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Treatments for Long COVID-Related Fatigue (2023–Present): A Frontier Evidence Review

Long COVID (post-acute sequelae of SARS-CoV-2, or PASC) is associated with persistent fatigue often accompanied by brain fog, exercise intolerance, and other symptoms. Research since 2023 has accelerated to identify interventions targeting proposed mechanisms such as immune dysregulation, mitochondrial dysfunction, microclot formation, autonomic imbalance, and others [1]. Below, we survey global treatment approaches across supplements, herbs, dietary strategies, off-label drugs, clinical trials, and anecdotal therapies – **ranked by level of supporting evidence**. Each treatment listing includes its **proposed mechanism**, **evidence source/type**, and references.

Tier 1: Well-Supported Interventions (Peer-Reviewed Studies/Trials)

- **Multidisciplinary Rehabilitation (Exercise & CBT):** *Mechanism:* Gradual physical reconditioning and psychological coping to improve fatigue. *Evidence:* Randomized trials indicate **cognitive-behavioral therapy (CBT)** can significantly reduce fatigue in long COVID [2]. Similarly, **structured exercise programs** (with pacing) have shown modest benefits – e.g. one RCT found intermittent aerobic exercise (3–5× weekly, 4–6 weeks) improved physical function compared to continuous exercise [3]. A large trial of an 8-week online combined **physical + mental rehab program** (585 patients) reported improved quality of life and mental health (and increased recovery rates) versus minimal care [4] [5], though notably **no significant improvement in fatigue** was seen [6]. These interventions are considered core management strategies given their safety and moderate efficacy.

- **Gut Microbiome Modulation (Synbiotic *SIM01*):** *Mechanism:* Restores gut flora to reduce systemic inflammation and immune dysregulation. *Evidence:* A large **placebo-controlled trial** in Hong Kong (463 patients) tested a **probiotic + prebiotic synbiotic (SIM01)** and found significantly higher rates of fatigue alleviation at 6 months compared to placebo (odds ratio ~2.27 for fatigue improvement) [7]. Participants receiving the synbiotic also saw greater resolution of cognitive symptoms (memory/concentration issues) and GI issues [7]. This suggests gut dysbiosis contributes to long COVID symptoms, and microbiome-targeted therapy can yield broad symptom benefits [7]. *(Note:* The trial was well-powered, but independent confirmation is needed, as this was a single-center study.)

- **Metabolic Modulator *AXA1125*:** *Mechanism:* A formulation of amino acids designed to boost mitochondrial function and cellular energy production. *Evidence:* In a Phase 2a **RCT** (Oxford, 2022–2023), 41 fatigue-predominant long COVID patients received AXA1125 or placebo for 4 weeks. The primary endpoint (a muscle phosphocreatine recovery metric) did not improve, **but fatigue symptoms did improve significantly** – the treated group had a greater reduction in fatigue scores (Chalder Fatigue Questionnaire) than placebo (mean difference –4.3 points) [8] [9]. No serious adverse events occurred [9]. This suggests enhancing bioenergetics can ameliorate fatigue, though larger multi-center trials are needed to validate the result [10].

- **Psychotropic and Neurologic Medications:** Thus far, **antidepressants** have not shown clear benefit in long COVID fatigue. For example, a trial of **vortioxetine** (an SSRI) found little to no improvement in cognitive or fatigue outcomes [11]. On the other hand, **psychostimulants** (modafinil, methylphenidate) are sometimes used off-label to manage severe fatigue or brain fog (by increasing wakefulness), but robust trial data in long COVID are lacking (these are based on ME/CFS practices).

- **Mitochondrial Cofactors (CoQ_{10}):** *Mechanism:* Supports electron transport and ATP synthesis. *Evidence:* Coenzyme Q_{10} was tested in a placebo-controlled trial (**119 patients, 500 mg/day for 6 weeks**). Results showed **no significant improvement in quality of life** versus placebo [12]. (Fatigue-specific outcomes were not significantly changed either in published data.) A prior meta-analysis did note CoQ_{10} can reduce certain inflammatory markers, but for long COVID fatigue the evidence thus far is not supportive [12]. Researchers suggest that if CoQ_{10} is used, it may need combination with other mitochondrial supports (e.g. NADH) to be effective [13], but definitive proof is lacking.

- **Antiviral Therapy (Nirmatrelvir/Ritonavir – *Paxlovid*):** *Mechanism:* Aims to eliminate residual SARS-CoV-2 viral reservoirs (a proposed driver of long COVID for some patients). *Evidence:* The **STOP-PASC** randomized trial (Stanford, 2023) evaluated a 15-day Paxlovid course in people with established long COVID. The results were **negative** – Paxlovid was safe but **did not significantly improve** fatigue or other symptoms compared to placebo at 10-week follow-up [14]. Most participants were already months post-infection and vaccinated, which might have limited the antiviral's impact [14]. **Note:** While Paxlovid is proven to *prevent* long COVID when given in acute infection (42% reduction in long COVID incidence in one trial) [15], evidence does not support it as a treatment once long COVID is established.

- **Other RCT-Tested Agents:** Several other interventions have undergone peer-reviewed trials with largely *negative* or inconclusive results:

- *Low-Dose Lithium:* Based on neuroinflammation theories, low-dose **lithium aspartate** (10–15 mg/day) was tested in a placebo-controlled trial. It **failed to improve fatigue or cognitive dysfunction** in long COVID patients [16], suggesting no benefit at that dose (higher doses are being hypothesized but would carry more side effects) [17].
- *Hyperbaric Oxygen Therapy (HBOT):* Breathing 100% oxygen in high-pressure chambers is proposed to improve oxygen delivery and promote tissue repair. A double-blind RCT of **10 HBOT sessions vs sham** found **no short-term advantage** of HBOT on fatigue or fitness – both groups improved similarly (placebo effect), with a hint that men improved more than women [18] [19]. However, a separate sham-controlled trial (Scientific Reports 2023) reported **improvements in neurocognitive function and some symptoms** after HBOT [20]. This discrepancy suggests more research is needed; current evidence is not uniformly strong, so HBOT cannot be fully endorsed yet.
- *Anticoagulation:* Impaired microcirculation from microclots is a theorized mechanism, but **no large RCTs** of anticoagulants exist to date. One small uncontrolled study (see Tier 2) suggested benefit from aggressive antithrombotic therapy, but without randomized data, anticoagulation is not yet a standard evidence-backed treatment.
- *Immunomodulators:* No **high-quality trials** have yet shown a clear benefit for drugs like corticosteroids, colchicine, or biologics in long COVID fatigue specifically. (Trials are ongoing for therapies like cytokine inhibitors and antivirals for Epstein-Barr virus reactivation, but results remain pending.)

Summary (Tier 1): So far, the most robust evidence supports **rehabilitative approaches** (graded exercise with pacing, CBT) and two novel therapies (**microbiome restoration** via synbiotics, and **metabolic therapy** via AXA1125) which showed significant fatigue improvement in trials [7] [8]. Several other interventions have been *tested rigorously and found ineffective* (e.g. antivirals, low-dose lithium, high-dose CoQ_{10}) [12] [14] [16]. This highlights the challenge of treating long COVID fatigue – even well-designed trials often show modest or no effects, underscoring the need for further research and combination approaches.

Tier 2: Emerging Clinical Evidence (Pilot Studies & Early Trials)

- **Low-Dose Naltrexone (LDN):** *Mechanism:* LDN (typically 1.5–4.5 mg) is thought to modulate neuroinflammation and glial cell activity, and rebalance immune responses. *Evidence:* Not yet FDA-approved for long COVID, but **observational studies** and case series suggest some patients have reduced fatigue, brain fog, and pain on LDN [21] [22]. For example, one cohort using LDN (often combined with nutraceutical NAD^+ boosters) reported it was *safe and possibly beneficial* for persistent post-COVID fatigue [23]. **Clinical trials** are underway: a Phase II RCT protocol has been published to formally test LDN for post-COVID fatigue [24]. Many practitioners have already adopted LDN empirically given its low cost and favorable safety, pending stronger evidence.

- **Antihistamine Therapy (H_1/H_2 Blockade):** *Mechanism:* Long COVID can resemble mast cell activation syndrome (MCAS) [25] – excess histamine and inflammatory mediators may contribute to fatigue, tachycardia, and brain fog. **H_1 antihistamines** (e.g. cetirizine, loratadine) plus **H_2 blockers** (famotidine, ranitidine) are being used to tame this response. *Evidence:* A notable **observational study** found *clear symptom improvements* in long COVID patients given combined H_1/H_2 blockers, especially in fatigue and cognitive symptoms [26]. Patients often report improved daily energy and reduced "flare-ups" of symptoms with this regimen [26]. While these findings are not from RCTs, they align with many anecdotal reports and the known safety of antihistamines. Ongoing studies (including MCAS biomarker research) aim to validate this approach.

- **"Triple" Anticoagulant Therapy (Anti-Microclot Regimen):** *Mechanism:* Targets the fibrin amyloid microclots and platelet hyperactivation observed in many long COVID patients [27] [28]. The regimen typically includes **dual antiplatelet agents** (low-dose aspirin + clopidogrel daily) *and* a **direct oral anticoagulant** (e.g. rivaroxaban) for 4+ weeks. *Evidence:* In a pilot study by South African researchers (Pretorius *et al.*), **24 patients** received this triple therapy for a month. **All patients showed resolution or major improvement of symptoms** (fatigue, shortness of breath, etc.) correlating with a reduction in microclot biomarkers [29] [30]. An uncontrolled larger series (91 patients) similarly reported high response rates [28]. These promising results, published as preliminary findings, lack a placebo control and carry bleeding risk, so broader adoption awaits RCT confirmation. Nonetheless, the data implicate microclot clearance as a potential path to relief for the fatigue and brain fog of long COVID.

- **BC007 (Autoantibody Neutralizing Aptamer):** *Mechanism:* BC007 (Rovunaptaban) is an aptamer drug that binds and inactivates certain autoantibodies against G-protein-coupled receptors (GPCRs). These autoantibodies have been detected in some long COVID patients and may cause autonomic and vascular dysfunction. *Evidence:* Initial case reports in Germany (2021) noted dramatic improvement in a severe long COVID patient's symptoms after a single BC007 infusion, sparking interest. In 2023–2024, a Phase IIa **crossover trial ("reCOVer")** in 30 patients found BC007 *significantly improved fatigue scores* compared to placebo, without safety issues [31]. However,

another trial ("BLOC") reportedly did *not* find efficacy, highlighting inconsistencies [32]. The published interim data (awaiting peer review) encourage larger trials to confirm effectiveness [33]. BC007 remains experimental but exemplifies a cutting-edge immune-targeted approach aiming to remove a root cause of long COVID (autoimmune dysregulation).

- **Hyperbaric Oxygen Therapy (HBOT):** *Mechanism:* Increases oxygen delivery to tissues and may promote healing of hypoxic or inflamed tissues (including brain). Also proposed to help break up microclots via high oxygen pressures. *Evidence:* **Mixed early evidence:** A small double-blind trial (10 HBOT sessions vs sham) found no significant added benefit in fatigue or exercise capacity over placebo in the short term [19], suggesting expectancy effects or spontaneous improvement in both groups. In contrast, another study (Shai Efrati's group) with a longer HBOT course reported **persistent improvements in cognitive function, sleep quality, and pain** at 3-month follow-up [34] [20]. Dozens of long COVID patients have self-reported improvements anecdotally after HBOT. Given the cost and divergent results, HBOT is considered an *emerging* option – possibly effective for some symptom domains (e.g. brain fog) [20] – but requiring further controlled trials to determine which patients, dosages, and outcome measures truly benefit.

- **Traditional Chinese Medicine (TCM) Herbals:** *Mechanism:* Multi-herb formulations aimed at replenishing "Qi" (energy), reducing inflammation, and supporting organ recovery. TCM often targets immune and autonomic balance. *Evidence:* China and other countries have integrated TCM into long COVID care. A **retrospective cohort** from Taiwan showed that personalized TCM herbal treatments led to notable fatigue reduction within 1 month, alongside improvements in respiratory and emotional symptoms [35]. Common formulas include **Bojungikgi-tang** (Bú Zhōng Yì Qì Tang 補中益氣湯) and **Kyungok-go**, traditionally used for post-illness fatigue. A Korean pilot trial (2024) testing these formulas demonstrated feasibility and suggested improvements in fatigue and cognitive symptoms, though it was not powered for definitive efficacy [36]. TCM approaches are thus supported by *emerging* evidence and decades of traditional use. Formal RCTs (e.g. a double-blind trial of a standardized herbal formula [37]) are in progress to validate safety and efficacy.

- **Ayurvedic and Adaptogenic Therapies:** *Mechanism:* Holistic restoration of vitality, stress reduction, and immune modulation using herbs. *Evidence:* In India, Ayurveda is applied to long COVID, emphasizing detoxification (Panchakarma) and rejuvenation herbs. **Ashwagandha (Withania somnifera)**, an adaptogen known to improve energy and stress tolerance, is under study – the APRIL trial (UK/India collaboration) is a large placebo-controlled trial of Ashwagandha for long COVID fatigue [38]. Traditional use and smaller case series indicate potential benefits in fatigue and sleep, but rigorous data are pending. Other adaptogens like **Panax ginseng** and **Rhodiola** are likewise used by integrative practitioners for post-viral fatigue, with a rationale of enhancing mitochondrial output and HPA-axis regulation (current evidence is mostly anecdotal or extrapolated from other fatigue conditions).

- **Preliminary Immune Therapies:** Some immune-targeted treatments are being explored:

- *Intravenous Immunoglobulin (IVIG):* High-dose IVIG is used in some post-viral autoimmune neuropathies. A few case reports/series in long COVID patients with autonomic or small-fiber nerve involvement show symptom improvements (e.g. reduced fatigue and orthostatic intolerance) after IVIG. These are uncontrolled observations, but a clinical trial is underway to test IVIG in long COVID with dysautonomia.

- *Therapeutic Apheresis:* Removing and filtering blood to eliminate suspected pathological factors (autoantibodies, microclots). In Germany, hundreds of long COVID patients have undergone H.E.L.P. **apheresis or plasmapheresis**. Anecdotally, some saw improved fatigue and cognitive function, especially those with high microclot burden. A small observational study of immunoadsorption (a process to strip autoantibodies from plasma) in 10 patients found 7 improved in physical function scores [39]. These invasive treatments lack RCT evidence and carry risks, so they remain experimental but illustrate the lengths being explored to reset the immune system in long COVID.

Summary (Tier 2): Emerging interventions show *promise* but are still under investigation. **LDN and antihistamines** have favorable early data for symptom relief [23] [26], aligning with immune and mast-cell theories of long COVID. Aggressive approaches like **triple anticoagulation** and **BC007** target cutting-edge hypotheses (microclots and autoantibodies) with encouraging pilot outcomes [29] [31], yet require validation. Complementary medicine from East and West – **TCM, Ayurveda, nutraceuticals** – contributes a pipeline of therapies (herbs, probiotics, metabolic supplements) that are entering formal trials due to positive case reports. Patients and clinicians should stay tuned as these early-phase studies progress, and consider such options on a case-by-case basis, ideally in clinical trial settings or with specialist guidance given the uncertainties.

Tier 3: Expert Consensus & Widely Adopted Practices

Even in the absence of definitive trial evidence, many interventions have gained **expert consensus or broad practitioner adoption** for managing long COVID fatigue. These are generally low-risk approaches rooted in pathophysiological rationale or extrapolated from ME/CFS management. Key examples:

- **Pacing and Energy Management:** *Principle:* **Activity pacing** is universally recommended by experts and patient groups to avoid post-exertional malaise (PEM). Patients are advised to balance activity with rest, use energy envelopes, and **prioritize rest in early recovery** to potentially improve long-term outcomes [40]. This approach is drawn from ME/CFS care, acknowledging that overexertion can trigger crashes in long COVID [41] [42]. While pacing is more management strategy than "treatment," it's considered foundational by clinicians to stabilize patients before other therapies are introduced.

- **Nutritional and Dietary Optimization:** Ensuring no vitamin or mineral deficiencies is a standard consensus step. For example, **Vitamin D** levels are checked and corrected – not only does deficiency correlate with higher long COVID risk [43] [44], but vitamin D plays a role in immune regulation and mitochondrial function. Similarly, **vitamin B12** or **iron** deficiencies (which can cause fatigue) are treated if present. Many clinicians recommend an **anti-inflammatory diet** (Mediterranean-style, high in omega-3s, antioxidants, and fiber) to reduce systemic inflammation. Though formal trials on diet are lacking, this aligns with general evidence that such diets support immune health. A **low-histamine diet** is sometimes advised if MCAS-like symptoms are prominent (the diet avoids trigger foods to complement antihistamine therapy). Hydration and electrolyte supplementation (or increased salt, e.g. in dysautonomia) are also commonly advised.

- **Mitochondrial Support Supplements:** It is common practice to use over-the-counter supplements aiming to boost cellular energy production. **Coenzyme Q_{10}**, **NAD^+ precursors** (e.g. nicotinamide riboside or NMN), **L-carnitine**, **D-ribose**, and **B-complex vitamins (B1, B2, B3, B12)** are frequently combined by integrative physicians. For instance, some ME/CFS clinicians report high-dose **vitamin B1 (thiamine)** can improve fatigue in a subset of patients (theory: thiamine helps

mitochondrial pyruvate processing). Another example is **magnesium** (important for ATP and muscle function) – many long COVID patients take magnesium glycinate or citrate to combat fatigue and poor sleep. While strong evidence is not yet available for these supplements in long COVID, small studies in chronic fatigue syndromes have shown hints of benefit (e.g. CoQ10+NADH improved fatigue in an older ME/CFS trial [13]). Thus, by consensus, mitochondrial nutrients are considered a *reasonable supportive therapy*. They are generally safe and might work synergistically with other interventions (the cost being the main downside if efficacy is marginal).

- **Anti-Inflammatory and Immune-Calming Agents:** Beyond vitamins, experts often add supplements with antioxidant or anti-inflammatory properties: **Omega-3 fish oil** (to lower inflammation and support brain health), **curcumin** (from turmeric, NF-κB pathway inhibitor), **quercetin** (flavonoid that stabilizes mast cells and is antiviral – the user is already familiar with this). These have theoretical benefits for immune dysregulation. For example, quercetin is frequently mentioned in long COVID protocols for its dual antihistamine and anti-inflammatory effects, although evidence is anecdotal. **N-acetylcysteine (NAC)** and **glutathione** are also used to support the body's antioxidant defenses and detox pathways, potentially helping clear lingering viral proteins or oxidative stress in mitochondria. Many long COVID–focused practitioners incorporate such supplements, guided by patient tolerability and incremental gains reported.

- **Treating Comorbid Conditions:** Specialists emphasize identifying specific complications that can be treated: for instance, if a patient develops **POTS (postural orthostatic tachycardia syndrome)** or orthostatic intolerance, treating that with **beta-blockers, ivabradine, midodrine, or fludrocortisone** can substantially reduce fatigue by improving circulation. Likewise, if there is evidence of **reactivated viruses** (like EBV or HHV-6) contributing to fatigue, some doctors consider antivirals such as **valganciclovir or valacyclovir** off-label (borrowing from ME/CFS practice); this is speculative but some patients with high EBV titers have been treated in this way. **Depression and sleep disorders** can worsen fatigue, so addressing those (with SSRIs, psychotherapy for depression, or melatonin and sleep hygiene or even CPAP if sleep apnea) is part of expert holistic management. In short, experienced clinicians perform a thorough workup (autoantibodies, adrenal/thyroid function, sleep studies, etc.) and treat any contributing factor – while none of these "cure" long COVID, they can meaningfully improve a patient's overall energy.

- **Off-Label Symptom-Targeted Medications:** Although not curative, certain prescriptions are commonly used to *manage* fatigue and related symptoms in long COVID:

- *Stimulants:* As noted, modafinil (Provigil) or amphetamine derivatives are sometimes prescribed to improve wakefulness and cognitive throughput in severe cases. This is based on practitioner experience, weighing potential benefits in function against side effects (insomnia, increased heart rate).
- *Mast Cell Stabilizers:* If histamine-related symptoms are pronounced, beyond H1/H2 blockers, some doctors add **montelukast** (a leukotriene inhibitor) or **cromolyn sodium** (mast-cell stabilizing agent) to further calm the immune system. These choices come from MCAS treatment protocols and have anecdotal support in long COVID patients with prominent allergies or wheezing.
- *ACE2 Upregulators:* A few researchers suggest **angiotensin receptor blockers (ARBs)** or **ACE inhibitors** might improve long COVID by countering dysregulated renin–angiotensin system activity (the virus impacts ACE2). This is highly experimental; still, if a patient has concurrent hypertension,

choosing an ARB (like losartan) might hypothetically confer some long COVID benefit (no direct evidence yet).

- *Antidepressants (Symptomatic use):* While vortioxetine didn't help long COVID cognitive symptoms in a trial [11], patients with concurrent depression or anxiety often receive SSRIs or SNRIs. These can improve overall well-being and sleep, indirectly helping fatigue. Some clinicians also use **tricyclics (amitriptyline)** or **gabapentin** at night if fibromyalgia-like pain or poor sleep is exacerbating fatigue.

- **Mind-Body and Adjunct Therapies:** A consensus exists that supportive therapies can enhance recovery or coping. **Behavioral health support** (therapy, support groups) is encouraged to manage the stress and lifestyle changes imposed by long COVID. Techniques like **meditation, mindfulness, yoga, tai chi** are commonly recommended – these can reduce stress hormones and improve autonomic balance, potentially mitigating fatigue flares. **Acupuncture** has been incorporated by some long COVID clinics; evidence is mostly anecdotal, but a few small studies in post-viral fatigue suggest acupuncture may help fatigue and pain (mechanism: modulating nervous system and blood flow). **Breathing exercises** (from pulmonary rehab or practices like pranayama) help those with dyspnea and may increase vagal tone, thus improving energy over time. **Massage and lymphatic drainage** therapy is another adjunct aimed at reducing muscle aches and improving circulation, which some patients find temporarily boosts their energy levels.

Summary (Tier 3): These widely-adopted practices form a **comprehensive care approach** to long COVID fatigue. They may not "cure" the condition, but they can improve quality of life and create a foundation for recovery. The consensus is to optimize the patient's overall health: correct deficiencies, treat comorbid issues, reduce inflammation, and *listen to the body's limits*. Many of these interventions come from established chronic fatigue syndrome management and have been adapted by long COVID experts given the overlapping features. Patients often end up on a **multi-modal regimen** – for example, pacing + nutritional supplements + an antihistamine + LDN – reflecting the complex, multifactorial nature of long COVID fatigue.

Tier 4: Anecdotal & Community-Reported Treatments

Finally, a multitude of **grassroots and anecdotal therapies** have arisen from patient communities (forums, Facebook groups, Reddit) and "biohacker" experimentation. These lack formal evidence but are noteworthy for the completeness of this report, as they highlight hypotheses being tested informally by patients and some forward-thinking clinicians:

- **Methylene Blue (MB):** *Mechanism:* MB is a blue dye with pharmaceutical history (used for methemoglobinemia) that also improves mitochondrial respiration and acts as a potent antioxidant. It can even have antiviral properties under light (in vitro, MB can inhibit SARS-CoV-2 spike–ACE2 binding and viral replication at low micromolar levels [45]). *Anecdotal Use:* In long COVID forums, some patients report **remarkable improvements in fatigue and brain fog** on low-dose oral methylene blue (typically 5–50 mg daily). They describe increased energy and mental clarity, presumably from enhanced cellular ATP production. Others see little effect or worry that benefits plateau. There are **no clinical trials yet** for MB in long COVID; all evidence is experiential. Caution is advised, as MB is not FDA-approved for this indication and can have side effects (it's a MAO inhibitor at higher doses and will turn urine blue). Nonetheless, it remains a popular experimental remedy for

those targeting mitochondrial dysfunction, with enough success stories that it's considered worth observing in future research.

- **Fibrinolytic Enzymes (Nattokinase, Serrapeptase, Lumbrokinase):** *Mechanism:* These are natural enzymes (derived from fermented soy, silkworm, earthworms, respectively) that can degrade fibrin and blood clots. They are thought to help **dissolve microclots** and degrade circulating spike protein remnants [46]. *Anecdotal Use:* Long COVID communities have embraced nattokinase in particular as an OTC supplement to "bust" microclots and improve blood flow. Some patients credit nattokinase (often taken 2,000–4,000 FU units/day) with gradual improvements in fatigue, headaches, and even clearing COVID vaccine or infection remnants – though these are subjective reports. **Serrapeptase** is similarly used for its anti-inflammatory and clot-dissolving potential. As of late 2023, no clinical trials had been registered specifically for nattokinase in long COVID [47], so evidence is purely theoretical and anecdotal. That said, a **mini-review** notes these enzymes have been *proposed* as potential treatments for long COVID clotting issues [48]. Users should be cautious about bleeding risks. This is a prime example of a community-driven hypothesis (microclots) leading to a do-it-yourself treatment that is unproven but biologically plausible.

- **Immunomodulatory Herbs & Supplements:** Patients often experiment with herbs known for immune-balancing or antiviral effects. For instance: **Nigella sativa (Black seed oil)** – has anti-inflammatory and mild antiviral properties (some acute COVID studies showed faster recovery with it). **Andrographis paniculata** and **astralagus** – used in traditional medicine for post-viral recovery. **Reishi mushroom** (Ganoderma) – an adaptogenic fungus said to improve energy and immunity; indeed, some long-haulers take reishi and report better endurance. In the FDA's patient survey, many participants mentioned trying antioxidants, amino acids, probiotics, and herbal supplements like **curcumin and reishi**, with *some* noting these "markedly improved my energy" but only up to a point [49] [50]. These reports suggest supplements can help to a degree, but often not enough to fully restore normal function. It underscores the need for multi-pronged approaches.

- **Dietary Strategies (Keto, Fasting):** Beyond general healthy diet consensus, some anecdotal success is reported with **ketogenic or low-carb diets**, positing that ketones provide a more efficient fuel for brain and muscle (bypassing some mitochondrial blocks). A subset of patients say that going keto or carnivore reduced their fatigue and brain fog; others find it unsustainable. **Intermittent fasting** (e.g. 16:8 or 18:6 time-restricted eating) is another community-suggested strategy – it might trigger autophagy and mitophagy (cellular cleanup), potentially clearing damaged cell components or viral antigens. While intriguing, these dietary approaches have no controlled data specifically in long COVID and can even worsen fatigue in some if not done carefully (nutrition is highly individual). As such, they remain experimental self-management tools.

- **Red Light Therapy (Photobiomodulation):** Low-level laser or LED in red/near-infrared wavelengths (often 660 nm and 850 nm) applied to the body or head is purported to boost mitochondrial ATP output and reduce inflammation. A few long COVID sufferers use **red light panels or helmets** at home, reporting subtle improvements in energy and cognition. There was at least one small pilot of transcranial photobiomodulation for long COVID cognitive symptoms, but evidence is preliminary [51]. Given its non-invasive nature, some are trying it despite minimal data. This is one of those "can't hurt, might help" biohacks circulating in online groups.

- **Ozone Therapy:** In alternative medicine, **ozone (O_3)** gas is used (either via blood ozonation or rectal insufflation) to purportedly inactivate viruses and improve oxygen delivery. A number of integrative clinics offer ozone therapy for long COVID, with anecdotal accounts of improved fatigue and mental clarity. However, ozone is not a conventional treatment and carries risks if not done properly (it's a reactive gas). Anecdotes are insufficient to judge efficacy, and no formal trials exist. It remains on the fringe, championed by some functional medicine practitioners.

- **Others:** Virtually every conceivable therapy has been tried by someone. To name a few: **Hydrogen water** (drinking water infused with H_2, an antioxidant) – some reports of better energy; **Chelation therapy** (to remove possible heavy metal burdens affecting mitochondria) – no evidence but tried in integrative circles; **Peptide therapies** (like BPC-157 or thymosin alpha-1) – these immune-regulating peptides are being used experimentally to aid recovery; **Cold exposure (cryotherapy or ice baths)** – a minority of patients practice cold plunges or Wim Hof breathing, aiming to reset immune responses and improve mitochondrial resilience, but results are mixed and this can be risky in those with dysautonomia. **Acupuncture** and **Ayurvedic detox routines** (like Panchakarma) were mentioned earlier and continue to have devoted followers who attest to benefits in fatigue reduction, even if placebo effect cannot be ruled out.

It's important to stress that **anecdotal reports are inherently biased** – often only the success stories are shared, while those who tried and failed might simply leave the conversation. Therefore, while *community innovation* has broadened the list of potential interventions (from **nattokinase to methylene blue to curcumin**), these should be approached with healthy skepticism. Patients considering them should ideally consult with a healthcare provider, start at low doses, and track their responses carefully.

Summary (Tier 4): The long COVID community has become an R&D engine of its own, crowdsourcing remedies for a novel condition. **Vitamins, supplements, diet mods, and repurposed drugs** abound in these anecdotal arsenals. Notably, many patients report partial improvements with combinations of antioxidants, probiotics, fibrinolytics, and herbals [49] [50] – e.g. *"[Certain] supplements markedly improved my energy and helped against fatigue but had an upper limit of effectiveness"* [50]. This sentiment is common: gains are often real but incremental. It reinforces that long COVID likely involves multiple pathological pathways; thus, a cocktail of interventions (each addressing one piece) might be required for substantial relief. What works for one may not work for another, hinting at heterogeneity in underlying causes (e.g. one patient's fatigue might be more immune-driven, another's more autonomic or microvascular).

Conclusion and Future Outlook

From 2023 onward, the landscape of long COVID fatigue treatments has evolved from symptom management toward mechanism-targeted therapies. **Immune dysregulation** is being met with antihistamines, LDN, and trials of immunotherapies; **mitochondrial dysfunction** is addressed with metabolic supplements and drugs like AXA1125; **microclot formation** is targeted by anticoagulants and enzymes; and overlapping issues like autonomic imbalance are tackled with rehab and medications. The **level of evidence** ranges widely – a few interventions have RCT-backed support (though often modest effects) [7] [8], while many others rest on early-phase data or even just theory and personal experimentation.

Encouragingly, the research pipeline is full: larger trials (e.g. of LDN, Ashwagandha, antivirals, IVIG, BC007, etc.) are ongoing or planned in 2024–2025. Each will add pieces to the puzzle of how to reliably restore energy to those suffering post-COVID. For now, clinicians and patients must navigate a **wide but shallow evidence base** – combining the best-supported therapies with individualized trials of emerging options, all while prioritizing safety. In practice, a long COVID patient's care plan might include a *core* of proven rehab strategies and psychosocial support (Tier 1), an *adjunct* of a few emerging therapies that fit their suspected dominant mechanism (Tier 2), pragmatic *supportive measures* (Tier 3), and possibly a cautious self-trial of one or two low-risk experimental remedies (Tier 4). This multi-tiered approach, continually adjusted, offers the best chance of improving the debilitating fatigue that defines long COVID.

As research progresses, we expect some anecdotal treatments to graduate to clinical proof or be discarded, and new interventions (e.g. antivirals, cytokine blockers, neurostimulants) to enter the scene. **Long COVID fatigue is a complex condition requiring an integrative approach**, and this frontier report captures the state-of-the-art as of 2023–2025. Patients and providers are encouraged to stay informed through updated literature and trial results, since the "best" treatment mix will likely be refined rapidly in the coming years. The collective goal is to move more options from the realm of hope to that of certainty – so that those affected by long COVID can reclaim their energy and quality of life.

Sources:

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