

# Responses to Participants' Questions

This document provides responses to questions raised by webinar participants. Please note that these responses are not intended to be clinical recommendations. Patients should discuss any treatment options with their physician. The questions related to the following presentations:

- **Presentation 1: *Dysautonomia in PASC: Overview and Diagnostic Approaches***  
Mitchell Miglis, MD
- **Presentation 2: *Why Autonomic Dysfunction in Long COVID Matters***  
Lauren Stiles, JD
- **Presentation 3: *Post-Acute Sequelae of PASC/Long COVID—Cardiovascular and Autonomic Sequelae***  
Peter Novak, MD, PhD
- **Presentation 4: *Treatment Strategies for Dysautonomia in Post-COVID Syndrome***  
Tae Chung, MD

## Presentation 1: Questions and Responses

**Q1. What happens if a patient has both drop (orthostatic hypotension [OH]) and abnormal increase (postural orthostatic tachycardia syndrome [POTS]) in blood pressure (BP) all in the same event?**

**Response:** In this case, the diagnosis would be orthostatic hypotension. If the heart rate increases by more than 10 points for each 20-mmHg systolic BP drop, the cause is most likely non-neurogenic (non-neurological). You can calculate the HR/BP ratio to help diagnose neurogenic OH as compared with non-neurogenic OH:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5867255/>. Neurogenic OH is most commonly caused by neurodegenerative disease, for example, Parkinson's disease.

**Q2. Is there also a change in symptoms from sitting to recumbency or prone [as compared with] supine positioning that is noted in the literature anywhere?**

**Response:** If symptoms worsen from sitting to recumbency or from prone to supine positioning, this is unlikely caused by autonomic imbalance. I would think more about vestibular dysfunction.

**Q3. What do you mean by “tremulousness”?**

**Response:** Patients describe this as an “inner shakiness”, even if not shaking on the outside or visibly.

**Q4. Can dysautonomia conditions morph from one type to another over a period of years (lifetime)? For example, a condition with more POTS symptoms (but undiagnosed as [a] teen) is later in life diagnosed with neurogenic orthostatic hypotension.**

**Response:** “Conversion” from POTS to autonomic failure is very unusual.

**Q5. Orthostatic hypotension [as compared with] POTS—What if someone presents with POTS for the first 5 minutes (heart rate 30+) but then after 5 minutes, BP drops. Could they have both?**

**Response:** If the tachycardia preceded the OH and occurred without the OH, then this is likely. The drop in BP could also have been a vasovagal syncope reaction triggered by the tachycardia.

**Q6. I have seen some data that POTS is likely underdiagnosed in general, especially outside specialty clinics. Are these differences between POTS patients and PASC patients likely to exacerbate this?**

**Response:** We’re hoping it will be the opposite. Greater awareness through RECOVER efforts and webinars like this, will help more clinicians, especially primary care providers, be better equipped to diagnose POTS, both COVID and non-COVID related.

**Q7. It is challenging to analyze POTS and Long COVID data since the diagnosis might not have been established and therefore not included in the EHR (electronic health record). How might you overcome this type of challenge to be sure they are accounted for and not assumed to be Long COVID symptoms?**

**Response:** This is a good point. We cannot rely on epidemiological studies for true prevalence estimates of post-COVID POTS because POTS is both underdiagnosed and over diagnosed, and there is no unique ICD code for the diagnosis. This is where we hope RECOVER will help, though we need to include validated measures prospectively, including active stand testing and Composite Autonomic Symptom Score-31 (COMPASS-31) for all patients, and formal autonomic testing for a subset of patients.

**Q8. Does physical therapy help with orthostatic hypotension too? Or just with POTS?**

**Response:** Physical therapy can definitely help. It can be even more helpful, in most cases, in people with OH. We want to strengthen skeletal muscles to pump the blood more effectively to the brain when standing. Aquatic therapy can be quite helpful, as hydrostatic water pressure will increase BP, and recumbent or sitting exercises are also helpful, just as in POTS.

**Q9. Could vaccination be more harmful than helpful to those diagnosed with PASC?**

**Response:** Not necessarily. We have just as many patients who have noted improvement of PASC symptoms with the vaccine [as have reported] worsening.

## Presentation 2: Questions and Responses

**Q10. It is critical for the presenters to comment on the validity of the COMPASS-31 [symptom scoring instrument] when used for short-term recall, and how/if it was modified for use in PASC studies.**

**Response:** The COMPASS-31 has been validated and weighted to screen for autonomic failure, and it has been widely used to screen for autonomic dysfunction more broadly in a variety of conditions. Ideally, COMPASS-31 would be combined with formal Autonomic Function Testing. However, for clinics where this is not available, COMPASS-31 can help clinicians get a broad assessment of the various autonomic domains. COMPASS-31 is not intended to formally diagnose any specific autonomic disorder. So if an autonomic disorder is suspected, a more formal clinical assessment is needed.

**Q11. Has any research looked at whether these conditions (dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS], etc.) relate to a more extreme fight/flight response; specifically hibernation? This would be an aspect of our brains thinking they are "protecting" us from greater danger.**

**Response:** Hibernation in animals occurs when the parasympathetic nervous system (rest and digest) suppresses sympathetic activation. But yes, there is clear evidence that POTS, ME/CFS, and a good subset of Long COVID patients have excessive sympathetic activation. Some also have a parasympathetic deficit.

**Q12. If POTS is caused by Sjögren's [syndrome], will physical exercise help, or do you also have to treat the underlying Sjögren's?**

**Response:** As someone who has POTS and Sjögren’s syndrome, and who studies both conditions, I would say that exercise is critically important. There is good data showing exercise helps mitigate Sjögren’s symptoms, and we have similar data in POTS. However, POTS/dysautonomia patients who have defined autoimmune diseases—such as Sjögren’s syndrome, lupus, rheumatoid arthritis, or Crohn’s disease— should absolutely be offered treatment that is directed toward treating their autoimmune disease, in addition to the symptom-directed treatments we use in POTS. There are numerous case reports/series on the use of intravenous immunoglobulin (IVIG) in Sjögren’s - associated dysautonomia, and there are two clinical trials happening right now, funded by Dysautonomia International and the Sjögren’s Foundation, exploring the use of IVIG in POTS and POTS + Sjögren’s.

### **Q13. A recent study implicated autoimmunity against satellite glial cells of the dorsal root ganglia in fibromyalgia, could something similar be going on in PASC and POTS?**

**Response:** Researchers in Europe recently published on dorsal root ganglia pathology findings in an animal model of Long COVID (<https://faseb.onlinelibrary.wiley.com/doi/10.1096/fasebj.2022.36.S1.R2167>). We asked RECOVER to sample autonomic and dorsal root ganglia during the autopsy protocol, and this was approved, so expect to see more data coming from that work. There is an unpublished autopsy study in POTS (patient did not die of POTS) that found diffuse autonomic and dorsal root ganglionitis. There are multiple published autopsy case reports in ME/CFS reporting ganglionitis (the authors did not specify whether this was dorsal root or autonomic, but it was probably dorsal root because most pathologists don’t look for autonomic ganglia, which are harder to locate). The short answer is, I think there is ganglia pathology involved but we need more research to confirm.

### **Q14. Any insight into how the menstrual cycle affects POTS or dysautonomia?**

**Response:** Most menstruating women with POTS feel more POTS symptoms just before and the first day or two of their period. Dr. Satish Raj did a study on this (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413773/>) as did Dr. Qi Fu (<https://www.ahajournals.org/doi/10.1161/hypertensionaha.110.151787>). Some patients assume it is caused by the blood loss during their period, but that is unlikely, as the blood loss during a period has been slowly accumulating for weeks before the period begins. Even in patients who have heavy periods, the blood loss is a relatively small quantity compared with their total blood volume. This worsening of symptoms is likely caused by changes in hormones that play a role in controlling autonomic function, vascular tone, and salt/fluid retention/blood volume. Women with POTS also have an increased rate of endometriosis, which can contribute to inflammatory markers increasing at different points in the cycle, especially at the start of the period. Some patients use continuous birth control pills to reduce the number of periods they have per year.

### **Q15. Can cognitive issues be a part of dysautonomia? How likely is dysautonomia from COVID to recur in the future?**

**Response:** A majority of people with various autonomic nervous system disorders experience cognitive dysfunction. This is, in part, because they often have reduced blood flow to the brain when they stand up. But it's not just a standing-up problem because we have data showing that POTS patients also have cognitive deficits while laying down (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7369241/>). This could be caused by changes in the brain, inflammation, or other factors. However, we're not sure because no one has studied this yet.

## Presentation 3: Questions and Responses

### **Q16. Why are so many patients hypocapnic?**

**Response:** The short answer is we don't know. Dr. Julian Stewart<sup>1</sup> from New York Medical College described thoracic hypovolemia that can affect respiratory sensors. Another explanation is differential perfusion of upper as compared with lower lung areas that can cause respiratory sensors malfunction. A third theory is that hypocapnia is compensation of metabolic derangement.

### **Q17: In the POTS population, is the small fiber neuropathy (SFN) progressive? Does it get better with symptomatic treatment?**

**Response:** SFN in POTS depends on the cause. It could improve, for example, if it is part of post-viral syndrome or can be progressive if it is caused by genetic causes, for example.

### **Q18. I agree that many diagnostic tests are not that helpful in providing diagnoses with Long COVID. What are your thoughts on more investigative tests, such as nuclear medicine or oxygen/ventilation perfusion tests, etc.? Have you found [anything] helpful in looking into Long COVID and the causes of symptoms?**

**Response:** The diagnostic criteria and optimal tests for Long COVID are evolving. The tests you mentioned are useful to assess the lung functions that may be affected in Long COVID.

### **Q19. Are there any data on a second COVID infection on dysautonomia symptoms/Long COVID? Do symptoms improve, decline, stay the same, etc.?**

**Response:** We're still collecting data. However, in general, COVID infection or additional COVID infection tend to worsen underlying dysautonomia.

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<sup>1</sup> Dr. Julian Stewart is a professor of pediatrics, physiology, and medicine, the associate chairman for patient oriented research, and director of the Center for Hypotension at New York Medical College. Dr. Stewart's investigational clinical interests involve the regulation of heart rate and blood pressure in children and adolescents.

## Presentation 4: Questions and Responses

### **Q20. You mentioned midodrine, what about Mestinon?**

**Response:** Mestinon (pyridostigmine) has a modest effect on heart rate and increased gastrointestinal motility, and some patients describe a vague sense of improvement. It's fairly well tolerated.

### **Q21. What are the most promising treatment approaches for COVID-related dysautonomia?**

**Response:** In addition to typical POTS treatments, I believe that immunomodulating treatments, such as IVIG, are the most promising.

### **Q22. [In regard to] autoantibodies, do we talk about functional ones (G protein-coupled receptors [GPCR]) or also serotonin-related?**

**Response:** We don't know at this time. I do think that post-COVID POTS may be related to novel autoantibodies. I hear that commercially available test kits for GPCR antibodies are not specific enough. But I agree that antibody-targeted treatments are promising.

## Discussant: Satish Raj, MD

### **Q23. What are you doing to rule out ME/CFS in PASC/POTS patients for whom you are recommending graded exercise therapy (GET) despite post-exertional malaise? CDC recommends against GET for ME/CFS.**

**Response:** There are good data that an exercise training program focused on aerobic reconditioning and often starting with non-upright exercise is a beneficial and important part of therapy for patients with POTS.

## All Presentations: Questions and Responses

### **Q24. Could you please comment on the use of the Levine Protocol for rehabilitation in Long COVID patients with dysautonomia?**

**Responses:**

- **Dr. Miglis:** Everyone will have a different response to this, but in my opinion the Levine Protocol is incredibly important in the treatment of POTS. However, we like to try and stabilize the cardiovascular system with

pharmacological and nonpharmacological treatments before starting the Levine Protocol. Also, one needs to be mindful about whether patients have severe post-exertional malaise, and then start low and go slow.

- **Professor Stiles:** Clinicians and patients can find a modified (and more practical) version of the Levine Protocol on the Dysautonomia International website, as modified by Dr. Jeffrey Boris, pediatric cardiologist and former Director of the Children’s Hospital of Philadelphia (CHOP) Postural Orthostatic Tachycardia Syndrome (POTS) Clinic (<https://www.dysautonomiainternational.org/exercise>). We also offer gentle/recline/seated virtual exercise classes and videos. Aquatherapy can also be very helpful because the water acts like a giant compression stocking. We encourage clinicians to really individualize a rehabilitation plan for their patients by meeting patients where they are. The range of disability in POTS/OI (orthostatic intolerance) ranges from being bedridden to people who can run marathons, so an individualized approach is needed.

**Q24. Any thoughts on low-dose naltrexone (LDN) to address some of the inflammatory components? I’ve seen it recommended when joint pain is also involved, but [I’m] unsure if there [are] any data on LDN on dysautonomia alone.**

**Responses:**

- **Dr. Miglis:** There are not yet any data, though I suspect we will see these studies soon. We have been using it in our Long COVID clinic with positive results.
- **Professor Stiles:** There are a few case reports. Dysautonomia International is funding a clinical trial on LDN in POTS at the University of Calgary (led by Dr. Satish Raj), and a second LDN trial in Long COVID at the Karolinska Institute in Sweden. We’ll share the results on our social media channels as soon as they’re available. However, this is some time away because clinical trials take a long time.

**Q26. What clinical interventions [can be] used to treat dysautonomia? Should we conduct randomized clinical trials (RCTs) to see if they reduce symptoms in Long COVID?**

**Responses:**

- **Dr. Chung:** We will be testing neonatal crystallizable fragment receptor (FcRn) antagonist to reduce immunoglobulin G (IgG) in immune-mediated post-COVID POTS patients. We’ll provide a study update on our website soon.
- **Professor Stiles:** Yes, we should conduct RCTs to see if these treatments help Long COVID dysautonomia patients, but we already have some RCTs and other trial data on these treatments in people who have other post-viral dysautonomias. We should apply that existing knowledge to clinical care and not make Long COVID dysautonomia patients wait for RCTs. Common dysautonomia treatments include increasing salt and fluid

intake, 20- to 30-mmHg compression stockings, beta blockers, ivabradine, fludrocortisone to expand blood volume, midodrine to support vasoconstriction, Mestinon (pyridostigmine), and more. There are detailed lectures on pharmacologic and nonpharmacologic approaches to managing POTS and other forms of dysautonomia on Dysautonomia International's Autonomic Disorders Video Library (<https://vimeo.com/dysautonomia>).

### **Q27. Can you share to what extent medical research is being done around diet/nutrition as a way to treat POTS patients?**

#### **Responses:**

- **Dr. Miglis:** That's a very good point. We need to pay more attention to diet and the influence of the gut brain axis/microbiome in symptoms, especially because post-viral autonomic conditions often produce motility problems. There is at least one publication showing that fermented diet can reduce IL-6 and inflammation, and future studies should evaluate this in POTS and PASC.
- **Professor Stiles:** There is also research documenting B12, B6, and vitamin D deficiency in some POTS patients. Correcting vitamin deficiencies may help improve symptoms, but it is rarely curative. There is research documenting worsening POTS symptoms after carbohydrate intake and insulin resistance in POTS patients. Even before this research, many patients figured out that a low carb diet and/or eating smaller meals throughout the day may help reduce symptoms. There has also been research suggesting a gluten free diet may help some POTS patients, including those with celiac disease and some who do not have celiac disease.

### **Q28. Are hormone therapies being studied for PASC dysautonomia? It seems that hormonal imbalances (insulin, adrenals, sex hormones) are significant downstream effects of POTS or orthostatic hypotension and may account for the sex differences in cases.**

#### **Responses:**

- **Dr. Novak:** I've only seen a few patients who had adrenal insufficiency who were also getting hormonal treatment or replacement, but I'm not sure how common it is.
- **Dr. Chung:** Sometimes our colleagues think adrenal fatigue is not a scientific term and they believe it is not primarily an endocrinological problem.
- **Professor Stiles:** It is a question that's very obvious and it's funny that we don't have better data. Pre-COVID, POTS was 90% female, so there is a role of sex and hormones. PASC is also female predominant, which I don't think is surprising because a majority of people with autoimmune conditions are female. Anecdotally, we've heard case reports of adolescent POTS patients who were transgender and transitioned from female to male using testosterone and their POTS symptoms improved. However, I'm not telling women with POTS to use

testosterone, as there are multiple reasons why you might not want to do that, but there should be more research into sex hormones.

- **Dr. Raj:** We did a study at Vanderbilt that included patients with POTS and healthy patients (Peggs et al., 2012). We asked people to rate levels of light-headedness during their menstrual cycle. The interesting finding is that the pattern was identical. Around menstruation and just before menstruation, women had more lightheadedness. In POTS patients, this lightheadedness was amplified, but the cyclical pattern was identical. It is not uncommon for POTS patients to go on longer-term birth control where they have lighter periods and breakthrough bleeds every 3 to 4 months instead of every month. It doesn't make everything better, but it decreases the worse times. Separate from that, hormones could refer to blood volume regulating hormones. At Vanderbilt, we've done some work related to that. In one cohort, over 70% of POTS patients had a low blood volume when measured objectively.

**Q29. Can you speak to how mental health conditions (anxiety, depression, PTSD) factor into Long COVID POTS diagnosis? It seems that the sympathetic overactivation on a physiological level could appear as “anxiety” to a medical provider and a dorsal nervous system shut down could look like depression, in spite of these states being brought on by dysregulation of the nervous system.**

**Responses:**

- **Dr. Raj:** There is no reason why a Long COVID or POTS patient cannot have an anxiety disorder. The reality is that a large portion of the North American population does. However, we have not found that it is higher among POTS patients. There is an issue where the somatic symptoms of anxiety are tachycardia and heart palpitations and lightheadedness, and part of the presentation we see. If someone's heart rate is very fast, before pulling out the Prozac, it may be worth trying to lower the heart rate and see. I have helped a lot of patients experiencing “anxiety” with beta blockers.
- **Professor Stiles:** To add to that, it's normal for patients who have new symptoms that are poorly understood to express fear about their symptoms. However, I don't think we should interpret that as being caused by an anxiety disorder. When I developed POTS 12 years ago, I was terrified by my symptoms because no one was telling me why it was happening for 2 years. Hopefully Long COVID patients will be diagnosed faster as awareness increases. Taking the time to explain to patients why they're having tachycardia and palpitations and assuring them it's not fatal might help with their quality of life. Patient education is a large part of managing dysautonomia.

**Q30. What do we need to do better to capture data on dysautonomia?**

**Responses:**

- **Professor Stiles:** I recognize that not every Long COVID clinic has substantial autonomic expertise. We need to have all the sites doing orthostatic vitals the right way and screening their PASC patients for this, not only for research procedures but for accurate diagnosis, proper intervention, and treatment. While we don't know all the treatments for Long COVID, we do know effective treatments for orthostatic disorders.
- **Dr. Miglis:** I agree. We're advocating at a minimum a 5- to 10-minute orthostatic stand test and the COMPASS-31. These are very low-cost tools to help us understand the true prevalence of these conditions.
- **Dr. Stiles:** We've also advocated for doing the full autonomic testing in a subcohort. Not all sites have that, but we hope that can be done in a subcohort of the RECOVER study population.
- **Dr. Novak:** Surveys are validated, but not designed to replace diagnosis. So the best way to detect it is to establish autonomic testing. There is usually not a yes or no answer, so if you want to detect mild progression, autonomic testing is the best way to capture it.

## Seminar Slides

To request a copy of the R3 seminar slides, please email [RECOVER\\_ACC@rti.org](mailto:RECOVER_ACC@rti.org).

## To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research>
- Information about RECOVER study protocols and measures: <https://recovercovid.org/research-works>
- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs>
- CDC information: Information for the general public and for healthcare providers about post-COVID conditions: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>

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