A Review of the Treatment of Primary Orthostatic Hypotension

Genevieve M. Hale, PharmD, BCPS¹, Jose Valdes, PharmD, BCPP¹, and Michael Brenner, PharmD, BCPS-AQ Cardiology²

Abstract

Objective: To review the efficacy and safety of pharmacological and nonpharmacological strategies used to treat primary orthostatic hypotension (OH). Data Sources: A literature review using PubMed and MEDLINE databases searching hypotension, non-pharmacological therapy, midodrine, droxidopa, pyridostigmine, fludrocortisone, atomoxetine, pseudoephedrine, and octreotide was performed. Study Selection and Data Extraction: Randomized or observational studies, cohorts, case series, or case reports written in English between January 1970 and November 2016 that assessed primary OH treatment in adult patients were evaluated. Data Synthesis: Based on the chosen criteria, it was found that OH patients make up approximately 15% of all syncope patients, predominantly as a result of cardiovascular or neurological insults, or offending medication. Nonpharmacological strategies are the primary treatment, such as discontinuing offending medications, switching medication administration to bedtime, avoiding large carbohydrate-rich meals, limiting alcohol, maintaining adequate hydration, adding salt to diet, and so on. If these fail, pharmacotherapy can help ameliorate symptoms, including midodrine, droxidopa, fludrocortisone, pyridostigmine, atomoxetine, sympathomimetic agents, and octreotide. Conclusions: Midodrine and droxidopa possess the most evidence with respect to increasing blood pressure and alleviating symptoms. Pyridostigmine and fludrocortisone can be used in patients who fail to respond to these agents. Emerging evidence with low-dose atomoxetine is promising, especially in those with central autonomic failure, and may prove to be a viable alternative treatment option. Data surrounding other therapies such as sympathomimetic agents or octreotide are minimal. Medication management of primary OH should be guided by patient-specific factors, such as tolerability, adverse effects, and drug-drug and drug-disease interactions.

Keywords
alternative medicine/therapies, cardiovascular drugs, cardiology, clinical practice, neurology, neuropharmacology

Introduction

Orthostatic hypotension (OH) is defined as a drop of ≥20 mm Hg or ≥10 mm Hg in systolic or diastolic blood pressure (BP), respectively, within 3 minutes of standing.¹ OH is manifested as a result of autonomic nervous system dysfunction, when cardiovascular adaptive mechanisms cannot compensate for reduced venous return on standing. It can be pathophysiologically classified into 2 categories: those with neurogenic (structural) causes or those with nonneurogenic (functional) causes.² Neurogenic OH (NOH) is a form of OH that arises because of the failure of the autonomic nervous system—either central autonomic failure (CAF) or peripheral autonomic failure (PAF)—to raise peripheral resistance in response to postural changes, a chief manifestation of chronic autonomic failure in primary neurodegenerative disorders.³ For the purposes of this review, nonneurogenic causes of OH are those that do not fit this definition. Most commonly, NOH affects patients with neurodegenerative diseases (particularly α-synuclein–related diseases), hypertension, or diabetes because of autonomic failure of compensatory mechanisms that help control BP. OH patients make up approximately 15% of all syncope patients. It is age dependent, affecting between 5% (<50 years of age) and 30% (>70 years of age) of patients, and disease state dependent, affecting up to 58% in specialized movement disorder clinics.²,⁴ Patients with OH may experience a constellation of symptoms caused by cerebral hypoperfusion, including, but not limited to, light-headedness, vision changes, weakness, cognitive impairment, dizziness, and syncope. Assessment of common symptoms related to cardiovascular

¹Nova Southeastern University College of Pharmacy, Palm Beach Gardens, FL, USA
²VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

Corresponding Author:
Genevieve M. Hale, Department of Pharmacy Practice, Nova Southeastern University College of Pharmacy, 11501 North Military Trail, Palm Beach Gardens, FL 33410, USA.
Email: Gh341@nova.edu
disorders should be completed. Orthostatic symptoms that occur after meals or on awakening could be related to venous pooling or postprandial hypotension. OH can occur in younger and middle-aged individuals, and prevalence increases with age. Additionally, those with renal failure or autoimmune diseases have been noted to have a higher prevalence than the general public. Appropriate treatment may reduce the increased risk of all-cause death, heart failure, and stroke associated with the presence of OH. Furthermore, if left untreated, this disease can be further complicated because OH leads to disabling symptoms, syncope/falls, and traumatic injuries and has been associated with an increase in all-cause mortality. Hence, to reduce long-term morbidity and mortality, optimal therapy is of utmost importance. The purpose of this article is to review the efficacy and safety of pharmacological and nonpharmacological strategies used to treat primary OH.

### Data Sources and Extraction

A literature review using PubMed and MEDLINE databases was performed. Gray literature was searched using search engines (ie, Google). Terms searched included hypotension, nonpharmacological therapy, midodrine, droxidopa, pyridostigmine, fludrocortisone, atomoxetine, pseudoephedrine, and octreotide. Eligible articles included those that were randomized or observational studies, cohorts, case series, or case reports that were written in English between January 1970 and November 2016 that assessed primary OH treatment in adult patients. Both pharmacological and nonpharmacological interventions were included. Letters to the editor were included if additional descriptive or historical information was needed but were not considered primary evidence for this review. Additionally, guidelines, review articles, and package inserts were referred to for information regarding pathophysiology, etiology, diagnosis, and pharmacology. All articles were read and evaluated by all 3 authors. The quality of each article was assessed based on relevance to the purpose of the study, with the exception of randomized controlled studies, which were given higher value of inclusion because of their innate strength of randomization and analysis. The interventions examined were derived from prior literature of OH and included the following: removing offending medications (see Table 1), transitioning administration times of medications; carbohydrate-rich meals, alcohol; hydration, water; salt, sodium chloride; abdominal binders, compression stockings; physical/counter maneuvers; water exercises, reclining exercises; canes, tripod chairs; bed tilt, elevating bed; midodrine; droxidopa; fludrocortisone; pyridostigmine; atomoxetine; pseudoephedrine, ephedrine; and octreotide. All 3 authors reviewed and analyzed any and all articles reviewed. Any discrepancies were resolved by consensus.

### Etiopathophysiology and Diagnosis

Typically, as an individual rises to an upright position from a supine position approximately 500 to 1000 mL of blood moves from the thoracic cavity and pools in the lower extremities while splanchnic blood flow increases (see Figure 1). This leads to a decrease in systolic and diastolic BP along with a decrease in venous return to the heart, reduced ventricular filling, and a transient decrease in cardiac output. When this occurs, compensatory mechanisms are elicited. These compensatory mechanisms cause activation of the sympathetic nervous system and deactivation of the parasympathetic nervous system to protect the individual from cardiovascular and neurological harm. In OH, autonomic failure from impairment of these compensatory mechanisms is present. OH has a higher association with elderly people because these individuals are more likely to experience decreased baroreceptor signaling associated with diastolic dysfunction and reduced stroke volume/venous return to the heart, bradycardia, increased vasodilation as a result of poor α, adrenergic response, and/or vagal withdrawal. The origin of this dysfunction can be traced to a variety of primary and/or secondary causes.

The etiology of primary OH includes Parkinson’s disease, multiple system atrophy, pure autonomic failure, Lewy body dementia, autoimmune autonomic gangliopathy, rare hereditary disorders (ie, familial dysautonomia), or idioopathic etiology. A stepwise approach should be taken when determining the cause of OH in a patient. After assessing for potential medications as an identifiable cause of orthostasis, volume status should be assessed because this is the most common cause of non-NONH. An examination focused on skin turgor, mucous membranes, and serum and urine analysis should be completed. If nonneurogenic causes are ruled out, neurogenic causes should be evaluated. Neurogenic

### Table 1. Common Medications That Induce Orthostatic Hypotension.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Blockers</td>
<td>Terazosin, doxazosin, prazosin, tamsulosin</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Diuretics (thiazide and loop), β-blockers, clonidine, long-acting calcium channel blockers</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Olanzapine, risperidone</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Rasagiline, selegiline</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Morphin</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Bromocriptine, levodopa</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>Sildenafil, vardenafil</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, nortriptyline</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Hydralazine, nitrates</td>
</tr>
</tbody>
</table>
causes of OH are associated with a variety of neurological disorders, such as Parkinson’s disease, and can be identified by reviewing patient history and performing a thorough physical examination. Diagnostic testing is warranted on the presentation of clinical symptoms, such as unexplained syncope or dizziness/unsteadiness on standing, and encouraged as well in all patients ≥70 years of age because up to one-third of older patients may have non–symptomatic OH (SOH). An electrocardiogram, orthostatic BP checks, and general laboratory testing, including a basic metabolic panel with blood glucose level and complete blood count, to rule out any metabolic, renal, or hematological causes are required. An accurate past medical history with particular interest in diseases that may lead to autonomic dysfunction (see Table 2) as well as detailed medication list of prescription and over-the-counter drugs and comprehensive physical exam should guide the clinician in choosing the appropriate cardiac and neurological tests to rule out causes of clinical symptoms. A patient’s history and physical exam alone can identify a potential cause in approximately 40% of patients with syncope. A tilt-table test may be performed when the clinical scenario is suggestive of OH. Electroencephalograms, carotid Doppler recordings, or magnetic resonance imaging/
Table 2. Classifications of OH.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Nonneurogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Autonomic failure\textsuperscript{b}</td>
<td>• Cardiovascular\textsuperscript{c}</td>
</tr>
<tr>
<td>• Brain-stem lesion/tumors\textsuperscript{c}</td>
<td>(aortic stenosis, HF, myocardial infarction, myocarditis, pericarditis, tachyarrhythmias)</td>
</tr>
<tr>
<td>• Carotid sinus hypersensitivity\textsuperscript{d}</td>
<td>• Reduced intravascular volume\textsuperscript{d} (bleeding, burns, dehydration, diabetes insipidus, diarrhea, salt-losing nephropathy, vomiting)</td>
</tr>
<tr>
<td>• Cerebral vascular accidents\textsuperscript{e}</td>
<td>• Venous pooling\textsuperscript{d} (alcohol consumption, fever, heat, prolonged recumbency or standing, sepsis)</td>
</tr>
<tr>
<td>• Dopamine β-hydroxylase deficiency\textsuperscript{b}</td>
<td>• Medications\textsuperscript{d} (see Table 1)</td>
</tr>
<tr>
<td>• Multiple sclerosis\textsuperscript{b}</td>
<td>• Peripheral nervous system\textsuperscript{c}</td>
</tr>
<tr>
<td>• Multiple system atrophy\textsuperscript{b}</td>
<td>• (HIV/AIDS, amyloidosis, diabetes mellitus, Guillain-Barré syndrome, renal failure, vitamin B12 or folate deficiency)</td>
</tr>
<tr>
<td>• Neurocardiogenic syncope\textsuperscript{b}</td>
<td>• Spinal cord\textsuperscript{d} (syringomyelia, tabes dorsalis, tumors, transverse myelitis)</td>
</tr>
<tr>
<td>• Parkinson’s disease\textsuperscript{b}</td>
<td>• Syringobulbia\textsuperscript{d}</td>
</tr>
</tbody>
</table>

Abbreviations: HF, heart failure; OF, orthostatic hypotension.\textsuperscript{a}Adapted from references 1 and 2.\textsuperscript{b}Primary cause of OH.\textsuperscript{c}Secondary cause of OH.

computed tomography should be restricted to patients having suffered a head injury from a fall or believed to have had a seizure, or if there is a new localizing neurological symptom on physical examination.\textsuperscript{14} Even after extensive evaluation, it has been noted that up to one-third of patients may not have an identifiable cause.\textsuperscript{15}

Nonpharmacological Therapy

Nonpharmacological measures are considered first-line therapy in OH.\textsuperscript{6-14} Initially, discontinuing offending medications (see Table 1), switching to a different medication in the same class with a lower incidence of OH (ie, α-blockers or β-blockers [mixed to selective]), or transitioning administration times of medications to bedtime should be taken into consideration. Additionally, dietary strategies such as avoiding large carbohydrate-rich meals, limiting alcohol, maintaining adequate hydration at 2 to 2.5 L of fluid daily, and adding salt (6 to 10 g of sodium chloride, cautiously) daily can help increase BP.\textsuperscript{14}

Jordan et al\textsuperscript{16} reported that an intake of approximately 16 ounces (480 mL) of water in several minutes can induce a sympathetic reflex, increasing BP as a result of hypotonicity and relieving symptomatic individuals with pure autonomic failure or multiple atrophy transiently. This sympathetic activation was demonstrated by increases in plasma norepinephrine concentration 30 minutes after water drinking as well as reduction of the pressor effect of drinking when adrenoreceptor blockade with phentolamine is present.\textsuperscript{16} However, Senard et al\textsuperscript{17} did not find the same benefit in patients with SOH and Parkinson’s disease, suggesting that the previous evidence may have been a result of gastric distension.\textsuperscript{17} Other studies have shown vasoconstriction on the radial artery transiently but no effect on BP overall, adding to the argument of another mechanism such as gastric repletion or systemic osmotic changes.\textsuperscript{18} The investigators in favor of water therapy stated that the latter study may have enrolled patients with milder autonomic impairment, enrolled patients on antiparkinsonian therapies that can exacerbate OH, and/or the pressor response may have been missed because the study only compared responses at 60 minutes rather than approximately 30 minutes following water ingestion; this effect was shown to clear after 60 minutes in the original study.\textsuperscript{16} Through microneurography in the peroneal nerve in the leg to assess the simultaneous effect on vascular resistance by venous occlusion plethysmography, another study in healthy Caucasians showed that vasoconstrictor nerve impulses increased significantly 20 minutes after water ingestion, reaching a peak at 30 minutes, and normalizing at 50 minutes.\textsuperscript{19} Additionally, a significant increase in calf vascular resistance at 20 minutes and peak at 40 minutes was shown, normalizing within 1 hour. Although mean arterial BP did not change, increases in central sympathetic vasoconstrictor nerve discharge was demonstrated, proving that this mechanism is normal, although transient, after water ingestion, and seems a reasonable possible mechanism in autonomic failure.\textsuperscript{19} Finally, commentaries by Mathias and colleagues reviewed the evidence surrounding the “water cure” and called into question the composition of the tap water used in these studies because the pressor effects might have been a result of chemicals or electrolytes in the water (studies using distilled water have shown a pressor response in patients with pure autonomic failure), temporal sequence of events, and the sensitivity of techniques used to measure the changes in intravascular volume.\textsuperscript{20,21} In conclusion, the precise mechanism of pressor effects caused by ingestion of water is still to be elucidated and may not have a substantial effect on all patients with OH.

Abdominal binders or compression stockings to reduce venous blood pooling, especially in the splanchnic circulation, have also proven to be useful.\textsuperscript{22,24} Engaging in physical maneuvers has been shown to reduce the orthostatic difference between the heart and brain, compress the splanchnic vessels by increasing abdominal pressure, and avoid presyncopeal symptoms by raising BP and alleviating symptoms. Activities such as standing with legs crossed; squatting; isometric exercises; toe raises or thigh, buttock, and calf muscle contractions; and bending over at the waist can be performed to alleviate symptoms.\textsuperscript{25,29} The use of canes and tripod chairs are also important in elderly individuals and in moderate to severe cases of OH.\textsuperscript{30} All patients
with OH should be instructed to rise slowly from supine or sitting to upright positions. Sitting or lying down can help alleviate symptoms. It is suggested that patients sleep with the head of the bed elevated, and they should be advised to rise slowly by sitting on the edge of the bed for some minutes after waking while performing thigh, buttock, or calf contractions as noted above. Exercise can be performed as tolerated. In particular, water exercises or reclining exercises are preferred to improve venous return. Referring patients to a hypotension specialist or physical or occupational therapy program for further instructions on exercise techniques should be considered. As clinicians, it is important to educate and train the patient and his/her caregiver on these strategies. Single or multiple nonpharmacological strategies can be utilized in any order. The choice and length of nonpharmacological therapy is dependent on patients’ disease severity, willingness, ability to perform these strategies, and presence of comorbid conditions. For example, it would not be wise to increase fluid or sodium intake in patients with heart failure. Most patients with mild disease are adequately controlled with nonpharmacological therapy, whereas in moderate or severe disease, pharmacological therapy is used in combination with nonpharmacological strategies.

**Pharmacological Therapy**

Evidence surrounding the pharmacotherapeutic options for OH is limited. The 2006 and 2011 European Federation of Neurological Society guidelines provide recommendations that will be discussed throughout this review. In 2013, the American Society of Hypertension released a position paper regarding the treatment of OH. Table 3 provides a summary of the literature discussed for each agent. Before initiating pharmacotherapy, management should initially consist of education, advice, and training on various factors that influence BP. When pharmacotherapy is utilized, the clinician must consider the risk of supine hypertension caused by medications used and/or disease state.

**Standard Therapy**

When nonpharmacological treatment options are insufficient to alleviate symptoms, the use of pharmacological treatments is justified. The most common pharmacological treatment options used in patients with OH are midodrine, droxidopa, pyridostigmine, and fludrocortisone (Table 4). Midodrine is an α1-agonist and one of the few drugs for OH with evidence based on placebo-controlled trials. In a recent review evaluating 5 randomized placebo-controlled trials for treating SOH, results showed symptom improvement in the midodrine arm; however, confidence was low ($I^2 = 73\%$) because of a moderate risk of bias, imprecision, and indirectness, leading the authors to conclude that midodrine might have a positive impact on clinical outcomes with low/moderate quality of evidence. Dosed initially at 2.5 to 5 mg twice a day to 3 times a day and titrated, as tolerated, up to a maximum dose of 30 mg daily, midodrine was the first medication approved by the Food and Drug Administration (FDA) for the treatment of SOH. The peak onset of midodrine occurs within 1 hour, and effects can last up to 4 hours. The most common adverse effects are pilomotor reactions, chills, and gastrointestinal discomfort. In addition, the most frequent adverse effects leading to discontinuation are supine hypertension, pilomotor reactions, and urinary problems. As such, patients with acute renal failure, severe organic heart disease, pheochromocytoma, thyrotoxicosis, preexisting persistent excessive supine hypertension, or urinary retention should avoid the use of midodrine, and dosing should not be administered within 4 hours of bedtime or after an evening meal. It is recommended to use with caution in patients with hepatic disease; however, specific dosage adjustments are not available. Additionally, midodrine may interact with drugs that enhance (eg, sympathomimetic agents) or diminish (eg, sympatholytic agents) its vasopressor effect as well as concomitant exposure to salt-retaining steroids, which may increase hypertensive effects (especially in the supine position), and cardiac glycosides, β-blockers, or calcium channel blockers (especially nondihydropyridine agents), which may cause or worsen bradycardia, arrhythmia, or atrioventricular block.

Droxidopa, a synthetic norepinephrine prodrug, was the second medication to be approved by the FDA for the treatment of NOH specifically caused by primary autonomic failure, dopamine β-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Dosed initially at 100 mg 3 times a day (in the morning, midday, and in the late afternoon, 3 or more hours prior to bedtime), one can titrate in increments of 100 mg 3 times a day every 24 to 48 hours based on patient response up to a maximum dose of 600 mg 3 times a day. Studies show that droxidopa has been effective in the treatment of NOH in patients with Parkinson’s disease, multiple system atrophy, dopamine β-hydroxylase deficiency, pure autonomic failure, and non-diabetic autonomic neuropathy. One recent meta-analysis investigated the safety and efficacy of droxidopa in NOH and found significant effectiveness for short-term management of symptoms, leading to class I evidence for its use. Efficacy of droxidopa was significantly reduced after 1 week when comparing the OH questionnaire (OHQ) composite score and standing systolic BP. However, after 8 weeks, OHQ item 1 (symptoms of dizziness/lightheadedness), OHQ composite score, and standing systolic BP did not significantly favor droxidopa compared with placebo, concluding that the available evidence is insufficient to show a significant effect of droxidopa for long-term use. Moreover, the FDA released a statement that the effectiveness of droxidopa has not been determined beyond 2
## Table 3. Pharmacotherapy Recommendations for Orthostatic Hypotension.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>Comparators</th>
<th>n</th>
<th>Significant Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elgebaly et al35</td>
<td>Meta-analysis</td>
<td>Droxidopa versus placebo</td>
<td>485</td>
<td>With SNOH OHQ composite score (P = 0.004), dizziness/lightheadedness score (P = 0.008), symptom impact composite score (P = 0.0007), and standing SBP (P = 0.03) were favored from baseline to end point. Efficacy analysis after 2 weeks did not favor droxidopa over placebo for effect size of change in dizziness/lightheadedness and standing SBP. Efficacy analysis after 8 weeks on SBP did not favor d Roxidopa over placebo in OHQ composite score, dizziness/lightheadedness, and standing SBP</td>
</tr>
<tr>
<td>Schoffer et al36</td>
<td>Randomized, double-blind crossover placebo</td>
<td>Midodrine versus placebo</td>
<td>593</td>
<td>SOH or recurrent reflex syncopal</td>
</tr>
<tr>
<td>Campbell et al36</td>
<td>Randomized, double-blind crossover placebo</td>
<td>Fludrocortisone 0.1 mg versus placebo</td>
<td>5</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Elgebaly et al37</td>
<td>Randomized, double-blind crossover placebo</td>
<td>Fludrocortisone 0.1 mg versus placebo</td>
<td>13</td>
<td>SOH</td>
</tr>
<tr>
<td>Singer et al38</td>
<td>Randomized, double-blind crossover placebo</td>
<td>Pyridostigmine 60 mg versus midodrine 5 mg versus placebo</td>
<td>58</td>
<td>NOH</td>
</tr>
<tr>
<td><strong>Emerging therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shibao et al39</td>
<td>Randomized, placebo-controlled</td>
<td>Atomoxetine 18 mg versus placebo</td>
<td>21</td>
<td>Increase in seated and standing SBP mean difference from baseline of 54 mm Hg and 45 mm Hg (P = 0.004 and P = 0.016, respectively)</td>
</tr>
<tr>
<td>Ramirez et al40</td>
<td>Randomized, single-blinded, controlled</td>
<td>Atomoxetine 18 mg versus midodrine 5-10 mg</td>
<td>65</td>
<td>Increase in upright systolic BP mean difference of 7.5 mm Hg (P = 0.03)</td>
</tr>
<tr>
<td>Jordan et al41</td>
<td>Observational</td>
<td>Phenytoin 12.5 and 25 mg, yohimbine 5.4 mg, indomethacin 50 mg, ibuprofen 600 mg, caffeine 250 mg, or methylphenidate 5 mg versus placebo</td>
<td>35</td>
<td>With severe OH resulting from multiple system atrophy or pure autonomic failure</td>
</tr>
<tr>
<td>Hoeldtke et al42</td>
<td>Observational</td>
<td>Octreotide 0.5 µg/kg versus midodrine 5 mg, Octreotide 0.5 µg/kg versus midodrine 5 mg + octreotide 0.5 µg/kg, Midodrine 5 mg versus octreotide 0.5 µg/kg + midodrine 5 mg, Octreotide 0.5 µg/kg + midodrine 5 mg versus placebo</td>
<td>16</td>
<td>With autonomic neuropathy and chronic OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviations: DBP, diastolic blood pressure; NOH, neurogenic orthostatic hypotension; OH, orthostatic hypotension; OHQ, orthostatic hypotension questionnaire; SBP, systolic blood pressure; SNOH, symptomatic neurogenic orthostatic hypotension; SOH, symptomatic orthostatic hypotension.</td>
<td></td>
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<tr>
<td>*Results are in favor of treatment therapy unless specified.</td>
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</tr>
<tr>
<td>*Domperidone, phenytoin, yohimbine are not sold in the United States.</td>
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</table>
weeks. Of note, reported adverse effects (ie, headache, hypertension, and supine hypertension) did not differ significantly between droxidopa and placebo groups. Droxidopa may exacerbate symptoms in patients with heart failure, arrhythmias, and ischemic heart disease and may cause supine hypertension. Additionally, postmarketing surveillance has reported hyperpyrexia and confusion resembling neuroleptic malignant syndrome, suggesting careful observation when dosages of droxidopa are changed or when concomitant levodopa is abruptly reduced or discontinued. Whereas this effect may be best explained as being caused by a sudden reduction in dopaminergic drive as a result of the abrupt discontinuation of levodopa, 1 case report describes a patient with multiple system atrophy without parkinsonism who developed fever following droxidopa administration, possibly because of a central pyrogenic effect via the noradrenergic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Droxidopa</td>
<td>α-/β-Adrenergic agonist</td>
<td>Synthetic amino acid analog metabolized directly to norepinephrine by dopadecarboxylase, inducing peripheral arterial and venous vasoconstriction</td>
<td>100 mg orally 3 times daily then uptitrated every 24 to 48 hours as needed (maximum dose: 1800 mg daily)</td>
<td>None</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Corticosteroid</td>
<td>Expanding volume intravascularly through increasing sodium reabsorption from the distal tubules; enhances the sensitivity of α-adrenoreceptors</td>
<td>0.1 mg orally daily, then uptitrated per week as needed to 0.3 mg daily (maximum dose: 1 mg daily)</td>
<td>None. Doses above 0.3 mg daily may cause unwanted adverse effects</td>
</tr>
<tr>
<td>Midodrine</td>
<td>α-Adrenergic agonist</td>
<td>Increases arteriolar and venous tone via vasoconstriction, increasing standing, sitting, and supine systolic/diastolic blood pressure</td>
<td>10 mg orally 3 times daily during daytime hours</td>
<td>Use with caution in patients with renal impairment. Recommended starting dose is 2.5 mg</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Prevents the metabolism of acetylcholine and increases tone via action on the nicotinic receptor</td>
<td>60 mg orally 3 times daily</td>
<td>Lower initial doses may be required in patients with renal disease, specific recommendations are not available</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Selective norepinephrine reuptake inhibitor</td>
<td>Selectively inhibits the reuptake of norepinephrine with little to no activity at the other neuronal reuptake pumps or receptor sites</td>
<td>18 mg orally daily</td>
<td>Moderate hepatic impairment (Child-Pugh class B): doses should be reduced to 50%. Severe hepatic impairment (Child-Pugh class C): doses should be reduced to 25%</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Somatostatin analog</td>
<td>Mimics natural somatostatin by inhibiting serotonin release and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. Decreases growth hormone and IGF-I in acromegaly. Octreotide provides more potent inhibition of growth hormone, glucagon, and insulin as compared with endogenous somatostatin. It also suppresses LH response to GnRH, secretion of thyroid-stimulating hormone and decreases splanchnic blood flow.</td>
<td>12.5 to 25 µg orally daily</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: IGF, insulin-like growth factor; VIP, vasoactive intestinal peptide; LH, luteinizing hormone; GnRH, gonadotrophin-releasing hormone.

*Not Food and Drug Administration–approved for indication of orthostatic hypotension.
system. Caution is advised when prescribing droxidopa concomitantly with other medications that may increase norepinephrine because the combination may have a synergistic effect along with sympathomimetic agents, α-agonists, and α₂-agonists.

Fludrocortisone, a mineralocorticoid, works by expanding volume intravascularly through increasing sodium reabsorption from the distal tubules and additionally enhancing the sensitivity of α-adrenoreceptors. Dosed initially at 0.1 to 0.3 mg daily and titrated up 0.1 mg weekly to a maximum dose of 1 mg daily, fludrocortisone has been shown to improve both standing and supine BP in patients with diabetes mellitus and in patients with Parkinson’s disease. Though clinical trials provide little evidence for the use of fludrocortisone in NOH, with the exception of Parkinson’s disease, it is often recommended as first-line treatment.

One study of 5 diabetic patients with SOH found significantly higher average systolic BP compared with placebo when preforming a tilt-table test and a significant reduction in postural BP fall compared with placebo. Another study showed a nonsignificant drop in maximal BP at 3 minutes of standing with fludrocortisone 0.1 mg and domperidone 10 mg compared with baseline. Adverse effects that may be seen with this agent include hypokalemia, weight gain, supine hypertension, pedal edema, and glucocorticoid effects. Fludrocortisone should be avoided in patients with heart failure, kidney failure, and hypertension. With regard to BP effects and OH symptoms in 65 patients receiving atomoxetine (from 81 ± 65 pg/mL at baseline to 78 ± 72 pg/mL). This study showed the effectiveness of low-dose atomoxetine in individuals with OH because it may worsen these conditions.

Furthermore, atropine interacts with pyridostigmine by antagonizing its muscarinic effects, which is useful when reversing pyridostigmine toxicity.

Emerging Therapy Options

Over the past decade, emerging therapies have been studied to evaluate possible secondary pharmacological options in patients with OH, including atomoxetine, sympathomimetic agents, and octreotide.

Atomoxetine, a selective norepinephrine reuptake inhibitor, is an agent whose place in therapy for OH has recently been explored in individuals with CAF and PAF. Given the mechanism of atomoxetine, increases in BP by elevating norepinephrine concentration in peripheral sympathetic neurons have been observed in patients with OH. Interestingly, this is not shown in healthy patients. Shibao et al investigated this observation in a randomized, crossover, placebo-controlled study of 21 patients with CAF and PAF receiving atomoxetine 18 mg. After measuring BP, heart rate, and plasma catecholamines (ie, norepinephrine) at baseline and 60 minutes after drug intake, it was found that atomoxetine significantly and acutely increased seated and standing systolic BP in patients with CAF by a mean of 54 mm Hg and 45 mm Hg, respectively, as compared with placebo. Furthermore, at the end of the observation period, the mean seated systolic BP increased to a mean of 149 mm Hg in the atomoxetine group, which was in the hypertensive range between 113 to 209 mm Hg. However, the same effect was not shown in patients with PAF because seated and standing systolic BPs were increased a mean of 4 and 0.6 mm Hg, respectively, with atomoxetine as compared with placebo. With regard to catecholamines, plasma norepinephrine levels showed a nonsignificant increased trend in patients with CAF after receiving atomoxetine (from 317 ± 143 pg/mL at baseline to 430 ± 83 pg/mL). In contrast, plasma norepinephrine levels were unchanged in patients with PAF after receiving atomoxetine (from 81 ± 65 pg/mL at baseline to 78 ± 72 pg/mL). This study showed the effectiveness of low-dose atomoxetine in individuals with OH and that caution should be used in patients with minimal autonomic dysfunction. Of note, depending on the severity of OH symptoms prior to atomoxetine initiation, symptoms may not completely resolve, but frequency of symptoms may decrease.

Case reports have also shown similar results.

In a randomized controlled trial by Ramirez et al, atomoxetine 18 mg and midodrine 5 to 10 mg were compared in regard to BP effects and OH symptoms in 65 patients with severe autonomic dysfunction (pure autonomic failure, multiple systems atrophy, or Parkinson’s disease). Of note, this study did not perform a subgroup analysis based on patient diagnosis in which the precise subtype of primary autonomic failure (ie, CAF or PAF) was determined. No differences between groups were found when looking at
seated systolic BP. However, it is important to note that atomoxetine produced a significantly greater upright systolic BP (mean difference of 7.5 mm Hg) compared with midodrine. Symptoms of OH were also significantly improved with the atomoxetine group compared with placebo, but this was not shown with midodrine when compared with placebo. This study suggested that atomoxetine is a viable and possibly superior treatment option in OH compared with the current mainstay of therapy. 

Although a low dose of atomoxetine may be beneficial in OH, clinicians should discuss the possible adverse effects with patients before initiation, including suicidal ideation, depression, aggressive behavior, priapism, and urination retention. Of note, suicidal ideation has been reported in children and adolescents, and reports of this adverse event are lacking in the adult population. Liver function tests should be administered at initiation and follow-up because hepatotoxicity can occur. Finally, this agent should be avoided in patients with serious structural cardiac or heart rate abnormalities or cardiomyopathy because sudden death, stroke, and myocardial infarction have been reported with atomoxetine use in these populations.

Sympathomimetic agents, such as phenylpropanolamine and pseudoephedrine, have been tested as another alternative option in OH in small observational studies. Jordan et al investigated 35 patients with severe OH caused by multiple system atrophy or pure autonomic failure in a single-blinded study to analyze the effect on seated systolic BP when given either placebo, phenylpropanolamine 12.5 and 25 mg, yohimbine 5.4 mg, indomethacin 50 mg, ibuprofen 600 mg, caffeine 250 mg, or methylphenidate 5 mg. In addition, investigators performed a subgroup analysis of patients receiving midodrine 5 mg in comparison to those receiving phenylpropanolamine 12.5 mg. When compared with placebo, seated and standing BPs were significantly increased when receiving phenylpropanolamine, indomethacin, and yohimbine. No significant difference was seen with ibuprofen, caffeine, and methylphenidate use compared with placebo. Furthermore, subanalysis revealed similar increases in systolic BP when midodrine and phenylpropanolamine were evaluated. This study demonstrated that phenylpropanolamine is as effective as standard therapy and Α-adrenergic agonists (as well as yohimbine or indomethacin) produce desirable effects in patients with OH caused by primary autonomic dysfunction. However, it is important to note that the effects of the midodrine control arm may have been subtherapeutic because the recommended dose of midodrine for the treatment of OH is 10 mg 3 times daily. Case reports have revealed similar findings with pseudoephedrine use in OH caused by idiopathic autonomic failure. Common adverse effects of sympathomimetic agents include confusion, headache, dizziness, nausea, palpitations, chest tightness, tremor, and in rare cases, ischemic colitis. Sympathomimetic agents should be used with caution in patients with open angle glaucoma, coronary artery disease, heart failure, prostatic hypertrophy, hyperthyroidism, and urinary retention. Concomitant use with monoamine oxidase inhibitors is contraindicated.

Octreotide is a somatostatin analogue, which promotes vasoconstriction, and has been evaluated in several small clinical studies in patients with OH caused by this mechanistic effect. Alam et al evaluated 24 ambulatory BP readings of 18 patients with idiopathic autonomic dysfunction caused by sympathetic denervation, who were receiving 1 µg/kg twice daily. Systolic and diastolic BPs rose a mean of 5 and 2 mm Hg, respectively, when octreotide was administered. A reduction in postural, postpostural, and exertion-induced hypotension and symptoms was observed. Mean decreases in nocturnal systolic and diastolic BPs of 10 and 6 mm Hg, respectively, were also found. This nocturnal decrease in BP is important to note because patients with OH typically have low BP on waking, and symptoms may worsen with this effect.

Hoeldtke et al compared the effects of octreotide 0.5 µg/kg and midodrine 5 mg with each other and in combination in 16 patients. Midodrine and octreotide alone did not produce significant increases in standing systolic BP. However, combination therapy showed a significant increase compared with no treatment and octreotide alone. Patients receiving octreotide and suffering from multiple system atrophy, postural tachycardia syndrome, diabetic autonomic neuropathy, and OH have been assessed, and analogous increases in BP with a decrease in OH symptoms have been demonstrated. Again, it is important to note the dose of midodrine utilized in this study is below the recommended dose in OH.

Octreotide 12.5 to 25 µg subcutaneous injections are most commonly used in clinical practice. The development of gallstones or biliary sludging, gastrointestinal discomfort, dysglycemia, and hypothyroidism are adverse effects that may occur with octreotide use. Sinus bradycardia, conduction abnormalities, and arrhythmias have been reported in acromegalic patients on long-term therapy.

Besides the treatment options aforementioned, other therapies have yet to be elucidated, such as estrogen or estrogen-like therapy. It has been proposed that these agents can modify the response of cardiovascular parameters to stressful situations and reduce the vascular effects of isometric muscle contraction, indirectly decreasing the activation of sympathetic vasoconstriction in smooth muscle cells of the arterial walls in postmenopausal and premenopausal women. As these and other emerging therapies arise, it would behoove clinicians to review the quality of evidence and compare these agents with more common treatment options.

**Summary/Concluding Remarks**

Management of OH should center on reducing symptoms and treating any contributing insult. The first steps of
treatment are removal of offending agents (see Table 1) and initiation of nonpharmacological strategies, such as increasing water and salt intake, use of compression stockings or abdominal binders, physical maneuvers, or sleeping with the head of the bed elevated. These strategies can be performed in any order alone or in combination in patients with mild symptoms. Evidence surrounding optimal pharmacological therapy is limited to small randomized controlled and observational studies, and case reports. Nevertheless, drug therapy options for patients with moderate to severe disease include midodrine, droxidopa, fludrocortisone, and pyridostigmine. If OH remains uncontrolled after trying out these therapeutic options as monotherapy or combination therapy, emerging agents such as atomoxetine can be considered. With respect to pharmacotherapeutic considerations, appropriate selection of medications based on adverse effects, monitoring parameters, and concomitant drug and disease interactions is paramount. Ensuring patient safety should be the highest priority for treatment of OH.

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