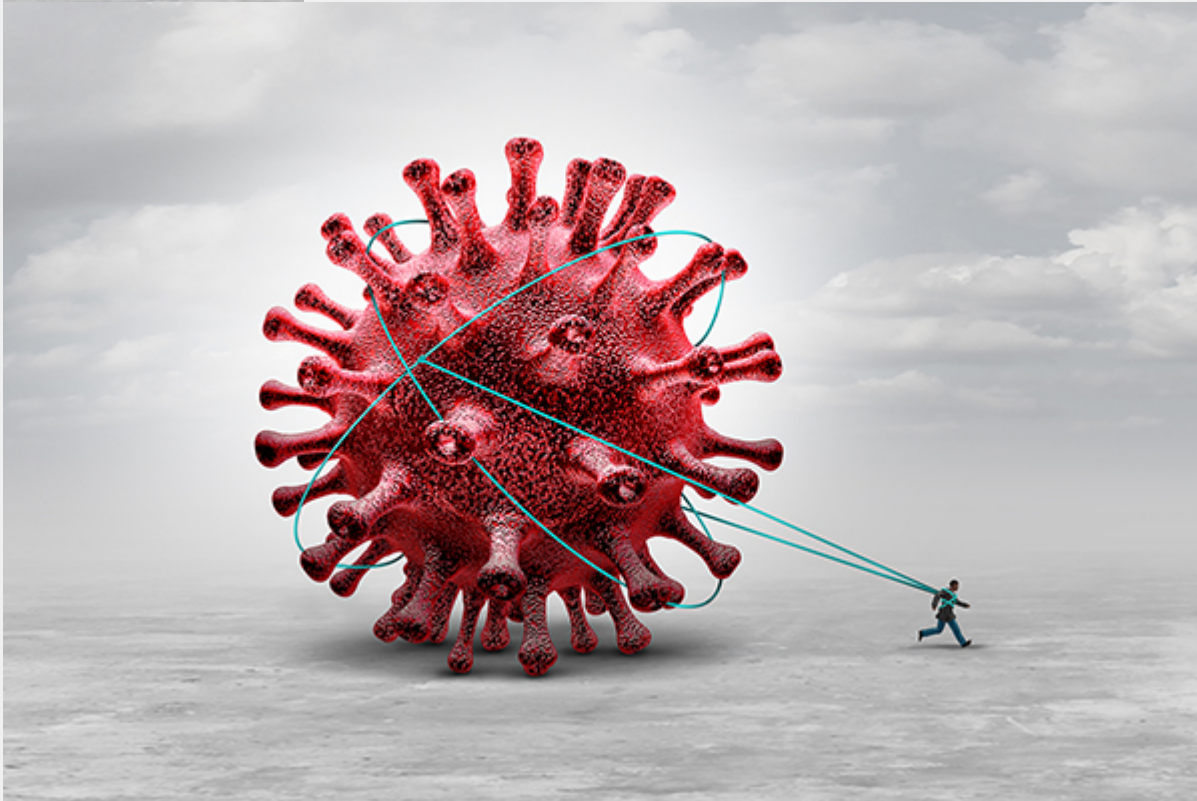


Vanquishing Long COVID



Long Covid is a complex disorder that resembles ME/CFS—a real clinical challenge. But because of the pervasiveness of Covid, there are a lot of research dollars committed to unraveling the mysteries of its aftermath. Early in the pandemic, the NIH allocated \$1.15 billion to study Long Covid; critics have argued that research efforts have bogged down amid bureaucratic snafus, and that the pace of rollout of effective treatments reflects a lack of urgency.

Common symptoms of Long Covid include, but are not limited to, fatigue, exercise intolerance, dizziness, lightheadedness, positional vertigo, shortness of breath, brain fog, memory deficits, sleep problems, heart palpitations, taste and smell alterations, tinnitus, headache, anxiety, depression, and episodic fevers. GI, endocrine, autoimmune and urological symptoms have also been reported. The scope of these disabilities makes it a challenge to study Long Covid and distinguish it from background disorders that ordinarily afflict the general population.

It was recently revealed that severely stressful events are associated with a likelihood of developing Long Covid. This should not be interpreted as a demonstration that Long Covid is merely a psychosomatic condition; instead, it illustrates the complex interplay between the brain and the immune system.

Cognitive behavioral therapy (CBT) is a controversial intervention because, while it may help patients positively reframe their symptoms, it gives the impression that

Long Covid is an imagined condition without distinct biological underpinnings. Not surprisingly, patient advocacy groups are up in arms over simplistically ascribing Long Covid to hypochondriasis or maladaptive beliefs. Nonetheless, CBT or even **mindfulness meditation** may provide an avenue for sufferers to harness the brain's formidable capacities for recovery.

When it comes to identifying a biological marker for Long Covid, studies yield conflicting results. Some highlight the role that chronically elevated cytokines might play—the immune system stuck like a broken record long after the pathogen has disappeared. Others suggest that a small subset of Long Covid sufferers may harbor chronic coronavirus infections—supporting the potential for antiviral drugs to ameliorate symptoms. Unfortunately, user experiences with medications like Paxlovid have been decidedly underwhelming.

Still, other studies have proposed that re-activation of underlying co-infections like Lyme, mycoplasma, Cytomegalovirus, or Epstein-Barr might account for the persistence of symptoms in Longhaulers.

One survey showed that a common denominator among Long Covid sufferers was **decreased cortisol**, suggestive of adrenal suppression. This ushers in the possibility that adaptogens or even low-dose hydrocortisone might help.

Similarly, physical therapy, graded exercise and breathing exercises have been proposed for Long Covid, although a majority of sufferers experience worsening with exertion. There's some merit to the notion that **restoring vagal tone** can help with symptoms. **At least one trial is underway** to evaluate the curative potential of vagal nerve stimulation via transcutaneous electrical stimulation in Longhaulers with autonomic symptoms like dizziness, light-headedness, and palpitations.

There's evidence that alterations in the microbiome may reinforce the persistence of Covid. Repleting the microbiome and repairing leaky gut may offer benefits in a subset of patients, especially those with GI or autoimmune manifestations.

Evidence is mounting that Long Covid affects the mitochondria, the powerhouses of the cells. To that end, mitochondrial support has been proposed, with varying results. **One preliminary study** showed that the synergy between CoQ10 and alpha lipoic acid hastened recovery from Long Covid; **another recent review** highlights the reparative role of lipid replacement therapy (LRT) with glycerolphospholipids like NTFactor®.

A trial is underway to examine the impact of nicotinamide riboside, a known mitochondrial enhancer, on Long Covid.

There's also the theory that histamine disturbances underly the puzzling ubiquity of Long Covid symptoms. Strategies directed at ameliorating **Mast Cell Activation Syndrome (MCAS)** including diet modification, nutraceuticals, and pharmaceutical drugs are thus employed.

In surveys of Long Covid sufferers in which they rate their response to supplements, nattokinase stands out. **A Japanese study** suggests it has a degradative effect on the coronavirus spike protein. It has been proposed that a mechanistic pathway underlying Long Covid symptomatology is small vessel blockage due to deposition of microclots; nattokinase is a proteolytic enzyme that may have antithrombotic effects.

Then there's the potential role of **low-dose naltrexone (LDN)**, a therapy that modulates the immune response by manipulating endorphin and enkephalin pathways.

Similarly, some have proposed cannabidiol (CBD) as a way of harnessing the anti-inflammatory and immunomodulatory potential of endocannabinoid receptors.

Can we just say NO to Long Covid? NO stands for nitric oxide, a signaling molecule that has been investigated for its antiviral, vasodilating, and anti-inflammatory impact in acute Covid. But some are now speculating that a primary deficit in long haulers is nitric oxide deficiency. If this theory pans out, then drugs or supplements like dietary nitrates, cocoa flavanols, and/or arginine/citrulline that drive NO synthesis may hasten resolution of Long Covid.

There's also some buzz around glutathione for Long Covid; a trial is underway to evaluate the effects of glutathione along with n-acetylcysteine and alpha lipoic acid on Longhaulers.

Melatonin has also been proposed for Long Covid, not just to reduce sleep problems and restore circadian rhythms, but because of its anti-inflammatory and immunomodulatory effects.

A raft of drugs are being investigated to be repurposed against Covid; they include antihistamines, immunosuppressants, antivirals like Paxlovid, anti-clotting drugs, glucocorticoids, statins and even Viagra.

An unproven off-shore intervention that some desperate Long Covid sufferers are increasingly turning to is apheresis—a therapeutic blood-washing procedure that has been deployed conventionally against certain autoimmune disorders and even high cholesterol.

When it comes to unconventional procedures for Long Covid, hyperbaric oxygen therapy (HBOT) is a candidate, but evidence for its effectiveness is limited to small studies.

As to diet, a modified low-carb Mediterranean diet, with its anti-inflammatory benefits, salutary effects on the microbiome, and superior nutrient density, has been proposed as a best bet to facilitate recovery from Long Covid.

Additionally, the role of supplemental protein—coupled with probiotics—in fending off post-Covid sarcopenia was evaluated in a recent study; after two months, a significant improvement in the skeletal muscle index (SMI) was observed.

Complicating matters is that anecdotal reports of cures or amelioration of Long Covid with various treatments are colored by the tendency for Long Covid symptoms to spontaneously abate. A recent optimistic assessment pegs recovery rates at 75% after one year. But a German study reported that only a minority of patients—20%—were completely free of neurocognitive symptoms 12 months after their diagnosis with Long Covid.

Bottom line: Long Covid is very unlikely to be one thing, and yield to an all-encompassing “cure”. It's going to test the ingenuity of medical practitioners who will deal with the inevitably increasing numbers of these patients. Insights derived from their treatment may have important ramifications for how we address the many sufferers of other complex debilitating disorders with elusive symptoms. Integrative and Functional Medicine offers the most comprehensive framework for understanding Long Covid.