture of human antibodies that are used to treat a variety of conditions, like certain infections (such as influenza and measles) and diseases like Kawasaki disease and multiple sclerosis. IVIg is made from donated blood, which is processed to separate the proteins from the other parts of the blood. One type of IVIg, called Gamunex-C, is believed to help the immune system fight infections. It is thought that IVIg might help people with POTS or autonomic dysfunction due to its immune system effects.

Summary of key evidence

There are no systematic reviews or published randomized controlled trials on intravenous immunoglobulin (IVIg) for people with long COVID. However, there are a few very small, low-quality studies. One study (Hogeweg, 2023) looked at 30 patients, another (Thompson) included 6 people aged 34 to 79, and a third study (McAlpine, 2024) reviewed 9 people who received IVIg and 7 who did not. All three of these small studies showed that IVIg therapy had a positive effect. However, this evidence is not considered very strong.

Accessibility and Feasibility

IVIg therapy is funded and managed by the National Blood Authority (NBA) in Australia, but patients must meet certain medical criteria to receive it. Long COVID is not included in these criteria, so IVIg for long COVID is accessed privately, and it requires a medical officer to seek access through a jurisdictional direct order (JDO). According to the National Product Price List, private access to IVIg costs $618.60 for a 10g/100ml bottle and $1,237.21 for a 20g/200ml bottle. Most studies used a dose of 0.5 g/kg, and one study used 2g/kg every 3 weeks for 6 months. For example, a 70 kg person would need 30g of IVIg (0.5 g/kg), which would cost $1,855.81 every 3 weeks. If the dose is 2g/kg, they would need 140g, which would cost $8,660.47 every 3 weeks.

Safety profile

Side effects are reported in 5 to 15% of people who get IVIg infusions. Out of those that get side effects, the most common side effect is a headache, which happens in about 24% of patients. Other possible side effects include chills, flushing, tiredness, stomach pain, fast heartbeat, and muscle pain. People who have kidney problems are advised not to get IVIg infusions at a rate higher than 100 ml per hour.

Detailed evidence profile

Key study - No current evidence

Summary of other evidence (non-randomised studies)

There are currently no systematic reviews and no published randomized controlled trials of intravenous immunoglobulin (IVIg) in those diagnosed with long COVID. However, there is one very small retrospective case control study (Hogeweg, 2023) of 30 patients, a very small observational case study (Thompson, which consists of only 6 observational single cases aged between 34 to 79 years old) and a very small retrospective case review (McAlpine, 2024). All three studies found patients had positive improvements in their symptoms in those that were treated with IVIg. Please see table 1 below for a summary of the results. These data must be interpreted with caution, as these are very small studies using retrospective or case study approaches.

Table 1. Summary of non-randomised studies

Study	Type of study	N	population	Intervention group	Comparator group	Main Outcome conclusions
Hogewey, 2023 (Germany)	Retrospective case study (matched case control)	30 (10-IVIg 10-budesonide 10-supportive measures only)	out-patients with severe post-COVID symptoms	(G1)3-4 monthly courses of IVIg (0.5g/kg Privigen from CSL Behring, Austria)	(G2)-inhaled glucocorticoids 2x0.2 mg/day (G3)-supportive measures only in outpatient	10/10 (100%) patients in IVIg group reported relief of symptoms, compared with 4/10 (40%) in G2 and 6/10 (60%) in G3. ISARIC* symptom change score within groups significantly higher in IVIg group ($p<0.001$) compared to G2($p< 0.05$) and G3 ($p<0.05$)
Thompson, 2023 (USA)	Observational Case study	6	Age 34-74, 5 male, 4 female with long COVID + neurological or cardiac symptoms	6 different cases receiving 0.5 g/kg IVIg every 2 weeks for a 3-month trial	No comparator	All 6 patients had subjective clinical improvements
McAlpine, 2024 (USA)	Retrospective chart review (case-control)	9 -IVIg 7-no IVIg	Diagnosis with long COVID based on WHO + reduced nerve fiber density (SFN)	IVIg -2g/kg split over 3 days for 1st infusion then 2 g/kg split over 2 days every 3 weeks thereafter for a median of 10 mnths [IQR 3-19]	Control group-No IVIg	IVIg group had a significant clinical response in neuropathic symptoms (9/9) compared to those with no IVIg (3/7), p=0.02.

SFN=small fiber neuropathy; ISARIC = International Severe Acute Respiratory and emerging Infection Consortium

Conclusion

Although IVIg has been proposed as a possible treatment for long COVID, there are limited studies exploring its efficacy. No high-quality studies such as randomized, prospective studies have been published for the use of IVIg for patients with long COVID. IVIg therapy requires further research to gather important efficacy features such as dosage, time, and IG type. There are two additional clinical trials (see table 2 below) currently in progress that may hopefully give further evidence to describe and elaborate on the value of IVIg for long COVID patients.

Summary of registered and ongoing trials

Table 2. Summary of registered trials in progress **(n=2 trials**)

Study ID (completion date), Status, **Target size**	Reference	Participants	Treatment Dose Duration	Follow-up	Comparator	Primary Outcomes
NCT06305780/ NCT06305793 (appendix) (2026-03) Status: "Recruiting" **N=380**	Duke University. RECOVER-AUTONOMIC (IVIg): Randomized Trial of the Effect of IVIg Versus Placebo on long COVID Symptoms. RECOVER-AUTONOMIC: Platform Protocol, Appendix A (IVIg). clinicaltrials.gov. 2024;	Adults with Autonomic dysfunction and long COVID-POTS symptoms after COVID (have 1 or more POTS symptoms	IVIg + coordinated care, IVIg + usual care IVIg (Gamunex) 2g /kg monthly for 9 months (36 weeks)	+ 3 month follow-up Total study duration 12 months	IVIg placebo + coordinated care Ivabradine + coordinated care, IVIg placebo + usual care, Ivabradine + Usual care, Ivabradin placebo + usual care	Change in Orthostatic Hypotension Questionnaire (OHQ)/Orthostatic Intolerance Questionnaire (OIQ) Composite Score
NCT05350774 (2025-12-15) Status: "Enrolling by invitation" **N=45**	National Institutes of Health Clinical Center (CC). Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2. clinicaltrials.gov. 2022;	18+, those with long COVID with ongoing neurologic symptoms	IVIg- 0.4g/kg /day for 5 days	2 weeks	Placebo	Comparison of proportion of participants with a clinically meaningful change in Health Utilities Index Mark 3 (HUI3) after receiving either IVIg or placebo at Week 2.

Coenzyme Q10 for long COVID – moderate level evidence

Brief background

Coenzyme Q10 (CoQ10) is an important substance that is found throughout the body that helps produce energy. It also acts as an antioxidant, helping protect cells from damage, and is a common dietary supplement. People claim that CoQ10 can help with heart and muscle health, as well as boosting energy. It is believed that the inflammation caused by a COVID-19 infection may harm the body's energy-producing cells. The main symptoms of long COVID, like tiredness, brain fog, muscle weakness, and trouble breathing, are also signs of problems in the body's energy-producing cells. Because of this, it is thought that taking CoQ10 as a supplement might help improve energy production and reduce these symptoms.

Summary of key evidence

Only two randomized control trials (RCTs) have been published on CoQ10 for long COVID. One trial with 119 people showed no major benefits with 500 mg of CoQ10 daily for 6 weeks compared to a placebo after a break period. Another trial also found no significant differences between 20 people who received CoQ10 along with rehabilitation treatment and 14 people who only received the rehabilitation treatment.

Accessibility and Feasibility

CoQ10 supplements can be bought at local pharmacies, health stores, and big grocery stores across Australia. They come in 150 mg and 300 mg tablets. A 30-day supply of 300 mg tablets usually costs around $30 to $50.

Safety profile

CoQ10 is generally safe and doesn't cause serious side effects in people. The highest safe dose is about 1200 mg per day. However, if taken in very high doses, it may cause mild stomach problems. It should not be used with the blood thinner warfarin because it can increase the risk of bleeding. It is also not recommended for pregnant or breastfeeding women, people with kidney disease, or those with liver problems because its safety for these conditions hasn't been proven.

Detailed evidence profile

Key studies- 2 RCTs

Hansen KS, Mogensen TH, Agergaard J, et al. ***High-dose coenzyme Q10 therapy versus placebo in patients with post COVID-19 condition: a randomized, phase 2, crossover trial***. Lancet Reg Health Eur 2023; 24: 100539.

Sumbalová Z, Kucharská J, Rausová Z, Palacka P, Kovalčíková E, Takácsová T, et al. ***Reduced platelet mitochondrial respiration and oxidative phosphorylation in patients with post COVID-19 syndrome are regenerated after spa rehabilitation and targeted ubiquinol therapy***. Front Mol Biosci. 2022;9:1016352.

Summary of methods

An RCT by Hansen 2023 was a 20-week double blinded, placebo controlled 2x2 randomized crossover trial which was conducted from May 25th ,2021 to September 22nd ,2021 at Aarhus University Hospital and Godstrup Hospital in Denmark. (table 1) 121 participants were randomised to either receive the intervention first for 6 weeks (and the placebo after for 6 weeks, including a 4 week wash out period) or the placebo first (and the intervention after for 6 weeks, including a 4 week wash out period). The final follow-up of outcomes (change in PASC symptoms and health index) was 4 weeks after the 2nd dosing period. The other RCT (Sunbalova 2022) from Slovakia compared 20 people who received CoQ10 + rehabilitation therapy vs 14 people who received only rehabilitation therapy for 16 to 18 days.

Table 1. Summary of 2 RCTs

Study, year, location	RCT design	N.	Participants	Intervention Coenzyme Q10 (ubiquinone/ubiquinol)	Comparator	Washout/follow up
Hansen, 2023 Denmark	2x2 crossover	121 (119 completed both intervention and comparator)	18+, history of COVID-19 and at least 2 long COVID symptoms for more than 90 days after initial COVID infection, recruited from PCC outpatient clinic	500 mg per day **ubiquinone** (5x 100mg doses per day) for 6 weeks	Placebo for 6 weeks	4 weeks washout/ 4 weeks follow-up
Sunbalova, 2022 Slovakia	Parallel 2 arm	34 (20 in intervention vs 14 in comparator)	18+, 3-7 months post hospitalization with severe COVID-19 + persistent symptoms (post covid-19)	Mountain spa rehab + 2x100 mg/day **ubiquinol** for 16-18 days **(MRQ)**	Mountain spa rehab for 16-18 days only **(MR)**	-

PCC=Post COVID-19 condition

Summary of results

In the Hansen RCT, the primary outcome was change in the number/and or severity of PCC-related symptoms after 6 weeks of CoQ10 treatment or placebo compared to baseline measured as a symptom score (PCC-specific questionnaire) and a health index (EQ-5D). After adjusting for sequence and period, the mean difference in the change in symptom scores was 1.18 points larger for the CoQ10 group compared to placebo but this was **not significant** (MD= -1.18, 95%CI: -3.54 to 1.17, p=0.32). For the health index after adjusting for period and sequence effect from a linear mixed-effects model, the estimated difference was **not significant** either (0.01; 95% CI; -0.02 to 0.04, p=0.45).

In the Sunbalavo RCT, 51.8% of symptoms were resolved in the rehab only group (MR), whereas 62.8% of symptoms were resolved in the rehab + CoQ10 group(MRQ). The authors did not assess whether the difference in symptom changes is statistically significant. Furthermore, Sunbalavo didn't compare differences in change scores (baseline and after) between groups as they only compared changes within groups. The 6 min walking distance was significantly improved in both groups (p<0.01) and the exercise dyspnea was significantly improved in the rehab only group (MR, p=0.004) but not in the rehab + coQ10 group (MRQ=0.08). See table 2 below for a summary of the main results.

Table 2. Summary results of 2 RCTs

Study	Outcome	Mean difference*(95%CI)	P-value	Comments
Hansen, 2023	Change in PCC-related symptom score	-1.18 (-3.45 to 1.17)	0.32	No statistically significant difference.
	Change in EQ-5D health index	0.01 (-0.02 to 0.04)	0.45	No statistically significant difference.
Sunbalova, 2022	% clinical symptoms reduced (before- after)	MR -51.8% MRQ -62.8%	unknown	Unknown
	Change in 6MWT in metres between baseline and after intervention/comparator	MR +87.2 (30.1) MRQ +61.4 (18.1)	MR-p=0.004 MRQ-p=0.003	No between group differences calculated. Both groups had significant differences-
	Change in exercise dyspnea using borg scale between baseline and after intervention/comparator	MR-2.1 (0.55) MRQ-1.0 (0.48)	MR p=0.004 MRQ p=0.08	No between group differences calculated. Only significantly improved in MR group-

*adjusting for period and sequence effects
6MWT=6 minute walking test, PCC= post covid-19 condition

Risk of bias

Figure 1 below displays the results of the Cochrane ROB-2 tool to assess the risk of bias in both the crossover RCT (Hansen, 2023) and the parallel RCT (Sumbalova, 2022). Hansen was found overall to have a low risk of bias across all domains. However, Sumbalova had issues with bias arising from the randomization process and therefore was assessed as having some risk of bias overall.

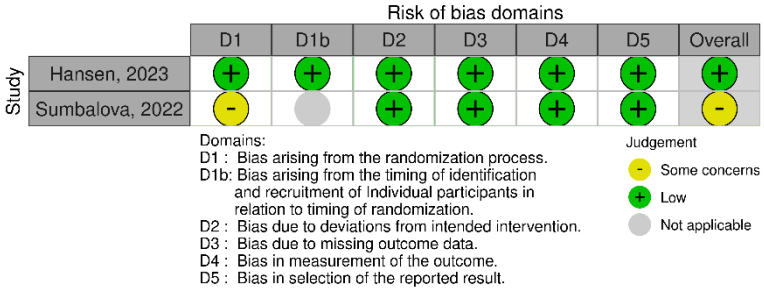

Figure 1. ROB-2 of a crossover RCT (Hansen, 2023) and parallel RCT (Sumbalova, 2022) Domain D1b represents bias arising from period and carryover effects and thus is not applicable for Sumbalova, 2022.

Summary of other evidence (1 non-randomised study)

[Barletta MA, Marino G, Spagnolo B, et al. Coenzyme Q10+α-lipoic acid for chronic COVID syndrome. Clin ExpMed 2023; 23: 667–678]

This non-randomized prospective observational study looked at the association of 100 mg **CoQ10** combined with 100 mg **alpha lipoic acid** vs a placebo for 60 days on chronic covid symptoms in 174 patients 18+ who contracted covid and who met ME/CFS diagnostic criteria, this criterion being used as a proxy for long COVID diagnosis. A reduction in fatigue severity scale (FSS) complete response was reached most frequently in the treatment group, n=62(53.5%) compared to n=2 (3.5%) in the control group (p<0.0001). The % of people who had a non- response in their fatigue (FSS score <20% from baseline to T1) was less in the treatment group (n=11, 9.5%) compared to those who did not receive it (n=15, 25.9%) which was statistically significant (p<0.01). Caution is required when interpreting these results as this study was not randomised and it was also combined with an alpha lipoic acid supplement (an antioxidant produced in the body and found in foods).

Conclusion

The results from only two RCTs indicate that overall, CoQ10did not indicate a statistically significant improvement in long COVID symptoms. Although findings from one prospective observational study (Barletta, 2023) who combined an antioxidant (alpha lipoic acid) with CoQ10 found a reduction in fatigue, caution is required when interpreting these results. There is one clinical trial currently in progress which is not set to conclude until late 2028

(see table 3 below). Overall, there is currently limited data and evidence to conclude that CoQ10 is an effective treatment for the symptoms of long COVID.

Summary of registered and ongoing trials

Table 3. Summary of registered trials in progress **(n=1 trial)**

Study ID (completion date), Status, **Target size**	Title	Intervention	Dose	Treatment Duration	Follow-up	Comparator	Outcomes
NCT05373043 (completion date; 2028-10-31) Status: "Recruiting" **N=300**	Long-term COVID and rehabilitation	Exercise + Mitoquinone (synthetic form of coenzyme Q10)	unknown	unknown	4 years	Exercise + Placebo	Change in flow mediated dilation (FMD), change in microvascular function (using passive leg movement-PLM), change in cerebral vascular endothelial function (using breath hold acceleration index-BHAI)

Multi-component intervention package for long COVID – high level evidence

Brief background

Multi-component intervention packages for long COVID involves a range of elements that are individualised to each person based on their symptoms, capacity, needs and goals. The package may include managing symptoms (e.g. pain, POTS), managing or sustainably increasing physical activity, sleep-wake cycle management, , re-engagement with work/study, managing postural orthostatic tachycardia syndrome, breathlessness, adjusting to the impact of the illness, managing mood/worry, and cognitive reattribution/adaptation. A multi-component intervention typically includes 'core' modules (e.g., sleep, pacing, sustainable increases in activity) and optional modules (e.g., breathlessness, worry, coping). Multi-component interventions for long COVID are typically delivered by a multidisciplinary team of allied health professionals, which could include a 'physical therapist' (e.g., exercise physiologists, physiotherapists, occupational therapists) and/or a psychologist, in collaboration with the GP and patient. The 'physical therapist' focuses on activity pacing, sustainable increase in activity (physical) – avoiding post-exertional exacerbation of symptoms, breathlessness, pain, and POTS. The psychologist focuses on sleep-wake cycle management, gradual increase in activity (cognitive)- avoiding post-exertional exacerbation of symptoms, coping with the illness, mood and cognitive reattribution – which identifies thinking patterns and how they influence behaviour to manage Long COVID. The GP may focus on one or more of these symptoms (e.g. pain, POTs, breathlessness, sleep, mood) and coordinate care with relevant allied health professionals to address other symptoms.

Summary of key evidence

The evidence for multi-component trials is based on a summary of five RCTs. These RCTs involved addressing multiple symptoms, using combined elements of cognitive behavioural techniques and movement, which were individualised to the participant Overall, multi-component intervention packages appear to improve symptoms of long covid.

Accessibility and Feasibility

Access to publicly funded allied health interventions for long COVID in Australia remains limited, with no coordinated care or system-level funding in place. In Australia, Medicare provides rebates for mental health and physical therapy services under specific programs that may support the delivery of a multi-component intervention package. The Mental Health Care Plan (MHCP) (Item 80010) offers rebates for up to 10 sessions per calendar year with a Clinical Psychologist. Each session has a Medicare rebate of $141.85. The Team Care Arrangement (TCA) (Item 723) and GP Management Plan (GPMP) (Item 721) support patients with chronic or complex conditions, providing rebates for up to 5 sessions per year with allied health professionals, such as exercise physiologists or physiotherapists. These

sessions typically cost around $145.00 each, with a rebate of $60.35 per session. Out-of-pocket costs can vary depending on private practice fees, potentially limiting access for individuals facing financial constraints.

Safety profile

Multi-component interventions are generally safe and beneficial for most people to participate in, particularly when provided under appropriate supervision.

Detailed evidence profile

Key studies reported within this SR:

- Kuut TA, Müller F, Csorba I, et al. Efficacy of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following Coronavirus Disease 2019: Results of a Randomized Controlled Trial. Clin Infect Dis2023;77:687-95. doi:10.1093/cid/ciad257 pmid:37155736CrossRefPubMedGoogle Scholar
- Samper-Pardo M, León-Herrera S, Oliván-Blázquez B, Méndez-López F, Domínguez-García M, Sánchez-Recio R. Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial. Sci Rep2023;13:7943. doi:10.1038/s41598-023-35058-y pmid:37193738CrossRefPubMedGoogle Scholar
- Samper-Pardo M, Oliván-Blázquez B, León-Herrera S, Sánchez-Arizcuren R, Casado-Vicente V, Sánchez-Recio R. Effectiveness of ReCOVery APP to improve the quality of life of long COVID patients: a 6-month follow-up randomized clinical trial. Mental Health Weekly Digest 2023;136.
- McGregor G, Sandhu H, Bruce J, et al. Clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-covid-19 condition (REGAIN study): multicentre randomised controlled trial. BMJ2024;384:e07650
- Leon-Herrera 2024, Olivan-Blazquez B, Sanchez-Recio R, Mendez-Lopez F, Magallon-Botaya R, Sanchez-Arizcuren R. Effectiveness of an online multimodal rehabilitation program in long COVID patients: a randomized clinical trial. Arch Public Health. 2024;82(1):159.
- Sánchez Milá Z, Rodríguez Sanz D, Martín Nieto A, Jiménez Lobo A, Ramos Hernández M, Campón Chekroun A, et al. Effects of a respiratory and neurological rehabilitation treatment plan in post Covid-19 affected university students. Randomized clinical study. Chronic Respiratory Disease. 2024;21.

Summary of methods

This summary is based on the findings from 5 RCTs.

Summary of results

Kuut, 2024 tested the effect of a 17-week cognitive behavioural therapy on severe fatigue in people with long COVID. The cognitive behavioural therapy program consisted of seven modules: elements focusing on (1) disrupted sleep-wake pattern, (2) dysfunctional beliefs about fatigue, (3) low or unevenly distributed level of activity, (4) perceived low social support, (5) problems with processing the acute phase of COVID-19, (6) fears and worries regarding COVID-19, and (7) poor coping with pain. A total of 114 participants were randomised (57 to the intervention arm and 57 to the control arm). This trial found a significant improvement in fatigue scores immediately after the intervention. These improvements were sustained 6 and 18 months after the intervention.

Samper-Pardo (2023a,b) also included behavioural components as part of a multicomponent intervention that was delivered via a mobile App. The intervention focused on diet, exercise, sleep, and cognitive stimulation and was delivered by psychologists, physiotherapists, nurses, occupational therapists and social workers through an online mobile application. Standard care was delivered by the participant's GP. A total of 100 participants were randomised (52 to the intervention group and 48 to the control). This study found no significant difference in quality of life, physical functioning or cognitive functioning of participants at 3 months compared with control.

McGregor, 2024 evaluated a combined physical and mental health rehabilitation programme versus usual care (single session of online advice and support) on quality of life, and a range of mental and physical symptoms. This intervention focussed on motivation, fear avoidance, managing emotions, fatigue, and stress and anxiety and was delivered online for <8 weeks by physiotherapists, health psychologists, and exercise physiologists. A total of 585 people were randomised (298 to the intervention group and 287 to usual care). The study found an improvement in quality-of-life scores after 3 months. These effects were sustained at 6 and 12 months from baseline.

Leon-Herrera, 2024 randomized 134 patients with long COVID to receive either an 8 week online multimodal rehabilitation program (8 group videoconferences + Moodle online learning platform) comprising exercises and therapeutic recommendations regarding physical activity, respiratory rehabilitation, cognitive rehabilitation, diet, sleep hygiene, the use of community resources and emotional management, or control (comprising usual care from the GP). The primary outcome was quality of life measured by the SF-36 health survey which was measured at baseline and 3 months later.

Sanchez Mila, 2024 randomised 200 patients with long COVID and dyspnoea or perceived fatigue, including olfactory and gustatory perception problems to a 31 day intervention comprising inspiratory training treatment plan (Powerbreathe Plus®) combined with aerobic exercise and olfactory gustatory treatment, or control (participants in this group received no intervention). Various Spirometry outcomes (FVC, FEV1, FEv1/FVC), dyspnea and lower limb fatigue were measured by the modified Borg scale. Dyspnea was also measured by the Modified Medical Research Council (mMRC) dyspnoea scale.

Summary of results

Leon-Herrera (2024) found that participants who received the intervention had a significant increase in quality of life, compared with baseline.

Sanchez Mila, 2024 found that participants who received the intervention had significant improvement in dyspnoea compared with baseline.

Overall Conclusion

Multicomponent interventions can be effective at improving overall quality of life and dyspnoea in individuals with long COVID. There is no yet strong evidence to suggest that they improve other physical, mental or cognitive symptoms. Individualised, supervised programs appear to be more effective than self-directed interventions (e.g. a mobile application). **While questions remain regarding the most effective elements of a multi-component intervention and the modality of delivery, the evidence suggests that multi-component interventions are a safe and beneficial non-pharmacological treatment option for many individuals with long COVID.**

Exercise training for long COVID - high level of evidence

Brief background

Exercise training mainly consists of either aerobic training or strength (resistance or weight) muscle training or a combination of both. Most training programs usually also include stretching, flexibility, and balance exercises. There are also specific forms of exercise training such as yoga and Pilates which also uses a combination of these training types.

Summary of key evidence

In total, 16 RCTs looked specifically at exercise training in long COVID patients (Aerobic training k=3, strength training k=3, Combined exercise k=8 and Pilates k=2). Exercise interventions can be effective in improving fatigue, quality of life, physical performance and mental health in individuals with long COVID. Some studies highlight the challenges associated with this population and suggest that improvements are not guaranteed or may be due to other factors. Individualised, symptom-titrated and supervised programs, appear to be more effective. While some questions remain regarding the most effective modalities and the mechanisms of action, the evidence suggests that exercise is a safe and beneficial non-pharmacological treatment option for many individuals with PASC.

Accessibility and Feasibility

Exercise training is very easy to access. Aerobic training can be completed at home with no equipment (walking, running etc.) Strength/resistance training can also be completed at home with minimal equipment (use of own body weight, light weights, exercise resistance band) or accessed at a gym (use of weights). Most exercise can be completed with very minimal cost. Pilates, yoga or swimming classes would require the cost of entry which is usually quite minimal.

Safety profile

All forms of exercise training are quite safe and beneficial for most people to participate in, particularly under appropriate supervision.

Detailed evidence profile

Aerobic training

Key Studies: 3 RCTs

1. Bai B, Xu M, Zhou H, Liao Y, Liu F, Liu Y, et al. Effects of aerobic training on cardiopulmonary fitness in patients with long COVID-19: a randomized controlled trial. 2024. Contract No.: 1.
2. Lai CY, Lin CH, Chao TC, Chang CC, Huang CY, Chiang SL. Effectiveness of a 12-week telerehabilitation training in people with long COVID: A randomized controlled trial. Ann Phys Rehabil Med. 2024;67(5):101853.
3. Mooren J, Garbsch R, Schäfer H, Kotewitsch M, Waranski M, Teschler M, et al. Medical Rehabilitation of Patients with Post-COVID-19 Syndrome-A Comparison of Aerobic Interval and Continuous Training. Journal of clinical medicine. 2023;12:6739-.

Summary of results

Study name	Sample size	Main findings
Bai et al. (2024)	Intervention group (n=12): 4-week exercise training program consisting of 12 supervised aerobic sessions on a cycling ergometer Control group (n=12): guideline-based recommendations for a healthy lifestyle and self-management after COVID-19	67.8% of patients in the training group had reduced or resolved symptoms, compared to 16.7% in the control group. The intervention group also had significant improvements in exercise time, maximum load, peak VO2, O2 pulse, and maximum heart rate.
Lai et al. (2024)	Intervention group (n=91): 12-week telerehabilitation training program with weekly remote monitoring for exercise maintenance and support. Sessions were thrice per week for 40 minutes Control group (n=91): Received physical activity counselling only	The intervention group had significantly greater walking behaviour, total amount of PA, exercise self-efficacy, and better sleep quality compared to the control group. However, there were no significant differences in any cardiorespiratory fitness parameters or health-related quality of life at 12 weeks between the groups.
Mooren et al. (2023)	Intervention groups (PASC patients): Continuous training (n=65): 4-6 weeks, 3-5 times a week, 18 minutes of cycle ergometer training at 50% of maximal workload. Interval training (n=45): cycle ergometer training with load at 60% and relief at 30% Comparison group (Patients with coronary artery disease, n=96): guideline-based rehabilitation, including continuous aerobic exercise training at 50% of maximal workload	Both continuous training and interval training intervention groups improved significantly in workload and oxygen uptake. Both groups also showed reduced fatigue, anxiety, and depression, as well as improved quality of life and well-being. No significant differences between intervention and comparison groups.

Strength training

Key Studies: 3 RCTs	
1.	Kaczmarczyk K, Matharu Y, Bobowik P, Gajewski J, Maciejewska-Skrendo A, Kulig K. Resistance Exercise Program Is Feasible and Effective in Improving Functional Strength in Post-COVID Survivors. Journal of clinical medicine. 2024;13:1712-.
2.	Kogel, A., M. Machatschek, R. Scharschmidt, C. Wollny, F. Lordick, M. Ghanem, U. Laufs and S. Fikenzer (2023). "Physical exercise as a treatment for persisting symptoms post-COVID infection: review of ongoing studies and prospective randomized controlled training study." Clin Res Cardiol 112(11): 1699-1709.
3.	3. Ramírez-Vélez, R., J. Oteiza, G. Legarra-Gorgoñon, S. Oscoz-Ochandorena, N. García-Alonso, Y. García-Alonso, M. Correa-Rodríguez, A. Soto-Mota and M. Izquierdo Exercise training in long COVID: the EXER-COVID trial. European heart journal.

Summary of results

Study name	Sample size and intervention	Main findings
Kaczmarczyk et al. (2024)	Intervention group (n=26): (8-week resistance training program, 2 x 60min sessions per week) Control group (n=20): advised to maintain usual activity	Significant improvement in muscle strength and functional outcomes for the intervention group compared to the control group. Additionally, the intervention group reported fewer symptoms of dizziness, muscle weakness, and exercise intolerance after the training period
Kogel et al. (2023)	Intervention group (n=22): thrice-weekly supervised 45-min exercise sessions consisting of strength and endurance exercises. Control group (n=22): Usual care	After 6 months, the exercise group showed significantly greater physical activity and psychological quality of life compared to the control group
Ramirez et al. (2024)	Crossover design (N=89): 6 weeks, two sessions per week of resistance training performed on non-consecutive days Intervention group 1: Exercise intervention for the first 6 weeks and usual care for the next 6 weeks. Intervention group 2: Usual care for the first 6 weeks and the intervention for the next 6 weeks	The prevalence of COVID-related symptoms decreased between phases, including weakness, dyspnea and memory loss. VO2 Max and muscle strength also improved.

Combined aerobic and strength training

Key Studies- 8 RCTs

1. Barz A, Berger J, Speicher M, Morsch A, Wanjek M, Rissland J, et al. Effects of a symptom-titrated exercise program on fatigue and quality of life in people with post-COVID condition - a randomized controlled trial. 2024 Dec 16.
2. Espinoza-Bravo C, Arnal-Gómez A, Martínez-Arnau FM, Núñez-Cortés R, Hernández-Guillén D, Flor-Rufino C, et al. Effectiveness of Functional or Aerobic Exercise Combined With Breathing Techniques in Telerehabilitation for Patients With Long COVID: A Randomized Controlled Trial. Phys Ther. 2023;103(11).
3. Jimeno-Almazán A, Franco-López F, Buendía-Romero Á, Martínez-Cava A, Sánchez-Agar JA, Sánchez-Alcaraz Martínez BJ, et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: A randomized controlled trial. Scand J Med Sci Sports. 2022;32(12):1791-801.
4. Kerling A, Beyer S, Dirks M, Scharbau M, Hennemann A, Dopfer-Jablonka A, et al. Effects of a randomized-controlled and online-supported physical activity intervention on exercise capacity, fatigue and health related quality of life in patients with post-COVID-19 syndrome. BMC sports science, medicine & rehabilitation. 2024;16:33.
5. M K, A B, L D, P G, B D, P dT, et al. Feasibility of a Group-Based Telerehabilitation Intervention for Long COVID Management. ResearchSquare. 2022.
6. Pleguezuelos E, Del Carmen A, Moreno E, Miravitlles M, Serra M, Garnacho-Castaño M. Effects of a telerehabilitation program and detraining on cardiorespiratory fitness in patients with post-COVID-19 sequelae: A randomized controlled trial. Scandinavian journal of medicine & science in sports. 2023;34:e14543.
7. Pleguezuelos E, Del Carmen A, Moreno E, Serra-Prat M, Serra-Payá N, Garnacho-Castaño MV. Telerehabilitation improves cardiorespiratory and muscular fitness and body composition in older people with post-COVID-19 syndrome. J Cachexia Sarcopenia Muscle. 2024.
8. Sick J, Steinbacher V, Kotnik D, König F, Recking T, Bengsch D, et al. Exercise rehabilitation in post COVID-19 patients: a randomized controlled trial of different training modalities. 2024 Dec 12.

Summary of results

Study name	Sample size and intervention	Main findings
Barz et al. (2024)	Intervention group (n=58): concurrent resistance and aerobic training 1-3 times a week, over 8 weeks Control group (n=60): Waitlist control	The intervention group reported greater improvements in fatigue severity, quality of life and handgrip strength compared to the control group.
Espinoza-Bravo (2023)	Intervention group 1 (n=21): Functional exercise consisted of low-intensity strengthening exercise targeting large muscle groups 3 times a week on non-consecutive days. The duration of the sessions increased from 25 minutes in week 1 to 40 minutes in week 8. Intervention group 2 (n=22): Aerobic exercise included a progressive walking protocol 40 minutes, 3 times a week on	Both exercise modalities were effective in improving stress symptoms and quality of life in patients with long COVID. Improvements in fatigue and functional performance were greater in the functional exercise group.

	non-consecutive days for 8 weeks. No control group.	
Jimeno-Almazán et al. (2022)	Intervention group (n=19): 8 weeks of multicomponent exercise (resistance training, moderate intensity variable training and light intensity continuous training) Control Group: No intervention. Control group (n=20): Usual care	The intervention group showed significant improvements in symptoms in the intervention group compared to the control group. There were also greater improvements in cardiovascular fitness, muscle strength, quality of life, depression, and functional status compared to the control group
Kerling et al. (2024)	Intervention group (n=30): 3-months of 150 min of moderate physical activity per week (60–75% of the maximum heart rate). Once a week, more intense exercise was scheduled (three to ten minutes of stair climbing or one to three minutes of sit-to-stand exercises) that allowed patients to exceed their exercise heart rate limit, if tolerated. Control group (n=32): Waitlist control	No significant change in V̇O2peak, depression severity or physical capacity between groups. Both groups showed a decrease in fatigue scores, and an increase in physical and mental component scores for quality of life.
King et al. (2022)	Intervention group (n=11): 10 weeks of supervised group-based telerehabilitation 2 times a week including walking training, upper and lower limb strengthening and combination aerobic movements. Control group (n=10): Usual care	The intervention group showed significant improvements in the 5-repetition sit-to-stand test compared to the control group. There were no other significant differences between groups at follow-up.
Pleguezuelos et al. (2023)	Intervention group (n=66): 15-week supervised home telerehabilitation program including aerobic and strength exercises 3 times a week using circuit training methodology. Control group (n=65): Usual care	The intervention group significantly improved their exercise capacity, mechanical efficiency, and power output compared to the control group. There was no significant difference in the change in relative V02 peak between the groups
Pleguezuelos et al. (2024)	Intervention group (n=60): 12-week supervised home telerehabilitation program including aerobic and strength training Control group (n=60): Usual care	The intervention group demonstrated greater improvements in exercise capacity, cardiorespiratory and muscular fitness, and body composition, but not VO2 Max compared to the control group
Sick et al. (2024)	Intervention group 1 (n=24): Aerobic endurance training 3 times a week on non-consecutive days increasing in intensity over the intervention period. Intervention group 2 (n=22): Concurrent resistance training 3 times a week on non-consecutive days (consisting of 4 machine-based exercises) and aerobic training Control group (n=20): Usual care	The overall number of symptoms decreased similarly across all groups. both exercise groups experienced a significant improvement in VO2peak No significant differences between the two exercise modalities were found, except for dyspnea which improved significantly in the concurrent training group.

Pilates

Key studies- 2 RCTs

1. Cunha ACR, Silva JC, Garcês CP, Sisconeto TM, Nascimento JLR, Amaral AL, et al. Online and Face-to-Face Mat Pilates Training for Long COVID-19 Patients: A Randomized Controlled Trial on Health Outcomes. 2024 Oct 19.
2. Jorge M, Nepomuceno P, Schneider R, Wibelinger L. Eight weeks of Pilates Method improves physical fitness and sleep quality of individuals with post-COVID-19 syndrome: a randomized clinical trial blinded. 2025.

Summary of results

Study name	Sample size and intervention	Main findings
Cunha et al. (2024)	Intervention group 1 (n= 16): Online mat Pilates 12-weeks, three times per week, 50 minute sessions. Intervention group 2 (n= 15): Face-to-face mat Pilates 12-weeks, three times per week, 50 minute sessions Control group (n=18): Booklet with stretching exercises to perform 3 times a week.	Only the face-to-face intervention resulted in significant improvements in fatigue, muscle strength and aerobic capacity.
Jorge et al. (2025)	Intervention group 1 (n=20): Pilates: two 40-60 minute sessions per week over 8 weeks. Intervention group 2 (n=20): Physical exercise: two weekly sessions with a physiotherapist, with exercises based on cardiorespiratory rehabilitation principles for 8 weeks Control group (n=19): Guidebook with exercises to be performed at home three times a week.	Only the Pilates group showed improvements in fatigue and sleep quality

Overall Conclusion

Exercise interventions can be effective in improving fatigue, quality of life, physical performance and mental health in individuals with long COVID. Some studies highlight the challenges associated with this population and suggest that improvements are not guaranteed or may be due to other factors. Individualised, symptom-titrated and supervised programs appear to be more effective. While some questions remain regarding the most effective modalities and the mechanisms of action, the evidence suggests that exercise is a safe and beneficial non-pharmacological treatment option for many individuals with PASC.