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Pharmacological Approaches to the Management of Long COVID

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ABSTRACT

Long COVID represents a multifaceted clinical syndrome characterized by persistent symptoms such as fatigue, dyspnea, cognitive impairment, and autonomic dysfunction that extend beyond the acute phase of infection. The heterogeneity of its manifestations and underlying pathophysiological mechanisms, including chronic inflammation, immune dysregulation, endothelial dysfunction, viral persistence, and autonomic imbalance, has complicated the development of targeted therapies. Current pharmacological treatment strategies are largely symptomatic and repurposed from established therapies for related conditions. These include the use of anti-inflammatory and immunomodulatory agents, cardiovascular and autonomic regulators, anticoagulants, and antiplatelet therapies to address microthrombosis, and agents for neurological and psychiatric symptoms. Additionally, novel therapeutics under investigation target viral reservoirs, mitochondrial dysfunction, and abnormal coagulation pathways. While clinical trials remain limited and evidence is evolving, a precision-medicine approach integrating patient phenotype and underlying mechanisms may enhance treatment efficacy. This review synthesizes the current pharmacological strategies, evaluates emerging therapeutic candidates, and highlights the importance of robust clinical trials to establish effective and safe interventions for Long COVID.

KEYWORDS

Long COVID, pharmacological agents, epidemiology, symptoms, treatment, supportive care

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiologic agent of Coronavirus Disease 2019 (COVID-19), which is so called because it was first reported in 2019 from Wuhan, China. Since then, it has wreaked havoc across the globe, leading to a total collapse of public health systems across nations[1]. As a result, delivery of healthcare to those who need it most has also suffered greatly[2]. Although COVID-19 primarily affects the respiratory system, it also affects other organs and systems. As a result, mental health issues[3], neurological complications[4] and even oral health problems[5] have been reported.

It has now become clear that approximately 10-20% of COVID-19 patients who had fully recovered, again start to exhibit new symptoms after 12 weeks, which can last over a long period of time, from weeks to months, and sometimes years. This condition is commonly referred to as Long COVID[6]. It is characterized by many overlapping symptoms that can be debilitating to the patient[7,8].

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The case definition for Long COVID, as given by the World Health Organization (WHO) indicates that the cases emerge within three months of recovery from the acute phase and the symptoms usually persist for about two months. Notably, the spectrum of symptoms observed in these patients differ from any other disease[9]. Although over 200 symptoms of Long COVID have been reported, three are most prominent, namely, fatigue, 'brain fog' and breathing difficulty, which can fluctuate and the patient may relapse, thereby complicating diagnosis and treatment[10].

Epidemiological data suggest that approximately 10-30% of individuals infected with SARS-CoV-2 develop Long COVID, though estimates vary depending on population characteristics, viral variants, and study methodologies[11]. The condition has been reported in individuals across all age groups, including those with mild initial illness[12]. The underlying pathophysiology remains incompletely understood, but proposed mechanisms include viral persistence, immune dysregulation, endothelial dysfunction, and microvascular injury[13]. Additionally, autonomic nervous system involvement and psychosocial stressors may exacerbate symptoms[14].

Given its substantial burden on healthcare systems and society, Long COVID has emerged as a major public health concern. It is associated with decreased quality of life, reduced work capacity, and increased healthcare costs[15]. Understanding the epidemiology, pathophysiology, and clinical spectrum of Long COVID is essential for developing evidence-based diagnostic criteria, therapeutic strategies, and rehabilitation programs. Therefore, this article reviews in detail all these aspects to gain better insight into how Long COVID could be tackled more effectively.

Epidemiology: Long COVID is typically defined as symptoms persisting ≥12 weeks (or ≥3 months) after acute SARS-CoV-2 infection, though some definitions begin at 4 weeks post-infection. Variability in definitions and symptom criteria leads to wide variance in prevalence estimates[16]. The prevalence of respiratory problems and fatigue is 20% each. Psychiatric and neurological problems have been reported in 18 and 16% of Long COVID patients, respectively. Memory problems, such as 'brain fog', arising from cognitive dysfunction, as well as dementia, have been reported in 11% of Long COVID cases[17].

Globally, approximately 400 million people are suffering from Long COVID, with 18 million in the US alone[18]. Multi-centric studies across Hyderabad, Vellore, Mumbai, and Thiruvalla in India have shown that 16.5% of hospitalized patients had Long COVID symptoms 1 year after discharge. The risk was elevated with ICU admission or longer stays[19]. Other Indian cohort-based studies indicate an incidence of ~30-37% among infected individuals[20]. In four Chinese cities (Beijing, Shanghai, Guangzhou and Hong Kong), the prevalence of Long COVID has been reported to be 90.4% (any level of severity), 62.4% (moderate/severe), and 31% (very severe)[21]. A study from Hainan Island during the Omicron wave reported a prevalence of 12.5%-lower than earlier figures (20-30%) due to younger age and mild variant, along with high vaccination rates[22]. Females, older age, pre-existing comorbidities, being unvaccinated, race/ethnicity, and lower socioeconomic status are consistently associated with a higher risk of Long COVID[17].

Symptoms: There are more than 200 symptoms of Long COVID. Symptom profiles vary widely. Severity spans from mild lingering symptoms to incapacitating disease, necessitating functional support. Symptoms often fluctuate, and some patients initially improve only to relapse after weeks or months[9]. Long COVID may resemble Myalgic Encephalomyelitis (ME) or Chronic Fatigue Syndrome (CFS)[23]. Children and adolescents can also be affected, typically experiencing fatigue, fever, sleep problems, headaches, anxiety, and multiple concurrent symptoms[24].

Of the many symptoms, several are more serious than others. These include severe fatigue, manifesting as profound tiredness that interferes with daily life activities. Others include cognitive dysfunction ("brain fog"), shortness of breath (dyspnea), chest pain, Post-Exertional Malaise (PEM),

Table 1: Types of symptoms and examples

Types of symptoms	Examples
General	Persistent fatigue, Post-Exertional Malaise (PEM), post-viral exhaustion
Neurological	Brain fog, headache, sensory disturbances, dysautonomia
Respiratory	Breathlessness, Acute Respiratory Distress Syndrome (ARDS), anosmia
Cardiovascular	Chest pain, palpitations, POTS
Musculoskeletal	Myalgia, arthralgia, back pain
Gastrointestinal	Nausea, diarrhea, abdominal pain, loss of appetite, ageusia
Mental	Anxiety, depression, sleep disorders, mood changes, suicidal thoughts

Table 2: Supportive care for Long COVID patients

Domains	Recommended strategies
Approach	Multidisciplinary teams, telemonitoring, personalized plans
Fatigue/PEM	Self-management with pacing, conservative rehabilitation
Breathlessness	Breathing exercises, pulmonary rehabilitation
Brain fog	Cognitive evaluation and therapy referrals
Autonomic dysfunction	Fluids, electrolytes, compression garments
Mental health	CBT, psychiatric support, sleep hygiene
Prevention	Vaccination, antiviral therapy if required

persisting 12-48 hrs after minimal physical exercise, migraine-like severe headaches, among others that persist even months later. Other problems, such as dysautonomia, Postural Orthostatic Tachycardia Syndrome (POTS), anosmia, ageusia, and sleep disturbances, have also been reported. Gastrointestinal problems, including nausea/vomiting, abdominal pain, bloating, diarrhea, constipation, and loss of appetite, have also been noted. Moreover, besides cognitive dysfunction, other psychological/psychiatric complications, such as anxiety, depression, mood disturbances, Post-Traumatic Stress Disorder (PTSD), and suicidal ideation are also quite common[8,10]. The major symptoms are summarized in Table 1.

Supportive care: To date, no definitive, approved treatments exist for Long COVID. Current management focuses on symptom-directed care, a multidisciplinary approach, and individualized rehabilitation rather than a universal cure[25]. Treatments are instituted as and when the symptoms appear, and a multi-pronged approach is adopted.

In case of fatigue and post-exertional malaise, self-management via energy conservation, pacing, the "3 Ps" strategy (prioritize, plan, pace), avoiding graded exercise therapy (GET), and virtual rehabilitation programs are often advised. For respiratory symptoms arising from persistent lung impairment, pulmonary rehabilitation is required. These include breathing retraining, involving diaphragmatic breathing and parasympathetic-stimulating techniques, which can help mitigate breathlessness, even in patients with normal pulmonary imaging[26]. Patients with cognitive complaints are referred for formal cognitive assessment and remediation in consultation with neuropsychology[27]. For autonomic dysfunction, including POTS, conservative measures like increased fluid and electrolyte intake, use of compression garments, and careful monitoring of orthostatic tolerance are recommended[28]. For mental health issues, Cognitive Behavioural Therapy (CBT) alongside structured rehabilitation has been shown with moderate certainty to improve both mental health and physical symptoms. Anxiety, depression, and insomnia should be managed using established psychiatric or behavioural interventions coupled with therapy. Rehabilitation of Long COVID patients typically requires a team-based approach, including primary care, physiotherapy, occupational therapy, respiratory therapy, mental health support, and specialty referral when needed. National guidelines (e.g., NICE in the UK, as well as new consensus frameworks) emphasise long-term follow-up, digital telemonitoring, and individualized rehabilitation plans[29]. The major treatment strategies are briefly summarized in Table 2.

Pharmacological treatment strategies: There are several pharmacological strategies that can be adopted to tackle Long COVID, which are discussed below.

- **Antivirals:** These aim to clear lingering viral replication or viral fragments believed to drive ongoing inflammation. Paxlovid (nirmatrelvir/ritonavir), remdesivir, and molnupiravir inhibit SARS-CoV-2 replication (via protease or RNA-dependent RNA polymerase inhibition), thus reducing inflammatory stimuli. However, trials in established Long COVID patients have shown no significant benefit compared to placebo. Prevention when administered early in acute infection appears more promising. However, treatment of Long COVID patients with a combination of Paxlovid and remdesivir has shown some promising results[30].
- **Immunomodulatory and anti-inflammatory agents:** These target sustained immune activation, auto-inflammation, and cytokine dysregulation. Baricitinib, a selective JAK1/JAK2 inhibitor, suppresses downstream STAT-mediated pro-inflammatory gene expression, modulating cytokine storm pathways. The REVERSE-LC clinical trial for neuro-inflammatory Long COVID, funded by the Vanderbilt University Medical Center, will be evaluating this drug. Currently, the recruiting of volunteers is in progress[31]. Bezisterim, a novel targeted anti-inflammatory agent, selectively inhibits inflammatory pathways without broad immunosuppression. The ADDRESS-LC clinical trial, funded by BioVie Inc., will be evaluating this selective anti-inflammatory drug. Currently, the recruiting of volunteers is in progress[32]. Low-dose naltrexone (LDN), a non-selective opioid receptor antagonist, modulates immune response by reducing microglial activation and decreasing pro-inflammatory cytokines, showing promise in small cohorts with fatigue and pain in post-acute sequelae of COVID-19 (PASC)[33]. DFV890 is an oral small-molecule inhibitor of the NLRP3 inflammasome. It blocks activation of caspase-1, reducing IL-1β and IL-18 release and pyroptosis. It targets exaggerated innate immune activation and is in early human safety/efficacy studies relevant to COVID-associated inflammation[34]. Dapansutrile (OLT1177) also inhibits NLRP3 via direct interaction with its ATPase domain, suppressing IL-1β/IL-18 and pyroptosis without affecting other inflammasomes. This drug has been traditionally used to treat gout flare-ups, but has recently also been investigated for post-COVID multi-organ inflammation[35]. Some studies have shown remission of Long COVID symptoms in a small number of patients, using casirivimab/imdevimab Monoclonal Antibody (mAb) cocktail (REGEN-COV). These mAbs exhibit high affinity for the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, to which they strongly bind, leading to neutralization of the virus[36]. However, robust clinical trials are still lacking. Fluvoxamine, a Selective Serotonin Reuptake Inhibitor (SSRI), is thought to modulate sigma-1 receptor and reduce cytokine production, possibly dampening inflammatory cascades. Small studies on COVID have shown reduced deterioration, but the definitive effect in Long COVID remains unproven.
- **Autoantibody neutralizing and mast cell stabilizing agents:** These involve autoantibodies and histamine-mediated mechanisms. The BC007, an experimental agent, neutralizes G Protein-Coupled Receptor (GPCR) autoantibodies linked to Long COVID autoimmunity. This has been proposed to reduce pathological antibody-driven signaling. The H and H antihistamines (e.g., famotidine, cetirizine) are used symptomatically to inhibit mast cell activation and histamine release. These are useful for alleviating the symptoms of Mast Cell Activation Syndrome (MCAS), which is a frequent complication of Long COVID[37].
- **Gut and endothelial targeted agents:** These address suspected mechanisms such as leaky gut or endothelial dysfunction. Larazotide stabilizes tight junctions in intestinal epithelium, reducing gut permeability ("leaky gut"). Early use has reduced circulating viral antigen and improved symptoms in the pediatric PASC trial[38]. The L-arginine and vitamin C have been trialled experimentally to improve endothelial dysfunction and oxidative stress in Long COVID, aiming to restore vascular homeostasis[39,40].
- **Cardiac and autonomic agents:** These drugs are repurposed for particular symptom clusters involving the heart and Autonomic Nervous System (ANS). Ivabradine is a HCN-channel blocker, which is used to treat POTS by slowing the heart rate and improving orthostatic tolerance. Metoprolol succinate (β antagonist) is considered for cardiac symptoms and POTS in Long COVID by improving heart rate control[38].

Table 3: Major pharmacological agents for treating Long COVID

Pharmacological agent	Class	Target	Mechanism of action
Paxlovid (nirmatrelavir /ritonavir)	Antiviral	3CL protease	Blocks viral replication by inhibiting 3CL protease
Remdesivir	Antiviral	RdRp	Blocks viral replication by chain termination of RdRp
Molnupiravir Favipiravir	Antiviral	RdRp	Blocks viral replication by mutagenesis in the viral genome
Ibudilast	Neuroimmune modulator /anti-inflammatory agent	PDE-4	Reduces neuroinflammation by inhibiting PDE-4
Infliximab	Anti-inflammatory monoclonal antibody	TNF-α	Inhibits TNF-α by blocking the binding to its receptor
Imatinib	Kinase inhibitor	Tyrosine kinase	Prevents respiratory failure by reversing pulmonary capillary leak through tyrosine kinase inhibition
Baricitinib	Immunomodulator	JAK1/JAK2	Suppresses STAT-driven cytokine expression
Bezisterim	Anti-inflammatory agent	Specific inflammatory pathway	Reduces neuroinflammation without immunosuppression
Low-dose naltrexone (LDN)	Opioid antagonist	Opioid receptors and microglia	Blocks cytokine release and modulates microglial activation
Ivabradine metoprolol	Cardiac/Autonomic agent	Cardiac conduction	Reduces POTS-related tachycardia and autonomic dysfunction
Deupirfenidone (LYT-100)	Antifibrotic agent	Lung tissue	Reduces pulmonary fibrosis and lung damage
Inosine pranobex	Immunostimulant	T-cells/NK cells	Immune enhancement, fatigue, neuroimmune symptoms
BC007	Autoantibody binder	Autoantibodies	Neutralizes GPCR autoantibodies
DFV890 Dapansutrile	Inflammasome suppressor	NLRP3 inflammasome	Blocks IL-1β/IL-18 release and pyroptosis
Fluvoxamine	SSRI	Sigma-1	Modulates inflammation via Sigma-1 pathways
H_1/H_2 antihistamines	Antihistamine	Histamine	Blocks mast cell degranulation
Larazotide	Tight junction regulator	Intestinal tight junctions	Reduces gut permeability/ antigen leak
L-arginine+Vitamin C	Antioxidant	Endothelium/ROS	Blocks oxidative endothelial damage

The major pharmacological agents, their classes, targets, and mechanisms of action are summarized in Table 3.

CONCLUSION

Long COVID is a heterogeneous syndrome involving possible viral persistence, immune dysregulation, autoimmunity, endothelial dysfunction, and symptom-specific pathology. Pharmacological strategies include antivirals, immunomodulators, intestinal barrier-stabilizing agents, and symptom-specific drugs. Most trials remain early-phase or exploratory, and therefore, larger stratified studies are needed to match treatments to patient subgroup mechanisms. Treatment of Long COVID as of September, 2025 remains primarily symptomatic and supportive, rooted in rehabilitation, energy management, and individualized care across multiple specialties. No single pharmacologic treatment has yet proven successful in large trials, although several immunomodulators and antivirals are under investigation. Emerging consensus guidance emphasizes long-term follow-up, symptom-based interventions, and holistic, personalized care.

SIGNIFICANCE STATEMENT

This study discovered the potential pharmacological interventions that can be beneficial for the management of Long COVID by addressing its complex pathophysiological mechanisms, including immune dysregulation, endothelial dysfunction, and viral persistence. By synthesizing current evidence on anti-inflammatory, immunomodulatory, cardiovascular, and neurological therapies, the study provides

valuable insights into optimizing treatment strategies through a precision-medicine approach. Moreover, it identifies emerging therapeutic candidates that may target underlying molecular and physiological abnormalities more effectively. This study will help researchers uncover the critical areas of drug repurposing, mechanism-based therapy development, and clinical validation that many researchers were not able to explore. Thus, a new theory on individualized pharmacological management of Long COVID may be arrived at.

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