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Review

Management of Orthostatic Hypotension in Parkinson's Disease

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Abstract. Orthostatic hypotension (OH) is a common non-motor feature of Parkinson's disease that may cause unexplained falls, syncope, lightheadedness, cognitive impairment, dyspnea, fatigue, blurred vision, shoulder, neck, or low-back pain upon standing. Blood pressure (BP) measurements supine and after 3 minutes upon standing screen for OH at bedside. The medical history and cardiovascular autonomic function tests ultimately distinguish neurogenic OH, which is due to impaired sympathetic nerve activity, from non-neurogenic causes of OH, such as hypovolemia and BP lowering drugs. The correction of non-neurogenic causes and exacerbating factors, lifestyle changes and non-pharmacological measures are the cornerstone of OH treatment. If these measures fail, pharmacological interventions (sympathomimetic agents and/or fludrocortisone) should be introduced stepwise depending on the severity of symptoms. About 50% of patients with neurogenic OH also suffer from supine and nocturnal hypertension, which should be monitored for with in-office, home and 24 h-ambulatory BP measurements. Behavioral measures help prevent supine hypertension, which is eventually treated with non-pharmacological measures and bedtime administration of short-acting anti-hypertensive drugs in severe cases. If left untreated, OH impacts on activity of daily living and increases the risk of syncope and falls. Supine hypertension is asymptomatic, but often limits an effective treatment of OH, increases the risk of hypertensive emergencies and, combined with OH, facilitates end-organ damage. A timely management of both OH and supine hypertension ameliorates quality of life and prevents short and long-term complications in patients with Parkinson's disease.

Keywords: Parkinson's disease, orthostatic hypotension, post-prandial hypotension, supine hypertension, nocturnal hypertension

INTRODUCTION

Orthostatic hypotension (OH) may affect every third patient with Parkinson's disease throughout the disease course [1–5].

OH manifests with syncope, unexplained falls, lightheadedness, cognitive impairment, blurred

vision, dyspnea, fatigue, shoulder, neck, or low-back pain, which develop upon standing and recover by lying down [6]. In some patients, OH may remain asymptomatic, depending both on how low the blood pressure (BP) falls upon standing and individual adaptive cerebral autoregulatory mechanisms [7, 8].

In PD, OH is mostly neurogenic, i.e., caused by post-ganglionic noradrenergic denervation of the heart and blood vessels [9], but hypovolemia and drugs with BP lowering effect may also cause OH of non-neurogenic origin.

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Meals can worsen OH by inducing excessive blood pooling in the splanchnic bed, a phenomenon called *postprandial hypotension*. Other exacerbating factors include heat exposure, fever, anemia, prolonged bed rest, hyperventilation, alcohol intake and physical exercise. In this case, the BP starts falling already while exercising, but patients typically experience syncope or presyncope soon after its cessation.

In about 50% of patients with neurogenic OH, baroreflex dysfunction and other, to date, not fully understood mechanisms, may cause hypertension in the supine position, which can be severe and last for several hours during nocturnal sleep [10, 11].

Identifying and managing OH is important, because it impacts on activity of daily living and increases the risk of injurious falls [12]. Supine hypertension (SH) is generally asymptomatic, but it may limit an effective treatment of OH, worsen it by fostering pressure natriuresis overnight and pose patients at higher risk of hypertensive emergencies [13]. In the long term, the combination of very low and very high BP values may also cause end-organ damage at cardiac, renal and cerebral level [14–16].

Here we provide a practical guide on how to screen, diagnose and treat OH in patients with PD, by taking into account supine and nocturnal hypertension. A similar approach can be adopted in patients with multiple system atrophy, an atypical parkinsonian disorder characterized by early, severe OH [17], poorly L-Dopa responsive parkinsonism, cerebellar ataxia and pyramidal signs in various combinations [18].

FIRST STEP: MAKE THE RIGHT DIAGNOSIS

Given its unspecific, and sometimes asymptomatic, presentation, OH should be actively screened at bedside by measuring the BP and heart rate (HR) supine and after 3 minutes upon standing [19]. OH is diagnosed in case of a systolic BP fall ≥ 20 mmHg and/or diastolic ≥ 10 mmHg with respect to baseline [20]. Standing systolic BP values < 90 mmHg are also highly suggestive of OH and often predict symptoms of orthostatic intolerance [7, 21]. In case of milder BP falls at the 3rd minute upon standing, it is recommendable to prolong the orthostatic challenge to 5–10 minutes, in order to screen for delayed OH, a possible precursor of classic OH [22].

Once a diagnosis of OH is established, non-neurogenic causes and exacerbating factors, such as

dehydration, anemia or infections should be ruled out. The medication schedule should be also reviewed for drugs with BP lowering effect, which may have been recently introduced or increased in dose: not only anti-hypertensive agents, but also dopaminergic drugs, tricyclics, opioids, neuroleptics or α -blockers.

Cardiovascular autonomic function tests ultimately distinguish neurogenic from non-neurogenic OH. In non-neurogenic OH, HR increases markedly upon standing, trying to counteract the fall in BP. By contrast, in neurogenic OH, no or only small orthostatic HR rises are observed despite severe BP falls, because of insufficient baroreflex stimulation (see Fig. 1). An increase in HR < 0.5 beats-per-minute/mmHg of systolic BP fall after 3 minutes of head-up tilt indicates neurogenic OH with high diagnostic accuracy [23]. Patients with neurogenic OH also miss the physiological BP overshoot at the end of a Valsalva maneuver, indicating an insufficient noradrenergic stimulation to the blood vessels (see Fig. 1) [11]. Performing a standing test under continuous BP monitoring may help identifying initial OH, a transient form of OH, which may also cause orthostatic intolerance [21].

All patients newly diagnosed with neurogenic OH should be screened for SH with in-office supine BP measurements [13]. Validated questionnaires, such as the Orthostatic Hypotension Questionnaire [24], and home BP measurements (see template in Fig. 2) provide useful additional information on the severity of OH in daily life and monitor for post-prandial hypotension and SH. If suspected, nocturnal hypertension is diagnosed with a 24-h-ambulatory BP monitoring.

TREATMENT OF OH

Correct non-neurogenic causes of OH and exacerbating factors

If the clinical assessment pinpoints dehydration, severe anemia or infections, these should be treated first.

When the onset of OH can be put in temporal relationship with the introduction or increase in dosage of any BP lowering drug, such therapeutic regimen should be carefully reconsidered after a case-by-case risk/benefit evaluation. In clinical practice, exacerbation of OH may occur during the titration of dopamine agonists [25, 26] and, less frequently, of L-Dopa [27, 28] due to vasodilatory effects and increased renal water and salt excretion [29, 30]. While, in some

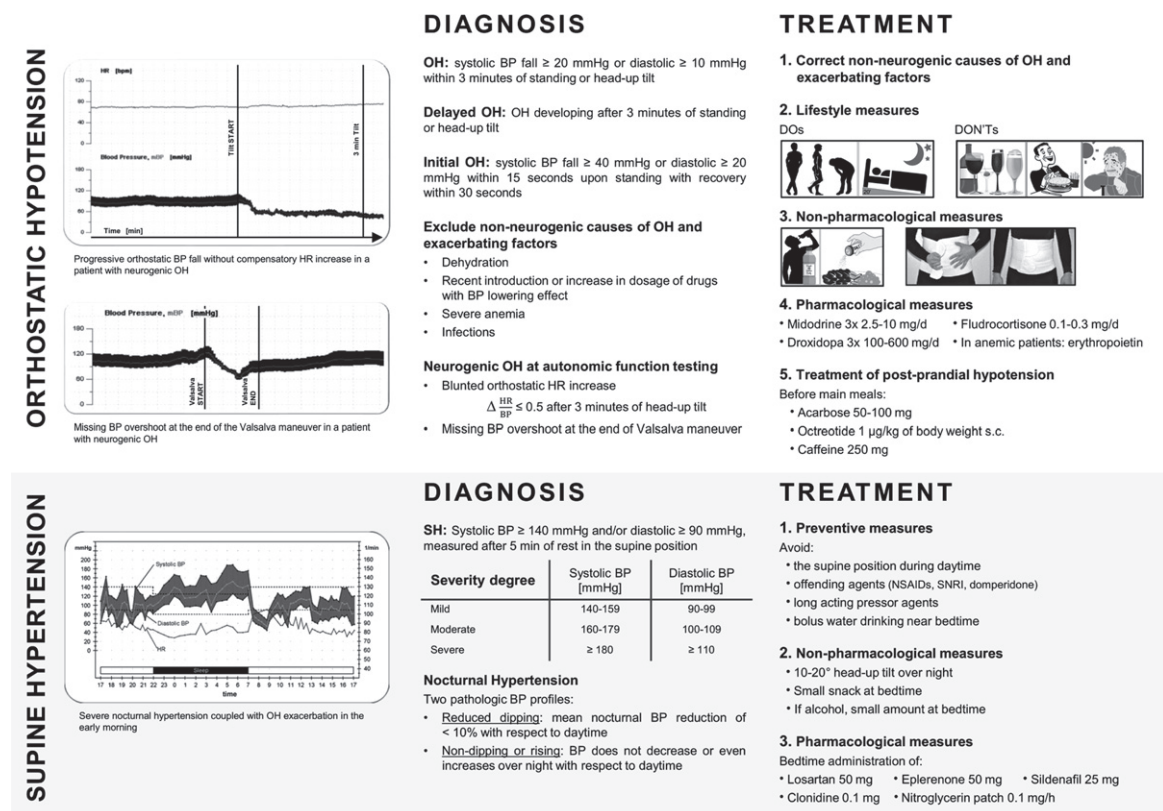


Fig. 1. Management of orthostatic hypotension and supine hypertension in Parkinson's disease. OH, orthostatic hypotension; BP, blood pressure; HR, heart rate; NSAIDs, non-steroidal anti-inflammatory drugs; SNRI, serotonin-noradrenaline reuptake inhibitors. Adapted from Fanciulli et al. 2014 [11] and Fanciulli et al., 2016 [37] with permission from Springer and John Wiley and Sons.

patients, orthostatic intolerance may ameliorate without intervention at follow-up, in others OH-specific measures may be necessary to maintain an adequate dopaminergic regimen.

Lifestyle measures

If no reversible cause of OH can be identified, or if symptoms of OH persist despite potentially exacerbating factors have been removed, lifestyle, non-pharmacological and pharmacological measures should be applied stepwise depending on the severity of OH symptoms [31].

Patients with OH should be carefully educated to:

- stand up slowly, especially after resting supine for longer times; in this case, patients may pause in the sitting position before standing up;
- avoid heat exposure, prolonged standing, alcohol, large, carbohydrate-rich meals and Valsalva-like maneuvers during micturition or bowel movements. Daily routine adaptations,

like showering on a chair or (for male patients) voiding in the seated position may be required;

- in case of dizziness and inability to sit or lie down, perform BP rising maneuvers such as stepping on the place, crossing the legs, tense the gluteal and abdominal muscles, bending forward or clenching the fists. A training session under continuous BP monitoring may help instructing the patient how to perform these maneuvers properly and selecting the most efficacious one [32];
- sleep in a 10–20° full-body head-up tilt position in order to stimulate the overnight production of antidiuretic hormone and reduce pressure natriuresis [33].

Non-pharmacological measures

Increasing water (up to 2,5 l/day) and salt (6–10 g/day) intake represents a key non-pharmacological measure to combat OH [34]. Drinking a bolus of water of 500 ml significantly

Home blood pressure diary

Name: _____

Date of birth: _____

height: _____ cm

weight: _____ kg

Date	Fluid intake (liters)	Measurements	In the morning (before breakfast)				After lunch				In the evening (before going to bed)			
			systolic	diastolic	HR	Symptoms	systolic	diastolic	HR	Symptoms	systolic	diastolic	HR	Symptoms
.....	___ l	5' min supine												
		3' min standing												
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.....	___ l	5' min supine												
		3' min standing												

* X = postural dizziness | O = no complaints; HR = heart rate

Fig. 2. Template of a home blood pressure diary for patients with orthostatic hypotension.

raises the BP in the following 30 to 90 minutes [35]: patients with OH may take advantage of such pressor effect by scheduling water intake on the basis of planned activities. Caution in water and salt supplementation should be used in patients with known heart, kidney or liver failure.

Abdominal binders also ameliorate OH by reducing the splanchnic venous pooling [36, 37], while compression stockings did not prove effective [34, 38] and may be difficult for elderly patients to put on.

Pharmacological measures

If non-pharmacological interventions provide insufficient control of OH symptoms, pharmacological measures should be implemented. One strategy is to increase the vascular tone with sympathomimetic agents, another is to expand the circulating blood volume, either by increasing the plasma volume or the red cell mass.

The choice of the pressor agent should be based on expected benefits, relevant comorbidities and potential adverse effects. If OH is the main cause of disability, higher dosages could be pursued in order to warrant good orthostatic tolerance during activities of daily living, while in patients, who are wheel-

chair bound due to advanced parkinsonism, avoiding polypharmacy and potential side effects may be more important.

Midodrine is a direct α_1 -adrenoceptor agonist [39–41], whereas droxidopa is a noradrenaline precursor that is converted into noradrenaline by the dopa-decarboxylase [42–45]. Both sympathomimetic agents are started at the lowest dose 3 times/day and increased gradually depending on the severity of OH symptoms (see Fig. 1). Patients with known cardiac disease, kidney failure or urinary retention shouldn't receive sympathomimetic agents.

Fludrocortisone is a synthetic mineralocorticoid that increases plasma volume by inducing sodium retention. It is used either in monotherapy or in combination with midodrine, but no studies compared the efficacy and safety of single versus combined drug regimens in the long term yet [34]. Fludrocortisone is contraindicated in patients with heart or kidney failure and electrolyte monitoring is recommended to exclude hypokalemia, especially in case of fever or diarrhea.

Erythropoietin, combined with iron supplements, may have a positive effect on OH in patients with concurrent anemia, but the risk of polycythemia and thrombotic complications must be considered [46].

To date, only elastic abdominal binders and droxidopa specifically proved effective and safe in treating PD-related OH in the short term [34, 47]. Recent observational studies report positive midterm effects of droxidopa [48] and long-term studies are ongoing, but droxidopa is not licensed in Europe at the moment.

For pyridostigmine, yohimbine, ergotamine, dihydroergotamine, ephedrine, desmopressin, indomethacin and fluoxetine, there are case reports and proof of concepts studies reporting on their efficacy on OH, but the safety profile is unclear to date [34]. Such pharmacological options can be considered in selected cases with refractory OH, if other agents proved ineffective or caused side effects.

TREATMENT OF POST-PRANDIAL HYPOTENSION

Conservative measures to treat postprandial hypotension include alcohol abstinence and fractionating meals.

If conservative measures prove ineffective, acarbose, an anti-diabetic agent that inhibits the intestinal α -glucosidase, can be used in selected cases [49] (see Fig. 1). Alternatively, subcutaneous octreotide, a somatostatin analogue, may be helpful [34], except for diabetic patients due to increased risk of postprandial hyperglycemic crisis.

Controversial evidence is available for caffeine: while low doses (250 mg) before meals may positively impact on postprandial hypotension [50], higher dosages have diuretic effects, which may worsen OH [51].

TREATMENT OF SUPINE AND NOCTURNAL HYPERTENSION

Preventive measures

Simple behavioral measures may prevent patients with neurogenic OH from developing overt SH [52]:

- Patients should avoid the supine position during daytime, when pressor agents are scheduled. If wished, a semi-seated position is recommendable for daytime naps;
- In patients who need pressor agents to control OH symptoms, short-acting drugs (e.g. midodrine or droxidopa) should be preferred over long-acting ones (e.g. fludrocortisone) and their

last administration should be scheduled no later than 4 pm. This may be even reduced or stopped, if OH symptoms are less severe in the second half of the day;

- Drugs, which are not primarily used as pressor agents, but which can cause significant BP increases in patients with baroreflex dysfunction should be avoided (e.g., NSAIDs, domperidone or SNRI);
- Bolus water drinking should be avoided in the 30 to 90 minutes before night sleep, because of the abovementioned pressor effect.

Non-pharmacological and pharmacological measures

When SH is present, non-pharmacological and pharmacological measures should be introduced gradually based on SH severity degree, especially overnight (see Fig. 1).

Treating nocturnal hypertension aims at reducing the risk of hypertensive emergencies, plasma volume loss overnight (with possible reduction of OH severity the day after) and end-organ damage in the long term. These potential benefits must be weighed against the risks of worsening OH and increasing the risk of syncope and falls. The highest and lowest BP levels observed at home or 24 h ambulatory BP monitoring may help estimating the risk of both hypertensive emergencies and of syncope in single patients.

Non-pharmacological measures can be sought to treat milder forms of nocturnal hypertension:

- 10–20° full-body head-up tilt during sleep;
- A small snack before bedtime to counteract SH by causing post-prandial hypotension. Following the same principle, enteral nutrition can be scheduled at nighttime in patients who are fed per gastrostomy;
- While the use of alcohol is not recommended to treat SH, patients who wish to enjoy small amounts of alcoholic beverages should do this before bedtime.

Pharmacological interventions may be considered in patients in whom BP values overnight remain high despite preventive and non-pharmacological measures. Few studies addressed the pharmacological treatment of nocturnal hypertension in patients with neurogenic OH. Bedtime administration of eplerenone [53], losartan [54], sildenafil [55], clonidine [56], transdermal nitroglycerin [57], and nifedipine [58] reduced systolic BP overnight.

Losartan, an angiotensin II-receptor antagonist, and clonidine, a CNS-active sympatholytic drug, also diminished nocturnal sodium excretion, while nifedipine worsened OH symptoms the day after due to its long half-life. Drugs to treat SH should therefore be short-acting and scheduled in the evening, while during daytime an effective treatment of OH should be prioritized.

FUTURE PERSPECTIVES

Despite combined treatment strategies, the symptomatic burden of OH remains high in a significant proportion of patients with PD and BP fluctuations due to concomitant SH represent a management challenge. This highlights the need for new therapeutic and safety studies in PD.

Supine plasma noradrenaline levels, which are generated from the spillover of post-ganglionic noradrenergic synapses, may guide an individualized choice of the pressor agent to combat OH. Low supine plasma noradrenaline levels may predict a better response to droxidopa [59]. On the other hand, higher supine plasma noradrenaline levels indicate dysfunctional, but preserved noradrenergic fibers and may provide the pharmacological rationale for treating OH with noradrenaline transporter blockers, which academic and industry-driven studies are currently investigating in PD and other autonomic disorders. These and other strategies will hopefully help optimizing the management of disorders of BP regulation in PD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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