Cardiovascular Safety Considerations in the Treatment of Neurogenic Orthostatic Hypotension

Brian Olshansky, MD[a,b,*], and James Muldowney, MD[c]

Neurogenic orthostatic hypotension (nOH), a drop in blood pressure upon standing resulting from autonomic malfunction, may cause debilitating symptoms that can affect independence in daily activities and quality-of-life. nOH may also be associated with cardiovascular comorbidities (e.g., supine hypertension, heart failure, diabetes, and arrhythmias), making treatment decisions complicated and requiring management that should be based on a patient's cardiovascular profile. Additionally, drugs used to treat the cardiovascular disorders (e.g., vasodilators, β-blockers) can exacerbate nOH and concomitant symptoms. When orthostatic symptoms are severe and not effectively managed with nonpharmacologic strategies (e.g., water ingestion, abdominal compression), droxidopa or midodrine may be effective. Droxidopa may be less likely than midodrine to exacerbate supine hypertension, based on conclusions of a limited meta-analysis. In conclusion, treating nOH in patients with cardiovascular conditions requires a balance between symptom relief and minimizing adverse outcomes. **© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)** **(Am J Cardiol 2020;125:1582−1593)**

Neurogenic orthostatic hypotension (nOH), a drop in blood pressure when moving to an upright position without a sufficient compensatory increase in heart rate, is common in patients with autonomic failure due to neurodegenerative disorders.[1] In nOH, the inability to maintain effective venous return when standing reduces left ventricular filling, cardiac output, blood pressure, and cerebral perfusion, causing dizziness, lightheadedness, syncope, and falls, which can affect patient independence, quality-of-life, and activities of daily living.[1−4] Successful management of nOH is challenging, especially if co-morbid cardiovascular conditions are present; available therapies may not be completely effective and may increase supine hypertension, a common morbidity in patients with nOH.[2,5] This review addresses critical issues in the management of symptoms related to nOH in patients with cardiovascular co-morbidities.

Clinical Signs and Diagnosis of nOH

Patients with primary autonomic dysfunction (characterized by α-synuclein pathology such as Parkinson disease, multiple system atrophy, and pure autonomic failure) or secondary autonomic neuropathies (due to diabetes, amyloidosis, or chemotherapy) are at risk for nOH. In addition to symptoms of cerebral hypoperfusion (dizziness, lightheadedness, and confusion), nOH also causes other symptoms (e.g., shoulder heaviness ["coat-hanger syndrome"], orthostatic angina, and dyspnea).[1,2] Patients with autonomic failure conditions presenting with debilitating or serious symptoms (e.g., syncope) or certain characteristics (e.g., elderly, polypharmacy use) should be evaluated for nOH by asking about orthostatic symptoms and measuring orthostatic vital signs (Figure 1).[2,6] An otherwise unexplained, inadequate compensatory heart rate increase (i.e., ≤10 to 15 beats/min) upon standing helps distinguish nOH from OH.[2,7]

If orthostatic vital signs indicate OH/nOH, a careful patient history, medication review, electrocardiogram, and directed testing should be conducted.[2] Common causes of non-neurogenic OH include medications (e.g., diuretics, vasodilators, anticholinergics, antihypertensive medications), hypovolemia, or deconditioning (e.g., due to a chronic illness).[2] If the cause is still unclear, specialized autonomic testing should be considered.[2]

Risk of Morbidity and Mortality in nOH

Falls and burden

Studies of morbidity and mortality outcomes in patients with nOH or OH are listed in Table 1.[3,4,8−22] Potential risk from falls is well recognized; patients with Parkinson disease and nOH/OH have greater healthcare resource use (e.g., falls that require medical treatment, more days of hospitalization, higher medical costs) than patients with Parkinson disease but without nOH/OH.[12,13] Falls also have functional and psychosocial consequences, such as a fear of walking or of falling again, resulting in secondary immobility, decreased activity, and subsequent negative outcomes (e.g., development/progression of co-morbidities, social isolation).[23]

In a patient and caregiver survey of nOH burden, most respondents (≥87%) reported that nOH had a negative

[a]Mercy Medical Center North Iowa, Mason City, Iowa; [b]University of Iowa, Iowa City, Iowa; and [c]Vanderbilt University School of Medicine, Nashville, Tennessee. Manuscript received September 6, 2019; revised manuscript received and accepted January 22, 2020.

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*Corresponding author: Tel: 319-384-8756; fax: 319-384-6247.

E-mail address: brian-olshansky@uiowa.edu (B. Olshansky).

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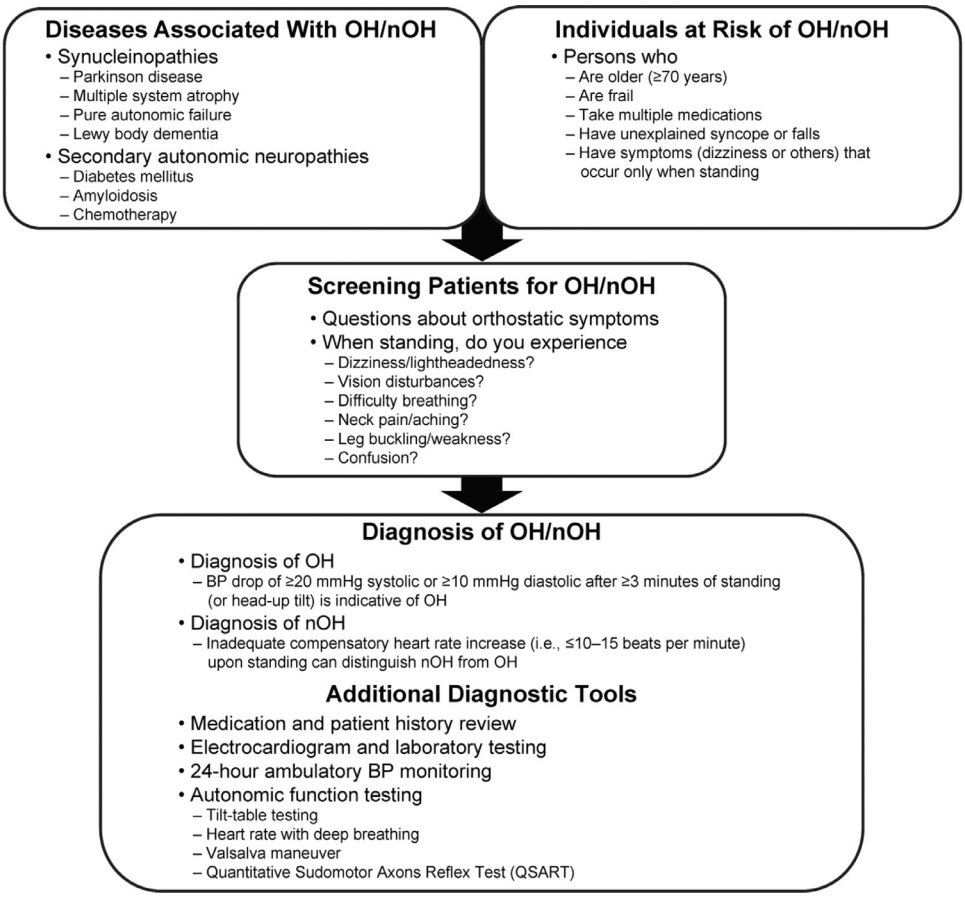

Figure 1. Symptoms, diagnosis, and treatment considerations for patients with nOH and OH and cardiovascular comorbidities. BP = blood pressure; nOH = neurogenic orthostatic hypotension; OH = orthostatic hypotension.

impact on the patient's ability to perform daily activities.[3] Patients often reported that nOH symptoms adversely affected their quality-of-life (59%), caused a lost sense of independence (42%), and drastically changed their lives (40%).[3] Another report indicated that symptomatic and asymptomatic nOH in patients with Parkinson disease was associated with more falls, impaired activities of daily living, and diminished health-related quality-of-life.[4]

Cardiovascular morbidity and mortality

A common, co-morbid cardiovascular condition in patients with OH is supine hypertension (prevalence estimates, 10% to 56%[22,24,25]), likely due to autonomic and baroreflex dysfunction with the resultant inability to buffer postural blood pressure.[2,26] The severity of OH has been correlated with the severity of supine hypertension in patients with multiple system atrophy.[20] Supine hypertension can affect renovascular function, sodium and water reabsorption, and renin-angiotensin release (e.g., elevated angiotensin II levels in patients with autonomic failure and supine hypertension versus healthy controls[26,27]) and has been associated with increased markers of end-organ damage, greater incidence of cardiovascular events, and increased mortality in patients with autonomic failure.[21] Other cardiovascular complications associated with OH/nOH include atrial fibrillation, atrial ectopy, and cardiac remodeling, including increased left ventricular mass and other ventricular and atrial changes (Table 1).[14–19] In patients with autonomic failure, increased left ventricular mass similar to hypertensive patients has been observed (both significantly higher than healthy controls).[19] However, contributions of essential hypertension to the ventricular mass changes observed in patients with autonomic failure cannot be completely ruled out, as essential hypertension can be a concomitant condition in some patients with nOH.[28] Although the mechanisms for cardiac remodeling associated with OH and nOH are uncertain, they may be related to blood pressure variability and supine hypertension.[15,16]

The prognosis of patients with nOH due to an α-synucleinopathy is highly dependent on the underlying cause of autonomic failure, with the greatest mortality risk associated with a diagnosis of multiple system atrophy and the lowest for pure autonomic failure (Table 1).[10,11] In Parkinson disease populations, patients with OH have shorter survival than those without OH, indicating that the presence of cardiovascular autonomic dysfunction (e.g., nOH) may represent a more malignant subtype of Parkinson disease.[11] Although individual studies of mortality and OH (i.e., not specifically nOH) have yielded mixed results, pooled analyses support an association between OH and an increased risk of death.[8,9] These analyses show that age and other risk factors may diminish the association between OH and mortality, suggesting that a

Table 1
Studies of morbidity and mortality associated with nOH or OH[3,4,8–22]

Study	Study type	Population	Mean age, y	Key findings
Burden				
Francois, 2017[13]	Retrospective analysis of a US medical claims database	PD + nOH (n = 281) vs PD alone (n = 17,421)	74–77	• nOH associated w/↑ falls, ↑ ED visits, ↑ inpatient stays, and ↑ costs (p ≤0.02 for all vs PD alone)
Merola, 2017[12]	Retrospective record review at 1 PD center (Cincinnati, OH, USA)	PD + OH (n = 93) vs PD alone (n = 224)	70–74	• OH associated w/↑ ED visits, ↑ hospitalization days, and ↑ healthcare costs (p <0.05 for all vs PD alone)
Claassen, 2018[3]	Patient and caregiver survey of nOH burden	nOH due to PD, MSA, or PAF (363 patients; 128 caregivers)	63–71*	• nOH symptoms associated w/falls, ↓ function, and ↓ patient QoL
Merola, 2018[4]	Prospective cohort from 2 specialty centers (Cincinnati, OH, USA, and Torino, Italy)	PD (n = 122)	66	• Symptomatic and asymptomatic OH associated w/↓ ADL, ↓ HRQoL, ↑ falls, and ↑ healthcare use (p ≤0.009 for all vs no OH)
SH				
Pavy-Le Traon, 2016[20]	Multicenter cohort study of European MSA Study group	MSA (N = 349)	64	• Statistically significant association of orthostatic symptom severity w/ SH
Fanciulli, 2016[22]	Retrospective record review at 2 centers (Innsbruck, Austria, and Rome, Italy)	PD or MSA (n = 275)	65–71	• Rates of coexistent OH + SH: 49% in MSA; 10% in PD • Association of OH w/SH in patients w/MSA (OR, 15; p = 0.002)
Palma, 2018[21]	Prospective study	nOH due to PD, MSA, or PAF (n = 57)	NR	• 67% had SH; SH associated w/↑ kidney damage (↑ BUN levels, ↓ GFR), ↑ LVH, ↑ WMHI, ↑ CV AEs, and ↑ death risk
CV Risks				
Ko, 2018[17]	Longitudinal study of a US community cohort (Framingham Heart Study)	1736 individuals; 256 w/OH at BL	72	• 224 participants developed AF during follow-up (mean, 8.3 y) • OH associated w/↑ AF (adjusted HR,† 1.6; p <0.01)
Fedorowski, 2010[18]	Longitudinal study of a Swedish community cohort (Malmö Preventive Project)	32,628 individuals; 1987 w/OH at BL	47–49 at BL	• 10% of OH group developed AF during follow-up (mean, 23 y) • OH associated w/↑ AF (adjusted HR,‡ 1.2; p = 0.035)
Magnusson, 2016[16]	Longitudinal study of a Swedish community cohort (Malmö Preventive Project)	974 individuals; 40 w/OH at BL	43–47 at BL	• OH predictive of cardiac remodeling at follow-up (mean, 23 y), including LVH, ↓ RVIDd, and ↓ ésept (adjusted HRs,§ 1.5–2.0, p ≤0.05)
Ali, 2018[15]	Cross-sectional study of patients hospitalized w/HF (Malmö, Sweden)	149 patients w/HF, 34 w/ HF + OH	74	• OH associated w/cardiac remodeling, including ↑ LA volume, ↑ IVSDd, and ↑ LVM (p ≤0.07)
Goldstein, 2010[14]	Retrospective record review at NIH Clinical Center (Bethesda, MD, USA)	PD, PD + nOH, MSA, or PAF (n = 138) vs controls (n = 41)	59–71	• Statistically significant ↑ atrial ectopy in PD + nOH, MSA, and PAF vs controls or PD alone
Milazzo, 2015[19]	Cross-sectional study of patients referred to an Italian autonomic unit (Torino, Italy)	Autonomic failure due to PD, MSA, or PAF (n = 27)	66	• ↑ LVM and ↑ atrial stiffness (measured by PWV) in autonomic failure patients vs healthy controls; damage similar to patients w/EH
Mortality				
Maule, 2012[10]	Retrospective record review of patients referred to an autonomic unit (Turin, Italy)	nOH and underlying autonomic neuropathy (n = 104)	71	• Patients w/nOH 3 × greater risk of death vs general population¶ • Adjusted HR** for death (any cause): MSA, 1.0; PD, 0.6; PAF, 0.3
Goldstein, 2015[11]	Prospective cohort of patients referred to NIH Clinical Center (Bethesda, MD, USA)	PD, PD + OH, MSA, or PAF (n = 206)	57–69 at BL	• Survival (10-y probability††): MSA (0.03–0.39) < PD + OH (0.23–0.74) < PAF (0.64–0.87) < PD no OH (0.67–0.93)

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Table 1 (*Continued*)

Study	Study type	Population	Mean age, y	Key findings
Xin, 2014[9]	Meta-analysis of 9 cohort studies	OH (N = 56,125)	46–86	• 6/9 individual studies showed statistically significant ↑ risk of death w/OH; pooled all-cause mortality RR, 1.4 (p <0.0001)
Ricci, 2015[8]	Meta-analysis of 13 prospective observational studies (10 of mortality)	OH (N = 121,913); mortality and OH analyses (n = 65,174)	46–93	• 6/10 individual studies showed statistically significant ↑ risk of death w/OH; pooled all-cause mortality RR, 1.5 (95% CI, 1.2–1.8)

ADL = activities of daily living; AE = adverse event; AF = atrial fibrillation; BL = baseline; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CI = confidence interval; CV = cardiovascular; ED = emergency department; EH = essential hypertension; ésept = early diastolic tissue velocity at mitral annulus in septal wall; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; HRQoL = health-related quality-of-life; IVSDd = interventricular septal diameter at diastole; LA = left atrial; LVH = left ventricular hypertrophy; LVM = left ventricular mass; MSA = multiple system atrophy; NIH = National Institutes of Health; nOH = neurogenic orthostatic hypotension; NR = not reported; OH = orthostatic hypotension; OR = odds ratio; PAF = pure autonomic failure; PD = Parkinson disease; PWV = carotid-femoral pulse wave velocity; QoL = quality-of-life; RR = risk ratio; RVIDd = right ventricular inner diameter in diastole; SH = supine hypertension; WMHI = white matter hyperintensities.

* Mean ages of patient respondents or patient being cared for by caregiver respondents.

† 10-y follow-up; adjusted for age, sex, BP, heart rate, height, weight, tobacco use, antihypertensive use, diabetes, history of myocardial infarction or HF.

‡ Adjusted for age, sex, BP, BMI, smoking, total cholesterol, diabetes.

§ Adjusted for age, sex, systolic BP, BMI, antihypertensive treatment.

¶ General population of same geographic region of similar age during same period.

** Adjusted for age, hypertension, use of fludrocortisone, midodrine, or angiotensin-converting enzyme inhibitors.

†† Survival probabilities from symptom onset or first evaluation, adjusted for age and sex.

confluence of factors, including cardiovascular autonomic dysfunction, may contribute to survival outcomes.[8,9]

Treatment of nOH

Treatment goals and considerations

The goal of nOH management is to improve symptoms; complete normalization of blood pressure is unrealistic. Culprit medications should be reduced or discontinued, if possible, such as antihypertensive medications (particularly daytime use), diuretics, β-blockers, and vasodilators.[7] Initial management includes nonpharmacologic measures, such as abdominal compression garments, bolus water ingestion, and increased physical activity (performed supine).[2,29] Tilting the head of the bed at a 30° angle can reduce night-time supine hypertension and associated volume depletion, leading to reduction of nOH symptoms in the morning.[2] However, if nOH symptoms are not sufficiently managed, pharmacologic intervention may be necessary (Table 2).[30–63] Droxidopa, midodrine, and fludrocortisone are the most commonly used medications to treat nOH or OH (Table 3).[64–68]

As nOH and supine hypertension are mechanistically related but hemodynamically opposite, these conditions may pose a clinical challenge in that treatment for one may exacerbate the other.[2,5] Patients with relatively rapid disease progression, such as those with multiple system atrophy, may benefit from aggressive nOH treatment.[2] Patients with disorders associated with a longer course of survival (e.g., pure autonomic failure) may require treatment of supine hypertension to lower the risk of end-organ damage or other adverse events.[69] Although supine hypertension might increase long-term cardiovascular risk, clinicians and patients need to balance treatment decisions between the choice of a more functional life with higher morbidity and mortality risks or a bed-bound life with lower morbidity and mortality.

Droxidopa

Droxidopa, a norepinephrine prodrug, is currently the only therapy approved by the US Food and Drug Administration to treat symptoms of nOH in patients with Parkinson disease, multiple system atrophy, pure autonomic failure, dopamine β-hydroxylase deficiency, and nondiabetic autonomic neuropathy.[67] Droxidopa is converted by L-aromatic-amino-acid decarboxylase to norepinephrine, which mediates a pressor response.[67] Efficacy and safety of droxidopa for the treatment of nOH symptoms have been demonstrated in several clinical trials (Table 2),[30–33] which mostly enrolled patients with α-synucleinopathies (approximately 2/3 of the clinical trial population had Parkinson disease). An integrated analysis of clinical trial data showed that droxidopa treatment increased standing blood pressure from baseline (respective systolic and diastolic blood pressure increases, 12 and 8 mm Hg vs placebo; both p <0.001) and significantly improved patient-reported symptoms of nOH (lightheadedness/dizziness, feeling faint, visual disturbances, weakness, and fatigue) and their ability to perform activities involving standing or walking.[70]

Table 2
Overview of studies with pharmacologic treatments for nOH or OH[30–63]

Author Year	Study design	Subjects	Diagnosis	Mean age, Y	Comparison	Key findings
Droxidopa						
Kaufmann, 2014[30]	Phase 3 RCT	263 (162*)	nOH due to PD, PAF, MSA, or NDAN	56–57	Droxidopa (100–600 mg tid); vs PBO	• Droxidopa vs PBO: ↓ nOH symptoms; ↑ standing BP (p <0.001) • Common AEs: headache, dizziness, and nausea; cardiac AEs, 3%
Biaggioni, 2015[31]	Phase 3 RCT	181 (101*)	nOH due to PD, PAF, MSA, or NDAN†	63–67	Droxidopa (100–600 mg tid); vs PBO	• Droxidopa vs PBO: ↓ nOH symptoms; change in standing BP NS • Common AEs: headache, dizziness, fatigue
Hauser, 2014[32]	Phase 3 RCT	51	nOH due to PD	72–73	Droxidopa (100–600 mg tid); vs PBO	• Droxidopa vs PBO: ↓ number of falls
Hauser, 2014[33]	Phase 3 RCT	174	nOH due to PD	72–73	Droxidopa (100–600 mg tid); vs PBO	• Droxidopa vs PBO: ↓ dizziness/lightheadedness (p = 0.018) • Common AEs: headache, dizziness, fatigue, nausea, HTN
Isaacson, 2016[34]	Phase 3 OLE	102	nOH due to PD, PAF, MSA, or NDAN†	66–68	Droxidopa (100–600 mg tid)	• Droxidopa: ↓ nOH symptoms through 12 months • 2 patients w/angina, first-degree AV block, or SV extrasystole
Isaacson, 2016[35]	Phase 3 OL	350	nOH due to PD, PAF, MSA, or NDAN	66	Droxidopa (100–600 mg tid)	• Common AEs: falls, GI disorders, UTIs, headache, syncope • Cardiac-related AEs in 5% of patients; SH in 5% of patients
Freeman, 1999[36]	RCT, crossover	10	nOH and MSA or PAF	60	Droxidopa (1000 mg); vs PBO	• Droxidopa vs PBO: ↓ fall in BP during tilt test (p <0.05)
Midodrine						
Jankovic, 1993[37]	RCT	97	OH and PAF, MSA, DM, or PD	59–65	Midodrine (2.5–10 mg tid) vs PBO	• 10-mg midodrine vs PBO: ↑ standing SBP (p <0.001); ↓ nOH symptoms • Common AEs: pruritus/tingling scalp, SH, urinary urgency
Low, 1997[38]	RCT	171	nOH and PAF, MSA, DM, or PD		Midodrine (10 mg tid) vs PBO	• Midodrine vs PBO: ↑ standing SBP (p <0.001); ↓ nOH symptoms • Common AEs: piloerection, pruritus, paresthesia, SH, urinary urgency
Wright, 1998[39]	RCT, crossover	25	nOH and PAF, MSA, DAN, or PD	62	Midodrine (2.5–10 mg) vs PBO	• Midodrine vs PBO: ↑ standing BP; ↓ nOH symptoms (dose-dependent) • AEs: SH (>200 mm Hg), goose bumps, paresthesia, pruritus
Smith, 2016[40]	Phase 4 RCT	24	nOH and PAF, MSA, PD, or AN	44	Midodrine (2.5–10 mg, >10 mg) vs PBO	• Midodrine vs PBO: ↑ time to syncopal symptoms/near syncope on tilt-table (p = 0.013)
Fludrocortisone						
Campbell, 1975[41]	RCT, crossover	6	OH and DM	52	Fludrocortisone (0.1 mg bid) vs PBO	• Fludrocortisone vs PBO: ↑ tilted (p <0.005) and supine BP (p <0.05); symptom improvement in 4 patients
Campbell, 1976[42]	OL	14	OH and DM	51	Fludrocortisone (0.1–0.4 mg bid)	• ↑ standing BP (p <0.001); symptom improvement in 13 patients
Hoehn, 1975[43]	OL	6	nOH and PD	NR	Fludrocortisone (0.05–0.2 mg)	• ↓ nOH symptoms
Hussain, 1996[44]	Prospective case series	64	Syncope clinic patients	80	Fludrocortisone (0.05, 0.1, 0.2 mg)	• Cardiac-related AEs: HTN, cardiac failure, HTN and stroke, hypokalemia; treatment withdrawn in 17 patients
Grijalva, 2017[45]	Retrospectivecohort	2121 (1324)‡	OH	67 (Median)	NR	• ↑ hospitalization rate vs midodrine patients • ↑ hospitalization rate in patients with CHF vs midodrine patients
Octreotide						
Hoeldtke, 1986[46]	RCT	8	AN and postprandial hypotension	56	Octreotide (0.2–1.6 μg/kg SC)	• ↑ postprandial BP (p <0.001) • AEs: abdominal cramps, nausea; SH in 3 patients
Hoeldtke, 1989[47]	RCT	11	OH and MSA or progressive AF	65–68	Octreotide (0.8 μg/kg SC), PBO	• Prevented postprandial hypotension and associated symptoms

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Table 2 (***Continued***)

Author Year	Study design	Subjects	Diagnosis	Mean age, Y	Comparison	Key findings
Hoeldtke, 1989[48]	RCT	28	OH and sympathotonic OH, MSA, PAF, DAN	21−89	Octreotide (0.2−1.6 μg/kg SC) vs PBO	• Octreotide vs PBO: ↑ semirecumbent BP in patients with MSA, PAF, DAN ($p < 0.025$); improved walking BP in some patients
Alam, 1995[49]	RCT (intrasubject)	18	OH and MSA or PAF	44−73	Octreotide (1 μg/kg SC, bid) vs PBO	• Octreotide vs PBO: ↑ seated and standing SBP ($p < 0.05$); ↑ postprandial SBP ($p < 0.05$)
Bordet, 1995[50]	RCT	9	nOH and MSA	72 (median)	Octreotide (1 μg/kg SC, bid) vs PBO	• Octreotide vs PBO: delayed time ($p = 0.02$) to reach minimal BP during head-up tilt
Yohimbine						
Okamoto, 2012[51]	RCT, crossover	17	nOH and PAF or PD	64	Yohimbine (5.4 mg), atomoxetine (18 mg), PBO	• No effect of individual treatments vs PBO; combination: ↑ seated SBP ($p < 0.001$) and improved OH symptoms ($p = 0.022$)
Jordan, 1998[52]	RCT	35	nOH and MSA or PAF	67	Yohimbine (5.4 mg) vs PBO	• Yohimbine vs PBO: ↑ seated and standing SBP ($p < 0.05$)
Onrot, 1987[53]	OL	11	OH and AF	70	Yohimbine (2.5, 5 mg)	• Dose-dependent ↑ seated BP ($p < 0.01$) with 5-mg
Shibao, 2010[54]	RCT, crossover	31	nOH and MSA, PAF, or PD	66	Yohimbine (5.4 mg), pyridostigmine (60 mg), PBO	• Yohimbine vs PBO or pyridostigmine: ↑ standing DBP ($p \leq 0.001$) and ↓ presyncopal symptoms; combination ↑ standing DBP ($p = 0.006$)
Erythropoietin						
Biaggioni, 1994[55]	OL	5	Anemia and AF	67	Erythropoietin (25, 50 U/kg SC); 3 times/week	• Improved standing BP
Hoeldtke, 1993[56]	OL	8	OH and DM, PAF or sympathotonic OH	48	Erythropoietin (50 U/kg SC); 3 times/week	• ↑ standing BP ($p < 0.01$)
Pyridostigmine						
Singer, 2006[57]	RCT, crossover	58	nOH and PAF, MSA, DAN, autoimmune NP	59	Pyridostigmine (60 mg), midodrine (2.5, 5 mg), PBO	• Combination pyridostigmine + midodrine vs PBO: ↑ standing DBP ($p = 0.002$); improved OI symptoms ($p < 0.001$)
Atomoxetine						
Shibao, 2007[58]	RCT, crossover	21	MSA, PD, peripheral AF	62 (MSA) 67 (PD/AF)	Atomoxetine (18 mg), PBO	• Atomoxetine vs PBO: ↑ seated/standing SBP ($p = 0.004$/$p = 0.016$) in MSA patients; no effects in peripheral AF or PD patients
Ramirez, 2014[59]	RCT, crossover	69	nOH and PAF, MSA, or PD	65	Atomoxetine (18 mg), midodrine (5−10 mg), PBO	• Atomoxetine vs PBO: ↑ seated BP and improved OH symptoms ($p < 0.05$); atomoxetine vs midodrine: ↑ seated BP ($p = 0.03$)
Pseudoephedrine						
Jordan, 2004[60]	OL	9	Severe nOH and MSA or PAF	66[§]	Pseudoephedrine (30 mg) ± 50 or 480 ml water	• Pseudoephedrine + water (480 mL): ↑ seated SBP ($p < 0.001$) vs 50 ml of water
Ephedrine						
Fouad-Tarazi, 1995[61]	RCT, crossover	8	Idiopathic OH or MSA	60	Ephedrine (8.4 mg)[¶] midodrine (22.3 mg),[¶] PBO	• Ephedrine and midodrine ↑ supine SBP ($p < 0.01$) • Midodrine ↑ standing BP vs ephedrine and PBO ($p < 0.001$)
Desmopressin						
Mathias, 1986[62]	OL	6	Symptomatic OH and progressive AF	Range: 55−68	Desmopressin (2, 4 μg IM)	• ↓ nocturnal polyuria ($p < 0.01$); prevented morning↓ in orthostatic BP ($p < 0.05$)
Sakakibara, 2003[63]	OL	3	MSA	62	Desmopressin (5 μg IN)	• ↓ nocturnal polyuria and nocturia

AEs = adverse events; AF = autonomic failure; AN = autonomic neuropathy; AV = atrioventricular; bid = twice daily; BP = blood pressure; CHF = congestive heart failure; DAN = diabetic autonomic neuropathy; DBP = diastolic blood pressure; DM = diabetes mellitus; GI = gastrointestinal; HTN = hypertension; IM = intramuscular; IN = intranasal; MSA = multiple system atrophy; NDAN = nondiabetic autonomic neuropathy; nOH = neurogenic orthostatic hypotension; NP = neuropathy; NR = not reported; NS = not statistically significant; OH = orthostatic hypotension; OI = orthostatic intolerance; OL = open-label; OLE = open-label extension; PAF = pure autonomic failure; PBO = placebo; PD = Parkinson disease; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; SH = supine hypertension; SV = supraventricular; tid = three times daily; UTI = urinary tract infection.

* Number of patients randomized to PBO or droxidopa.

† 1 patient in the study had dopamine β-hydroxylase deficiency.

‡ Represents the number of patients on fludrocortisone.

§ Mean age of all patients (n = 13) in the study; not the 9 patients who received 30 mg of pseudoephedrine.

¶ Represents the mean maintenance dose.

Table 3
Contraindications and adverse events of common pharmacologic treatments for nOH or OH[64–68]

	Droxidopa	Midodrine	Fludrocortisone
Regulatory status	FDA approved for symptomatic nOH	FDA approved for symptomatic OH	Off-label use
Recommended dose	100–600 mg, tid; maximum daily dose: 1800 mg	10 mg, tid	0.05–0.3 mg daily
Contraindications and precautions			
Comorbid conditions	Severe renal impairment: use with caution	Urinary retention, diabetes, renal or hepatic impairment	Heart failure, kidney failure, or hypertension: contraindicated
Concomitant pharmacy	DDCIs and other agents that increase BP: use with care	Use with other vasoconstrictors or agents that reduce HR: monitor BP carefully	Use with midodrine may increase SH risk; use with AChEI may cause muscle weakness
Adverse events			
Cardiac	Emergence or exacerbation of SH: common (RR, 1.4 [95% CrI, 0.7–2.7])	Emergence or exacerbation of SH: common (RR, 5.1 [95% CrI, 1.6–24])	Emergence or exacerbation of SH: common
Other	Headache, dizziness, and nausea most common (2%–13%)	Paresthesia, piloerection, dysuria, pruritus most common: (12%–18%)	Headache, nausea, dizziness, edema, hypokalemia

AChEI = cholinesterase inhibitors; BP = blood pressure; CrI = credible interval; DDCIs = dopamine decarboxylase inhibitors; FDA = US Food and Drug Administration; HR = heart rate; nOH = neurogenic orthostatic hypotension; OH = orthostatic hypotension; RR = risk ratio; SH = supine hypertension; tid = 3 times daily.

Droxidopa treatment was associated with reductions in falls, fear of falling, and nOH symptoms, as well as improved measures of physical function and mental well-being (vs before treatment initiation) in a 6-month prospective study of real-world use.[71] Although these data are informative regarding results observed in the more diverse cross-section of patients treated in normal clinical practice (vs clinical trial populations), interpretation of the findings is limited by the open-label study design.

Patients taking droxidopa may exhibit supine hypertension.[67] In clinical trials of droxidopa, hypertension was the most frequently reported cardiac adverse events.[72] In a 12-month extension study, incidence rates of supine hypertension ranged from 3.8% to 12.3%, with no significant increase in the incidence of supine hypertension with increasing duration of exposure noted.[34]

Our anecdotal clinical experience suggests that long-term treatment with droxidopa and resultant improvement in the nOH symptoms may also improve supine hypertension. These observations may be due to correction of the hypotensive state possibly attenuating alterations of the renin-angiotensin-aldosterone system and in renal fluid and salt reabsorption processes caused by chronic daily hypotension. It is also possible that improved control of supine hypertension reduces pressure natriuresis overnight, thereby leading to improvement of nOH during the daytime. Accordingly, adequate control of nOH and supine hypertension is essential to preventing the cycle, and exploration in formal studies is warranted to better understand the effects of treatment in both conditions.

Currently available data indicate that there are limited signals of cardiovascular safety concern with droxidopa, including incidence of serious cardiac adverse events (Table 3), although this association has not been carefully studied.[70] In the droxidopa clinical trials, the rates of hypertension (2% to 7%), blood pressure increase (0% to 7%), first-degree atrioventricular block (1% to 3%), atrial fibrillation (1% to 3%), or supraventricular extrasystoles (1% to 3%) were low.[72] Patients with preexisting cardiovascular disorders showed a higher incidence of these findings, but the most common cardiovascular events were relatively mild (e.g., supine hypertension), and the rate of discontinuation because of these events was low (≤3%).[72]

Little to no effect of droxidopa on heart rate has been observed in patients with nOH or healthy individuals.[70,73] In healthy individuals, meaningful changes in QTc interval were not observed with therapeutic or supra-therapeutic doses of droxidopa,[73] and it is likely droxidopa would have less effect in nOH populations because of centralized autonomic nervous system denervation.[74] Further study of droxidopa is required regarding use in patients with cardiovascular disease and effects on myocardial volume oxygen and contractility.

Droxidopa is metabolized directly to norepinephrine and likely exerts its effects on blood pressure by inducing peripheral vasoconstriction, although the precise mechanism of action is unknown.[67] Plasma concentrations of droxidopa peak at 1 to 4 hours after dosing.[67,75] Because droxidopa elevates norepinephrine levels, there may be some concerns about increasing catecholamine levels in patients with cardiac co-morbidities, including atrial

fibrillation.[76] The increases in plasma norepinephrine levels with droxidopa has been shown to be modest (72 pg/ml)[77] to moderate (956 pg/ml),[78] with a peak increase of 956 pg/ml (supine measurement) noted after a single 400-mg dose.[78] In patients with autonomic failure (n = 10), the maximum increase in plasma norepinephrine level after a single 1000-mg dose of droxidopa was 222 to 230 pg/ml (supine and upright tilt, respectively).[36] In 2 patients with dopamine β-hydroxylase deficiency and extremely low levels of plasma norepinephrine at baseline (<5 pg/ml), a 600-mg dose of droxidopa increased plasma norepinephrine by 72 and 122 pg/ml (maximum increase) in each patient.[77] Given that the upper limit of normal supine norepinephrine is 520 pg/ml, the increase of 956 pg/ml noted previously appears to be an outlier. A 50 to 200-pg/ml increase in norepinephrine levels may be more typical of the effect of droxidopa, especially given that norepinephrine levels double in normal, healthy individuals when standing.[79] In patients with autonomic failure, it is this norepinephrine increase that does not occur,[80] and droxidopa administration and its associated increase in norepinephrine levels compensate for this deficiency.

The most common noncardiovascular adverse events reported in clinical trials of droxidopa included headaches, dizziness, urinary tract infections, fatigue, and nausea.[70] Droxidopa may be associated with relatively few long-term adverse events, with the most common adverse events in the long-term open-label extension trial (experienced by ≥5% of patients) including falls, gastrointestinal disorders, urinary tract infections, headache, syncope, dizziness, fatigue, nausea, asthenia, back pain, and contusions.[34]

Midodrine

Midodrine is an α-1 agonist approved by the U.S. Food and Drug Administration in 1996 to treat the symptoms of OH.[68] Midodrine acts by activating vascular α-adrenergic receptors, increasing vascular tone, and elevating blood pressure.[68] The approval of midodrine was based on an increase in standing systolic blood pressure, a surrogate marker of clinical benefit (e.g., improvement of orthostatic symptoms).[68] In clinical trials, patients with OH receiving midodrine experienced significant, dose-dependent increases in standing systolic and diastolic blood pressure compared with patients receiving placebo (Table 2).[37−39] Midodrine raises systolic blood pressure to a similar degree in standing and supine positions (increases of 20 to 22 mm Hg and 16 to 18 mm Hg, respectively).[38] Consequently, midodrine treatment can induce or worsen supine hypertension, particularly at doses >20 mg/day.[38,39] Other than hypertension, common adverse events associated with midodrine include piloerection, scalp paresthesia and pruritus, and urinary hesitancy/retention.[68,81]

Droxidopa versus midodrine

Only indirect comparative analyses of safety or efficacy of midodrine and droxidopa in patients with nOH have been reported.[64] A Bayesian meta-analysis and mixed treatment comparison of randomized trial data showed that only midodrine had a significant risk ratio for supine hypertension (5.1; 95% credible interval, 1.6 to 24).[64] The risk ratio for supine hypertension in patients receiving droxidopa was 1.4 (95% credible interval, 0.71 to 2.7). The difference in supine hypertension risk between droxidopa and midodrine may be related to the significantly greater effect of midodrine on standing systolic blood pressure.[64]

Mechanistically, droxidopa, a norepinephrine precursor, likely acts on α- and β-adrenergic receptors (directly or indirectly), whereas midodrine acts specifically and directly on α-adrenergic receptors.[67,68] Droxidopa readily penetrates the central nervous system and may affect neurons,[67,82] whereas desglymidodrine, the active metabolite of midodrine, crosses the blood-brain barrier poorly.[68] Compared with more specific effects of midodrine, different sites of action and broader effects of droxidopa may be associated with better systematic tolerance. For example, droxidopa does not affect the prostate, but the primarily peripheral distribution of desglymidodrine and the direct stimulation of α-adrenergic receptors with midodrine may result in contraction of the prostate.

Off-label treatments

Off-label medications have been used to treat patients with nOH with varied success. The choice of therapy should take into account the patient history and potential safety concerns.[65] Numerous drugs have been studied as off-label treatments for nOH (Table 2),[41−43,45,46,48−63] but only limited support for efficacy is available.[1,65,66] Fludrocortisone, which is commonly used, is contraindicated in patients with heart failure and may pose a high cardiovascular safety risk (Table 3)[65] when used alone or in combination with midodrine.[2,65,66,83] Fludrocortisone used in combination with pyridostigmine can cause weakness.[84] Atomoxetine has shown early promise but may not be safe in patients with cardiac or cerebrovascular co-morbidities.[65,85] Erythropoietin (in combination with iron supplementation) may be helpful in patients with nOH and anemia, but the risk of supine hypertension should be considered carefully.[56,65] Additional limitations of other off-label treatments include relatively impractical delivery methods (e.g., octreotide subcutaneous injection) or the potential for serious adverse events (e.g., electrolyte imbalance with desmopressin use).[86,87]

Recommendations for the Treatment of Patients With nOH and Cardiac Co-morbidities

Recommendations for the pharmacologic treatment of patients with nOH who have supine hypertension, heart failure, diabetes, arrhythmias, or implantable defibrillators are detailed in Table 4.[65−68,87,88]

Supine hypertension

All patients with autonomic failure may experience worsened supine hypertension with antihypotensive treatment for nOH (Tables 3 and 4); however, good gravitational hygiene (e.g., not resting or sleeping in a fully supine position) and proper timing of medication (i.e., final daily dose of antihypotensive medication ≥5 hours before bedtime) can decrease the severity of supine hypertension.[2,89] A short-acting antihypertensive medication

Table 4
Recommendations for pharmacologic treatment of nOH in patients with comorbidities[65–68,87,88]

	Approved for nOH/OH		Off-label treatments	
	Droxidopa	Midodrine	Fludrocortisone	Octreotide
Supine hypertension	• Monitor supine BP due to risk of supine hypertension[67]	• Can cause marked elevation of supine BP[68]	• Contraindicated in patients w/ hypertension[66]	–
Heart failure	• Can be used with caution; risk assessment necessary	• Not recommended[88]	• Contraindicated[88]	–
Arrhythmias	• No data available in patients w/long QT syndrome	• May exacerbate bradycardia; not optimal w/pre-existing slow HR	• ↑ Arrhythmia risk due to hypokalemia; monitor electrolytes	–
Diabetes	• Limited data available; not approved for nOH due to diabetic autonomic neuropathy	• Use with caution	–	• Contraindicated due to GI AEs (i.e., hyperglycemia)[65,87]
Implantable defibrillators	• SOC treatment for OH not contraindicated			

AE = adverse event; BP = blood pressure; GI = gastrointestinal; HR = heart rate; nOH = neurogenic orthostatic hypotension; OH = orthostatic hypotension; SOC = standard of care.

(e.g., captopril, hydralazine, losartan, short-acting nifedipine, or a nitroglycerin patch) can be prescribed at night as needed.[2,89] Clonidine can have prolonged effects, which may exacerbate nOH symptoms in the morning.[2,89]

Heart failure

Some studies suggest an association between OH and heart failure, but a causal relation has not been established.[90–92] Management of OH in patients with heart failure may primarily warrant nonpharmacologic approaches.[29,88]

Since some medications used to treat symptoms of heart failure may induce or worsen nOH,[2,88] medication adjustments should be considered (e.g., minimize use of and dose of vasodilators, diuretics, and β-blockers).[93] More selective β-blockers (e.g., bisoprolol or metoprolol succinate) may be preferable to carvedilol in patients with systolic heart failure. Because correction of volume depletion can improve nOH symptoms, we employ weight-based dosing and use "damp weight" over dry weight when prescribing diuretic therapy in patients with coexistent nOH and heart failure. If severe symptoms persist after medication adjustments and nonpharmacologic measures, droxidopa may be given with caution and careful monitoring (Table 4). In patients with heart failure, fludrocortisone (because of risk of hypokalemia, worsening hypertension) and midodrine (because of risk of urinary retention, worsening hypertension) may be contraindicated.[88]

Arrhythmias

Standard-of-care treatment for nOH is not contraindicated in patients with contraction, fibrillation, flutter, bradycardia, or tachycardia arrhythmias. If a β-blocker is used, dosage should be kept low if orthostatic symptoms worsen.[94] Other medications used for atrial fibrillation (e.g., amiodarone, verapamil, propafenone, sotalol, and flecainide) can result in peripheral polyneuropathies, which could exacerbate some nOH symptoms (e.g., weakness).[95,96] Although a mechanistic association between nOH and arrhythmias has been suggested, there are no data suggesting how management of OH would affect the risk of atrial fibrillation.[17,18]

Fludrocortisone use may increase arrhythmia risk due to hypokalemia (approximately 50% of patients); electrolytes should be monitored.[45,66] Since midodrine may exacerbate bradycardia, it may not be optimal for patients with preexisting bradycardia (Table 4).[68] Although clinical trial data show little effect of droxidopa on heart rate or QT interval,[70,72,73] no data are available for effects in patients with long QT syndrome.

Diabetes

Although autonomic neuropathy and nOH can occur in patients with diabetes mellitus (types 1 and 2),[97] no randomized controlled trials of droxidopa in patients with diabetic autonomic neuropathy have been conducted. In the 3 clinical trials of droxidopa, patients with diabetes were eligible for participation in only 1, and only a few patients with Parkinson disease and diabetes mellitus type 1 or 2 (n = 10) were enrolled.[98] Droxidopa is not approved for the treatment of OH in patients with diabetic autonomic neuropathy (i.e., off-label use; Table 4). When treating patients with nOH and diabetes mellitus agent-specific safety concerns may arise.[65,87]

Implantable defibrillators and pacemakers

Standard-of-care treatment for OH is not contraindicated in patients with implantable defibrillators (Table 4). Although pacemakers with closed-loop stimulation rate-adaptive sensors are associated with a lower prevalence of OH versus accelerometers or no rate sensors, pacemakers alone are generally inadequate to treat nOH.[99,100]

Conclusions

It is critical to recognize and treat symptoms of nOH to avoid potentially devastating consequences (e.g., falls, decreased function in daily activities, diminished quality-of-life[3]); however, management can be challenging. Although treating nOH can exacerbate supine hypertension, there is little evidence that treatment of nOH will worsen other comorbid cardiovascular disease. Existing evidence (albeit somewhat limited) indicates that droxidopa has a

good safety profile in patients with cardiovascular disease and may be less likely to exacerbate supine hypertension than midodrine.[64] Nevertheless, further safety data are required on droxidopa treatment in patients with coronary artery disease or low left ventricular ejection fraction. Additional studies investigating the safety profiles and effectiveness of other nOH treatments in patients with cardiovascular disease are also needed.

Data Statement

There are no data associated with this narrative review.

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