Published in final edited form as:

Curr Hypertens Rep. 2013 August ; 15(4): 304–312. doi:10.1007/s11906-013-0362-3.

Current Concepts in Orthostatic Hypotension Management

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Abstract

Orthostatic hypotension is a condition commonly affecting the elderly and is often accompanied by disabling presyncopal symptoms, syncope and impaired quality of life. The pathophysiology of orthostatic hypotension is linked to abnormal blood pressure regulatory mechanisms and autonomic insufficiency. As part of its diagnostic evaluation, a comprehensive history and medical examination focused on detecting symptoms and physical findings of autonomic neuropathy should be performed. In individuals with substantial falls in blood pressure upon standing, autonomic function tests are recommended to detect impairment of autonomic reflexes. Treatment should always follow a stepwise approach with initial use of nonpharmacologic interventions including avoidance of hypotensive medications, high-salt diet and physical counter maneuvers. If these measures are not sufficient, medications such as fludrocortisone and midodrine can be added. The goals of treatment are to improve symptoms and to make the patient as ambulatory as possible instead of targeting arbitrary blood pressure values.

Keywords

Orthostatic hypotension; Elderly; Midodrine; Fludrocortisone; Autonomic insufficiency; Autonomic failure; Neurogenic orthostatic hypotension; Hypertension

Introduction

The assumption of upright posture depends on rapid cardiovascular adaptations driven primarily by the autonomic nervous system. In healthy individuals, standing activates afferent autonomic neural pathways to induce baroreceptor unloading, and subsequent increases in efferent sympathetic outflow and vasoconstriction, to increase venous return and maintain resting blood pressure [1]. Impairment of these compensatory mechanisms can result in orthostatic hypotension (OH), defined as a reduction in systolic blood pressure ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg within three minutes of standing or head-up tilt to an angle of at least 60° [2]. The prevalence of OH increases with age, and underlying causes include medications (α -blockers, diuretics, tricyclic antidepressants), systemic diseases involving peripheral autonomic nerves (diabetes mellitus, amyloidosis), and in rare cases primary neurodegenerative disorders (Parkinson's disease, pure autonomic failure, multiple systems atrophy) [3]. OH is often accompanied by presyncopal symptoms and syncope, leading to impaired quality of life. Even in asymptomatic patients, OH is an independent risk factor for falls, cardiovascular events and all-cause mortality [4–9]. Given the increasing aging population worldwide, it is important to identify underlying mechanisms and optimal treatment strategies for this condition. This review will describe

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Conflict of Interest: A.C. Arnold and C. Shibao declare that they have no conflict of interest.

advances in understanding the pathophysiology and comorbidities of OH, with a focus on approaches for management of these patients.

Epidemiology of Orthostatic Hypotension

OH is a relatively common finding in the general population. In middle-aged adults, the prevalence of OH is approximately 5 % in community based studies [6–8]. In community dwellers older than 65 years, the prevalence of OH is 16.2 % [10], and increases exponentially with age affecting most commonly men [11;12]. Conditions such as Parkinson's disease and diabetes mellitus are commonly associated with orthostatic hypotension. In Parkinson's patients, the prevalence of orthostatic hypotension varies considerably, ranging between 14 and 58 % in specialized movement disorder clinics [13–15] to 47 % in community-based populations [16]. Importantly, patients with Parkinson's disease and concomitant OH are more likely to be on hypotension-inducing medications including levodopa. The only available population based study in patients with diabetes mellitus reported that the prevalence of OH was 8.4 % and 7.4 % in type I and type II patients, respectively [17].

A recent cross-sectional study provides evidence that OH is relatively common among hospitalized elderly in the United States with an overall annual rate of 36 per 100,000 adults. In these patients, the prevalence of OH increased exponentially with age, and was consistently higher in males [18]. The burden of OH also increases dramatically among elderly in nursing homes and geriatric wards affecting up to 54 % and 68 % of patients, respectively [19;20]. This high prevalence likely reflects increased risk factors for OH in these settings including neurodegenerative diseases, multiple comorbidities and vasoactive medications. Importantly, OH is an independent risk factor for cardiovascular morbidity and mortality from stroke [8], coronary heart disease [6], and chronic kidney disease [9]. The presence of OH also increases risk for falls and all-cause mortality in both middle-aged and elderly individuals [4–7;21]. Overall, these epidemiologic findings demonstrate the emergent need to identify and manage this condition, particularly in the elderly.

Pathophysiology of Orthostatic Hypotension

Normal physiological changes during upright posture

Under normal conditions, the assumption of upright posture does not result in major changes in blood pressure due to the integration of complex autonomic, circulatory and neurohumoral responses [1]. Standing produces pooling of approximately 700 mL of blood in the lower extremities, pulmonary and splanchnic circulations, as well as translocation of fluid from intravascular to interstitial spaces [22]. This shift in blood compartmentalization attenuates venous return to the heart and ventricular filling, to transiently reduce stroke volume. As a result, there is unloading of the arterial baroreceptors to enhance sympathetic outflow and subsequently increase systemic vascular resistance, venous return and cardiac output. This compensatory response results in a small decrease in systolic blood pressure (5–10 mmHg), a similar magnitude increase in diastolic blood pressure, and an increase in heart rate (10–25 bpm). Other mechanisms evoked in response to standing include activation of the renin-angiotensin aldosterone system, local axon reflex, venoarteriolar reflex and myogenic response.

Causes of Orthostatic Hypotension

In the majority of cases, orthostatic hypotension is caused by multiple factors. As shown in Table 1, commonly prescribed medications such as tricyclic antidepressants, α_1 -blockers to treat prostate hyperplasia in males, antiparkinsonian drugs and antihypertensives such as diuretics, sympatholytics and vasodilators can induce or exacerbate OH [23;24]. In addition,

OH can result from any disease or condition that produces deficits in hemodynamic responses including inadequate intravascular volume to support ventricular filling, excessive decreases in cardiac output or venous return, or failure of the skeletal muscle pump to increase venous return to the heart. The elderly are particularly prone to develop OH due to age-related physiologic changes such as decreases in baroreflex sensitivity and overall parasympathetic tone, impairment of α_1 -adrenergic vasoconstriction, and reductions in cardiac and venous compliance that affect their ability to compensate for the normal orthostatic fluid shift [25;26]. Elderly patients also have reductions in thirst perception and the ability to conserve salt and water during periods of restriction which increases risk for dehydration and decreases blood volume to contribute to OH.

Alternatively, autonomic neuropathy can contribute to OH by affecting the normal vasoconstrictor and neurohumoral responses to support standing blood pressure (Table 1). These conditions can result from a primary autonomic disorder or secondary to a systemic illness that produces autonomic neuropathy such as diabetes mellitus or certain paraneoplastic disorders (small cell lung cancer, monoclonal gammopathies, light chain disease or amyloidosis). Primary forms of autonomic failure are rare neurodegenerative disorders associated with cellular lesions involving protein inclusions rich in α -synuclein. The two main types of this disease are defined by the origin of these cellular lesions. In multiple systems atrophy (MSA), protein inclusions are localized to the cytoplasm of glial cells in the striatonigral system to produce parkinsonian features, in olivopontocerebellar structures to produce truncal ataxia, or in brainstem regions involved in autonomic regulation [27]. In contrast, patients with pure autonomic failure (PAF) have protein inclusions that form Lewy bodies in peripheral postganglionic fibers [28]. The pathophysiological characteristics of the Lewy bodies are identical to Parkinson's disease; however, PAF is not associated with movement disorders. The clinical picture of primary autonomic failure is dominated by severe OH and disabling symptoms of cerebral hypoperfusion, in which severely affected patients can only stand for a few seconds. These patients also have absence of arterial baroreceptor reflexes, and as a result do not appropriately increase heart rate in response to standing [29].

For patients presenting with acute or subacute onset of autonomic failure, other diagnoses should be considered including autoimmune autonomic ganglionopathy (AAG) and paraneoplastic syndrome. In AAG, the autoimmune neuropathy is characterized by antibodies directed against nicotinic (N_N) acetylcholine receptors in autonomic ganglia, resulting in OH and severe autonomic dysfunction [30]. Interestingly, recent studies identified autoantibodies to vascular α_2 -adrenergic and M3-muscarinic receptors in symptomatic OH suggesting that idiopathic OH may also have an immune component in some patients. Furthermore, these studies provided preliminary in vitro evidence for a functional role of these antibodies in vasodilation [31;32]. These findings may provide a new target for treatment of OH; however, further studies are needed to determine the precise role and specificity of these autoantibodies.

Genetic Association Studies in Orthostatic Hypotension

Several small population based studies have identified potential genetic associations with idiopathic OH. Polymorphisms of the G-protein related genes *GNAS1* and *GNB3*, which influence cardiovascular sympathetic tone and reactivity, were associated with OH in a cohort of Japanese residents [33]. Furthermore, genetic variants of *NEDD4L*, a neural precursor gene involved in regulation of sodium absorption in the distal nephron, have been linked to OH [34;35]. A recent consortium study showed a generally weak association of polymorphisms of genes involved in blood pressure regulation with OH in subjects of European ancestry [36]. However, there was a significant association of OH in this study

with a region near the early B-cell factor 1 (EBF1) gene locus, an area previously linked to Sjögren's syndrome.

In primary forms of autonomic failure such as MSA, candidate gene studies have identified variants of the α -synuclein gene SNCA, the M129V polymorphism of the prion protein (PRNP) gene, and genes involved in oxidative stress and inflammation in these patients [37;38]. These initial studies provide promising directions for further research to genetic underpinnings of autonomic failure, as well as OH in general, but many of these studies included small sample sizes and need to be validated in larger independent cohorts. Finally, in rare cases patients may present with an autosomal recessive genetic disorder secondary to deficiency in dopamine β -hydroxylase, the enzyme required for conversion of dopamine to norepinephrine. This disorder is characterized by selective sympathetic noradrenergic and adrenomedullary failure with intact parasympathetic and sympathetic cholinergic function [39]. Common symptoms include severe OH, ptosis and nasal stuffiness, and the biochemical phenotype includes minimal or absent plasma norepinephrine and epinephrine with elevated plasma dopamine levels. Droxidopa (L-DOPS), an oral synthetic norepinephrine precursor, is used for pharmacologic management of OH and associated symptoms in these patients.

Evaluation of Orthostatic Hypotension

Orthostatic vital signs should be obtained in any patient with history of syncope or presyncopal symptoms. Typical symptoms of cerebral hypoperfusion include lightheadedness, dizziness, blurred vision, fatigue, headache, cognitive impairment and dull pain in the neck and shoulders which are all relieved by recumbence. The definition of orthostatic hypotension involves measurement of blood pressure and heart rate while supine for at least 5 minutes and then again after standing for 1 and 3 minutes. An alternative in routine clinical practice would be to measure both seated and standing blood pressures. While this approach is better than no measurement, up to two-thirds of patients with OH may be undetected if supine blood pressure is not assessed [40]. Orthostatic symptoms are often worse in the morning suggesting diurnal variability. Therefore, it is important to instruct patients to keep a blood pressure diary with orthostatic blood pressure measurements taken over several days and at various different time points to increase the sensitivity for detection of OH. Some patients may also present with delayed OH, observed after 3 minutes of standing, perhaps representing a mild or early form of sympathetic failure [41]. In patients unable to tolerate standing or in those with suspicion of OH despite normal vital signs, head-up tilt table testing to an angle at least 60 ° should be considered [42]. Furthermore, in contrast to diagnostic practice for neurally mediated syncope, pharmacologic challenge with either sublingual nitrate or intravenous isoproterenol is not recommended during tilt table testing in OH due to increased sensitivity to venodilators in these patients. Finally, ambulatory 24-hour blood pressure monitoring may also be useful to detect OH, if posture is routinely recorded.

Once the diagnosis of OH is established, patients should undergo an intensive medical history and physical examination. The goal of the initial examination is to identify secondary causes that may induce or worsen OH (Table 1). Autonomic symptoms should be documented including urinary retention, constipation, decreased sweating and erectile dysfunction, although these symptoms may be nonspecific in the elderly. Patients should be evaluated for diseases causing peripheral neuropathy such as amyloidosis (SPEP, UPEP and fat pad biopsy), malignancy (paraneoplastic antibody panel), diabetes mellitus (oral glucose tolerance test) and Vitamin B deficiency (B12 levels). A neurological evaluation may also be useful to assess for early signs of motor disorders which could indicate Parkinson's disease or MSA. Finally, a profound postural decrease in blood pressure (>30 mm Hg)

without an adequate compensatory heart rate increase (<15 bpm) may suggest primary autonomic failure. In these cases, autonomic function tests are particularly helpful to confirm sympathetic and/or parasympathetic dysfunction by assessing arm cuff or continuous blood pressure and heart rate responses to sinus arrhythmia, Valsalva maneuver, isometric handgrip and cold pressor tests [43].

Treatment of Orthostatic Hypotension

A structured stepwise approach should be implemented for the management of OH, which may include both nonpharmacologic and pharmacologic interventions (Table 2). The goal of treatment in OH patients is to improve symptoms and functional status, rather than to improve blood pressure. Many of the following recommendations are based on small cross-sectional trials in well characterized patients with primary autonomic failure and severe OH. Thus, these findings do not necessarily clinically reflect to the more common problem of the elderly patient with idiopathic OH. Moreover, current treatment approaches for OH have not been adequately evaluated in large, randomized clinical trials and the efficacy of chronic therapy remains unclear [44].

Non-Pharmacologic Approaches

Nonpharmacologic approaches should be tried in every patient as first line of treatment (Table 2). First, medications that predispose to or exacerbate OH should be discontinued when appropriate. In patients with OH and comorbid hypertension, certain antihypertensives should be avoided, but treatment should generally not be discontinued (see special considerations). Second, patients should be educated on physical countermeasures to reduce gravitational blood pooling in the lower extremities, such as moving gradually from supine to standing positions, avoiding standing motionless, standing with legs crossed, squatting and active tensing of leg muscles. These simple maneuvers can provide instantaneous improvement in orthostatic symptoms and tolerance [45;46]. Devices to reduce venous pooling, such as custom-fitted thigh or waist-high compression stockings and abdominal binders, may also be useful when graded pressure of at least 30 to 40 mmHg is applied to the lower body [47;48]. However, these devices are difficult to put on and may be uncomfortable to wear, limiting patient compliance.

Finally, patients should be encouraged to employ approaches to improve central volume. Salt consumption can be increased to 6 to 9 g of sodium chloride per day (with 1 g sodium chloride tablets taken with each meal if needed). However, increasing salt intake alone is usually insufficient for treatment of OH, and fludrocortisone may need to be concurrently prescribed to promote sodium retention. Water intake can also be increased up to 2 to 3 liters per day, with rapid water ingestion (16 ounces in 3 to 4 minutes) used as a rescue measure to increase systolic blood pressure and relieve orthostatic symptoms [49]. The pressor effects of water peak at 30 minutes and can last for up to 2 hours, with effects mediated by activation of the sympathetic nervous system [50]. In patients with hypertension, sleeping with the head of the bed tilted up 6 to 9 inches can also prevent volume depletion by reducing nocturnal pressure natriuresis [51;52]. Overall, nonpharmacologic approaches are very cost-effective and have assumed an important role in the treatment strategy for patients with OH.

Pharmacologic Approaches

In patients with more severe forms of OH, pharmacologic interventions may be needed (Table 2). The first line of therapy for patients without baseline hypertension or heart failure is fludrocortisone (initiated at 0.1 mg/day and increased up to 0.3 mg/day), a potent synthetic mineralocorticoid that increases intravascular volume by promoting renal sodium

reabsorption [52;53]. The volume expansion effects of this drug revert within a few weeks, with long-term effects attributed to sensitization of the vasculature to norepinephrine and angiotensin II. Common adverse effects of fludrocortisone include hypokalemia, headache, heart failure and de novo or worsened supine hypertension.

In patients with supine hypertension or heart failure, it is preferable to use short-acting vasoconstrictor drugs that can be administered as needed prior to upright activities. The selective α_1 -adrenergic agonist midodrine is currently the only FDA-approved drug for the treatment of OH. Initiation of midodrine treatment should start with a single 2.5 mg dose and it can be increased up to 10 mg TID. Midodrine should be taken as needed 30 to 45 minutes before upright activity, and increases blood pressure for 2 to 3 hours. However, patients should avoid the seated or supine position after taking this medication, as well as focus on morning and early afternoon dosing, to avoid supine hypertension.

In patients with primary autonomic failure, an emerging pharmacologic strategy is the use of agents that harness residual sympathetic tone to increase blood pressure. In autonomic failure, the norepinephrine transporter inhibitor atomoxetine increases seated and standing blood pressure and improves orthostatic tolerance even when given in pediatric doses (18 mg). This drug increases synaptic norepinephrine levels to increase blood pressure, and is particularly effective in MSA patients due to the presence of residual sympathetic tone [54]. The α_2 -adrenergic antagonist yohimbine has also shown to increase seated and standing blood pressure and to reduce presyncopal symptoms in autonomic failure patients [55;56]. This drug acts by increasing central sympathetic outflow and norepinephrine release from postganglionic sympathetic neurons. Similar to atomoxetine, the pressor effects of yohimbine are magnified in MSA patients [56]. However, yohimbine is only available through compounding pharmacies. Sympathomimetic amines such as pseudoephedrine (30 mg) have also shown some efficacy in autonomic failure [57].

Another potential therapeutic agent for primary autonomic failure is the cholinesterase inhibitor pyridostigmine that facilitates cholinergic neurotransmission at the level of the autonomic ganglia. Pyridostigmine (60 mg) preferentially increases upright blood pressure and improves orthostatic symptoms without worsening supine hypertension [58]. The effect of this drug is relatively modest and may not be effective in patients with severe autonomic failure [56]. The somatostatin analogue octreotide (12.5–25 μ g, SC) is also very effective for the treatment of OH by constricting the splanchnic circulation to prevent venous pooling. Octreotide has comparable short-term efficacy as midodrine [59], but is limited by parenteral administration and side effects such as hyperglycemia, abdominal pain and diarrhea. In patients refractory to stand alone treatment, combination therapy can be considered. Low combined doses of midodrine and fludrocortisone may be effective to improve OH symptoms, but development of supine hypertension must be carefully monitored. Sympathomimetic agents such as midodrine and ephedra alkaloids also have an additive blood pressure effect when combined with a 480 mL water bolus [60]. Moreover, combination yohimbine and atomoxetine synergistically increases seated blood pressure, and improves standing time and symptoms, in peripheral autonomic failure patients [61].

Special Considerations for the Treatment of Orthostatic Hypotension

Orthostatic Hypotension and Postprandial Hypotension

An important comorbidity in patients with impaired autonomic reflexes is postprandial hypotension, defined as a fall in systolic blood pressure ≥ 20 mmHg within 2 hours after a meal [62;63]. The decrease in blood pressure usually initiates within 15 minutes of meal ingestion, peaks between 30 to 60 minutes, and lasts for up to 2 hours. Postprandial hypotension is accompanied by numerous symptoms, even in the seated position, including

dizziness and sleepiness and tends to occur simultaneously with OH which increases the risk of falls and syncope [64]. Patients with primary autonomic failure exhibit an exaggerated postprandial response, with an average decrease in systolic blood pressure of 50 mmHg [65]. The causes of postprandial hypotension are likely multifactorial, but include release of gastrointestinal and pancreatic peptides that promote vasodilation. In autonomic failure patients, the postprandial hypotension induced by either an oral glucose load or high carbohydrate breakfast is associated with exaggerated increases in pancreatic vasodilatory peptides (pancreatic polypeptide, neurotensin and enteroglucagon) [63]. Conversely, drugs that antagonize the release of these peptides such as octreotide and caffeine (adenosine antagonist) are effective for treatment of this condition [59;66]. The α -glucosidase inhibitor acarbose, which decreases glucose absorption in the small intestine, also attenuates postprandial falls in blood pressure when given 20 minutes prior to meals in PAF patients [67].

Elderly Hypertensive Patients

In patients with a history of essential hypertension, antihypertensive medications are often discontinued to prevent exacerbation of OH and reduce risk of falls, but this is a misguided approach. When considering individual classes, diuretics and peripheral vasodilators such as α -blockers may worsen OH [23; 24]. The association between nondihydropyridine calcium channel antagonists and OH is less certain, some studies show conflicting results [24]. In contrast, drugs blocking the renin-angiotensin system (ACE inhibitors and ARBs) and β -blockers with intrinsic sympathomimetic activity may be more appropriate in elderly patients to improve blood pressure regulation, given that these drugs do not appear to worsen or predispose to OH [68;70].

In elderly individuals up to 80 years of age, controlling blood pressure to levels less than 140/90 mmHg is associated with a decreased risk for cardiovascular morbidity and mortality. In addition, the incidence of OH and risk of falls is significantly greater in elderly with uncontrolled compared to controlled hypertension [68;69]. This protective effect may in part result from the ability of chronic antihypertensive therapy, particularly ACE inhibitors, to increase cerebral blood flow and carotid distensibility [70]. Furthermore, untreated hypertension often worsens OH by promoting nocturnal pressure natriuresis and diuresis. Thus, judicious use of antihypertensive agents is important in these patients, starting at low doses and with careful monitoring of OH and adverse events during gradual dose escalations.

Primary Autonomic Failure Patients with Supine Hypertension

At least 50 % of patients with primary autonomic failure also exhibit paradoxical supine hypertension, defined as systolic blood pressure $\geq$ 150 mmHg or diastolic blood pressure $\geq$ 90 mmHg [71]. However, the presence of supine hypertension often goes undetected as blood pressure is commonly only measured in the seated position. Supine hypertension limits the use of pressor agents, increases end organ damage and risk of acute cardiovascular events, and induces nocturnal natriuresis to worsen morning OH. Since the severity of supine hypertension is positively associated with the magnitude of OH [72], it has been suggested that a more appropriate definition for OH in these patients is a decrease in systolic blood pressure $\geq$ 30 mmHg [2]. During the daytime, the most effective approach to manage hypertension in autonomic failure is to avoid the supine position, especially when using compression devices or pressor agents for treatment of OH. In most patients, pharmacologic treatment is only needed during the night [73]. Automated 24-hour ambulatory monitoring is useful to guide treatment of supine hypertension, as blood pressure can dip to normal levels during the night in a significant proportion of these patients [74]. Conservative nonpharmacologic approaches for management of supine hypertension include ingestion of

a snack prior to bedtime to induce transient postprandial hypotension and raising the head of the bed by 6 to 9 inches during the night to lower blood pressure and reduce nocturnal pressure natriuresis. For patients with sustained hypertension, short-acting pharmacologic agents can be given at bedtime including transdermal nitroglycerin patch, sildenafil, nifedipine, clonidine and losartan [75–78]. All of these drugs have been shown to effectively lower supine blood pressure in autonomic failure patients in small clinical trials; however, none of these drugs improve morning orthostatic tolerance.

Conclusions

Orthostatic hypotension is a significant medical problem associated with substantial morbidity and mortality, particularly in the elderly. For early detection, any patient with presyncopal symptoms exacerbated by postural changes, a history of falls or syncope should undergo measurements of orthostatic vital signs during routine clinical visit. Patients with a substantial decrease in blood pressure upon standing (>30 mm Hg) associated with a poor compensatory heart rate response (<15 bpm) should be referred for autonomic testing for suspicion of autonomic failure. Treatment should follow a stepwise approach with non-pharmacologic interventions as first line therapy. If these measures prove inadequate, the next step should be the use of pharmacologic interventions with the selection of the starting agent depending on patient comorbidities. Fludrocortisone should not be used in patients with history of hypertension or heart failure. The overall goal of treatment should focus on improving symptoms and restoring functional capacity of the patient. With proper evaluation and treatment, the occurrence of syncope, falls and fracture can be significantly reduced.

Acknowledgments

C. Shibao was supported by American Heart Association Clinical Research Program grant 10CRP4310026, National Institutes of Health grant K23 HL103976–02, and PHRMA Foundation Career Development Award. A.C. Arnold was supported by American Heart Association Postdoctoral Fellowship Award 11POST7330010.

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Table 1**Acute and Chronic Causes of Orthostatic Hypotension****Acute OH**

Medications

- Tricyclic antidepressants, β_1 -blockers, antiparkinsonian, antihypertensives

Intravascular volume depletion

- Dehydration, vomiting, diarrhea, hemorrhage

Cardiovascular

- Myocardial infarction, congestive heart failure

Endocrine

- Adrenal insufficiency, hypoadosteronism

Chronic OH

Age-Related Physiologic Changes

- Decline in baroreflex sensitivity and parasympathetic function
- Impaired β_1 -adrenergic vasoconstriction
- Decreased cardiac and venous compliance
- Decreased thirst perception and inability to conserve salt and water

Autonomic Neuropathy

Primary Disorders

- Pure autonomic failure (PAF)
- Multiple systems atrophy (MSA)
- Parkinson's disease, Lewy body dementia

Secondary Disorders

- Diabetes mellitus (type 1 and type 2)
- Paraneoplastic disorders (amyloidosis, small cell lung cancer)
- Autoimmune autonomic ganglionopathy

Table 2**Approaches for Management of Orthostatic Hypotension****Nonpharmacologic Interventions**

Discontinue Medications that Exacerbate OH

- Tricyclic antidepressants, α_1 -blockers, diuretics

Physical Countermeasures to Decrease Venous Pooling

- Avoid getting up too quickly or standing motionless
- Stand with legs crossed
- Squatting and active tensing of leg muscles

Devices to Decrease Venous Pooling

- Waist-high compressor stockings (30 to 40 mmHg) or abdominal binders

Increase Central Volume

- Increase fluid and salt intake, raise head of bed by 6 to 9 inches during the night to prevent excessive elevation of blood pressure and pressure natriuresis

Pharmacologic Interventions:

Volume Expansion

- Fludrocortisone (0.1–0.3 mg/day, PO)

Vasoconstriction

- Midodrine (2.5–10 mg, PO)
- Atomoxetine (18 mg, PO)
- Yohimbine (5.4 mg, PO)
- Pyridostigmine (60 mg, PO)
- Octreotide (12.5–25 μ g, subcutaneous)
- Pseudoephedrine (30 mg, PO)

Combination Therapy

- Fludrocortisone (0.1–0.3 mg/day) and midodrine (5–10 mg)
- Midodrine (5–10 mg) or pseudoephedrine (30 mg) and water bolus (16 ounces)