
Orthostatic Intolerance

Part 2: Management



Brayden Yellman, MD

University of Utah Health Project ECHO

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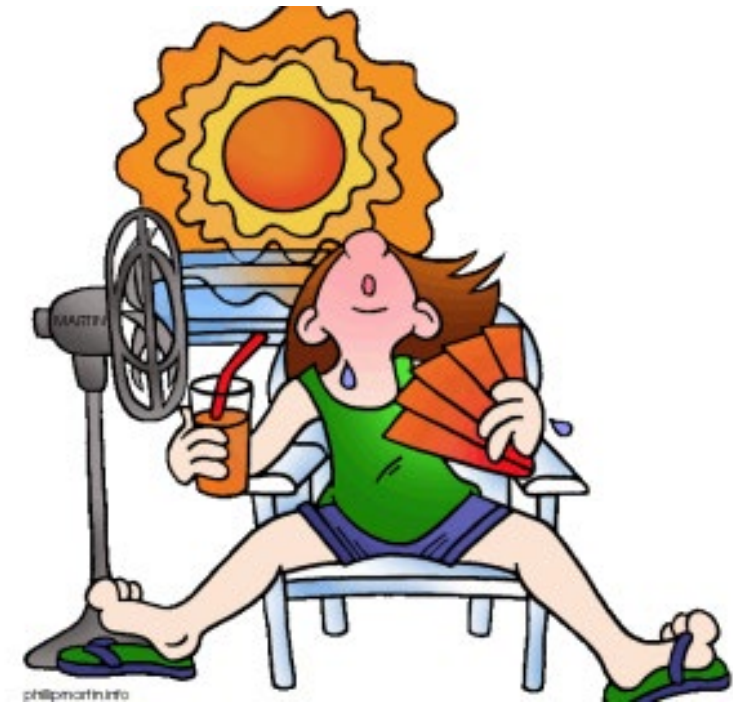
Management of OI

Improve perfusion. Expand volume. Constrict blood vessels. Control rapid heart rate. Modulate Autonomic Nervous System (ANS).

Interventions for OI:

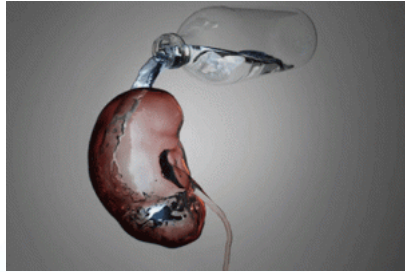
Recognize and avoid the common triggers

- Heat, getting overheated
- Dehydration
- Prolonged standing in place
- Prolonged sitting with feet on floor
- Prolonged bedrest (confuses the ANS)
- Muscle atrophy and weakness
 - Abdomen/core, upper and lower legs
- Medications that cause/worsen OI



Orthostatic Intolerance Management: Increase Intravascular Volume

- Increase Free Water



- Increase Sodium Intake



- Ratio of free water to sodium **MUST BE EQUIVALENT**
 - Excess free water will be removed in urine
 - Kidney regulates excess sodium as well

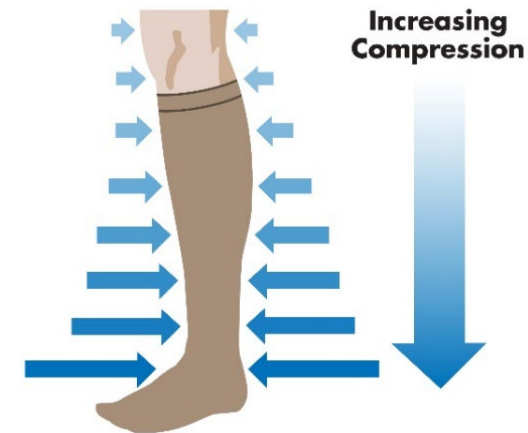
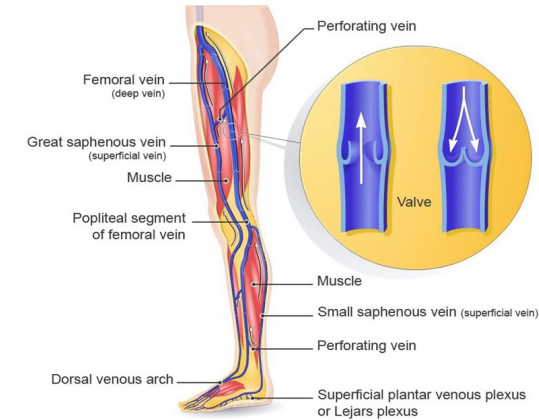
Orthostatic Intolerance Management: Increase Intravascular Volume

- IV normal saline infusions (both diagnostic and therapeutic)
- Increase oral free water and sodium intake
 - Aim for 80-100 ounces of free water daily
 - Aim for 1500-2000 mg of sodium for this amount of free water
 - Oral rehydration solutions/buffered salt tabs
 - Liquid IV, Normalyte, Nuun, Vitassium Salt Stick, WHO rehydration formula, Trioral, V8 (original)



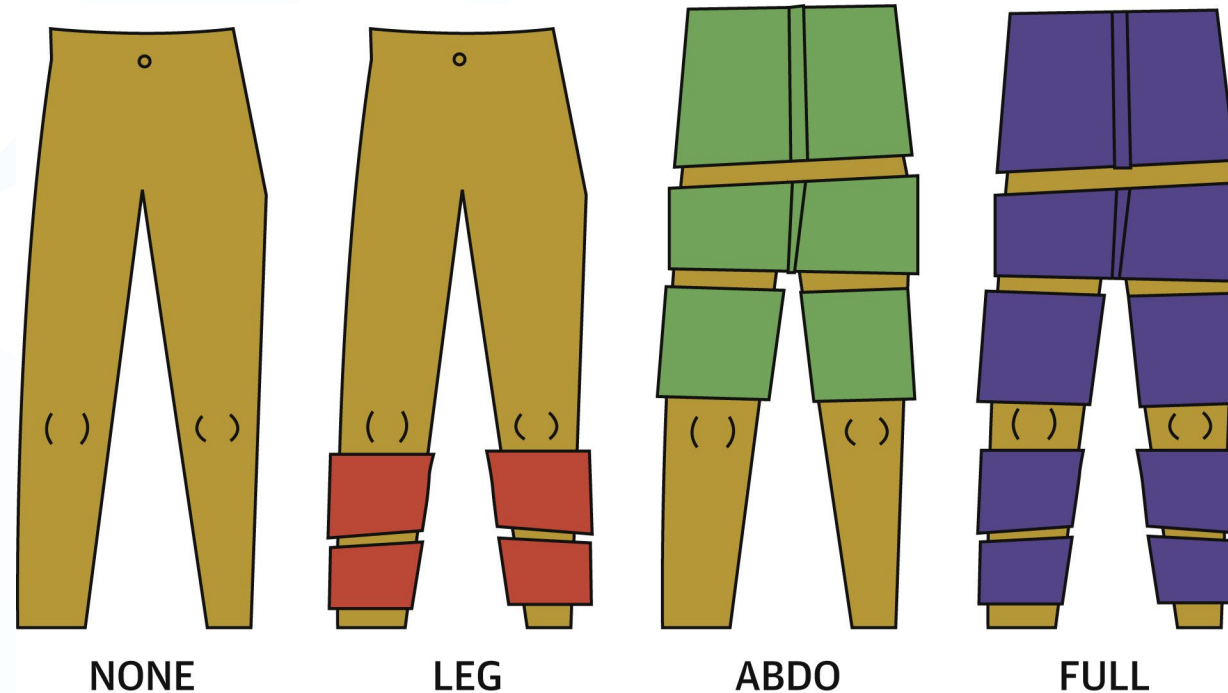
Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return

- Increase in blood pooling in the lower extremities and splanchnic veins during orthostasis that is not participating in circulation
- Use **Compression Clothing** to restore intravascular volume and venous preload to the heart



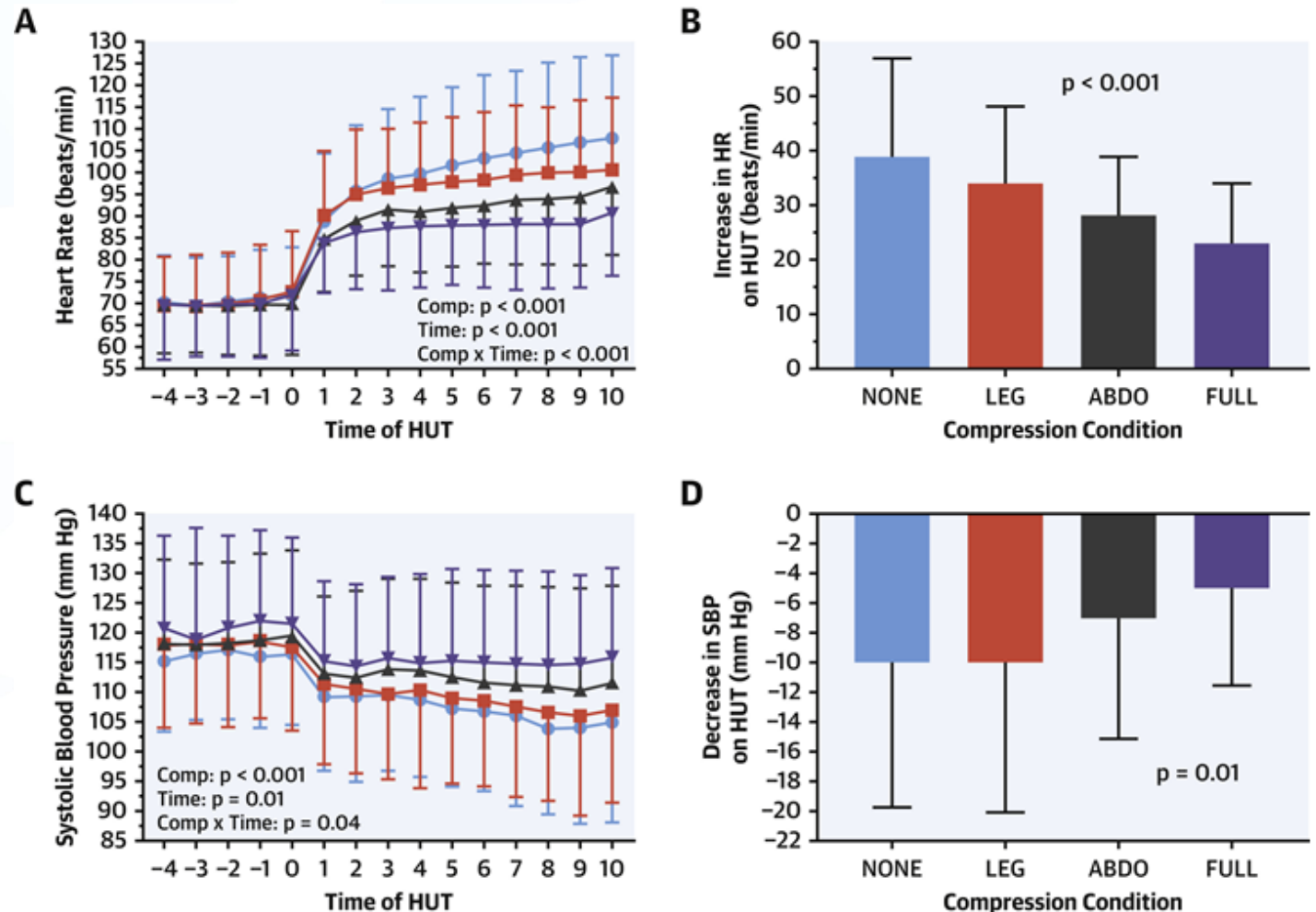
Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return

Compression & surface area

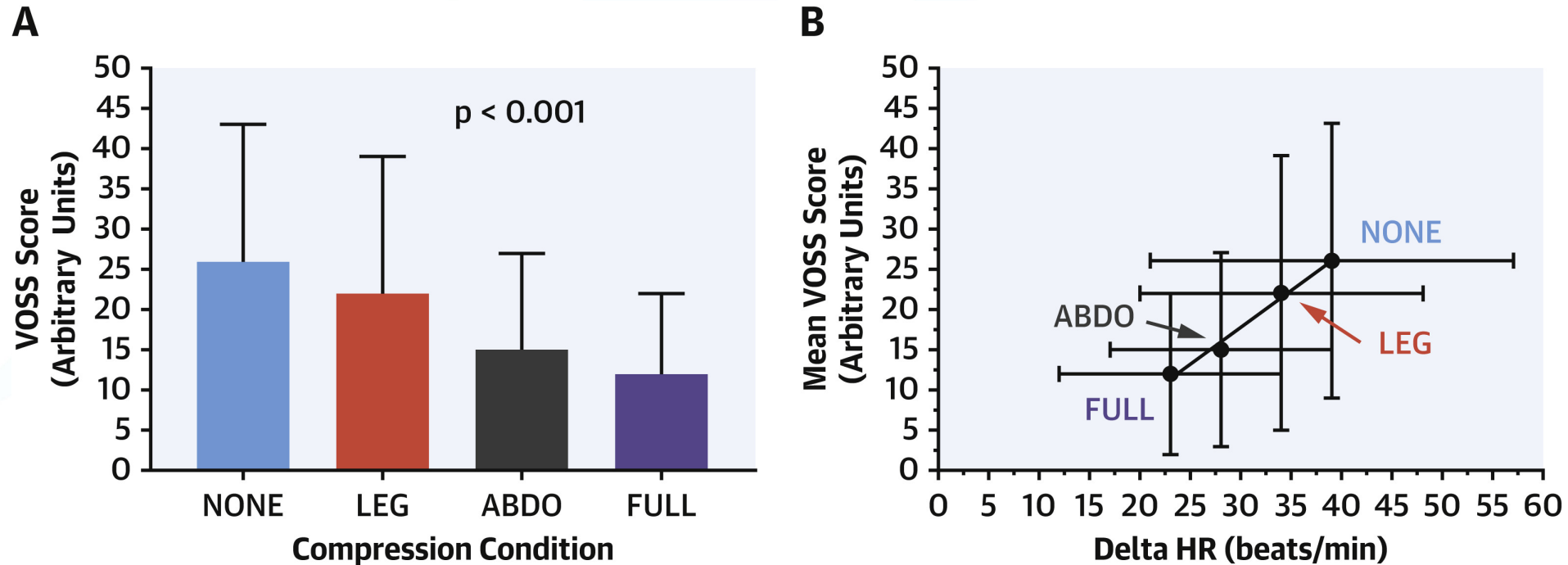


Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return

Heads Up Tilt-Table (HUT)



Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return



Vanderbilt Orthostatic Symptom Scores (VOSS Score)

Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return

- Abdominal compression alone may provide clinical benefit even in those who do not tolerate lower extremity compression (FM, SFPN, peripheral neuropathy...)



Orthostatic Intolerance Management: Maintain Intravascular Volume, Improve Venous Return

Without Compression Clothing:

- Lying Down: 112/72 and 60 bpm
- 1 min Standing: 87/55 and 111 bpm
- 2 min Standing: 93/80 and 105 bpm
- 5 min Standing: 79/63 and 134 bpm



With (Under Armor) Compression Clothing:

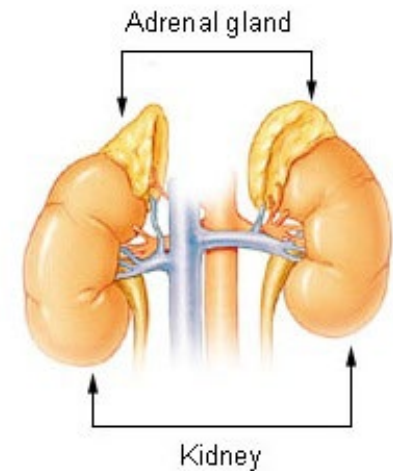
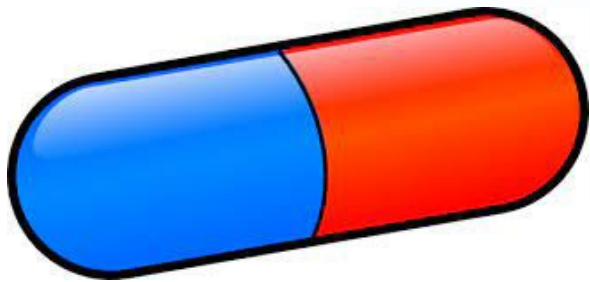
- Lying Down: 131/78 and 57 bpm
- 2 min Standing: 123/96 and 89 bpm
- 4 min Standing: 123/90 and 87 bpm
- 7 min Standing: 135/93 and 84 bpm



Orthostatic Intolerance Management: Maintain Intravascular Volume

Fludrocortisone:

- 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 not fluid and sodium loading
- Common Side Effects:
 - Headaches, often worse in the supine position



Orthostatic Intolerance Management: Maintain Intravascular Volume

Midodrine:

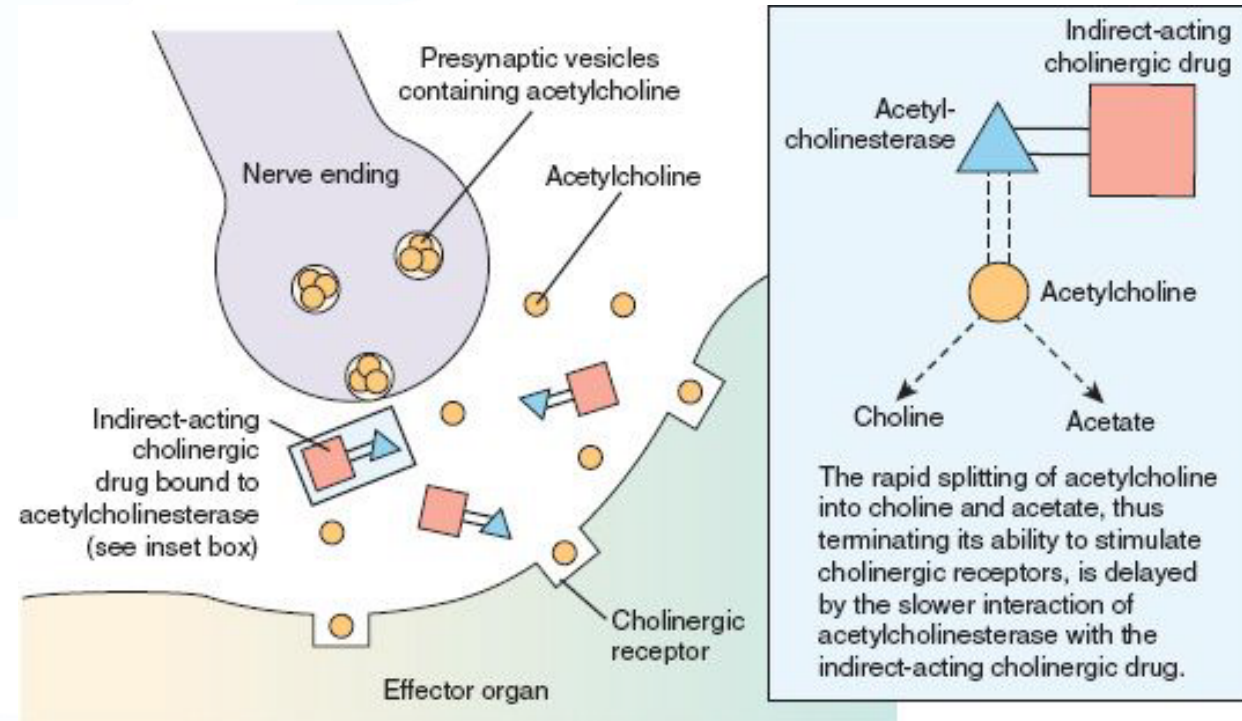
- Forms a metabolite, desglymidodrine, that is an α_1 -agonist
- Increases in both arterial and venous tone
- Overall increase in both systolic and diastolic pressures in the upright positions
- Particularly potent in the splanchnic vasculature compared to the periphery
- Diffuses poorly across the blood-brain barrier with few central nervous system effects
- Great for those with facial flushing, rapid temperature changes, trouble standing in one place, difficulty showering
- Common Side Effects:
 - Supine hypertension
 - Scalp tingling, goosebumps
 - Other pseudo-neurological sensory side effects



Orthostatic Intolerance Management:

Pyridostigmine (off-label use):

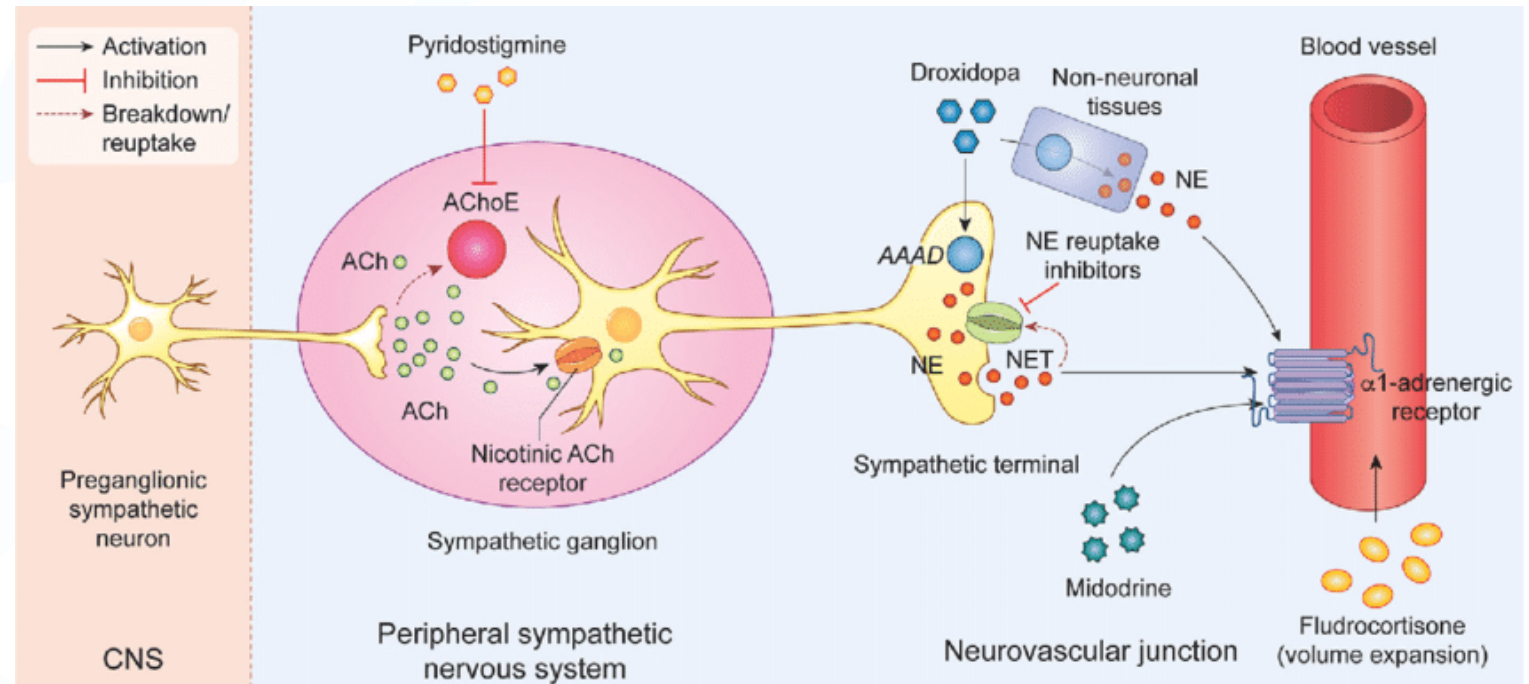
- Inhibits acetylcholine esterase (AChE) in the synaptic cleft, thus reducing the hydrolysis of acetylcholine
- Initially used to increase acetylcholine concentration to overcome autoantibody binding to the acetylcholine receptor (AChR) in myasthenia gravis



Orthostatic Intolerance Management:

Pyridostigmine (off-label use):

- Enhances cholinergic stimulation of post-synaptic norepinephrine (NE) release at the post-ganglionic synapse, thus increasing **venoconstriction** at exercising muscles
- Ultimately, this leads to improvement of blood flow return to the heart and increased preload filling of the heart

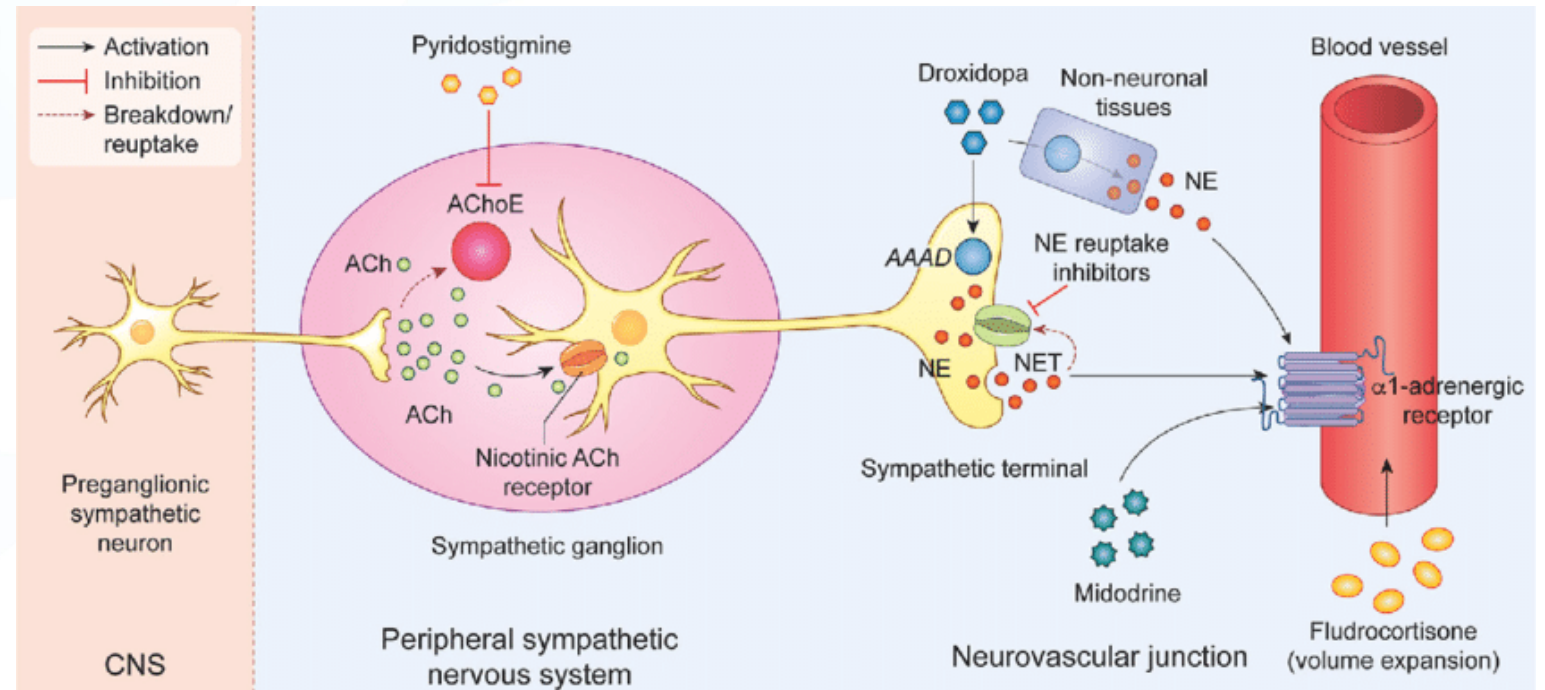


"The Exercise Response to Pharmacologic Cholinergic Stimulation in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome - Full Text View." *Full Text View - ClinicalTrials.gov*, <https://clinicaltrials.gov/ct2/show/NCT03674541>.

Orthostatic Intolerance Management:

Pyridostigmine (off-label use):

- Non-invasive measurements of exercise capacity, such as O₂ intake, end-tidal CO₂, and ventilatory efficiency all improve with pyridostigmine
- Current phase II trial nearing completion in which invasive hemodynamic measurements, peak oxygen uptake (VO₂ max), and skeletal muscle oxygen extraction are being measured



"The Exercise Response to Pharmacologic Cholinergic Stimulation in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome - Full Text View." *Full Text View - ClinicalTrials.gov*, <https://clinicaltrials.gov/ct2/show/NCT03674541>.

Orthostatic Intolerance Management:

Pyridostigmine (off-label use):

Mechanisms of Action:

- Improved venoconstriction and venous pre-load return
- **Reversal of AV shunting mediated by SFPN**



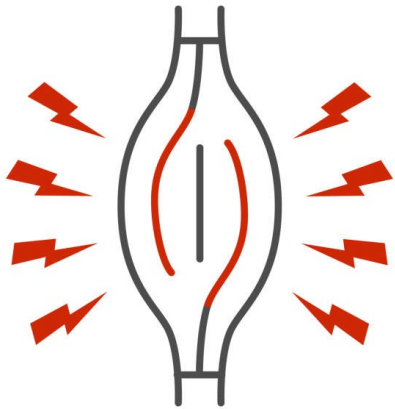
- Small Fiber Polyneuropathy (SFPN) leads to loss of myovascular innervation
- Can result in vessel patency that leads to arteriovenous shunting of blood.
- Capillary beds can be entirely bypassed in this distal “left to right” shunt
- Lack of delivery of oxygen and nutrients and removal of metabolic waste

Orthostatic Intolerance Management: Maintain Intravascular Volume

Pyridostigmine (off-label use):

Common Side Effects:

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



Orthostatic Intolerance Management: Reduce Sympathetic Activity & Maximize Cardiac Output

Beta Blockers:

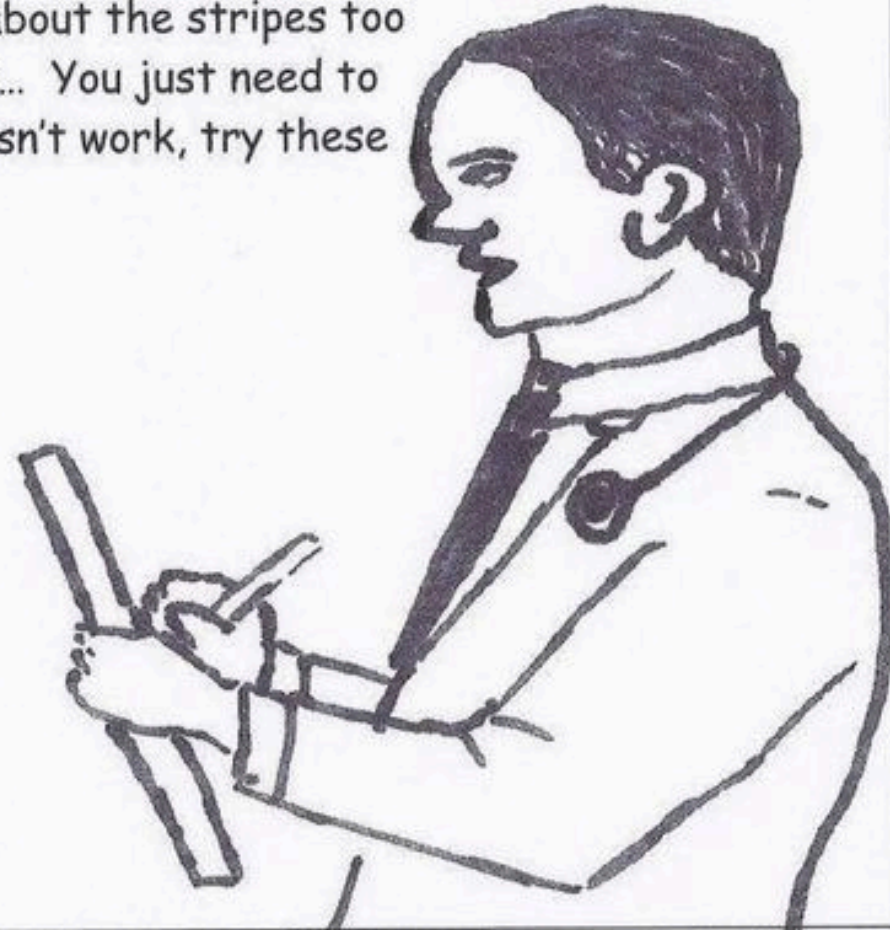
- Block adrenergic subtype receptors β_1 , β_2
- β_1 receptors are primarily in cardiac tissue and mediate inotropy (contractility) and chronotropy (heart rate)
- β_2 receptors located in the smooth muscles of blood vessels and the bronchial tree
- 2nd generation beta blockers, like atenolol and bisoprolol, have a higher affinity for β_1 receptors and are more cardioselective
- Avoid 3rd generation beta blockers like carvedilol, labetalol, nebivolol, as these also cause vasodilation through α -adrenergic and nitric oxide influences
- Most frequently use **propranolol, metoprolol, atenolol**
- Consider duration of action, prn vs. scheduled use when choosing
- Common side effects:
 - Fatigue
 - Lightheadedness/dizziness
 - Bradycardia
 - Asthma exacerbation (rather rare in OI patients)



Table 1¹⁰ : 3 Generations of beta-blockers

	Properties	Drugs
1 st Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2 nd Generation	β_1 -selective without vasodilation β_1 selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3 rd Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

You're a perfectly healthy horse* except for those stripes. But I wouldn't worry about the stripes too much. We see this sometimes... You just need to diet and exercise. If that doesn't work, try these antidepressants.



*Medical school mantra: "When you hear hoof beats, think horses, not zebras." ~ Dr. Theodore Woodward

Orthostatic Intolerance Management: Exercise to Increase Cardiac Output and Improve CV Tone

- Physiological decompensation from supine positioning unquestionably worsens OI symptoms
- Cardiovascular training can improve cardiac output (via improved stroke volume) and by improving vascular tone to support optimal blood flow to the muscles
- Ergo... “just exercise more and you’ll feel better!”



Exercise can be a primary trigger for **POST-EXERTIONAL MALAISE (PEM)** in those suffering from ME/CFS or Long-Covid/Post-Acute Sequelae of Covid (PASC)

Orthostatic Intolerance Management:

Exercise to Increase Cardiac Output and Improve CV Tone

- If your patient can tolerate exercise **WITHOUT** triggering PEM, then it can be advisable
- Preferable initial exercise therapies include:
 - Supine Exercises
 - Core strengthening exercises
 - Water/Pool-based exercises
 - Isometric Exercises > Aerobic Exercises
 - Yoga (supine preferable) or Pilates (reclined)
- Can monitor heart rate with a wearable device
 - If HR exceeds a certain bpm, it can be thought of as a surrogate marker for physiological stress
 - Recommend stopping and waiting until HR returns to baseline before continuing exercise routine
 - Best to give at least one day of recovery between exercise sessions



21-year-old male with ME/CFS and POTS

- High school competitive athlete
- Became ill senior year of high school 4 years ago, gradually continually losing functional capacity and experiencing more severe symptoms (despite the care of a POTS specialist)



“I am struggling to perform any daily activity – showering, eating, walking up the stairs. I am struggling to walk, stand, or sit without nearly falling. I feel as though my muscles are too weak to hold me and my brain fog is too great to provide any sense of what is going on around me.”

Initial NASA (Passive Standing) Lean: Upon Symptomatic Presentation

SBP 112→89 standing @ 9 min
Meets criteria for OH (delayed)

HR 55 bpm→117 bpm @ 9 min
Meets criteria for POTS (+62 bpm)

Orthostatic Vital Signs/The NASA 10-minute Lean Test

	Blood Pressure (BP)		Pulse	Comments
	Systolic	Diastolic		
Supine 1 minute	117	67	54	
Supine 2 minute	112	66	55	
Standing 0 minute	100	70	105	shortness breath
Standing 1 minute	105	75	102	feeling dizzy
Standing 2 minute	100	77	94	feeling nauseous
Standing 3 minute	115	79	79	
Standing 4 minute	105	74	95	tingling in hands
Standing 5 minute	84	64	105	very short breath
Standing 6 minute	100	82	99	
Standing 7 minute	98	69	94	hard time breathing
Standing 8 minute	89	74	113	
Standing 9 minute	89	65	117	feels like going to pass out
Standing 10 minute	92	61	100	

NASA (Passive Standing) Lean: After Initial Treatment Measures

- Aggressive oral free water
- 1000 mg/day salt supplementation
- Compression leggings
- Pyridostigmine 30 mg x 2 doses prior to testing

Orthostatic Vital Signs/The NASA 10-minute Lean Test

	Blood Pressure (BP)		Pulse	Comments
	Systolic	Diastolic		
Supine 1 minute	113	64	71	
Supine 2 minute	112	58	67	
Standing 0 minute	98	61	89	
Standing 1 minute	103	69	86	
Standing 2 minute	114	76	89	
Standing 3 minute	108	72	79	
Standing 4 minute	106	67	89	little shortness of breath
Standing 5 minute	103	70	82	
Standing 6 minute	108	72	87	
Standing 7 minute	114	75	83	
Standing 8 minute	97	63	83	
Standing 9 minute	97	70	84	dizziness
Standing 10 minute	101	67	90	

Other resources

OI/POTS: <http://dysautonomiainternational.org/>

BHC YouTube site education videos: <https://www.youtube.com/user/OFFERUtah>

BHC website → provider resources: <https://batemanhornecenter.org/>

ME/CFS: [https://www.mayoclinicproceedings.org/article/S0025-6196\(21\)00513-9/fulltext](https://www.mayoclinicproceedings.org/article/S0025-6196(21)00513-9/fulltext)