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ORTHOSTATIC HYPOTENSION (OH): CONSIDERATIONS FOR MANAGEMENT

What Is The Prevalence Of Orthostatic Hypotension (OH)? [1,2,3,4]

- The prevalence of OH varies depending on the age and comorbidities of the population. The prevalence of OH can range from ~16-20% in community residents & as high as ~50% in nursing homes, and increases exponentially with age. OH is of importance due to its **association with falls, fractures, transient ischemic attacks, syncope and myocardial infarction**, which all can cause serious morbidity and mortality risk.

What Is Orthostatic Hypotension [2,3,6,7]

- A sustained ↓ in systolic BP ≥20mmHg or in diastolic BP ≥10 mmHg within 3 minutes of standing from sitting or supine position.
- May be symptomatic, asymptomatic or atypical.
- Common symptoms: dizziness, light-headedness, blurred vision, fatigue, nausea, palpations, and headache.
- Less common & atypical symptoms: syncope, dyspnea, chest pain, neck & shoulder pain. Investigate for OH with unexplained falls.

What Is Neurogenic Orthostatic Hypotension (nOH)? [8,9,10]

- A failure of the sympathetic nervous system related to 1° or 2° autonomic disorders (e.g. pure autonomic failure, Parkinson's disease, diabetic & non-diabetic autonomic neuropathies, spinal cord injury). Signs of nOH include symptoms triggered by autonomic stressors (e.g. meal, hot bath, exercise). Treatment of nOH is similar to OH.

What Causes Orthostatic Hypotension? [7,11,12]

- OH may be multifactorial, especially in older or medically complex individuals. It may be acute/reversible, chronic/non-reversible, non-neurogenic or neurogenic. Most common causes for OH include non-neurogenic or 2° autonomic failure. (See Table 1.)

What Is The Overall Goal Of OH Management? [1,2,3]

- Treat **if symptomatic** to relieve symptoms, manage any underlying causes & improve function while ↓ risk of complications (e.g. ↓ falls).

[Achieving a set BP target is not a goal. Consider life expectancy & quality of life.]

Table 1: Causes of OH {may commonly be multifactorial, especially in older or if medically complex}
4Ds: **D**econditioning, **D**ysfunctional Heart (eg. MI, HF, Aortic stenosis), **D**ehydration (eg. disease, dialysis, drugs) & **D**rugs (eg. blood pressure, angina, Parkinson's, psychiatric.

Acute/ reversible	**Dehydration**, **medications** (see Table 3), deconditioning, fever
Chronic/non-reversible	Cardiac failure, diabetes mellitus, Parkinsonism, multiple system atrophy, trauma (blunt to chest)
Non-neurogenic OH	**Cardiovascular**: MI, aortic stenosis, constrictive pericarditis, advanced cardiac failure, hypertrophic obstructive cardiomyopathy (HOCM), arrhythmias, large varicose veins **Endocrine and renal**: adrenal insufficiency, diabetes insipidus, hypoaldosteronism, renal concentrating defect **Venous pooling**: alcohol, postprandial dilation (splanchnic blood vessels), hot environment, prolonged standing **Reduced intravascular volume**: hemorrhage, burns, salt-losing nephropathy
Neurogenic OH (nOH)	**Primary causes**: pure autonomic failure, multiple system atrophy. **Common causes**: 2° autonomic failure (e.g. stroke, diabetes, alcoholic polyneuropathy, idiopathic parkinsonism, amyloid neuropathy, pernicious anemia)

Management Overview

a) Assess Acute Medical Issues, Medications, & Hydration Status. [7,11,14]

b) Assess for Drug Induced Causes Of OH (see Table 3)

- **α-blockers** e.g. terazosin; **antihypertensives**: e.g. diuretics (preferred alternatives: ACEI/ARB, or adjust or split dose); **antiparkinson's**, **antipsychotics**, **barbiturates**, **ethanol**, **insulin**, **MAOIs** monoamine oxidase inhibitors, **nitrates**, **opiates**, **phosphodiesterase inhibitors**, **sedatives**, **TCAs** (alternative: SSRI), & **trazodone**
- Consider stopping, reducing or changing the offending drug/dose

c) NON-PHARMACOLOGICAL Management [2,5,7,11,13,14]

- **Get Up Gradually**: avoid getting up or moving too quickly (e.g. count to 15 when going from lying to sitting, & sitting to standing)
- **Stay Cool**: avoid exposure to extra hot environments (e.g. hot showers).
- **↑ Fluid** (1.5-3L daily) or salt intake (up to 2.3-4.6 g NaCl daily in food or as 1g tablets) unless contraindicated (e.g. heart failure, hypernatremia). Drink ~500mL of water as bolus, ↑ BP in 5-30+ minutes
- **Syncope Avoidance Maneuvers**: leg crossing, bending forward, squatting, toe raise, limb & abdominal contraction; give yourself a hug while standing.
- Eat small, frequent low carbohydrate meals (e.g. 6 small meals vs. 3 large meals) to prevent postprandial worsening of OH.
- ↑ caffeine intake: 1-2 cups of coffee/tea with meals if postprandial OH

d) Consider Additional Non-drug Measures

- Raise head of the bed by 6 to 9 inches during nighttime.
- Use abdominal binder or compressive waist-high stockings (pressure of 30-40 mmgHg may be required)
- Functional electrical stimulation in spinal cord injury
- For men ♂, sitting to urinate may be preferred.
- Exercise (e.g. swimming, recumbent bicycle or rowing).

e) PHARMACOLOGIC Management Options [1, 2,3,5,7,10,11,12,14,15,17,19]

When non-pharmacological measures are inadequate, pharmacologic agents may be used in addition to nonpharmacological therapies, especially in nOH.

Note: [Meds treating OH can also cause supine HTN]

Fludrocortisone FLORINEF (see Table 2) – most commonly used drug for OH.
Midodrine AMATINE (see Table 2) – less commonly used, but noted in literature.
Beta blockers (non-selective): limited role, despite negative chronotrophy & inotropy.
Caffeine: 100-260mg TID as tablets or 1-2 cups of coffee/tea (e.g. with meals).
Clonidine: 0.1-0.6 mg/ day. Can ↑ venous return without significant ↑ in peripheral vascular resistance. Caution: hypotension.
Desmopressin acetate DDAVP: 100-800mcg po, IM 2-4mcg. Prevents nocturnal polyuria.
Erythropoietin: Shown to be useful in people with anemia and autonomic dysfunction. AE: supine hypotension. Parenteral administration.
NSAIDS: can ↑BP, but caution due to **GI and renal adverse effects**.
Octreotide SANDOSTATIN: Used in DM, pure autonomic failure, multiple system atrophy. More effective with midodrine than either drug if used alone. Costly; SC or IV.
Pyridostigmine MESTINON: 30mg BID-TID, ↑ to 60mg TID. Some success in autonomic failure. Not studied in older/complex medical patients.
Nitroglycerin patch: if supine HTN, nighttime dosing 8pm-8am used for nighttime congestion
Dihydroxyphenylserine DROXIDOPA: 100-600mg TID, 100, 200, 300 mg FDA'2014. N/A Canada

Other Considerations:

- Antihypertensives should not be discontinued all at the same time in people with OH. A stepwise approach should be considered if discontinuing and tapering these medications. While the risk of falls is ~2.5 times higher in the elderly with uncontrolled HTN, some relaxation of the BP goals may have to occur in order to manage the OH symptoms. Often stopping antihypertensives can treat OH in more than half of people with these symptoms.
- **Pacemaker therapy**: Atrial tachypacing option for OH and bradycardia. Dual chamber pacemakers can treat severe OH.

Table 2: Select Drugs For Treatment Of Orthostatic Hypotension

DRUG	DOSE/ MOA/ PHARMACOKINETICS	ADVANTAGES/ DISADVANTAGES	CONTRAINDICATIONS (CI)/ ADVERSE EFFECTS (AE)/ DRUG INTERACTIONS (DI)/ MONITOR (M)
Fludrocortisone FLORINEF 0.1mg^{C} tablets P L	**Dose:** 0.1 to 0.3mg daily. ↑dose weekly or until pedal edema (if start low: 0.05mg) **Maximum**: 1mg/ day **MOA:** Synthetic mineralocorticoid (sodium & water retention)	**Adv**: Considered first line therapy after failure of non-pharmacological measures **DI**: Dose limiting AE. K^+ supplementation usually required Older individuals: fluid overload	**CI**: systemic fungal infections, long term corticosteroid use, HF, renal failure **M**: fluid in & outs for adequate intake **AE**: headache, **supine HTN**, CHF, edema, ↓K^+, ↑ weight **DI**: may ↓antineoplastic (e.g. aldesleukin), BCG, corticosteroid effect, ↑AE of natalizumab, taper off steroids prior to starting natalizumab
Midodrine AMATINE,g 2.5^{C}, 5mg^{C} tablets P L	**Dose**: 2.5mg TID, ↑ 2.5mg weekly until max dosage (for best results, AM dose given early and PM dose no later than 6pm) **Maximum**: 10mg TID **MOA :** α-1-agonist	**Adv**: Can be used with fludrocortisone in refractory individuals PRN scheduling, taken 30 to 45 minutes before upright activities[2] **DI**: Caution elderly taking meds that ↓ HR	**CI**: CAD, HF, acute renal failure, severe heart disease, urinary retention, thyrotoxicosis, pheochromocytoma **AE**: **supine HTN**, piloerection, pruritus, paraesthesia **DI**: ergot derivatives & MAOI may ↑ hypertensive effect, TCA may ↑vasopressor effect, BB & CCB (non-DHP) may ↑bradycardia, sympathomimetics may ↑adverse/ toxic effect

If an individual cannot stop an antihypertensive, it may be replaced by agents that are less likely to cause OH. Although for some, **non-pharmacologic measures with appropriate antihypertensive medications may be sufficient.**

WHICH MEDICATIONS MAY WORSEN OH AND WHAT ARE THE ALTERNATIVES? [7,11,15,16,19,20]

When possible, stop the medication of concern or reduce the dose of the medication before switching to another agent. Control of OH may require decrease in the intensity of BP management. **Note: Medications in Table 3 all have the potential to cause OH; some may cause or worsen OH more than others.**

Table 3: Medications That May Worsen OH and Possible Alternatives

	Medications That May Worsen OH	Alternatives (less likely to cause OH)
CV	ß blockers (e.g. propranolol > metoprolol)	⇨change to an ACEI or an ARB
	α agonists (e.g. clonidine, methyldopa)	⇨consider timing options. May split dose of antihypertensives e.g. ACEI or ARB; or nighttime dosing of at least one antihypertensive
	Diuretics (e.g. **furosemide** > hydrochlorothiazide, chlorthalidone)	
	α blockers (e.g. doxazosin, prazosin, terazosin)	⇨change to tamsulosin or alfuzosin (if for BPH)
	Non-DHP CCB (e.g. verapamil, diltiazem)	⇨DHP CCB {e.g. amlodipine, felodipine; **Avoid** nifedipine IR (Beers criteria)} ⇨ consider giving at nighttime
CNS	TCA's (e.g. **amitriptyline** > nortriptyline; clomipramine, doxepin >6mg/day, imipramine, trimipramine)	⇨SSRI or SNRI (if treating depression or anxiety) or mirtazapine ⇨If TCA indicated, may consider nortriptyline

Consider a step-wise approach by tapering/discontinuing one antihypertensive at a time. If using both a BB & clonidine, taper BB first, several days before tapering clonidine to ↓ risk of rebound HTN.

SUMMARY: HOW SHOULD ORTHOSTATIC HYPOTENSION BE MANAGED? [5,7,11]

A medication assessment should be done to determine if **any** medications may be contributory. When suitable, consider a trial of stopping or reducing medication(s) of concern or switching to another agent. {In c**omorbidities** such as HF, reducing doses or stopping medications could mean sacrificing life-saving effects of drugs such as ACEI & β-blockers; facilitate risk vs benefit discussions with patient/care-giver to allow for informed decisions.} Non-pharmacological measures are important in management of OH and can be used while medications are being changed or adjusted and after the change if symptoms are still present. If OH symptoms continue to remain problematic, drug therapy may be added to non-drug measures to manage OH. [Most OH related drug trials were studied in nOH.] Assessment of fluid status and management of dehydration is important.

New Drug (USA): DROXIDOPA L-Dihydroxyphenylserine, 100, 200, 300 mg caps po TID; **FDA Approval Feb/14 for Treatment of symptomatic nOH.** Shown success in patients with autonomic failure and in dopamine B hydroxylase deficiency but not been studied in elderly/ complex medical patients. Effectiveness beyond 2 weeks not demonstrated. **Caution: FDA Black Box:** may cause **supine hypertension**. AE: nausea, headache, dizzy, hypertension. (Rare: possible neuroleptic malignant syndrome, & may exacerbate heart disease or stroke).

ç=scored **1°**=primary **2°**=secondary **AI**=active metabolite **ACEI**=angiotensin converting enzyme inhibitor **AE**=adverse effect **ARB**=angiotensin receptor blocker **AM**=morning **BB**=beta blocker **BP**=blood pressure **CAD**=coronary artery disease **CCB**=calcium channel blocker **CHF**=congestive heart failure **CNS**=central nervous system **CV**=cardiovascular **DHP**=dihydropyridine **DM**=diabetes mellitus **e.g.**=example **GI**=gastrointestinal **HA**=headache **HF**=heart failure **HTN**=hypertension **hr**=hour **HR**=heart rate **HSR**=hypersensitivity **hx**= history **i.e.**=that is **IM**=intramuscular **IR**=immediate release **ISA**=intrinsic sympathomimetic activity **IV**=intravenous **K⁺**=potassium **LA**= long acting **Na⁺**=sodium **nOH**=neurogenic orthostatic hypotension **NT**=neurotransmitter **MAOI**=monoamine oxidase inhibitors **MI**=myocardial infraction **mins**=minutes **mg**=milligrams **mmHg**=millimeters of mercury **MOA**=mechanism of action **NaCl**=sodium chloride **OH**=orthostatic hypotension **PDE5 inh**=phophodiesterase type 5 inhibitors **po**=orally **pts**=patients **RF**=renal failure **SA**= short acting **SBP**= systolic blood pressure **SC**= subcutaneous **sx**=symptoms **TCA**=tricyclic antidepressant **TID**=three times daily **vs**.=versus **XR**=extended release

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Notes:

- Suggest measure BP at 1 minute and 3 minutes after standing**.**
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