

Interventions for long COVID treatments

Prepared for the OUTPOST APT, HEAL COVID and ALCAP MRFF-funded projects

September 2024 (search done on 3 October 2024)

The following report provides an update of evidence syntheses activities conducted by the Living Evidence Group in October. The Bond and ALEC teams have now refined and finalised a search strategy for RCTs of treatments for long COVID and conducted monthly searches for RCTs on long COVID until the end of September 2024. We have completed full text screening of the studies published in July-September. We are currently completing a full text screen of the remaining studies (i.e. identified prior to July 2024) and expect that this will be completed in time for the next update.

In the absence of substantial high-quality trial evidence for interventions of interest (e.g. antivirals), the Living Evidence Group has commenced a systematic review for low dose naltrexone in long COVID. Low dose naltrexone was listed as an intervention of high interest by clinicians in the clinical survey. As there are no published RCTs on this drug to date, the Living Evidence Group will identify and review research literature from pre-post studies of low dose naltrexone in long COVID. This review is underway, and the results will be reported to the project team shortly.

The following table provides a summary of the currently published trials for Long COVID treatments. These trials were identified through a comprehensive systematic search on PubMed, Cochrane and Embase, plus pre-print servers. The search is also supplemented with updates from long COVID reviews that are being conducted by EPPI-Centre and Epistemonikos. In September, 4 new RCTs on long COVID were published. These studies focused on; antidepressants, rehabilitation, therapeutics (ozone therapy), and complementary (Homeopathic) medicine. (see Appendix A).

Table 1. Updated summary of RCTs for long COVID treatments identified by title and abstract.

Taxonomy categories	Number of SRs n=56	Number of RCTs n= 218	Number of RCTs (July) n=226	Number of RCTs (August) n=228	Number of RCTs (September)** n=232
Non-pharmacological interventions					
Physical Activity and physical therapy (exercise rehab, exercise training, physiotherapy, pulmonary rehab...)	31	67 ^c	<u>68</u>	68	<u>69</u>
Therapeutic procedures (PRP, brain stimulation, HBOT)	6	33 ^c	<u>34</u>	<u>36</u>	<u>37</u>
Complementary and Alternative medicine (qigong, chine herbal meds, aromatherapy, meditation, breathing, acupuncture etc)	5	20 ^c	20	20	<u>21</u>
Behavioural, psychological, educational and self-care (EMDR,+ psyc, cognitive, neurorehab, drug/supplements)	2	12 ^c	<u>13</u>	13	13
Diet and dietary supplements	2	33	<u>36</u>	36	36

(Palmitoylethanolamide and Luteolin, vit A, B, C, D)					
Other non-drug	0	7	7	7	7
Pharmacological interventions					
Acetylcholinesterase inhibitor	0	1	1	1	1
Antidepressant	0	3 (1 prevention of LC, 2 for LC depressive Sx)	3	3	4
Antifibrotic	0	3 ^c	3	3	3
Antihistamine	0	1	1	1	1
Antivirals	1 (preventive)	3 (1 protocol, 1 for acute covid, 1 for LC fatigue, 5 registered trials recruiting)	4	4	4
Beta Blockers	0	2	2	2	2
Corticosteroids	5 (olfac dysfunc)	1	1	1	1
Enzyme Therapeutics	0	1 [*]	1	1	1
Mood stabilizer	0	1	1	1	1
Targeted drugs	0	2 [#]	2	2	1
Multiple	2	2 [^]	2	2	2
NSAIDs	0	1	1	1	1

Olfactory function/anosmia	0	22	23	23	23
Other (BrainMax, AXA1125)	0	3	3	3	3
Both drug and non-drug interventions	2	0	0	0	0

^o includes 1 conference paper (total of 5 conference papers across 5 categories).

[^] prevention study; Bramante, 2023

* bovine hyaluronidase azoximer (longidase)

Targeted drugs- includes both Lerolimab-CCR5-, and RNase

** A list of the RCTs added after full text screening to date, are provided in Appendix A

Table 2: Appendix A. RCTs added until September 2024

Date added	Author, year	Study title	Category
September 2024	Guttuso, 2024	Lithium Aspartate for Long COVID Fatigue and Cognitive Dysfunction: A Randomized Clinical Trial.	Pharmaceutical Lithium/ Antidepressant
September 2024	León-Herrera, 2024	Effectiveness of an online multimodal rehabilitation program in long COVID patients: a randomized clinical trial.	Rehabilitation
September 2024	Rana, 2024	Individualized Homeopathic Medicinal Products in the Treatment of Post-COVID-19 Conditions: A Double-Blind, Randomized, Placebo-Controlled, Feasibility Trial.	Complementary and alternative medicine
September 2024	Soldatenko, 2024	Effectiveness of enriching drug treatment with systemic ozone therapy in patients with post-covid asthenic syndrome.	Therapeutic/ Both drug and non-drug intervention
August 2024	Zha, 2024	Short-term intermittent hypoxia exposure for dyspnea and fatigue in post-acute sequelae of COVID-19: A randomized controlled study	Intermittent hypoxia exposure compared with normoxia
August 2024	Lee, 2024 Secondary analysis of already included RCT (new outcomes of ankle dorsiflexion strength & activities of daily living) original RCT-Zulbaron-Rojas	Gastrocnemius electrical stimulation increases ankle dorsiflexion strength in patients with post-acute sequelae of SARS-COV-2 (PASC): a double-blind randomized controlled trial	Therapeutic (Gastrocnemius Electrical-Stimulation)
July 2024	Abdelazim, 2024	Efficacy of forskolin as a promising therapy for chronic olfactory dysfunction post COVID-19	Diet/Dietary
July 2024	Charoenporn, 2024	Effects of an 8-week high-dose vitamin D supplementation on fatigue and neuropsychiatric manifestations in post-COVID syndrome: A randomized controlled trial.	Diet/Dietary
July 2024	Geng 2024	Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial	Antiviral
July 2024	He, 2024	A pilot randomized controlled trial of major ozone autohemotherapy for patients with post-acute sequelae of COVID-19	Therapeutics

July 2024	Redel, 2024	Effect of lactoferrin treatment on symptoms and physical performance in long COVID patients: a randomised, double-blind, placebo-controlled trial.	Dietary
July 2024	Stavrou, 2024	The Impact of Different Exercise Modes in Fitness and Cognitive Indicators: Hybrid versus Tele-Exercise in Patients with Long Post-COVID-19 Syndrome.	Physical activity and physical therapy
July 2024	Uswatte, 2024	Long COVID Brain Fog Treatment: Findings from a Pilot Randomized Controlled Trial of Constraint-Induced Cognitive Therapy.	Behavioural