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Orthostatic Hypotension in the Elderly: Diagnosis and Treatment

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ABSTRACT

Orthostatic hypotension is a common problem among elderly patients, associated with significant morbidity and mortality. While acute orthostatic hypotension is usually secondary to medication, fluid or blood loss, or adrenal insufficiency, chronic orthostatic hypotension is frequently due to altered blood pressure regulatory mechanisms and autonomic dysfunction. The diagnostic evaluation requires a comprehensive history including symptoms of autonomic nervous system dysfunction, careful blood pressure measurement at various times of the day and after meals or medications, and laboratory studies. Laboratory investigation and imaging studies should be based upon the initial findings with emphasis on excluding diagnoses of neurodegenerative diseases, amyloidosis, diabetes, anemia, and vitamin deficiency as the cause. Whereas asymptomatic patients usually need no treatment, those with symptoms often benefit from a stepped approach with initial nonpharmacological interventions, including avoidance of potentially hypotensive medications and use of physical counter maneuvers. If these measures prove inadequate and the patient remains persistently symptomatic, various pharmacotherapeutic agents can be added, including fludrocortisone, midodrine, and nonsteroidal anti-inflammatory drugs. The goals of treatment are to improve symptoms and to make the patient as ambulatory as possible rather then trying to achieve arbitrary blood pressure goals. With proper evaluation and management, the occurrence of adverse events, including falls, fracture, functional decline, and myocardial ischemia, can be significantly reduced.

KEYWORDS: Aging; Blood pressure; Elderly; Office practice; Orthostatic hypotension

In 1995, the American Academy of Neurology and the Joint Consensus Committee of the American Autonomic Society defined orthostatic hypotension as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of assuming an erect posture.[1] This definition does not account for a fall in blood pressure *after* 3 minutes or symptoms associated with smaller decreases in blood pressure upon standing. Hence, the significance of any decrease in blood pressure upon standing should be evaluated according to its association with symptoms of dizziness, presyncope, syncope, or falls.

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EPIDEMIOLOGY

Previous studies have revealed an increased prevalence of orthostatic hypotension with age. In community dwelling individuals >65 years of age, its prevalence is approximately 20%; in those >75 years of age it is as high as 30%. In frail elderly individuals living in nursing homes, the prevalence of orthostatic hypotension is even higher, up to 50% or more. An age-associated increase in supine blood pressure has been implicated as a major determinant of the development of orthostatic hypotension with aging.[2] Orthostatic hypotension also is associated with significant morbidity at older age. It has been linked to falls, fractures, transient ischemic attacks, syncope, and myocardial infarction. In addition, elderly people with orthostatic hypotension are more likely to be physically frail and thus to have decreased functional capacity, a factor that is often overlooked during the evaluation of older patients.

Table 1 Age-Related Changes that Can Affect Normal Blood Pressure Regulation

Decreased baroreflex sensitivity
Decreased α-1-adrenergic vasoconstrictor response to sympathetic stimuli
Decreased parasympathetic activity
Decreased renal salt and water conservation
Increased vascular stiffness
Reduced left ventricular diastolic filling

PATHOGENESIS

In healthy people, approximately 500 to 1000 milliliters of blood is transferred below the diaphragm upon assuming an erect posture.[3] This leads to decreased venous return to the heart, reduced ventricular filling, and a transient decrease in cardiac output and blood pressure. As a consequence, baroreceptors in the carotid arteries and aorta are activated, resulting in increased sympathetic outflow and decreased parasympathetic outflow from the central nervous system. This compensatory reflex restores cardiac output and blood pressure by increasing heart rate and vascular resistance.

Blood pressure varies directly with heart rate, stroke volume, and vascular resistance. Therefore, impairments in the response of any of these parameters during postural change may result in orthostatic hypotension. As shown in Table 1, aging is associated with a decrease in baroreflex sensitivity, which manifests as a diminished heart rate response and α-1-adrenegic vasoconstrictor response to sympathetic activation. Also, an age-related reduction in parasympathetic tone results in less cardioacceleration during the vagal withdrawal that normally occurs with standing. Due to reductions in renin, angiotensin, and aldosterone with aging, and an elevation in natriuretic peptides, the aged kidney loses some of its ability to conserve salt and water during periods of fluid restriction or volume loss, leading to rapid dehydration. In addition, the aged heart becomes stiff and non-compliant, resulting in impaired diastolic filling. This reduces stroke volume when preload is decreased due to standing or volume contraction.

Taken together, the reductions in baroreflex-mediated cardioacceleration and vasoconstriction, renal salt and water conservation, and cardiac filling greatly increase the risk of hypotension in the elderly. Severe, symptomatic orthostatic hypotension may develop in the face of any additional stress that lowers blood pressure or impairs the compensatory response, including certain medications, reduced intravascular volume, or other situations that reduce cardiac preload.

ETIOLOGY

Causes of orthostatic hypotension can be broadly divided into acute and chronic (Figure 1). Acute orthostatic hypotension most commonly develops over a relatively short period of time and is more often symptomatic at the outset. Generally, it results from acute conditions such as adrenal insufficiency, myocardial ischemia, medication administration, sepsis, or dehydration. In contrast, chronic orthostatic hypotension develops gradually over a prolonged period of

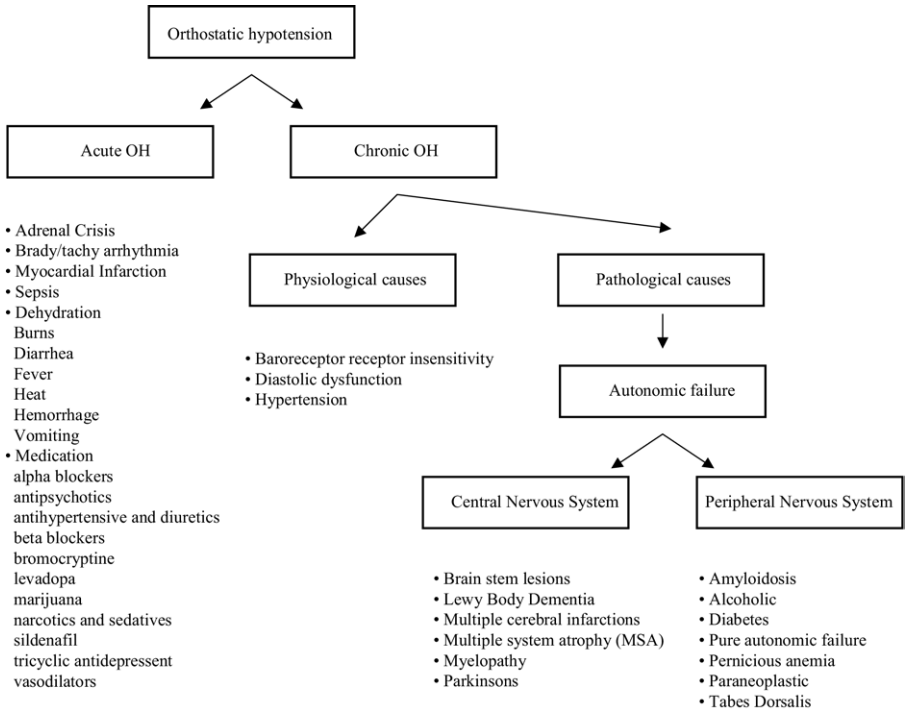

Figure 1 Etiology of orthostatic hypotension (OH).

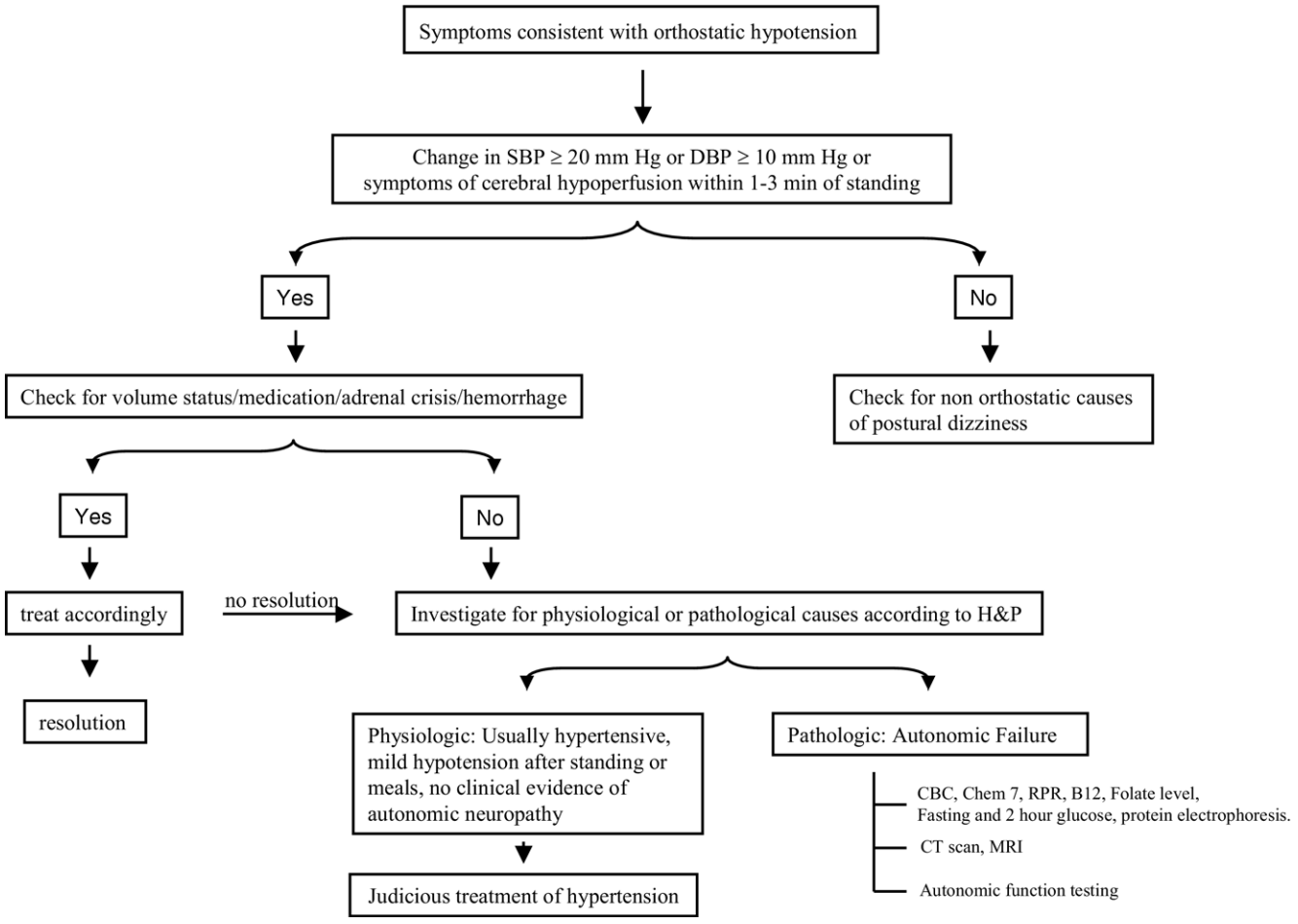

Figure 2 Approach to the evaluation of orthostatic hypotension. BMP = basic metabolic profile; CBC = complete blood count; CT = computerized tomography; H&P = history and physical examination; MRI = magnetic resonance imaging; RPR = rapid plasma reagin.

time and the patient is usually asymptomatic during the initial period. Chronic orthostatic hypotension can be due to either physiologic or pathologic causes. Physiologic causes are those attributable to the age-associated changes in blood pressure regulation described above, as well as the age-related increase in systolic blood pressure, which further impairs adaptive responses to hypotensive stresses. These physiologic changes predispose elderly people to symptomatic hypotension in the face of common everyday stresses, such as posture change, meals, new medications, fluid restriction, or any acute illness. Pathologic causes of chronic orthostatic hypotension are secondary to central or peripheral nervous system diseases that result in autonomic insufficiency (Figure 1).

CLINICAL FEATURES

Orthostatic hypotension may be symptomatic or asymptomatic. However, even in asymptomatic patients it remains a risk for future falls and syncope, and should therefore be minimized as much as possible. Common symptoms at all ages include dizziness, light headedness, weakness, syncope, nausea, paracervical pain, low back pain, angina pectoris, and transient ischemic attacks. In elderly people, disturbed speech, visual changes, falls, confusion, and impaired cognition are more commonly seen.[4] However, the predictive value of these symptoms in the elderly is poor, due to intake of multiple medications with various side effects and overlapping symptoms arising from comorbid conditions. Therefore, careful blood pressure measurements are of critical importance, even in patients with atypical symptoms.

EVALUATION

Our approach to the evaluation of orthostatic hypotension is shown in Figure 2. Initial evaluation should include measuring blood pressure and heart rate after the patient has been quietly supine for at least 5 minutes and again after 1 minute and 3 minutes of standing. Early morning measurements, especially after a high carbohydrate meal, are useful to identify postprandial hypotension. Although postprandial hypotension may occur concomitantly with orthostatic hypotension, it is a distinct entity that often occurs while sitting after a meal, and may actually resolve upon standing up and walking.[5] Detection of orthostatic hypotension may

Table 2 Additional Clinical Clues and Tests to Order

Clinical Presentation	Possible Etiology	Test to Order
Ecchymoses, purpura, macroglossia, numbness, paresthesias, pseudohypertrophy of muscle	Amyloidosis	Rectal biopsy
Diarrhea, vomiting, burns, fever	Volume depletion	Electrolytes, BUN, Creatinine
Gummas, unequal pupils (Argyll Robertson pupil) loss of position and vibration senses, history of sexually transmitted disease	Tabes dorsalis	RPR, VDRL
Early satiety, postprandial fullness, constipation, incontinence, exercise intolerance	Diabetic neuropathy	EKG for deep breath variability, GTT
Chest pain, palpitation, shortness of breath, pedal edema	Cardiogenic causes	EKG, echocardiogram
Reduced sweating, incontinence, constipation, posture difficulties, tremors, rigidity	Multiple system atrophy	Autonomic testing
Confusion, cerebellar symptoms, nystagmus, amnesia, confabulation, history of alcohol abuse	Alcoholic neuropathy	CBC, random alcohol level
Smooth beefy red tongue, lemon pallor, recent loss of mental capacity, paresthesias, ataxia	Pernicious anemia	CBC, cobalamin level, folate level

BUN = blood urea nitrogen; CBC = complete blood count; EKG = electrocardiogram; GTT = glucose tolerance test; RPR = rapid plasma reagin; VDRL = venereal disease research laboratory.

require multiple measurements on different days. This can be accomplished with ambulatory blood pressure monitoring, or by loaning the patient an automatic blood pressure monitor with instructions to maintain a diary with recordings of supine and standing blood pressure at different times of the day for several days. Measurements before breakfast, after medications, after meals, and before bed are most useful. Furthermore, the heart rate response to postural change can provide important clues to the etiology. Minimal cardio-acceleration ($<$10 beats per minute) on standing from a supine position in the presence of hypotension suggests baroreflex impairment, whereas tachycardia ($>$20 beats per minute) indicates volume depletion or orthostatic intolerance. Note, however, that lack of tachycardia also may occur in volume-depleted elderly patients due to baroreflex impairment.

Once the diagnosis of orthostatic hypotension is established, a detailed history should be obtained, focusing on medications (both prescription and nonprescription), volume losses (vomiting, diarrhea, fluid restriction), coexisting medical disorders, and autonomic dysfunction. A comprehensive physical examination should be performed, seeking clinical clues to possible underlying physiological and pathological disorders (Table 2). These include signs of amyloidosis, malignancy, and heart failure. A neurological evaluation should include a mental status examination (to identify neurodegenerative diseases such as Lewy Body Dementia), motor testing (Parkinson's disease or multiple strokes), sensory testing (peripheral neuropathy), and pupillary size (Horner's syndrome). Subsequent laboratory tests should be obtained based on the results of these assessments. These may include hemoglobin and hematocrit levels to evaluate for anemia; blood electrolytes, urea nitrogen, and creatinine to assess for dehydration; a rapid plasma reagin (RPR) test for syphilis; and a glucose tolerance test for diabetes. Brain imaging studies should be ordered if clinical suspicion points towards central nervous system pathology.

Autonomic function testing is helpful when the history and physical examination are equivocal, to evaluate the extent of autonomic involvement, and to monitor the course of an autonomic disorder and its response to therapy. Commonly used bedside studies to assess autonomic function are heart rate variation in response to deep breathing (respiratory sinus arrhythmia) and blood pressure response to the cold pressor test. Heart rate variation during deep breathing assesses the function of parasympathetic (vagal) efferents to the heart. Sinus arrhythmia is measured by electrocardiography with the patient lying supine during 1 minute of slow and deep breathing with 5 seconds inspiration and 7 seconds expiration. In healthy elderly people, the ratio of longest expiratory R-R interval to shortest inspiratory R-R interval is $>$1.15. Potential confounders that may reduce heart rate variability include medications (beta-blockers, calcium channel blockers, anticholinergic agents), advanced age, the patient's position (sitting vs. supine), and hypocapnia. The cold pressor test evaluates sympathetic innervation of the vasculature. After immersion of one hand in ice cold water at 4°C for 1 minute, a normal response is a systolic blood pressure elevation $\geq$15 mm Hg and diastolic elevation $\geq$10 mm Hg. Other tests that can be considered include plasma norepinephrine and vasopressin levels supine and upright to distinguish central from peripheral causes of autonomic failure. In central causes, supine norepinephrine is normal but fails to increase with postural change, and vasopressin is low. In peripheral causes, supine norepinephrine levels are low and vasopressin is normal. However, in practice the high variability of these levels undermines their utility.

MANAGEMENT

Due to the presence of multiple co-morbid conditions and nonspecific signs and symptoms, treatment of orthostatic

Table 3 Nonpharmacologic Treatment Options for Orthostatic Hypotension

Withdraw offending medication (either substitution or discontinuation)
Rise slowly from supine to sitting to standing position
Avoid straining, coughing, and prolonged standing in hot weather
Cross legs while standing
Squat, stooping forward
Raise head of bed 10 to 20 degrees
Small meals and coffee in the morning
Elastic waist high stocking
Increase salt and water intake
Exercise, eg, swimming, recumbent biking, and rowing

hypotension in the elderly is often challenging. Instead of aiming to achieve arbitrary blood pressure goals, the treatment of orthostatic hypotension should be directed toward ameliorating symptoms, correcting any underlying cause, improving the patient's functional status, and reducing the risk of complications. Broadly, interventions can be divided into nonpharmacological and pharmacological approaches.

Nonpharmacological Interventions

Generally it is best to start with nonpharmacological interventions and, if this fails, then proceed to drug therapy (Table 3). The first management step involves removing any medication that could precipitate orthostatic hypotension. Common offending drugs include nitrates, tricyclic antidepressants, neuroleptics, and alpha-blockers (often used for urinary frequency or retention). Orthostatic hypotension may develop when a patient begins taking an anti-hypertensive medication, but it may improve with continued use.[6] Therefore, it is imperative to start with a low dose and slowly titrate the dose upward. In patients with acute orthostatic hypotension due to dehydration, fluid replacement therapy should be initiated. Patients who have had prolonged bedrest or inactivity (eg, following hospitalization) should be instructed to stand up gradually to mitigate excessive pooling of blood in the lower extremities. Activities that decrease venous return to the heart, such as coughing, straining, and prolonged standing, should be avoided, particularly in hot weather. Dorsiflexion of the feet before assuming an upright posture may promote venous return to the heart, accelerate the heart rate, and increase blood pressure. Squatting and stooping forward can result in an increase in blood pressure. In patients who present with symptoms after prolonged standing, simply sitting down can often raise the blood pressure. Physical counter-maneuvers like crossing one's legs while standing and maintaining muscle contraction for 30 seconds can increase systemic venous return, thereby causing increased cardiac output and blood pressure. Waist high compression stockings and abdominal binders may be helpful. In patients with autonomic failure and supine hypertension, raising the head of the bed by 10 to 20 degrees at night can reduce hypertension, prevent overnight volume loss, and help restore morning blood pressure upon standing. Liberal intake of salt and water to achieve a 24-hour urine volume of 1.5 to 2 liters may attenuate fluid loss commonly seen in autonomic insufficiency. In elderly patients with orthostatic hypotension related to deconditioning, an exercise regimen comprising swimming, recumbent biking, or rowing might lead to disappearance of symptoms.

Pharmacological Interventions

Numerous pharmacological agents are available if the patient remains symptomatic despite the above measures (Table 4). One of the most potent agents is fludrocortisone, a synthetic mineralocorticoid, which has a principal mode of action of reducing salt loss and expanding blood volume.[7] The initial dose is 0.1 mg per day with increments of 0.1 mg every week until there is development of trace pedal edema or the maximum dose of 1 mg per day is reached. Common side effects include hypokalemia, supine hypertension, heart failure, and headache. Elderly patients should be monitored for fluid overload and hypokalemia. In patients taking higher doses, potassium supplements are usually required.

If the patient remains symptomatic, midodrine, an alpha-agonist with selective vasopressor properties, is often effective.[8] The starting dose is 2.5 mg 3 times per day, and the dose should be titrated upwards in 2.5-mg increments at weekly intervals until a maximum of 10 mg 3 times per day

Table 4 Selected Pharmacologic Agents for Orthostatic Hypotension

Drug	Dose	Contraindication	Common Side Effects
Fludrocortisone	Initial: 0.1 mg daily Max.: 1 mg daily	Hypersensitivity	Supine hypertension, hypokalemia, HF, headache
Midodrine	Initial: 2.5 mg tid Max.: 10 mg tid	Severe OHD, urinary retention, thyrotoxicosis, acute renal failure	Supine hypertension, piloerection, pruritus, paresthesia
Ibuprofen	400-800 mg tid	Hypersensitivity to NSAIDs, active bleeding, impaired renal function	GI intolerance, bleeding, headache, dizziness, renal insufficiency
Caffeine	100-250 mg daily	Hypersensitivity	GI irritation, insomnia, agitation, nervousness
Erythropoietin	25-75 U/Kg tiw	Uncontrolled hypertension	Stroke, myocardial infarction, hypertension

GI = gastrointestinal; HF = heart failure; NSAIDs = non-steroidal anti-inflammatory drugs; OHD = organic heart disease.

Table 5 Indications for Referral to a Specialist

Indications for referral to a geriatrician
Multiple comorbid conditions
Failure of standard therapy to alleviate symptoms
Complications, including recurrent falls, fracture, functional decline, ischemic events, decreased quality of life
Cognitive decline and confusion
Frail elderly patient >70 years old
Lack of social support
Indications for referral to a cardiologist
Uncontrolled supine hypertension despite standard therapy
Advanced coronary artery disease or severe ischemic symptoms
Severe left ventricular diastolic or systolic dysfunction (ejection fraction < 30%)
Recent onset of tachy-/bradyarrhythmia
Indications for referral to a neurologist
Specialized diagnostic testing for autonomic failure
Chronic and progressive autonomic failure

is achieved. For best results, the morning dose should be given early and the evening dose no later then 6 PM. Combination therapy of fludrocortisone and midodrine using lower doses of both agents (due to synergistic effects) also is beneficial. Adverse effects include supine hypertension, piloerection, pruritus, and paresthesia. Midodrine is contraindicated in patients with coronary heart disease, heart failure, urinary retention, thyrotoxicosis, or acute renal failure. Midodrine should be used cautiously in elderly patients who are taking medications that decrease heart rate, such as beta-blockers, calcium channel blockers, and cardiac glycosides.

Prostaglandin inhibitors, such as indomethacin and other nonsteroidal anti-inflammatory drugs (NSAIDs), can block the vasodilating effects of prostaglandins and raise the blood pressure in some patients with orthostatic hypotension.[9] In elderly patients, indomethacin should be avoided because of associated confusion, and all NSAIDs should be used with caution due to gastrointestinal and renal side effects.

The methylxanthine caffeine, administered in a dose of 200 mg every morning as 2 cups of brewed coffee or by tablet, may attenuate symptoms in some patients. Caffeine is an adenosine-receptor blocker that inhibits adenosine-induced vasodilatation by blocking these receptors. To avoid tolerance and insomnia, caffeine should not be given more then once in the morning.

Erythropoietin has been shown to be effective in a subgroup of patients with anemia and autonomic dysfunction.[10] Although the exact mechanism of action is not known, its effect is probably due to increased red cell mass and blood volume. The principal disadvantage of this drug is the parenteral route of administration. Serious side effects include hypertension, stroke, and myocardial infarction.

Additional pharmacologic agents that may prove useful in selected patients include clonidine and yohimbine. A peripheral α-2-adrenergic agonist, clonidine may improve orthostatic hypotension in patients with central nervous system causes of autonomic failure, in whom there is little or no central sympathetic outflow, by promoting peripheral venoconstriction and thereby increasing venous return to the heart. Yohimbine is a central α-2-adrenergic antagonist that can increase central sympathetic outflow in some patients with residual sympathetic nervous system efferent output.

REFERRAL TO A SPECIALIST

Major indications for referral to a specialist are listed in Table 5. In brief, consultation with a geriatrician should be sought for frail elderly patients, those with multiple comorbid conditions including cognitive decline, failure of standard therapy, any symptom-related complication, or lack of social support. In elderly patients requiring counseling and reinforcement, referral to a geriatrician

Table 6 Key Points in Office Management of Orthostatic Hypotension

- Orthostatic hypotension is defined as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of assuming an erect posture. However, the significance of any decrease in blood pressure upon standing should be evaluated in context with associated symptoms.
- Regardless of whether orthostatic hypotension is symptomatic or asymptomatic, the elderly patient remains at significant risk for future falls, fractures, transient ischemic attacks, and myocardial infarction.
- Orthostatic hypotension can be acute or chronic. Acute causes include hypotensive medications, dehydration, and adrenal insufficiency. Chronic causes can be further subdivided into those related to aging or age-related blood pressure elevation (physiologic causes) and those due to central or peripheral autonomic nervous system diseases (pathologic causes).
- The diagnostic evaluation of orthostatic hypotension should include a comprehensive history and physical examination, careful blood pressure measurements, and laboratory studies.
- Goals of treatment in the elderly patient include ameliorating symptoms, correcting any underlying cause, improving the patient's functional status, and reducing the risk of complications, rather than trying to attain an arbitrary blood pressure goal.
- In most cases, treatment of orthostatic hypotension begins with nonpharmacological interventions, including withdrawal of offending medications (when feasible), physical maneuvers, compression stockings, increased intake of salt and water, and regular exercise.
- If nonpharmacological measures fail to improve symptoms, pharmacologic agents should be initiated. Fludrocortisone, midodrine, nonsteroidal anti-inflammatory drugs, caffeine, and erythropoietin have all been used to treat orthostatic hypotension due to autonomic failure.

can often prove worthwhile when time constraints limit primary care physician effectiveness. Cardiology consultation is indicated for patients with uncontrolled supine hypertension despite standard therapy, advanced symptomatic coronary artery disease, severe heart failure, and in those with recent onset of tachy- or bradyarrhythmias. Referral to a neurologist is suggested primarily for specialized autonomic testing in patients with an unclear diagnosis or progressive autonomic failure.

Key points in the office management of orthostatic hypotension in the elderly are outlined in Table 6.

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