bm.genomicpress.com

Brain Medicine

OPEN

PERSPECTIVE

A multimodal approach for treating post-acute infectious syndrome

Charlotte Steenblock[1], Nicole Toepfner[2], Yannick P. Kok[3], Philip Mavberg[4], Horst Bruckmoser[5], Alfons Breu[6], Johannes Korth[7], Harald Heidecke[8], Milo A. Puhan[9], and Stefan R. Bornstein[1,10,11]

Long-term complications, such as extensive fatigue and cognitive issues, are known from various infections, including SARS-CoV-2, influenza virus, or *Borrelia burgdorferi*. The pathology is mostly unknown and differs between patients. Unfortunately, there is currently no common and effective treatment. In this perspective, we imply that post-acute infectious syndromes are due to a variety of factors, including among others diminished tissue perfusion, tissue infiltration by viruses, inflammation, and oxidative stress, and that not one specific biomarker can be used to measure these syndromes. Thus, we suggest that a score based on a number of criteria/factors should be used to assess post-acute infectious syndromes. Consequently, probably not one single treatment can be used to treat this group of patients, and we suggest a multimodal treatment regimen comprising a combination of pharmacotherapy, such as metformin and naltrexone with anti-inflammatory effects, alongside physical therapies such as extracorporeal apheresis and transcutaneous neurotherapy. This combined approach aims to reduce biomarker levels and enhance cognitive functions. This implies that a reset of the systems can be achieved by a multimodal approach based on a score for post-acute infectious syndromes.

Brain Medicine (2024), 35–41; doi: https://doi.org/10.61373/bm024p.0064; Published online: 30 August 2024.

Keywords: Long-Covid, post-acute infectious syndrome, COVID-19, SARS-CoV-2, virus, therapy

Introduction

After the COVID-19 pandemic, a number of patients experience persistent symptoms and physiological changes even after recovering from the acute phase of the disease (1). The potential symptoms cover a broad spectrum, including fatigue, breathlessness, headaches, sleep disturbances, difficulty concentrating, cognitive issues, skin rashes, diarrhea, and tinnitus (2–4). SARS-CoV-2 causing COVID-19 is not unique in this ability to cause post-acute sequelae. Various other acute infections, including Ebola, polio, dengue, but also influenza or bacterial infections, such as *Borrelia burgdorferi*, which might give rise to Lyme disease syndrome (5), have been linked to an unexplained chronic disability in a subpopulation of patients (6). Post-acute infectious syndromes (PAIS) are not new; they usually come to attention when many people are infected, such as during pandemics, and have been described since the Russian flu (7). The consistent symptom profiles across different PAIS, regardless of the infecting agent, along with the overlapping clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), indicate the potential contribution of a shared etiopathogenesis (8).

The prevalence of PAIS depends on the pathogen and varies from a few percentages in patients having had influenza (9) to up to 70% of patients with persistent symptoms 2 years after infection with West Nile virus (10). For Long-Covid, the evidence suggests that, before the introduction of the vaccines, about 20% of patients diagnosed with COVID-19 and 5–10% of all infected persons developed long-term complications (11–14), which fell below 5% with the introduction of vaccines and new variants like omicron (15, 16). Interestingly, women seem to have a higher prevalence (6), which might at least partly be explained by the fact that women are generally more susceptible to immune-mediated conditions (17). The recovery period for patients with Long-Covid may vary significantly depending on the severity of the disease, hospitalization, comorbidities, and age (11, 18).

The persistent symptoms experienced by patients with PAIS can result in significant financial losses, affecting individuals, businesses, and economies globally. Furthermore, syndromes following acute infections can greatly diminish quality of life, as chronic symptoms may result in lost productivity, increased healthcare costs, and mental health issues, all of which can interfere with personal, social, and professional life. Health disparities related to PAIS have been shown to particularly affect racial and ethnic minorities. These disparities are driven by factors such as socioeconomic status, discrimination, and limited access to healthcare. They are not confined to specific regions but have global implications (18).

Factors Responsible for PAIS

The underlying mechanisms for PAIS remain poorly understood but the current hypotheses proposed to elucidate the consequences of chronic fatigue and post-exertional malaise in patients with Long-Covid encompass diminished tissue perfusion (19), viral infiltration of tissues, inflammation in both the brain and peripheral organs (20), the prolonged presence of SARS-CoV-2 spike proteins (21), and the reactivation of other infectious agents such as Epstein–Barr virus, cytomegalovirus (CMV), and various other infectious components (22–26).

Furthermore, recent findings demonstrate that heightened lipid levels represent a significant risk factor (27–29). Likewise, Long-Covid induces a substantial elevation in lipids, posing a long-term risk for cardiovascular disease (30). Recently, it was demonstrated that in patients with Long-Covid, a persistent dysregulation and activation of the complement system could be observed (31). Moreover, thromboinflammatory proteins were increased in Long-Covid (31).

Changes in blood cellular components (32–34) and the rarefaction of vessels (35) have also been proposed as potential factors contributing to the onset of Long-Covid subsequent to SARS-CoV-2 infection. Interestingly, two distinct blood marker profiles during the acute phase of

[1]Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [2]Department of Pediatrics, University Clinic Carl Gustav Carus, Technische Universitat Dresden, Dresden, Germany; [3]INUS Laboratories AG, Horgen, Switzerland; [4]Ayus Medical Basel AG, Basel, Switzerland; [5]MICRO-MEDICAL Instrumente GmbH, Senftenberg, Germany; [6]BREU GmbH, Putzbrunn, Germany; [7]Dialysepraxis am Kortumpark, Bochum, Germany; [8]CellTrend GmbH, Luckenwalde, Germany; [9]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; [10]School of Cardiovascular and Metabolic Medicine and Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK; [11]Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich, Switzerland.

Corresponding Author: Charlotte Steenblock, Department of Internal Medicine III, Technische Universität Dresden, Fetscherstrasse 74, Dresden 01307, Germany. Tel.: +49-351-458-16130; E-mail: charlotte.steenblock@uniklinikum-dresden.de

Received: 26 April 2024. Revised: 2 August 2024 and 7 August 2024. Accepted: 12 August 2024.

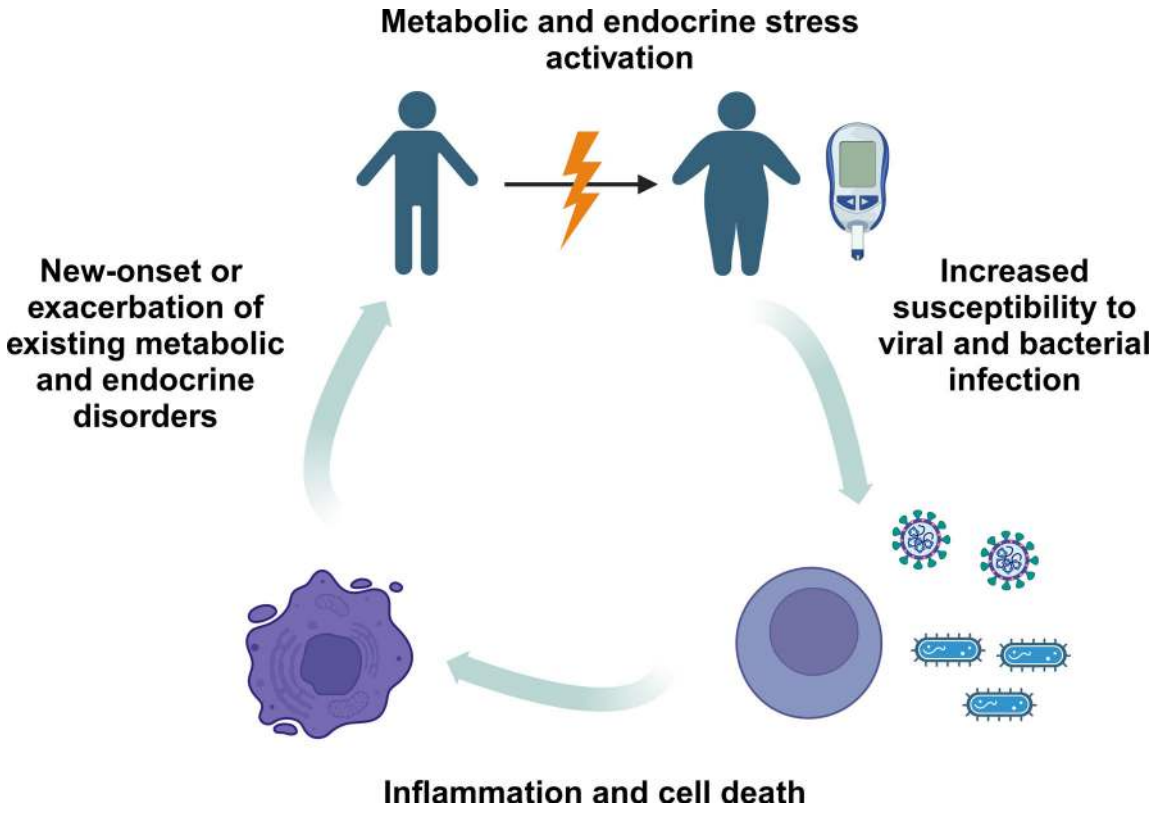

Figure 1. Metabolic and endocrine stress activation. The endocrine stress axis, which can be triggered by various factors such as psychological stress, physical exhaustion, or metabolic diseases, plays a pivotal role in the body's response mechanisms. When the endocrine stress axis is persistently activated, the body's immune system can become compromised, leading to heightened susceptibility to infections. Chronic or excessive inflammation can lead to tissue damage and cell death, which might aggravate or initiate metabolic and endocrine disorders, thus perpetuating a vicious cycle. Created with BioRender.com

COVID-19 have been associated with cognitive deficits up to 1 year after the acute infection with SARS-CoV-2. One is elevated fibrinogen and the other is elevated D-dimer, both in relation to C-reactive protein (36). Other studies have shown that plasma samples from patients with both acute COVID-19 and Long-Covid contain large anomalous (amyloid) deposits (microclots) that are resistant to fibrinolysis (37).

The emergence of autoantibodies against G-protein coupled receptors has raised concerns about their potential involvement, given their pathogenic role demonstrated in various autoimmune disorders (38). Particularly noteworthy is the implication of autoantibodies targeting neurotransmitters, such as β-adrenergic receptors, which have been suggested to impact the severity of COVID-19 and contribute to Long-Covid (6, 39). Furthermore, increased levels of autoantibodies against protease-activated receptor-1 (PAR-1), which promotes platelet activation, has been linked to severe COVID-19 (40–42), suggesting that these autoantibodies could also play a role in Long-Covid.

It has been speculated that the activation of interferon (IFN) signaling linked to SARS-CoV-2 could trigger the production of autoantibodies targeting type I IFNs (17) and exacerbate local inflammation (18, 19), thereby possibly contributing to the manifestation of PAIS.

Nonetheless, our research, along with others', suggests that functional autoantibodies against type I IFNs are unlikely to contribute to the pathogenesis of Long-Covid (43, 44). Additionally, we observed no correlation between Long-Covid fatigue scores and IFN-stimulated gene signatures (43).

The Effect of Metabolic and Endocrine Diseases on PAIS

Metabolic and endocrine disorders, as well as chronic stress, can trigger activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in dysregulated cortisol release. Moreover, they may impact the renin-angiotensin-aldosterone and the sympatho-adrenomedullary system (45). Additionally, stimulation of the neuroendocrine stress axis could result in persistent low-grade inflammation throughout the body (45). For instance, both stress and obesity appear to exert comparable effects on brain function, attributed to the presence of neuroinflammation observed in both circumstances (46, 47). Chronic inflammation and imbalance between proinflammatory and anti-inflammatory factors in endocrine and metabolic diseases and in stress increases the susceptibility for additional pathogenic infections, which may lead to an abnormal immune response reaching pathogenic levels (48), which in turn increases the risk of experiencing PAIS. The direct infection of endocrine organs, such as pancreatic islets (49–52), adipose (53–56), or adrenal tissue (57) may lead to new onset of endocrine diseases (58). Moreover, the initial viral entry and replication in cells of metabolic and endocrine organs can induce direct damage, ultimately resulting in cell death, either through the immune system's activation or the initiation of cell-autonomous death signaling pathways (Figure 1). Additionally, immune cells activated to produce antibodies or cytokines, along with infected cells releasing biomolecules, may also affect noninfected cells locally and in distant tissues (59).

In conclusion, PAIS impacts various organ systems and multiple mutually nonexclusive biomedical explanations for the pathogenesis of PAIS can be hypothesized (60), which alone or in combination might be responsible for the development of PAIS. They probably involve unregulated immune response, persistent generation of proinflammatory cytokines (chronic inflammation), autoimmune-like reactions, persistent viral replication, and microclot formation (61). Thus, managing PAIS involves addressing a range of symptoms that include physical, cognitive, and psychological aspects. Consequently, we recommend measuring a panel of biomarkers to obtain a clinical indication for treatment

in patients severely affected by PAIS. Further research involving large groups of patients with and without PAIS is needed to determine exactly which biomarkers should be included in such a score and their respective weights.

Potential Treatments of PAIS

Several potential treatments for Long-Covid have been explored (62) and recently, a systemic review of all registered clinical trials for treatment of PAIS was conducted (63). This study showed that while most research focuses on monotherapies, a combination of interventions is also being examined. Both pharmacotherapies and rehabilitative approaches but also psychotherapy or complementary and alternative medicine is being tested (63, 64). Most of these studies are still running and because of the heterogeneity among the studies, it is extremely difficult to draw a conclusion at this point. Because of the complexity of symptoms of PAIS, also the treatment is challenging and probably not one single treatment can be used for all patients exhibiting PAIS. Here, we will discuss some of the treatments that have shown a positive effect on Long-Covid. Current or emerging treatments, such as nutritional supplements or restoration of the gut microbiota, will not be discussed here as they have been recently described elsewhere (62).

Metformin

One of the pharmaceutic therapies that shows a positive effect on Long-Covid is the treatment with metformin. Worldwide, metformin is the first-line drug in the treatment of type 2 diabetes mellitus (65) due to its effectiveness, safety, and affordability (66).

Apart from its ability to inhibit gluconeogenesis and enhance insulin sensitivity, metformin has been recognized as a powerful suppressor of the chronic inflammatory response in macrophages. In acute inflammation, metformin reduces the transcription of interleukin (*Il) 1b* and *Il10* by activating AMP-activated protein kinase (AMPK) (67), whereas in chronic inflammation, it reduces the production of reactive oxygen species (ROS) by mitochondria, which leads to a reduction in the levels of HIF1-α and results in decreased expression of *Il1b*, whereas expression of *Il10* is enhanced (68). Recent studies demonstrated that the SARS-CoV-2 spike protein 1 induces α-synucleinopathy through microglia-mediated inflammation and mitochondrial ROS, which can be suppressed by metformin (69). This ability of metformin to reduce the levels of inflammatory markers has led to the hypothesis that metformin could be used for the treatment of Long-Covid. Furthermore, targeted machine learning analysis indicated that metformin use is associated with a reduced risk of post-infection mortality in COVID-19–positive patients (70). Indeed, in a double-blind trial, adults with overweight or obesity and SARS-CoV-2 infection who took metformin for 2 weeks were less likely than those who took a placebo to later report a diagnosis of Long-Covid (71). Similar findings were observed in a study assessing the 3-month and 6-month risk of PAIS in patients with type 2 diabetes mellitus. This study compared metformin users with those using sulfonylureas or dipeptidyl peptidase-4 inhibitors and found that metformin users had a lower risk of PAIS ((72). These results suggest that additional interventions aimed at reducing mitochondrial ROS production should be identified and subjected to further investigation.

Low-dose Naltrexone

Another promising therapy is low-dose naltrexone (LDN) (73). Naltrexone is an oral μ-opioid receptor antagonist. It is FDA approved for the treatment of opioid and alcohol dependence standardly in high doses of 50–150 mg/day. In low doses of 1–5 mg/day, opioid receptor signaling is not completely blocked, which leads to endogenous production of opioids and opioid receptors. These endogenous opioids modulate the immune system by inhibiting the proliferation of B and T cells (74). Furthermore, on immune cells, LDN is a specific antagonist for Toll-like receptor 4, thereby inhibiting the production of proinflammatory cytokines (75).

The anti-inflammatory effects of LDN have been widely used off-label for the treatment of autoimmune diseases and pain in diseases such as multiple sclerosis, Crohn's disease, and fibromyalgia (73, 76–78). In addition, LDN has been applied for the treatment of ME/CFS (79, 80). Recently, LDN was tested for treatment of Long-Covid, where it demonstrated to have a positive effect on clinical symptoms and self-reported measures of fatigue (81–84).

Extracorporeal Apheresis

Apheresis involves the extracorporeal extraction of targeted blood constituents, such as particular cells or specific plasma components. Originally devised for eliminating lipids to address severe dyslipidemias and autoantibodies, methods for removing various pathogenic molecules from plasma have yielded surprising additional benefits. Subsequent research revealed the capacity to enhance blood viscosity by eliminating high molecular weight proteins, reduce oxidative stress by removing oxLDL, mitigate inflammation by extracting cytokines and inflammatory lipids and eliminate autoantibodies (85–88).

Up to 70% of patients with ME/CFS, including patients with Long-Covid, reported a significant improvement in their symptoms after extracorporeal apheresis (89). We demonstrated that patients who reported significant improvement after two cycles of therapeutic apheresis showed a substantial reduction in neurotransmitter autoantibodies, lipids, and inflammatory markers. Additionally, we observed a 70% decrease in fibrinogen levels, and dark field microscopy revealed that erythrocyte rouleaux formation and fibrin fibers largely disappeared post-apheresis (90). However, randomized, sham-controlled trials that are sufficiently powered and include psychological and physiological outcomes are still lacking.

Transcutaneous Electrical Nerve Stimulation

For nontransponders of pharmacotherapy, alternative strategies are important. As mentioned above, PAIS is a complex condition containing a neurological dimension but also cognitive and affective symptoms that might not be pharmacologically treated. For treatment of these patients, noninvasive brain stimulation, and in particular auricular transcutaneous nerve stimulation (atVNS) has been suggested (91). atVNS is a brain stimulation technique primarily used as a treatment for epilepsy and depression, but it is also being explored for other conditions like migraines and Alzheimer's disease (92).

The exact mechanism of how VNS works is not fully understood, but it's thought to modulate brain activity and the release of the neurotransmitters gamma-aminobutyric acid and noradrenaline (93). Furthermore, HPA axis activation is inhibited (94–96). In addition, anti-inflammatory effects of atVNS are mediated via the α7 nicotinic acetylcholine receptor (97), which leads to modulation of cholinergic anti-inflammatory pathways thereby inhibiting the release of cytokines, such as TNF-α in the prefrontal cortex, hippocampus, and hypothalamus, thus suppressing neurological inflammation (98).

A pilot randomized controlled trial of atVNS showed a trend suggesting that atVNS may have mild to moderate effect in reducing mental symptoms in a subset of patients with Long-Covid (99). Another pilot study involving 24 female patients with Long-Covid showed significant improvements in various cognitive functions, anxiety, depression, and sleep immediately post-intervention, with benefits persisting or increasing at the 1-month follow-up. Improvements in fatigue were delayed, achieving statistical significance at the 1-month follow-up compared with baseline (100). These findings support allocating resources to conduct further trials and advance the understanding of atVNS as a potential treatment for Long-Covid.

Multimodal Treatment

Given the absence of a single definitive biomarker for PAIS, and recognizing the significant heterogeneity among patients with PAIS, we propose a pragmatic treatment approach. Our recommendation involves a multimodal treatment regimen comprising a combination of pharmacotherapy, such as metformin and naltrexone with anti-inflammatory effects, alongside physical therapies such as rehabilitative measures, extracorporeal apheresis and transcutaneous neurotherapy. This combined approach aims to reduce biomarker levels and enhance cognitive functions. Selection criteria for this treatment should be based on presenting symptoms and a biomarker panel score (Figure 2). As mentioned above, additional research is necessary to identify the specific biomarkers that should be measured and to establish the threshold scores for diagnosing Long-Covid or other PAIS.

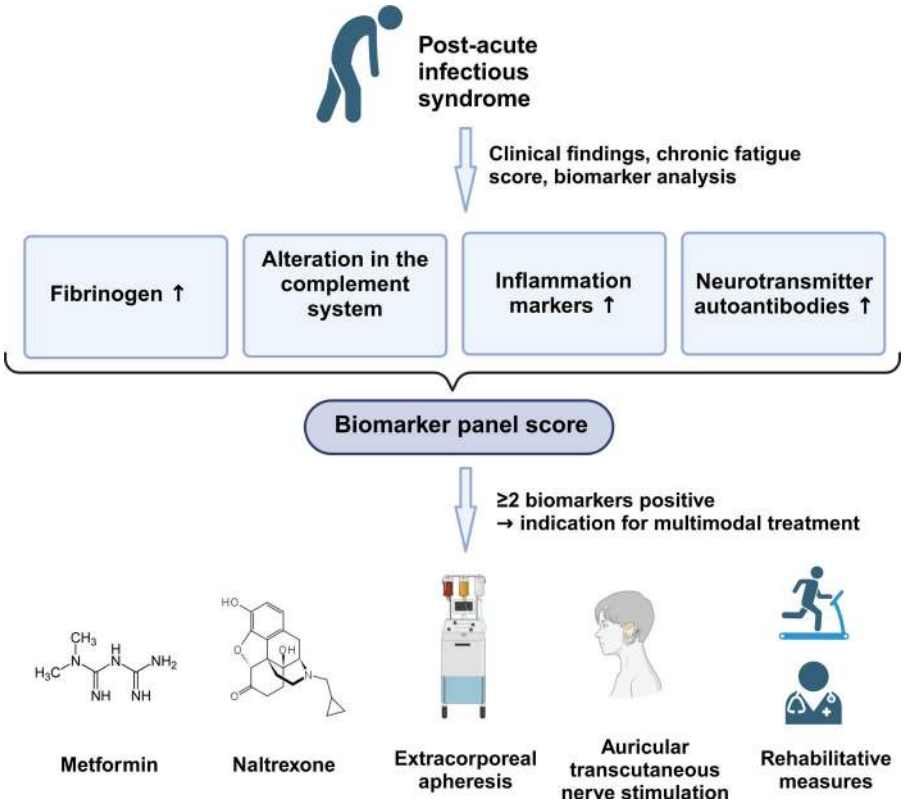

Figure 2. Multimodal strategy for treating PAIS. As PAIS appears to be multifactorial in nature with a wide variety of symptoms, we propose an approach involving the measurement of a panel of biomarkers such as different blood parameters, complement factors, inflammation markers, or neurotransmitter autoantibodies. If two or more of these biomarkers test positive, we recommend implementing a combined approach comprising both pharmaceutical (e.g., metformin or naltrexone) and physical interventions (e.g., extracorporeal apheresis or auricular transcutaneous nerve stimulation). Furthermore, rehabilitative measures addressing both physical and psychological needs should be considered. Created with BioRender.com

Ideally, the suggested multimodal treatment should be accessible to everyone. Since both metformin and naltrexone are relatively inexpensive, providing the pharmaceutical component should be feasible. However, access to specialists offering extracorporeal apheresis or atVNS is limited, making these components challenging to implement. This underscores the need for inclusive healthcare strategies and support for all communities worldwide.

Conclusion

Long-term complications are known from various infections. The pathology is mostly unknown and differs between patients. Unfortunately, currently there is no common and effective treatment. Limited data on the prevalence and outcomes of unexplained PAIS make interpretation difficult. The absence of comprehensive, prospective studies with long-term follow-ups, objective measures, and appropriate control groups, along with small sample sizes, obscures case outcomes. Methodological differences and varied symptom criteria further hinder comparison across studies, making it challenging to draw definitive conclusions about prevalence accuracy and long-term prognosis. This data gap undermines foundational knowledge for designing clinical studies and assessing interventions' impact on post-infectious chronic disease and disability management.

To develop a clinical scoring system for PAIS, multicenter studies involving a larger patient cohort, inclusive of those who have not responded to treatment, will be imperative. These studies will aim to correlate individual biomarkers with treatment outcomes. Specifically, multivariable analysis will be essential for establishing a practical clinical scoring system to monitor both short-term and long-term treatment efficacy. Moreover, a more comprehensive exploration of disease mechanisms underlying Long-Covid and other PAIS could enhance or supplement the existing panel of clinical biomarkers. Furthermore, in the future, modern artificial intelligence-based technologies, particularly those employing machine learning, will be ideally suited to tailor and define individualized treatment protocols based on specific markers for various patient subgroups afflicted with post-infectious syndromes.

In conclusion, a comprehensive approach is needed to address global health disparities while also encouraging specialists to combine well-established treatments with potentially lesser-known therapies to achieve optimal results.

Author Contributions

CS and SRB wrote the initial draft of the paper. NT, YPK, PM, HB, AB, JK, HH, and MP wrote smaller sections of the perspective. CS prepared the figures. All authors reviewed successive drafts of the Review. All authors approved the final submitted version and had final responsibility for the decision to submit for publication.

Acknowledgments

This work was supported by the German Research Foundation (DFG, project no. 314061271 and project no. 288034826).

References

1. Bornstein SR, Cozma D, Kamel M, Hamad M, Mohammad MG, Khan NA, et al. Long-COVID, metabolic and endocrine disease. Horm Metab Res. 2022;54(8):562–6. DOI: 10.1055/a-1878-9307. PMID: 35724687; PMCID: PMC9363148
2. Kim Y, Bae S, Chang HH, Kim SW. Characteristics of long COVID and the impact of COVID-19 vaccination on long COVID 2 years following COVID-19 infection: prospective cohort study. Sci Rep. 2024;14(1):854. DOI: 10.1038/s41598-023-50024-4. PMID: 38191556; PMCID: PMC10774352
3. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open. 2021;4(5):e2111417. DOI: 10.1001/jamanetworkopen.2021.11417. PMID: 34037731; PMCID: PMC8155823

4. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611–27. DOI: 10.1016/S2215-0366(20)30203-0. PMID: 32437679; PMCID: PMC7234781
5. Bai NA, Richardson CS. Posttreatment Lyme disease syndrome and myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review and comparison of pathogenesis. Chronic Dis Transl Med. 2023;9(3):183–90. DOI: 10.1002/cdt3.74. PMID: 37711861; PMCID: PMC10497844
6. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med. 2022;28(5):911–23. DOI: 10.1038/s41591-022-01810-6. PMID: 35585196
7. Staub K, Ballouz T, Puhan M. An unwanted but long-known company: postviral symptoms in the context of past pandemics in switzerland (and beyond). Public Health Rev. 2024;45:1606966. DOI: 10.3389/phrs.2024.1606966. PMID: 38651133; PMCID: PMC11033310
8. Walitt B, Singh K, LaMunion SR, Hallett M, Jacobson S, Chen K, et al. Deep phenotyping of post-infectious myalgic encephalomyelitis/chronic fatigue syndrome. Nat Commun. 2024;15(1):907. DOI: 10.1038/s41467-024-45107-3. PMID: 38383456; PMCID: PMC10881493
9. Magnus P, Gunnes N, Tveito K, Bakken IJ, Ghaderi S, Stoltenberg C, et al. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine. Vaccine. 2015;33(46):6173–7. DOI: 10.1016/j.vaccine.2015.10.018. PMID: 26475444
10. Murray KO, Garcia MN, Rahbar MH, Martinez D, Khuwaja SA, Arafat RR, et al. Survival analysis, long-term outcomes, and percentage of recovery up to 8 years post-infection among the Houston West Nile virus cohort. PLoS One. 2014;9(7):e102953. DOI: 10.1371/journal.pone.0102953. PMID: 25054656; PMCID: PMC4108377
11. Ballouz T, Menges D, Anagnostopoulos A, Domenghino A, Aschmann HE, Frei A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. BMJ. 2023;381:e074425. DOI: 10.1136/bmj-2022-074425. PMID: 37257891; PMCID: PMC10230608
12. Menges D, Ballouz T, Anagnostopoulos A, Aschmann HE, Domenghino A, Fehr JS, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. PLoS One. 2021;16(7):e0254523. DOI: 10.1371/journal.pone.0254523. PMID: 34252157; PMCID: PMC8274847
13. Nittas V, Gao M, West EA, Ballouz T, Menges D, Hanson SW, et al. Long COVID through a public health lens: an umbrella review. Public Health Rev. 2022;43:1604501. DOI: 10.3389/phrs.2022.1604501. PMID: 35359614; PMCID: PMC8963488
14. Hanson SW, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. JAMA. 2022;328(16):1604–15. DOI: 10.1001/jama.2022.18931. PMID: 36215063; PMCID: PMC9552043
15. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. BMJ Med. 2023;2(1):e000385. DOI: 10.1136/bmjmed-2022-000385. PMID: 36936268; PMCID: PMC9978692
16. de Bruijn S, van Hoek AJ, Mutubuki EN, Knoop H, Slootweg J, Tulen AD, et al. Lower prevalence of post-Covid-19 condition following Omicron SARS-CoV-2 infection. Heliyon. 2024;10(7):e28941. DOI: 10.1016/j.heliyon.2024.e28941. PMID: 38617937; PMCID: PMC11015416
17. Angum F, Khan T, Kaler J, Siddiqui L, Hussain A. The prevalence of autoimmune disorders in women: a narrative review. Cureus. 2020;12(5):e8094. DOI: 10.7759/cureus.8094. PMID: 32542149; PMCID: PMC7292717
18. Sweis JJG, Alnaimat F, Esparza V, Prasad S, Azam A, Modi Z, et al. From acute infection to prolonged health consequences: understanding health disparities and economic implications in long COVID worldwide. Int J Environ Res Public Health. 2024;21(3):325. DOI: 10.3390/ijerph21030325. PMID: 38541324; PMCID: PMC10970637
19. Charfeddine S, Hadj Amor HI, Jdidi J, Torjmen S, Kraiem S, Hammami R, et al. Long COVID 19 syndrome: is it related to microcirculation and endothelial dysfunction? Insights from TUN-EndCOV study. Front Cardiovasc Med. 2021;8:745758. DOI: 10.3389/fcvm.2021.745758. PMID: 34917659; PMCID: PMC8670225
20. Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021;144(12):3576–88. DOI: 10.1093/brain/awab302. PMID: 34398188; PMCID: PMC8719840
21. Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, et al. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. Clin Infect Dis. 2023;76(3):e487–90. DOI: 10.1093/cid/ciac722. PMID: 36052466; PMCID: PMC10169416
22. Aldhaleei WA, Alnuaimi A, Bhagavathula AS. COVID-19 induced hepatitis B virus reactivation: a novel case from the United Arab Emirates. Cureus. 2020;12(6):e8645. DOI: 10.7759/cureus.8645. PMID: 32550096; PMCID: PMC7296884
23. Gatto I, Biagioni E, Coloretti I, Farinelli C, Avoni C, Caciagli V, et al. Cytomegalovirus blood reactivation in COVID-19 critically ill patients: risk factors and impact on mortality. Intensive Care Med. 2022;48(6):706–13. DOI: 10.1007/s00134-022-06716-y. PMID: 35583676; PMCID: PMC9116062
24. Meng M, Zhang S, Dong X, Sun W, Deng Y, Li W, et al. COVID-19 associated EBV reactivation and effects of ganciclovir treatment. Immun Inflamm Dis. 2022;10(4):e597. DOI: 10.1002/iid3.597. PMID: 35349757; PMCID: PMC8959425
25. Shariq M, Sheikh JA, Quadir N, Sharma N, Hasnain SE, Ehtesham NZ. COVID-19 and tuberculosis: the double whammy of respiratory pathogens. Eur Respir Rev. 2022;31(164):210264. DOI: 10.1183/16000617.0264-2021. PMID: 35418488; PMCID: PMC9488123
26. Zubchenko S, Kril I, Nadizhko O, Matsyura O, Chopyak V. Herpesvirus infections and post-COVID-19 manifestations: a pilot observational study. Rheumatol Int. 2022;42(9):1523–30. DOI: 10.1007/s00296-022-05146-9. PMID: 35650445; PMCID: PMC9159383
27. de Arriba Fernandez A, Alonso Bilbao JL, Frances AE, Cabeza Mora A, Gutierrez Perez A, Diaz Barreiros MA, et al. Assessment of SARS-CoV-2 infection according to previous metabolic status and its association with mortality and post-acute COVID-19. Nutrients. 2022;14(14):2925. DOI: 10.3390/nu14142925. PMID: 35889880; PMCID: PMC9325256
28. Loosen SH, Jensen BO, Tanislav C, Luedde T, Roderburg C, Kostev K. Obesity and lipid metabolism disorders determine the risk for development of long COVID syndrome: a cross-sectional study from 50,402 COVID-19 patients. Infection. 2022;50(5):1165–70. DOI: 10.1007/s15010-022-01784-0. PMID: 35355237; PMCID: PMC8966865
29. Stasiak A, Perdas E, Smolewska E. Risk factors of a severe course of pediatric multi-system inflammatory syndrome temporally associated with COVID-19. Eur J Pediatr. 2022;181(10):3733–8. DOI: 10.1007/s00431-022-04584-8. PMID: 35948653; PMCID: PMC9364844
30. Xu E, Xie Y, Al-Aly Z. Risks and burdens of incident dyslipidaemia in long COVID: a cohort study. Lancet Diabetes Endocrinol. 2023;11(2):120–8. DOI: 10.1016/S2213-8587(22)00355-2. PMID: 36623520; PMCID: PMC9873268
31. Cervia-Hasler C, Bruningk SC, Hoch T, Fan B, Muzio G, Thompson RC, et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. Science. 2024;383(6680):eadg7942. DOI: 10.1126/science.adg7942. PMID: 38236961
32. Joob B, Wiwanitkit V. Blood viscosity of COVID-19 patient: a preliminary report. Am J Blood Res. 2021;11(1):93–5. PMID: 33796395; PMCID: PMC8010604
33. Kronstein-Wiedemann R, Tausche K, Kolditz M, Teichert M, Thiel J, Koschel D, et al. Long-COVID is associated with impaired red blood cell function. Horm Metab Res. 2024;56(4):318–23. DOI: 10.1055/a-2186-8108. PMID: 37890507
34. Kubánková M, Hohberger B, Hoffmanns J, Fürst J, Herrmann M, Guck J, et al. Physical phenotype of blood cells is altered in COVID-19. Biophys J. 2021;120(14):2838–47. DOI: 10.1016/j.bpj.2021.05.025. PMID: 34087216; PMCID: PMC8169220
35. Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, Kumpers P, et al. Persistent capillary rarefication in long COVID syndrome. Angiogenesis. 2023;26(1):53–61. DOI: 10.1007/s10456-022-09850-9. PMID: 35951203; PMCID: PMC9366128
36. Taquet M, Skorniewska Z, Hampshire A, Chalmers JD, Ho LP, Horsley A, et al. Acute blood biomarker profiles predict cognitive deficits 6 and 12 months after COVID-19 hospitalization. Nat Med. 2023;29(10):2498–508. DOI: 10.1038/s41591-023-02525-y. PMID: 37653345; PMCID: PMC10579097
37. Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol. 2021;20(1):172. DOI: 10.1186/s12933-021-01359-7. PMID: 34425843; PMCID: PMC8381139
38. Cabral-Marques O, Moll G, Catar R, Preuss B, Bankamp L, Pecher AC, et al. Autoantibodies targeting G protein-coupled receptors: an evolving history in autoimmunity. Report of the 4th international symposium. Autoimmun Rev. 2023;22(5):103310. DOI: 10.1016/j.autrev.2023.103310. PMID: 36906052
39. Wallukat G, Hohberger B, Wenzel K, Furst J, Schulze-Rothe S, Wallukat A, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun. 2021;4:100100. DOI: 10.1016/j.jtauto.2021.100100. PMID: 33880442; PMCID: PMC8049853

40. Cabral-Marques O, Halpert G, Schimke LF, Ostrinski Y, Vojdani A, Baiocchi GC, et al. Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity. Nat Commun. 2022;13(1):1220. DOI: 10.1038/s41467-022-28905-5. PMID: 35264564; PMCID: PMC8907309
41. Reinshagen L, Nageswaran V, Heidecke H, Schulze-Forster K, Wilde AB, Ramezani Rad P, et al. Protease-activated receptor-1 IgG autoantibodies in patients with COVID-19. Thromb Haemost. 2023. DOI: 10.1055/a-2205-0014. PMID: 37931906
42. Tran F, Harris DMM, Scharmacher A, Grasshoff H, Sterner K, Schinke S, et al. Increased protease-activated receptor 1 autoantibodies are associated with severe COVID-19. ERJ Open Res. 2022;8(4):00379-2022. DOI: 10.1183/23120541.00379-2022. PMID: 36575710; PMCID: PMC9571165
43. Achleitner M, Mair NK, Dänhardt J, Kardashi R, Puhan MA, Abela IA, et al. Absence of type i interferon autoantibodies or significant interferon signature alterations in adults with post-COVID-19 syndrome. Open Forum Infect Dis. 2024;11(1):ofad641. DOI: 10.1093/ofid/ofad641. PMID: 38179103; PMCID: PMC10766412
44. Peluso MJ, Mitchell A, Wang CY, Takahashi S, Hoh R, Tai V, et al. Low prevalence of interferon alpha autoantibodies in people experiencing symptoms of post-coronavirus disease 2019 (COVID-19) conditions, or long COVID. J Infect Dis. 2023;227(2):246–50. DOI: 10.1093/infdis/jiac372. PMID: 36089700; PMCID: PMC9494362
45. Cozma D, Siatra P, Bornstein SR, Steenblock C. Sensitivity of the neuroendocrine stress axis in metabolic diseases. Horm Metab Res. 2024;56(1):65–77. DOI: 10.1055/a-2201-6641. PMID: 38171373
46. Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacology (Berl). 2016;233(9):1637–50. DOI: 10.1007/s00213-016-4218-9. PMID: 26847047; PMCID: PMC4828495
47. Dionysopoulou S, Charmandari E, Bargiota A, Vlahos N, Mastorakos G, Valsamakis G. The role of hypothalamic inflammation in diet-induced obesity and its association with cognitive and mood disorders. Nutrients. 2021;13(2):498. DOI: 10.3390/nu13020498. PMID: 33546219; PMCID: PMC7913301
48. Steenblock C, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, et al. COVID-19 and metabolic disease: mechanisms and clinical management. Lancet Diabetes Endocrinol. 2021;9(11):786–98. DOI: 10.1016/S2213-8587(21)00244-8. PMID: 34619105; PMCID: PMC8489878
49. Muller JA, Gross R, Conzelmann C, Kruger J, Merle U, Steinhart J, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab. 2021;3(2):149–65. DOI: 10.1038/s42255-021-00347-1. PMID: 33536639
50. Qadir MMF, Bhondeley M, Beatty W, Gaupp DD, Doyle-Meyers LA, Fischer T, et al. SARS-CoV-2 infection of the pancreas promotes thrombofibrosis and is associated with new-onset diabetes. JCI Insight. 2021;6(16):e151551. DOI: 10.1172/jci.insight.151551. PMID: 34241597; PMCID: PMC8410013
51. Steenblock C, Richter S, Berger I, Barovic M, Schmid J, Schubert U, et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun. 2021;12(1):3534. DOI: 10.1038/s41467-021-23886-3. PMID: 34112801; PMCID: PMC8192507
52. Zinserling VA, Bornstein SR, Narkevich TA, Sukhanova YV, Semenova NY, Vashukova MA, et al. Stillborn child with diffuse SARS-CoV-2 viral infection of multiple organs. IDCases. 2021;26:e01328. DOI: 10.1016/j.idcr.2021.e01328. PMID: 34777995; PMCID: PMC8570448
53. Basolo A, Poma AM, Bonuccelli D, Proietti A, Macerola E, Ugolini C, et al. Adipose tissue in COVID-19: detection of SARS-CoV-2 in adipocytes and activation of the interferon-alpha response. J Endocrinol Invest. 2022;45(5):1021–9. DOI: 10.1007/s40618-022-01742-5. PMID: 35169984; PMCID: PMC8852916
54. Martinez-Colon GJ, Ratnasiri K, Chen H, Jiang S, Zanley E, Rustagi A, et al. SARS-CoV-2 infection drives an inflammatory response in human adipose tissue through infection of adipocytes and macrophages. Sci Transl Med. 2022;14(674):eabm9151. DOI: 10.1126/scitranslmed.abm9151. PMID: 36137009; PMCID: PMC9529056
55. Saccon TD, Mousovich-Neto F, Ludwig RG, Carregari VC, Dos Anjos Souza AB, Dos Passos ASC, et al. SARS-CoV-2 infects adipose tissue in a fat depot- and viral lineage-dependent manner. Nat Commun. 2022;13(1):5722. DOI: 10.1038/s41467-022-33218-8. PMID: 36175400; PMCID: PMC9521555
56. Steenblock C, Bechmann N, Beuschlein F, Wolfrum C, Bornstein SR. Do adipocytes serve as a reservoir for severe acute respiratory symptom coronavirus-2? J Endocrinol. 2023;258(2):e230027. DOI: 10.1530/JOE-23-0027. PMID: 37227170
57. Kanczkowski W, Evert K, Stadtmuller M, Haberecker M, Laks L, Chen LS, et al. COVID-19 targets human adrenal glands. Lancet Diabetes Endocrinol. 2022;10(1):13–6. DOI: 10.1016/S2213-8587(21)00291-6. PMID: 34801110; PMCID: PMC8601687
58. Steenblock C, Toepfner N, Beuschlein F, Perakakis N, Mohan Anjana R, Mohan V, et al. SARS-CoV-2 infection and its effects on the endocrine system. Best Pract Res Clin Endocrinol Metab. 2023;37(4):101761. DOI: 10.1016/j.beem.2023.101761. PMID: 36907787; PMCID: PMC9985546
59. Perakakis N, Harb H, Hale BG, Varga Z, Steenblock C, Kanczkowski W, et al. Mechanisms and clinical relevance of the bidirectional relationship of viral infections with metabolic diseases. Lancet Diabetes Endocrinol. 2023;11(9):675–93. DOI: 10.1016/S2213-8587(23)00154-7. PMID: 37524103
60. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. Front Microbiol. 2021;12:698169. DOI: 10.3389/fmicb.2021.698169. PMID: 34248921; PMCID: PMC8260991
61. Bhattacharjee N, Sarkar P, Sarkar T. Beyond the acute illness: exploring long COVID and its impact on multiple organ systems. Physiol Int. 2023;110(4):291–310. DOI: 10.1556/2060.2023.00256
62. Li B, Bai J, Xiong Y, Guo D, Fu B, Deng G, et al. Understanding the mechanisms and treatments of long COVID to address future public health risks. Life Sci. 2024;353:122938. DOI: 10.1016/j.lfs.2024.122938. PMID: 39084516
63. Fawzy NA, Abou Shaar B, Taha RM, Arabi TZ, Sabbah BN, Alkodaymi MS, et al. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO international clinical trials platform. Clin Microbiol Infect. 2023;29(5):570–7. DOI: 10.1016/j.cmi.2023.01.007. PMID: 36642173; PMCID: PMC9837206
64. Pouliopoulou DV, Macdermid JC, Saunders E, Peters S, Brunton L, Miller E, et al. Rehabilitation interventions for physical capacity and quality of life in adults with post-COVID-19 condition: a systematic review and meta-analysis. JAMA Netw Open. 2023;6(9):e2333838. DOI: 10.1001/jamanetworkopen.2023.33838. PMID: 37725376; PMCID: PMC10509723
65. Chaudhary S, Kulkarni A. Metformin: past, present, and future. Curr Diab Rep. 2024;24(6):119–30. DOI: 10.1007/s11892-024-01539-1. PMID: 38568468
66. Wrobel MP, Marek B, Kajdaniuk D, Rokicka D, Szymborska-Kajanek A, Strojek K. Metformin – a new old drug. Endokrynol Pol. 2017;68(4):482–96. DOI: 10.5603/EP.2017.0050. PMID: 28819951
67. Postler TS, Peng V, Bhatt DM, Ghosh S. Metformin selectively dampens the acute inflammatory response through an AMPK-dependent mechanism. Sci Rep. 2021;11(1):18721. DOI: 10.1038/s41598-021-97441-x. PMID: 34548527; PMCID: PMC8455559
68. Kelly B, Tannahill GM, Murphy MP, O'Neill LA. Metformin inhibits the production of reactive oxygen species from NADH:Ubiquinone oxidoreductase to limit induction of interleukin-1β (IL-1β) and boosts interleukin-10 (IL-10) in lipopolysaccharide (LPS)-activated macrophages. J Biol Chem. 2015;290(33):20348–59. DOI: 10.1074/jbc.M115.662114. PMID: 26152715; PMCID: PMC4536441
69. Chang MH, Park JH, Lee HK, Choi JY, Koh YH. SARS-CoV-2 spike protein 1 causes aggregation of alpha-synuclein via microglia-induced inflammation and production of mitochondrial ROS: potential therapeutic applications of metformin. Biomedicines. 2024;12(6):1223. DOI: 10.3390/biomedicines12061223. PMID: 38927430; PMCID: PMC11200543
70. Qiu S, Hubbard AE, Gutierrez JP, Pimpale G, Juarez-Flores A, Ghosh R, et al. Estimating the effect of realistic improvements of metformin adherence on COVID-19 mortality using targeted machine learning. Glob Epidemiol. 2024;7:100142. DOI: 10.1016/j.gloepi.2024.100142. PMID: 38590914; PMCID: PMC10999684
71. Bramante CT, Buse JB, Liebovitz DM, Nicklas JM, Puskarich MA, Cohen K, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. Lancet Infect Dis. 2023;23(10):1119–29. DOI: 10.1016/S1473-3099(23)00299-2. PMID: 37302406
72. Olawore O, Turner LE, Evans MD, Johnson SG, Huling JD, Bramante CT, et al. Risk of post-acute sequelae of SARS-CoV-2 infection (PASC) among patients with type 2 diabetes mellitus on anti-hyperglycemic medications. Clin Epidemiol. 2024;16:379–93. DOI: 10.2147/CLEP.S458901. PMID: 38836048; PMCID: PMC11149650
73. Toljan K, Vrooman B. Low-dose naltrexone (LDN)-review of therapeutic utilization. Med Sci (Basel). 2018;6(4):82. DOI: 10.3390/medsci6040082. PMID: 30248938; PMCID: PMC6313374
74. Li Z, You Y, Griffin N, Feng J, Shan F. Low-dose naltrexone (LDN): a promising treatment in immune-related diseases and cancer therapy. Int Immunopharmacol. 2018;61:178–84. DOI: 10.1016/j.intimp.2018.05.020. PMID: 29885638
75. Trofimovitch D, Baumrucker SJ. Pharmacology update: low-dose naltrexone as a possible nonopioid modality for some chronic, nonmalignant pain syndromes. Am J Hosp Palliat Care. 2019;36(10):907–12. DOI: 10.1177/1049909119838974. PMID: 30917675
76. Bruun KD, Amris K, Vaegter HB, Blichfeldt-Eckhardt MR, Holsgaard-Larsen A, Christensen R, et al. Low-dose naltrexone for the treatment of

fibromyalgia: protocol for a double-blind, randomized, placebo-controlled trial. Trials. 2021;22(1):804. DOI: 10.1186/s13063-021-05776-7. PMID: 34781989; PMCID: PMC8591911
77. Marcus NJ, Robbins L, Araki A, Gracely EJ, Theoharides TC. Effective doses of low-dose naltrexone for chronic pain – an observational study. J Pain Res. 2024;17:1273–84. DOI: 10.2147/JPR.S451183. PMID: 38532991; PMCID: PMC10964028
78. Patten DK, Schultz BG, Berlau DJ. The safety and efficacy of low-dose naltrexone in the management of chronic pain and inflammation in multiple sclerosis, fibromyalgia, crohn's disease, and other chronic pain disorders. Pharmacotherapy. 2018;38(3):382–9. DOI: 10.1002/phar.2086. PMID: 29377216
79. Bolton MJ, Chapman BP, Van Marwijk H. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Rep. 2020;13(1):e232502. DOI: 10.1136/bcr-2019-232502. PMID: 31911410; PMCID: PMC6954765
80. Polo O, Pesonen P, Tuominen E. Low-dose naltrexone in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Fatigue. 2019;7(4):207–17. DOI: 10.1080/21641846.2019.1692770
81. Bonilla H, Tian L, Marconi VC, Shafer R, McComsey GA, Miglis M, et al. Low-dose naltrexone use for the management of post-acute sequelae of COVID-19. Int Immunopharmacol. 2023;124(Pt B):110966. DOI: 10.1016/j.intimp.2023.110966. PMID: 37804660; PMCID: PMC11028858
82. Isman A, Nyquist A, Strecker B, Harinath G, Lee V, Zhang X, et al. Low-dose naltrexone and NAD+ for the treatment of patients with persistent fatigue symptoms after COVID-19. Brain Behav Immun Health. 2024;36:100733. DOI: 10.1016/j.bbih.2024.100733. PMID: 38352659; PMCID: PMC10862402
83. O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G, Lambert JS. Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study. Brain Behav Immun Health. 2022;24:100485. DOI: 10.1016/j.bbih.2022.100485. PMID: 35814187; PMCID: PMC9250701
84. Tamariz L, Bast E, Klimas N, Palacio A. Low-dose naltrexone improves post-COVID-19 condition symptoms. Clin Ther. 2024;46(3):e101–6. DOI: 10.1016/j.clinthera.2023.12.009. PMID: 38267326
85. Grassler J, Kopprasch S, Passauer J, Fischer S, Schuhmann K, Bergmann S, et al. Differential effects of lipoprotein apheresis by lipidfiltration or dextran sulfate adsorption on lipidomic profile. Atheroscler Suppl. 2013;14(1):151–5. DOI: 10.1016/j.atherosclerosissup.2012.10.006. PMID: 23357157
86. Julius U, Siegert G, Kostka H, Schatz U, Hohenstein B. Effects of different lipoprotein apheresis methods on serum protein levels. Atheroscler Suppl. 2015;18:95–102. DOI: 10.1016/j.atherosclerosissup.2015.02.018. PMID: 25936311
87. Kopprasch S, Bornstein SR, Schwarz PE, Bergmann S, Julius U, Graessler J. Single whole blood dextran sulfate adsorption favorably affects systemic oxidative balance in lipoprotein apheresis patients. Atheroscler Suppl. 2013;14(1):157–60. DOI: 10.1016/j.atherosclerosissup.2012.10.007. PMID: 23357158
88. Kopprasch S, Graessler J, Bornstein SR, Schwarz PE, Tselmin S, Frind A, et al. Beyond lowering circulating LDL: apheresis-induced changes of systemic oxidative stress markers by four different techniques. Atheroscler Suppl. 2009;10(5):34–8. DOI: 10.1016/S1567-5688(09)71807-0. PMID: 20129371
89. Steenblock C, Walther R, Tselmin S, Jarzebska N, Voit-Bak K, Toepfner N, et al. Post COVID and apheresis – where are we standing? Horm Metab Res. 2022;54(11):715–20. DOI: 10.1055/a-1945-9694. PMID: 36113501
90. Achleitner M, Steenblock C, Dänhardt J, Jarzebska N, Kardashi R, Kanczkowski W, et al. Clinical improvement of Long-COVID is associated with reduction in autoantibodies, lipids, and inflammation following therapeutic apheresis. Mol Psychiatr. 2023;28(7):2872–7. DOI: 10.1038/s41380-023-02084-1. PMID: 37131073; PMCID: PMC10152027
91. Colzato LS, Elmers J, Beste C, Hommel B. A prospect to ameliorate affective symptoms and to enhance cognition in long COVID using auricular transcutaneous vagus nerve stimulation. J Clin Med. 2023;12(3):1198. DOI: 10.3390/jcm12031198. PMID: 36769845; PMCID: PMC9917620
92. Yan L, Li H, Qian Y, Zhang J, Cong S, Zhang X, et al. Transcutaneous vagus nerve stimulation: a new strategy for Alzheimer's disease intervention through the brain-gut-microbiota axis? Front Aging Neurosci. 2024;16:1334887. DOI: 10.3389/fnagi.2024.1334887. PMID: 38476661; PMCID: PMC10927744
93. Colzato L, Beste C. A literature review on the neurophysiological underpinnings and cognitive effects of transcutaneous vagus nerve stimulation: challenges and future directions. J Neurophysiol. 2020;123(5):1739–55. DOI: 10.1152/jn.00057.2020. PMID: 32208895
94. Doerr JM, Juenemann M, Hakel L, Schmidt L, Menzler K, Krause K, et al. Effect of transcutaneous vagus nerve stimulation on stress-reactive neuroendocrine measures in a sample of persons with temporal lobe epilepsy. Epilepsia Open. 2023;8(3):1013–20. DOI: 10.1002/epi4.12774. PMID: 37310988; PMCID: PMC10472404
95. Hou L, Rong P, Yang Y, Fang J, Wang J, Wang Y, et al. Auricular vagus nerve stimulation improves visceral hypersensitivity and gastric motility and depression-like behaviors via vago-vagal pathway in a rat model of functional dyspepsia. Brain Sci. 2023;13(2):253. DOI: 10.3390/brainsci13020253. PMID: 36831796; PMCID: PMC9954117
96. Li S, Wang Y, Gao G, Guo X, Zhang Y, Zhang Z, et al. Transcutaneous auricular vagus nerve stimulation at 20 Hz improves depression-like behaviors and down-regulates the hyperactivity of HPA axis in chronic unpredictable mild stress model rats. Front Neurosci. 2020;14:680. DOI: 10.3389/fnins.2020.00680. PMID: 32765210; PMCID: PMC7378324
97. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. 2003;421(6921):384–8. DOI: 10.1038/nature01339. PMID: 32765210
98. Guo X, Zhao Y, Huang F, Li S, Luo M, Wang Y, et al. Effects of transcutaneous auricular vagus nerve stimulation on peripheral and central tumor necrosis factor alpha in rats with depression-chronic somatic pain comorbidity. Neural Plast. 2020;2020:8885729. DOI: 10.1155/2020/8885729. PMID: 33144854; PMCID: PMC7599410
99. Badran BW, Huffman SM, Dancy M, Austelle CW, Bikson M, Kautz SA, et al. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. Bioelectron Med. 2022;8(1):13. DOI: 10.1186/s42234-022-00094-y. PMID: 36002874; PMCID: PMC9402278
100. Zheng ZS, Simonian N, Wang J, Rosario ER. Transcutaneous vagus nerve stimulation improves Long COVID symptoms in a female cohort: a pilot study. Front Neurol. 2024;15:1393371. DOI: 10.3389/fneur.2024.1393371. PMID: 38756213; PMCID: PMC11097097