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Immunotherapies for Postural Orthostatic Tachycardia Syndrome, Other Common Autonomic Disorders and Long COVID: Current State and Future Direction

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Review

Immunotherapies for Postural Orthostatic Tachycardia Syndrome, Other Common Autonomic Disorders and Long COVID: Current State and Future Direction

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Abstract: Postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope, and orthostatic hypotension are the most common autonomic disorders encountered in clinical practice. Autoimmune etiology and association of these conditions with systemic autoimmune and inflammatory disorders, autonomic neuropathy and post-acute infectious syndromes, including Long COVID, suggest that immunotherapies should be considered as a therapeutic option, at least in a subset of patients. However, treatment of common autonomic disorders has traditionally included pharmacologic and non-pharmacologic symptomatic therapies as the standard approach. Unfortunately, these symptomatic therapies have been of limited or insufficient efficacy to meaningfully improve functional status or result in recovery, especially in patients with severe symptomatology. Case reports, case series, and clinical experience suggest that intravenous and subcutaneous immunoglobulin as well as other immunologic therapies, such as plasmapheresis, corticosteroids and rituximab, may be effective in some patients with severe POTS and other common autonomic disorders who are refractory to standard therapies. In this review, we summarize the literature available on the topic of immunotherapies in POTS, other common autonomic disorders, and Long COVID. We also highlight the need for large, multi-center, placebo-controlled trials of immunoglobulin, plasmapheresis, intermittent corticosteroids and other repurposed immunotherapies in patients with common autonomic disorders who have significant functional impairment.

Keywords: postural orthostatic tachycardia syndrome; dysautonomia; autonomic disorders; immunotherapy; immunoglobulin; autoimmunity; therapeutics

1. Introduction

Postural orthostatic tachycardia syndrome (POTS), one of the most common disorders affecting the autonomic nervous system, is a disabling condition with no FDA-approved treatment. Neurocardiogenic syncope, orthostatic hypotension, inappropriate sinus tachycardia and post-COVID dysautonomia are other common autonomic disorders (OCAD) frequently encountered in clinical practice. Treatment of these conditions traditionally includes non-pharmacological and pharmacologic regimens consisting of symptomatic treatment, which is currently accepted as the standard of care. However, for many patients with POTS and OCAD, these symptomatic therapies have been of limited and often insufficient efficacy to result in significant improvement or recovery. Case reports, case series, and clinical experience suggest that immunotherapies and immunomodulating agents may present potentially effective therapeutic options for some patients

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with standard treatment-refractory POTS and OCAD. We review the available literature on the use of immunotherapies in POTS and OCAD, including post-COVID dysautonomia as part of Long COVID, and discuss complexities, challenges, and future direction of immunologic therapies as treatments for the underlying autoimmune and immune-mediated etiology of these disorders.

1.1. Postural Orthostatic Tachycardia Syndrome

POTS is a chronic disorder of the autonomic nervous system characterized by orthostatic tachycardia, which is defined as an increase in heart rate by ≥ 30 bpm in adults and ≥ 40 bpm in adolescents 12-19 years old, from supine to standing position, associated with orthostatic symptoms that last for at least 3 months [1,2] (**Table 1**). Although it is defined by postural tachycardia, the clinical features of POTS are numerous and include dizziness, headache, fatigue, nausea, generalized weakness, sleep disturbances and others [3,4]. The onset of POTS may be sudden or insidious and can follow various triggers, such as infection, puberty, pregnancy, vaccinations, surgery, concussion and injury [5]. Importantly, patients with POTS have diminished quality of life and functional impairment similar to patients with congestive heart failure and chronic obstructive pulmonary disease, with greater than 50% of patients unable to maintain employment [6,7].

Prior to the COVID-19 pandemic, POTS was estimated to affect approximately 0.2-1% of the US population (1-3 million people) [8]. After the COVID-19 pandemic, the incidence of POTS was found to have increased 15-fold due to POTS and autonomic dysfunction being common manifestations of Long COVID [9]. POTS predominantly affects women of reproductive age, ages of 15-25 [8], but men are also becoming increasingly affected due to post-COVID POTS. Common comorbidities include migraines (at least 40%), gastrointestinal disorders (at least 30%), small fiber neuropathy (at least 50%), Ehlers-Danlos syndrome and hypermobility spectrum disorders (HSD) (at least 30%), autoimmune disorder (at least 20%), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (at least 20%), and mast cell activation syndrome (at least 20%) [5].

There are no FDA-approved therapies for POTS, but commonly accepted therapeutic approach to POTS consists of non-pharmacologic and pharmacologic treatment options. Pharmacotherapy includes first-line medications such as beta-blockers, which decrease resting and postural tachycardia by reducing sympathetic overactivity; fludrocortisone, a mineralocorticoid that augments retention of water and sodium and expands plasma volume; midodrine, which is an apha-1 agonist that causes vasoconstriction and increased peripheral resistance; pyridostigmine, a parasympathetic nervous system enhancer, and others [10,11].

1.2. Neurocardiogenic Syncope

Neurocardiogenic syncope (NCS) (also known as vasovagal syncope or neurally-mediated syncope) is defined as a sudden fall in blood pressure, heart rate, and cerebral hypoperfusion on standing or a tilt table test[1,2] (**Table 1**). It is usually of rapid onset, short duration and may be preceded by prodromal symptoms, such as pallor, diaphoresis, nausea, headache, and weakness. The loss of consciousness is typically brief and is not usually followed by confusion. NCS can occur after various triggers, including standing, pain, dehydration, heat, and the sight of blood. This form of syncope is common, with 42% of women and 32% of men experiencing at least one episode by age 60. Although when it occurs occasionally NCS is usually benign, recurrent and frequent NCS can greatly impair quality of life [1]. One common mechanism of syncope involves ineffective reflex response, where baroreceptors fail to perceive drops in venous return upon standing, or where pathologic vasodilation is triggered. The resulting hypotension causes loss of consciousness and has often been observed together with a vagally mediated bradycardia. Recurrent episodes of syncope often involve sympathetic nervous system dysfunction [1].

Diagnosis is based primarily on clinical history, and a tilt table test can be utilized when the origin of syncope is unclear, though it can only point towards a susceptibility to vasovagal syncope and cannot definitively diagnose the condition [1]. Similar to treatment of POTS, treatment of NCS involves increased fluid and salt intake, education about counterpressure maneuvers to be done

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when prodromal symptoms occur, and wearing compression garments. For those with recurrent episodes with significant impact on daily functioning, medical management can include a trial of midodrine, fludrocortisone, beta blockers or SSRIs, while pacemaker implantation can be considered in treatment-refractory patients with severe and disabling NCS with predominant cardioinhibitory component [12].

1.3. Orthostatic Hypotension

Orthostatic hypotension (OH), defined as a reduction in blood pressure ≥20/10 mmHg that occurs within three minutes of standing or during a head tilt test, is often associated with symptoms commonly related to cerebral hypoperfusion, such as lightheadedness, dizziness, presyncope, or syncope [2] (**Table 1**). OH can be associated with non-neurogenic causes, such as volume depletion or medication side effects, and neurogenic causes, such as senescence, neuropathic disorders, or neurodegenerative diseases. Medications, including vasodilators, nitrates, diuretics, phenothiazine, and neuroleptic antidepressants, can result in OH as side effect [13]. The severity of blood pressure reduction may also be influenced by the time of day, food ingestion, prolonged exposure to heat, fever, and alcohol consumption [2]. OH most often presents in the elderly, specifically 1 in 5 adults over age 60, and patients with neurodegenerative disorders [2,14].

Mild cases of OH are commonly managed by discontinuing hypotensive medications and lifestyle changes, such as increasing water intake, avoiding alcohol, dietary changes, use of abdominal binders or leg stockings, and head-up tilt sleeping. The pharmacological treatment approach for OH for patients with persistent symptoms is similar to POTS and includes sympathomimetic agents (midodrine, yohimbine, vasopressin agonists, clonidine), fludrocortisone, erythropoietin, pyridostigmine, selective serotonin reuptake inhibitors, and other medications (NSAIDs, antihistamines, caffeine, hydralazine, ergotamine). Droxidopa, a norepinephrine precursor medication with combined central and peripheral alpha and beta agonist effects, has been FDA approved for OH since 2014. It is indicated for treatment of neurogenic OH, and has shown improved symptoms and blood pressure elevation in four placebo-controlled RCTs [15].

1.4. Inappropriate Sinus Tachycardia

Inappropriate Sinus Tachycardia (IST) is a chronic syndrome defined as an unexplained sinus heart rate of ≥100 bpm at rest or >90 bpm on average for 24 hours without orthostatic changes [1] (**Table 1**). IST may be associated with debilitating clinical symptoms, most often palpitations, and commonly occurs in women between the ages of 15-45. Pathophysiology of IST involves various proposed mechanisms, including an imbalance between sympathetic and parasympathetic inputs, accelerated intrinsic sinus node rate due to deficient function of the acetylcholine and adenosine-sensitive potassium channels, impaired baroreflex control and others [16]. Since sinus tachycardia can be caused by various factors, including electrolyte abnormalities, dehydration and hormonal abnormalities, these causes should be ruled out, and cardiac monitoring, such as event monitor or implantable loop recorder, should be used to correlate symptoms with heart rates [16]. A 10-minute stand test or a tilt table test can be used to distinguish IST from POTS, OH and NCS [17], but sometimes a patient may have more than one autonomic disorder, such as, for example, both POTS and IST.

Treatment of IST includes medications that reduce heart rate and symptoms, such as ivabradine (an I_f channel antagonist), beta blockers, and calcium channel blockers. The combination of beta-blockers and ivabradine may be considered for ongoing management in some patients with IST [17]. Sinus node modification, surgical ablation, and sympathetic denervation are not typically recommended as a part of routine care for patients with IST [18].

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1.5. Long COVID

Long COVID describes the health consequences of COVID-19 that persist beyond the initial infection. The World Health Organization defines post COVID-19 conditions as symptoms that persist more than 12 weeks after probable or confirmed SARS CoV-2 infection, which last at least 2 months and have no alternative explanations [19]. Similarly, the 2024 National Academies of Sciences, Engineering, and Medicine consensus defines Long COVID as "an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems" [20]. Long COVID can follow either asymptomatic or symptomatic SARS CoV-2 infection, and the current diagnosis is entirely clinical [20], given that there are no reliable and validated biomarkers available to clinicians at this time. A Long COVID Household Pulse Survey showed that the rate of Long COVID is nearly 7% of all adults—roughly 17 million people— as of March 2024 [21]. In another study from 2023, the National Health Interview Survey, 8.4% of adults in the US reported ever having Long COVID and 3.6% reported currently having Long COVID [22].

The pathophysiology of Long COVID is multifactorial, but frequently involves autonomic dysfunction, including symptoms and signs such as palpitations, orthostatic intolerance, labile blood pressure, fatigue, headaches, and "brain fog" [23]. Consequently, many patients with Long COVID have POTS or OCAD [24,25], with nearly 70% of patients having a high autonomic symptom burden [26]. Autoimmune, inflammatory and immune dysregulations are identified as other major pathophysiologic mechanisms of Long COVID, which together with autonomic dysfunction, closely parallel the pathophysiology of POTS and OCAD. Increased prevalence of elevated serum autoimmune and inflammatory markers have been reported in patients with both POTS and Long COVID [27], and neuroinflammation at the brainstem, specifically at the dorsolateral inferior medulla, has been suggested as potential central nervous system localization for POTS and Long COVID [28]. Moreover, consensus guidelines on assessment and treatment of post-COVID autonomic dysfunction have been developed using nonpharmacologic and pharmacologic treatment options similar to POTS and OCAD unrelated to COVID-19 [29].

2. Autoimmunity

2.1. Autoimmune Markers in POTS and OCAD

The pathophysiology of POTS has been deemed as largely heterogeneous and traditionally classified as neuropathic, hypovolemic and hyperadrenergic [30]. In the past decade, however, investigators zeroed in on autoimmunity as one of the major mechanisms. Patients with POTS were found to have a higher prevalence of various non-specific autoimmune markers, including antinuclear antibodies, and comorbid autoimmune disorders than the general population [31]. More specifically to the autonomic nervous system, ganglionic N-type and P/Q type acetylcholine receptor antibodies, alpha 1, beta 1 and beta 2 adrenergic antibodies, muscarinic M2 and M4 antibodies, angiotensin II type 1 receptor antibodies and opioid-like 1 receptor antibodies have been identified in patients with POTS and OCAD [3,32–36]. Many of these antibodies have been also identified in patients with chronic fatigue syndrome, small fiber neuropathy, complex regional pain syndromes and cardiovascular disorders – conditions that have overlapping clinical features with POTS.

2.2. Comorbidity with Undifferentiated Connective Tissue Disease (UCTD)

POTS and OCAD are commonly comorbid with other autoimmune disorders, with the most common being Hashimoto's thyroiditis [31]. Association with Sjogren's syndrome, antiphospholipid syndrome and celiac disease have also been reported [37–39]. In addition, many patients with autonomic dysfunction, small fiber neuropathy and positive autoimmune or inflammatory markers are diagnosed with undifferentiated connective tissue disease (UCTD) when they do not qualify for the diagnostic criteria of defined autoimmune disorders, such as systemic lupus erythematosus,

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mixed connective tissue disease, Sjögren syndrome, systemic sclerosis, polymyositis, dermatomyositis, or rheumatoid arthritis. In clinical practice, the presence of undifferentiated connective tissue disease can be common.

Like POTS, UCTD predominantly affects women of reproductive age and is thought to be heterogeneous in mechanisms and presentations. UCTD is caused by an autoimmune etiology and may precede the onset of lupus or another defined classical autoimmune disease. UCTD includes the following diagnostic criteria: (1) clinical presentation suggestive of a defined connective tissue disease, but not meeting its criteria, (2) positive serological markers on two separate occasions including positive antinuclear antibody marker, and (3) the duration of symptoms is at least three years [40].

Positive serological markers are essential in the diagnostic criteria for UCTD and should include routine screening tests, such as complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, urinalysis with microscopic analysis, rheumatoid factor (RF), antinuclear antibodies (ANA), anti-Ro/SSA/anti-SSB antibodies and anti-U1-RNP [41]. Treatment typically includes symptomatic management with nonsteroidal anti-inflammatory medications, such as ibuprofen, naproxen, and celecoxib; corticosteroids, such as prednisone, methylprednisolone and hydrocortisone; calcium channel blockers, such as diltiazem and nifedipine; and immunomodulatory therapy with an anti-malarial drug, hydroxychloroquine. In more severe cases, immunosuppressive medications, such as methotrexate and azathioprine, can be used, especially when there is evidence of significant organ damage or involvement [42]. Further research is needed to elucidate whether POTS and OCAD with positive autoimmune markers represents a sizable subset of patients with UCTD, what longitudinal monitoring is required in this subset, and whether early intervention with treatment, such as hydroxychloroquine or low-dose naltrexone, can alter the natural history and potentially prevent further progression of the disease process.

2.3. Association with Autonomic Neuropathy

POTS and OCAD can often occur as part of, or in the context of, autonomic neuropathy. Experts who originally described POTS have considered it to be a limited or restricted form of autonomic neuropathy [43,44]. About half of patients with POTS have a length-dependent distribution [30,45] with distal postganglionic sudomotor denervation demonstrated with the quantitative sudomotor axon reflex test (QSART) or the thermoregulatory sweat test [46]. These tests commonly reveal sudomotor denervation to the foot and toes: adrenergic impairment to the lower extremity can be seen in neuropathic POTS as impaired norepinephrine spillover in the leg while the arm response remains normal [47]. However, non-length-dependent or patchy distribution of small fiber neuropathy can also occur, especially in conjunction with systemic autoimmune disorders [48]. Autoimmune and immune-mediated etiology has been suggested as one of the major underlying mechanisms in autonomic neuropathy, with immunotherapy being recommended as the first line treatment [49–52].

2.4. Autoimmunity in Long COVID

Autoimmunity has been implicated as one of the major mechanisms of Long COVID leading to a higher risk, overall incidence and range of autoimmune conditions after SARS-CoV-2 infection [53]. A variety of antibodies has been linked to Long COVID, including autoantibodies to inflammatory cytokines such as IgG to IL-2, D8B, thyroglobulin, and IFNδ [27,54,55]. These autoantibodies have been associated with anti-SARS CoV2 IgG antibodies [27,54,55]. G protein-coupled receptor antibodies, including against alpha- and beta-adrenergic antibodies and muscarinic antibodies, previously identified in patients with POTS, as well as autoantibodies to antinuclear and extractable nuclear antigens have been also found in patients with Long COVID [27,56,57]. The pro-inflammatory mediators, non-specific antibodies and antibodies important to the function of the autonomic nervous system are thought to be implicated in the development of post-COVID autonomic disorders, such as POTS and OCAD [27].

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3. Immunotherapies

3.1. Immunologic Therapies and Ongoing Clinical Trials for POTS and OCAD

3.1.1. Immunoglobulin

Intravenous (IVIG) or subcutaneous (SCIG) Immunoglobulin comes from a concentrate of pooled immunoglobulins derived from 1000 to 100000 healthy donors and serves as an immunomodulating therapy that can neutralize autoantibodies, reduce cellular immunity, and decrease endothelial inflammation by increasing IgG levels in the bloodstream [58]. Immunoglobulins play a vital role in humoral adaptive immunity, and therefore, IVIG reflects a collective exposure of the donor population to their environment and can be expected to contain various antibodies of multiple specificities against a broad spectrum of infectious agents (bacterial, viral, and others), self-antigens and anti-idiotype antibodies. The composition of IVIG products closely corresponds to that of immunoglobulins in normal human plasma, especially IgG (along with its subclasses), IgA, traces of other Igs, cytokines, and soluble receptors [59].

IVIG has been indicated as a replacement therapy in immunodeficiencies, as an immunomodulatory and anti-inflammatory therapy for immunomodulation in hematological and organ-specific autoimmune disorders, and as an anti-inflammatory in rheumatic inflammatory conditions, infectious and neurological disorders. It's been also utilized as a hyperimmune therapy against specific infectious agents [59].

Given its widespread use in neurologic conditions, such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), acute disseminated encephalomyelitis (ADEM), MMN, dermatomyositis, myasthenia gravis and others, IVIG has been also used successfully in treating less common peripheral neuropathies, such as autoimmune autonomic ganglionopathy (AAG) and autoimmune autonomic neuropathy (AAN) [60,61]. To this end, a trial of IVIG or SCIG seems reasonable in POTS – a restricted form of AAN – and OCAD, especially in patients with comorbid SFN, UCTD or systemic autoimmune disorder.

Over the past decade, case reports and case series describing the benefits of IVIG in POTS and OCAD have been accumulating. All reported reduced autonomic symptoms, orthostatic intolerance, fatigue, functional impairment and lowered antibody titers when available. Similar findings were observed in other case reports of IVIG or SCIG in patients with OCAD (**Table 2**). Importantly, these reports suggest that IVIG and SCIG are well-tolerated without significant serious adverse events although side effects, including post-infusion headache and flu-like symptoms, were common. Slower infusion rates with pretreatment with IV saline, antihistamines and anti-inflammatories, may mitigate these side effects and improve tolerability [62].

Recently, a small randomized controlled study found no significant benefit of 16 patients treated with IVIG vs. 14 patients treated with albumin with autoimmune POTS despite a trend toward a higher response rate in the IVIG-treated group [63]. However, the true benefit of IVIG may not have been captured as the study was underpowered, used lower IVIG doses than those for autoimmune disorders, was of short duration and had other major limitations [64]. Further research with large, multicenter, randomized controlled trials of longer duration and addressing major limitations is needed to provide a comprehensive and objective assessment of the efficacy of IVIG in patients with POTS [64].

3.1.2. Plasma Exchange

Plasma exchange (TPE), also known as plasmapheresis, is a technique that removes circulating autoantibodies and other humoral factors rapidly from the vascular compartment and has been used as the first effective acute treatment for neurologic disorders, such as Guillain-Barré syndrome and myasthenia gravis before intravenous immunoglobulin became available [65]. It is still used when IVIG is not available or ineffective in a variety of neuroimmune disorders, including CIDP and autoimmune encephalitis [65]. Isolated cases of a total of 5 patients with severe POTS have been

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described in scientific literature; their POTS symptoms improved significantly with TPE, with patients being able to return to work and other daily activities, such as walking and exercising [66–68] (**Table 2**). Despite no significant adverse events reported, further studies are necessary to determine the efficacy and safety of TPE in patients with severe POTS and OCAD.

3.1.3. Biologic Immunotherapies

Biologic therapies in POTS and OCAD cases have not been explored in-depth but may be a good option to explore in patients with severe symptoms. Rituximab, an anti-CD20 monoclonal antibody, could be of benefit in autoimmune autonomic disorders as it targets B-cells that are created by the adaptive immune system and responsible for autoantibody production. There is limited data on its use in POTS and OCAD, however, it has been utilized in select cases with other autoimmune neurological conditions with autonomic involvement [69,70]. Currently, Rituximab use has been reported in one POTS patient and three OCAD patients [67,71,72]. All patients reported autonomic symptomatic resolution with two demonstrating absence or decrease in autoimmune antibodies post-treatment.

Adalimumab is a monoclonal antibody against Tumor Necrosis Factor-alpha (TNF-α), a pro-inflammatory cytokine made by the innate immune system, that is responsible for regulating inflammation, cell differentiation, and tissue destruction. It is FDA-approved for treatment of rheumatoid arthritis, inflammatory bowel disease and other autoimmune and inflammatory disorders. One case report described the use of adalimumab in a patient with POTS and seronegative ankylosing spondylitis, which led to complete symptom resolution of POTS symptoms within one week of the induction dose and no adverse effects [73] (**Table 2**).

Tocilizumab is an IL-6 receptor antagonist that activates the JAK/STAT3 pathway and regulates inflammation, B-cell activation, and autoantibody production. Although it has been used in neurologic and autoimmune disorders, such as neuromyelitis optica spectrum disorder [74] and rheumatoid arthritis [75], it has yet to be explored in POTS and OCAD. Currently, the application of biologic therapies in POTS and OCAD remains extremely limited, primarily due to inaccessibility of these agents, high cost, and potential for adverse effects, but future pharmaceutical research and investment in clinical trials are warranted to assess their full therapeutic potential. Notably, there is one Phase II double-blind placebo-controlled clinical trial investigating a novel monoclonal antibody against natriuretic peptide receptor 1 that began recruiting POTS patients in late 2024[76] (**Table 3**).

3.1.4. Other traditional immunomodulators

Although immunomodulating therapies have not been typically included in the standard pharmacologic approaches for POTS and OCAD, these treatment options have been gaining utility, especially in the context of comorbid UCTD, systemic autoimmune disorders and Long COVID. These pharmacotherapies include oral, IV and SQ corticosteroids, low-dose naltrexone, and immunosuppressants, such as hydroxychloroquine. These medications may be attractive as they have more established safety profiles, clinical familiarity, and easier accessibility through insurance coverage compared to other immunologic therapies. Corticosteroids are effective in reducing inflammation and autoimmunity and have been used for decades for acute exacerbation of multiple sclerosis, neuromyelitis optica, myasthenia gravis and others. They have been reported as treatment of autonomic dysfunction either as monotherapy or in combination with other immunotherapies in patients with neurologic Sjogren's and autonomic neuropathy associated with neurosarcoidosis [77–81]. Improvement with corticosteroids has been observed in these small case series; however, long-term use is not recommended due to significant steroid-induced side effects, including long-term risk of diabetes, osteoporosis, hypertension and Cushing's syndrome [82].

Naltrexone is a potent mu-opioid receptor antagonist at high doses, primarily used to prevent relapse in opioid use disorder. Below 5 mg, low-dose naltrexone (LDN) acts as a glial modulator, inhibits Toll-like-receptor-4 (TLR-4), and only partly antagonizes opioid receptors. Its anti-TLR4 effects inhibit proinflammatory cytokine production, while its partial opioid receptor

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downregulation signals for increased opioid production and can downregulate the immune system in POTS and OCAD [83,84]. There are no clinical trials on the use of LDN in POTS and OCAD, with only one case report documenting beneficial LDN use in POTS[85] (**Table 2**). Clinical experience suggests that many patients report improvement in chronic pain, chronic fatigue and mast-cell related symptoms with the use of LDN.

Antimetabolite immunosuppressants, such Mycophenolate Mofetil, Azathioprine, or Hydroxychloroquine, could be also of potential therapeutic benefit in autoimmune POTS and OCAD, but the use of these medications in patients with POTS and OCAD has not been invesigaged. Anecdotal reports of patients with POTS and OCAD and comorbid autoimmune disorders, such as UCTD and Sjogren's syndrome, suggest that there may be potential benefits in this subset of patients.

3.2. Immunologic Therapies and Ongoing Clinical Trials for Long-COVID

Immunotherapies documented in Long-COVID case reports and cohort studies include IVIG, immunoadsorption, convalescent plasma (CP), TPE, and LDN. Due to their proposed therapeutic role in autoimmune POTS and OCAD, these therapies could be considered potential therapeutic options for Long-COVID-associated dysautonomia, but their use is extremely limited due to a lack of access and insurance coverage.

Three case reports have documented the utility of IVIG, TPE, and CP treatments in Long-COVID. Novak reported improvement in headache and fatigue, with complete symptom resolution of all other symptoms [86]. Minor adverse effects, such as headaches, were alleviated by dose down titration. Tomisti et al. treated two patients with CP who reported complete symptom resolution within 1 month after their final treatment dose and reported no side effects[87]. Lastly, Seeley et al. treated one patient with TPE who reported improved cognitive function, peripheral pain, and ambulation capacity, from 5 to 12 meters [88]. They also did not report side effects (**Table 2**).

Four prospective studies, though limited in sample size, have demonstrated clinical improvements in Long-COVID and post-COVID syndromes following treatment with LDN (n=38), immunoadsorption (n=20), and immunoglobulin (n=9) [89–91]. O'Kelly et al. conducted an open-label prospective study with 38 patients receiving 1 mg of LDN, assessing improved outcomes by self-reported questionnaires [89]. They found the biggest effect of symptom reduction in joint pain. Additionally, Isman et al. investigated LDN in an open-label prospective study with 36 long-COVID subjects over 12 weeks. They reported significant improvements in their quality of life and fatigue, measured by their SF-36 and CFS scores. Approximately half of their participants were identified as clinical responders [92] (**Table 2**).

A placebo-controlled clinical trial was conducted for Efgartigimod in 53 patients with post-COVID POTS subjects, but preliminary outcomes showed no benefit of Efgartigimod compared to placebo l[93]. The clinical trial was stopped in 2024 and its outcome data has yet to be released [94] (**Table 2**). Currently, eight immunotherapy clinical trials are ongoing for Long COVID and post-COVID autonomic disorders. These clinical trials are investigating IVIG, immunoadsorption, Infliximab compared to Imatinib, Tocilizumab, Baricitinib, and an anti-SARS-CoV-2 monoclonal antibody therapy. Four clinical trials are being held in North America (United States and Canada), including one as part of the NIH-RECOVER autonomic study, with the other trials taking place in Germany, Finland, and the United Kingdom[95–101] (**Table 3**).

3.3. Immunologic Therapies for ME/CFS

ME/CFS has overlapping clinical features with POTS, OCAD and Long COVID and is therefore relevant to this review. A number of immunologic therapies have been studied in ME/CFS, including IVIG, SCIG and IgG depletion by immunoadsorption [90,91,102]. Four double-blind randomized placebo-controlled trials (RCTs) of IVIG for ME/CFS have been conducted in the 1990s: one study reported that immunoglobulin is effective in a "significant number of patients," the other that IVIG "is unlikely to be of clinical benefit in CFS" [103,104]. The third study reported a beneficial effect of IVIG in adolescent patients, but a fourth trial reported that IVIG was ineffective [105,106]. Despite

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these conflicting results from clinical trials, some authors believe that IVIG presents a potentially curative treatment for a proportion of patients with ME/CFS and that further randomized controlled trials should be conducted with urgency, especially since many patients with Long COVID qualify for a diagnosis of ME/CFS [107].

More recently, in a case-control study of patients with post-COVID SFN who had comorbid ME/CFS, IVIG administered to 9 patients resulted in decreased allodynia and neuropathic symptoms compared to patients who were not treated with IVIG [91]. Subcutaneous low-dose immunoglobulin therapy has also been shown to be effective in 17 patients with ME/CFS [102]. In a cohort of 20 patients, immunoadsorption was used to remove select immunoglobulins and autoantibodies from plasma, which led to symptomatic improvement in some patients [90]. Further research involving more robust, controlled study designs with larger sample sizes are needed to elucidate the efficacy of these immunologic therapies for treatment of ME/CFS.

3.4. Potential Immunologic Therapies for POTS, OCAD and Long COVID

Since POTS, OCAD and Long COVID have been increasingly linked to autoimmunity and immune system dysregulation, new and repurposed immunologic therapies present a potentially effective treatment option and should be explored in future clinical trials. These therapies might be used either as a last resort in patients who failed standard non-pharmacologic and pharmacologic therapies or as a first line treatment in patients POTS and OCAD of suspected autoimmune or inflammatory etiologies, or comorbid SFN, UCTD and other systemic autoimmune disorders. Many immunologic therapies have been already approved for other indications that could have the potential to treat POTS and OCAD including immunoglobulin, plasmapheresis, immunoadsorption, corticosteroids, hydroxychloroquine, mycophenolate, azathioprine, methotrexate, monoclonal antibody treatments, and various receptor inhibitors (**Table 4**). Availability and accessibility of these immunotherapies to patients with POTS, OCAD and Long COVID may present a potentially effective treatment option and prevent future disability incurred as a result of progressive disease course.

4. Future Direction

Although immunomodulating therapies appear to be beneficial in at least a subset of patients with POTS and OCAD, the next step is to invest in large, multi-center, placebo-controlled trials of immunoglobulin, plasmapheresis, intermittent corticosteroids and other repurposed immunologic therapies. However, these trials may be more difficult to execute than similar trials for patients with immune-mediated peripheral neuropathies, multiple sclerosis, myasthenia gravis and other autoimmune disorders. The reasons for these complexities are multi-faceted. First, the heterogeneity of patient population, diverse pathophysiology and autoantibodies and a lack of the precise unifying biomarker underlying POTS and dysautonomia in general can make it difficult to interpret and generalize the outcomes. Second, the 30 beats per minute heart rate elevation as the diagnostic criteria for POTS may not be a good marker to assess treatment outcome as this change in heart rate is highly variable and imprecise. Moreover, there is a lack of established inclusion criteria for patients with presumed autoimmune POTS. Additionally, comorbidity with small fiber neuropathy, UCTD and autonomic neuropathy, which are predominantly driven by autoimmune and inflammatory etiologies, needs to be considered. Furthermore, the effect of saline and albumin as comparators needs to be examined as these agents may not be truly placebo and may have significant blood volume and some immunologic effects [64]. Another difficulty is the high prevalence of patients with allergies and sensitivities to medications, excipients and preservatives among patients with POTS, and therefore, patients may require individualized and modified trial protocols. Immunotherapy dose, duration, and cross-over timelines also need to be evaluated given that at least 3-6 months of treatment may be required to see the full effect and at least 6 months may be needed for the effect of immunotherapy to dissipate. Moreover, optimal timing of immunotherapy initiation relative to disease onset would need to be determined. It is possible that starting immunotherapy sooner rather than later in the disease course would yield better efficacy and treatment outcomes than starting it at

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any point in the disease course. Finally, validated questionnaires to assess autonomic symptom burden, fatigue, functional abilities, and quality of life should be used as primary outcomes, and objective heart rate and blood pressure responses as secondary outcomes because there is a high rate of discrepancy and variability between symptom severity and vital signs. Despite these challenges, however, we believe that conducting large, well-designed clinical trials of immunotherapies is a priority for patients with POTS and OCAD, including those with post-COVID onset.

5. Conclusion

Combining the limited data outlined in this review, the current and future clinical trials and our clinical experience, we conclude that immunologic therapies present an important and, potentially, very effective therapeutic option for patients with POTS, OCAD and Long COVID. To this end, we believe that patients with severe POTS, OCAD and Long COVID should have access to a variety of therapeutic options involving immunomodulation, including a 3-6 month trial of IVIG, SCIG or PLEX - therapies that are already available to patients with demyelinating neuropathies, autonomic neuropathy, autoimmune autonomic ganglionopathy, and other neurologic and autoimmune disorders.

Table 1. Diagnostic criteria for common autonomic disorders and Long COVID.

Disorder	Diagnostic Criteria	Clinical Features
POTS [1,2]	1. HR increase ≥30 bpm within 10 min for adults (≥40 bpm for adolescents 12–19 years of age) of standing or TTT. 2. Absence of OH, a ≥ 20 mmHg drop in systolic blood pressure. 3. Symptoms of orthostatic intolerance for ≥3 months.	Palpitations, exercise intolerance, dyspnea, tachycardia, chest discomfort, syncope, tremors, anxiety, blurred vision, headaches, lightheadedness, fatigue, weakness, gastroparesis (abdominal pain, nausea, IBS), bladder dysfunction.
NCS [1,2]	1. Transient loss of consciousness typically preceded by prodromal symptoms and signs. 2. A sudden fall in blood pressure, heart rate and cerebral hypoperfusion on standing or TTT.	Prodromal symptoms may include pallor, diaphoresis, nausea, headache and weakness. Loss of consciousness is typically brief and is not usually followed by confusion.
OH [2]	Sustained drop in blood pressure ≥20/10 mmHg within 3 min of standing or TTT.	Syncope, presyncope, dizziness.
IST [1,2]	1. Average sinus HR exceeding 90 bpm over 24h or HR while awake and at rest ≥100 bpm. 2. Palpitations and other distressing symptoms associated with sinus tachycardia.	Palpitations, dyspnea, lightheadedness, chest discomfort, transient loss of consciousness.
Long COVID[20,108]	Symptoms that persist > 12 weeks after probable or confirmed SARS CoV-2 infection and last at least 2 months with have no other culpable etiology.	Fatigue, shortness of breath, exercise intolerance, “brain fog,”, headache, palpitations, loss of smell, poor memory, dizziness, altered mood, sleep disturbance.

POTS, postural orthostatic tachycardia syndrome; NCS, neurocardiogenic syncope; OH, orthostatic hypotension; HR, heart rate; bpm, beats per minute; TTT, tilt table test; IST, inappropriate sinus tachycardia.

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Table 2. Immunotherapy in POTS, OCAD, and Long-COVID: Review of Literature.

Indication	Study Design	Immunotherapy, Administration, Dosage, and Course	Outcome Measures	Key Findings	Adverse Effects
POTS	Double-blind randomized controlled trial of IVIG (n= 16) vs. albumin (n= 14)[63]	IVIG (Gamunex-C®) 0.4 gm/kg for 12 weeks. 1. Weekly for 4 weeks 2. q2weeks for 8 weeks	- Change in Symptoms Measured by Change in COMPASS-31 Score from baseline to week 13. - Orthostatic vitals (active stand test) and laboratory studies for safety were collected at screening, baseline and weeks 5, 13, and 15.	- No difference between treatment groups at week 13 in scores. - IVIG group had a non-statistically significant higher response rate (46.7% vs. 38.5%) vs. placebo.	-No difference in AE between patients vs. controls -Mild headache -One patient with pneumonia
	Case Report[109] n= 1	1. IVIG 400 mg/kg/day for 5 days. 2. IV 0.5 g/kg initiated after 1 month, every q5-6 weeks.	- Change in serum antibody testing - Change in vital signs on HUT test, at baseline and post-treatment. - Change in ability to do daily activities of living	- Decrease in Anti-gAch-R antibody index at baseline from 2.162 to 1.438 - Patient's HUT showed HR change from lying and standing reduced from 56 to 34 bpm.	None reported
	Case Series[110] n= 6	IVIG 0.4 g/kg 1. Daily for 5 days (2 g/kg maximum dose). 2. Given over 2 days monthly (0.8 g/kg maximum dose).	- Change in heart rate increase (bpm) after 10 minutes of HUT test, duration (min) of TST, and anhidrotic area (%) in the TST at baseline and 6 months after IVIg treatment. - Change in standardized symptom questionnaires from baseline to 6 months of IVIg treatment.	- Symptom severity was reduced by nearly 40%. 83.3% had improved performance, exercise tolerance, and later on gastrointestinal symptoms. - Autonomic function testing showed improved cardiovascular functioning by 50% and a reduction of anhidrotic areas by one third.	- Aseptic meningitis and hospitalization (n=2) - Hypertension (n=2)
	Case Report[111] n= 1	1.IVIG 2 g/kg for 5 days. 2. IV 1 g/kg given	- Change in HUT test - Change in COMPASS31	- Reduction of serum antibodies - Improvement	No major AE

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	11 times, at a rate of 2-3g/h 3. Subcutaneous 0.25 g/kg, changed to weekly for 6 months.	questionnaire - Change in antibody titers	COMPASS31 scores. - Cessation of syncopal episodes while standing.	
Case Report[68] n=1	PLEX (3L pf plasma with 4% albumin) given over 2-4 hours for 6 sessions within a 2-week period.	- Change in COMPASS31 questionnaire - Change in OHSA and OHDAS scores - Change in CANTAB score - Change in 10-minute tilt table test	- Improvement in COMPASS31(40 %), OHSA (38%), and OHDAS (29%) scores. - CANTAB score indicated some improvement in attention, alertness, and memory metrics. - Tilt table test only showed minor improvements when reassessed post-2 weeks treatment. - Symptoms returned within a month of PLEX treatment, and pt was restarted on a maintenance dose every q2-3weeks for over 18 months.	None
Case Series[66] n= 7	SCIG (5/7) PLEX q2weeks or monthly for at least 3 months.	- Change in COMPASS-31 score and FAS score from baseline to 3-12 months post-treatment.	- Average 50% reduction in COMPASS 31 score, 217% increase in FAS scores within 3 to 9 months of treatment. - 6 pts reduced or discontinued oral medications for POTS. - 5 pts had a FAS score higher than 80%, and able to return to work or school.	No major AE
Case Report[85] n= 1	Immunoglobulin (Privigen®) IV 1.5 g/kg monthly for 1	- Change in 10-point Likert scale to score	Improved syncope, body pain, weakness,	No major AE

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		year.	severity and frequency of symptoms.	vertigo, syncope, GI symptoms, tinnitus. - After 10 IVIg infusions, resolution of tachycardia on HUT, improvement in sudomotor function.	
	Case Report[73] n= 1 POTS with seronegative ankylosing spondylitis	Adalimumab SC, unknown dose and duration.	- Change in Likert scale, to score severity and frequency of symptoms, from baseline and after treatment.	- Complete resolution of POTS symptoms within days to one week of treatment initiation.	None
	Case Report[67] n= 1	1. Rituximab IV 375 mg/m² q4 weeks for 1 year. 2. PLEX 2-3x per week for 1 year.	Not specified.	- Improvement in symptoms, such as going from being bedbound to walking 2 miles, exercising daily for an hour, and returning to work.	None
OCAD	Open-label Cohort Study[112] in AD n= 32	Immunoglobulin IV 2 gm/kg monthly for at least 3 months.	- Change in upper gastrointestinal symptom severity and QOL every two months for 2 years.	- Improvement of OTE scores, with a mean of 1.8 (SD 3.2), was significantly better than 0 at baseline (p=0.004). - The PAGI-QOL indicated “great or very great deal better” (p<0.001) and a clinically significant response (p=0.001).	Greater than 60% reported side effects, none life-threatening.
	Case Series[81] in Autoimmune GI dysmotility n= 23	Immunoglobulin IV 0.4 g/kg given over 3 days or Methylprednisolone IV 1 mg daily for 3 days then weekly or both for for 6-12 weeks.	- Response was defined subjectively (symptomatic improvement) and objectively (gastrointestinal scintigraphy/manometry studies).	- 74% had improved symptoms and scintigraphy, five; symptomatic alone, eight; scintigraphy alone, four). - 6/7 with repeat	Aseptic meningitis (n=1)

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			autonomic testing after treatment demonstrated improvements.	
Case Series[113] in AD n= 38	Immunoglobulin IV 0.25 gm/kg weekly for at least 3 months, then increased to 1 gm/kg/month.	- Change in disease activity, measured by COMPASS-31and FAS scores, from baseline and regular intervals. - Repeat skin biopsies after 12 months or more of IVIg therapy.	- Improved in FAS and COMPASS 31 scores reported in 83.5% of patients. - Pre-treatment average FAS score changed from a 21% (mostly bedridden) to 74% (able to return to work or school) in 1 year. - Improved sweat gland and/or epidermal nerve fiber density in 2 out of 4 patients 1 year after IVIG.	- Headache - Neck pain - Fatigue - Myalgias - Aseptic meningitis - Transaminitis - MCAS flare
Case Report[114] in AN with Sjogren's syndrome n= 1	Immunoglobulin 1. IV 2g/kg given over 5 days, then 0.4 g/kg/month x 1.5 yrs	- Change in disease activity, measured by COMPASS-31 score and FAS score, from baseline.	- After 6 months, patient could walk long distances; COMPASS-31 improved from 51 to 11 after 1.5 yrs on IVIG.	None
Case Report[80] in Autonomic dysfunction in Sjogren's syndrome n= 1	Oral steroid with dose and course not specified.	Not specified.	- Patient reported significant clinical improvement after Midodrine and Florinef failed to improve autonomic symptoms.	None
Case Series[79] in Acute AN n= 10	Immunoglobulin IV 2 g/kg given for 5 days. with or without IV Methylprednisolone or Dexamethasone.	Change in autonomic nerve function tests and modified Rankin scale.	- Sensory and motor symptoms recovered significantly, reduced autonomic symptoms - 9 patients improved after treatment of IVIG and IV steroids; - 4 patients with	None

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				severe illness got worse.	
	Case Series[71] in Autonomic dysfunction in Sjogren's syndrome n= 4	Immunoglobulin IV 0.4 to 0.8 g/kg monthly; Rituximab IV 1g on day 1 and 15.	- Change in autonomic function testing and CASS score	- Marked improvement in clinical and functional status correlated with improved autonomic testing in all patients.	None
	Case Series[78] in Autonomic dysfunction in neurosarcoidosis n= 11	Oral Prednisolone with or without IVIg or IV Methylprednisolone	Not specified.	- 10/11 of patients were categorized as responsive to immunotherapy by the authors.	None
	Case Report[77] in AN n= 1	IV Methylprednisolone for 5 days followed by IV Immunoglobulin x 5 days.	- Change in autonomic testing and symptomatology	- Substantial improvement in symptoms. -Post-treatment autonomic testing improved.	None
	Case report[69] in Autoimmune AN n= 1	IVIg 2 g/kg/day, then TPE every other day for 6 sessions; then Rituximab 1000 mg twice, two weeks apart; then prednisone 60 mg daily	- Change in COMPASS31 score	- Improved symptoms and COMPASS-31 score after treatment with each medication sequentially.	None
	Case Series[72] in Autoimmune AN n=2	IVIg 2 g/kg monthly Rituximab IV 750 mg/m² twice, two weeks apart.	- Change in autonomic function tests, EMG and symptoms	- Improved symptoms after IVIG and Rituxan; improved functional status and neurologic exam	Abdominal cramps
Long-COVID	Case Report[86] n= 1	IVIG 2g/kg monthly; then after 2 months, 1 g/kg/month	- Change in symptomatology	- Resolution of some symptoms; - Headaches/fatigue improved by 50%.	Headache
	Placebo case control study for IVIg (n= 9) vs. Placebo (n= 7)[91]	Immunoglobulin IV 2g/kg q3 weeks for 10 months.	- Change in autonomic symptoms, skin biopsy, iCPET testing, labs	- Resolution (6/9) or improvement (3/9) in clinical response (p = 0.001) and significant clinical response in neuropathic	None

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			symptoms (9/9) with IVIG compared to no IVIG (3/7; p = 0.02)	
Prospective Cohort Study[90] n= 20	Immunoadsorption Five sessions (4.5-9 hrs each) given over 10 days, with no more than 2 days apart.	- Change COMPASS31, QOL, FFS scores - Change in muscle fatigue and vascular dysfunction, assessed by handgrip strength (HGS) on dynamometer and EndoPAT® measurements	- Improvement in SF-36 scores between 2-3 months, with significant improvement found through 6 months - 70% of participants were responders at four weeks post-treatment. - Improved autonomic symptoms (p = 0.001); increased HGS six months post-treatment	Internal Jugular vein thrombosis (n=1)
Case series[87] n= 2	Convalescent Plasma (CP) IV 300mL, 3 doses over 15 days: 1. 3332.6 BAU/mL 2. 1794.2 BAU/mL 3.) >5680 BAU/mL	- Cycle Threshold (CT) values from PCR NPS. - Symptomatology. - Chest CT scan.	- Negative NPS 5 days after last dose of CP. - Complete resolution of symptoms one month after CP.	None
	Convalescent Plasma (CP) IV 500mL, 2 doses given 5 days apart. 1. 5680 BAU/mL 2. 4556 BAU/mL	- Cycle Threshold (CT) values from PCR NPS. - Symptomatology. - Chest CT scan.	- Complete resolution of fever with clinical improvement 1 day after the first dose of CP. - Negative NPS 2 days after last dose of CP	None
Case Report[88] n= 1	TPE daily for 5 days.	- Change in cognitive function, measured by MoCA and CANTAB. - Change in ambulation distance (m).	- Pain, walking and cognitive function, assessed by MoCA and CANTAB, improved.	None
Placebo blinded randomized clinical trial[93,94] n= 53	Efgartigimod IV 10 mg/kg weekly for 24 weeks.	- Change in COMPASS31 and MaPS - Change in laboratory test results, vital sign measurements.	- No clinically meaningful improvement when compared to placebo for the MaPS score and COMPASS31.	Unknown

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			- Change in fatigue, cognitive function, etc.	- Clinical trial was closed prematurely and further outcome measures are yet to be released.	
	Open-label prospective study[89] n= 38	LDN 1-3 mg po daily for 2-3 months.	- Change in Likert scale: sleep, concentration, pain/discomfort, mood, energy levels, limitation in activities of daily living, and perception of overall recovery from COVID.	- Significant reduction in reported low pain, mood, chest tightness and cough ($p < 0.05$).	- Diarrhea - Fatigue - 2 patients discontinued it due to AE
	Observational open-label prospective study[92] n= 36	LDN 4.5mg po QHS daily for 12 weeks.	- Reduction of fatigue measured by Chalder fatigue scale and SF-36 at 12 weeks post-treatment.	- Significant increase in SF-36 survey scores after 12 weeks of treatment ($p < 0.0001$); significant decrease in Chalder fatigue scale scores after 12 weeks of treatment ($p < 0.0001$). - 52% were responders at 12 weeks.	- Nausea - Fatigue, - Dizziness - Insomnia - Diarrhea - SOB

POTS: Postural Tachycardia Orthostatic Syndrome; OCAD: Other Common Autonomic Disorders; AD: Autoimmune dysautonomia; AN: Autonomic Neuropathy; AE: Adverse Event; SAE: Serious Adverse Event; LDN: Low Dose Naltrexone; COMPASS31: Composite Autonomic Symptom Score 31; FAS: Functional ability scale; CASS: Composite Autonomic Severity Score; HUT: Head Up Tilt; TST: Thermoregulatory Sweat Test; ECG: Electrocardiography; NPS: Nasopharyngeal Swabs; MoCA: Montreal Cognitive Assessment; CANTAB: Cambridge Neuropsychological Test Automated Battery; MaPS: Malmo POTS Symptom Score; PROMIS: Patient-Reported Outcomes Measurement Information System; SF-36: 36 item Short Form Health Survey; PAGI-QOL: Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; OTE: Overall Treatment Effectiveness; SOB: Shortness Of Breath; SQ: Subcutaneous; HGS: Hand Grip Strength Test; OHSA: Orthostatic Hypotension Symptom Assessment; OHDAS: Orthostatic Hypotension Daily Activity Scale.

Table 3. Ongoing and Pending Immunotherapy Trials for POTS and Long COVID.

Identifier #	Location	Indication	Immunotherapy	Administration, Dosage, and Course	Selective Outcome Measures
NCT06593600[76]	Europe	POTS	NPR1 Antagonist Monoclonal Antibody	Single high or low dose SQ injection	- HR change from supine to standing (DeltaHR) at Day 8, 15, and 29 - Serum concentration through 90 days

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					- AE occurrence and severity through 90 days
NCT06305793[99]	Durham, NC, U.S.A.	Post-COVID Autonomic Dysfunction NIH-RECOVER	Immunoglobulin (Gamunex®)	IV 2g /kg monthly for 9 months (36 weeks)	- Change in OHQ/OIQ, COMPASS-31, MaPS, PROMIS-29, VOSS, PASC Symptom Questionnaire from baseline to end of treatment - Change in Active Stand Test (BP and HR) and 6-mi walk test - Incidence of SAEs and ESIs up to 3 months post-treatment. - Changes in Autonomic Function Testing from baseline to end of treatment
NCT06524739[100]	Multiple Sites in U.S.A.and Canada	Post-COVID POTS	Immunoglobulin (HIZENTRA®)	SCIG IgPro20, a 20% ready-to-use liquid formulation	- Proportion of participants no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test at baseline vs. week 25 - Change of COMPASS-31 score at week 25. - Number and percentage of participants with TEAEs for up to 57 weeks post-treatment.
NCT05841498[97]	Mainz, Germany	Long-COVID-19	Immuno-adsorption	5 sessions by central venous catheter	- Improvement of Post-COVID symptoms, fatigue and cognitive impairment as measured by various questionnaires at 2 weeks post-IA. - Change of HGS measured as hand-grip-strength test with a dynamometer at 2 weeks post-IA. - Number of SAE's, and discontinuations at 2 weeks post-IA. - Prevalence of anti-adrenergic and anti-muscarinic autoantibodies at baseline; concentration of

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					autoantibodies pre and post-IA treatment.
NCT05710770[96]	Berlin, Germany	Post-COVID CFS	Immuno-adsorption	5 sessions over 9-12 days	- Improvement in physical and mental fatigue as measured by the Chalder fatigue score scale and other questionnaires at 3 months post-IA. - Number of TEAE's, SAE's, and discontinuations at 1, 3, and 6 months post-IA. - Improvement in COMPASS31 scores at 10 days, 3 and 6 months post-IA. - Improvement in autonomic dysfunction by measuring the Schellong Test at 3 and 6 months post-IA. - Changes in serum autoimmune/inflammatory biomarkers at 3 and 6 months post-IA.
NCT05220280[95]	Finland	Hospitalized COVID-19 patients	Infliximab vs. Imatinib	Infliximab IV 5mg/kg x 1 dose Imatinib: 400mg po qd x 14 days	- Symptom questionnaire at 1 and 2 year follow-ups. - EQ-5D-5L questionnaire at 1 and 2 year follow-ups. - Lung function by spirometry and diffusing capacity. - 6MWT. - Whole-genome genotyping.
ISRCTN46454974[115]	United Kingdom	Long-COVID-19	Tocilizumab	SQ q weekly or fortnightly x 12 weeks	- Questionnaires to assess symptoms or physical and mental health, brain fog and physical performance - Breathing test and imaging
NCT06631287[101]	Nashville, TN, U.S.A.	Long-COVID-19	Baricitinib (OLUMIANT®)	4mg PO daily for 24 weeks	- CNS-Vital Signs Global Cognitive Index at 6 months. - Exercise capacity including the 6MWT at 6- and 12- months. - CPET at 6- and 12-months.

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				- QOL and other symptom measures at 6- and 12-months - Orthostatic intolerance using the OIQ at 3-, 6-, and 12-months. - COMPASS-31 scores at 3-, 6-, and 12-months.
NCT05877508[98]	San Francisco, CA, U.S.A.	Long-COVID-19	Anti-SARS-CoV-2 Monoclonal Antibodies	IV 1200 mg since dose	- Change in symptom scores via various questionnaires - Change in COMPASS-3 Score from baseline to day 90 - Change in 6MWT and active stand test from baseline to day 90. - Change in CRP, ESR, D-Dimer, Fibrinogen from baseline to day 90.

POTS: Postural Orthostatic Tachycardia Syndrome; OCHOS: Orthostatic Hypoperfusion Syndrome; SFN: Small Fiber Neuropathy; ME: Myalgic Encephalomyelitis; CFS: Chronic Fatigue Syndrome; PASC: Post-Acute Sequelae of SARS-CoV-2 infection; HR: Heart Rate; ADA : Antidrug antibodies; AE: Adverse Event; OHQ: Orthostatic Hypotension Questionnaire; OIQ: Orthostatic Intolerance Questionnaire; COMPASS31: Composite Autonomic Symptom Score 31; MaPS: Malmo POTS Symptom Score; BP : Blood Pressure; PROMIS: Patient-Reported Outcomes Measurement Information System; SAE: Severe Adverse Event; VOSS: Vanderbilt Orthostatic Symptom Score; TEAE: Treatment-Emergent Adverse Events; ECG: Electrocardiogram; MoCA: Montreal Cognitive Assessment; QoL: Quality of Life; EQ-5D-5L: EuroQoL 5-level EQ-5D version; 6MWT: 6-minute walk test; CPET: Cardiopulmonary Exercise Testing; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; HGS: Hand Grip Strength Test.

Table 4. Potential immunotherapies for clinical trial consideration in POTS and OCAD.

Immunotherapy	Mechanism of Action	FDA Approved Indications
Immunoglobulin (IV or SC)[116]	Antagonism of IgG antibody Fc receptors	- Primary humoral immunodeficiency - Idiopathic thrombocytopenic purpura - CIDP, AIDP, MMN and other neurologic disorders
Plasmapheresis * [117]	Extracorporeal filtration or exchange of blood plasma	- Guillain-Barre syndrome - AIDP and CIDP - Myasthenia gravis - NMDA receptor antibody encephalitis - Paraproteinemic demyelinating neuropathy - Progressive multifocal leukoencephalopathy associated with natalizumab - Thrombotic thrombocytopenic purpura - Wilson disease
Immunoadsorption ** [118,119]	Extracorporeal filtration and removal of IgG antibodies and IgG-bound immune complexes from blood plasma	- Rheumatoid arthritis - Hemophilia A and B

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Corticosteroids[120] - Methylprednisolone - Prednisone - Hydrocortisone	Synthetic or naturally occurring analogs of adrenal corticosteroids	- Many indications
Hydroxychloroquine[121–123]	Derivative of 4-aminoquinoline	- Rheumatoid arthritis - Systemic lupus erythematosus - Chronic discoid lupus erythematosus - Malaria
Mycophenolate Mofetil[124,125]	Uncompetitive, reversible inosine monophosphate dehydrogenase (IMPDH) inhibitor	- Neuroimmune disorders - Prophylaxis of organ rejection in allogeneic kidney, heart or liver transplants
Azathioprine[126,127]	Purine analog, derivative of 6-mercaptopurine (6-MP) and thioguanine (6-TGN)	- Neuroimmune disorders - Prophylaxis of renal homotransplantation rejection - Rheumatoid Arthritis
Methotrexate[128–131]	Antagonist of dihydrofolic acid reductase (DHFR)	- Rheumatoid arthritis - Severe psoriasis - Polyarticular juvenile idiopathic arthritis - Cancer
Rituximab[132]	Monoclonal Antibody against CD20 antigens on pre-B and mature-B-lymphocytes	- Neuroimmune disorders - Rheumatoid Arthritis - Granulomatosis with Polyangiitis - Non-Hodgkin's Lymphoma - Chronic Lymphocytic Leukemia - Pemphigus Vulgaris
Adalimumab[133,134]	Antagonist of Tumor necrosis factor-alpha (TNF-alpha) cell surface receptors for p55 and p75	- Rheumatoid Arthritis - Juvenile Idiopathic Arthritis - Psoriatic Arthritis and Plaque Psoriasis - Ankylosing Spondylitis - Crohn's Disease and Ulcerative Colitis - Uveitis
Infliximab[135–138]	Antagonist of all Tumor necrosis factor-alpha (TNF-alpha) receptors	- Rheumatoid arthritis - Ankylosing Spondylitis - Psoriatic Arthritis and Plaque Psoriasis - Crohn's Disease and Ulcerative Colitis
Imatinib[139]	Tyrosine Kinase Inhibitor (TKI)	- Newly diagnosed Philadelphia Positive Chronic Myeloid Leukemia - Philadelphia Positive Acute Lymphoblastic Leukemia - Myelodysplastic/Myeloproliferative Diseases - Aggressive systemic mastocytosis
Tocilizumab[75,140–144]	Antagonist of soluble and membrane-bound Interleukin-6 (IL-6) receptor	- Rheumatoid Arthritis - Polyarticular Juvenile Idiopathic Arthritis - Systemic Juvenile Idiopathic Arthritis - Giant Cell Arthritis - Coronavirus Disease 2019 in hospitalized patients.
Omalizumab[145–147]	Antagonist of IgE antibody	- Asthma - Chronic rhinosinusitis with nasal polyps - Chronic spontaneous urticaria

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* FDA regulates devices and procedures related to TPE, but not their use in particular conditions. ** FDA regulates devices and procedures related to immunoadsorption, but they granted two specific approvals for its intended use in a medical condition.

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Conflicts of Interest: none.

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