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A brief survey of interventional agents intended to treat Long COVID

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ABSTRACT

The present study provides a brief survey, based on a search of the US National Institutes of Health dataset Clinicaltrials.gov, of clinical trials for interventions that could prevent, mitigate or cure Long COVID, a syndrome of increasing concern to patients and their physicians, as the acute phase years of the main pandemic recede and some patients remain afflicted by the failure of the disease signs to completely abate. The disease is pleomorphic in its presentations and severity, with the consequence that there is no one generally accepted approach to treatment, and clinical trial design can be a challenge. At time of writing, there is no approved therapeutic intervention or combination of interventions for Long COVID. Over the last 3 years, there have been several reviews of the state-of-play in relation to therapies for long COVID; however, this is a rapidly moving field and the intention of this brief article is to provide a succinct update on a subset of potential interventional therapies that are currently undergoing clinical trial. There are at least 82 unique active agents in development, and they are characterised by diverse mechanisms of action; however, the emergency approach that was employed during the COVID-19 pandemic is not being replicated for development of treatments for Long COVID.

Keywords: COVID, post-acute COVID-19 syndrome, post-acute sequelae of SARS-CoV-2, post-acute sequelae of COVID-19, long haul COVID, persistent COVID-19, post-acute COVID syndrome, long hauler COVID, chronic COVID syndrome.

Introduction: Long COVID

Some individuals who have been infected with SARS-CoV-2 (COVID-19) experience long-term effects from their infection, lasting many months or even years, and characterised by a broad range of sequelae affecting pulmonary and extrapulmonary organ systems.[1] This syndrome is known as 'Long COVID' or Post-COVID Conditions (PCC).[1] Long COVID is broadly defined as signs and symptoms that continue or develop after acute COVID-19 infection (definition provided by the US Department of Health and Human Services, DHHS, and Centers for Disease Control and Prevention, CDC[2]).

- Long COVID occurs more often in people who had severe COVID-19 illness, but anyone who has been infected with the virus that causes COVID-19 can experience it.
- People can be reinfected with SARS-CoV-2, the virus that causes COVID-19, multiple times. Each time, they have a risk of developing Long COVID.

Most people with COVID-19 improve to their baseline health within a few days to a few weeks after infection; at least 4 weeks after infection is the time after which Long COVID would normally be first identified. Healthcare providers consider a diagnosis of Long COVID based on each patient's health history, including a diagnosis of COVID-19, either by a positive test or by symptoms or exposure, as well as based on a health examination.

For some people, Long COVID can last weeks, months or years after COVID-19 illness and can sometimes result in long-term disability. Sometimes the symptoms disappear and return. The condition is extremely pleomorphic across the assessed cohort. Some individuals with Long COVID have symptoms that are neither explained by tests nor easy to manage.

Some people may be more at risk for developing Long COVID:

- People who have experienced more severe COVID-19 illness, especially those who were hospitalised or needed intensive care.

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- People who had underlying health conditions prior to COVID-19.
- People who did not receive a COVID-19 vaccine.
- Individuals who had repeated COVID-19 infections.

The pleomorphic nature of disease, and concomitant definitional issues for Long COVID, could make clinical development challenging, given the requirement for definition of consistent endpoints for trials. The present study was conducted to provide a brief survey, based on a search of the US National Institutes of Health dataset known as Clinicaltrials.gov (see https://clinicaltrials.gov/, accessed 26 December 2023), of progress in conducting clinical trials for interventions that could prevent, mitigate, or cure Long COVID, a syndrome of broad and increasing concern to previous COVID-19 patients and their treating physicians as the acute phase years of the main pandemic fade and some patients remain afflicted by the failure to completely abate of the disease signs. Moreover, the continuing bursts of COVID-19 worldwide have also led to a new cohort of patients with COVID-19 acute phase disease; thus, the number of Long COVID patients continues to increase.

The known current treatment options for Long COVID generally consist of symptomatic treatment and experimental therapies, the latter of which are captured in the present paper, to the extent possible within the limitations of the accessible database. Symptomatic treatment varies widely, since the disease is quite pleomorphic in its presentations and severity, with the consequence that there is no one generally accepted treatment methodology. At time of writing, there is no approved therapeutic intervention or combination of interventions for Long COVID.

Over the last 3 years, there have been several reviews of the state-of-play in relation to therapies for Long COVID (e.g. Chakraborty and Bhattacharya,[3] Bramante *et al.*,[4] Novak,[5] Ceban *et al.*,[6] Chee *et al.*[7]); however, this is a rapidly moving field and the intention of this brief article is to provide a succinct update on a subset of potential therapies that are currently undergoing clinical trial.

Methods

Using the term 'Long COVID', and the synonyms 'Post-acute COVID-19 syndrome', 'Post-acute sequelae of SARS-CoV-2 infection', 'Post-Acute Sequelae of COVID-19', 'long haul COVID', 'persistent COVID-19', 'post-acute COVID syndrome', 'long hauler COVID' and 'chronic COVID syndrome', the authors of this paper searched the entire database of the US government's Clinicaltrials.gov (see https://clinicaltrials.gov/) to assess all clinical trials under US Investigational New Drug Applications (INDs) related to Long COVID, both interventional and observational, and in Phases 1–4 of clinical trial study. The results were then identified as interventional or not (interventional was the only term used, and only drug, biological and medical device trials, as reviewed for each of the 500 hits from the search, were further explored, see below). The interventional trials were further classified as to whether the experimental agent was: a small molecule drug; a biological drug, including vaccine; a medical device; or dietary supplement or traditional medicine. Please note that we used a narrower definition of 'interventional' than has been used previously for the purpose of such a survey.[3] There are many behavioural and other approaches used as interventions for this constellation of conditions. We decided to concentrate on small molecule drugs, biologic drugs or vaccines, and medical devices. The classification of trials as drug, biological or medical device was by author discretion based on information available from the database and was a straightforward determination, even when precise chemical structures were not disclosed. No trials were excluded if they fit the criteria for inclusion, and actives were identified in almost all cases.

The authors are most familiar with these interventions and have a long history in those areas and we believe that it is reasonable to assert that these types of intervention are the most likely to receive broad global acceptability for Long COVID. Regulatory approval of these interventions is comparatively straightforward, but safety and efficacy must be proven prior to broad use of such interventions. Psychotherapeutic, behavioural, and similar controlled or uncontrolled approaches were not covered in our concept. Thus, the number of discrete interventions is quite small as delineated here. It is important to note that we were unable to categorise some agents because proprietary information from INDs cannot be released by the government and some of the experimental agents were only identified by code number.

A search on 'Long COVID' (and synonyms as delineated above) in all phases of clinical trials and received exactly 500 'hits'. We then manually went through every citation and exempted from the list the types of interventions that did not fit the categories described above.

A further screen for Phase 3 studies was made to attempt to identify those interventional agents under experimental use for Long COVID that were furthest along the developmental pathway for treatment of the condition. It should be understood that, as above, proprietary IND information cannot be provided to the public by the US government, and the actual regulatory status of an interventional agent in a clinical trial (e.g. whether a marketing application is imminent for a particular intervention intended for treatment of Long COVID) cannot be ascertained by such searches. Further, the search results were rescreened using new discriminators on the original search terms to include only Phase 3 and larger Phase (e.g. 4) trials. The results represented the small number of interventions ($n = 26$) that were farthest along in the clinical trial process. These are either interventions previously approved or cleared for other indications and being tested for Long COVID, or interventions which have moved quickly through the process.

Results

Table 1 provides a delineation of interventional agents intended to treat Long COVID from the clinical trial database, shown by type of intervention, number of separately identifiable active interventions of each chosen type, and any comments needed to further refine these results. It can

Table 1. Number and type of interventions (https://www.clinicaltrials.gov/, accessed November 2023).

Type of intervention	Number of actives	Number of trials	Comments
Small molecule drug	31	40	There are more than 31 trials due to multiples for a small number of interventions. Nirvitelvir or Ritonvir: 4 trials
			Naltrexone: 3 trials
			Fluvoxamine: 2 trials
			Remdesivir: 2 trials
			Methylprednisone: 2 trials
			Bupivacaine: 2 trials
Biological drug/stem cells	17	20	Mesenchymal umbilical stem cells: 2 trials
			Efgartigimod (humanised antibody Fc): 2 trials
			NT-17 (Long-acting Interleukin-7): 2 trials
Medical device	18	26	There are more than 18 trials due to multiples for a small number of interventions
			Vagus nerve stimulation: 2 trials
			Hyperbaric oxygen: 2 trials
			HD-DCS (High Definition Transcranial Direct Current Stimulation or DCS: 6 trials
			Immunoadsorption with Therasorb column: 2 trials
Dietary supplement/traditional medicine	29	30	Probiotic supplement: 2 trials
Unclassified	5	5	Unable to identify the active principle, generally suspected traditional medicines or dietary supplements

be seen that a large number (78%) of the 500 clinical trials extracted from the database were noninterventional; these were not considered in further analyses of the data. Most of the trials were in early clinical phases (Phase 1 and 2); at the time of search, only a small number (26) had progressed to or commenced Phase 3 or beyond. This often does not reflect potential success in approval and marketing; rather, well-known or previously approved interventions with data for a new indication may be allowed to progress into more advanced clinical trials more quickly for indications with unmet medical need and, often, greater severity (e.g. Long COVID). Table 1 provides specific numbers of discrete, identified (or unclassified) types of interventions across the *interventional* results from the database. It is noteworthy that a number of trials have been, or are being, conducted with the same agent; this is due either to different investigators or sponsors pursuing the same intervention, or multiple trials conducted by the same sponsor using the same intervention. The number of trials, retrieved from the database, that were classified as interventional was 121 (see Table 1).

A majority of the trials involve small molecules (33%) and, in descending order, dietary supplements or alternative medicines (27%), medical devices (17%) and biologic drugs (14%).

Table 2 presents a discrete subset of the data involving only interventional Phase 3 (advanced or confirmatory) clinical trials on specific agents (where identification as to small molecule, biological drug, etc. can be made directly from the available dataset, based on the authors' expertise). In interventional drug development, these interventions are typically the farthest along towards the possibility of approval by the regulatory authorities, since they have already shown some promise in earlier clinical trials.

Based on the information extracted from the database search, the following agents are most likely to move into the final phase of development and potential marketing (see Table 3).

These interventions were selected for Table 3 either because they are furthest along in the clinical trial confirmatory process; they have shown the most promise in previous clinical studies, or they have been previously approved, which renders approval or licensing more likely for new indications, given evidence of statistically significant and clinically relevant efficacy and acceptable safety in the patient cohorts selected in the Long COVID environment.

Conclusion

The pleomorphic nature of disease, and the consequential definitional issues for Long COVID, present a challenge for clinical development, given the requirement for definition of consistent endpoints for trials. Of the discrete interventional agents appearing in the clinical trials database, only ~1/3 are in Phase 3 clinical trials at present. Based on the number of patients enrolled, some of these listings are almost certainly for Phase 2 or 3 clinical trials, not typical Phase 3 confirmatory trials. Although there are at least 82 unique active agents (including dietary supplements, but excluding medical devices) in development, and they are characterised by diverse mechanisms of action, the emergency approach that was employed during the COVID-19 pandemic is not being replicated for development of

Table 2. Active principles in Long COVID Phase 3 clinical trials.

Active principal	Type of intervention	Combination of active ingredients/interventions?
Metformin	Small molecule	No
Lau-7B	Small molecule	No
Nitrite Supplementation	Dietary supplement	No
Fluvoxamine	Small molecule	No
Na Pyruvate Nasal Spray	Small molecule	No
Sirulimus C-19	Small molecule	No
Pycnogenol	Dietary supplement	No
Trigeminal Nerve Stimulation	Medical device	No
Testofen	Dietary supplement	No
Anakinra	Small molecule	No
Human Growth Hormone	Biologic	No
Homeopathic Treatment	Dietary supplement or alternative	Not discernable from database
Statins	Small molecule	Not discernable from database
Prospekta	Biologic	No
Allopurinol	Small molecule	No
Lidocaine Stellate Ganglion Block	Small molecule	No
Paxlovid	Small molecule	Yes
Immunorecon	Dietary supplement	Not discernable from database
Adaptogens	Dietary supplement	Yes
ASA	Small molecule	No
Montelukast	Small molecule	No
COVID-19 Vaccines	Biologic	Yes

Table 3. Lead interventions for Long COVID that appear to be farthest progressed toward market.

Intervention	Structure	Comments
LAU-7B (Sponsor: Laurent Pharma)	Retinoid	Anti-inflammatory Phase 2 and 3 Adaptive Trial
Metformin (Sponsor: University of Minnesota)	Small molecule	Recipients of metformin were 41% less likely to develop Long COVID.[4] Antiviral, antidiabetic, anti-inflammatory actions
Anakinra (Sponsor: Hellenic Institute for the Study of Sepsis)	Biologic, recombinant Il-1 receptor agonist	Approved for treatment of Rheumatoid Arthritis
Statins (Sponsor: The George Institute, Sydney Australia)	Small molecule. Fermentation product of aspergillus, HMG-COA reductase activity	Approved for lipid reduction and other indications
Paxlovid (Sponsor: Kanecia Obie Zimmerman, Duke Universityand Stanford University).	Small molecules (2)	Combination of two antivirals, Nirmatrelvir co-packaged with Ritonavir, previously approved for moderate to severe acute COVID-19
Montelukast (Sponsor: Fundacio d'Investigacio en Atencio Primaria Jordi Gol i Gurina)	Small molecule	Leukotriene receptor antagonist, previously approved for asthma.

treatments for Long COVID. Thus there is likely to be significant delay before medical professionals will be able to offer patients commercially available treatments for Long COVID, unless there is a redirection of government or private funding.

We look forward to following up this study with further assessments of the development of interventions for mitigating or curing Long COVID in the months and years to come.

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Data availability. Outputs from the search based on the search terms listed in the methods section can be provided in PDF format, on request.

Conflicts of interest. Ross Barnard is a member of the editorial board of *Microbiology Australia* but did not at any stage have editor-level access to this manuscript while in peer review. *Microbiology Australia* encourages its editors and editorial board members to publish in the journal and they are kept totally separate from the decision-making processes for their manuscripts. The authors have no further conflicts of interest to declare.

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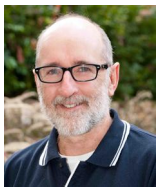

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