Recognition and Management of Orthostatic Hypotension in Primary Care

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Classify patients by type of orthostatic hypotension
- Assess patients to arrive at a firm diagnosis
- Implement evidence-based treatment to alleviate symptoms, prevent complications, and improve quality of life

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of orthostatic hypotension.

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INTRODUCTION

Orthostatic hypotension (OH) is associated with significant morbidity and potential loss of autonomy. In addition to increased risk of falls, OH is associated with an increased risk of heart failure, atrial fibrillation, kidney failure, hospitalization, stroke, cognitive impairment, and death.[1-6] The prevalence of chronic OH is underestimated and OH often is overlooked in common disorders, such as Parkinson's disease (PD) and diabetes mellitus.[7] Fortunately, there are effective nonpharmacologic and pharmacologic interventions available to improve quality of life and reduce the risk for

devastating consequences, such as a fall or hip fracture. However, many clinicians neglect to screen for OH, missing the opportunity to treat.

DEFINITION AND EPIDEMIOLOGY

Maintenance of blood pressure (BP) upon standing requires a complex interaction between baroreceptors, the sympathetic nervous system, and the cardiovascular system. Defective compensatory responses can result from cardiac dysfunction, reduced intravascular volume, excessive vasodilation, baroreceptor dysfunction, autonomic nervous system impairment, or as a result of medications.[8,9]

OH generally has been defined as a sustained reduction of systolic BP (SBP) of 20 mm Hg or diastolic BP (DBP) of 10 mm Hg within 3 minutes of standing from a supine or seated position, or a tilt table head-up tilt of ≥60 degrees.[10] The authors do not suggest that tilt table testing be performed routinely; rather, OH should be a straightforward clinical diagnosis. Tilt testing could produce significant false positive results because the support of lower extremity musculature critical for maintaining normotension in the erect posture is eliminated during tilt table testing.

OH sometimes is comorbid with postural orthostatic tachycardia syndrome (POTS). POTS, which also causes lightheadedness or fainting as the primary symptom, is a condition in which an excessively reduced volume of blood returns to the heart when moving from the supine to the standing position. POTS is accompanied by a rapid increase in heart rate of ≥30 beats per minute (bpm). Most people who experience POTS are women between the ages of 15 and 50 years.[11]

Neurogenic OH (NOH), a commonly overlooked subtype of OH, is associated with nervous system impairment, and is predominantly seen in neurodegenerative disorders such as PD, multiple system atrophy (MSA), and pure autonomic failure (PAF).[10] NOH also might accompany peripheral and autonomic neuropathies associated with diabetes, amyloidosis, and immune-mediated neuropathies.[12] In primary or secondary diseases of the autonomic nervous system, NOH often is accompanied by supine hypertension. The prevalence of NOH is approximately 50% among patients with PD, and approximately 33% among those with diabetes, amyloidosis, or spinal cord injury.[1,13,14] Fortunately, only a portion of these patients are symptomatic at the time of OH diagnosis.

Patients at increased risk for OH should be screened even in the absence of symptoms; this includes those with PD, MSA, PAF, dementia with Lewy bodies, and peripheral neuropathies associated with autonomic dysfunction (eg, diabetes, amyloidosis, HIV). Patients with an unexplained fall or syncopal episode, elderly patients (age >70 years), and those on multiple medications that affect intravascular volume, vascular tone, sympathetic activity, or cardiac function also warrant screening.[15]

DIAGNOSIS

Typical OH symptoms, which occur when standing, less frequently when sitting, and abate when lying down, include dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache. Less common symptoms include syncope, dyspnea, chest pain, and neck and shoulder "coat hanger" pain.[16,17] Heat exposure, large or carbohydrate-dense meals, alcohol, dehydration, and medications with potential for vasodilation, volume depletion, bradycardia, or sympatholytic medications (eg, antihypertensives, tricyclic antidepressants, diuretics, dopaminergic anti-parkinsonian agents, and phosphodiesterase inhibitors) could exacerbate OH symptoms.[10,13,16] Nocturnal diuresis results in peak symptoms in the morning.[12,17] Among patients with autonomic dysfunction, supine hypertension commonly co-exists with NOH, and might exaggerate this overnight diuresis.[16]

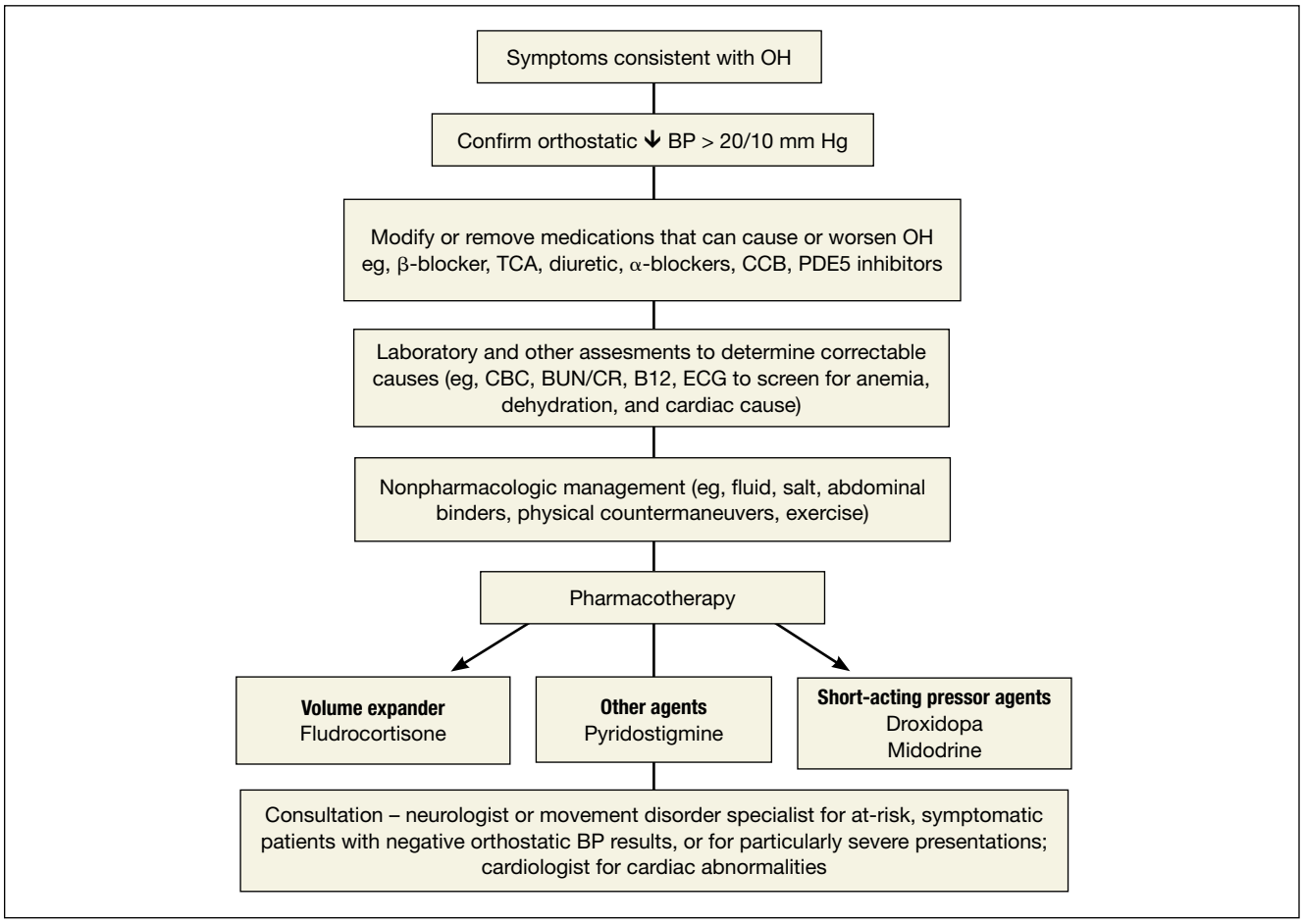
The diagnosis of OH requires measuring BP in both the supine and upright positions.[10] To establish a baseline, BP and heart rate are measured after 5 minutes of rest in the supine or seated position. Ideally, standing BP and heart rate are measured at 30 seconds, 60 seconds, 2 minutes, and 3 minutes; however, for practicality, some experts advocate using the 3-minute reading as the primary discriminator.[13] In situations where a supine to standing diagnostic assessment cannot be performed easily, a sit-to-stand procedure could be used.[18] Patients sit for at least 5 minutes and then stand for 3 minutes, with BP measured just before standing and at 1 and 3 minutes upon standing.[15] One investigation showed a decrease in SBP >15 mm Hg or DBP >7 mm Hg to yield the highest sensitivity and specificity for the diagnosis of OH.[18] Note that these criteria differ slightly from the criteria included in the definition of OH.

An increase in heart rate >15 bpm within 3 minutes of standing is consistent with non-neurogenic OH (eg, volume depletion).[15] An increase in heart rate <15 bpm on standing is suggestive of NOH caused by reduced sympathetic response.[15,17] Medications that impede an appropriate heart rate response and cardiac arrhythmias must be taken into account.

If standard orthostatic BP testing (including extended at-home BP monitoring or 24-hour ambulatory monitoring) does not reveal OH in an at-risk individual with unexplained postural symptoms, referral to a movement disorder specialist is necessary.[15] Presence of a potential cardiac etiology warrants referral to a cardiologist.[19]

History and physical examination are key to differentiating between NOH and non-neurogenic OH. Laboratory,

FIGURE **Diagnostic and treatment algorithm for orthostatic hypotension**[1,8,12,15]



Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CCB, calcium channel blocker; ECG: electrocardiogram; OH, orthostatic hypotension; PDE5, phosphodiesterase inhibitor; SCR, serum creatinine; TCA, tricyclic antidepressant.

elecrocardiogram, and imaging assessments further aid in ruling out non-neurogenic causes such as dehydration, acute blood loss, cardiovascular disorders (eg, constrictive pericarditis, cardiomyopathy, aortic stenosis), endocrine disorders (eg, adrenal insufficiency, diabetes), and excessive vasodilatation (eg, systemic mastocytosis, carcinoid syndrome) (**FIGURE**).[1,8,12,15] Patients should be queried about exacerbating factors that suggest an autonomic cause, eg, prolonged standing, cardiovascular exercise, heat exposure, alcohol, morning time, or large meals.[16] Laboratory evaluations could include basic metabolic panel, complete blood count, morning cortisol level, vitamin B12, folic acid (peripheral neuropathy), and fasting plasma glucose or glycated hemoglobin.[15,20]

TREATMENT

There is insufficient evidence to support intervention for asymptomatic OH. The goal of treatment in symptomatic OH is not to normalize standing BP, but rather to alleviate symptoms, prevent falls, and improve standing time to allow for activities of daily living. Additionally, in patients with NOH, the goal is to minimize comorbid supine hypertension.[21] Management of OH addresses modifiable contributing factors (eg, medications, dehydration, anemia), and employs nonpharmacologic strategies, and, if necessary, pharmacologic treatment (**FIGURE**).[1,8,12,15] Because orthostatic stress varies with circumstances during the day, a patient-oriented approach that emphasizes education and nonpharmacologic strategies to minimize orthostatic stress is vital.[9]

Nonpharmacologic strategies

Patients should be counseled to avoid situations that could exacerbate symptoms associated with OH such as prolonged or motionless standing, alcohol, large or carbohydrate-dense meals, physical activity sufficient to cause muscle vasodilation,

TABLE **Nonpharmacologic interventions for treating orthostatic hypotension**[1,9,12,16,17,21-27]

Intervention	Specific Instructions	Comments
Dietary counseling and recommendations	2 to 2.5 liters of fluid/d 10 g/d sodium intake (1-2 teaspoons of added salt to a healthy diet; 0.5-1 g salt tablets) Avoid diuretics, including coffee Avoid high glycemic index meals/beverages	Clear urine provides patient with a visual target for maintaining adequate hydration Benefits of salt loading can be seen as early as 3 days after initiation 24-hour urinary sodium excretion ≥170 mmoL and 24-hour urine output of 1.5 liters are indicative of adequate salt loading and plasma volume
Water bolus	Drink 500 mL of water over 3 to 4 minutes	Raises SBP ≥20 mm Hg within 5-15 minutes; peaks at 20-30 minutes; lasts for 1-2 hours Anticipatory management (eg, prolonged standing, hot weather, preprandial, upon awakening)
Physical counter-maneuvers and exercise	Perform physical counter-maneuvers, eg, crossing legs, trunk bending, squatting, knee flexing, toe raises, tensing muscles (contract a group of muscles bilaterally for 30 seconds, relax, and then repeat) Gradual staged movements with postural changes Elevate head of the bed 6-9 inches Avoid daytime recumbency Avoid Valsalva maneuvers Isotonic exercises	Counter-maneuvers can be done to attenuate OH symptoms at onset Rise gradually from lying to sitting to standing, especially in the morning when orthostatic tolerance is lower or after meals or straining with defecation Exercise in a recumbent or seated position or in a pool to attenuate exercise-induced hypotension, which accompanies deconditioned states
Compression garments	Abdominal binder and/or custom-fitted thigh or waist high compression stockings	Splanchnic-mesenteric venous bed compression reduces venous pooling and drop in SBP after postural changes Should be tight enough to exert gentle pressure Place before rising from bed in the morning, and take off when lying supine May use as needed during times of orthostatic stress More effective than lower extremity compression Might be difficult for patients to put on, uncomfortable, and cosmetically unapealing

Abbreviations: OH, orthostatic hypotension; SBP, systolic blood pressure.

heat exposure (eg, hot weather, hot bath), sudden postural changes, and Valsalva maneuvers.[9,17]

Evidence-based nonpharmacologic strategies can be employed to expand blood volume (increased fluid and salt intake), decrease nocturnal diuresis (raise the head of the bed), decrease venous pooling (abdominal binder, physical counter maneuvers [see online video demonstration at: https://www.youtube.com/watch?v=1Lq0AN9AJoA&t=352s]), or induce a pressor response (water bolus intake).[9] These strategies, and the evidence supporting them, are further detailed in the **TABLE**.[1,9,12,16,17,21-27]

Pharmacologic strategies

Pharmacologic intervention is indicated when nonpharmacologic strategies and lifestyle modification do not sufficiently resolve OH symptoms. Pharmacologic strategies aim to expand intravascular volume (fludrocortisone) or increase peripheral vascular resistance with the pressor agents midodrine or droxidopa.[17] Because of the prevalence of supine hypertension among patients with OH (up to 50%), slow titration and frequent monitoring is advised.[12,16] Home BP monitoring is recommended for several days after starting or changing therapy.[15]

Fludrocortisone

Fludrocortisone, a synthetic mineralocorticoid, is an aldosterone receptor agonist. It increases plasma volume by increasing renal sodium and water reabsorption and improves vascular alpha-adrenoreceptor sensitivity to circulating catecholamines. Fludrocortisone monotherapy

could be considered for patients who do not adequately raise plasma volume with fluid and salt supplementation. Fludrocortisone may also be added to midodrine in patients with persistent OH symptoms.[9,12]

The initial dose of fludrocortisone is 0.1 mg/d, which can be titrated to 0.2 mg/d. Daily dosages >0.2 mg rarely are more effective and amplify side effects.[17] A weight gain of 3 to 5 pounds and mild dependent edema is indicative of adequate plasma volume expansion.[9,19] The onset of action typically is 3 to 7 days, but may require up to 2 weeks.[15,17] Because hypokalemia can develop in nearly 50% of patients and hypomagnesemia in 5%, electrolyte monitoring is required, and patients should be counseled to increase dietary potassium. Other common adverse events include supine hypertension, nausea, peripheral edema, and headache.[1,16]

Midodrine

Midodrine is a peripherally selective alpha-1-adrenoreceptor agonist that constricts arteriolar and venous vasculature resulting in supine, sitting, and standing SBP and DBP increases.[17] Double-blind multicenter placebo-controlled trials have shown midodrine to increase standing BP and improve OH symptoms.[28,29] In dose-response trials, midodrine, 10 mg, compared with placebo produced an average 1-minute standing SBP increase at 1 hour of 15 mm Hg.[30] This drug is approved for treating symptomatic OH.[30]

Midodrine is dosed in 4-hour intervals 3 times a day; eg, shortly before or upon arising in the morning, midday, and late afternoon before 6 PM. Dosages are titrated to clinical response or maximum daily dosage of 30 mg. The evening dose should be taken 3 to 4 hours before bedtime because of risk of supine hypertension in up to 25% of patients.[19] The medication should be discontinued in patients who do not have significant symptomatic improvement.[13,16] Midodrine can be used as monotherapy or in combination with fludrocortisone or, in low dosages, with pyridostigmine.[19,31] Adverse events include urinary urgency or retention (6%), piloerection (13%), pruritus/tingling (mostly of scalp; 9% to 10%), and chills (5%).[19]

Droxidopa

Droxidopa is a prodrug converted to norepinephrine in the central nervous system and peripheral tissues, including sympathetic peripheral nerve endings. Droxidopa is approved for treatment of symptomatic NOH caused by primary autonomic failure (PD, MSA, PAF), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.[32] Droxidopa is only available through specialty pharmacies and requires that the prescriber submits a treatment form indicating primary diagnosis, symptomatic condition, treatment history, and patient clinical notes.[33]

An integrated efficacy analysis of 3 clinical trials comparing droxidopa with placebo in patients with a primary neurodegenerative disease and symptomatic NOH (N=460) showed significant reduction in most NOH symptom scores: Orthostatic Hypotension Questionnaire composite score, dizziness/lightheadedness, visual disturbances, weakness, and fatigue.[34] Droxidopa also significantly improved 3 of 4 patient-oriented measures and significantly increased upright SBP (11.5 ± 20.5 vs 4.8 ± 21.0 mm Hg; $P<.001$) and DBP (8.0 ± 15.55 vs 1.8 ± 17.3 mm Hg; $P<.001$).[34] A lower incidence of falls was observed in the droxidopa group.[34]

The starting dosage of droxidopa is 100 mg three times daily, titrated by 100 mg three times daily to a maximum dosage of 600 mg three times daily. The last daily dose should be at least 3 hours before bedtime and the head of bed should be elevated to minimize supine hypertension.[32] The rates of supine hypertension (SBP >180 mm Hg) in clinical trials were ≤7.9% with droxidopa vs ≤4.6% with placebo.[34] Adverse effects include hypertension, headache, dizziness, and nausea.[14]

Pyridostigmine

Pyridostigmine, an acetylcholinesterase inhibitor that potentiates neurotransmission in autonomic ganglia, amplifies sympathetic activation in response to orthostatic stress. Pyridostigmine has been used off-label as monotherapy in patients with mild symptoms, and as an adjunct to low-dose midodrine (2.5 mg once or twice daily).[15,31] In a double-blind, 4-way crossover study in patients with NOH (n=58), pyridostigmine, 60 mg either alone or with 2.5 mg, or midodrine, 5 mg, produced smaller reductions in standing DBP vs placebo with no effect on supine SBP or DBP.[31] Because pyridostigmine is not associated with worsening supine hypertension, it could be considered when supine hypertension becomes problematic.[31] The starting dosage of pyridostigmine is 30 mg two or three times daily, and can be increased to 60 mg three times daily.[9] Adverse effects include diaphoresis, hypersalivation, diarrhea, muscle cramping, and urinary incontinence.[15,16]

SPECIAL CONSIDERATIONS

Supine and nocturnal hypertension

Although most patients with essential hypertension experience BP elevation throughout the day and night—albeit to a lesser degree at night by 10% to 20%—patients with supine HTN experience HTN *only* at night. Although the potential long-term effects of supine HTN should not be minimized, it should be recognized that the risks of supine HTN remain uncertain with no clinical trials documenting benefit from treating supine HTN. The short-term risks associated with

NOH (ie, falls and hip fractures) could take precedence over the longer-term theoretical risks associated with supine HTN (ie, cerebrovascular and cardiovascular events).[35] Paradoxically, untreated supine HTN can worsen OH by causing pressure natriuresis and diuresis, resulting in volume depletion.[35] To minimize episodes of supine HTN, patients should avoid recumbency during the day, raise the head of the bed, and avoid fluids within 1 hour of bedtime.[13] If these measures are insufficient, a short-acting antihypertensive at bedtime could be considered (eg, angiotensin II receptor blocker, short-acting angiotensin-converting enzyme inhibitor, nifedipine, clonidine, or a nitrate patch [removed 1 hour before rising]).[13]

Postprandial hypotension

Among patients with autonomic dysfunction, 40% to 80% of patients also have postprandial hypotension.[36] This is commonly defined as a decline in SBP ≥20 mm Hg within 2 hours of consuming a meal or decline of SBP to <90 mm Hg when preprandial SBP is >100 mm Hg.[37] Large and carbohydrate-heavy meals induce splanchnic vasodilation and redistribution of blood flow to the digestive system.[16] Patients are advised to avoid carbohydrate-heavy meals, alcohol, and sudden standing or physical activity after a meal.[12] Treatment with the alpha-glucosidase inhibitor acarbose could be considered because it delays intestinal glucose absorption by inhibiting complex carbohydrate breakdown, thereby delaying release of vasodilatory gut hormones.[35,38]

SUMMARY

A fall of SBP ≥20 mm Hg or in DBP ≥10 mm Hg within 3 minutes of standing is diagnostic of OH. History and physical examination are key to differentiating between neurogenic and non-neurogenic OH. To achieve the primary goals of reducing symptoms and preventing falls, treatment of OH is directed at increasing blood volume, decreasing venous pooling, and increasing vasoconstriction. Reversible causes of OH (dehydration, hypotensive medications) should be investigated. Patient education and nonpharmacologic strategies alone can be effective in mild cases of OH. If symptoms persist, consider low-dosage fludrocortisone. Other pharmacologic options include droxidopa, pyridostigmine, or an α-adrenoreceptor agonist such as midodrine. For patients with NOH, worsening of supine HTN should be evaluated and proactively managed. Because OH can have devastating consequences for some patients, identifying persons at increased risk is imperative. Avoiding falls by successfully managing OH has the potential to reduce morbidity and mortality. ●

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