

Review

Interventions For Improving Long Covid Symptomatology: A Systematic Review

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Abstract: **Introduction:** Although the understanding of several aspects of long COVID syndrome is increasing, there is limited literature regarding the treatment of these signs and symptoms. The aim of our systematic review is to understand which therapies have proved effective against the symptoms of long COVID. **Methods:** A systematic search for randomized controlled or clinical trials in several databases was conducted until 15/05/22. Specific inclusion criteria included: (1) intervention studies, either as randomized controlled (RCTs) or clinical trials; (2) diagnosis of long-COVID, according to the World Health Organization criteria; (3) presence of long-COVID for at least 12 weeks after SARS CoV2 infection. **Results** We initially found 1,638 articles to screen. After removing 1,602 works based on their title/abstract, we considered 35 full-texts and, among them, two intervention studies were finally included. The first RCT focused on the greater improvement of treatment combining olfactory rehabilitation with oral supplementation with Palmitoylethanolamide and Luteolin in patients with olfactory dysfunction after COVID-19. The second study evaluated the positive impact of aromatherapy vs standard care in adult females affected by fatigue. **Conclusion** Our systematic review found only two intervention studies focused on patients affected by long COVID. More intervention studies are needed to investigate potentially positive interventions on long covid symptoms.

Keywords: Long COVID; COVID-19; Therapy; Interventions; SARS CoV2

1. Introduction

Coronavirus disease 19 (COVID-19) is a condition that has been putting a strain on health systems around the world for more than two years and has disrupted everyday lives. Parallel to the battle to stem the illness in its most acute phases, the prospect of a

new challenge is growing: long COVID.[1] In this regard, some recent systematic reviews and meta-analyses have indicated that most people who contract COVID-19 recover completely, but at least 10-20% of patients experience a range of medium- and long-term effects after recovering from the acute stage of the disease.[2] These medium and long-term effects are collectively defined as post COVID-19 syndrome or "long COVID". In the WHO definition, this condition affects individuals with a history of SARS CoV-2 infection which signs or symptoms occurring 3 months after the COVID-19 infection lasting for at least 2 months. [3]

Interestingly, similar post-viral syndromes have already been observed in conditions caused by herpesviruses, such as Cytomegalovirus and Epstein-Barr [4], as well as other coronaviruses, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).[5] There is currently limited knowledge of the underlying pathology and epidemiology of long COVID, however studies available are constantly increasing. Long COVID represents a global problem and has the potential to inflict anyone who has developed the SARS-CoV-2 infection regardless of the severity of the acute illness [6, 7], even children and adolescents.[8]

Several epidemiological studies have shown that the most common symptoms of long COVID are represented by fatigue and dyspnea [9], but other less typical symptoms include myalgia, headache, chest and joint pains, cough, smell and taste dysfunctions, insomnia, wheezing, rhinorrhea, cognitive and mental disorders, and cardiac and gastrointestinal issues. Importantly, these symptoms may persist more than six months.[10]

Although many aspects of long COVID syndrome's understanding are increasing, there is limited literature regarding the treatment. Given this background, the aim of our systematic review is to understand which therapies have proved effective against the symptoms of long COVID, which appears to be as the chronic manifestation of a disease with complex repercussions. [11]

2. Materials and Methods

2.1. Protocol registration

This study was conducted following the recommendations in the Cochrane handbook for systematic literature reviews to conduct the screening and selection of studies.[12] The original protocol was registered in PROSPERO (CRD42022335907). This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

2.2. Research question

The research question for this systematic review is: What are the interventions that can improve long-COVID signs and symptoms? To guide the identification of adequate keywords to build search strategies to search bibliographic databases, the research question was framed into the PICOS (Participants, Intervention, Comparison, Outcome, Study design) format.

The research question formulated into PICO(S) format was, as follows: (P) laboratory confirmed and/or clinically diagnosed COVID-19; long-COVID was defined as the presence of signs and/or symptoms after three months and lasting at least two months and that cannot be explained by other medical conditions, in agreement with the indications of the World Health Organization [WHO] [14]; (I): any pharmacological or non-pharmacological; (C) non active, i.e., placebo or standard/usual care; (O) severity of signs and symptoms of long-COVID; (S) randomized controlled (RCTs) or clinical trials (CCTs).

2.3. Information sources and search strategies

We searched PubMed, Embase, Scopus, and Web of Science, until 15th May 2022, for articles written in English. The search for individual studies in these bibliographic

databases was supplemented by manual searches of reference lists of included relevant systematic reviews already published regarding this topic.

Considering the main PICO elements, we built the following search strategy for Medline: (((("COVID-19"[All Fields] OR "Novel Coronavirus-Infected Pneumonia"[All Fields] OR "2019 novel coronavirus"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields]) AND ("lingering symptoms"[All Fields] OR "persistent symptoms"[All Fields] OR "long-term symptoms"[All Fields] OR "long-term Covid"[All Fields] OR "long-term"[All Fields] OR "long-term"[All Fields] OR "long"[All Fields])) OR ("long COVID"[All Fields] OR "long-COVID"[All fields] OR "PACS"[All fields] OR "post acute COVID syndrome"[All fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])). Then, we adapted the search strategy and the syntax for the other databases. The management of the references possibly eligible was performed using the Rayyan website (<https://www.rayyan.ai/>).

2.4. Eligibility Criteria

Specific inclusion criteria included the following: (1) intervention studies, either as RCTs or CCTs; (2) diagnosis of long-COVID, according to the WHO criteria; (3) presence of long-COVID for at least two months.[14] Studies with no WHO definition of long COVID or with an unclear follow-up, observational studies, head to head trials were excluded.

2.5. Study selection

We followed the recommendations reported in the Cochrane handbook for Systematic reviews to select studies that were finally included in this review.[12] The selection of the studies was independently carried out by four authors (OT, RB, SC, MC) in two couples, with consensus meetings to discuss the studies for which divergent selection decision was made. A third senior member (NV, FDG) of the review team was involved, when necessary. The studies selection process involved, first, a selection based on title and/or abstracts, then a selection of studies retrieved from this first step based on the full-text manuscripts.

2.6. Data extraction

Two authors (SC, MC) extracted in a standardized Microsoft Excel sheet the following information, (double checked by one senior author; NV): data regarding the identification of the manuscript (e.g., first author name and affiliation, year of publication, journal name, title of the manuscript), characteristics of the population considered (e.g., sample size, mean age, location, gender, etc.), setting (e.g., hospital, intensive care unit, hospital, etc.), long-COVID sign or symptom investigated, method for COVID19 diagnosis, hospitalized (yes/no/not reported), follow-up (in months), type of intervention. We planned, as declared in the protocol, to extract data for a meta-analysis, but since only two RCTs were available, we reported the data descriptively.

2.7. Risk of bias assessment

Two authors (OT, RB) independently appraised the risk of bias of the included studies and one senior (NV) checked these data, using the Cochrane Collaboration's tool through seven aspects of potential biases [12]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (including early termination and absence of prospective sample size calculation). The risk of bias was then categorized as high, low, or unclear.

2.8. Data synthesis

Since a limited number of studies was available, it was decided to descriptively report the findings.

3. Results

3.1. Literature search

As shown in Figure 1, we initially found 1,638 articles to screen. After removing 1,602 articles based on their title/abstract, we considered 35 full-texts and, among them, two intervention studies were finally included. [15, 16]

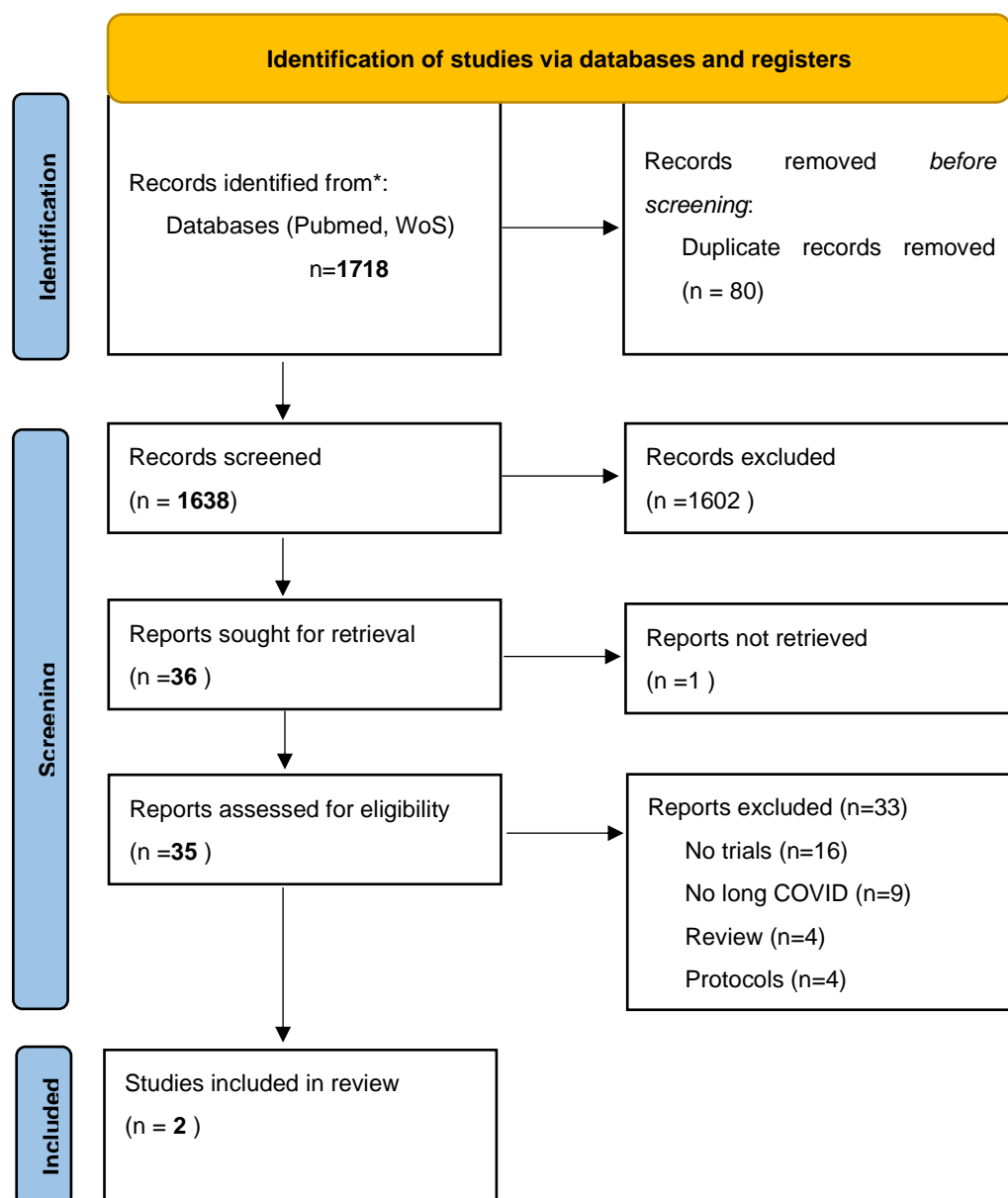


Figure 1. PRISMA flow-chart.

3.2. Descriptive characteristics and risk of bias

Table 1 shows the main descriptive characteristics of the two RCTs included [15, 16], whilst no CCT was available. One study was carried out in Europe and one in North America. In both studies, the definition of long COVID was made according to the criteria proposed by the WHO. These two studies considered mainly females and adults, without including children or older people. As shown in Supplementary Table 1, in one RCT [15]

we observed a potential high risk of bias for the random sequence generation and unclear regarding allocation since it was not declared, whilst the other work indicated low risk of bias. [16]

Table 1. Descriptive characteristics and main findings of the studies included.

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| Author | Year | Country | Sample size | Definition of long COVID | Sign or symptom investigated | Methods for COVID19 diagnosis | Age | % females | Follow-up (months) | Type of intervention | Outcome | Descriptive results |
|-----------|------|---------|-------------|--|--|-------------------------------|-------------|-----------|--------------------|---|--|---|
| D'Ascanio | 2021 | Italy | 12 | A condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis | anosmia/hyposmia persisting \geq 90 days after negative COVID-19 nasopharyngeal swab | nasopharyngeal swab | 42.2 (14.1) | 67% | 1 | olfactory training/stimulation through Sniffin' Sticks, administered twice every day (10-minute session) for 30 days plus daily treatment with PEA/Luteolin oral supplement | Sniffin scores | Patients taking supplement had greater improvement in Sniffin score than controls (mean change in Sniffin score = 2 for CG and 4 for TG; KW: $p = 0.01$) |
| Hawkins | 2022 | US | 44 | fatigue not prior to COVID-19 infection and recovered at least 5 months before | fatigue | nasopharyngeal swab | 19-49 | 100% | 0.5 | aromatherapy | Multidimensional Fatigue Symptom Inventory, Short Form | Individuals who inhaled the essential oil blend for 2 weeks had significantly lower fatigue scores. Significant results were found on the subscales of global, behavioral, general, and mental fatigue, as well as vigor. |

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3.3. Main findings

One RCT [16] including twelve participants (followed up for one month) found that in patients with anosmia/hyposmia persisting ≥ 90 days after negative COVID-19 nasopharyngeal swab, the use of an olfactory training/stimulation through Sniffin's Sticks, administered twice every day (10-minute session) for 30 days plus daily treatment with PEA/Luteolin oral supplement had a greater improvement in the Sniffin score (which measures olfactory sensitivity) than controls that received standard care (mean change in Sniffin score = 2 for controls and 4 for treatment; $p = 0.01$). [16]

The other study included 44 adult females affected by fatigue during long COVID and followed-up for two weeks.[15] In this study, aromatherapy was compared to standard care. Overall, the authors found that people with long COVID affected by fatigue who inhaled the essential oil blend for 2 weeks had significantly lower fatigue scores and that significant results were found on the subscales of global, behavioral, general, and mental fatigue, as well as vigor. [15]

4. Discussion

We conducted a systematic review of interventional studies reporting data that could improve signs and symptoms of long COVID, based on the WHO definition.[14] Among all the studies considered, only two were eligible, with a limited sample size and a short follow-up.

The first study focused on olfactory dysfunction. [16] Anosmia and hyposmia are among the most frequent symptoms of both COVID19 and long COVID19 and have helped to characterize at the level of general debate what was apparently a simple flu-like syndrome.[17] For more than two decades, semi-quantitative assessment has been the most common study method for olfactory stimulation.[18] Among the most widely used instruments of use is the Sniffin Sticks test. In the study by authors D'Ascanio L. et al. this same instrument showed the utility in the treatment of olfactory dysfunction of long COVID19. [16] The authors reported that the use of olfactory training/stimulation through Sniffin sticks, administered twice daily, showed at 30-day follow-up an improvement in score compared with controls in patients with persistent anosmia/hyposmia ≥ 90 days after COVID-19-negative nasopharyngeal swab. [16] Although the pathogenetic mechanisms underlying COVID-related anosmia/dysosmia are still unclear [19], some rehabilitation of the olfactory pathway was achieved in this study. The rehabilitation through sensorial stimulation is reported from other articles, also in a perspective of self-management of symptoms.[20] This is to be considered an important finding in the management of long COVID: as some qualitative assessment studies have documented, the residual symptom of olfactory loss has a strong association with the psychological distress of the long COVID patient.[21]. Further research on a larger scale is required to verify the findings of this study and inform medical policy regarding long term olfactory long COVID symptoms.

The second study concerns another common symptom of long COVID: chronic fatigue. Through an RCT, Hawkins et al. evaluated the effect of aromatherapy on long COVID related chronic fatigue. It is known that aromatherapy is useful in other conditions such as the treatment of agitation in patients affected by dementia, whilst conflicting results are present for other diseases [22]. Despite the increased risk of bias compared with the previous study (due to limited data on random sequence generation), the finding that the group that inhaled the essential oil blend for two weeks had significantly lower fatigue scores, is important both from a general and mental fatigue perspective [15]. However, these observations were made only in females limiting the generalizability of these findings in men. However, this study is one of the various attempts to manage chronic fatigue syndrome due to COVID-19. Several authors agreed that possible treatments of this condition must differentiate possible organic and functional causes.[23] Although a clear and unambiguous pathogenesis has not yet been identified, there is agreement on the role of other viral infections. EBV is thought to be the major culprit, but cases related to SARS

and MERS are also reported in the literature. Only now, however, in view of the important and massive social burden of COVID19, is the management of a specific virus-related form of chronic fatigue being questioned for the first time [24].

Young adult UK citizens with persistent symptoms following COVID-19 may benefit from an online breathing and wellness program conducted at the English National Opera (ENO), according to the recent ENO Breathe trial. However, because the authors did not apply the WHO criteria of long covid in their trial, this study is not considered to be eligible for our review [25].

One important recent finding is that vaccination against COVID-19 could be useful in preventing long COVID as shown in a recent large study in the United States of America [26]. The systemic antibody responses probably influence the severity of post-COVID/long COVID symptoms, as shown by recent literature. [27-29] Despite the literature is not univocal regarding this topic [27-29], one of the potential mechanisms is the protective role of vaccination against cardiovascular diseases that seems to be present also in long term period [29-34].

In order to promote new countermeasures (vaccines, drugs, and diagnostics) for long COVID based on public health requirements, governments, agencies, NGOs, and industry should continue to exchange information, diagnostic tools, and data. This synergy, as in COVID 19 pandemic and in other epidemic [35], could be crucial in control long Covid symptomatology.

The findings of our systematic review must be interpreted within its limitations. First, there is a paucity of studies currently available in the published literature. The need to introduce intervention studies for patients with long COVID into the clinical and scientific landscape now arises as imperative: the identification of appropriate symptom management and proper follow-up in the short and long term can thus help to assess possible patient outcomes. In this regard, we found many protocols that will add possible novel treatments for long COVID, that in the next future can contribute to new scientific evidence [36].

5. Conclusions

In conclusion, our systematic review found only two intervention studies that can help patients affected by long COVID. The varied clinic of long COVID, as well as the unclear pathogenesis, raises an additional question, i.e., "who is the referral specialist for Long Covid?" To date, management has been left to chance or mere continuity with the acute care inpatient unit. This might suggest the need to identify the correct characteristics of a multidisciplinary team: this would allow, on the one hand, more efficient care of individual patients, and on the other hand, a more in-depth and timely study of the pathology.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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