Managed Care Approach to the Treatment of Neurogenic Orthostatic Hypotension

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Abstract

Neurogenic orthostatic hypotension (NOH) is an orphan disease that primarily affects patients with neurodegenerative disorders such as Parkinson's disease and multiple system atrophy. The first step in the management of NOH is to discontinue or minimize the use of drugs that lower blood pressure. Nonpharmacologic therapy for NOH includes physical countermaneuvers, compression abdominal binders and lower extremity stockings, recognition and avoidance of orthostatic stressors, hydration, and salt supplementation. The management of NOH should also include interventions to prevent falls. Pharmacotherapy for NOH includes the mineralocorticoid drug fludrocortisone to expand plasma volume and the sympathomimetic drugs midodrine and droxidopa. Clinical efficacy, tolerability, and the role of each drug in the treatment paradigm are reviewed here.

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Orthostatic hypotension (OH) caused by non-neurogenic mechanisms like volume depletion or cardiac failure is common, especially in elderly patients.[1,2] In comparison, neurogenic orthostatic hypotension (NOH) is a rare disorder that occurs primarily in patients already given a diagnosis of a degenerative disease such as Parkinson's disease (PD), diffuse Lewy body disease, pure autonomic failure, or multiple system atrophy (MSA).[3] Patients with severe NOH suffer from debilitating symptoms that substantially impair their ability to complete activities of daily living and reduce their quality of life (QOL). Classic NOH symptoms, such as orthostatic dizziness and syncope, and less appreciated symptoms, such as coat-hanger pain and cognitive impairment, can force patients to curtail activities that involve standing or walking.[4]

As a rare disease, NOH has unique management challenges with few well-established treatments, and it requires a patient-oriented approach in which nonpharmacologic strategies may be augmented by pharmacotherapy. In addition, patients with NOH might be treated with drugs for comorbid disorders that exacerbate NOH and, as a result, they are at risk for drug interactions and adverse effects.[5-7]

Treatment Goals and Plans

The goals of NOH treatment are to reduce symptoms, improve functional ability and QOL, and reduce the occurrence of falls and syncope.[7] The associated risks of fractures, trauma, and functional decline make fall prevention an important priority in the management of patients with NOH.[8] Considering that this disease reflects degenerative autonomic dysfunction, restoration of normal blood pressure responses is not a realistic treatment goal. Instead, maintaining standing and supine blood pressures within the range of cerebral autoregulation (approximately 90 mm Hg) will aid in reducing symp-

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toms. Approximately half of patients with NOH also suffer from supine hypertension (SH).[9] In these patients, an additional goal is to minimize increases in supine blood pressure.

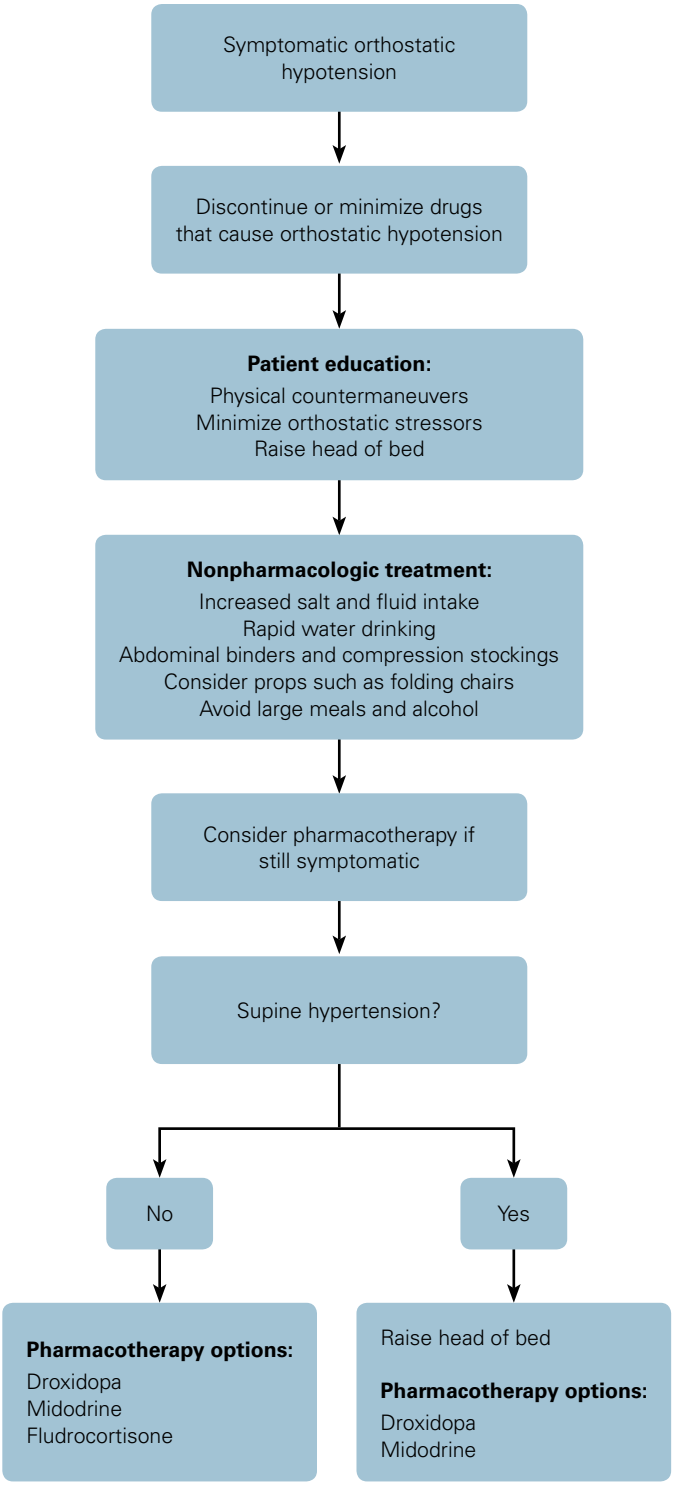
The Figure[7,10,11] depicts a treatment algorithm for managing NOH.[7] Patients with NOH are often elderly with multiple comorbidities and a high rate of polypharmacy.[5-7] Therefore, the first step in management is to assess the patient's treatment regimen for drugs that cause OH.[9] A strong emphasis on patient education is necessary to teach patients how to perform physical countermaneuvers and implement other nondrug measures that improve QOL, including minimizing orthostatic stressors. The head of the bed should be maintained at 30 degrees or higher to minimize SH and reduce nocturnal diuresis. Pharmacotherapy is needed for patients who remain symptomatic despite nonpharmacologic interventions. Management options for NOH, through both nonpharmacologic treatment and pharmacotherapy, act by either volume expansion or vasoconstriction (see Table 1[7,10]).[7,10]

Drug-induced Orthostatic Hypotension

Receiving multiple drugs that can cause OH increases the risk of a patient suffering from symptomatic OH.[5,12] Drug classes commonly linked to causing OH include diuretics, alpha$_1$-antagonists, antidepressants, antipsychotics, levodopa and dopaminergic drugs for PD, and vasodilators (see Table 2[5,6,13-20]).[5,12-14] Within drug classes, specific agents may have an especially high risk of causing OH; some of these are listed on the American Geriatric Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults because they pose a risk for elderly patients in general. Drugs listed on the Beers Criteria because they increase the risk of OH in the elderly include amitriptyline, clomipramine, doxazosin, doxepin over 6 mg/day, imipramine, prazosin, terazosin, and trimipramine.[15]

In male patients, benign prostatic hypertrophy may be treated with an alpha$_1$-antagonist, leading to exacerbation of OH. Prazosin, which has high affinity to alpha$_1$-receptors and a rapid onset of action, is considered the alpha$_1$-antagonist with the highest risk of causing OH.[16] A recent analysis of medical claims data found that even "uro-specific" alpha$_1$-antagonists, such as silodosin and tamsulosin, were linked to a higher risk of hip fracture during early use, likely due to OH.[21] An increased risk of hospital-

Figure. Algorithm for Initial Treatment of Neurogenic Orthostatic Hypotension[7,10,11]



Adapted from Schroeder et al. *Drugs*. 2013;73(12):1267-1279, and Jordan J et al. *Am J Med*. 1998;105(2):116–124.

Table 1. Mechanism of Action for NOH Treatment[7,10]

Volume Expansion	Vasoconstriction
Nonpharmacologic management	
Increased salt and fluid intake	Abdominal binders Compression stockings Rapid water drinking
Pharmacotherapy	
Fludrocortisone NSAIDs	Droxidopa Midodrine Pyridostigmine Atomoxetine

NOH indicates neurogenic orthostatic hypotension; NSAID, nonsteroidal anti-inflammatory drug.

ization for hypotension has been reported in men soon after starting tamsulosin, with a 2-fold increase in risk during the first month of therapy.[22] An analysis of the FDA Adverse Events Reporting System found a signal for most alpha-antagonists, with a reporting odds ratio for OH of 2.66 for doxazosin, 3.31 for tamsulosin, 4.21 for alfuzosin, and 6.13 for terazosin.[23]

Atypical antipsychotic drugs with high alpha$_1$-antagonist activity increase the risk of OH, especially clozapine, iloperidone, and quetiapine. Increased rates of OH have been reported with the low-potency drugs chlorpromazine and thioridazine.[14] Volume depletion and autonomic dysfunction are risk factors for developing symptomatic OH with alpha$_1$-antagonists and antipsychotic drugs.[14,16] Tricyclic antidepressants can cause OH and increase the risk of falling, with the highest risks identified for amitriptyline, imipramine, and doxepin. Monoamine oxidase inhibitors and trazodone can also cause OH.[17]

A new class of diabetes drugs, the sodium glucose co-transporter 2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), causes an osmotic diuresis via increased renal excretion of glucose.[24] They can cause symptomatic hypotension in certain groups of susceptible patients, including patients with impaired renal function, the elderly, patients undergoing co-administration of diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and those with low systolic blood pressure.[25] However, a meta-analysis of clinical trial data did not find a significant risk of OH.[24] Considering how important it is for patients with NOH to maintain optimal intravascular volume, it may be prudent for them to avoid this class of drugs.

Dopaminergic drugs used to treat motor symptoms of PD can lower blood pressure and may exacerbate NOH. Levodopa can cause reductions in blood pressure in patients who have PD, and higher doses were linked to an increased risk of falls in one study.[18,26] Dopamine agonists also commonly cause OH, which can be symptomatic.[19] Symptomatic OH has also been noted with selegiline and amantadine.[6,19]

Antihypertensive drugs, particularly diuretics, can cause OH. In epidemiologic studies of patients with PD, diuretics increased the odds of OH by more than 5-fold and the odds of falling by more than 3-fold.[6,26] Probably because negative effects on cardiac conduction and contractility prevent a compensatory increase in heart rate when standing, the nondihydropyridine calcium channel blockers diltiazem and verapamil can cause OH.[20] Despite the risk of OH with some antihypertensive drugs, maintaining blood pressure control is an important goal because uncontrolled hypertension exacerbates OH and increases the risk of falling.[7,27]

Physical Countermaneuvers and Patient Education

Physical countermaneuvers that reduce venous pooling are an important strategy patients can use to increase orthostatic tolerance and prevent syncope. These measures include crossing one's legs while standing, squatting, and tensing muscles in the legs, thighs, and buttocks.[28,29] Routine use of leg-crossing in patients with autonomic failure can increase blood pressure by approximately 20/10 mm Hg. Bending forward can also increase orthostatic tolerance; this maneuver lowers the head to heart level and increases cardiac output through abdominal compression.[30] Video instructions and tutorials that demonstrate these techniques can be viewed at www.syncopedia.org[31] and www.stars.org.uk.[32] An important limitation for physical countermaneuvers is that patients who are elderly or debilitated may have difficulty performing them.

In addition to physical countermaneuvers, patients can employ external devices to increase their functional

Table 2. Drugs That Cause Orthostatic Hypotension[5,6,13-20]

Drug Class	Drugs With High Risk of Orthostatic Hypotension	Mechanism
Alpha$_1$-adrenergic antagonists	doxazosin,[a] prazosin,[a] terazosin[a]	Decreases systemic vascular resistance
Antipsychotic drugs	clozapine, quetiapine, iloperiodone, chlorpromazine, thioridazine	Decreases systemic vascular resistance
Diuretics	furosemide, hydrochlorothiazide	Volume depletion
Antidepressants	amitriptyline,[a] clomipramine,[a] imipramine,[a] doxepin >6 mg/day,[a] trimipramine,[a] trazodone	Decreases systemic vascular resistance
Calcium channel blockers	diltiazem, verapamil	Negative inotropic and chronotropic effects
Anti-Parkinson drugs	amantadine, levodopa, pramipexole, ropinirole, selegiline	Decreases systemic vascular resistance, decreases sympathetic outflow
Monoamine oxidase type A inhibitors	phenelzine, tranylcypromine	Norepinephrine depletion
Nitrates	isosorbide dinitrate, nitroglycerin	Decreases preload

[a]Listed on 2012 Beers Criteria.

ability. Patients with adequate balance can use folding chairs when they feel lightheaded or have been walking for extended distances.[33] In addition, elastic and pull-string abdominal binders can be used to increase standing blood pressure.[34,35] Abdominal binders reduce pooling of blood in the splanchnic circulation, a greater contributor to venous pooling than the lower extremities. Thigh-high or waist-high compression stockings that provide at least 15 to 20 mm Hg of compression can also help reduce venous pooling on standing.[7] However, abdominal binders and compression stockings can be difficult for patients to put on without assistance.[36]

Patients with NOH need to learn how to manage activities and conditions that cause orthostatic stress or exacerbate the disease. When they change positions, they should do so slowly to allow time for autonomic adaption. For instance, in going from a supine position to walking, patients should sit before standing and stand for several minutes before walking.[37] Large meals, especially those high in carbohydrates and consumed with alcohol, can cause postprandial OH by causing vasodilation in the splanchnic circulation.[38] Compared with 3 standard meals, eating 6 small meals has been shown to improve orthostatic symptoms and standing tolerance.[35] Exercise, especially with activities that are recumbent or done in water, are encouraged in order to prevent deconditioning, which can exacerbate NOH.[7] However, patients should avoid exercising in the morning, when orthostatic symptoms are typically worse.

Patients with NOH must be diligent to maintain intravascular volume because volume depletion can exacerbate symptoms. The American Society of Hypertension recommends that NOH patients drink 1.5 to 2 L of water daily.[7] In addition, they should consume 6 to 10 g of salt daily, taking 1 g of salt (as tablets) with each meal if needed. Drinking 300 to 500 mL of water over 3 to 4 minutes can induce a pressor effect that has an onset within 10 to 15 minutes, peaks at 40 minutes, and can last over an hour.[3,10,39] Rapid water drinking induces hypo-osmolality in the portal vein, which triggers a sympathetic reflex. Drinking water is an important option for managing morning symptoms of NOH, as well as postprandial OH. As one expert notes, "Being free, readily available, and highly effective in many patients, water is the first-line 'drug' for NOH."[10]

Additionally, patients should be advised to elevate the head of the bed at least 30 degrees to lower SH and reduce nocturnal diuresis. This may also improve baroreflex failure. Patients should be encouraged to document blood pressure measurements and orthostatic symptoms in a diary.[3] This may be helpful in identifying orthostatic stressors and nondrug strategies to minimize orthostatic symptoms.

Fall Prevention

OH is a major and independent risk factor for falls in elderly patients; in a large study of nursing home residents, OH increased the risk of subsequent falls by 2.6-fold.[40] In ambulatory patients who have PD, OH almost doubled the risk of falls (multivariate odds ratio 1.84; 95% CI, 1.02-3.31).[26] A high incidence of fractures and trauma caused by falls has been documented in patients with severe NOH due to autonomic failure.[41] The CDC has created a comprehensive fall prevention program

Table 3. Pharmacotherapy for NOH[7,9,44-50]

	Droxidopa	Midodrine	Fludrocortisone
Mechanism of action	Norepinephrine prodrug; vasoconstrictor	$Alpha_1$-agonist prodrug; vasoconstrictor	Mineralocorticoid; volume expansion
Onset of action	1 hour	1 hour	Slow
Duration of action	6 hours when standing; 8 hours when supine	4 hours	Long-acting
Efficacy	Improvement in orthostatic dizziness or lightheadedness	Improvement in 1 minute standing blood pressure	Improvement in standing blood pressure
When to take precautions	Supine hypertension, fever and confusion syndrome, possible exacerbation of ischemic heart disease, arrhythmia, or heart failure	Supine hypertension, urinary retention	Supine hypertension, heart failure (relative contraindication), hypokalemia
Common adverse effects	Headache, dizziness, nausea, hypertension	Paresthesia, pruritus (especially scalp), chills, goosebumps, urinary retention, urinary frequency	Edema, weight gain, headache
Drug interactions	Carbidopa: dosage increase of droxidopa may be required	Digoxin, beta-blockers: possible additive bradycardia $Alpha_1$-antagonists: block effects of midodrine	Diuretics: exacerbation of hypokalemia
Dose	100-600 mg orally 3 times per day, taken consistently with or without food; titrate upward every 1-2 days; last dose ≥3 hours before bed	2.5 mg orally, initially to detect pressor hypersensitivity, titrated to 10 mg orally 3 times daily; last dose ≥3-4 hours before bed	0.1-0.3 mg orally once daily; titrate upward slowly
Availability	Brand only through specialty pharmacy	Generic only	Generic only
Cost of 30 day-supply	$1548-$9291	$272	~$50

called Stopping Elderly Accidents, Deaths and Injuries (STEADI) that has the potential to reduce morbidity from falls in patients with OH.[42] It includes tools and educational materials for clinicians and an algorithm of fall risk assessment and interventions. One important component of this program is minimizing the use of drugs that increase the risk of a fall, including benzodiazepines and anticholinergic drugs. A practice guideline from the American Geriatric Society recommends that assessment and treatment of OH should be part of multifactorial interventions to prevent falls in elderly patients and those of any age who have gait or balance difficulties.[43] This recommendation is based on results from 3 randomized controlled trials that demonstrated a reduction in falls with multifactorial interventions, which included treatment of OH in addition to other interventions, such as medication reduction, optimization of fluids, and behavioral interventions.

Pharmacotherapy of NOH

The primary defect in NOH is the failure of sympathetic neurons to release norepinephrine and cause vasoconstriction. This defect is addressed directly by 2 sympathomimetic drugs approved by the FDA for the management of NOH: droxidopa and midodrine. The role of sympathomimetic drugs is to reduce orthostatic symptoms, prevent falls, and improve QOL.[9] In addition to sympathomimetic drugs, the mineralocorticoid fludrocortisone, which acts indirectly through volume expansion, is used off-label in NOH.[10] Fludrocortisone is also considered for patients who cannot maintain plasma volume with salt and fluids alone or for those who do not get adequate symptom relief from a sympathomimetic drug.[7,10] It is also an alternative for initial therapy in patients who do not have SH. Table 3[7,9,44-50] compares these pharmacotherapy options for NOH.

The presence of SH impacts treatment decisions for NOH (see Figure[7,10,11]). Uncontrolled SH induces a pressure diuresis that causes volume depletion and worsens orthostatic symptoms in the morning.[9,51] Nonpharmacologic measures to manage SH include avoiding the supine position during the day and raising the head of the bed by 6 to 9 inches (>30 degrees).[7] Also important for patients to know is that the increase in blood pressure from rapid

water drinking is substantial enough that those with SH should avoid lying down within 2 hours afterward.[52]

Patients receiving pharmacotherapy for NOH should be advised to raise the head of the bed to minimize the risk of SH and to reduce nocturnal diuresis. For first-line treatment in patients with SH or heart failure, a sympathomimetic drug is preferred over fludrocortisone. However, measures must still be taken to minimize the risk of SH with droxidopa and midodrine. Sympathomimetic drugs should be given as needed 30 to 45 minutes before patients with NOH intend to be upright.[7] These drugs should not be used when patients intend to remain seated or supine. Product labeling for both droxidopa and midodrine includes a black box warning about the risk of SH; because of this risk, these drugs should not be taken at night.[44,45] Specifically, the last dose of either drug should be taken at least 3 hours before bed. In addition, supine blood pressure should be monitored after dosage increases.

The 2-part Orthostatic Hypotension Questionnaire (OHQ) is used to assess symptomatic improvement of NOH in clinical trials and may be used to assess the response to pharmacotherapy in clinical practice. The 6-item Orthostatic Hypotension Symptom Assessment (OHSA) asks about dizziness/lightheadedness (OHSA item 1), vision disturbance, weakness, fatigue, trouble concentrating, and head or neck discomfort. The Orthostatic Hypotension Daily Activity Scale (OHDAS) assesses the interference of NOH with standing and walking. Patients score items on a scale of 0 to 10. An improvement of 0.8 to 1.0 units is considered a minimal important change on the OHSA, OHDAS, and OHQ composite score.[53] Ambulatory blood pressure monitoring also has a role in assessing the response to pharmacotherapy.[54]

Droxidopa

Droxidopa is a synthetic amino acid prodrug that is converted to norepinephrine through decarboxylation by dopa decarboxylase. It was approved by the FDA in 2014 for the treatment of symptomatic NOH caused by primary autonomic failure, dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.[44] More specifically, it was approved for orthostatic dizziness, lightheadedness, or for when a patient feels as if they may black out, (otherwise known as OHSA item 1). In a single-dose study of patients with NOH, the pressor effect of droxidopa had an onset at 1 hour and peaked 3.5 hours after the dose.[47] The duration of action was 6 hours while standing and 8 hours while supine. A high-fat meal reduces peak levels by 35% and delays the time to peak levels by approximately 2 hours. Patients should be counseled to take droxidopa consistently either with or without food to account for this food effect.[44]

Clinical Efficacy

Droxidopa was evaluated in 3 phase 3 studies (301, 302, 306). Two of these trials (301, 302) enrolled patients with NOH due to PD, pure autonomic failure, MSA, nondiabetic autonomic neuropathy, or dopamine-beta-hydroxylase deficiency.[55,56] The third trial (306) enrolled only patients with NOH caused by PD.[57,58]

Study 302 (the first phase 3 trial performed) had an open-label dose-optimization phase to identify droxidopa responders, followed by a 7-day open-label phase in which responders continued droxidopa treatment. Patients were then randomized to a 14-day double-blind withdrawal phase where they received droxidopa or placebo. Droxidopa was not more effective than placebo for the primary end point, OHSA item 1; however, a post hoc analysis found that the mean change in the OHQ composite score was significantly lower with droxidopa than with placebo (0.11 ± 2.18 vs 1.22 ± 2.39; $P = .013$).[56]

Study 301 (the second phase 3 trial performed) began with a dose-optimization phase to identify patients who responded to and tolerated droxidopa (n = 263). After a 7-day washout phase, responders received double-blind treatment with droxidopa (n = 82) or placebo (n = 80) for 1 week. The change in composite OHQ score from randomization to week 1, the primary outcome, was −1.83 for droxidopa and −0.93 for placebo (treatment difference of 0.9; 95% CI, 0.30-1.48; $P = .003$). More patients had an improvement in the composite OHQ score of at least 3 units with droxidopa than with placebo (27.2% vs 11.4%; $P = .016$). Standing blood pressure also improved with droxidopa.[55] The results of Study 301 led to a subsequent trial in patients with PD.

In study 306, which was the third phase 3 trial performed, patients initially entered a randomized double-blind dose-optimization phase in which they received droxidopa or placebo for up to 2 weeks before entering an 8-week treatment phase.[58,59] After a planned interim analysis of the first 51 participants found no significant difference between droxidopa and placebo in the initial primary end point of OHQ composite score, that analysis was designated as study 306a because of potential unblinding. After discussion with the FDA, the primary outcome was switched to a change in OHSA item 1 between baseline and week 1 and the subsequent 171 patients to enter the study were designated as study 306b,

which became the pivotal trial supporting FDA approval.[59] In Study 306b, the mean change in OHSA item 1 from randomization to week 1 was −2.3 for droxidopa and −1.3 for placebo (P <.05).[58] Standing supine blood pressure also was significant over placebo at week 1.

Based on pooled data from studies 301 and 306, the number needed to treat (NNT) for at least 50% improvement in OSHA item 1 at 1 week was 5 (95% CI, 3-11). The number needed to harm (NNH) for development of hypertension was 28 (95% CI, 16-95). For discontinuation due to an adverse event, the NNH was 34. A response to droxidopa was 6.8 times more likely than an adverse event leading to discontinuation.[60]

The long-term efficacy of droxidopa has been evaluated in a 1-year open-label extension study (study 303) that enrolled 102 patients from studies 301 and 302. Patients received droxidopa for 3 months and then were randomized to receive droxidopa (n = 38) or placebo (n = 37) for 2 weeks. There was no significant difference between groups in the primary end point, mean change in composite OHQ score from baseline.[43] However, after more than 1 year of open-label treatment with droxidopa, the changes from baseline in OHSA item 1 and OHQ composite scores were maintained.[61,62] Droxidopa has demonstrated efficacy only in studies lasting less than 2 weeks.[55,58] Product labeling recommends that patients be evaluated periodically to determine whether they continue to benefit from droxidopa.[44]

Adverse Effects

The most commonly reported adverse effects with droxidopa in premarketing clinical trials were headache, dizziness, nausea, and hypertension.[44] Adverse effects most often leading to discontinuation of droxidopa included hypertension and nausea. In Japan, where droxidopa has been available since 1989, a symptom complex similar to neuroleptic malignant syndrome has been reported, but rarely.[44,59]

Drug Interactions

Many patients with PD receive carbidopa, a dopa decarboxylase inhibitor, in order to prevent conversion of levodopa to dopamine in the peripheral nervous system. A high single dose of carbidopa (200 mg) has been shown to inhibit the conversion of droxidopa to norepinephrine and abolish its pressor effect.[47] Analysis of clinical trial data has not resolved the question of whether lower doses of carbidopa impair the efficacy of droxidopa.[55] Droxidopa product labeling advises that dosage adjustment of droxidopa may be necessary if it is co-administered with carbidopa, and because of concerns about additive effects on SH, the product labeling recommends against co-administration of midodrine.[43] Droxidopa has been given with fludrocortisone in some clinical trials; approximately 20% of patients in the droxidopa pivotal trials also used fludrocortisone.[57,58]

Availability

Droxidopa is considered a specialty drug that the manufacturer has made available through a specialty pharmacy distribution network.[63] The prescriber and patient must complete prescription forms to obtain the drug. In order for patients to receive a trial of droxidopa, prior authorization procedures may require documentation that the patient has not responded to or tolerated other drugs for NOH.

Midodrine

Midodrine is a direct alpha$_1$-agonist that increases blood pressure by vasoconstriction. It is a prodrug that is metabolized to an active metabolite, desglymidodrine.[38] Midodrine acts peripherally; it does not cross the blood–brain barrier. Increases in systolic blood pressure with midodrine are dose-related, with effects peaking approximately 1 hour after the dose and lasting 4 hours.[48]

Clinical Efficacy

In 1996, Shire received fast-track approval from the FDA to market midodrine for symptomatic OH, with 7 years of marketing exclusivity as an orphan drug. Approval was based on studies that demonstrated improvement in a surrogate outcome, 1-minute standing systolic blood pressure. The company agreed to complete additional studies to establish symptomatic efficacy.

In 2003, when marketing exclusivity ended, Shire discontinued the brand name product, leaving only generic products available. In 2010, the FDA proposed withdrawing approval of midodrine because Shire had failed to submit adequate postmarketing studies to establish symptomatic benefit. In 2012, Shire agreed to conduct 2 studies to establish the efficacy of midodrine for relieving OH symptoms.[64]

These studies have been completed, but not published. Preliminary results have been posted on www.clinicaltrials.gov.[65,66] In a placebo-controlled tilt table test, the time to onset of syncope or near-syncope was significantly longer with midodrine (1105.6 vs 1626.6 sec; mean difference 521 sec; 95% CI, 124.2-917.7; P = .0131).[65] In a midodrine

withdrawal study, 98 patients with severe OH were treated with the midodrine regimen they had taken before the study. Patients were randomized to receive midodrine for 16 days or midodrine for 15 days followed by placebo on the last day. The primary outcome of the study was the percentage of patients who failed to maintain a response 30 minutes after the dose on day 16, with failure defined as either a 4-point increase on OHSA item 1 or an increase in syncopal or near-syncopal events within 15 minutes after standing. The percentage of patients who failed to maintain a response was 30.3% for midodrine and 44.1% for placebo (mean difference of 13.8%; 95% CI, −37.6 to 9.8; $P = .3145$).[66] Patients and clinicians maintain that midodrine may have QOL and symptomatic benefits that the clinical trials have failed to identify.[67]

An independent systematic review evaluated symptom improvement and adverse effects of midodrine in clinical trials of symptomatic OH. There was high heterogeneity ($I^2 = 73\%$) among 5 studies that were included in the analysis. The odds ratio for symptom improvement with midodrine was 3.9 (95% CI, 1.8-8.3), providing an NNT of 3 (95% CI, 2-7).[68]

Adverse Effects

Adverse effects reported with midodrine are related to its alpha-agonist activity. These include pilo-erection, pruritus (especially on the scalp), paresthesia, urinary retention, and SH.[48,69] The previously cited systematic review evaluated adverse effects with midodrine in clinical trials of symptomatic OH.[63] The relative risk of a minor adverse event (primarily pilo-erection, paresthesias, chills, and GI discomfort) was 4.58 (95% CI, 2.03-10.37), providing an NNH of 8 (95% CI, 3-27). Based on data from 3 studies, midodrine increased the risk of SH (relative risk 5.31; 95% CI, 1.39-20.27), with an NNH of 14 (95% CI, 9-50).[68]

Drug Interactions

Because midodrine is a direct $alpha_1$-agonist, its effects are opposed by $alpha_1$-antagonists.[45] There is concern that co-administration of midodrine and digoxin or beta-blockers may cause bradycardia.

Fludrocortisone

Fludrocortisone is a mineralocorticoid that causes volume expansion by increasing renal sodium reabsorption.[10] These effects normalize over time, so other mechanisms may be responsible for its effects in NOH. Unlike the sympathomimetic drugs, it has a long duration of action (biologic half-life of 18 to 36 hours).[46] In addition, it had equivalent effects on standing and supine blood pressure in a study of patients with OH due to diabetic autonomic neuropathy.[70] These properties raise concern about exacerbation of SH.[10] Doses of 0.1 to 0.2 mg are suggested, but some patients can respond with up to 0.6 mg daily.

Clinical Efficacy

Clinical trials provide little evidence for the efficacy of fludrocortisone in NOH. In a double-blind crossover trial, fludrocortisone 0.1 mg twice daily improved orthostatic blood pressure measurements in 5 patients with NOH due to diabetic neuropathy.[70,71] Increases in standing blood pressure were reported with fludrocortisone plus head-up sleeping in an observational study of 8 patients with NOH.[72] A Movement Disorder Society Task Force found insufficient evidence to evaluate the safety and efficacy of fludrocortisone for OH in PD.[73]

Adverse Effects

Fludrocortisone can cause hypokalemia, pedal edema, SH, and glucocorticoid effects.[45] In order to minimize the risk of these adverse effects, the lowest effective dose of fludrocortisone should be used. Weight gain is expected due to fluid retention; therefore, heart failure is a relative contraindication.[7] To prevent hypokalemia, potassium levels should be monitored and potassium supplementation provided if needed.

Additional Pharmacotherapy Options

Other drugs have been evaluated for treatment of NOH, but they do not have a well-defined role in management. These include non-steroidal anti-inflammatory drugs (primarily indomethacin), erythropoietin in patients with anemia, and desmopressin in patients with nocturnal polyuria.[74-76] Octreotide and acarbose have been evaluated for postprandial hypotension.[77,78]

Atomoxetine inhibits norepinephrine reuptake by inhibiting the pre-synaptic norepinephrine transporter. In patients with NOH due to autonomic failure who have residual sympathetic activity, this has the potential to raise blood pressure by increasing synaptic norepinephrine levels.[7] Atomoxetine displayed a pressor effect only in patients with central autonomic failure in a study that compared its effects in patients with central and peripheral autonomic failure.[79] A placebo-controlled crossover study compared single doses of atomoxetine and midodrine in 65 patients with severe autonomic failure and NOH.[80] At 1 minute, upright systolic blood pressure was significantly higher with

atomoxetine than midodrine (means difference 7.5 mm Hg; 95% CI, 0.6-15; P = .03). Change in the OHQ total score was significantly greater with atomoxetine than placebo (0.4 points; 95% CI, −0.1 to −0.8; P = .02). The OHQ total score with midodrine was not significantly different from placebo (0.5 points; 95% CI, −0.1 to 1.0; P = .08). Further study is necessary to define the role of atomoxetine in NOH.

The cholinesterase inhibitor pyridostigmine may increase standing blood pressure by increasing cholinergic transmission in the autonomic ganglia.[10] A potential advantage of pyridostigmine is that it has demonstrated little potential to cause SH. A randomized controlled trial evaluated a single dose of pyridostigmine alone or in combination with midodrine in 60 patients with NOH.[81] It caused a modest increase in standing blood pressure that was associated with symptom improvement. A survey reported moderate to marked symptom improvement in 17 of 20 patients who continued long-term treatment with pyridostigmine after the single-dose study.[82] In a second study of patients with NOH and autonomic failure, pyridostigmine did not improve standing blood pressure or symptoms.[83] Cholinergic adverse effects can limit the use of pyridostigmine in NOH.[10]

SUMMARY

NOH is an uncommon disorder with multiple treatment considerations. Clinicians often must make use of nonpharmacologic treatments and pharmacotherapy to improve the daily activities and QOL of patients who suffer symptoms of NOH. Until recently, midodrine and fludrocortisone were the mainstays for drug therapy of NOH. The recent approval of droxidopa adds to the clinician's armamentarium, providing patients with another alternative to treat symptoms of NOH.

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