Long COVID & Post Infectious Syndromes ECHO

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Orthostatic Intolerance/Dysautonomia: Pharmacological Treatment Approaches

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- The patient cases discussed in this lecture are presented solely for educational purposes.
- Some examples reflect composite clinical scenarios designed to illustrate common disease presentations rather than a single individual.
- When real patient information is referenced, it is shared with the patient's explicit authorization for use in this setting.

LEARNING OBJECTIVES

- Briefly review Dysautonomia and Orthostatic Intolerance as seen in Long COVID and Long COVID ME/CFS.
- Outline pharmacologic treatment options for both conditions.
- Review in more detail the treatment options, strategies for treatment selection, and how treatments are applied.
- Briefly review non-pharmacologic and emerging treatment strategies.

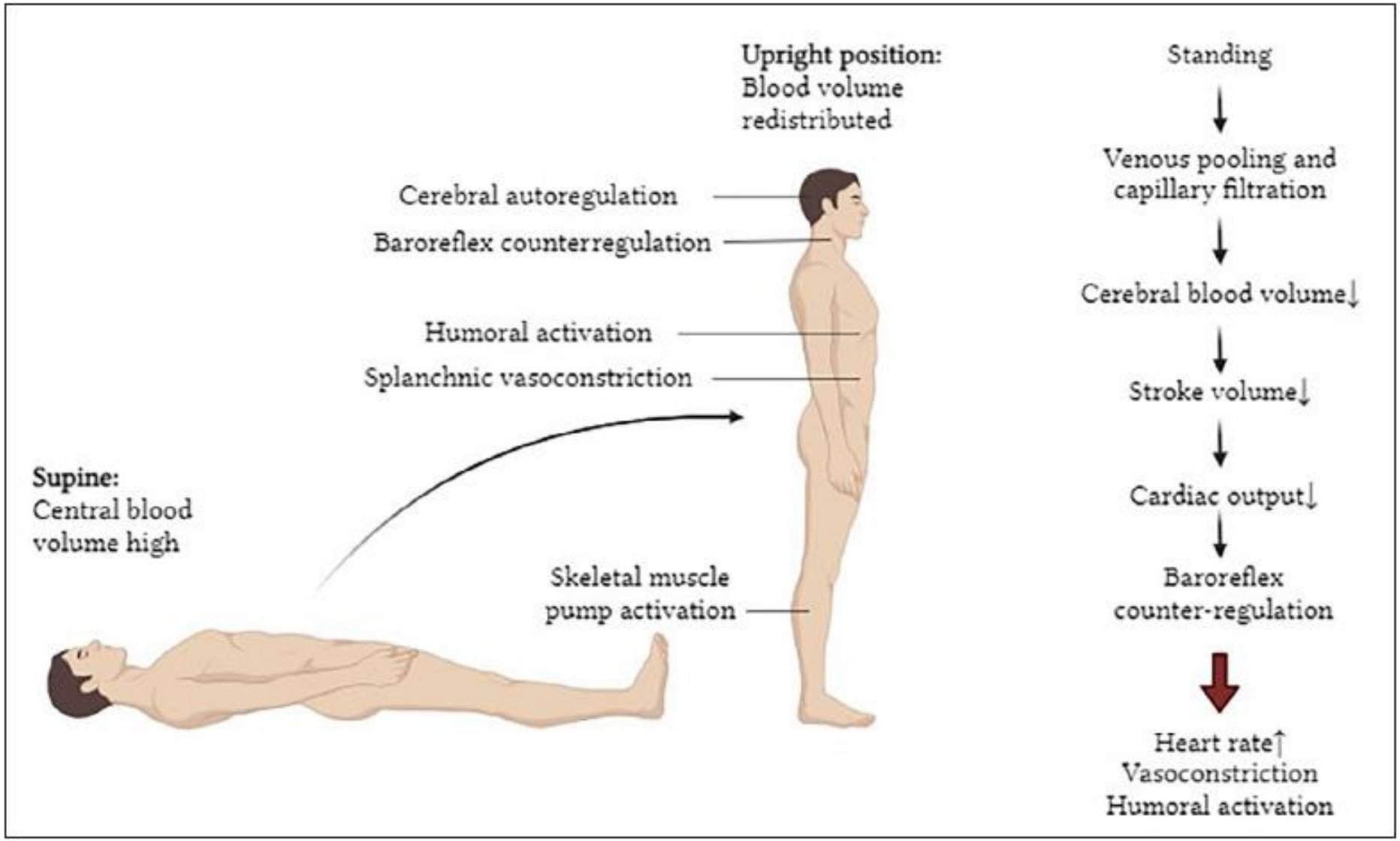
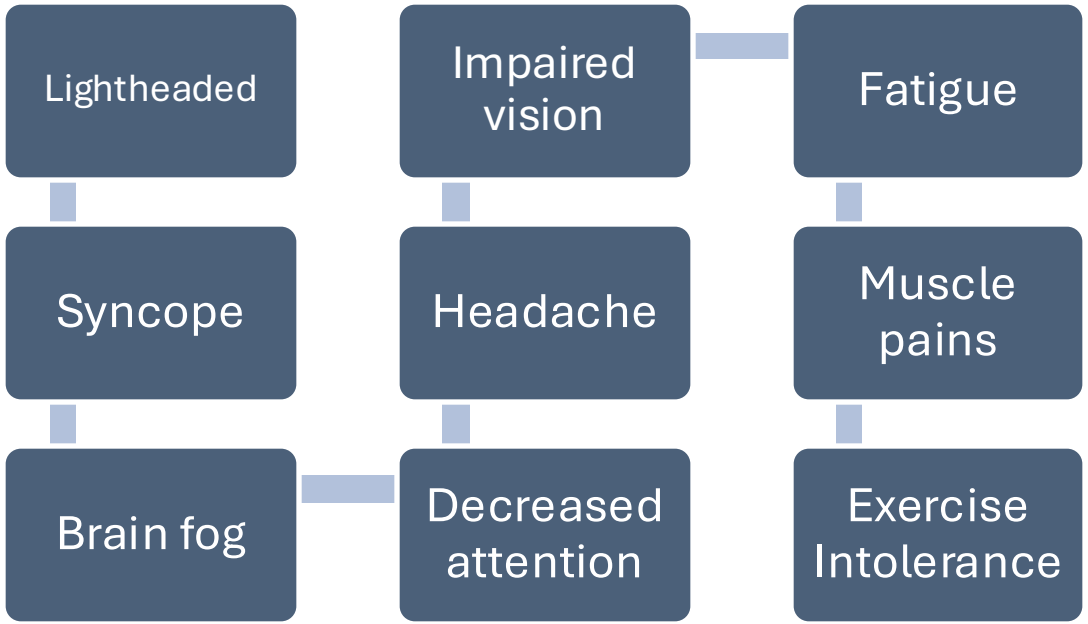


Figure 1. **Physiological mechanisms involved in regulating blood flow with orthostasis (left) and order of activation of physiological changes that occur with standing (right).**

Khan MS, Miller AJ, Ejaz A, Molinger J, Goyal P, MacLeod DB, Swavely A, Wilson E, Pergola M, Tandri H, Mills CF, Raj SR, Fudim M. Cerebral Blood Flow in Orthostatic Intolerance. J Am Heart Assoc. 2025 Feb 4;14(3):e036752. doi: 10.1161/JAHA.124.036752. Epub 2025 Feb 3. PMID: 39895557; PMCID: PMC12074713.

Symptoms of Orthostatic Intolerance

Cerebral Hypoperfusion



Activation of the Sympathetic Nervous System

Palpitations
Shortness of breath
Anxiety
Tremors
Sweating
Cold extremities
Nausea
Abdominal discomfort
Chest Pain
Disrupted Sleep/Insomnia *

Rowe, P. C. (2024). Living well with orthostatic intolerance: A guide to diagnosis and treatment. Johns Hopkins University Press.

Symptoms of Dysautonomia

Table 2: Clinical Features of Autonomic Disorders

Review of Systems	Clinical features
Cardiovascular	• Orthostatic intolerance • Postural tachycardia • Orthostatic hypotension • Postprandial hypotension • Exercise intolerance • Syncope • Presyncope • Palpitations • Chest pain, pressure or discomfort
Neurologic	• Dizziness or lightheadedness • Cognitive dysfunction (a.k.a. "brain fog") • Paresthesia • Generalized weakness • Neuropathic pain • Headache, including migraine
Respiratory	• Shortness of breath • Hyperventilation
Gastrointestinal	• Nausea • Dysphagia • Acid reflux • Early satiety • Abdominal fullness, distension or pain • Gastric and intestinal dysmotility • Diarrhea or constipation
Genitourinary	• Urinary frequency, urgency or hesitancy • Incomplete bladder emptying • Urinary retention • Overactive bladder • Polyuria • Nocturia • Interstitial cystitis • Erectile dysfunction • Vaginal dryness • Pelvic pain
Thermoregulatory	• Hypohydrosis • Hyperhidrosis • Anhidrosis • Gustatory sweating • Heat intolerance • Cold intolerance
Pupillomotor	• Blurred vision • Light sensitivity • Dilated pupils

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OI Testing Interpretation to Guide Treatment Approach

Vascular volume support

- Low resting BP
- Drop in BP on passive standing test
- Elevated HR secondary to drop in BP

Improving venous return to the right side of the heart

- Venous pooling in the extremities with evidence of premature AV shunting
- Drop in Pulse Pressure Index (SBP-DBP/SBP) during standing - < 25%

Heart Rate control

- Elevated resting HR
- HR elevation on standing and persisting throughout passive standing test
- BP drop is secondary to high HR

Hyper or hypotensive response to standing

Other Sympathetic Nervous System symptoms

Vascular Volume Support

Increase vascular volume

Aggressive water and sodium intake is foundational for other therapeutic interventions!

- 3-4 Liters of water per day **PLUS** 500mg to 1000mg sodium per liter of water.
  - Table Salt - One teaspoon of Morton's table salt has 2600mg of sodium
  - Electrolyte powders, tablets, and chews – READ LABELS carefully for sodium amount and added sugar. Avoid Stevia due to stomach upset.
  - High sodium foods
- **IV normal saline.** 1 liter 3x/week for 2 weeks or more as needed.
  - Helpful in PEM, persistent and severe OI symptoms
  - Understanding extent of OI in overall illness
  - Initiating new medication for people with medication sensitivity

Vascular Volume Support & Venous Return to the Heart

Fludrocortisone: 0.1mg QD or BID – FDA approved for Orthostatic Hypotension

- Potent mineralocorticoid, similar in effect to aldosterone.
- Promotes increased reabsorption of sodium and loss of potassium from the distal renal tubules.
- Ultimately helps "trick" the kidney into holding on to fluid and sodium.
- Not as potent if patient is not fluid and sodium loading.

Midodrine: 2.5-10 mg every 4 hrs – FDA approved for hypotension – Alpha 1 agonist
Droxidopa: 100 - 200mg TID every 4 hrs – FDA approved for hypotension – Alpha-/Beta-Agonist

- Increases both arterial and venous tone, particularly the splanchnic vasculature.
- Diffuses poorly across the blood-brain barrier with few central nervous system effects.
- Most effective when well hydrated.

Vascular Volume Support & Venous Return to the Heart

Pyridostigmine (Acetylcholinesterase Inhibitor: off-label use – FDA approved for Myasthenia Gravis but recommended in the literature for POTS and Orthostatic Hypotension)

Mechanisms of Action:

- Alters the Autonomic Nervous System (ANS) by raising acetylcholine, the neurotransmitter at the neuromuscular junction, and is a weak stimulator of the parasympathetic system. This action results in…
  - Increased skeletal muscle contraction
  - Improved venous constriction and venous preload return
  - Reversal of AV shunting mediated by SFPN improving tissue oxygenation and removal of metabolic waste

Dosing and tips to improve tolerance: **Goal dose 60mg TID or ER 180mg QD**

- Start low and slow on dosing: 15-30mg every 6-8 hrs starting one dose at a time. May take weeks to get to 60mg TID.
- Change to Extended-Release formulation (180 mg) once at 60mg TID.

Pyridostigmine (cont.)

Clinical Benefits noted in our patients:

- Improved upright stamina
- Improved PEM resilience

Common Side Effects:

- GI cramping, increased loose stool output
- Muscle fasciculations
- Increased sweating, salivation, tearing

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Heart Rate Control/Sympathetic Nervous System Activity

Beta Blockers: Reduce sympathetic activity & maximize cardiac output

- **Propranolol 10mg every 6-8 hrs**
  - Good one to start with
  - Has minimal effect on BP
- **Metoprolol Succinate ER** 25mg - **12.5 mg QD or BID**
  - Extended release provides smoother HR control
  - Due to fatiguing effects, I don't go over 25mg BID
- **Atenolol 25mg QD or BID dosing**
  - Start low dose
  - Has stronger BP lowering effects. Use carefully
- **Common side effects of Beta Blockers**
  - Fatigue
  - Lightheadedness/dizziness
  - Bradycardia
  - Asthma exacerbation

Sympathetic Nervous System Overdrive

Alpha 2 Adrenergic Agonist – Off label

- Primarily for SOD symptoms such as insomnia, nightmares, tremors, panic attacks, adrenalin surges. Helps reduce sympathetic outflow from the CNS.
- Use lowest dose possible
- BP and RHR needs to be monitored
- Can be fatiguing
- Wean slowly

- **Clonidine tablets**
  - IR 0.1-0.3mg – often use ½ tabs
  - 12 hr 0.1mg
  - 24 hr 0.17mg
- **Clonidine Patch** Weekly – 0.1 – 0.3mg
- **Prazosin** – **FDA approved for PTSD, nightmares**
  - 1mg to 2 mg QHS

Heart Rate Control

IVABRADINE – a selective I_f channel blocker, FDA approved for Inappropriate Sinus Tachycardia

- **5mg to 7.5mg BID**
- Primary use is to lower heart rate in POTS
- Less hypotensive affect
- Can be used in combination with Beta Blockers
- Not as good for treating sympathetic overdrive as Beta and Alpha Blocker.

Marchetta, Michele MD*; Lopez, Rocio I. MD*; Hogwood, Austin C. PhD*; Thomas, Georgia MD, PhD†; Abbate, Gerardina*; Markley, Roshanak MD†; Canada, Justin M. PhD†; Abbate, Antonio MD, PhD*. Heart Rate Lowering With Ivabradine and Burden of Symptoms in Patients With Postural Orthostatic Tachycardia Syndrome. Journal of Cardiovascular Pharmacology 86(1):p 28-32, July 2025. | DOI: 10.1097/FJC.0000000000001705

Taub PR, Zadourian A, Lo HC, Ormiston CK, Golshan S, Hsu JC. Randomized Trial of Ivabradine in Patients With Hyperadrenergic Postural Orthostatic Tachycardia Syndrome. *J Am Coll Cardiol* 2021;77:861-71.

Stellate Ganglion Block

FDA approved for CRPS

- Using a local anesthetic, the SGB blocks cervical sympathetic chain activity allowing the regional autonomic nervous system to reboot.
- Results have shown improvement of sympathetic nervous system dysregulation symptoms in many but not all Long COVID patients.
- Those treated earlier after onset of symptoms respond the best
- Multiple injections often needed for longer lasting benefit

  - Case Series *Liu LD, Duricka DL. Stellate ganglion block reduces symptoms of Long COVID: A case series. J Neuroimmunol. 2022 Jan 15;362:577784. doi: 10.1016/j.jneuroim.2021.577784. Epub 2021 Dec 8. PMID: 34922127; PMCID: PMC8653406. **https://pubmed.ncbi.nlm.nih.gov/34922127/**
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Other OI/Dysautonomia Treatments

- Manage comorbid conditions
- Pacing and PEM avoidance
- Compression clothing
- Vagal maneuvers
  - Cold Therapy - face in ice water bath, cold shower, ice to back of neck, chest, abdomen.
  - Meditation, Yoga Nidra, diaphragmatic breathing
- Benzodiazepines – Use low dose and prn
  - Longer acting such as diazepam and lorazepam work best

Additional References

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3. Kate M. Bourne, Robert S. Sheldon, Juliette Hall, Matthew Lloyd, Karolina Kogut, Nasia Sheikh, Juliana Jorge, Jessica Ng, Derek V. Exner, John V. Tyberg, Satish R. Raj, Compression Garment Reduces Orthostatic Tachycardia and Symptoms in Patients With Postural Orthostatic Tachycardia Syndrome, Journal of the American College of Cardiology, Volume 77, Issue 3, 2021, Pages 285-296, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2020.11.040.