



# Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies: prioritisation of treatment targets

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Neurogenic orthostatic hypotension and supine hypertension are common manifestations of cardiovascular dysautonomia in Parkinson's disease and related synucleinopathies. Because these disorders are haemodynamic opposites, improvement in one might be achieved at the expense of worsening of the other. Thus, management decisions necessitate assessment of the individual risks for patients with coexistent neurogenic orthostatic hypotension and supine hypertension. Whereas neurogenic orthostatic hypotension poses risks for falls and can be associated with cognitive impairment in the short term, chronic supine hypertension can be associated with stroke and myocardial infarction in the long term. Because few clinical trial data exist for outcomes in patients with coexistent neurogenic orthostatic hypotension and supine hypertension, clinicians need to balance, on the basis of comorbidities and disease staging, the potential immediate benefits of treatment for neurogenic orthostatic hypotension and the long-term risks of supine hypertension treatment in each patient. Future research needs to focus on ascertaining a safe degree of supine hypertension when treating neurogenic orthostatic hypotension; the effectiveness of nocturnal antihypertensive therapy in patients with coexistent neurogenic orthostatic hypotension and supine hypertension; and the prevalence, scope, and therapeutic requirements for managing neurogenic orthostatic hypotension that manifests with falls or cognitive impairment, but without postural lightheadedness or near syncope.

## Introduction

Autonomic dysfunction is common in patients with Parkinson's disease and other synucleinopathies.<sup>1,2</sup> In addition to genitourinary and gastrointestinal impairments,<sup>1,3</sup> patients with autonomic dysfunction commonly experience various coexistent haemodynamic abnormalities, including neurogenic orthostatic hypotension and supine hypertension.<sup>2,4–11</sup> Neurogenic orthostatic hypotension is defined as a systolic blood pressure decrease of 20 mm Hg or more, or a diastolic decrease of 10 mm Hg or more, within 3 min after rising from a supine to a standing position, unrelated to cardiogenic causes or hypovolaemia.<sup>12</sup> In a 2011 meta-analysis<sup>13</sup> of 25 methodologically heterogeneous studies, the prevalence of neurogenic orthostatic hypotension in patients with Parkinson's disease was estimated to be about 30%. Postprandial hypotension, characterised as a systolic decrease of 20 mm Hg<sup>10,14</sup> or more after a meal,<sup>5</sup> commonly coexists with neurogenic orthostatic hypotension.<sup>8,10</sup>

Notably, neurogenic orthostatic hypotension is strongly associated with supine hypertension, a haemodynamically opposite form of blood pressure dysregulation. There is no expert consensus on the diagnostic criteria for supine hypertension, but the condition has been defined as a systolic blood pressure of 140 mm Hg (or 150 mm Hg) or higher, or a diastolic pressure of 90 mm Hg or higher, while in a recumbent position.<sup>15,16</sup> Supine hypertension can be associated with a loss of the normal night-time decrease (typically  $\geq 10\%$ ) in mean blood pressure—termed non-dipping<sup>10,17</sup>—or with a nocturnal increase in blood pressure, which is termed nocturnal hypertension or reverse dipping.<sup>10</sup> We review the available clinical and pathophysiological evidence for the coexistence of neurogenic

orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies, and discuss complexities in the management of these opposite abnormalities. Specifically, we articulate that prioritisation of the management of orthostatic hypotension over that of supine hypertension—and thereby allowing some supine hypertension—might be necessary to avoid the more urgent complications associated with insufficiently treated orthostatic hypotension.

## Understanding the clinical dilemma

Compared with chronic essential hypertension, the syndrome of combined neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and other synucleinopathies has received little attention. Whereas essential hypertension affects nearly a third of the world's population, is the primary or secondary cause of approximately 380 000 deaths per year in the USA alone, and contributes to first stroke in eight of ten people,<sup>18</sup> orthostatic hypotension has a prevalence of 6–35% in the general population and its sequelae are far less recognised.<sup>19</sup>

In patients with coexistent neurogenic orthostatic hypotension and supine hypertension, the risk of cardiovascular and cerebrovascular complications associated with supine hypertension has been frequently judged similar to those of chronic hypertension, with the result that supine hypertension generally takes precedence in management decisions. Physicians might also base treatment decisions solely on one or few blood pressure data points without consideration of the patient's general context—ie, treating what they regard as disturbingly high or low blood pressure values.<sup>20</sup> The dilemma in such choices is that, because neurogenic orthostatic hypotension

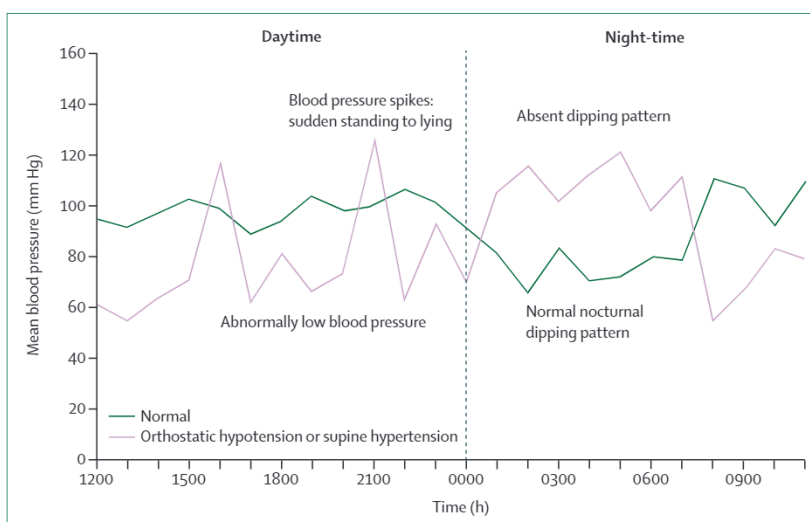
and supine hypertension are haemodynamic opposites (figure 1),<sup>10</sup> improvement of one is accomplished only at the expense of the other.<sup>7,21</sup>

Substantial evidence supports the association of neurogenic orthostatic hypotension with increased morbidity (table 1). Particularly, the syndrome appears to be associated with recurrent falls and cognitive impairment in patients with Parkinson's disease.<sup>22–24</sup> However, the potential contribution to morbidity of coexistent supine hypertension has remained largely unrecognised. To make appropriate treatment decisions, the underlying pathophysiological mechanisms of supine hypertension need to be scrutinised on a case-by-case basis, including the potential contributions of medications, baroreflex dysfunction, and disease phenotypes associated with restricted versus widespread involvement of blood pressure regulatory mechanisms. Different pathways are likely to be involved in the pathogenesis of neurogenic orthostatic hypotension and supine hypertension, some of which might also be related to different disease phenotypes. For example, a 2014 study<sup>25</sup> showed a higher prevalence of supine hypertension in patients with Parkinson's disease with restless legs syndrome than in Parkinson's disease patients without restless legs syndrome, suggesting an association between autonomic and sleep dysfunctions in this specific subgroup of patients with Parkinson's disease. In patients with progressive, disabling neurodegenerative disorders, more immediate clinical concerns might be the short-term risks associated with neurogenic orthostatic hypotension (eg, falls), rather than longer-term risks associated with supine hypertension (eg, cerebrovascular disease, cardiovascular disease).<sup>26,27</sup>

### Prioritisation of neurogenic orthostatic hypotension over supine hypertension

When managing coexistent neurogenic orthostatic hypotension and supine hypertension, there are strong reasons to prioritise treatment of neurogenic orthostatic hypotension (panel 1). An argument in favour of accepting some degree of supine hypertension is epidemiological evidence suggesting that the long-term risk of this syndrome in patients with Parkinson's disease might not be as severe as that in populations without Parkinson's disease, in whom supine hypertension is likely to be sustained rather than paroxysmal and mechanisms such as atherosclerosis might be more prevalent.

Several studies<sup>27–30</sup> have shown little or no difference in cardiovascular risk between patients with Parkinson's disease and those without the disorder; other studies have shown a modified cardiovascular risk in Parkinson's disease, with an overall decrease in the cumulative incidence of stroke and myocardial infarction (table 2).<sup>26,31,32</sup> Further research is needed to understand fully the cardiovascular risk in patients with coexistent neurogenic orthostatic hypotension and supine hypertension,



**Figure 1: Syndrome of neurogenic orthostatic hypotension with supine hypertension**

In patients with coexistent neurogenic orthostatic hypotension and supine hypertension, during the day, episodes of neurogenic orthostatic hypotension alternate with episodes of seated hypertension and supine hypertension (red line). At night, the normal pattern of physiological dipping in blood pressure is absent or reversed, and supine hypertension becomes more sustained because of prolonged recumbency. Mean blood pressure=(systolic blood pressure + diastolic blood pressure)/2.

because assessment of supine hypertension in patients with synucleinopathies and neurogenic orthostatic hypotension has largely been neglected. However, in view of two reports<sup>36,37</sup> of the frequency of neurogenic orthostatic hypotension, supine hypertension, and coexistence of the two in patients with Parkinson's disease (24–25%, 15–34%, and 10–31%, respectively), it is reasonable to suggest that a substantial proportion of patients with Parkinson's disease has one or both of these conditions. Notably, in one study,<sup>37</sup> only 21 (29%) of 72 patients did not have either condition.

Another consideration in the prioritisation of neurogenic orthostatic hypotension as a treatment target in patients with orthostatic hypotension–supine hypertension syndrome is the decreased use of tobacco products in patients with Parkinson's disease compared with age-matched and sex-matched cohorts,<sup>26,32,34</sup> resulting in a lower prevalence of stroke. The reason for this difference in tobacco use is unknown, but one hypothesis is that people who eventually develop Parkinson's disease have reduced susceptibility to dopamine-mediated nicotine addiction.<sup>38</sup> Thus, the lower risk of cerebrovascular or cardiovascular disease (eg, stroke, myocardial infarction) could represent an abstinence-related reduction in the prevalence and severity of atherosclerosis.<sup>26</sup> Because patients with Parkinson's disease are likely to be under the regular care of a neurologist, enhanced stroke prevention measures might also be a contributory factor to decreased incidence of cerebrovascular disease in these patients.<sup>27</sup> Conversely, the occasional finding of increased stroke risk in patients with Parkinson's disease<sup>33,35</sup> could represent a detection bias.<sup>26,35</sup> In animal studies, catecholamine depletion

confers some protection against experimentally induced stroke.<sup>39,40</sup> In patients without Parkinson's disease, an increased risk of cardiovascular disease and stroke has been associated with blood pressure variability and non-dipping.<sup>41,42</sup> However, orthostatic hypotension might be more detrimental than supine hypertension in terms of cardiovascular risk in elderly patients without Parkinson's disease.<sup>43</sup> No studies have been done to assess whether a

link exists between supine hypertension and cardiovascular risk in patients with Parkinson's disease with coexistent neurogenic orthostatic hypotension and supine hypertension.

Unlike the hypothetical long-term sequelae of chronic supine hypertension (eg, coronary artery disease, heart failure, stroke, renal disease, peripheral arterial disease), the risks associated with orthostatic hypotension in

Study design	Study aim	Blood pressure assessment methods	Study participants	Neurogenic orthostatic hypotension	Supine hypertension	Non-dipping or reverse dipping	Postprandial hypotension
Senard et al (1992) <sup>4</sup>	Prospective To measure blood pressure and heart rate with a Spacelabs device during daytime and night-time in patients with Parkinson's disease with and without orthostatic hypotension	ABPM	38 patients with Parkinson's disease with or without symptomatic neurogenic orthostatic hypotension*	19 (50%)	Not assessed	Reverse dipping in 18 (95%) of 19 with neurogenic orthostatic hypotension; normal dipping in 12 (63%) of 19 without	Ten (53%) <sup>†</sup> of 19 with neurogenic orthostatic hypotension; one (5%) of 19 without
Plaschke et al (1998) <sup>5</sup>	Prospective To analyse ABPM findings in patients with and without autonomic dysfunctions to determine whether autonomic failure in parkinsonian patients is associated with alterations in diurnal and nocturnal blood pressure patterns	ABPM and tilt-table testing	24 patients (13 men and 11 women; mean age 67 years) with Parkinson's disease	Six (25%) reported a history of postural hypotension; 11 (46%) had autonomic failure on autonomic testing	Mean supine blood pressure significantly higher in the autonomic failure group <sup>‡</sup>	Altered pattern <sup>§</sup> in nine patients with autonomic failure (82%); no change in those without autonomic failure	Not identified <sup>¶</sup>
Goldstein et al (2003) <sup>7</sup>	Prospective To assess whether supine hypertension attends orthostatic hypotension in chronic autonomic failure	Orthostatic testing	51 patients (40 men and 11 women; mean age 63 years) with Parkinson's disease, 24 of whom were referred for neurogenic orthostatic hypotension	24 (47%)	Mean supine blood pressure in patients with neurogenic orthostatic hypotension matched that in controls with essential hypertension; mean supine pressure in those without neurogenic orthostatic hypotension matched that in normotensive controls	Not assessed	Not assessed
Ejaz et al (2006) <sup>8</sup>	Retrospective To identify the characteristic patterns of blood pressure changes on 24-h ABPM in Parkinson's disease	ABPM	13 patients (nine men and four women; mean age 77 years) with Parkinson's disease and symptomatic neurogenic orthostatic hypotension	13 (100%)	Not formally assessed <sup>  </sup>	Reverse dipping in 12 (92%)	13 (100%)**
Schmidt et al (2009) <sup>10</sup>	Prospective To compare 24-h ABPM findings with those from highly sophisticated and time-consuming autonomic testing	ABPM and tilt-table testing	23 patients (17 men and six women; mean age 65 years) with Parkinson's disease and 26 age-matched and sex-matched healthy controls (13 men and 13 women; mean age 60 years)	Ten patients (43%), five of whom were asymptomatic during their orthostatic test	Not assessed	Non-dipping or reverse dipping in 11 (48%) of 23 with Parkinson's disease (48%) and two (8%) of 26 healthy controls	Significantly more episodes in patients than in healthy controls <sup>††</sup>
Berganzo et al (2013) <sup>11</sup>	Prospective To analyse the frequency of nocturnal hypertension and orthostatic hypotension in Parkinson's disease	ABPM and orthostatic testing	111 patients (62 men and 49 women; mean age 62 years) with Parkinson's disease and 17 219 general-population controls tested for hypertension by ABPM	45 patients (41%; not assessed in controls)	Not assessed	Non-dipping or reverse dipping in 79 (71%) people with Parkinson's disease and 8265 (48%) controls	Not assessed

ABPM=ambulatory blood pressure monitoring. \*Verified as a systolic or diastolic decrease  $\geq 30$  mm Hg after standing for 5 min. <sup>†</sup>Defined as a systolic decrease  $\geq 25$  mm Hg within 90 min after a meal. <sup>‡</sup>Defined as below the fifth percentile of normal on at least two of five cardiovascular tests. <sup>§</sup>Defined as a mean night-time blood pressure differing from mean daytime blood pressure by  $<10/5$  mm Hg. <sup>¶</sup>By ABPM analyses, including vs excluding all 3-h postprandial periods. <sup>||</sup>Average bedside blood pressure was 142.6/70.6 mm Hg; a mean nocturnal blood pressure  $>120/75$  mm Hg was recorded in all 13 patients. \*\*Defined as a systolic decrease  $\geq 20$  mm Hg within 75 min after a meal. <sup>††</sup>Defined as a systolic decrease  $>20$  mm Hg within 30 min after a meal, without recovery during a subsequent 60-min period; numerical findings were not presented.

**Table 1:** Studies of clinical manifestations of cardiovascular dysautonomia in patients with Parkinson's disease



patients with Parkinson's disease can be immediate and a major health threat (eg, injuries from falls). Symptomatic neurogenic orthostatic hypotension also confers uncomfortable and incapacitating symptoms—including postural dizziness, syncope, generalised fatigue, weakness, and vision impairment<sup>44</sup>—which can contribute to an increased risk of falls, the most frequent reason for hospital admission in patients with Parkinson's disease.<sup>45–47</sup> Neurogenic orthostatic hypotension adds to the risk of falls attributable to causes such as freezing of gait, festination, and loss of postural reflexes.<sup>48,49</sup> In a study<sup>22</sup> of impaired mobility and imbalance in 120 outpatients with Parkinson's disease who were selected for their ability to stand unsupported, the 63 (53%) patients who had orthostatic hypotension were more likely to have fallen within the preceding 3 months than were those without, although this difference was not significant.<sup>22</sup> Although walking speed was similar in patients with neurogenic orthostatic hypotension and those without, the group with neurogenic orthostatic hypotension showed significant increases in several measures of postural sway, suggesting that they had impaired control of static balance.

In addition to the immediate risks of falls, patients with Parkinson's disease and neurogenic orthostatic hypotension might be at increased risk of dementia compared with patients without orthostatic hypotension. In a study<sup>23</sup> of 87 newly diagnosed, drug-naïve patients with Parkinson's disease, neurogenic orthostatic hypotension was identified in 32 (37%) patients, and supine hypertension (defined as a supine systolic blood pressure >150 mm Hg) was identified in 18 (21%) patients. Of the 14 patients with dementia, ten had neurogenic orthostatic hypotension and 11 had supine hypertension; of the 25 patients with normal cognition, five had neurogenic orthostatic hypotension and none had supine hypertension. Of the 13 patients with coexistent neurogenic orthostatic hypotension and supine hypertension, nine had Parkinson's disease dementia and the remaining four had mild cognitive impairment. Although this study was small, the findings were intriguing.

A prospective cohort study<sup>50</sup> of the link between neurogenic orthostatic hypotension and dementia showed that patients with Parkinson's disease with neurogenic orthostatic hypotension at baseline had an increased risk of developing dementia compared with those without neurogenic orthostatic hypotension. Furthermore, the risk of developing dementia was seven-times higher in patients with a systolic standing drop of more than 10 mm Hg than in patients with normal blood pressure.<sup>50</sup> In the non-Parkinson's population, the relation between blood pressure and dementia risk has been explored prospectively.<sup>51</sup> Among elderly people who did not have dementia who were followed up for an average of 3 years, those with a baseline systolic blood pressure of 140 mm Hg or less were at significantly higher risk of developing dementia than were those whose baseline systolic blood pressure ranged from

#### Panel 1: Case study

A 79-year-old man with chronic essential hypertension and a 7-year history of Parkinson's disease developed dementia, visual hallucinations, and delusions 5 years after the onset of motor symptoms, which affected functional independence. Treatment included levodopa-carbidopa and lisinopril. He was not on antiarrhythmics or negative chronotropics. He had intermittent episodes of postural lightheadedness and presyncope, but his primary care physician chose to continue lisinopril. On neuropsychological examination, he was globally impaired (Mini-Mental State Examination score 19/30), with involvement of attention, working memory, and executive and visuospatial functions. His supine blood pressure was 165/100 mm Hg, and his pulse was 52 beats per min (bpm) and regular. After 3 min of standing, blood pressure was 100/65 mm Hg and pulse was 55 bpm. Electrocardiography revealed sinus bradycardia at 48 bpm, but was otherwise normal. The man's clinical diagnosis was Parkinson's disease dementia. He was started on oral rivastigmine, which was titrated to 4.5 mg twice a day.

After 3 weeks, he experienced worsening orthostasis and fatigue and had two syncopal events. Lisinopril was discontinued but postural symptoms persisted. The addition of fludrocortisone 0.1 mg per day led to no improvement after 2 weeks. Supine blood pressure was 110/60 mm Hg and pulse was 50 bpm; blood pressure dropped to 70/45 mm Hg with a pulse of 55 bpm after 3 min of standing. Addition of midodrine, titrated to 10 mg three times a day, led to a supine blood pressure of 160/90 mm Hg and a pulse of 54 bpm, and 120/70 mm Hg and a pulse of 56 bpm after 3 min of standing. He did not experience orthostatism or fatigue. However, concerns about his supine blood pressure prompted a reduction of midodrine to 5 mg three times daily. He subsequently experienced a syncopal episode, which was complicated by hip fracture.

This case illustrates a common clinical dilemma. Although severe orthostatism was successfully addressed with pharmacotherapy for neurogenic orthostatic hypotension, the treating physician did not accept the resulting supine hypertension and reduced the dose of midodrine, leading to re-emergence of orthostatism with a medical complication. No guidelines exist to advise physicians about the range of supine hypertension that can be regarded as safe in the treatment of neurogenic orthostatic hypotension.

141 mm Hg to 179 mm Hg. At baseline, a systolic blood pressure of 140 mm Hg or less was significantly related to a Mini-Mental State Examination score of less than 24. The pathophysiology underlying these correlations is not known but might involve an age-related, progressive impairment of the brain's capacity to autoregulate cerebral blood flow.<sup>52</sup>

Although definitive identification of the association between neurogenic orthostatic hypotension and cognitive deficits can be challenging because of confounding factors (eg, demographic and cardiovascular risk factors),<sup>53</sup> the two entities could be related because the same degenerating brain regions control cognitive and cardiovascular autonomic processes.<sup>54</sup> Additionally, although the cognitive impairment in neurogenic orthostatic hypotension can be transient (ie, reversed during supine posture), the episodic cerebral hypoperfusion experienced can eventually lead to sustained brain changes that could manifest as cognitive deficits.<sup>53,54</sup>

Preliminary evidence is emerging to support this premise in synucleinopathies. In a proof-of-concept study<sup>55</sup> of 15 patients with synucleinopathies (seven with dementia with Lewy bodies, five with Parkinson's disease



dementia, and three with Parkinson's disease and mild cognitive impairment), there was evidence for a voxel-wise association between the severity of the orthostatic drop in systolic blood pressure and cerebral perfusion as measured by arterial spin-labelling MRI. Specifically, a greater drop in systolic blood pressure upon standing was associated with lower steady-state regional cerebral perfusion to the occipitoparietal region—a finding that subsequently predicted performance on visuospatial and attentional tasks after correcting for the severity of cognitive impairment.<sup>55</sup>

In summary, the risk of developing dementia could have a U-shaped relation with blood pressure, with heightened risk at both ends of the spectrum. We speculate that neurogenic orthostatic hypotension and dementia might more commonly coexist at the more severe end of the phenotypic range of Parkinson's disease.<sup>50</sup> The American Geriatrics Society recommendation to accept supine hypertension in elderly (>80 years) patients without Parkinson's disease<sup>56</sup> might also be appropriate for younger patients with coexistent neurogenic orthostatic hypotension and supine hypertension.

### Prioritisation of supine hypertension over neurogenic orthostatic hypotension

Two arguments support the treatment of supine hypertension in patients with coexistent neurogenic orthostatic hypotension. The first argument is that prevention of the long-term consequences of hypertension, which might be similar to those seen in people without Parkinson's disease, should be a priority.<sup>27–30</sup> Cross-sectional studies of patients with pure autonomic failure have shown associations between supine hypertension and both renal impairment<sup>57</sup> and left ventricular hypertrophy.<sup>58</sup> However, these studies were based on ancillary testing in patients with Parkinson's disease with no symptoms of either renal or cardiovascular impairment, and are thus of unclear importance. Nevertheless, no long-term benefits from the treatment of supine hypertension have been shown in patients with coexistent neurogenic orthostatic hypotension and supine hypertension.

A second argument for the treatment of supine hypertension is that, untreated, the condition can cause pressure natriuresis and nocturia, which ultimately result in volume depletion and worsening of neurogenic orthostatic hypotension. This relation probably explains

	Study design	Participants (n)	Main findings
<b>No significant effects</b>			
Eadie and Sutherland (1964) <sup>28</sup>	Case-control	Consecutive patients with Parkinson's disease (95); age-matched and sex-matched controls with acute orthopaedic disorders (96)	No difference in mean clinical atherosclerosis
Marttila and Rinne (1976) <sup>29</sup>	Case-control	All traceable patients with Parkinson's disease in a Finnish area (444); age-matched and sex-matched general-population controls in the same area (444)	No difference in prevalence of cardiac insufficiency, coronary heart disease, or stroke
Mastaglia et al (2002) <sup>30</sup>	Post-mortem examination	Brains of patients with Parkinson's disease (100); brains of age-matched controls (100)	No difference in frequency of cerebral infarcts or haemorrhages
Nataraj and Rajput (2005) <sup>27</sup>	Record review	Patients with Parkinson's disease (490); age-matched and sex-matched patients with essential tremor (270); age-matched and sex-matched patients chosen randomly from a general practitioner's database (490)	No difference in prevalence of coronary artery disease or symptomatic cerebrovascular disease (stroke or transient ischaemic attack); lower prevalence of stroke in patients with Parkinson's disease, which became non-significant after adjustment for smoking status*
<b>Decreased risk</b>			
Hoehn and Yahr (1967) <sup>31</sup>	Record review	Patients with Parkinson's disease seen at a single centre in New York, NY, USA (802); general population death statistics from New York, NY, USA (N/A)	Less death from heart disease in patients with Parkinson's disease
Kessler (1972) <sup>32</sup>	Community-based survey	Patients with Parkinson's disease in Baltimore, MD, USA (228); patients without Parkinson's disease seen by the same physicians, matched for race, age, and sex (228)	Less frequent history of heart disease or stroke among men with Parkinson's disease*
Struck et al (1990) <sup>36</sup>	Case-control (retrospective)	Consecutive patients with Parkinson's disease (200); patients with skin carcinoma (200)	Lower cumulative prevalence of ischaemic stroke and myocardial infarction*
<b>Increased risk</b>			
Bodenmann et al (2001) <sup>33</sup>	Record review	Consecutive parkinsonian patients (368); age-matched controls (not reported)	Higher frequency of ischaemic stroke in patients with Parkinson's disease
<b>Mixed findings</b>			
Levine et al (1992) <sup>34</sup>	Case-control (retrospective)	Consecutive patients with Parkinson's disease (119); age-matched and sex-matched patients discharged from the same hospital without Parkinson's disease (238)	Lower cumulative prevalence of myocardial infarction, coronary artery disease, and atrial fibrillation; no difference in cumulative prevalence of ischaemic stroke*
Gorell et al (1994) <sup>35</sup>	Death certificate review	Patients with Parkinson's disease as a contributing cause of death in MI, USA (8629); general-population death statistics from MI, USA (208 933)	No difference in frequency of heart disease; higher likelihood of death from cerebrovascular disease†

N/A=not available. \*Tobacco use, an important potential confounder, was significantly lower in the group of patients with Parkinson's disease. †Suspected to reflect detection bias.

**Table 2: Studies of prevalence of cardiovascular risk factors and cardiovascular disease in patients with Parkinson's disease**

the tendency for increased neurogenic orthostatic hypotension in patients with uncontrolled hypertension.<sup>59</sup> These observations also imply that withholding antihypertensives might paradoxically worsen orthostatic hypotension, so treating severe and nocturnal supine hypertension needs to be considered.<sup>60</sup>

## Cardiovascular autonomic dysfunction

### Cardiovascular homeostasis

Disruptions of cardiovascular homeostasis in Parkinson's disease have at least three pathophysiological causes related to catecholaminergic deficiency:<sup>61</sup> cardiac noradrenergic sympathetic denervation, which decreases the heart's ability to increase cardiac output; central and peripheral noradrenaline deficiency, which causes sympathetic denervation and interferes with vasoconstriction; and arterial baroreflex failure, which impairs homeostatic functions, including heart-rate adjustment in response to changing blood pressure. These mechanisms are under the control of sympathetic and parasympathetic components of the autonomic nervous system. Sympathetic activation induces arterial vasoconstriction and increases cardiac output, resulting in an increase in blood pressure, whereas parasympathetic activation reduces peripheral resistances and heart rate, thereby lowering blood pressure. The homeostasis of this complex network is preserved by continuous feedback to brainstem nuclei from baroreceptors in the heart, vena cava, carotid sinuses, and aortic arch. Impairment of this network underlies the development of neurogenic orthostatic hypotension, and baroreflex dysfunction, nocturnal fluid retention, adrenergic hypersensitivity, and drug therapies for the syndrome all contribute to or aggravate pre-existing supine hypertension.<sup>7,62</sup>

### Peripheral parasympathetic denervation

Although correlative clinicopathological studies have not been done,  $\alpha$ -synuclein pathology in Parkinson's disease and dementia with Lewy bodies might affect the dorsal vagal nucleus,<sup>63</sup> resulting in substantial parasympathetic dysfunction—including a reduced mean change in heart rate in response to deep breathing and standing, and a reduced mean Valsalva ratio.<sup>64</sup> Early vagal dysfunction can be assessed by means of heart-rate-variability electrocardiography or power spectral analysis.<sup>65</sup> Patients with Parkinson's disease can have deficient cardiac reactivity (mediated both by sympathetic and parasympathetic dysfunction) and blood pressure dysregulation as a result of inadequate noradrenergic tone (required for sustaining normal blood pressure increases upon standing), a scenario for the concurrence of neurogenic orthostatic hypotension and supine hypertension.

### Peripheral sympathetic denervation

In patients with Parkinson's disease, the progressive loss of cardiac noradrenergic sympathetic innervation seems at least as extensive as the progressive loss of dopaminergic

neurons in the nigral pars compacta.<sup>66</sup> This loss of cardiac sympathetic innervation appears to be associated with the same pathological changes found in Parkinson's disease, including aggregation of misfolded  $\alpha$ -synuclein,<sup>67,68</sup> and it can precede the loss of dopaminergic nigral neurons.<sup>69–74</sup> The severity of cardiac sympathetic denervation is unrelated to the severity of putaminal dopaminergic deafferentation.<sup>73</sup> In an imaging study, patients with Parkinson's disease and neurogenic orthostatic hypotension showed progressive loss of myocardial noradrenergic innervation, involving the apical or inferolateral wall of the left ventricle.<sup>61</sup> A thoracic PET study<sup>75,76</sup> showed no detectable myocardial sympathetic nerve endings and no noradrenaline spillover (ie, the estimated rate at which the released neurotransmitter escapes from synaptic clefts into the cardiac venous drainage).

Findings of cardiac sympathetic denervation in Parkinson's disease have been confirmed with various sympathetic imaging radiolabels,<sup>61</sup> and by pathological studies<sup>66,67,77</sup> in heart tissue in which immunostaining was used to mark sympathetic axons. Clinically assessed sympathetic dysfunction is also more common in patients with Parkinson's disease dementia than in those with other dementias, such as Alzheimer's disease, as shown by a reduced (or blunted) blood pressure overshoot during phase IV of the Valsalva manoeuvre and reduced mean change in diastolic blood pressure during isometric exercise.<sup>64</sup> The predominantly central dysautonomia of another synucleinopathy, multiple system atrophy—in which cardiac sympathetic denervation is minimal<sup>78</sup>—is associated with impairment in heart-rate variability that is similar to or greater than that of Parkinson's disease. This finding suggests that peripheral denervation has a marginal role in breathing-related and standing blood pressure fluctuations in multiple system atrophy, by contrast with Parkinson's disease.

### Noradrenaline deficiency

The early and severe degeneration of the locus coeruleus and sympathetic ganglia in Parkinson's disease, which leads to impaired noradrenergic output, might be as extensive as the degeneration of substantia nigra neurons that results in dopaminergic deficiency.<sup>79</sup> In patients with neurogenic orthostatic hypotension, the mean resting serum noradrenaline concentration is significantly lower than that in patients who do not have neurogenic orthostatic hypotension.<sup>80,81</sup> Because release into the cardiac venous drainage contributes negligibly to the systemic concentration of noradrenaline,<sup>82</sup> the lower systemic concentration can be interpreted as reflecting mainly a decrease in extracardiac noradrenergic sympathetic activity.<sup>61,83</sup>

In patients with neurogenic orthostatic hypotension, systemic noradrenaline concentrations do not increase on standing.<sup>80,83,84</sup> In healthy people, within 5 min of changing from a supine to a standing position, the plasma noradrenaline concentration approximately

doubles<sup>85,86</sup>—a homeostatic adjustment that remains unchanged with ageing.<sup>87</sup> Further evidence of extra-cardiac sympathetic denervation in patients with neurogenic orthostatic hypotension is the increase in systolic blood pressure induced by low noradrenaline doses, suggesting vascular adrenoceptor supersensitivity from noradrenaline deficiency.<sup>80,81</sup> Moreover, yohimbine, an  $\alpha_2$ -receptor antagonist, has a reduced capacity to increase the baseline plasma noradrenaline concentration.<sup>88</sup> The collective consequence is a decrease in vasoconstriction when assuming an upright posture.

### Baroreflex failure

Baroreflex functionality can be assessed by different tests, including analysis of heart-rate variability during deep breathing, which could provide information on the integrity of parasympathetic pathways, and the combined analysis of blood pressure measurements and heart-rate variability during specific activating manoeuvres, such as

Valsalva and lying to standing, which probe both sympathetic and parasympathetic components of the autonomic nervous system. The Valsalva manoeuvre is associated with four phases of blood pressure and heart-rate response (appendix).<sup>61</sup> Sympathetic failure in neurogenic orthostatic hypotension includes a progressive blood pressure decrease throughout phase II, an absence of blood pressure overshoot during phase IV, and an absence of reflex tachycardia during phase II, leading to a greater tendency for both neurogenic orthostatic hypotension and supine hypertension.

Standing requires a coordinated sequence of reflexes to maintain blood pressure and therefore cerebral perfusion. The initial fall of blood pressure that occurs immediately after standing (due to blood pooling in the lower extremities) is usually followed by a compensatory sympathetic activation and inhibition of parasympathetic output, resulting in peripheral vasoconstriction and an increase in heart rate. This phase is usually associated with a transient blood pressure overshoot, followed by a gradual stabilisation of pressure and heart rate. Inadequate functioning of these compensatory mechanisms can result in neurogenic orthostatic hypotension.

The mechanisms leading to supine hypertension are probably multifactorial and relate to overlapping pathophysiological processes involved in neurogenic orthostatic hypotension. Abnormal natriuresis, increased blood volume, and impaired baroreflex compensatory responses, in addition to post-synaptic adrenoceptor hypersensitisation, have all been implicated.<sup>21</sup>

### Effects of pharmacotherapy

Dopaminergic drugs have well recognised hypotensive effects, which could exacerbate or even cause orthostatic hypotension.<sup>83,89–91</sup> Levodopa lowers blood pressure through both peripheral and central mechanisms.<sup>92,93</sup> In a 2014 study,<sup>91</sup> levodopa dosing in 17 patients with Parkinson's disease (two of whom had neurogenic orthostatic hypotension) led to decreased mean arterial pressure, accompanied by decreases in cardiac stroke volume and cardiac contractility. However, heart rate and systemic vascular resistance did not change significantly, suggesting that levodopa might promote hypotension via negative cardiac inotropism rather than vasodilation. Other dopaminergic therapies, including dopamine agonists and monoamine oxidase B inhibitors, also increase the risk of hypotension.<sup>94–96</sup>

There is no evidence that levodopa interferes with the cardiovascular response to noradrenaline.<sup>83</sup> In a study of the cardiovascular effects of levodopa in patients with Parkinson's disease, the severity of orthostatic hypotension did not differ between levodopa-treated and levodopa-untreated patients with Parkinson's disease and orthostatic hypotension. The two groups showed similarly reduced reflexive cardiovagal gain and sympathoneural responses.<sup>83</sup>

Acetylcholinesterase inhibitors can provide clinical benefits in cognitive performance and the management of

See Online for appendix

## Panel 2: Conservative approaches to the management of neurogenic orthostatic hypotension and supine hypertension in patients with both conditions

### Neurogenic orthostatic hypotension

#### Lifestyle

- Increase water and salt intake
- Stand up slowly
- If possible, perform exercises (eg, leg crossing, squatting) to reduce lower body blood pooling
- Avoid alcohol
- Avoid autonomic stressors (eg, long exposure to hot water)
- Consider thigh-high compression stockings with or without abdominal binder
- Sleep with head of the bed elevated by 15–23 cm

#### Adjustment of pharmacotherapy

- Whenever possible, replace fludrocortisone with a short-acting pressor (eg, midodrine, droxidopa)
- When possible, the patient should use pressor agents as required
- Use the lowest dose of pressor agent that controls symptoms
- Consider treating postprandial hypotension with acarbose (an  $\alpha$ -glucosidase inhibitor that decreases intestinal glucose absorption)
- Consider treating mild disease with pyridostigmine
- Assess all drugs for unwanted, avoidable cardiovascular effects

### Supine hypertension

#### Lifestyle

- Avoid the supine position during the day, especially after taking a pressor agent
- Have a snack before bedtime (to induce postprandial hypotension)
- Sleep with head of the bed elevated by 15–23 cm

#### Adjustment of pharmacotherapy

- If antihypertensives are needed, avoid  $\alpha$ -blockers and diuretics
- Assess all medications for unwanted, avoidable cardiovascular effects
- Consider bedtime therapies, such as transdermal nitroglycerin patches, the phosphodiesterase-5 inhibitor sildenafil, the  $\beta$ -blocker nebivolol, the angiotensin-receptor antagonist losartan, or the vasodilators hydralazine or minoxidil
- In multiple system atrophy (in which residual sympathetic tone can increase supine hypertension), the sympatholytic agent clonidine can be useful



hallucinations in patients with Parkinson's disease dementia or Parkinson's disease with mild cognitive impairment.<sup>97</sup> However, in a population-based cohort study<sup>98</sup> of registry data from patients with dementia, Gill and colleagues showed that acetylcholinesterase inhibitors were associated with an increased risk of syncope, bradycardia, pacemaker insertion, and hip fracture. Although the authors controlled for dopaminergic therapy in their analysis of hip fractures, they did not control for syncope or the other outcomes assessed. In our clinical experience, because of their background cardiovascular dysautonomia, patients with Parkinson's disease with pre-existing neurogenic orthostatic hypotension who are treated with acetylcholinesterase inhibitors are at a higher risk of syncope (as a result of bradycardia or exacerbation of neurogenic orthostatic hypotension) than are patients without Parkinson's disease who are treated with these drugs.

### Management of supine hypertension with minimum worsening of neurogenic orthostatic hypotension

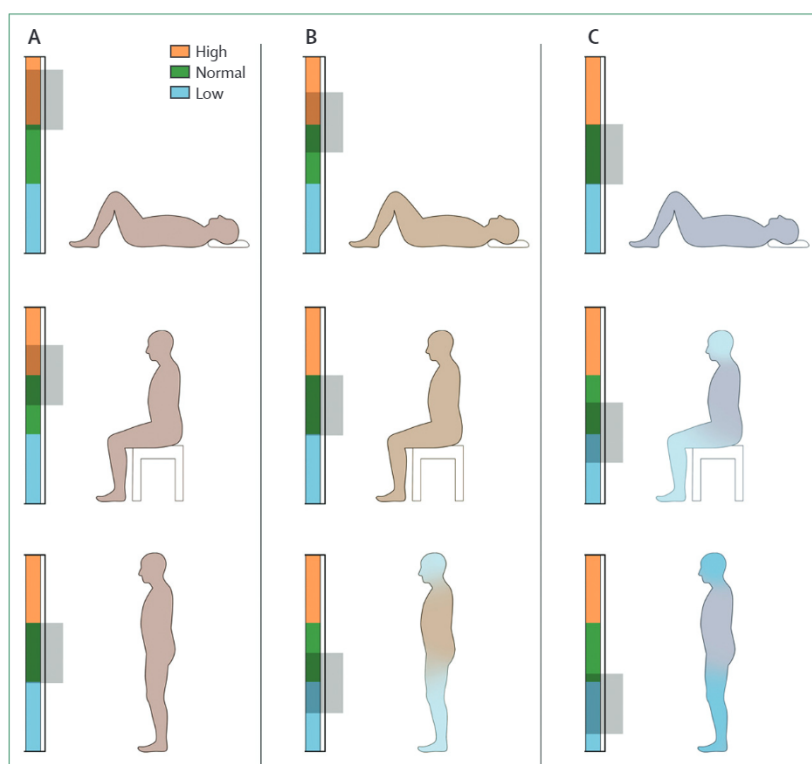
Non-pharmacological measures can be beneficial in the management of both supine hypertension and neurogenic orthostatic hypotension (panel 2), but these approaches can be easily overlooked. During the day, for example, patients should avoid the supine position, particularly after taking a pressor drug. In patients with autonomic failure, sleeping with a head-up tilt reduces night-time pressure natriuresis and improves morning orthostatic tolerance.<sup>99</sup> An ideal antihypertensive regimen should achieve overnight blood pressure reduction and have a duration of action tailored to avoid worsening of neurogenic orthostatic hypotension the next morning.

A patient's prognosis should be considered when deciding whether to prescribe antihypertensive drugs. In general, acute responses to a cardiovascular drug in patients experiencing autonomic failure can be difficult to predict.<sup>100</sup> Accordingly, management should be individualised, in view of the absence of an obvious first-choice treatment. However, clinical experience suggests that  $\alpha$ -blockers and diuretics should be avoided in patients with Parkinson's disease, because their mechanisms of action can exacerbate nocturia in patients with coexistent neurogenic orthostatic hypotension and supine hypertension. The use of  $\beta$ -blockers is also of concern in patients with Parkinson's disease, because the usual postural tachycardic response to standing is often absent in these patients, and thus these drugs can lessen a crucial compensatory response for the maintenance of adequate perfusion.

### Management of neurogenic orthostatic hypotension with worsening of supine hypertension

Management of coexistent neurogenic orthostatic hypotension and supine hypertension is a major

therapeutic challenge because drug treatment aimed at one could worsen the other (figure 2). Although both conditions have risks, falls and hospital admissions associated with Parkinson's disease tend to be more commonly attributed to neurogenic orthostatic hypotension than to supine hypertension.<sup>46</sup> Moreover, the rationale for aggressive treatment of supine hypertension in patients with Parkinson's disease has arisen from studies of chronic hypertensive non-Parkinson's populations and, especially, populations without neurogenic orthostatic hypotension or supine hypertension. Application of this evidence to treatment decisions would necessitate data showing that supine hypertension in patients with neurogenic orthostatic hypotension confers the same long-term cardiovascular and cerebrovascular risks as it does in patients with chronic essential hypertension. Even then, the theoretical cumulative harm of supine hypertension is a long-term risk in Parkinson's disease, compared with the near-term risk of falls and other sequelae of neurogenic orthostatic hypotension.



**Figure 2: Blood pressure management challenges in three clinical presentations**

Three types of patient with Parkinson's disease with autonomic dysregulation leading to neurogenic orthostatic hypotension and supine hypertension are shown. In the lying–sitting–standing sequence, patient A shows very high, high, and normal blood pressure; patient B shows high, normal, and low pressure; and patient C shows normal, low, and very low pressure. Patient B, who has normal blood pressure when sitting, and patient C, who has low blood pressure when sitting, are at risk of neurogenic orthostatic hypotension when standing (the risk is greater in patient C). Patient A illustrates the hypothesised treatment state, in which a high blood pressure in the sitting and lying positions allows normal blood pressure in the erect position and fewer consequences related to neurogenic orthostatic hypotension. Patient C represents the untreated or undertreated state, in which the absence of supine hypertension can herald (symptomatic or subclinical) neurogenic orthostatic hypotension. Although the risks for patient C are well established and of immediate concern, the risks for patient A need to be further studied. Different colours within patients represents perfusion.

Several studies<sup>26,27,31,32,34</sup> suggest that the risks of supine hypertension are lower in patients with Parkinson's disease than in other patient populations. Conversely, the autonomic impairment of pure autonomic failure—a Lewy-body pathology that shares several underlying pathogenetic mechanisms with the autonomic impairment in Parkinson's disease<sup>101</sup>—has been associated with hypertensive end-organ damage.<sup>57,58</sup> However, unlike patients with Parkinson's disease, those with pure autonomic failure are not treated with dopaminergic drugs, which could lower blood pressure, and pure autonomic failure is typically long-lived. A study<sup>102</sup> in which the long-term survival of patients with synucleinopathies was assessed showed that the 10-year survival probability from diagnosis was 74% in the 47 patients with neurogenic orthostatic hypotension, compared with 87% in the 28 patients with pure autonomic failure, and 93% in the 54 patients with Parkinson's disease but without neurogenic orthostatic hypotension.

Concerns about the long-term risks of supine hypertension might encourage aggressive treatment at the expense of exacerbations of neurogenic orthostatic hypotension or unmasking of a subclinical or asymptomatic state. Conversely, treatment of neurogenic orthostatic hypotension, while permitting some degree of supine hypertension, can be disconcerting for patients and clinicians. The rationale for blood-pressure-increasing regimens in patients with Parkinson's disease will need to be validated in prospective, naturalistic studies.<sup>7</sup> Symptomatic neurogenic orthostatic hypotension is

most often characterised by dizziness, lightheadedness, or feeling faint or likely to lose consciousness, which can be measured with item 1 of the Orthostatic Hypotension Symptom Assessment, a component of the validated Orthostatic Hypotension Questionnaire.<sup>103</sup> Pivotal clinical trials of droxidopa<sup>104,105</sup> (a new treatment approved by the US Food and Drug Administration for symptomatic neurogenic orthostatic hypotension) and an observational study of Parkinson's disease and neurogenic orthostatic hypotension<sup>106</sup> have used these scales to assess the severity of, and improvements in, symptoms. Besides a reduction in lightheadedness or dizziness in the short term, assessments of the effect of treatment on gait and falls in the near term and medium term, and on cognitive function, stroke risk, and renal function in the long term (table 3), are important.

Another important research question is whether asymptomatic neurogenic orthostatic hypotension should be targeted pharmacologically, in a fashion similar to symptomatic presentations, in view of the condition's association with fatigue, falls, and cognitive impairment. Indeed, a definition of symptomatic neurogenic orthostatic hypotension restricted to the presence of postural lightheadedness or weakness could preclude the application of blood-pressure-increasing interventions in patients with Parkinson's disease with falls or cognitive impairment who might benefit from such treatments. A 2015 study<sup>106</sup> showed that only 33 (31%) of 105 patients with Parkinson's disease who met the blood pressure criteria for neurogenic orthostatic hypotension were symptomatic. This clinical finding suggests that cerebral

	How to address knowledge gap	Study complexity
What is the ratio of symptomatic to asymptomatic neurogenic orthostatic hypotension?	Systematic measurement of orthostatic blood pressure in large consecutive cohorts of patients with neurogenic orthostatic hypotension to determine prevalence of lightheadedness	Low, cross-sectional
What proportion of gait impairment and falls can be attributed to neurogenic orthostatic hypotension?	Systematic measurement of orthostatic blood pressure in large consecutive cohorts of patients with neurogenic orthostatic hypotension to determine prevalence of gait impairment and falls	Low, cross-sectional
Should asymptomatic neurogenic orthostatic hypotension be treated in elderly patients at risk of dehydration and drug-induced hypotension?	Placebo-controlled randomised controlled trial of blood-pressure-increasing treatment for patients older than 75 years with neurogenic orthostatic hypotension, with monitoring of cardiovascular endpoints, and daytime and night-time blood pressure	High, multisite, ≥1-year follow-up
Are there advantages to night-time short-acting antihypertensives in patients with daytime neurogenic orthostatic hypotension?	Placebo-controlled randomised controlled trial of night-time antihypertensives (eg, transdermal nitroglycerin patches, sildenafil, nebulolol, clonidine) in patients with neurogenic orthostatic hypotension plus supine hypertension, with monitoring of cardiovascular endpoints and night-time blood pressure	Medium, multisite, ≥1-year follow-up
Should antihypertensive treatment be stopped in patients with neurogenic orthostatic hypotension and pre-existing hypertension?	Prospective measurement of fatigue, falls, and cognitive impairment in patients with neurogenic orthostatic hypotension before and after discontinuation of antihypertensives vs a control group (an age-matched and disease-duration-matched cohort continuing on antihypertensives)	High, multisite, ≥1-year follow-up
Should asymptomatic neurogenic orthostatic hypotension be treated to avoid current or future complications?	Prospective measurement of fatigue, falls,* and cognitive impairment before and after blood-pressure-increasing treatment in patients with asymptomatic neurogenic orthostatic hypotension	High, multisite, ≥2-year follow-up
What range of supine hypertension is safe when treating neurogenic orthostatic hypotension?	Prospective measurement of cardiovascular events (stroke and myocardial infarctions) in patients with Parkinson's disease with no or mild supine hypertension (systolic blood pressure 141–179 mm Hg) or moderate supine hypertension (180 mm Hg)	High, multisite, ≥3-year follow-up

\*Includes ascertainment of the proportion of falls in Parkinson's disease due to neurogenic orthostatic hypotension and the extent to which a reduction in falls can be achieved with aggressive neurogenic orthostatic hypotension treatment (ie, allowing for safe level of supine hypertension).

**Table 3: Knowledge gaps in treatment of neurogenic orthostatic hypotension in patients with or at risk of supine hypertension**

autoregulation mechanisms might adapt in these patients to compensate for the chronic, recurrent variability in blood pressure.<sup>106,107</sup> It has been suggested that this cerebral autoregulation adaptation could be linked to the development of supine hypertension because of chronic vasoconstriction of cerebral blood vessels.<sup>107</sup>

How often asymptomatic neurogenic orthostatic hypotension in patients with Parkinson's disease evolves into symptomatic disease upon initiation of, or with increases in, dopaminergic treatment or during other challenges to cerebrovascular autoregulatory mechanisms (eg, dehydration) is unknown. The roles of new treatments for neurogenic orthostatic hypotension (eg, automated abdominal binders,<sup>108</sup> noradrenaline infusions<sup>109,110</sup>) or management of supine hypertension (eg, use of carotid sinus stimulation devices<sup>111</sup>) in patients with Parkinson's disease also remain to be fully investigated. Most challenging for optimal care is the outstanding need to define what constitutes a safe range of permissible supine hypertension amid the expected outcomes of treating neurogenic orthostatic hypotension. Before such data become available, it seems reasonable to treat supine hypertension in patients who also have neurogenic orthostatic hypotension, especially those expected to live long enough for potential cardiovascular consequences to be of concern, provided that this treatment does not worsen daytime neurogenic orthostatic hypotension (panel 2). Non-pharmacological measures, such as sleeping with the head of the bed elevated, can also improve neurogenic orthostatic hypotension. The unanswered question confronting many patients is whether to use antihypertensives: it will be valuable to determine whether a short-acting antihypertensive at night is a useful adjunct to a short-acting pressor during the day for neurogenic orthostatic hypotension—an approach that has been advocated, but never studied.<sup>112</sup> Among available antihypertensives, short-term trials have shown that some effectively lower night-time blood pressure, including angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers.<sup>112</sup> However, others (eg, clonidine) do not reduce pressure natriuresis and can have a persisting and undesirable hypotensive effect.

## Conclusions and future directions

Prioritisation of treatment in patients with neurogenic orthostatic hypotension and supine hypertension remains challenging in view of the paucity of clinical trial data for disability and outcomes of the combined haemodynamic dysfunction, and the extent to which the short-term and long-term response of favouring one over the other can be affected by comorbidities and disease staging. Although questions remain about the optimal management of bidirectional haemodynamic influences in Parkinson's disease, the available evidence supports a preliminary conclusion that, in patients with cardiovascular dysautonomia, adequate treatment of

### Search strategy and selection criteria

We originally searched PubMed and Embase with the terms “orthostatic hypotension”, “neurogenic orthostatic hypotension”, “supine hypertension”, “sympathetic”, “dysautonomia”, “autonomic dysfunction”, “cardiovascular”, “Parkinson”, and “Parkinson disease” for articles published in peer-reviewed journals in any language from July 1, 2004, to June 30, 2014. Our search was subsequently updated to Dec 31, 2015. We also searched the reference lists of selected papers. The final reference list was generated on the basis of relevance to the topics covered in this Review.

neurogenic orthostatic hypotension should be prioritised, allowing mild-to-moderate supine hypertension, with initiation of short-acting antihypertensives only for patients with severe supine hypertension during the day or night.

Important goals for future studies (table 3) include ascertaining the proportion of gait impairment and falls that can be attributed to neurogenic orthostatic hypotension; the safe range for supine hypertension in patients treated for neurogenic orthostatic hypotension; the extent to which asymptomatic neurogenic orthostatic hypotension might need to be treated in elderly patients at risk of dehydration and drug-induced hypotension; and whether asymptomatic neurogenic orthostatic hypotension in general deserves to be treated to avoid current or future complications. Although much remains to be learned about the complex management of patients with neurogenic orthostatic hypotension and supine hypertension, there is an urgent need to recognise the independent influence of these treatable sources of impaired quality of life and disability in Parkinson's disease and other synucleinopathies.

### Contributors

AJE planned the Review, identified the primary sources of information (through literature searches and selection of relevant articles), wrote the first draft, and executed further revisions based on feedback from co-authors. PAL, RAH, AM, MM, and AEL reviewed the paper and provided critical feedback.

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