LONG-COVID CONDITION THERAPEUTICS: A MULTI-MODAL INVESTIGATION OF TREATMENT EVIDENCE, OFF-LABEL PRESCRIBING PATTERNS, AND CLINICAL OUTCOMES

Ph.D. thesis

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1. Introduction

The COVID-19 pandemic has left millions suffering from long-lasting symptoms collectively known as long COVID or post-COVID condition.
This chronic, multi-system disorder affects up to one-fifth of those infected, causing fatigue, breathlessness, cognitive difficulties, and various organ complications. Despite extensive research, its exact mechanisms and effective treatments remain largely unclear.
Evidence suggests that early antiviral therapy and vaccination can mitigate the risk of persistent sequelae, yet no standardised pharmacological therapy exists.

The dissertation examines the treatment options and therapeutic evidence for long COVID, with a particular focus on clinical trials and their results. It examines the off-label use of drugs related to COVID-19 infection in Hungary, comparing it with international clinical trial data, and examines the medication patterns of 470 post-COVID patients.

2. Objectives

2.1. Long COVID and possible preventive options

This dissertation systematically synthesizes and critically compares recent scientific evidence on long COVID, with emphasis on new treatments, clinical trial results, and consensus guidelines since

2.2. Off-label drug use for long COVID

It investigates off-label therapy practices for long COVID symptoms, comparing Hungarian approaches to international trends and assessing their integration into domestic healthcare.

2.3. Post-COVID interstitial lung disease: medication usage analysis

Medication usage is quantitatively analysed in a cohort of 470 post-COVID patients, with a focus on descriptive patterns and potential associations between interstitial lung disease and pharmacological management.

3. Methods

3.1. Long COVID and possible preventive options

Sebők et al.'s (2023) earlier analysis was updated with new publications and clinical trial data from 2023–2025. Systematic database searches identified 70 relevant long COVID drug trials and the latest literature, which were reviewed to update tables and findings and ensure the synthesis reflected recent global advances in pharmacotherapy.

3.2. Off-label drug use for long COVID

A national database review identified COVID-related off-label drug requests in Hungary, and each application was evaluated for key details. A global literature search found six original studies of off-label drug use for long COVID. Together, these results allowed direct comparison of national and international off-label practices.

3.3. Post-COVID interstitial lung disease: medication usage analysis

This retrospective study based on data from 470 post-COVID outpatients managed at the post-COVID outpatient clinic of the Pulmonology Department of Semmelweis University between February 2021 and January 2023, grouped by ILD status and symptom persistence. Key clinical, demographic, and medication information was assembled and analysed using descriptive statistics and subgroup comparisons, providing a profile of treatment patterns and disease characteristics in this unique cohort.

4. Results

4.1. Long COVID and possible preventive options

Definitions and terminology for long COVID have become more standardized, with most authorities now recognizing persistent, multi-organ symptoms beyond 2–3 months after SARS-CoV-2 infection. However, some heterogeneity and debate in naming and case definitions remain. Recent years have seen a shift in focus from purely symptomatic care to research on prevention and targeted interventions. Vaccination and early antiviral treatment offer moderate protection against developing long COVID, while other preventive or therapeutic strategies—such as glucocorticoids or repurposed drugs—have shown inconsistent results. Despite expanding research efforts, no breakthrough therapy has emerged, and effective evidence-based management remains elusive.

The updated systematic review identified 70 drug-based clinical trials for long COVID registered between late 2022 and September 2025. Despite rigorous methodology—including 27 quadruple-blind randomized controlled trials and 17 Phase III studies—only 2.9% have published results, creating a significant evidence gap. The therapeutic landscape spans antivirals (9 trials), neurological interventions (8 trials), anti-inflammatory agents (6 trials), cardiovascular therapies (6 trials), and immunomodulators (6 trials). Large-scale Phase III studies include the REVIVE trial (1,500 participants testing fluvoxamine/metformin), baricitinib for neurological symptoms (550 participants), and allopurinol for cardiovascular risk (1,116 participants). Most completed trials—including those testing Paxlovid, lithium, montelukast, metoprolol, atorvastatin, cannabidiol, and vortioxetine—yielded negative or statistically insignificant results. No therapeutic breakthrough has emerged.

A minority of ongoing trials (IV immunoglobulin, low-dose naltrexone, sirolimus) continue recruitment, with results pending.

4.2. Off-label drug use for long COVID

Analysis of the national database revealed 165 COVID-related off-label requests from 2008 to May 2025, with a striking temporal concentration: 87.9% submitted in 2020, declining sharply to zero by 2025. The patient cohort was predominantly male (63.5%) with a mean age of 57 years. The most frequently requested drugs were tocilizumab (34.5%), favipiravir (35.7%), ruxolitinib (6.1%), and remdesivir (4.8%), primarily for acute COVID-19 pneumonia and cytokine release syndrome. Combination therapies accounted for 12 cases. Critically, only five off-label requests addressed long COVID complications—all involving pirfenidone for post-COVID pulmonary fibrosis (2022–2023). Global literature review identified only six original publications on off-label pharmacological interventions for long COVID, indicating limited adoption and narrow therapeutic scope. This evidence-practice gap underscores conservative regulatory approaches and highlights significant divergence from broader international research trends.

4.3. Post-COVID interstitial lung disease: medication usage analysis

Retrospective analysis of 470 post-COVID outpatients (February 2021–January 2023) revealed distinct medication usage patterns. Patients were stratified by ILD status: 11.1% confirmed/suspected ILD versus 88.9% non-ILD. Polypharmacy was prevalent, particularly among ILD patients, with medication counts strongly correlating with age ($r = 0.96$; $p < 0.001$). Cardiovascular medications dominated: beta-blockers (33.3% in ILD patients), antiplatelet agents (33.3%), and ACE inhibitors/ARBs showed significantly higher use in the

ILD subgroup compared to non-ILD patients ($p < 0.05$). Surprisingly, respiratory-specific therapies (bronchodilators, inhaled corticosteroids) were rarely prescribed, despite persistent pulmonary symptoms. The overall medication burden was high (13.4% polypharmacy rate), yet targeted pulmonary pharmacotherapy remained underutilized. These findings reveal a therapeutic paradox: extensive cardiovascular and metabolic treatment alongside inadequate respiratory symptom management, suggesting a need for revised clinical protocols specifically addressing post-COVID ILD.

5. Conclusions

Despite intensive efforts, there is still no proven guideline or effective drug therapy for long COVID, as new treatments—including vaccines, antivirals, immunomodulators, and off-label drugs—have shown mostly limited or negative results in clinical trials and have not led to consensus recommendations. Wide variability in definitions, study designs, and reported outcomes continues to impede comparison and the standardization of care. Progress is further slowed by the lack of large-scale, well-designed studies such as RECOVER and SOLIDARITY, as well as by persistent consensus and regulatory barriers. In Hungary, off-label drug use for long COVID remains limited, often diverging from international practice and lacking global coordination. Notably, among the 470 patients analysed, drug utilization is high, and polypharmacy is common—especially in those with ILD—yet medications specifically targeting respiratory symptoms are seldom used. This evidence-practice gap highlights the ongoing need for high-quality research and harmonized clinical approaches in the management of long COVID.

6. Bibliography of the candidate's publications

Publications related to the thesis:

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