Neurogenic Orthostatic Hypotension: State of the Art and Therapeutic Strategies

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ABSTRACT: Neurogenic orthostatic hypotension (nOH) is a subtype of orthostatic hypotension in which patients have impaired regulation of standing blood pressure due to autonomic dysfunction. Several primary and secondary causes of this disease exist. Patients may present with an array of symptoms making diagnosis difficult. This review article addresses the epidemiology, pathophysiology, causes, clinical features, and management of nOH. We highlight various pharmacological and non-pharmacological approaches to treatment, and review the recent guidelines and our approach to nOH.

KEYWORDS: Neurogenic OH, autonomic dysfunction

Introduction

Orthostatic hypotension (OH) is defined as a fall in systolic blood pressure (SBP) of ≥20 mm Hg or diastolic blood pressure (DBP) of ≥10 mm Hg, within 3 minutes of standing.[1] This definition was updated in 2011 to include a fall in SBP of ≥30 mm Hg for patients with an elevated baseline BP including those with supine hypertension (SH).[2] In patients with Multiple System Atrophy (MSA), a fall of ≥30 mmHg in SBP or ≥15 mmHg in DBP is used to define OH.[3,4] Delayed OH is when orthostatic symptoms take longer than 3 minutes to emerge.[5] This indicates an early form of sympathetic adrenergic failure—more than 50% of such patients will develop classic OH over the next decade.[5] These differences in diagnostic criteria create an area of some uncertainty regarding optimal definitions.

Non-neurogenic OH is caused by reduced cardiac output and/or impaired vasoconstriction without a primary autonomic disorder. On the other hand, neurogenic OH (nOH) typically results from inadequate vasomotor sympathetic release of nor-epinephrine due to autonomic dysfunction.[6] This reduction in sympathetic innervation also causes the heart rate (HR) to increase less than expected.[7] nOH is not solely a disease of low BP but also of high BP (ie, supine hypertension) such that the narrow range of BP normality is perturbed, and patients often display both OH and SH at differing times. This dysfunction can arise from impaired central neural pathways that regulate sympathetic control, or from deficient activation of vascular adrenoceptors due to degenerative postganglionic sympathetic neurons.[6] nOH is a debilitating disorder that carries significant morbidity and is an independent risk factor for mortality.[8-10]

Methods

We searched PubMed CENTRAL, MEDLINE, Embase, and Web of Science in July 2020. We included all English language studies on nOH reporting diagnosis and therapies. We included reviews, controlled trials, cohort studies or case-control studies. Inclusion was considered irrespective of prospective or retrospective recruitment or publication date. The key terms searched were neurogenic orthostatic hypotension, expert documents, guidelines, and practice recommendations. The reference lists of all relevant articles were scrutinized for relevant studies. Full texts of all eligible studies were retrieved. Data from the included studies were extracted and collated using a standardized extraction form. The selection process was recorded in a PRISMA flow diagram (Figure 1). This systematic literature search identified 491 citations. Deduplication left 443 citations, of which 281 were excluded because they did not contain relevant data on therapy, were case reports, or not about nOH. Full texts of 162 articles were retrieved and 54 were excluded because they did not report enough detail or were conference abstracts. Thus, 108 studies were included.

Epidemiology and causes

The cross-sectional prevalence of OH in unselected patients aged 65 years or older is between 5% and 30%.[8,11] OH is an independent risk factor for mortality, stroke, and adverse cardiovascular (CV) outcomes including coronary artery disease and myocardial infarction.[8,10,12-18] The increase in age related prevalence may be attributed to the decrease in the effectiveness of the counter-regulatory mechanisms including reduced vasomotor tone, decreased baroreflex sensitivity, decreased ß-adrenoreceptor mediated responses, reduced cardiac compliance, increased arterial stiffness, and attenuation of the vestibulosympathetic reflex.[12,19,20]

Although OH is a frequent problem encountered in primary care, nOH is relatively uncommon and is more often diagnosed by neurologists and cardiologists. As previously
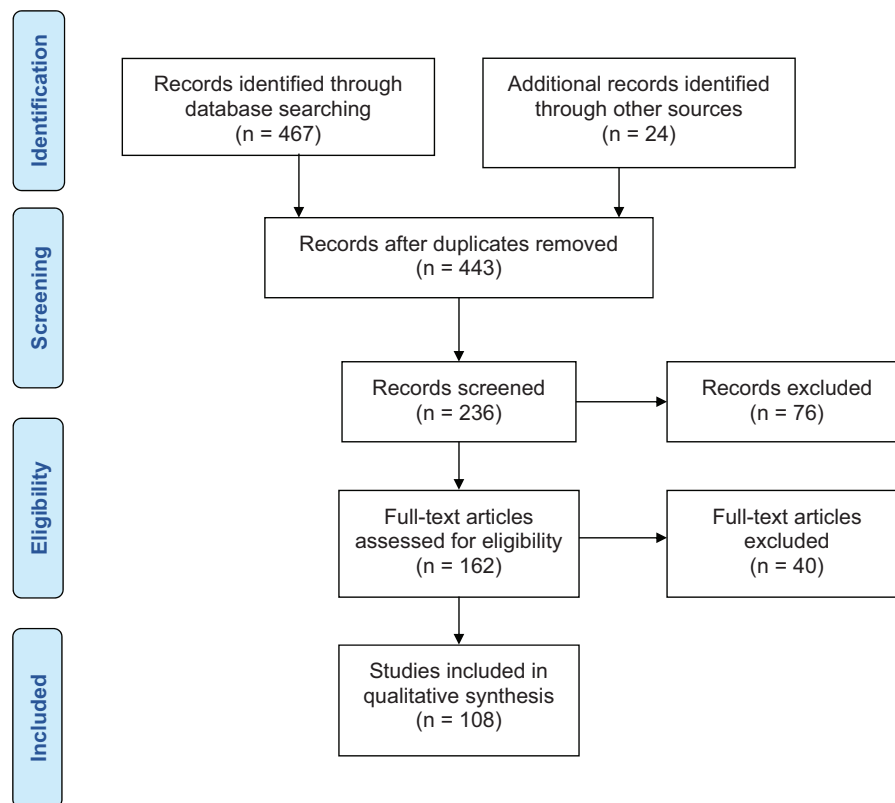
Figure 1. PRISMA flow chart.

mentioned, when OH occurs either because of reduced norepi-nephrine release from postganglionic sympathetic nerves, or due to central autonomic neurodegeneration leading to defective vasoconstriction in the upright posture, it is referred to as nOH.[7] nOH is best understood as a neurotransmitter disorder and has been classified as an orphan disease (ie, one which affects fewer than 200 000 people in the United States[7,11,21]), however the true prevalence of nOH is unknown and is likely underestimated.[7]

Among the primary causes of nOH are a group of neurodegenerative diseases characterized pathologically by the deposition of the protein α-synuclein in the central or peripheral nervous system, including Parkinson's Disease (PD), MSA, Pure Autonomic Failure (PAF), and Dementia with Lewy Bodies (DLB). These 4 conditions are thus called α-synucleinopathies and have nOH as a common manifestation. Despite clinical similarities, there are major pathological differences; thus, they are further subdivided into 2 phenotypes: Lewy Body Diseases (PD, PAF, and DLB), and MSA on basis of the neuronal cell type involved and degree of neuronal loss.[22,23] In a large meta-analysis of 25 studies, the prevalence of nOH in PD was 30%.[24] In another prospective cohort study of 175 patients with MSA, the prevalence of nOH was 78%. About 50% of patients with DLB have nOH.[25]

There are also a variety of metabolic, autoimmune, and neoplastic conditions that produce secondary nOH[7,26-28] (Figure 2). Amongst these, diabetes is one of the most common causes and about 8% of diabetics develop nOH.[29]

Clinical presentation and severity

The majority of patients with OH do not have dizziness[12]—in one study, only 2% of participants had symptoms, whereas 16.2% were asymptomatic.[13] In another study of 12 433 patients, symptoms were not significantly different in patients with or without OH (11.3% vs 9.4%).[15] Similarly, patients with nOH may or may not experience symptoms. The chronic nature of nOH allows remarkable adaptive changes in cerebral autoregulatory mechanisms. Thus, patients, are frequently able to tolerate wide swings in BPs and remain conscious at pressures that would otherwise induce syncope in healthy subjects.[30] In a study of 1125 patients with PD, only 18% reported any OH symptoms.[31] In contrast, nOH symptoms were much more frequently seen in patients with MSA (81%) and DLB (31%).

Symptoms also vary according to the location of the lesion, especially the presence of Lewy bodies in locations such as locus ceruleus, sympathetic ganglia, and parasympathetic plexus which may be responsible for autonomic, axial, or cognitive symptoms.[32] A recent study of 363 nOH patients with PD, MSA, or PAF reported lightheadedness as the most common symptom followed by several others (Table 1).[33] Additional symptoms of autonomic failure and neurological symptoms can help differentiate them from patients with non-neurogenic OH (Table 2).[30,34] Common symptoms include dizziness, blurring of vision/tunnel vision, impaired cognition, syncope and rarely, seizures.[34] Symptoms related to muscle hypoperfusion are coat hanger ache (pain in the suboccipital, paracervical, and shoulder muscles), lower back pain or calf claudication.[34-37] Symptoms such as

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                                          ┌──────────────────────────┐
                                          │ 1. Multiple System atrophy│
                              ┌──────────┐ │ 2. Dopamine β hydroxylase│
                              │ Central or│ │    deficiency            │
                              │ peripheral│ │ 3. Autoimmune gangliopathy│
                              │ autonomic │─│ 4. Parkinson's disease   │
                  ┌─────────┐ │ nervous system│ 5. Pure autonomic failure│
                  │ Primary │─│ inolvement│ │ 6. Lewy Body Dementia    │
                  │ causes  │ └──────────┘ │ 7. Familial dysautonomia │
                  └─────────┘              └──────────────────────────┘
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Figure 2 — Classification of causes of nOH

- Primary causes
  - Central or peripheral autonomic nervous system inolvement
    1. Multiple System atrophy
    2. Dopamine β hydroxylase deficiency
    3. Autoimmune gangliopathy
    4. Parkinson's disease
    5. Pure autonomic failure
    6. Lewy Body Dementia
    7. Familial dysautonomia
- Secondary causes
  - Neuropathies
    1. Diabetic autonomic neuropathy
    2. Amyloidosis
    3. Drug induced acute autonomic neuropathy
    4. Toxic acute autonomic neuropathy
    5. Botulism
    6. Porphyria
  - Neoplastic
    1. Posterior fossa tumors
    2. Spinal cord tumors
    3. Paraneoplastic acute or chronic autonomic neuropathy
  - Spinal Cord
    1. Traumatic tetraplegia
    2. Syringomyelia
    3. Subacute combined degeneration
  - Inflammatory/autoimmune
    1. Multiple sclerosis
    2. Guillain-Barre Syndrome
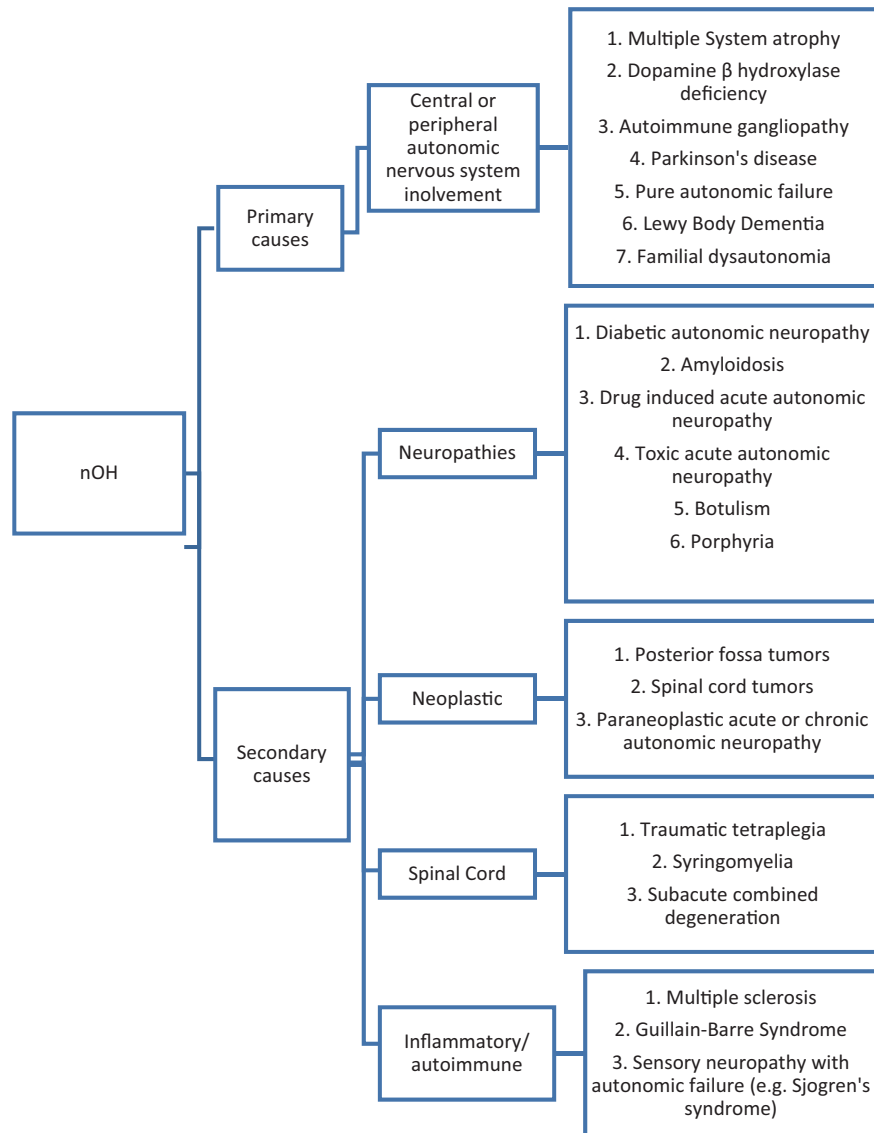   3. Sensory neuropathy with autonomic failure (e.g. Sjogren's syndrome)

nOH

Figure 2. Classification of causes of nOH.

angina due to cardiac hypoperfusion, orthostatic dyspnea due to lower perfusion of the lung apices, and oliguria due to renal hypoperfusion may occur.[20,34,38] Neurologic symptoms may include pill rolling tremor, rigidity, bradykinesia and postural instability in PD.[39] MSA is characterized by parkinsonism, autonomic dysfunction and cerebellar signs such as ataxia and dysarthria.[1] Additional features may include an action tremor with superimposed jerks (rather than the "pill-rolling" PD tremor), dystonia, camptocormia (severe anterior flexion of the spine) and dysphagia[20,39,40] PAF is diagnosed based on a history of symptomatic OH and low serum norepinephrine levels during supine rest. Signs of central neurodegeneration are typically absent.[20,41] Some of these same symptoms such as lightheadedness, blurring of vision, weakness or fatigue may also be seen in patients with postural orthostatic tachycardia syndrome, however the latter can usually be differentiated from nOH by a sustained HR increase of 30 beats per minute within 10 minutes of standing in the absence of OH.[2]

A study by Merola et al in 121 patients with PD showed that patients with asymptomatic OH had similar impairment in activities of daily living, quality of life and falls as compared to patients with symptomatic OH.[32] In another study by Freeman et al in 89 patients with OH, no correlation was found between the magnitude of SBP drop and symptoms. Absence of warning symptoms may place these patients at a higher risk of complications.[42] Thus, screening all patients with α-synucleinopathies for orthostatic BP drop may help in better detection of patients with asymptomatic OH. Symptoms may occur after stressors such as meals, standing or just after waking up, coughing, warm weather, and hot baths.[34,43]

Morbidity and mortality

The debilitating symptoms of nOH make it difficult for patients to complete simple activities of daily living as they live in fear of falling. Syncope, head trauma, and fractures were higher in patients with autonomic failure.[44] In one study, 87% of patients

with nOH reported that it had a negative impact on their ability to perform everyday activities and their quality of life (59%) and robbed them of their independence (42%).[33] In a prospective study of 844 nursing home patients (age > 60 years), those with OH had a 2.6 fold higher risk of recurrent falls.[45] Limitation of physical activities frequently leads to debilitation.[46] Similarly, in a community based middle age population, Juraschek et al reported that OH was an independent risk factor for falls over 20 years of follow-up.[47] Patients with nOH have a 3-fold increased risk of mortality compared to age matched controls, with highest the mortality being in patients with MSA followed by PD and PAF. The median survival in MSA is 7 to 9.5 years compared to PD and PAF where it is 10 to 15 years.[8]

Pathophysiology

A complex interplay between blood volume, reflex and humoral systems, vascular tone and capacitance of the striated muscle bed, splanchnic-mesenteric bed, and cerebrovascular beds helps maintain postural normotension.[43] Upon standing, 500 to 1000 mL of blood pools in the lower extremities and splanchnic circulation. This leads to decreased venous return, reduced

ventricular filling, diminished cardiac output, and a drop in BP (Figure 3). In an individual with an intact autonomic nervous system, baroreceptors sense this drop in the carotid sinus and aortic arch. An afferent signal is thus sent via fibers of the glossopharyngeal and vagus nerves to the nucleus tractus solitarus in the dorsomedial medulla.[20] A compensatory neural response follows in which there is efferent parasympathetic inhibition[20,43] (Figure 3). Parasympathetic inhibition in the nucleus solitarius and nucleus ambiguus also results in sinus node acceleration. There is also a concomitant increase in sympathetic outflow from the medulla via the thoracic spinal cord to the heart and peripheral vasculature.[20,43] In this sympathetic efferent pathway, norepinephrine is the major regulatory neurotransmitter and its levels promptly increase. The net effect of this increased sympathetic and decreased parasympathetic tone is peripheral vasoconstriction and a small increase in HR and cardiac contractility. This results in an increase in the venous return and cardiac output which helps blunt the BP drop.[36] In nOH, central or peripheral autonomic lesions reduce the effects of these compensatory mechanisms[28] (Figure 4) and patients experience a sustained drop in BP. Inadequate release of peripheral norepinephrine upon orthostatic stress is thus a common feature in most conditions that produce nOH.

In the Parkinsonian diseases, this results from both sympathetic neurocirculatory failure (with or without noradrenergic denervation) and impaired baroreflex cardiovagal activity. Central autonomic lesions are most commonly seen in MSA (the peripheral noradrenergic system may or may not be intact), whereas PD and PAF cause predominant peripheral noradrenergic sympathetic denervation (but may have contributions from central denervation as well).[48-50] In PD, 3 processes contributing to catecholaminergic deficiency have been described. First, failure of arterial baroreflex can impair homeostatic functions including HR adjustment. Second, central and peripheral norepinephrine deficiency causes sympathetic denervation impairing vasoconstriction. Third, cardiac noradrenergic sympathetic denervation decreases the heart's ability to increase cardiac output. Post-mortem histological studies in PD patients have confirmed loss of sympathetic noradrenergic nerves in the heart, that is, there is a profound loss of tyrosine hydroxylase

Table 1. Symptom burden in patients with nOH.[29]

SYMPTOMS	PERCENTAGE OF RESPONDENTS REPORTING SYMPTOMS MULTIPLE TIMES A DAY
1. Dizziness or lightheadedness	29
2. Fatigue when standing	28
3. Difficulty walking	26
4. Blurry vision	19
5. Pain running down neck and across shoulders	17
6. Confused, foggy, inability to think clearly	16
7. Feeling faint	11
8. Difficulty breathing	10

Table 2. Symptoms of autonomic failure and neurological deficits indicative of nOH.

Symptoms of autonomic failure	Urinary symptoms	Increased frequency, retention, incontinence
	Gastrointestinal	Constipation, nocturnal diarrhea, gastroparesis, dry mouth
	Vision problems	Blurring of vision, inability of pupils to react to light
	Genitourinary	Erectile dysfunction, retrograde ejaculation
Symptoms of neurological deficits	Cognitive impairment	Forgetfulness, poor judgment, depression, irritability
	Parkinsonian symptoms	Pill rolling tremor, rigidity, bradykinesia, postural instability
	Cerebellar signs	Ataxia, dysarthria, dysmetria, dysdiadochokinesia
	Sensory neuropathy	Numbness, tingling, burning pain

immunoreactive cardiac innervation.[51] Another study in patients with PD and nOH reported that there was a loss of noradrenergic nerves in extra cardiac tissues as well.[48]

The pathophysiology of SH is more complex and stems from an impaired baroreflex mechanism and a chronically activated renin-angiotensin system.[52] Impaired baroreflex buffering of the BP, inappropriate natriuresis, higher blood volume, and residual sympathetic tone acting on hypersensitive postsynaptic adreno-receptors in nOH, all play an important role.[53] During the day, while patients spend most of their time in a seated or upright position and blood pressure is low, sodium excretion is decreased, and blood volume is increased.[54] Moving from standing to a supine position at night increases the venous return and thus increases cardiac output and blood pressure. nOH patients with an impaired baroreflex do not appropriately compensate for this shift and thus develop SH.[52] These patients also have chronically activated renin-angiotensin system that exacerbates this problem. In this feedback loop, SH causes nocturnal pressure-diuresis and hypovolemia leading to worsening of early morning orthostatic symptoms.[43] A consensus statement in 2018 defined SH as mild (SBP 140-159 mm Hg or DBP 90-99 mm Hg), moderate (SBP 160-179 mm Hg or DBP 100-109 mm Hg), and severe (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg).[55]

Figure 3. Schematic showing normal baroreflex mediated maintenance of BP and physiologic principles behind pharmacotherapy in patients with nOH (highlighted in gray boxes). (The arrow does not denote any hierarchy in treatment.)

Screening and diagnosis

The American Autonomic Society and the National Parkinson Foundation guideline recommends that nOH screening start with questions to identify OH symptoms followed by orthostatic BP measurement in the office to diagnose it.[26] It describes 5 high risk patient groups who are suitable for such screening (Table 3) and enumerates questions to be asked to elicit these symptoms (Table 4). A positive response to any question warrants additional testing.[26] Our 4-step approach to distinguish nOH from OH is described below.

1. A detailed history and physical examination are vital. This helps differentiate nOH from other causes of light headedness (eg, vasovagal, hypoglycemia, obstructive cardiac lesions etc.). Symptoms which point towards a diagnosis of nOH include symptoms of autonomic failure and neurological deficits (Table 2).
2. BP monitoring should not stop at 3 minutes and may be extended to 10 minutes as some patients will have delayed OH.[2,56] If the history is suggestive of OH, but orthostatic testing in the office is negative, a Head Up Tilt (HUT) test (with a tilt of at least 60°) should be considered. This test is also useful in patients with physical limitations who are unable to remain standing for orthostatic testing in the office.[26,56] As the symptoms of OH can fluctuate widely throughout the day and office BP readings may not be able to recapitulate the BP readings that occur at the time that the patient experiences symptoms, Ambulatory Blood Pressure Monitoring (ABPM) can be considered to detect such BP drops with meals, exercise, and upon getting out of bed in the morning. ABPM is thus a very useful tool to diagnose covert nOH.[7,57] Additionally, one can use the mean BP to ascertain the diagnosis. Palma et al in their study of 210 patients with PD, showed that an upright mean BP < 75 mm Hg is an important marker for detecting symptomatic OH.[58]
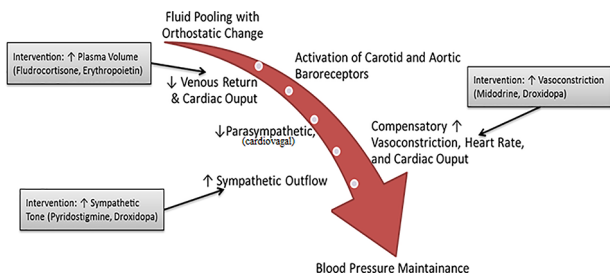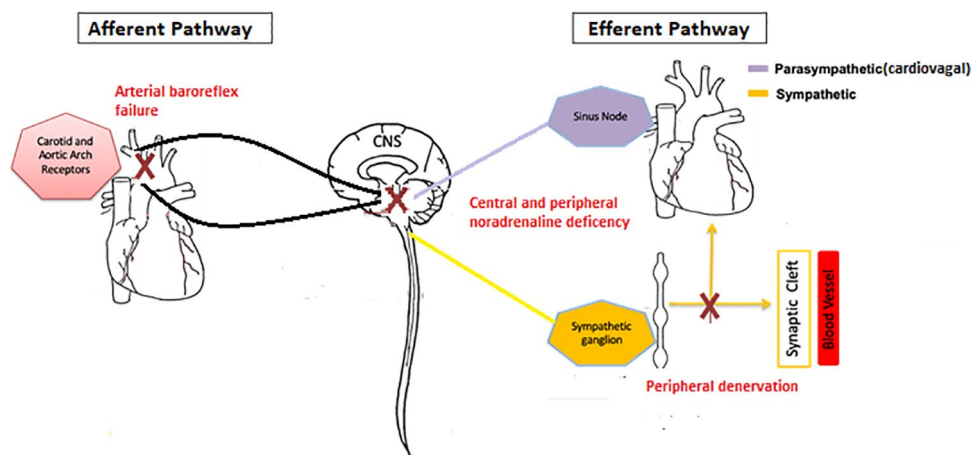

Figure 4. Pathway for autoregulation of blood pressure and conditions that cause nOH.

Table 3. Categories of patients who should be routinely screened for OH.[19]

1. Patients with suspected or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction, including PD, MSA, PAF, DLB
2. Patients who have reported an unexplained fall or have had an episode of syncope
3. Patients with peripheral neuropathies known to be associated with autonomic dysfunction
4. Patients who are elderly (70 years and older) and frail or on multiple medications
5. Patients with postural dizziness or non-specific symptoms that only occur on standing

Table 4. Screening questions for nOH.

1. Have you fainted/blacked out recently?
2. Do you feel dizzy or lightheaded upon standing?
3. Do you have vision disturbances when standing?
4. Do you have difficulty breathing when standing?
5. Do you have leg buckling of leg weakness when standing?
6. Do you ever experience neck pain or aching when standing?
7. Do the above symptoms improve or disappear when you sit or lay down?
8. Are the above symptoms worse in the morning or after meals?
9. Have you experienced a fall recently?
10. Are there any other symptoms you commonly experience when you stand up or within 3 to 5 min of standing and get better when you sit or lay down?

3. HR response is an important marker to differentiate between neurogenic and non-neurogenic causes as patients with nOH have a blunted HR response. If a patient develops OH upon standing, an increase in HR < 15 bpm suggests a diagnosis of nOH, whereas patients with non-neurogenic OH will typically demonstrate an increase in HR of 15 bpm within 3 minutes of standing.[26] Data from Norcliffe-Kaufmann et al.'s study of 402 patients suggested the use of a quantitative tool to assess this feature—they showed that a $\Delta HR/\Delta SBP$ ratio <0.5 bpm/mm Hg could be used as a diagnostic marker of nOH indicating a diminished HR increase.[59]

4. A comprehensive review of medications is important as polypharmacy in elderly patients is common.[60] Offending drugs include diuretics, alpha1-antagonists, antidepressants, antipsychotics, and levodopa (Table 6).[60] Numerous medications can also diminish the compensatory increase in HR (eg, beta blockers, non-dihydropyridine calcium channel blockers, central alpha-2 agonists, and antiarrhythmic agents).[26]

One should ensure the patient is intravascularly volume repleted and should tailor further testing according to the suspected cause (Table 5). For example, a cardiac murmur of aortic or mitral stenosis or hypertrophic cardiomyopathy should point away from nOH and toward a cardiac etiology for OH. Similarly, neurologic symptoms (Figure 2) should raise suspicion of nOH. For example, a pill rolling tremor, rigidity, and bradykinesia indicates PD, whereas, cool skin, stocking-glove sensory loss, and extremity numbness points toward diabetes causing nOH.[27,34,61] Nonetheless, even after extensive evaluation, 10% to 20% of patients will have no identifiable cause initially but will eventually get diagnosed as OH or nOH as symptoms appear over the course of their disease.

Various techniques can be used to study adrenergic failure in patients with nOH including serum levels of catecholamines and their metabolites, neuropharmacological tests, and cardiac neural imaging.[34,61] Baroreflex-cardiovagal integrity can be measured from the slope of the cardiac interbeat interval (with 1 beat delay)

to SBP during Phase II of the Valsalva maneuver or by analyzing the ratio between HR increase and BP drop from lying to standing position.[59] Cholinergic system testing includes thermoregulatory sweat response and quantitative sudomotor axon reflex test.[20] Neuropharmacological tests assess hemodynamic and neurochemical responses to various stimulants such as isoproterenol, tyramine, edrophonium, and glucagon.[27] Plasma norepinephrine dihydroxyphenylglycol levels, and neuroimaging tests such as 6-[18F] fluorodopamine positron emission tomographic (PET) scanning and [123I] metaiodobenzylguanidine (MIBG) scintigraphy can be used to localize sympathetic noradrenergic denervation.[27] In nOH patients without central neurodegeneration and normal peripheral noradrenergic innervation, the diagnosis of autoimmune autonomic ganglionopathy should be considered and one should test for circulating antibodies to the neuronal nicotinic receptor (nAChR).[27]
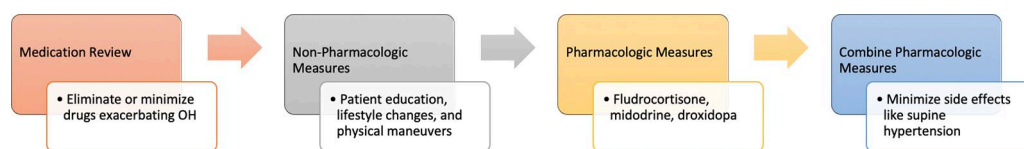
Management

Goals of treatment

The usual outcome measures in nOH studies can be objective (BP goals) or subjective (symptom control) although both these outcome measures are imperfect and pose interpretative challenges. As mentioned previously, the severity of nOH symptoms often varies day-to-day or throughout the day and can be affected by ambient temperature, physical exertion, and food and fluid intake. In a similar way BP values obtained during clinic evaluation may not recapitulate BP values when the patient experiences symptoms.[62] The goals of treatment should be to reduce the burden of symptoms, allow the patient to be able to stand for longer periods of time, reduce the risk of falls and improve physical performance to restore independence in activities of daily living. Thus, solely fixing orthostatic BP abnormalities or normalizing standing BP should not be the primary goal as changes in postural BP are not always correlated with

Table 5. Testing for nOH.

INITIAL TESTING	UTILITY IN DIAGNOSIS
Complete blood count	To rule out anemia, infection
Comprehensive metabolic panel	To assess volume status, electrolyte abnormalities, kidney dysfunction, intravascular volume (albumin), hypoglycemia
Electrocardiogram	To identify cardiac etiology
CT or MRI head/spine	To rule out structural central neurologic problems
Autonomic testing	To identify a specific etiology
Secondary testing	
Vitamin B12, methyl malonic acid, fasting plasma glucose, glycosylated hemoglobin	To screen for peripheral neuropathies
Morning cortisol, thyroid stimulating hormone	To rule out endocrine abnormalities
Paraneoplastic panel	To assess autoimmune etiologies
Serum/urine electrophoresis and further cardiac imaging (eg, pyrophosphate scan)	To identify monoclonal gammopathy and amyloidosis

Figure 5. Approach to the management of nOH.

symptoms.[26,63,64] Furthermore, it is currently not known whether treatment prevents long term mortality associated with OH, although intuitively it makes sense to prevent falls related to OH. Current treatment recommendations are based mostly on studies in small numbers of patients with primary forms of autonomic failure and severe OH, with limited evidence of long-term efficacy from randomized controlled clinical trials.

Various consensus statements from The American Autonomic Society and the National Parkinson Foundation,[26] European Society of Cardiology (ESC) 2018 guidelines for diagnosis and management of syncope,[65] European Academy of Neurology,[56] and American College of Cardiology (ACC) 2017 guidelines for patients with syncope[66] provide broad strategies for the management of OH patients.

We employ a 4-step approach to management of nOH: eliminate offending drugs, use conservative/non-pharmacological measures, then use pharmacologic therapy starting with a single agent and finally if needed, use drugs in combination (Figure 5). These steps are not hierarchical, for example, conservative measures should continue to be the backbone of therapy even in patients who are being treated with multiple drugs.[26]

Medication review

A list of common offending agents is listed in Table 6. In patients with mild symptoms, minimizing or eliminating these medications is often enough. This may require collaboration with other prescribers to prevent exacerbation of other conditions like depression, hypertension, urinary retention, etc.

Non-pharmacological measures

This includes lifestyle modifications, physical counter-pressure maneuvers, and external wearables.

1. Lifestyle modifications: older patients are more symptomatic after prolonged bed rest and should use a gradual, staged transition from a supine position to reduce symptoms.[43,65]

   a. Adequate hydration: many patients with nOH are often blood volume depleted due to inadequate oral fluid intake.[67] Maintaining adequate hydration is a first step in both the ESC and ACC guidelines.[65,66] A daily fluid intake of 2 L is recommended, but if cardiac status allows this can be as high as 3 L, especially in warmer weather.[26]

   b. Acute water ingestion: water bolus treatment is used in patients with nOH.[26,43] Acute water ingestion is a class I indication with the peak effect occurring in 30 minutes after ingestion of ≥240 mL and additional benefit seen with ≥480 mL. Effects are driven by adrenergic activation.[26,66]

   c. Salt intake: 2.3 to 10 g of salt/day can be added to the diet of nOH patients. Careful selection of patients is

Table 6. Drugs that cause OH.

MEDICATION CLASS	OFFENDING DRUGS
Alpha-1 antagonists	Doxazosin, prazosin, tamsulosin, terazosin
Diuretics	Furosemide, torsemide, hydrochlorothiazide, acetazolamide, spironolactone
Nitrates	Nitroprusside, isosorbide dinitrate, nitroglycerin
Beta-blockers	Propranolol, metoprolol, atenolol, bisoprolol, carvedilol, labetalol (the last 2 also have α-1 antagonist properties)
Tricylic antidepressants	Amitriptyline, nortriptyline, imipramine, desipramine
Phosphodiesterase inhibitors	Sildenafil, vardenafil, tadalafil
Alpha-2 agonists	Clonidine, guanfacine

important as cardiac patients are at risk of worsening edema and heart failure.[26,43,65,66]

d. Head up tilt: elevation of head up by 6 to 9 inches above the feet (or 10°-30°) is a class IIa indication to prevent nocturnal diuresis and the morning fall in BP especially in patients with SH.[7,65]

e. Physical conditioning: patients who are deconditioned experience larger BP falls.[26] Thus, lower body strength training and non-gravitation exercises such as stationary bicycle, rowing machines and water exercises are recommended. Contrarily, upright posture exercises such as running on a treadmill should be avoided.[7,26]

f. Meals: 60% of nOH patients experience orthostatic symptoms within 2 hours of high carbohydrate meals (post prandial hypotension).[61] Thus, patients should be educated to eat smaller but more frequent meals with a low glycemic index.[26,61,68]

g. Avoidance of hot weather, hot showers or saunas. This prevents cutaneous vasodilation and OH.[7,26]

2. Physical counter-pressure maneuvers: patients who have warning signs upon standing can use certain physical counter-pressure maneuvers.[65,66] Examples include leg crossing, squatting, tiptoeing, lower body muscle tensing (thigh and leg muscle or buttock clenching), bending forward, and hand grip. These maneuvers work by increasing the venous return and increasing cardiac output.[7,69,70] Breathing-related counter-maneuvers such as slow, deep breathing and the creation of inspiratory resistance through the use of an impedance threshold device, inspiratory sniffing work by their effect on the respiratory pump to facilitate venous return to the heart from the abdomen and upper extremities.[68] Patients should avoid Valsalva like maneuvers such as straining during bowel movements which will lower the BP.[7]

3. External wearables: compression garments such as waist high compression stockings and abdominal binders can improve orthostatic symptoms. They work by preventing the gravitational pooling of venous blood but are effective only when tight fitting.[26,65,66] A randomized trial in nOH patients who wore an automated inflatable abdominal binder (40 mm Hg compression) was shown to be as effective as midodrine in reducing orthostatic symptoms.[71,72]

Pharmacotherapy

For patients with severe symptoms (falls, syncope) or whose symptoms are not controlled by non-pharmacologic measures, we use pharmacotherapy (Table 7). Until 2014, the 2 drugs primarily used were fludrocortisone and midodrine, with only midodrine having FDA approval for OH. However, in 2014 droxidopa was the first drug to receive FDA approval specifically for the treatment of nOH in the US.[66]

Midodrine. Midodrine has been shown to improve symptoms in patients with nOH.[65,66] It is an oral prodrug whose active metabolite, desglymidodrine, acts as an alpha 1-adrenoreceptor agonist that increases arteriolar and venous vascular resistance by causing vasoconstriction thus elevating SBP and DBP.[73] Jankovic et al in 1993 evaluated midodrine in a 4-week, double-blind, placebo-controlled study of 97 patients with OH—it increased standing SBP by 22 mm Hg and reduced orthostatic symptoms compared to placebo.[74,75] Peak effect occurs in 1 hour.[76] It received FDA approval in 1996 for the treatment of symptomatic OH. Typical doses of midodrine range from 2.5 to 15 mg 1 to 3 times a day, with dosing being titrated up for symptom relief. It has a short half-life and the effect lasts for 2 to 4 hours, hence it can be taken every 4 to 6 hours.[20,75] The most important side effect is the SH that occurs in up to 25% of patients[77] and can limit its use. Thus patients should not take it within 5 hours of bedtime and omit a dose if BP is ≥180/110 mm Hg.[74-77] Other significant side-effects include piloerection, pruritus, paresthesia, chills, and urinary retention (especially in elderly men).[77]

Droxidopa. Droxidopa, also known as l-DOPS (l-threo-dihydroxyphenylserine, NORTHERA; Lundbeck), is a synthetic precursor of norepinephrine and the newest drug available for nOH treatment.[66] It is an oral pro-drug that is converted both peripherally and centrally to norepinephrine by decarboxylation.[78] Droxidopa can exert a pressor effect in 3 ways: as a central stimulator of sympathetic activity, as a peripheral sympathetic neurotransmitter and as a circulating hormone.[79] Kaufman et al evaluated the use of droxidopa in 162 patients with symptomatic nOH due to PD, MSA, PAF, or nondiabetic autonomic neuropathy. The primary efficacy endpoint was patient self-ratings on the OH questionnaire (OHQ). At the end of 7 days, patients in droxidopa group reported significantly better composite OHQ scores

Table 7. Drugs used to treat OH.

MEDICATION	MECHANISM OF ACTION	DOSAGES	ADVERSE EFFECTS	COMMENTS
Midodrine	α-1 adrenoreceptor agonist leading to vasoconstriction	2.5-15 mg TID	Supine hypertension, piloerection, scalp itching, and urinary retention	FDA approved. ACC/AHA IIa. Single agent or combination therapy
Droxidopa	Pro-drug converted to norepinephrine; stimulates adrenergic receptors	100-600 mg TID	Supine hypertension, headache, dizziness, nausea, fatigue	FDA approved, ACC/AHA IIa. Single agent or combination therapy
Fludrocortisone	Synthetic mineralocorticoid, acts as an aldosterone agonist leading to volume expansion	0.1-0.3 mg QAM	Supine hypertension, hypokalemia, hypomagnesemia, peripheral edema	ACC/AHA IIa. Single agent or combination therapy
Pyridostigmine	Acetylcholinesterase inhibitor, enhances sympathetic activity	30-60 mg, QD to TID	GI upset, sialorrhea, excessive sweating, and urinary incontinence	ACC/AHA IIb. Combination therapy or refractory cases. Likely Inferior to fludrocortisone. Minimal supine hypertension

compared to placebo.[62,80-82] An integrated analysis of 3 studies evaluated OHQ scores from baseline to 1 week of droxidopa treatment. And showed a significant unit change of in the OHQ composite score compared with placebo (-2.68 ± 2.20 vs -1.82 ± 2.34; $P < .001$).[83] Based on these studies, it received FDA approval in February 2014 for nOH stemming from primary autonomic neuropathies (PD, MSA, PAF, dopamine beta hydroxylase deficiency, and non-diabetic neuropathy). A more recent study also provided longer follow up data (12 months) in 102 patients. nOH symptom severity and impact on daily activities improvements exceeded 50% and were maintained throughout the 12-months.[84]

Typical dosages range from 100 to 600 mg TID, starting at 100 mg TID and upward titration every 24 to 48 hours until symptom relief or intolerable hypertension occurs. Droxidopa levels peak at 3 hours; half-life is 2 to 3 hours. However due to decarboxylation of droxidopa within cellular sites, plasma norepinephrine levels peak at 6 hours and remain elevated for 46 hours.[85] The major route of elimination is renal. It should also be avoided within 5 hours of bedtime to avoid SH.

In patients with PD being treated with levodopa/carbidopa, droxidopa may not be effective as carbidopa inhibits its conversion of norepinephrine.[85] However, co-administration of the peripheral catechol-o-methyl transferase inhibitor, entacapone, with droxidopa did not affect plasma droxidopa concentrations or the droxidopa-induced increase in plasma norepinephrine levels or SBP.[86] Potential adverse events (AEs) include headache, dizziness, decreased appetite, fatigue, urinary tract infections, and SH.[83,87]

Droxidopa can exacerbate conditions such as ischemic heart disease, arrhythmias, and congestive heart failure.[78] In the short term studies, were no CV events; in the intermediate term studies, CV event rates were 4.4% and 1.8% (droxidopa vs placebo).[88] In long-term studies, CV events occurred in 10.8% of droxidopa patients (open-label studies, no placebo arm was available for comparison). Most events were minor atrial arrythmias and none were major adverse CV events.[88]

Some studies suggest that droxidopa may also have a role in reducing intradialytic hypotension[89] in hypotensive individuals with spinal cord injury.[90,91] Although there have been no head to head trials comparing midodrine with droxidopa, a Bayesian meta-analysis to compare outcomes of standing and supine BP outcomes reported a significant difference between the 2, with midodrine showing a greater mean change in standing SBP. There was also a higher risk for SH with midodrine (midodrine RR = 5.1 [95% CI = 1.6-24] vs droxidopa RR = 1.4 [95% CI = 0.7-2.7]).[92]

Off-label medications

Fludrocortisone. Fludrocortisone is a synthetic mineralocorticoid used off-label for the treatment of nOH that acts as an aldosterone receptor agonist to increase renal sodium reabsorption and thus increase plasma volume. Other possible mechanisms include sensitization of the vasculature to circulating catecholamines such as norepinephrine and angiotensin II.[93] Even though the strength of data supporting use of fludrocortisone is limited, ACC guidelines give it a IIa recommendation as its benefits outweigh the risks.[66] Treatment dosages range from 0.1 to 0.3 mg/day with the onset of action between 3 to 7 days.[26] The main side effects of fludrocortisone include SH, hypokalemia, edema. More serious side effects such as hypothalamic-pituitary-adrenal axis suppression and immunosuppression occur mainly with doses >0.3 mg daily.[26] Hypokalemia is dose dependent and is seen in 25% of patients.[78] Chronic use can cause cardiac hypertrophy and worsening heart failure. It increases the warfarin effect and may require a dose reduction of concomitant warfarin therapy.[78]

Pyridostigmine. Pyridostigmine is an acetylcholinesterase inhibitor used to treat myasthenia gravis. It increases sympathetic activity via nicotinic acetylcholine receptors and thus raises peripheral vascular resistance.[26] It has the advantage of not producing SH.[94-96] It is used off label for nOH/OH,

usually as adjunctive therapy in refractory cases. Small studies have reported a modest improvement in orthostatic symptoms.[94-96] A recent phase II non-inferiority study compared pyridostigmine to fludrocortisone in PD and found pyridostigmine to be inferior.[66,97] Typical dosing is 30 to 60 mg once to 3 times per day. Adverse effects are related to cholinergic stimulation, including nausea, vomiting, abdominal cramps, diarrhea, sialorrhea, excessive sweating, and urinary incontinence.[26]

The aforementioned 4 drugs mentioned for nOH are labeled pregnancy category C by the FDA. Other medications infrequently used to treat nOH include dihydroergotamine, indomethacin,[70] intranasal desmopressin, and erythropoietin.[20,70] Little data exists to determine efficacy and safety of different combinations compared to monotherapy for nOH. Studies evaluating the outcomes of droxidopa have reported a larger proportion of subjects taking fludrocortisone in the droxidopa group.[82] Occasional case reports and anecdotal use of triple therapy are available. Limited date shows that addition of as-needed midodrine to combination therapy of fludrocortisone and droxidopa may help refractory patients.[98] Similarly, safety data of combination therapy is scarce.[26] The selection of 1 drug over the other is driven by clinician preference and side effect profile. There have been no head-to-head comparison studies to guide the initial medication choice in nOH. We recommend home blood pressure diaries or AMBP readings and the OHQ to assess treatment response. If symptoms do not improve after reaching the maximum labeled dose, we switch to another single agent or add a second drug. Caution should be used with in patients with congestive heart failure, aortic disease, cerebrovascular disease, chronic renal failure, and SH.[26]

Worsening SH is a concern during treatment. SH may lead to hypertensive emergencies and acute ischemic and aortic syndromes, however data is currently not robust enough to define cut-off values as to when to treat it.[55] Prevention of short term immediate complications (eg, falls) from OH may take precedence over the longer term complications of SH, especially in elderly patients with limited life expectancy.[99] To counteract SH, patients should not take their last dose of pressor medication within 5 hours of bedtime, should sleep in a head-up position (30° or more), and omit a dose if supine or sitting BP is ≥180/110 mm Hg (ie, severe SH). When these conservative measures are unable to control SH, and if it is in the severe range persistently or frequently, small doses of short acting anti-hypertensives can be used at bedtime[26] (eg, hydralazine [25-50 mg], captopril [6.25-12.5 mg]).

Conclusion

nOH is a debilitating form of OH caused by autonomic dysfunction. Screening appropriate patients in the clinic with orthostatic BP testing and utilizing an orthostatic symptom questionnaire is helpful in not missing patients, and in identifying the severity of disease, and evaluating treatment success. The first step in managing a nOH patient involves review of their current medications and eliminating drugs that can cause

OH. Second, conservative measures such as patient education, physical counter-maneuvers, and lifestyle changes are often enough to treat mild symptoms. Next, pharmacotherapy is used in those with residual or severe symptoms. Future research should be aimed at multicenter studies with larger cohorts with longer follow up and head-to-head comparisons of the various therapeutic agents.

Author Contributions

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