

Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa

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Abstract: Neurogenic orthostatic hypotension (nOH) is due to failure of the autonomic nervous system to regulate blood pressure in response to postural changes due to an inadequate release of norepinephrine, leading to orthostatic hypotension and supine hypertension. nOH is common in Parkinson's disease (PD). Prevalence varies throughout the course of PD, ranging from 40% to 60%, and resulting in symptomatic nOH in approximately half. Symptomatic nOH, including lightheadedness, can limit daily activities and lead to falls. Symptomatic nOH can also limit therapeutic options for treating PD motor symptoms. Clinical evaluation should routinely include symptom assessment and blood pressure measurement of supine, sitting, and 3-minute standing; 24-hour ambulatory blood pressure monitoring can also be helpful. Non-pharmacological management of symptomatic nOH involves education, physical maneuvers, and adequate hydration. Current pharmacological treatment of symptomatic nOH includes salt supplement, fludrocortisone, midodrine, pyridostigmine, and other empiric medications. Despite these options, treatment of symptomatic nOH remains suboptimal, often limited by severe increases in supine blood pressure. Droxidopa, an oral prodrug converted by decarboxylation to norepinephrine, is a promising therapeutic option for symptomatic nOH in PD, improving symptoms of nOH, daily activities, falls, and standing systolic blood pressure in several recent trials. These trials demonstrated short-term efficacy and tolerability, with comparable increases in standing and supine blood pressures. Longer-term studies are ongoing to confirm durability of treatment effect.

Keywords: (pre)syncope, norepinephrine, autonomic, lightheadedness, treatment, falls

Introduction

Neurogenic orthostatic hypotension (nOH) results from failure of the autonomic nervous system (ANS) to regulate blood pressure in response to postural change, due to an inadequate release of norepinephrine (NE). This leads to both orthostatic hypotension upon standing and supine hypertension when lying. nOH is a hallmark of several neurodegenerative diseases, including multiple systems atrophy, Parkinson's disease (PD), and primary autonomic failure. PD is the second most common neurodegenerative disease, and nOH is a commonly encountered clinical problem in patients with PD, perhaps affecting up to 40%–60% of patients throughout the multi-decade disease course.^{1–4} Symptomatic nOH occurs in approximately 20% of patients with PD,^{1,5} and increases with PD duration, disease severity, age, and levodopa usage.⁵ However, symptoms such as lightheadedness may be variable though the day, and may abate and recur over time. Thus, there is not always a consistent correlation between orthostatic lightheadedness/dizziness and finding orthostatic hypotension when blood

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pressure is measured at a single reading. Although several pharmacological and non-pharmacological options are available to help manage this condition, current treatment of symptomatic nOH remains suboptimal.

Normal ANS response to standing

Postural change (ie, standing or lying supine) induces gravitational redistribution of blood volume, leading to changes in blood pressure. Upon standing, pooling of venous blood in the legs is countered by the normal sympathetic ANS to maintain standing blood pressure.⁶ Lying supine also causes gravitational redistribution of blood volume, and the normal ANS minimizes blood pressure from rising too high. Norepinephrine is the major neurotransmitter in the ANS regulation of blood pressure in response to postural changes.⁷ Sympathetic activation in response to standing leads to: venoconstriction with increased venous return; an increase in heart rate and myocardial contractility with increased cardiac output; and vasoconstriction with increased blood pressure. Normal activation of the intact ANS, along with sufficient circulating blood volume, prevents the gravity-induced fall in standing systolic blood pressure (s-SBP), maintaining cerebral perfusion and of other vital organs.⁸

Impaired ANS response to standing in nOH

In patients with PD and nOH, autonomic dysfunction causes blood pressure to fall upon standing, due to an inappropriate NE response to postural change. Orthostatic hypotension has been defined as a drop in SBP of at least 20 mmHg or a drop in diastolic blood pressure of at least 10 mmHg after 3 minutes of standing.⁹ There is often a loss of the cardioacceleratory response too.¹⁰ Non-neurogenic causes of orthostatic hypotension are also common in patients with PD, and contribute to blood pressure drop.¹¹ These non-neurogenic causes of orthostatic hypotension should be identified first, and include dehydration, medications, and cardiac pump failure. A clinical diagnosis of nOH can be made when these non-neurogenic causes of persistent orthostatic hypotension are excluded, and can be confirmed through autonomic testing and plasma NE levels.¹²

In PD, autonomic dysfunction is mainly a result of cardiac sympathetic denervation with inadequate activation of NE pathways^{7,13–15} and also baroreflex failure.¹⁶ This can emerge during the course of PD or can occur early in its course.^{17–20} Parkinsonism due to multiple system atrophy is also accompanied by prominent autonomic dysfunction, but nOH results from failure of central NE pathways.^{21,22}

Symptomatic nOH

Upon standing, the normal ANS response maintains s-SBP within the range of cerebrovascular autoregulation. In nOH, a fall in blood pressure upon standing may not cause symptoms if s-SBP does not drop too low so that cerebral perfusion is maintained. When blood pressure falls upon standing, compensatory cerebrovascular autoregulation may maintain (or partially maintain) cerebral perfusion, minimizing symptoms.²³ Symptomatic nOH occurs when s-SBP falls below the range of cerebrovascular autoregulation, resulting in cerebral hypoperfusion and consequent lightheadedness/dizziness or syncope.

Asymptomatic nOH can become symptomatic in response to worsening autonomic dysfunction or due to orthostatic stress.²⁴ Indeed, in patients with PD, nOH is often compounded by non-neurogenic causes of OH and by orthostatic stressors. Symptomatic nOH may only emerge in response to an orthostatic stressor.²⁵ Mild dehydration can occur due to inadequate fluid intake, dysphagia, and concomitant diuretics. Early morning orthostasis may be problematic due to nocturnal supine fluid shifts.²⁶ Postprandial hypotension can trigger symptomatic nOH,^{27,28} as can prolonged standing or walking. Increased vasodilation due to heat, alcohol, or other factors may cause symptoms of nOH to emerge.²⁹ Many medications can lower blood pressure, especially during times of orthostatic stress or at their peak effects, including antihypertensive and dopaminergic therapies for PD^{30–33} (Figure 1).

Clinical evaluation of nOH

Routine clinical evaluation of patients with PD should always include an assessment of blood pressure (lying, sitting, and 3-minute standing). Although orthostatic hypotension is diagnosed with a reduction of s-SBP of at least 20 mmHg within 3 minutes of standing,⁹ lesser drops in s-SBP may still be symptomatic, and orthostatic hypotension may not occur until beyond 3 minutes.³⁴ Heart rate should normally rise 4–6 beats per minute upon standing, with a greater increase in response to orthostatic hypotension; with autonomic dysfunction, this cardioacceleratory response is typically blunted.⁹ Symptomatic nOH may not always correlate with isolated measurements of s-SBP, due to the diurnal circadian rhythm of blood pressure and also to the marked fluctuations in blood pressure that occur throughout the day.³⁵ Twenty-four hour ambulatory blood pressure monitoring can be helpful in the evaluation of patients with symptomatic nOH to better understand temporal fluctuations in blood pressure, especially when clinical symptoms do not regularly correlate with sporadic blood pressure measurements.³⁵

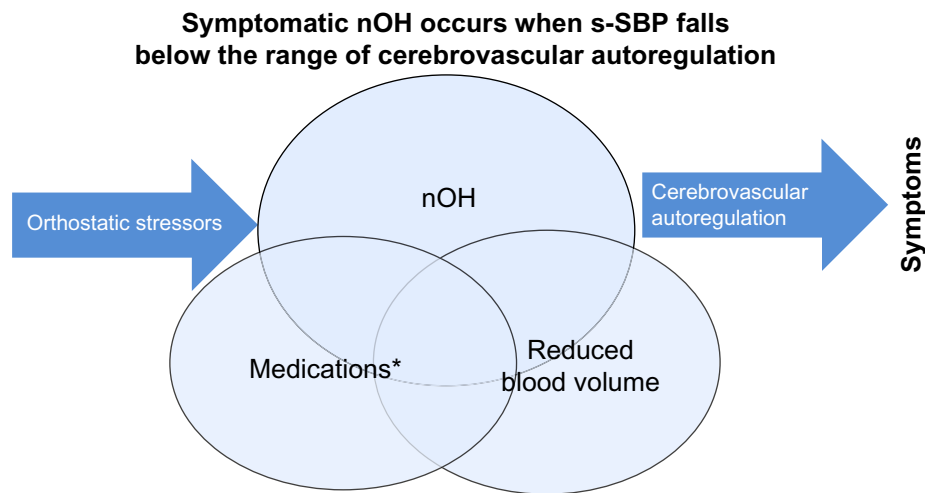


Figure 1 Overlapping causes of symptomatic nOH (Venn diagram): 1) autonomic failure of NE pathways upon standing; 2) dopaminergic and other medications causing lower SBP; and 3) suboptimal hydration leading to reduced circulating blood volume.

Note: *Medications include dopaminergic, diuretics, central adrenergic inhibitors, alpha-1 antagonists, nitrates.

Abbreviations: nOH, neurogenic orthostatic hypotension; SBP, systolic blood pressure; s-SBP, standing SBP.

Medical history should query possible offending medications, daily activities, potential orthostatic stressors, and symptoms of nOH. Common symptoms of nOH include lightheadedness, visual disturbances, impaired cognition,³⁶ fatigue, sleepiness (ie, postprandial), and difficulty standing or walking; syncope and falls may also occur. Symptoms of inadequate perfusion of other organs can cause symptoms, such as upper back/neck pain. The Orthostatic Hypotension Questionnaire (OHQ) can be useful to monitor symptoms over time.³⁷ Distinguishing imbalance on standing (due to postural instability) from lightheadedness (due to nOH) is important.³⁸ Other stigmata of autonomic dysfunction may be present, including constipation, gastroparesis, and urinary frequency.^{39,40}

Testing of ANS integrity may be a useful adjunct to clinical evaluation. Testing may include RR-interval variation, spectral analysis of RR interval and blood pressure²⁰, Valsava response, thermoregulatory sweat test, tilt-table, and sampling plasma.^{11,21,41–43} MIBG scintigraphy has distinguished central and peripheral causes of nOH, but is not readily available. In PD, reduced radioisotope uptake reflects the sympathetic cardiac denervation in PD.^{11,16,44}

Management of nOH

Patients with symptomatic nOH should be treated to improve clinical symptoms and to maintain daily activities, such as walking. Treatment will also reduce the risk of injury, falls, and other morbidities associated with nOH. The treatment of symptomatic nOH is aimed at raising s-SBP into the range of compensatory cerebrovascular autoregulation.

Treatment is multifaceted. Clinical therapeutic decision making must be based on standing (not sitting) SBP measurements. All possible offending pharmacologic agents should be minimized or stopped. Effective management requires extensive patient education with a combination of non-pharmacological and pharmacological therapies²⁴ (Figure 2).

Disease education of patients and their caregivers is directed towards an understanding of the role of postural changes on blood pressure, and is a necessary adjunct to clinical management. Rapid changes in posture should be avoided. Arising from supine to standing should be preceded by sitting for several minutes before standing. Standing after prolonged sitting should occur slowly, and several minutes of standing should precede walking. Patients also need to be advised that they should identify places to safely sit and rest in the case of unexpected symptom onset in order to avoid falls.⁴⁵ Patients and caregivers should especially be educated about the impact of orthostatic stressors on nOH symptoms.²⁴ Extended periods of standing or walking may result in symptoms, as can physical exercise, meals,²⁷ and any rise in core body temperature (fever, hot shower, hot or dry climates).^{24,29}

1. Decrease incidence and severity of symptoms;
2. Restore functional capacity for activities, including standing and walking;
3. Prevent severe drops in s-SBP in patients who fall or have episodes of syncope;
4. Minimize increases in supine blood pressure.

Figure 2 Treatment goals for patients with symptomatic nOH.

Abbreviations: nOH, neurogenic orthostatic hypotension; s-SBP, standing systolic blood pressure.

Polypharmacy should be avoided, and all medications that have potential to lower blood pressure should be discontinued as possible. The use of diuretics and antihypertensives should be discouraged, although shorter-acting antihypertensives prior to bedtime may be needed for supine hypertension.^{10,24} Other concomitant therapies, including medications for depression (tricyclics), sleep/allergy (antihistamines), and urinary frequency (anticholinergics and alpha-adrenergic antagonists) should be minimized.

Dopaminergic medications also lower blood pressure.^{30,33} If motor symptoms of parkinsonism permit, modifying the Parkinson's medication regimen may be one way to minimize blood pressure fluctuations in patients with nOH. Levodopa dose may need to be fractionated if orthostatic symptoms occur at peak dose. Dopamine agonist dose, especially of the immediate-release formulations that have higher peaks, may need to be reduced. Selegiline, anticholinergics, and amantadine also commonly lower blood pressure.

Patient education is often combined with non-pharmacologic measures, and these are sometimes sufficient. Increased hydration and salt intake is essential to maintain sufficient circulating blood volume, although caution must be used in patients with congestive heart failure. In response to lightheadedness or other symptoms of nOH, immediately drinking a 12–16 ounce bolus of water can rapidly raise s-SBP.^{24,46,47} Instruction on physical maneuvers, such as toe-raises, crossing legs, squatting, and bending at the waist can also improve nOH symptoms when they occur.^{24,48} Body compression garments, corset or belt, and thigh-high compression stockings are useful,^{24,49,50} but may be difficult for some patients to routinely wear. Elevation of the head 30° above horizontal will help minimize supine hypertension and nocturnal supine diuresis.^{26,51}

Medication management of nOH is added when patients have persistent symptoms despite these non-pharmacological approaches.¹⁰ Fludrocortisone is a synthetic mineralocorticoid that acts to retain sodium and water. This increases circulating blood volume and consequently blood pressure.^{51,52} Clinical effect of daily dosages of 0.1–0.4 mg should be administered once (or twice) earlier in the day. Onset of effect typically occurs over a period of 3–7 days. Its use is limited by increased supine blood pressure, which must be monitored in patients by sitting and supine blood pressure evaluations. Routine monitoring of electrolytes should also be performed to evaluate for development of hypokalemia. Excessive fluid retention by fludrocortisone can result in pedal edema and congestive heart failure, and may limit its use.

Midodrine is an alpha-adrenergic agonist that can increase blood pressure by increasing peripheral

vascular resistance. While some patients may respond to a dosage of 2.5 mg, most will require 5–10 mg dosage.^{53–55} Clinical response to a dose of midodrine should be assessed before and 1 hour after administration, as onset of action occurs within 30 minutes, peaks at 1 hour, and lasts 3–4 hours.⁵³ Due to its short duration of clinical effect, midodrine is administered several times daily, but should not be given within several hours of bedtime or near other times of lying supine.⁵³ Adverse effects of midodrine include piloerection, pruritus, and increased supine blood pressure, which can be dose limiting.⁵⁵

Pyridostigmine has also been used to treat nOH. Pyridostigmine is a peripheral inhibitor of acetylcholinesterase, which can cause a mild increase in standing blood pressure without significantly increasing supine blood pressure.⁵⁶ Adverse effects are cholinergic, including diarrhea, excessive sweating, and sialorrhea. When symptomatic nOH persists despite use of fludrocortisone, midodrine, and pyridostigmine, or the use of these medications are limited by adverse effects, several empiric medications have been tried.^{10,24} Erythropoietin can expand blood volume and increase blood pressure in symptomatic patients, but can increase supine blood pressure.^{57,58} Desmopressin,⁵⁹ indomethacin,⁶⁰ and caffeine⁶¹ have been evaluated in small trials. In patients with persistent or severe symptomatic nOH, attempts to augment NE pathways through the use of sympathomimetics or of NE transporter inhibitors (ie, NE-transporter blockers, serotonin-NE reuptake inhibitors) have been tried with variable success.^{62–65}

Droxidopa (L-threo-3-4-dihydroxyphenylserine [L-threo DOPS]), an oral prodrug converted by decarboxylation to NE in both the central and the peripheral nervous systems,^{66–68} is a promising therapeutic option for symptomatic nOH in PD. Droxidopa improves nOH in PD by replenishing NE.^{67,69} Over more than two decades, studies in Japan^{70,71} and in Europe⁷² have studied the effects of droxidopa in patients with nOH and PD. In these trials, droxidopa has been demonstrated to increase s-SBP, even in patients taking a decarboxylase inhibitor. Smaller studies in the US have also found similar benefit in nOH.^{67,73} Droxidopa for nOH has been marketed in Japan since 1989 for the indications of: 1) improvement of frozen gait and dizziness on standing in Parkinson's disease (Yahr stage III); 2) improvement of orthostatic hypotension, syncope, and dizziness on standing in Shy-Drager syndrome and familial amyloid polyneuropathy; and 3) improvement of orthostatic hypotension symptoms in the hemodialytic patient (dizziness, lightheaded feeling, dizziness on standing up, malaise, and weakness). In the US, a “new drug

application" has been filed with the FDA, and is pending regulatory approval.

More recently, droxidopa has been evaluated in several Phase III clinical trials in the US to establish its efficacy and safety in treating symptomatic nOH, including in patients with nOH associated with PD. The results of these trials have been presented in abstract form, but have not yet been fully published. In these trials, efficacy was assessed primarily by the two-part OHQ: Orthostatic Hypotension Symptom Assessment (OHSA; Item 1: dizziness/lightheadedness) and Orthostatic Hypotension Daily Activity Scale.³⁷

An initial trial utilized a withdrawal design and enrolled patients with nOH due to PD, multiple systems atrophy, and other neurological disorders with nOH. After open-label droxidopa titration, droxidopa responders were randomized to treatment with droxidopa or placebo for 2 weeks. While OHQ was significantly improved, the primary endpoint of OHSA Item 1 (dizziness/lightheadedness) was not met.⁷⁴ In a second trial, patients with nOH were enrolled in an induction design study. After open-label droxidopa titration followed by 1 week washout, droxidopa responders were randomized to treatment with droxidopa or placebo for 1 week. Significant improvement over placebo was found for OHQ, including OHSA Item 1 (dizziness/lightheadedness), and for s-SBP.⁷⁵ A subsequent 3-month open-label study enrolled patients from these two trials. Overall, patients maintained stable scores on OHQ and OHSA Item 1 (dizziness/lightheadedness) for up to 12 months. However, a randomized 2-week withdrawal after 3 months of open-label treatment did not find significant difference in OHQ between droxidopa and placebo,⁷⁶ perhaps suggesting a prolonged residual effect of droxidopa. In a safety study, patients were evaluated with 24-hour ambulatory blood pressure monitoring 1 week after droxidopa washout and again after 4 weeks of droxidopa treatment. Droxidopa treated patients had a significantly greater increase in mean daytime SBP without causing sustained elevations in supine SBP overnight.⁷⁷ Long-term, open-label treatment with droxidopa has also been reported with overall good tolerability and safety.⁷⁸

Droxidopa has also been evaluated for symptomatic nOH in 225 patients with PD, one of the largest studies conducted of nOH in PD. After 1 week of randomized droxidopa or placebo treatment, there was a significant improvement in OHSA Item 1 (dizziness/lightheadedness), s-SBP, and clinician global improvement.^{79,80} At week 8, numerical differences persisted but were not statistically significant. Some patients had a reduction in falls,⁸¹ and treatment effect was

1. Monitor 3-minute-SBP, sitting blood pressure, supine blood pressure, and heart rate
2. Minimize polypharmacy
3. Postural adjustment, physical maneuvers, and elevate head of bed
4. Education and avoidance of orthostatic stressors (dehydration, meals, and heat)
5. Compression garments, water bolus
6. Expansion of circulating blood volume
 - a. Hydration
 - b. Salt
 - c. Fludrocortisone (monitor potassium, edema, and supine blood pressure)
7. Current pharmacotherapy
 - a. Midodrine
 - b. Pyridostigmine
 - c. Empiric medications
8. Emerging pharmacotherapy
 - a. Droxidopa

Figure 3 Management of symptomatic nOH.

Abbreviations: nOH, neurogenic orthostatic hypotension; s-SBP, standing systolic blood pressure.

seen despite use of decarboxylase inhibitor,⁸² dopaminergic medications for PD,⁸³ or prior use of midodrine.⁸⁴

Overall, droxidopa has demonstrated short-term efficacy on symptoms of nOH and on s-SBP, including in patients with PD.⁸⁵ In long-term open-label treatment, droxidopa had good tolerability and safety, without significant supine hypertension. While some studies found sustained improvements in symptoms and s-SBP, longer-term studies are needed to confirm the durability of droxidopa treatment on nOH symptoms.

Summary

nOH in PD is due to an inadequate release of NE resulting in failure of the ANS to maintain s-SBP. nOH is common and can become symptomatic when compensatory cerebrovascular autoregulation cannot maintain adequate cerebral perfusion upon standing, often in response to orthostatic stress. Clinical evaluation of symptoms and 3-minute s-SBP should routinely be performed, so that treatment can be instituted to improve symptoms, daily activities, and reduce risk of injury, falls, and other morbidities (Figure 3). Current treatments for nOH are suboptimal and can increase supine blood pressure. Droxidopa is an emerging therapy for symptomatic nOH, and increases s-SBP without greater increases in supine hypertension.

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