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Pharmacologic Treatment of Orthostatic Hypotension

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The autonomic nervous system continuously monitors blood pressure. Namely, to compensate for gravity, the brain requires more blood pressure when standing than when lying down. However, when there is autonomic dysfunction, cardiovascular dysfunction, or changes in blood volume, the human body may no longer be able to maintain blood pressure.[1] Inability to regulate blood pressure when standing up may cause a drop in blood supply to the brain. Commonly, patients with the orthostatic hypotension (OH) present with lightheadedness, dizziness, or in case of severe condition, syncope.[2,3]

Complications of hypotension include fall injuries, angina, and even stroke.[4] The goal of treatment is to relieve symptoms and prevent complications without causing the opposite condition, hypertension. Options for treatment include both non-pharmacologic and pharmacologic options.[2,3] Although it is possible to cure some patients by treating the cause for their condition, it is entirely possible for the patient to be treated long term without determining the underlying cause.[4] The purpose of this article is to review the diagnosis of OH and the available treatments, including pharmacology, safety, monitoring, and the evidence behind their use.

Epidemiology

Orthostatic hypotension is the most common form of non-emergent hypotension. Although uncommon in the general population, it has been associated with certain comorbidities, such as neurodegenerative disease, frailty in the elderly, and heart failure. Published reports have found a prevalence that range between 6% and 35%. The factor most associated with OH may be age, as it affects less than 5% of those under the age of 50 years and more than 30% of people older than 70 years.[4]

Orthostatic hypotension has been associated with an increased risk of cardiovascular disease as well as all-cause mortality.[4] A recent study found that OH is associated with increased risk of all-cause death, incident coronary heart disease, heart failure, and stroke for those younger than 65 year of age, while the association is statistically significant but much less pronounced in those older than 65.[4] The study, a meta-analysis by Ricci and colleagues, found a 78% increase in all-cause mortality for patients <65 years old, and 26% increase in the older subgroup when comparing subjects with OH to those without.[4] The most serious complication of OH is falls. In the elderly and the frail, falls are especially hazardous. Even though those >65 years old only account for less than 13% of the population, 75% of deaths from falls are from that population. In 2000, direct medical costs for fall injuries totaled $20 billion. By 2020, the costs are projected to reach $44 billion.[5]

Etiology

Orthostatic hypotension has a variety of etiologies. Secondary OH, often non-neurogenic causes, include anemia, heart failure, and volume depletion. Medications are also a common secondary cause. A list of offending medications is included in **Table 1**. Neurogenic causes of hypotension are considered primary OH, and are often a common symptom in Parkinson's and cerebral ataxia.[4]

Diagnosis

Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position.[2,3] The brain is very sensitive to changes to blood pressure and depends on autonomic reflexes to maintain a constant pressure. When it cannot adapt to decreasing pressure, there is a temporary loss of certain functions in the brain. This can cause varying symptoms including dizziness, loss of vision, and syncope.

The signs and symptoms of OH vary widely and are generally nonspecific. Without specific diagnostic testing, it may be difficult to differentiate it from other conditions. Common symptoms include dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache. Most commonly, these symptoms appear three minutes after standing.[3] However, those with neurodegenerative disorders may respond later, closer to 10 minutes after standing. Most clinics have the ability to measure patients' blood pressure while they are sitting and standing. However, the AAFP recommends using a tilt table as it has better predictive value (61% positive predictive value and 100% negative predictive value for tilt table vs 61% and 50% for sitting test, respectively.[2]

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Table 1 | Medications that can cause OH.[2,3,4]

Class	Examples
Antihypertensive	lisinopril, hydralazine, metoprolol, clonidine, chlorthalidone, spironolactone, diltiazem, losartan, doxazosin, aliskiren, sacubitril
PDE-5 inhibitors	sildenafil, tadalafil
Anticholinergics	oxybutinin
Anti-parkinsonism agents	levodopa-carbidopa, pramipexole, and ropinirole
Sedatives	morphine, fentanyl, and lorazepam, and phenobarbital
Antidepressants	amitriptyline, trazodone, but not SSRIs or SNRIs such as duloxetine
Antipsychotics	haloperidol, chlorpromazine, and clozapine
Muscle relaxants	baclofen, methocarbamol and tizanidine
Antiarrhythmics	amiodarone, sotalol
Antianginal agents	isosorbide mononitrate, nitroglycerin
Others	ethanol

Guidelines and Treatment Recommendations

Two notable guidelines for the treatment of OH exist currently: the European Academy of Neurology (EAN) and the American Academy of Family Physicians (AAFP). Both include the same diagnostic criteria and provide similar treatment recommendations.[2,3] Medications contribute to a large proportion of hypotension cases. Thus, when suspecting OH, both EAN and AAFP guidelines recommend discontinuing offending medications (**Table 1**) if possible.[2,3]

Besides the discontinuation of offending medications, a select number of non-pharmacologic options are available for treatment. Abdominal and lower extremity compression have been found to be usefu.[6] In a trial of leg and abdominal compression on older patients, the group with both compression devices had significantly less drop in systolic blood pressure after a tilt test (127 ± 21 vs. 106 ± 25 mmHg $p < 0.002$), respectively, after 20 min. In addition, specific exercise programs containing maneuvers to avoid OH, have been tested to improve symptoms.

Pharmacologic Treatment

In the event that non-pharmacologic treatments are insufficient, pharmacologic treatments are available. The both EAN and AAFP agree in recommending midodrine and fludrocortisone in treating OH.[2,3] The FDA approved a third medication, droxidopa, after the release of the guidelines in 2014. The guidelines do not provide specific recommendations for one agent over the others as no head-to-head studies exist at this time. Therefore, clinicians must consider the safety profile, as well as how individual patients would respond to each medication.[2,3] A summary of the currently recommended agents for OH are provided in **Table 2**.

Midodrine (ProAmantine®)

Midodrine is approved by the FDA as an oral tablet for the treatment of symptomatic OH. Midodrine is a prodrug, therefore must be metabolized in the liver to the active metabolite desglymidodrine, an alpha-1 adrenergic agonist. It increases peripheral vascular constriction and thus, peripheral resistance. Starting doses are 2.5 mg three times per day; however, doses can be titrated up to10 mg three times a day, depending on the patient's response to therapy. It is contraindicated in patients with acute renal failure, structural heart disease, urinary retention, thyrotoxicosis, and pheochromocytoma. Because of its adrenergic effects, the FDA issued a black box warning for supine hypertension. It may also be combined with other agents for synergistic effects if monotherapy produces an inadequate therapeutic response. Although it is available as a generic product, prices are still higher than other medications used for OH.[7]

Evidence supporting the use of midodrine is controversial. The current guidelines, published in 2006 and 2011, accepted midodrine as a first line option based on a phase III study showing midodrine significantly increased systolic blood pressure in patients with neurogenic OH.[8] However, a meta-analysis published in 2014 by Parsaik concluded there was not enough data to establish the efficacy of midodrine.[9] In the analysis, an average of 21.5 mm Hg difference in systolic pressure ($p < 0.01$) was found in favor of midodrine. In regards to patient's quality of life, the mean change in global assessment symptoms scale scores also favor midodrine (+0.7 for patient's own score, $p < 0.01$; +0.8 for investigator's assessment, $p < 0.01$). Even though the effect size was large, the authors were hesitant to conclude that midodrine is effective for OH due to the heterogeneity as well as the small population of the studies. In 2016, the manufacturer began publishing its phase 4 data in favor of the use of midodrine. In a small, double blinded, randomized study using tilt tablet tests, the subjects in the midodrine group was conscious more a significantly longer period of time than the placebo group (difference, 521.0 s; 95 % confidence interval 124.2-971.7 s; $p = 0.0131$).[10]

Fludrocortisone (Florinef®)

Fludrocortisone is a derivative of cortisol and retains both cortisol's mineral- and glucocorticoid effects. The mineralocorticoid properties of fludrocortisone acts on the kidneys to increase the resorption of sodium and water. With the increased volume, cardiac output and blood pressure increases. Fludrocortisone is generally dosed between 0.1 and 0.3 mg as a single daily dose. Like midodrine, it can also cause supine hypertension. However, unlike midodrine, fludrocortisone cause electrolyte imbalances and requires periodic tests to prevent potassium imbalance. Because it does retain glucocorticoid activities, fludrocortisone may also cause symptoms such glucose intolerance, delayed wound healing, and insomnia. It is the most affordable of all options at approximately $25 per month.[11]

While it is FDA-approved for the treatment of Addison Disease and salt-wasting forms of congenital adreno-genital syndrome, the use of fludrocortisone for OH is off-label.[11] The evidence for use of fludrocortisone began in the 1970's with two small trials published in 1975 and 1976.[12,13] In each trial, six patients were given fludrocortisone acetate (0.05-0.2 mg per day) for the treatment of OH. In one of the trials performed on subjects with diabetic autonomic neuropathy, all six patients had subjective increases in systolic blood pressure although only four felt symptomatic relief.[13] The other trial studied the use of fludrocortisone in subjects with Parkinson's disease on levodopa and found that

Table 2 | Medications commonly used for OH.[9,10,14]

Drug	Dosage	MOA	Common SE	Contraindications	Price[a]
Midodrine (ProAmantine®)	Starting: 2.5 mg every 8 hours Usual: 10 mg Every 8 hours Maximum: 30 mg/ day have not been studied; should not exceed 40 mg/day	A prodrug for desglymidodrine, which directly activates peripheral α1-receptors to constrict vascular and increase resistance, and thus, blood pressure	Supine hypertension (7% to 13%), Paresthesia (18%), piloerection (13%), pruritus (12%), dysuria (≤13%), urinary retention, urinary urgency	Severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma, thyrotoxicosis, persistent and excessive supine hypertension	Tablets: 2.5 mg: $101.20 5 mg: $217.54 10 mg: $435.92
Fludrocortisone (Florinef®)	Starting: 0.1 mg once daily. Usual: 0.1-0.3 mg per day Maximum: 1 mg daily. CrCl < 30 mL/min not studied	Mineralocorticoid receptor agonist, which acts in the kidneys to decrease fluid loss and increase fluid volumes in the body	Nausea, headache, dizziness, insomnia, acne, increased sweating, Cushing's syndrome	Systemic fungal infection	Tablets: 0.1 mg: $34.92
Droxidopa (Northera®)	Starting: 100 mg every 8 hours Maximum: 600 mg every 8 hours	Prodrug for norepinephrine, a natural pressor	Headache (6.1%) Dizziness (3.8%) Nausea (1.5%) Hypertension (1.5%)	Hypersensitivity to droxidopa	Capsules: 100 mg: $2244.32 200 mg: $4488.64 300 mg: $6732.96

[a]Price is based on 30 day supply from AWP of a single manufacturer. Generic price used if available. Data from October 2016.
MOA = mechanism of action; **SE** = side effects

all six patients experienced both normalization of blood pressure, as well as symptomatic relief.[12] Two patients with low serum albumin had experienced ankle edema with no other adverse events reported.

Droxidopa (Northera®)

Droxidopa has been widely used to treat symptoms of OH before it received FDA approval for the treatment of patients with neurogenic OH. Initial dosing is 100 mg three times per day and can be titrated up to a maximum dose of 600 mg three times per day based on symptom relief. Like midodrine, the FDA has issued a black box warning for supine hypertension leading to stroke. Thus, it is not recommended to be used in patients with heart disease or those who have other medications or conditions that can increase blood pressure. The package insert does not specify any contraindications. The most common symptoms include headache, nausea, and vomiting.[14]

The phase III trials for the approval of droxidopa were internally coded trials 301, 302, and 306 that investigated the short-term efficacy of droxidopa treating patients with neurogenic OH.[14,15,16] The inclusion criteria were diagnosis with neurogenic OH due to Parkinson's, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy. Exclusion criteria included the use of any antihypertensive medications or had any significant systemic, hepatic, cardiac, or renal disease.

Study 301 was a double blind, randomized, placebo-controlled, parallel study in Western countries that enrolled 162 subjects. The patients were initiated on droxidopa 100 mg three times per day and after titrating all patients to a goal of 0 on the first question of OH Questionnaire (OHQ), they were washed out and the randomized to receive placebo or droxidopa. The primary outcome was set to be the difference between the changes in OHR composite after one week. The droxidopa group showed an improvement of -1.83 units versus -0.90 in the placebo group (difference = -0.93; 95% CI 0.30–1.48; q = 0.003). In terms of systolic blood pressure, the droxidopa group had an increase of 11.2 mmHg vs 3.9 mmHg in the placebo group (Difference = 7.3; 95% CI 1.1–13.5; p < 0.001). It was noted in this trial that the placebo group had increased blood pressure as well, indicating that droxidopa has a long carry over effect. In both treatment groups, no serious or cardiac adverse events were reported. The most frequent reported adverse events in both the treatment and placebo groups were headache (7.4% vs 0%, respectively), dizziness (3.7% vs 1.2%), fatigue (2.5% vs 2.5%), syncope (2.5% vs 1.2%), and falls (0% vs 3.7%).[14]

Study 302 was a double blind, randomized, placebo-controlled withdrawal trial with 181 patients with the same inclusion criteria as 301. After an open-label titration phase with droxidopa, the cohort was randomized 1:1 to either droxidopa or placebo for two weeks. The primary outcome was the mean change in the first question of the OH Symptom Assessment, which reported dizziness/lightheadedness. At the end of the study, the droxidopa group had a mean increase of 1.9 points while the placebo had an increase of 1.3 points (p=5.02). In this trial, the most common adverse events in the randomized phase were falls (2.0% in droxidopa group vs 11.8% in placebo), urinary tract infections (4.0% vs 3.9%), and dizziness (4.0% vs 2.0%). The authors attributed large change in placebo group to the long carryover effect

of droxidopa.[14]

Study 306 was initially a double blind study that enrolled 51 subjects to evaluate the efficacy of droxidopa (nOH306A trial) in patients diagnosed with neurogenic OH. Due to the lack of power, the investigators recruited an additional 171 subjects (nOH306B trial) exclusively diagnosed with Parkinson's disease in the United States. In 306B, there was a statistically significant difference of -0.94 units in item one of the OHQ between the droxidopa and placebo group (95% CI -1.78 to -0.1; p = 0.028). In this trial, the most common adverse events were headache (13.2% in droxidopa group vs. 7.4% in placebo), dizziness (9.6% vs 4.6%), nausea (8.8% vs 4.6%), hypertension (7.0% vs 0.9%), contusion (11.1% vs 5.3%), and diarrhea (7.4 % vs 3.5%). The trial concluded that subjects taking droxidopa had a significant improvement in symptoms of dizziness and light-headedness.[17]

A potential issue with droxidopa that may limit its use in therapy is its price. With a wholesale price of $5072 for a 30 day supply of 300 mg capsules, it is priced far above similarly dosed fludrocortisone ($34.92 for 0.1 mg tablets) and midodrine ($217.54 for 5 mg tablets).[16] Because of the lack of pharmacoeconomic data from independent sources, it remains to be seen whether droxidopa is a cost-effective treatment for OH.

Comparison of Pharmacologic Agents

The choice of initial therapy is solely dependent on patient and clinician preferences. To date, no clinical trials or observational studies have conducted head-to-head comparisons of the medications for first line treatment of OH. The AAFP guidelines make no distinction between any of their pharmacologic treatments.[2] The EAN guideline, however, concluded that midodrine has better quality of evidence supporting its use.[3]

Despite the evidence supporting the use of droxidopa, due to its high cost, insurance may only cover its cost for clinically proven cases of neurogenic OH.[16] Fludrocortisone is the least costly of the three options and may be the initial treatment for those without insurance. Fludrocortisone requires additional outpatient monitoring that the other agents may not need due to the risk of hypokalemia, and hyperglycemia. Hence, periodic metabolic panels are needed to detect toxicity.[11]

Fludrocortisone has the advantage of once per day dosing while midodrine and droxidopa must be taken three times per day. Fludrocortisone is also the only medication out of the three that does not carry a black box warning against the risk of supine hypertension that may lead to stroke. Even though all three have excellent oral bioavailability, patients should not take droxidopa with fatty meals as it decreases absorption and drug exposure.[14]

Fludrocortisone may also have more drug-drug interactions due to its significant CYP3A4 metabolism; however, all three may still have pharmacodynamic interactions. For example, midodrine and droxidopa should not be combined with other sympathomimetics due to the risk of severe supine hypertension. Fludrocortisone should be used with caution in patients taking other corticosteroids and drugs affecting electrolyte balance. There is no need to dose adjust any of the three medications due to either renal or hepatic dysfunction, as all three are titrated to effect.

Summary

Orthostatic hypotension is a disabling condition that can result in significant morbidities such as fall injuries, angina, and even stroke. Despite the consequences, there is sparse literature comparing pharmacologic treatment available in the outpatient setting. Fludrocortisone, midodrine, and droxidopa have been commonly used to treat OH. Both the AAFP and EAN recommend midodrine and fludrocortisone as first line monotherapy. The third option, droxidopa, has demonstrated efficacy but is limited by its high cost. The choice of therapy is generally a decision between the physician and patient, considering multiple factors including cost, dosing schedule, drug-drug interactions, and monitoring parameters.

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Personalized Medicine Corner

Implementing Pharmacogenomics in the Clinic: Who, What, and How?

Developing a pragmatic model to incorporate pharmacogenomics services into routine clinical care is a common need among healthcare professionals interested in pharmacogenomics. At the recent UF Precision Medicine Conference in Orlando, Florida, Mark Dunnenberger, PharmD, Senior Clinical Specialist in Pharmacogenomics at the NorthShore Center for Personalized Medicine, discussed the logistics of the successful outpatient pharmacogenomics clinic he has developed at his institution.

Dunnenberger identified four key decision points to consider before starting a new pharmacogenomics service: personnel, patients, testing, and reimbursement.

First, a clinical pharmacogenomics service requires sufficient personnel to bill for clinical services, collect medication and family history data, interpret pharmacogenomic test results, develop a genotype-informed treatment plan, and counsel patients on the risks, benefits, and limitations of pharmacogenomic testing.

Second, Dunnenberger noted that appropriate patient selection will be key to long-term success. The targeted patient population should have an identified need for and potential benefit from clinical pharmacogenomics services (e.g., polypharmacy, poor treatment response). Referral criteria and methods for identifying and referring patients should be determined up front.

Third, the approach to how the pharmacogenomic testing will be conducted should be determined, with three key factors identified by Dunnenberger as influencing the appropriate decision: 1) whether testing will be reactive or preemptive; 2) if testing will be conducted as a single-gene test or multi-gene panel; and 3) whether testing will be performed in-house or by a third-party laboratory. Answers to these questions will vary and depend greatly on the patient population being served and clinic environment.

The fourth key decision point identified by Dunnenberger, developing a sustainable reimbursement model, is also likely to present the most challenges in the current billing environment. Steps that clinicians can consider in this process include identifying a billable provider, determining whether billing will be time- or complexity-based, and deciding whether the cost of testing will be billed directly to patients or to their major medical provider. In some cases, clinics have opted to outsource testing and billing to commercial laboratories that may have resources to coordinate prior authorization requests and/or income-based sliding scale cost models for patients to ease the financial and administrative burden of test reimbursement.

Leaders in pharmacogenomics, such as Dr. Dunnenberger, are showing that implementation of pharmacogenomic services in the outpatient setting is feasible. Dunnenberger has also described his experiences in detail in a recently published article.[1]

For questions on ordering and interpreting a pharmacogenomic test, contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu).

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