Managing Orthostatic Hypotension in Parkinson's Disease

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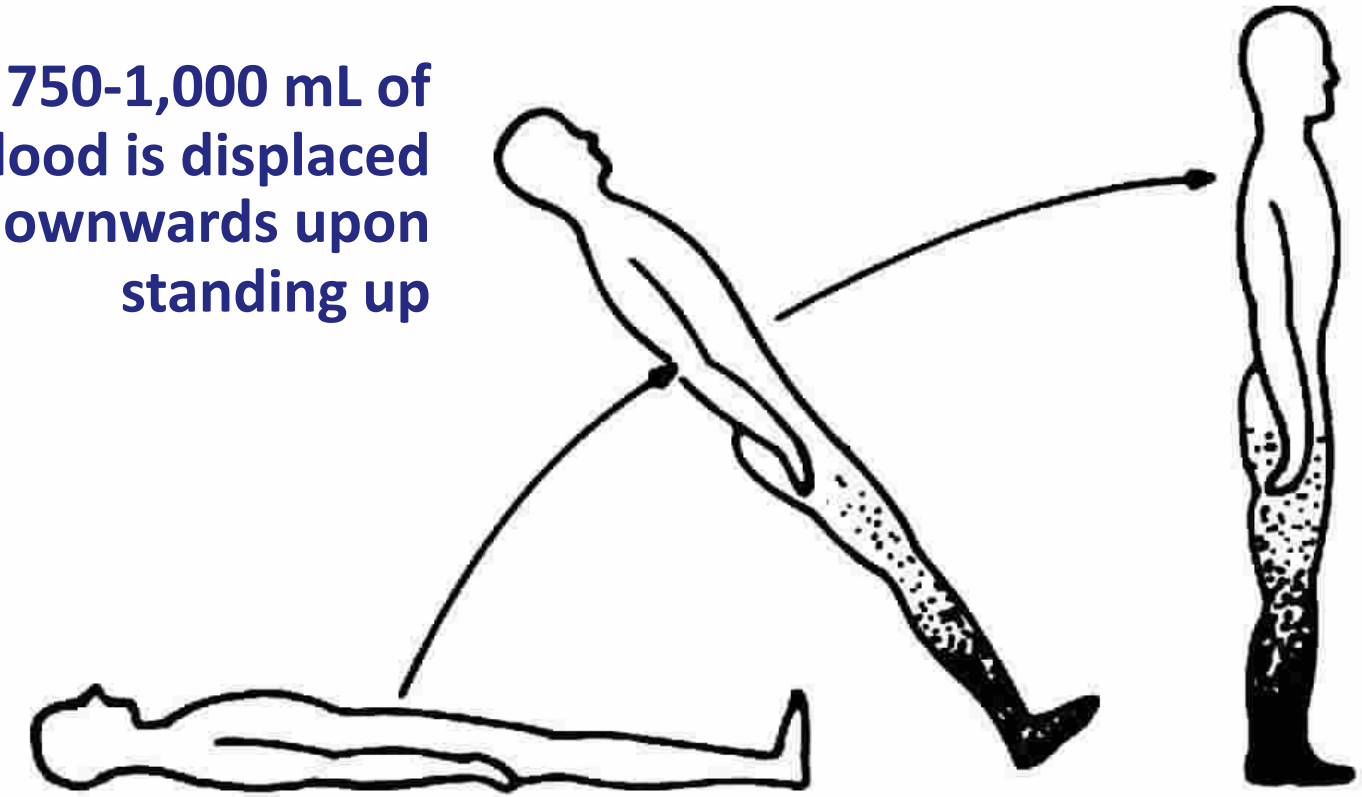
Hemodynamic Changes During Orthostasis

750-1,000 mL of blood is displaced downwards upon standing up



Several mechanisms in place to maintain orthostatic BP (baroreflex)

BP = blood pressure

Rowell LB. *Human Circulation Regulation During Physical Stress*. 1986.

Orthostatic Hypotension

A sustained fall of at least 20 mm Hg in SBP or 10 mm Hg in DBP within 3 minutes of standing or upright tilt

—AAS/AAN definition (2011)

SBP = systolic blood pressure
DBP = diastolic blood pressure

Freeman R, et al. *Clin Auton Res.* 2011;21:69-72.

Orthostatic Hypotension

- Many causes of OH, including severe heart failure, adrenal insufficiency, dehydration, and severe anemia
  - Prevalence is high
    - 5% in patients < 50 years old
    - Increases with age
    - Overall prevalence of OH in patients > 65 years is about 20%

OH = orthostatic hypotension

Lanier JB, et al. *Am Fam Physician*. 2011;84:527-36; Ricci F, et al. *J Am Coll Cardiol.* 2015;66:848-60.

Orthostatic Hypotension

- It is a sign (not a symptom)
- Symptoms alone are not required nor sufficient to diagnose OH
- BP measurements in the supine and standing positions are required to diagnose OH
- Can be symptomatic or asymptomatic

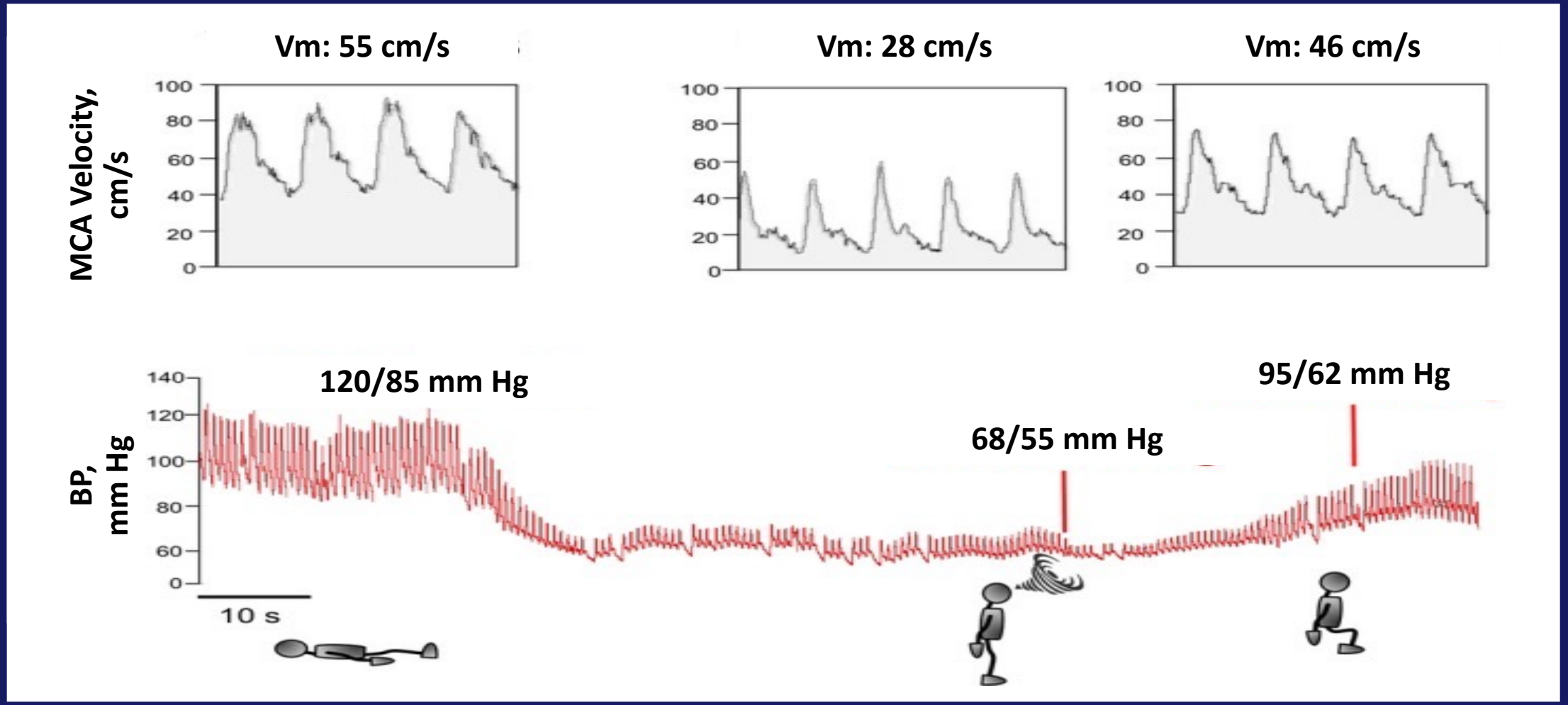
Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

Symptomatic Orthostatic Hypotension

- Typical well-known symptoms include:
  - Dizziness, lightheadedness, feeling about to faint when standing
  - Loss of consciousness (syncope)
  - Visual changes
- Less well-known symptoms include:
  - Coat-hanger pain
  - Shortness of breath
  - Angina
  - Cognitive slowing
  - Fatigue

Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

Symptomatic Orthostatic Hypotension



MCA = middle cerebral artery
Vm = velocity

Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

Two Types of Orthostatic Hypotension

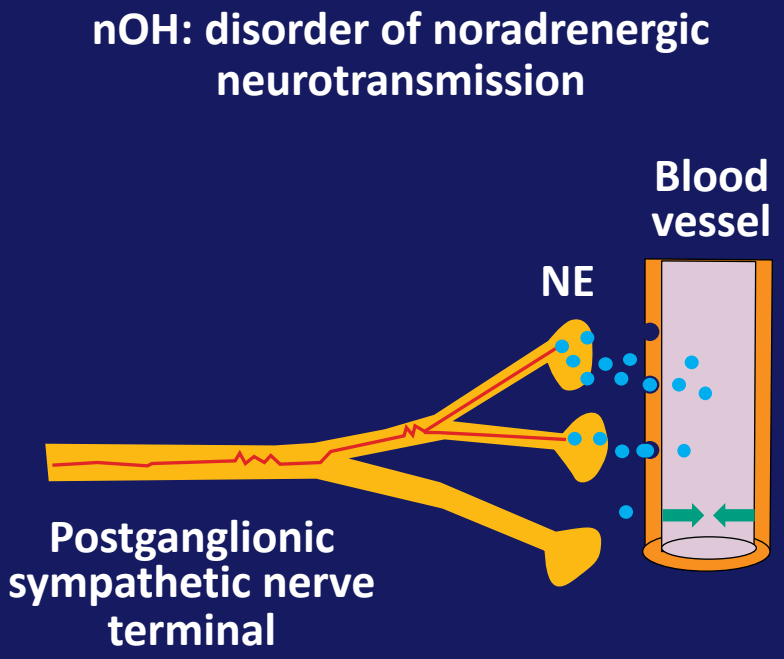
Non-Neurogenic Orthostatic Hypotension

- Very common in population > 65 years old
- Causes:
  - Anemia of unknown origin
  - Volume depletion
  - Heart failure
  - Significant varicose veins
  - Adrenal insufficiency
- Medications can cause or aggravate it
  - Diuretics
  - Antihypertensives
  - Nitrates
  - Sildenafil and others
  - Tricyclic antidepressants

Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

Neurogenic Orthostatic Hypotension

- Disorder of noradrenergic neurotransmission resulting in deficient norepinephrine release from postganglionic sympathetic nerves
- Orphan condition affecting < 200,000 people in the United States
  - An estimated 30%-50% of patients with PD have nOH
  - nOH can be a feature of the premotor stage in patients with PD, DLB, and MSA



NE = norepinephrine
PD = Parkinson disease
DLB = dementia with Lewy bodies
MSA = multiple system atrophy

Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

Neurogenic Orthostatic Hypotension Causes Significant Morbidity and Early Mortality

- Patients with PD and nOH are hospitalized more often, make more emergency department visits, and have earlier mortality than those with PD but without nOH
- Overall, the health-related cost among patients with PD and OH is 2.5 times higher than patients with PD without OH

Goldstein DS, et al. *Neurology.* 2015;85:1554-61;
Merola A, et al. *Parkinsonism Relat Disord*. 2018;47:45-9.

Why Identifying Neurogenic Orthostatic Hypotension Is Important

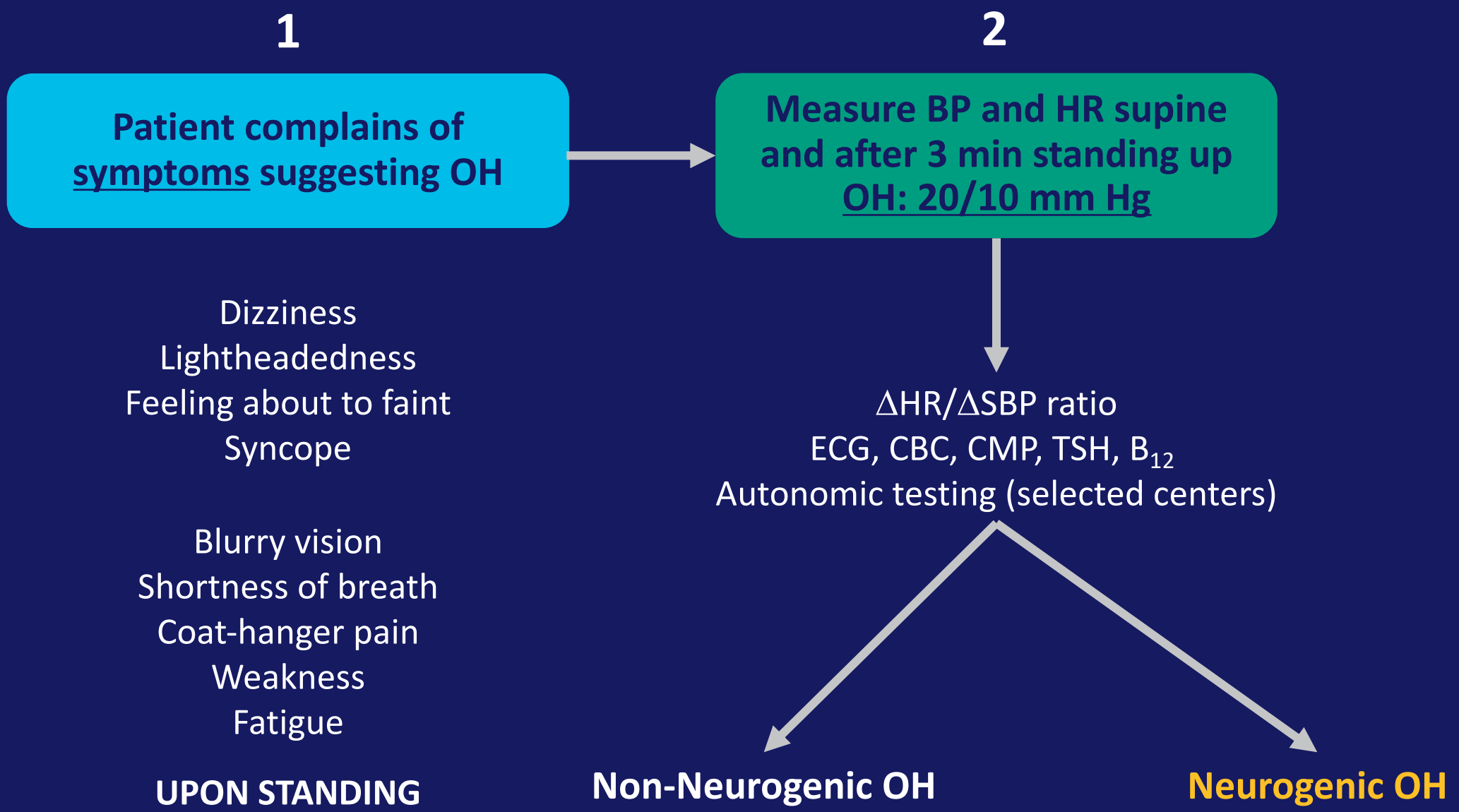
- Early treatment could prevent serious morbidity that could be fatal
- nOH is the hallmark of neurologic disorders that affect sympathetic neurons
- nOH can be the first sign of a neurodegenerative disorder and predate cognitive and/or motor impairment

Palma JA, et al. *Mov Disord Clin Pract*. 2017;4:298-308.

When to Suspect Orthostatic Hypotension

- Unexplained syncope/fall
- Typical symptoms (dizziness, lightheadedness, fatigue, confusion, gait disorders, neck pain, vision disturbance when standing)
- Patient's history (age, neurodegenerative disease, diabetes, renal failure, amyloidosis, heart disease, hypertension, autoimmune disease)
- Patients on vasodilators, diuretics, alpha- and beta-blockers, tricyclic antidepressants

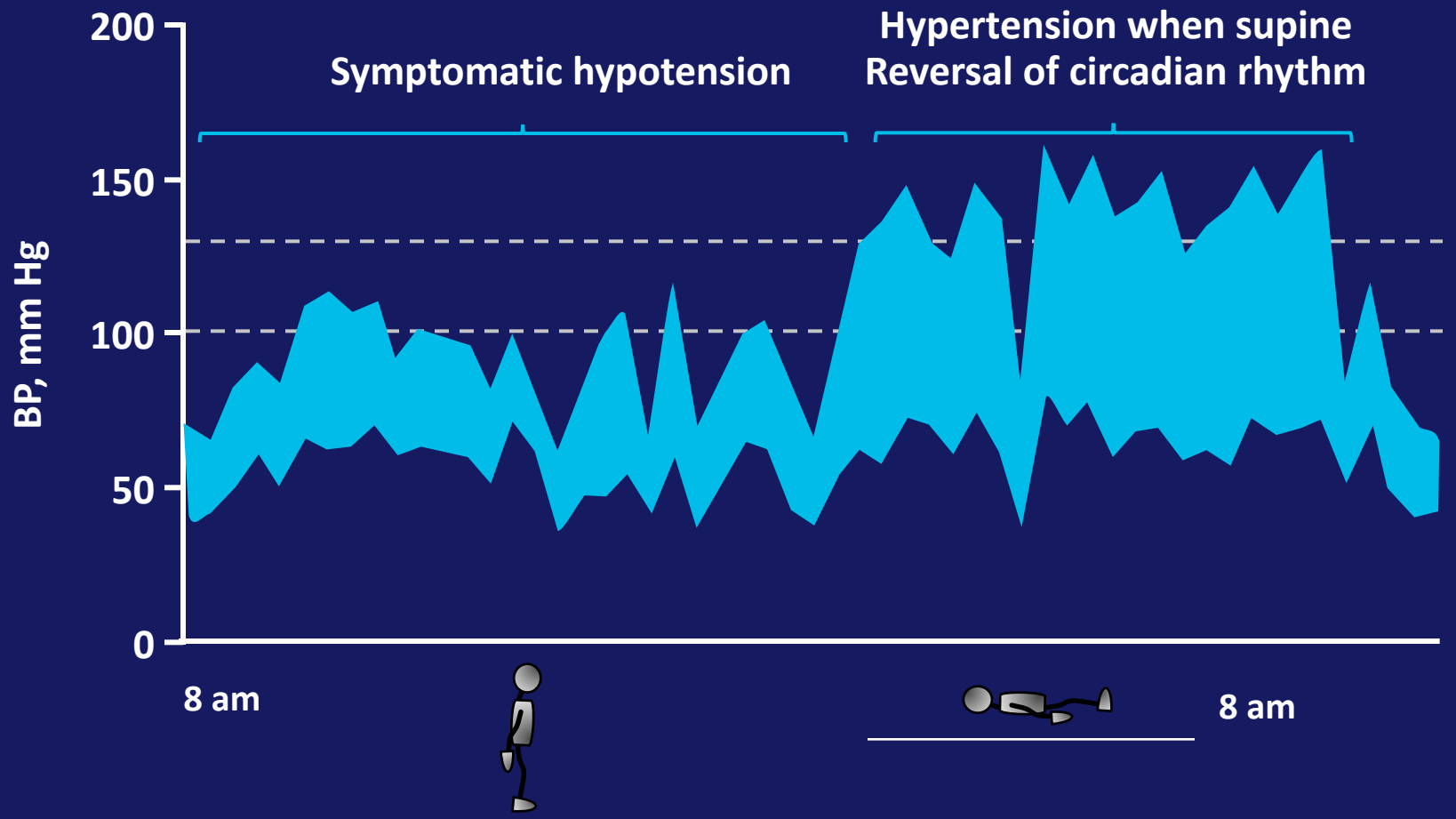
Ricci F, et al. *J Am Coll Cardiol.* 2015;66:848-60.



CBC = complete blood count CMP = comprehensive metabolic panel
TSH = thyroid-stimulating hormone HR = heart rate

Gibbons CH, et al. *J Neurol*. 2017;264:1567-82.

Ambulatory 24-Hour BP Monitoring



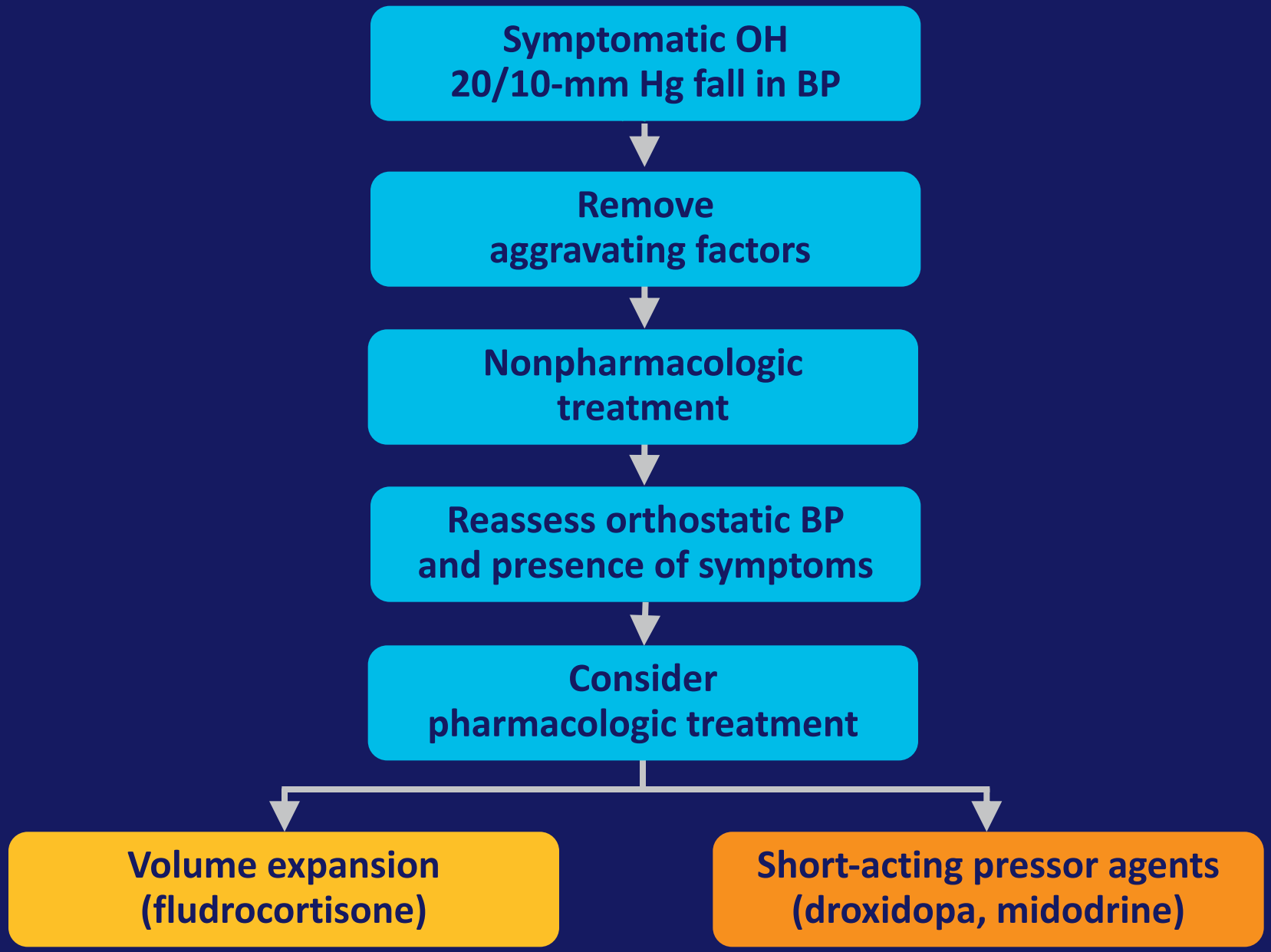
Norcliffe-Kaufmann L, et al. *Clin Auton Res*. 2014;24:189-92.

Management of Neurogenic Orthostatic Hypotension

Neurogenic Orthostatic Hypotension: Principles of Treatment

- Goal of treatment is to improve symptoms and quality of life—not to normalize BP
- Asymptomatic OH does not require pharmacologic treatment

Gibbons CH, et al. *J Neurol.* 2017;264:1567-82; Low PA, et al. *Lancet Neurol.* 2008;7:451-8.



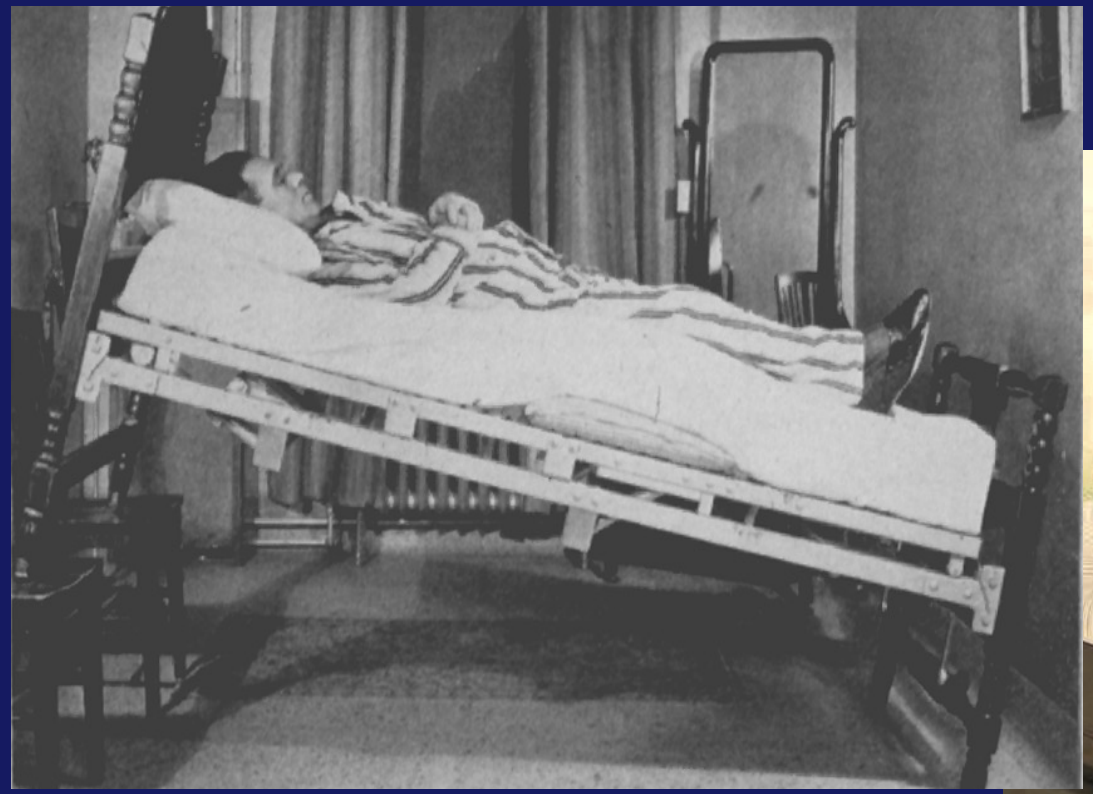
Kaufmann H, et al. *Clin Auton Res*. 2017;27:39-43.

Nonpharmacologic Treatment

- Elevating the head of the bed 30-45 degrees with an electric bed/mattress
- Compression garments (binders/stockings)
- Increased fluid and salt intake:
  - Approximately 2 L of water daily
    - Patients with nOH who rapidly consume 500 mL of water can raise SBP by 30 mm Hg within 10-15 minutes
  - Liquids other than water do not provide the same BP response
  - It is recommended that nOH patients add 1-2 teaspoons of salt per day to their diet
- Physical conditioning
  - Lower-body strength training, moderate nonstrenuous activities
    - Stationary recumbent bicycle, rowing machine, water-based activities
    - Avoid upright exercises, treadmill, or running

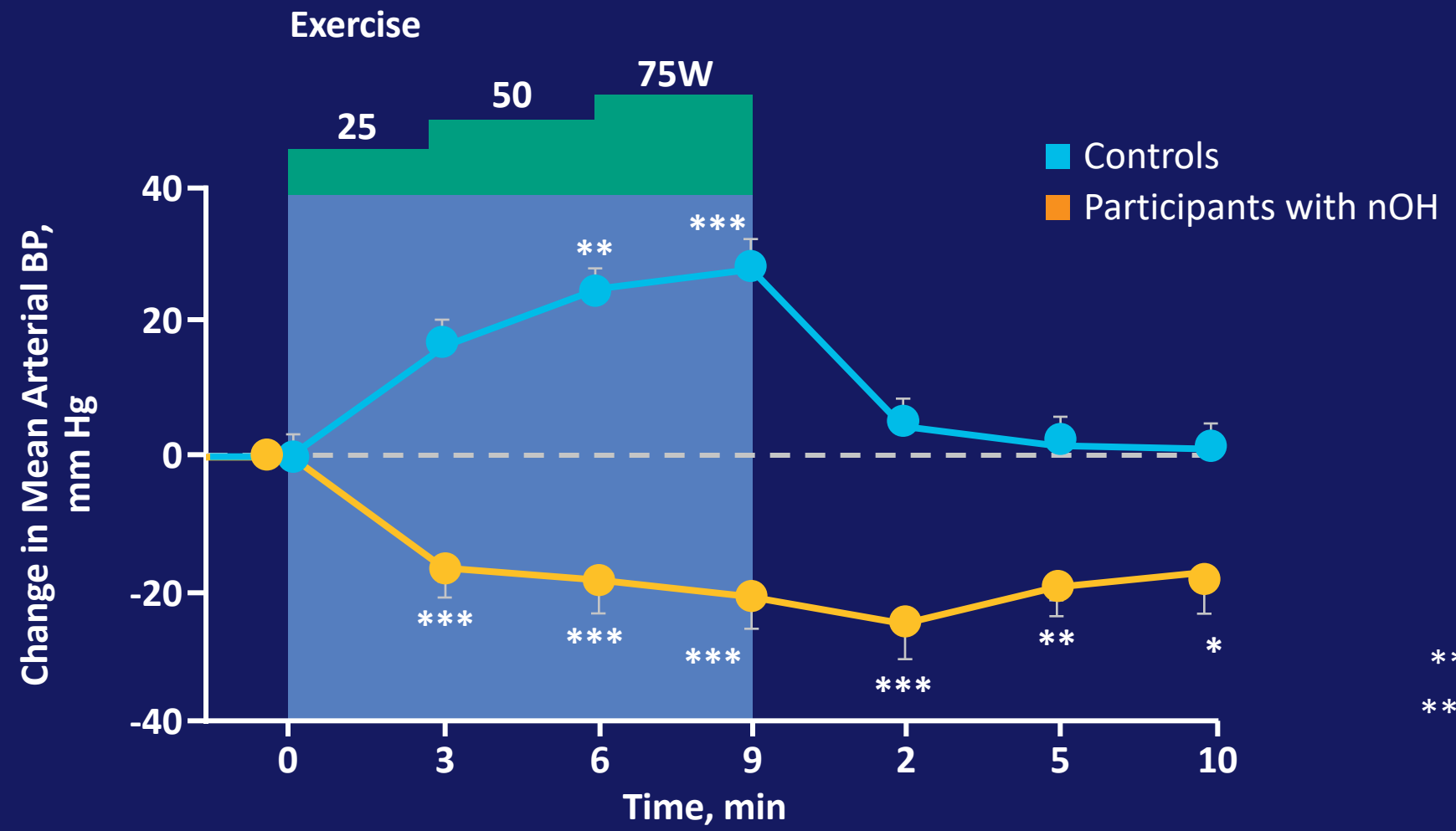
Gibbons CH, et al. *J Neurol*. 2017;264:1567-82.

Elevating the Head of the Bed Is the Most Effective Treatment



MacLean A, et al. *JAMA*. 1940;115:2162-7.

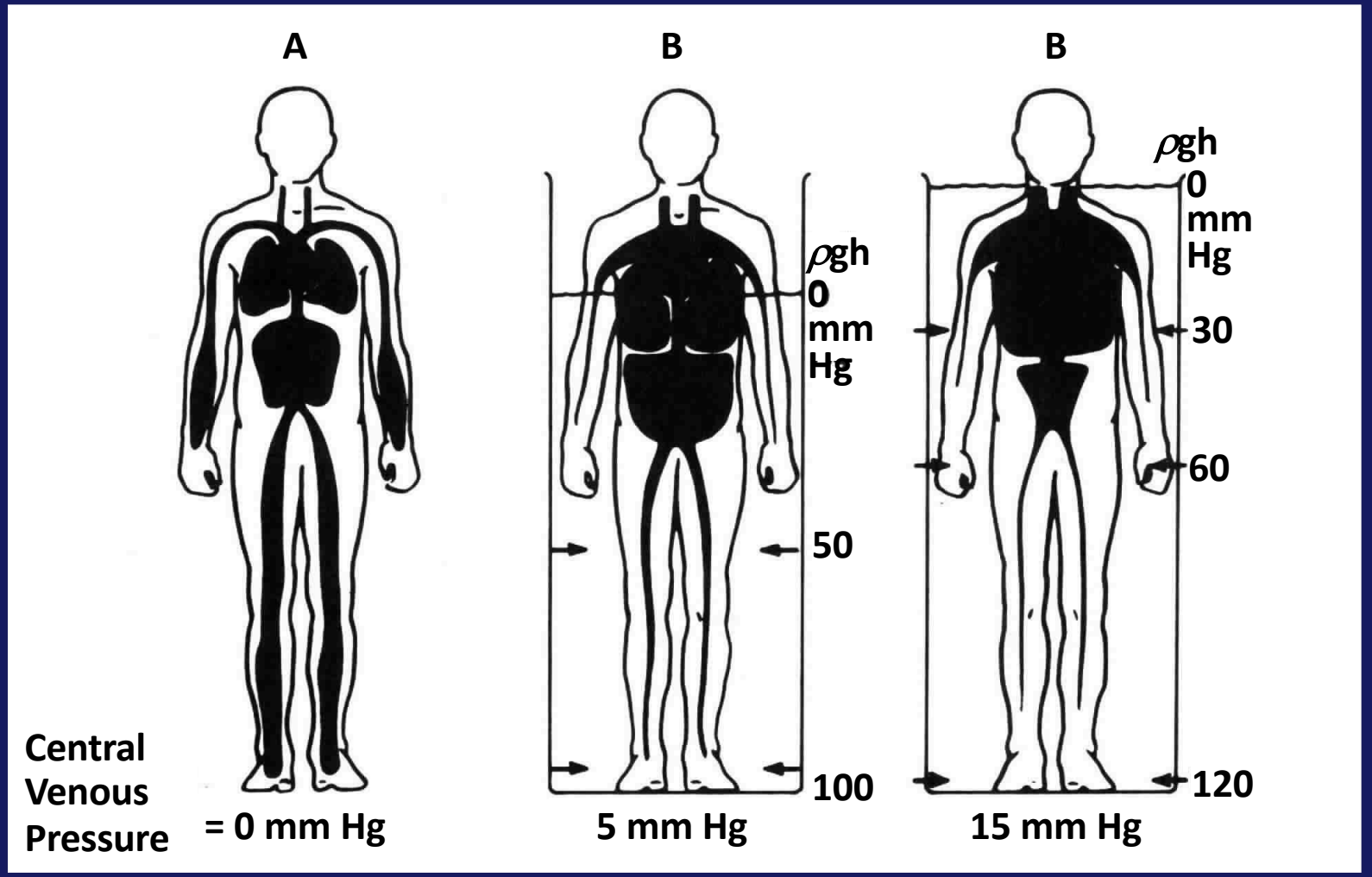
Dynamic Physical Exercise Lowers BP in Patients With Neurogenic Orthostatic Hypotension



*$P < .05$.
**$P < .005$.
***$P < .0005$.

Puvi-Rajasingham S, et al. *J Physiol.* 1997;7:155-61.

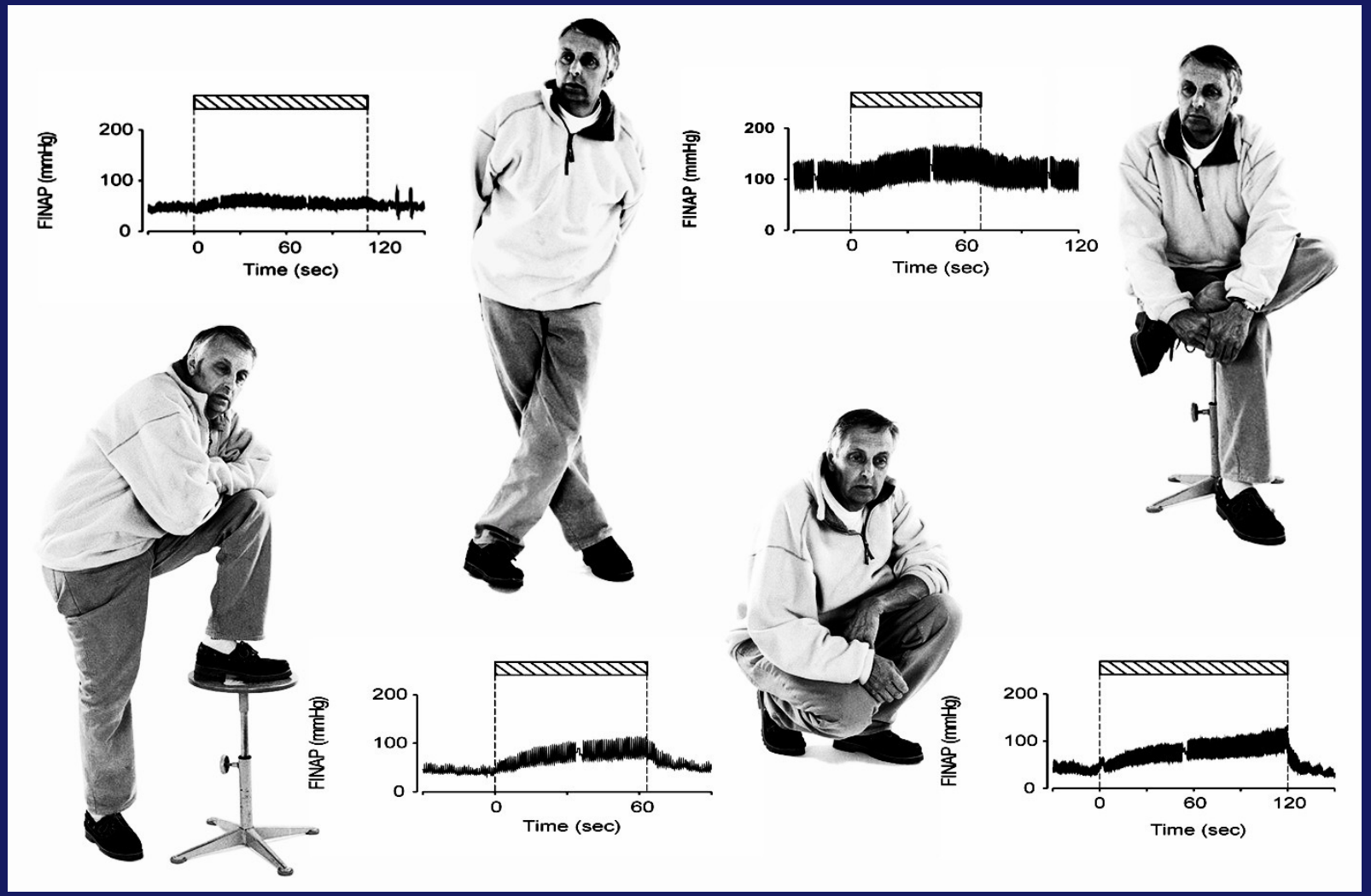
Exercise in a Swimming Pool Prevents the Fall in BP



ρ = density of the fluid
g = acceleration of gravity
h = height of the column of fluid above the layer where pressure is being measured

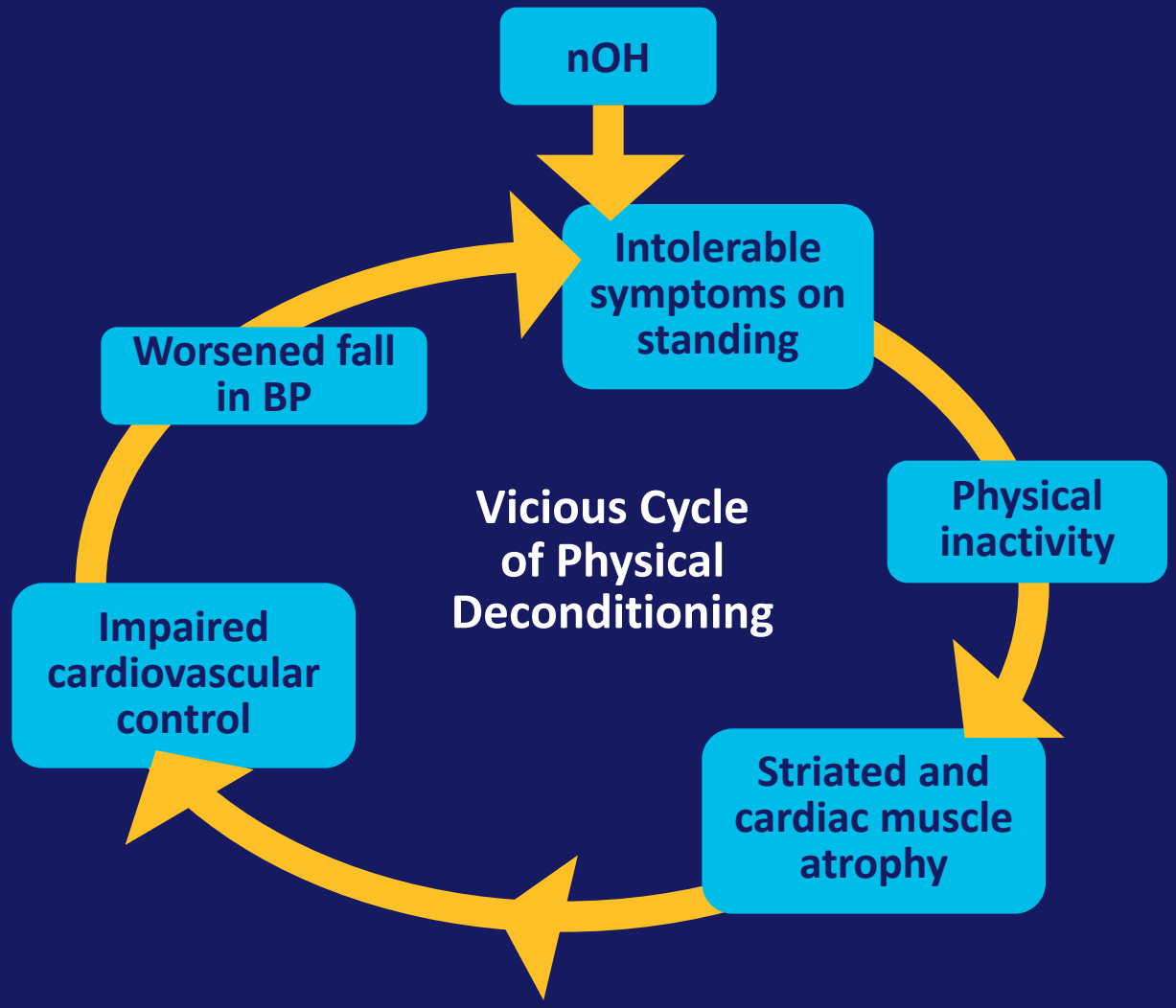
Rowell LB. *Human Circulation Regulation During Physical Stress*. 1986.

Physical Counter-Maneuvers to Prevent Orthostatic Hypotension



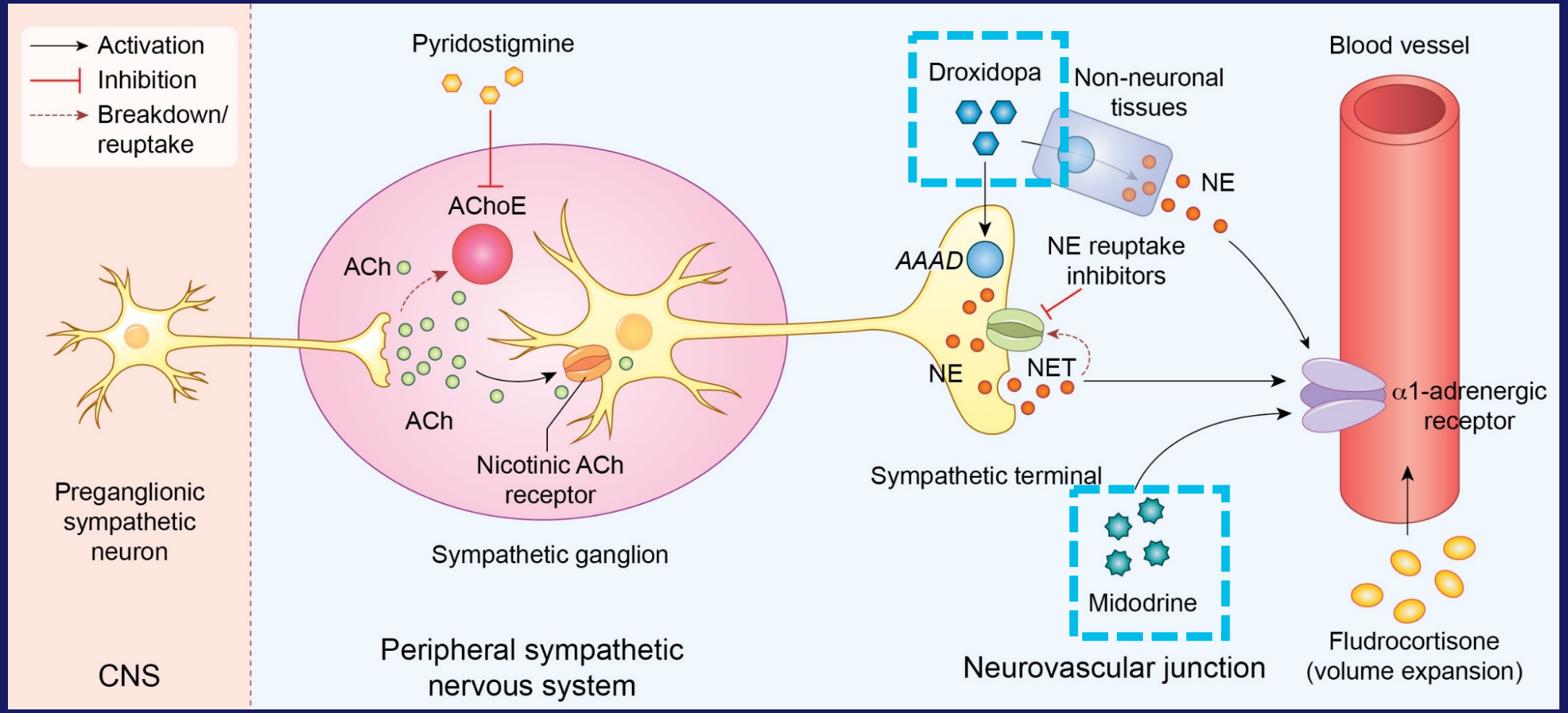
Wieling W, et al. *Clin Auton Res*. 2004;14:62-70.

Breaking the Vicious Cycle of Orthostatic Hypotension



Kaufmann H, et al. *Clin Auton Res*. 2017;27:39-43.

Pharmacology of Neurogenic Orthostatic Hypotension



AAAD = aromatic amino acid decarboxylase ACh = acetylcholine AChoE = acetylcholine esterase
CNS = central nervous system
NET = norepinephrine transporter

Palma JA, et al. *Mov Disord*. 2018;33:372-90.

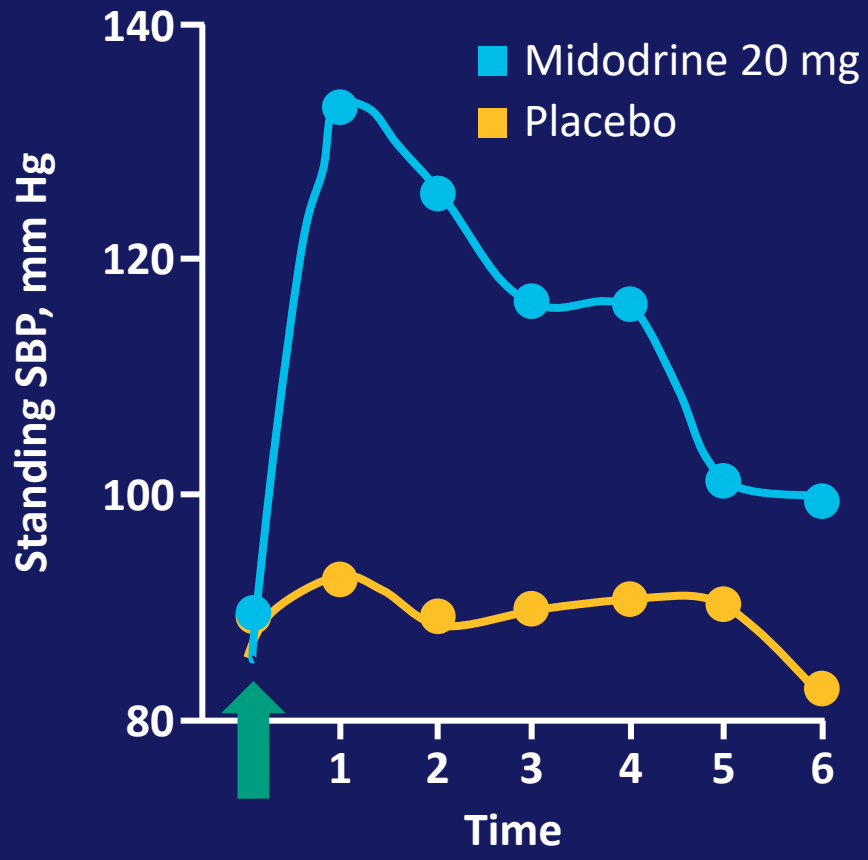
2 FDA-Approved Drugs for Orthostatic Hypotension

- Direct sympathomimetic agent: midodrine
- Norepinephrine precursor: droxidopa

Palma JA, et al. *Mov Disord*. 2018;33:372-90.

Midodrine

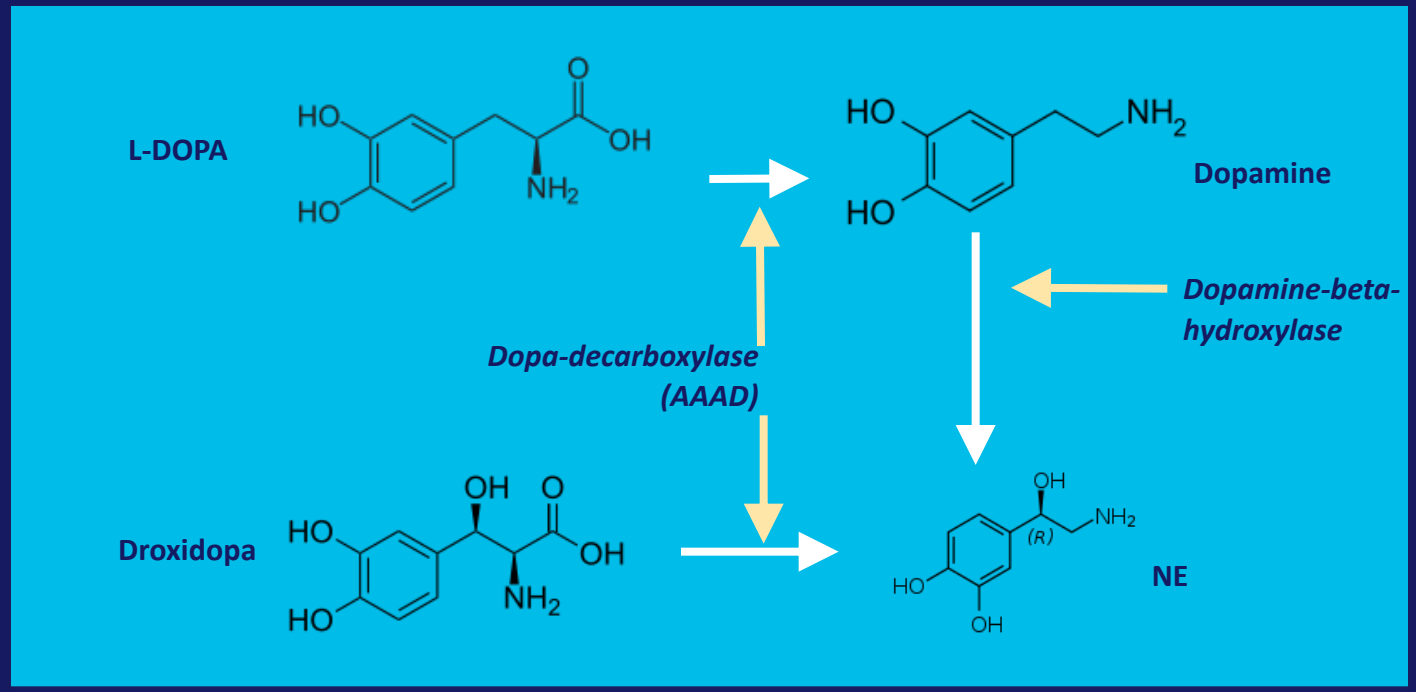
- FDA approval: 1996
- Selective alpha-1-adrenergic agonist
- Does not cross blood-brain barrier
- Predictable pressor effect ~1 hour post-administration
- Duration of action: ~3 hours
- Dosage: 2.5-10 mg up to 3 times/day
- Side effects:
  - Supine hypertension
  - Pilomotor reactions (goosebumps)
  - Urinary retention (rare)



Wright RA, et al. *Neurology.* 1998;51:120-4.

Droxidopa

- FDA approval: 2014
  - First drug for nOH approved in 20 years
- Synthetic precursor of NE
- Predictable peak plasma concentration and pressor effect ~1 hour post-administration
- Duration of action: 4-6 hours
- Dosage: 100-600 mg 3 times/day



Kaufmann H, et al. *Expert Rev Cardiovasc Ther*. 2015;13:875-91.

Cardiovascular Safety Considerations in the Pharmacologic Treatment of Neurogenic Orthostatic Hypotension

- All drugs for OH increase the risk of supine hypertension
- Patients should be instructed to avoid the flat position at all times and sleep with the head of the bed raised 30-45 degrees
- Some patients respond better to specific drugs (eg, patients with low NE levels respond well to droxidopa)
- Some patients require combinations of drugs

Palma JA, et al. *Mov Disord*. 2018;33:372-90.

Clinical Management of Supine Hypertension in Patients With Neurogenic Orthostatic Hypotension

- Supine hypertension with droxidopa (> 160 mm Hg)
  - ~10% of patients
  - More common in those with higher baseline supine BP
  - Initial clinical management includes clinic and home BP monitoring with nonpharmacologic interventions (elevation of head of bed)
- Avoid dosing within 4 hours prior to bedtime
  - Physicians and patients should monitor supine BP as droxidopa dose is up-titrated
  - For more severe BP elevations, droxidopa can be down-titrated or discontinued
  - Short-acting antihypertensive agents can be administered at bedtime if necessary

Package insert.

Off-Label Use: Fludrocortisone

- Evidence-based data on fludrocortisone for nOH treatment are limited
- Increases renal sodium reabsorption, intravascular volume, and BP
- No more than 0.1-0.2 mg/day
- Long acting: clinical effects take 3-5 days to be noticeable (biological half-life is 36 hours)
- Side effects:
  - Hypokalemia and arrhythmia (short term)
  - Edema (short term)
  - Left ventricular hypertrophy and heart and renal failure (long term)
  - Increases risk of all-cause hospitalization in patients with OH

NICE. www.nice.org.uk/advice/esuom20/chapter/Key-points-from-the-evidence; Schoffer KL, et al. *Mov Disord*. 2007;22:1543-9; package insert.

Off-Label: Pyridostigmine

- Acetylcholinesterase inhibitor
- Little effect as isolated drug
- Appears to enhance effect of other medications to increase sympathetic nerve activity in response to orthostatic stress
- Side effects: abdominal cramps, diarrhea, sialorrhea, excessive sweating, and urinary incontinence

Singer W, et al. *Arch Neurol*. 2006;63:513-8;
Byun JI, et al. *Neurology*. 2017;89:1078-86;
Okamoto LE, et al. *Hypertension*. 2019;73:235-41.

Conclusion

- OH can be treated (if diagnosed)
- nOH has different pathophysiology and prognosis than non-neurogenic OH
- Treatment of OH starts with nonpharmacologic measures
- Pharmacologic treatment of OH includes midodrine, droxidopa, or fludrocortisone
- All patients must sleep with the head and torso raised 30-45 degrees