Clinical Autonomic Research
https://doi.org/10.1007/s10286-019-00652-6

RESEARCH ARTICLE

Prevalence and factors related to orthostatic syndromes in recently diagnosed, drug-naïve patients with Parkinson disease

Cecilia Quarracino[1] · **Matilde Otero-Losada**[1] · **Francisco Capani**[1,2] · **Santiago Pérez-Lloret**[1,3]

Received: 9 October 2019 / Accepted: 2 December 2019

Abstract

Purpose The aim of this study was to explore the prevalence of and factors related to orthostatic syndromes in recently diagnosed drug-naïve patients with Parkinson disease (PD).

Methods This was a cross-sectional study that included 217 drug-naïve patients with PD and 108 sex- and age-matched non-parkinsonian controls from the Parkinson's Progression Markers Initiative (PPMI) prospective cohort study who were devoid of diabetes, alcoholism, polyneuropathy, amyloidosis, and hypotension-inducing drugs. Orthostatic symptoms were evaluated using the Scales for Outcomes in PD–Autonomic Dysfunction (SCOPA-AUT). Ioflupane-I^{123} single-photon emission computerized tomography was used to evaluate striatal dopamine active transporter (DaT) levels. Blood pressure was assessed both in the supine position and 1–3 min after the switch to a standing position. Orthostatic hypotension (OH) was defined by international consensus, and orthostatic intolerance (OI) was defined as the presence of orthostatic symptoms in the absence of OH.

Results Compared with non-parkinsonian controls, patients with PD experienced a mild fall in systolic blood pressure upon standing ($p = 0.082$). The prevalence of OH was 11.1% in PD patients and 5.6% in controls ($p = 0.109$). The prevalence of OI was higher in patients with PD than in controls (31.3 vs. 13.3%; $p = 0.003$). Logistic regression revealed that OH and OI were related to a lower striatal DaT level and higher SCOPA-AUT gastrointestinal score.

Conclusions Orthostatic syndromes were common in the recently diagnosed drug-naïve patients with PD enrolled in the study, but only the prevalence of OI was higher in PD patients than in the non-parkinsonian controls. Unlike motor or functional disability indicators, markers of dopaminergic striatal deficit and gastrointestinal dysfunction were associated with OH and OI.

Keywords Autonomic nervous system · Dysautonomia · Orthostatic hypotension · Orthostatic symptoms · Parkinson disease

✉ Santiago Pérez-Lloret
santiagopl@conicet.gov.ar

Cecilia Quarracino
cecquarr@hotmail.com

Matilde Otero-Losada
molly1063@gmail.com

Francisco Capani
franciscocapani@hotmail.com

[1] Institute of Cardiological Research, University of Buenos Aires–National Research Council, ININCA, UBA-CONICET, Marcelo T. de Alvear, CP 1122 Buenos Aires, Argentina

[2] School of Medicine, Fundación H.A. Barceló, Buenos Aires, Argentina

[3] Department of Physiology, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina

Introduction

Dysautonomia is one of the most frequent and disabling non-motor symptoms in Parkinson disease (PD) [1]. Orthostatic hypotension (OH) affects the quality of life and mortality [1–3] and is defined as a fall in systolic and/or diastolic blood pressure (BP) of ≥ 20/10 mmHg within 3 min of standing or a head-up tilt of ≥ 60° on a tilt table (systolic BP cutoff point may be set at 30 mmHg in hypertensive patients) [4]. The condition may be asymptomatic or accompanied by orthostatic symptoms such as light-headedness, dizziness, presyncope, and syncope [4]. Diabetes, alcoholism, hypertension, aging, amyloidosis, and a variety of medications can increase the risk of OH [2, 5]. The prevalence of OH in recently diagnosed patients with PD has been insufficiently

Published online: 17 December 2019

studied. Awerbuch and colleagues studied 20 unmedicated patients with PD with a Hoehn and Yahr score of 1 and 2 and found abnormal parasympathetic cardiac activity in 80% of them [6]. In two other studies, the prevalence of OH in two small cohorts of drug-naïve patients was 16 and 40%, respectively [7, 8]. However, the lack of control groups in these studies, the limited sample sizes, and differences in assessed parameters make it difficult to appreciate the burden of OH in patients with early PD. More recently, a larger study (185 recently diagnosed patients with PD and 172 controls) reported an OH prevalence of 19.5% among PD patients [9].

Some patients complain of orthostatic symptoms even though an exaggerated fall in BP or significant heart rate modifications are not found during routine orthostatic stress testing [5, 10–12]. In such cases, typically the symptoms alleviate rapidly after the patient resumes the resting position. This disorder is referred to as orthostatic intolerance (OI) and was found to affect 16% of the young participants in the Syncope Study of Unselected Population in Malmö cohort [10] and 47% of patients from a specialized autonomic testing unit cohort [13]. One study reported cardiovascular symptoms in 7.4% patients with early PD with no evidence of OH during orthostatic testing [7], and a more recent study reported orthostatic symptoms in 39.6% of 1746 recently diagnosed patients with PD although orthostatic stress was not tested [14].

Not only does the prevalence of OH lack controlled testing, but there is a void of information on the prevalence of and factors associated with OI in patients with PD. In this cross-sectional study, we have thoroughly analyzed the available data in the Parkinson's Progression Markers Initiative (PPMI) [15] to explore the prevalence of and factors related to orthostatic syndromes in recently diagnosed drug-naïve patients with PD and non-parkinsonian controls.

Methods

Study design and participants

The PPMI is an ongoing multi-center observational study focused on identifying disease biomarkers in recently diagnosed patients with PD attending clinical centers at locations ranging from USA to Oceania [15]. In the PPMI, patients with PD and sex- and age-matched controls are evaluated and followed up. The protocol is approved by the review board of each center, and all participants sign a written informed consent. The information obtained is shared with involved and uninvolved investigators. To be eligible to enter the PPMI the patient must have been diagnosed with PD within the previous 2 years; have PD at Hoehn and Yahr stage I or II at the time of enrollment; have single-photon emission computed tomography (SPECT) scan results that are consistent with a dopamine transporter protein (DAT) deficit; be untreated, and not be expected to require pharmacological treatment during the first 6 months of the PPMI. Exclusion criteria for healthy controls are the existence of any significant neurological disorder; having a first-degree relative with idiopathic PD; or a Montreal Cognitive Assessment (MoCA) score of < 26.

All participants underwent a clinical evaluation, including basal and orthostatic BP testing, heart frequency determination, blood chemistry analysis, and lumbar puncture. All data on demographics, treatments, and comorbidities were recorded. Several validated scales were used to evaluate the participants, including the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [16], MoCA [17], Geriatric Depression Scale [18], State-Trait Anxiety Inventory for Adults [19], and Scales for Outcomes in PD-autonomic dysfunction (SCOPA-AUT) [20]. Ioflupane-I^{123} SPECT was used to evaluate striatal DaT levels (DaTSCAN) [15]. Levels of α-synuclein, β-amyloid fragment 1-42, total tau, and phosphorylated tau were quantified in cerebrospinal fluid samples [15].

In the present study, we considered recently diagnosed drug-naïve patients with PD and non-parkinsonian controls for whom there were complete data on the baseline orthostatic BP assessment and orthostatic symptoms. We excluded patients with conditions or medications associated with orthostatic syndromes, including diabetes, alcoholism, polyneuropathy, and amyloidosis, as well as users of calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, AT-1 receptor blockers, nitrates, α-adrenoreceptor antagonists, opioids, or tricyclic antidepressants [2, 5].

Assessment of orthostatic symptoms and blood pressure

Blood pressure was measured 1–3 min after resting in the supine position and at 1–3 min after switching to the standing position [15]. The month previous to the study, orthostatic symptoms were assessed using the SCOPA-AUT [20], which evaluates lightheadedness immediately after standing up (Item #14) and at any other time (Item #15) and syncope (Item #16). By adding item scores, we obtained a cardiovascular subscore.

The orthostatic syndromes examined in this study [4, 5, 21] were defined as follows. OH was defined as a fall in systolic BP of ≥ 20 mmHg (or ≥ 30 mm Hg in hypertensive patients) and/or a fall in diastolic BP of ≥ 10 mmHg fall upon 1–3 min upright standing. OI was defined by a SCOPA-AUT cardiovascular subscore of ≥ 1 in the absence of OH.

The ratio of heart rate change (Δ) and systolic BP drop during orthostatic stress was also determined among those patients with OH. A Δ heart range/Δ systolic BP drop after

changes in posture ratio of < 0.492 has been shown to discriminate between neurogenic and non-neurogenic OH [22],

Statistical analysis

The *t* test or Pearson Chi-square test was used for between-groups bivariate comparisons. The lack of homoscedasticity was compensated for by correcting for the degrees of freedom in the *t* test. Fisher´s exact test was used to measure the association between two categorical variables if two or more cells had fewer than five cases. Multivariate analysis was performed using multinomial logistic regression. The criterion to include a variable was based on its biological relevance and/or statistical significance ($p < 0.05$) in the bivariate test. Interactions were evaluated and ruled out. Results were expressed as odds ratio and 95% confidence intervals. The level of significance was conventionally set at 0.05 (SPSS v.23 software; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

This cross-sectional study enrolled 217 patients with PD and 108 non-parkinsonian controls from the PPMI database. As shown in Table 1, the mean age (± standard deviation) was 59.34 ± 9.8 and 57.73 ± 11.62 years, respectively ($p = 0.206$). In the PD group, 131 patients (60.4%) were male versus 61 males (56.5%) in the control group ($p = 0.502$). Of the 217

Table 1 Demographic characteristics and orthostatic syndromes in patients with Parkinson disease and the non-parkinsonian controls

Demographic characteristics and orthostatic syndromes	PD group($n = 217$)	Non-PD control group ($n = 108$)	*p* value
Males	131 (60.4%)	61 (56.5%)	0.502
Age (years)	59.34 ± 9.80	57.73 ± 11.62	0.206
Black race	2 (0.9%)	4 (3.7%)	0.097
Hypertension	17 (7.8%)	10 (9.3%)	0.661
Disease duration (months)	6.91 ± 8.68	–	NE
MDS-UPDRS scores			
Part I (non-motor symptoms)	1.19 ± 1.67	0.45 ± 0.95	< 0.001
Part II (activities of daily living)	5.87 ± 4.19	0.35 ± 0.89	< 0.001
Part III (motor examination)	19.80 ± 8.36	0.97 ± 1.92	< 0.001
Cognitive impairment (MoCA score)	3 (1.4%)	0 (0%)	0.553
Drugs for orthostatic hypotension at baseline	0 (0%)	0 (0%)	NE
Supine blood pressure (mmHg)			
Systolic	127.76 ± 16.16	128.22 ± 15.74	0.979
Diastolic	76.05 ± 10.68	75.97 ± 11.07	0.440
Changes in blood pressure after standing up (mmHg)			
Systolic	− 3.46 ± 11.49	− 1.23 ± 12.00	0.082
Diastolic	3.06 ± 8.70	4.26 ± 8.76	0.269
Orthostatic hypotension symptoms (SCOPA-AUT)			
Lightheadedness immediate (Item 14)	61 (28.1%)	16 (14.8%)	0.008
Lightheadedness delayed (Item 15)	37 (17.1%)	3 (2.8%)	< 0.001
Syncope (Item 16)	4 (1.8%)	1 (0.9%)	0.999
Orthostatic syndromes			
None	124 (57.1%)	85 (78.7%)	< 0.001[a]
Orthostatic hypotension	24 (11.1%)	6 (5.6%)	0.109
Symptomatic	12 (5.5%)	0	0.057
Asymptomatic	12 (5.5%)	6 (100%)	
Orthostatic intolerance	68 (31.3%)	17 (15.7%)	0.003[a]

Data are expressed as the mean ± standard deviation (SD) (continuous variables) or as the frequency and percentage (categorical variables). Bivariate comparisons were performed using a *t* test or Chi-square test

$p < 0.05$ indicates statistical significance

PD Parkinson disease, *MDS-UPDRS* Motor Disorder's Society-Unified Parkinson's Disease Rating Scale, *MoCA* Montreal Cognitive Assessment, *SCOPA-AUT* Scales for Outcomes in Parkinson's disease-dysautonomia

[a]Significance was confirmed after applying a Holm–Bonferroni correction for multiple comparisons

patients with PD, 25 (11.6%) had a first-degree relative with PD. The mean PD duration was 6.91 ± 6.68 months.

Frequency of orthostatic hypotension and orthostatic intolerance

There were no significant differences in BP either before or after standing up between non-parkinsonian controls and patients with PD (Table 1). Of note, the fall in systolic BP was milder in the control group than in the PD group (− 1.23 ± 12.00 vs. − 3.46 ± 11.49, $p = 0.082$; Table 1). Conversely, the SCOPA-AUT cardiovascular score was higher in patients with PD than in the controls (Table 1).

No differences were found in the prevalence of OH (PD 11.1% vs. controls 5.6%, $p = 0.109$; Table 1). As shown in Table 1, among the 24 PD patients with OH and the six non-parkinsonian controls with OH, 12 (50%) patients in the PD group and no person in the control group were symptomatic ($p = 0.057$). Nine patients with PD (37.5%) showed a Δ heart rate/Δ systolic BP ratio of < 0.492. OI was significantly more frequent among patients with PD than among the controls (31.3 vs. 15.7%, $p = 0.003$; Table 1).

Factors associated with orthostatic hypotension and orthostatic intolerance

Factors related to OH and OI in patients with PD are shown in Table 2. A multinomial logistic regression analysis revealed that the SCOPA-AUT gastrointestinal score and low striatal DaT levels were independently and significantly associated with both OH and OI (Table 2). A sensitivity analysis was performed by excluding SCOPA-AUT scores as predictors. Low DaT levels remained as a significant factor

Table 2 Factors related to orthostatic syndromes in patients with Parkinson disease

Factors related to orthostatic syndromes	No orthostatic syndromes ($n = 125$)	Orthostatic hypotension ($n = 24$)	Orthostatic intolerance ($n = 68$)	p value	Multinomial logistic regression analysis (OR, 95% CI)	
					OH	OI
Male gender	78 (62.4%)	14 (58.3%)	39 (57.4%)	0.773		
Age (years)	59.11 ± 10.22	60.95 ± 9.85	59.30 ± 9.13	0.784	0.99 (0.94–1.05)	0.99 (0.95–1.02)
Age at PD onset (years)	58.55 ± 10.24	60.27 ± 9.86	58.71 ± 9.26	0.806		
PD family history	28 (22.4%)	7 (29.2%)	19 (28.4%)	0.584		
DaTSCAN	1.48 ± 0.39	1.23 ± 0.26	1.35 ± 0.40	0.005	0.16 (0.04–0.69)[a]	0.32 (0.13–0.83)[a]
CSF biomarkers						
Aβ42	385.27 ± 106.69	339.00 ± 78.54	391.65 ± 112.82	0.092	1.00 (1.00–1.01)	1.00 (1.00–1.01)
α–syn	1898.94 ± 684.00	1850.64 ± 636.78	1983.32 ± 815.20	0.726		
pTau	16.93 ± 12.57	13.55 ± 6.84	16.03 ± 10.01	0.412		
Total Tau	43.01 ± 14.97	42.41 ± 16.26	44.30 ± 17.26	0.943		
Anxiety score	23.21 ± 8.90	26.45 ± 11.87	25.29 ± 10.92	0.137	1.01 (0.96–1.06)	1.01 (0.97–1.05)
Depression score	2.11 ± 2.44	3.09 ± 2.74	2.54 ± 2.66	0.284		
SCOPA–Aut						
Gastrointestinal	1.50 ± 1.77	2.95 ± 2.34	2.48 ± 1.74	0.006	1.46 (1.06–2.00)[a]	1.32 (1.05–1.66)[a]
Urinary	3.60 ± 2.51	3.50 ± 2.61	4.43 ± 3.49	0.111		
Thermoregulation	0.99 ± 1.12	1.77 ± 2.18	1.22 ± 1.18	0.066	1.24 (0.87–1.77)	1.03 (0.79–1.36)
Visual	0.36 ± 0.69	0.55 ± 0.60	0.51 ± 0.76	0.411		
Sex	1.04 ± 1.45	1.18 ± 1.50	0.94 ± 1.44	0.296		
Hypertension	12 (9.6%)	1 (4.2%)	4 (5.9%)	0.510		
MDS-UPDRS						
I	1.02 ± 1.29	1.71 ± 2.88	1.24 ± 1.52	0.829		
II	5.31 ± 3.89	6.21 ± 5.32	6.66 ± 4.22	0.067	0.89 (0.76–1.03)	0.99 (0.90–1.09)
III	18.83 ± 9.00	20.09 ± 9.18	21.41 ± 8.37	0.342		

Data are expressed as the mean ± SD (continuous variables) or as the frequency and percentage (categorical variables). Bivariate comparisons were performed using a *t* test or Chi-square test. Multivariate analysis was performed using multinomial logistic regression

OR Odds ratio, *CI* confidence interval, *OH* orthostatic hypotension, *OS* orthostatic sensitivity, *DaTSCAN* striatal DaT levels determined by Ioflupane-I^{123} SPECT (single-photon emission computed tomography), *CSF* cerebrospinal fluid, *α-syn* α-synuclein, *Aβ42* β-amyloid fragment 1-42, *p Tau* phosphorylated tau

[a]Multinomial logistic regression analysis revealed that the SCOPA-AUT gastrointestinal score and low DaTSCAN levels were independently and significantly ($p < 0.05$) associated with both OH and OI

associated with both conditions, without any other predictor in the model.

Finally, postural instability (as assessed by MDS-UPDRS item 3.12) was not associated with the presence of cardiovascular symptoms in the SCOPA-AUT ($p = 0.457$).

Discussion

In this study, we focused on orthostatic syndromes, which have not been thoroughly assessed in recently diagnosed drug-naïve patients with PD. Our results suggest that in our PD patient population OH and OI occurred early during disease development and that both entities were associated with nigrostriatal denervation, as measured by DaTSCAN.

Orthostatic stress testing revealed that fall in systolic BP in the non-parkinsonian controls was non-significantly milder as compared to patients with PD, suggesting that cardiovascular autonomic function is affected early in PD. However, a larger sample size is required to confirm this observation. Our results together with those from other studies showing overt alterations in BP regulation in advanced stages of PD [3, 23] suggest that OH evolves in time as the disease progresses. Likewise, the concept that patients with early PD already experience a mild autonomic alteration is consistent with our observation of a twofold increase in OH prevalence in the PD patient group compared with the non-parkinsonian controls, albeit not statistically significant due most likely to the reduced sample size in our study. The prevalence of OH among the PD patients in our study (11%) fell somewhat below the values reported in comparable earlier studies, i.e., 16, 19.5, and 40% [7–9]. This difference might be partly due to the restrictive exclusion criteria in our study: we excluded patients with other factors potentially associated with OH. For this reason, this study may provide the nearest reliable approximation to OH innately secondary to PD.

Norcliffe-Kaufmann et al. recently reported that a drop in the Δ heart range/Δ systolic BP ratio after changes in posture of < 0.492 may discriminate accurately between neurogenic and non-neurogenic OH [22]. In their study, this ratio was obtained from the results of a standardized tilt test at a 3-min interval for each patient, which was not the case for the PPMI cohort. Some limitations to the study have been raised recently, such as a potential referral bias and a possible lack of sensitivity between active versus passive standing [24]. To the best of our knowledge, our study is one of the first to assess this measure in patients with PD. We observed that only nine of 24 patients with PD with OH showed a ratio compatible with a diagnosis of neurogenic OH. It is possible that even after excluding common causes of non-neurogenic OH, others might still be present, such as volume depletion, unusual adverse effect of drugs, etc.. Since non-neurogenic OH tends to resolve when its cause is eliminated, we believe that calculation of the Δ heart range/Δ systolic BP drop ratio in patients with PD is of the highest importance before assumptions as to the neurogenic nature of OH can be made.

Few studies have been conducted on OI in patients with PD or the general population, possibly in part due to diagnostic difficulties as the symptoms may not only be unspecific but also sporadic in appearance [11]. Symptoms are often misascribed to comorbidities, and when they do not present continuously, the likelihood of detecting OI during the anamnesis or physical exam is reduced. In our sample of non-parkinsonian controls, OI was detected in 15.7% of patients, which is consistent with previously reported findings in the general population [10]. In our sample of patients with PD, however, the prevalence of OI was twofold the only available estimation to date, which was reported by Bae et al. [7] who studied 27 patients with early PD. The reasons for this discrepancy are not easily explained. The impact of OI in PD remains unknown and should be investigated, given its high prevalence in early PD. The multinomial logistic regression analysis in our study identified a significant association between orthostatic syndromes and the degeneration of nigrostriatal fibers, as inferred from DaTSCAN, suggesting a link between OH and OI with PD progression. Left ventricular post-ganglionic sympathetic denervation has been proposed as a central mechanism of OH genesis in PD [23]. In addition, experimental results suggest that alterations in the central regulation of the peripheral autonomic nervous system occur in PD [25]. In rats, stimulating the substantia nigra pars compacta enhanced striatal dopamine release, eliciting proportional hypertension and tachycardia, which in turn could be blocked by haloperidol [26]. These results are in agreement with our findings regarding a decline in nigrostriatal innervation in PD individuals with orthostatic syndromes and further highlight the importance of striatal influences on autonomic control.

We also observed an independent association between orthostatic syndromes and gastrointestinal dysautonomia symptoms. In patients with PD, dysautonomia is a multidomain phenomenon [3, 27]. These findings suggest an altogether broad autonomic compromise in the neurodegenerative process.

In our sample, neither OH nor OI were associated with disease severity as assessed by MDS-UPDRS scores. To date, the evidence regarding the relation between PD progression and dysautonomia is inconclusive, with some authors reporting motor [14, 28] or functional [29] associations and others [7, 9] finding none, as in the present study. We may have missed such associations because our sample comprised patients with recently diagnosed with PD. Disease progression and survival have been associated with autonomic alterations in a clinical retrospective

review of data from 100 consecutive patients with an autopsy-confirmed PD diagnosis. Finally, autonomic abnormalities may even appear before disease onset [28, 30, 31].

A large number of patients with PD in our sample complained of orthostatic symptoms even though only a minority of these had OH. We believe this observation strengthens the need for objective BP measurement since OI can be secondary to different pathologies (e.g., adverse drug effects, vertigo, volume depletion, inebriation-like syndrome, balance impairment, etc.) [32], some of which have a specific treatment.

There are a number of limitations to our study. The fall in orthostatic BP was determined by asking the patient to stand up, which may have increased experimental error partly due to intraindividual variability [33–35]. In addition, BP assessment at 1–3 min after orthostatic stress likely added to the experimental error associated to interindividual differences. Tilt-testing combined with a delayed assessment, longer than 3 min, has been reported to increase both the reproducibility and sensitivity of BP measurements [36]; however, this procedure is not available at every center and is not the usual standard of care. Notwithstanding, OH prevalence in non-parkinsonian controls in our study lies within the expected range of 5–30% [37–40], suggesting that the procedures used were sufficiently accurate. Another limitation is that the SCOPA-AUT does not capture the full spectrum of orthostatic symptoms. However, this scale is commonly used in clinical practice and has been recommended for use in PD [41]. The possibility that dizziness or lightheadedness was confused with postural instability by patients with PD was ruled out. Orthostatic symptoms were assessed during the month preceding the BP assessment. While concurrent assessment of BP and symptoms may have resulted in more precise results, extending the period of recollection may offer more sensitivity to orthostatic symptoms recollection. Finally, due to reduced sample sizes, some tests may have been underpowered.

In summary, we observed a significantly higher frequency of OI in patients with recently diagnosed drug-naïve PD than in the non-parkinsonian controls, together with signals of mild cardiovascular autonomic dysfunction, as suggested by a statistically non-significant greater fall in systolic BP after postural changes in the former population as well as a statistically non-significant higher prevalence of OH. Orthostatic syndromes were linked to central and peripheral neurodegeneration, as suggested by their association with lower DaTSCAN uptake by basal ganglia on the SPECT scan and gastrointestinal dysautonomia symptoms. OI has received considerably less attention than OH in studies on PD. Further research is warranted to assess the impact and prognostic significance of this condition in PD.

Acknowledgements The data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (https://www.ppmi-info.org/data). For up-to-date information on the study, visit https://www.ppmi-info.org.

Funding The PPMI—a public–private partnership—is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Avid Radiopharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Biolegend, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, Meso Scale, Piramal, Pfizer, Servier. TEVA, Takeda, Sanofi Genzyme, and UCB.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

References

1. Li K, Reichmann H, Ziemssen T (2015) Recognition and treatment of autonomic disturbances in Parkinson's disease. Expert Rev Neurother 15:1189–1203
2. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O (2010) Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur Heart J 31:85–91
3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ (2018) Autonomic dysfunction in Parkinson's disease: a prospective cohort study. Mov Disord 33:391–397
4. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21:69–72
5. Gutkin M, Stewart JM (2016) Orthostatic circulatory disorders: from nosology to nuts and bolts. Am J Hypertens 29:1009–1019
6. Awerbuch GI, Sandyk R (1992) Autonomic functions in the early stages of Parkinson's disease. Int J Neurosci 64:7–14
7. Bae HJ, Cheon SM, Kim JW (2011) Orthostatic hypotension in drug-naive patients with Parkinson's disease. J Mov Disord 4:33–37
8. Bonuccelli U, Lucetti C, Del Dotto P, Ceravolo R, Gambaccini G, Bernardini S, Rossi G, Piaggesi A (2003) Orthostatic hypotension in de novo Parkinson disease. Arch Neurol 60:1400–1404
9. Hiorth YH, Pedersen KF, Dalen I, Tysnes OB, Alves G (2019) Orthostatic hypotension in Parkinson disease: a 7-year prospective population-based study. Neurology 93:e1526–e1534
10. Goswami N, Blaber AP, Hinghofer-Szalkay H, Montani JP (2017) Orthostatic intolerance in older persons: etiology and countermeasures. Front Physiol 8:803
11. Hamrefors V, Spahic JM, Nilsson D, Senneby M, Sutton R, Melander O, Fedorowski A (2017) Syndromes of orthostatic intolerance and syncope in young adults. Open Heart 4:e000585
12. Stewart JM (2013) Common syndromes of orthostatic intolerance. Pediatrics 131:968–980
13. Lee H, Low PA, Kim HA (2017) Patients with orthostatic intolerance: relationship to autonomic function tests results and reproducibility of symptoms on tilt. Sci Rep 7:5706

14. Malek N, Lawton MA, Grosset KA, Bajaj N, Barker RA, Burn DJ, Foltynie T, Hardy J, Morris HR, Williams NM, Ben-Shlomo Y, Wood NW, Grosset DG, Consortium PRC (2017) Autonomic dysfunction in early Parkinson's disease: results from the united kingdom tracking Parkinson's study. Mov Disord Clin Pract 4:509–516
15. Parkinson Progression Marker Initiative (2011) The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 95:629–635
16. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N, Movement Disorder Society URTF (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23:2129–2170
17. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, Weintraub D (2009) Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology 73:1738–1745
18. Meara J, Mitchelmore E, Hobson P (1999) Use of the GDS-15 geriatric depression scale as a screening instrument for depressive symptomatology in patients with Parkinson's disease and their carers in the community. Age Ageing 28:35–38
19. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, Weintraub D, Sampaio C, Poewe W, Rascol O, Stebbins GT, Goetz CG (2008) Anxiety rating scales in Parkinson's disease: critique and recommendations. Mov Disord 23:2015–2025
20. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ (2004) Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 19:1306–1312
21. Fedorowski A (2019) Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. J Intern Med 285:352–366
22. Norcliffe-Kaufmann L, Kaufmann H, Palma JA, Shibao CA, Biaggioni I, Peltier AC, Singer W, Low PA, Goldstein DS, Gibbons CH, Freeman R, Robertson D, Autonomic Disorders C (2018) Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. Ann Neurol 83:522–531
23. Goldstein DS (2014) Dysautonomia in Parkinson disease. Compr Physiol 4:805–826
24. Balagny P, Wanono R, d'Ortho MP, Vidal-Petiot E (2018) Reply to validation of the new diagnostic tests for neurogenic orthostatic hypotension. Ann Neurol 84:957–958
25. Pazo JH, Belforte JE (2002) Basal ganglia and functions of the autonomic nervous system. Cell Mol Neurobiol 22:645–654
26. Lin MT, Yang JJ (1994) Stimulation of the nigrostriatal dopamine system produces hypertension and tachycardia in rats. Am J Physiol 266:H2489–2496
27. Korchounov A, Kessler KR, Yakhno NN, Damulin IV, Schipper HI (2005) Determinants of autonomic dysfunction in idiopathic Parkinson's disease. J Neurol 252:1530–1536
28. Kotagal V, Lineback C, Bohnen NI, Albin RL, Investigators C-PPSG (2016) Orthostatic hypotension predicts motor decline in early Parkinson disease. Parkinsonism Relat Disord 32:127–129
29. Merola A, Romagnolo A, Rosso M, Lopez-Castellanos JR, Wissel BD, Larkin S, Bernardini A, Zibetti M, Maule S, Lopiano L, Espay AJ (2016) Orthostatic hypotension in Parkinson's disease: does it matter if asymptomatic? Parkinsonism Relat Disord 33:65–71
30. Goldstein DS, Holmes C, Lopez GJ, Wu T, Sharabi Y (2018) Cardiac sympathetic denervation predicts PD in at-risk individuals. Parkinsonism Relat Disord 52:90–93
31. Goldstein DS, Sharabi Y, Karp BI, Bentho O, Saleem A, Pacak K, Eisenhofer G (2009) Cardiac sympathetic denervation preceding motor signs in Parkinson disease. Cleve Clin J Med 76[Suppl 2]:S47–50
32. Palma JA, Norcliffe-Kaufmann L, Kaufmann H (2016) An orthostatic hypotension mimic: the inebriation-like syndrome in Parkinson disease. Mov Disord 31:598–600
33. Alli C, Avanzini F, Bettelli G, Colombo F, Corso R, Di Tullio M, Marchioli R, Mariotti G, Radice M, Taioli E et al (1992) Prevalence and variability of orthostatic hypotension in the elderly. Results of the 'Italian study on blood pressure in the elderly (SPAA)'. The 'Gruppo di Studio Sulla Pressione Arteriosa nell'Anziano'. Eur Heart J 13:178–182
34. Lipsitz LA, Storch HA, Minaker KL, Rowe JW (1985) Intra-individual variability in postural blood pressure in the elderly. Clin Sci (Lond) 69:337–341
35. Puisieux F, Boumbar Y, Bulckaen H, Bonnin E, Houssin F, Dewailly P (1999) Intraindividual variability in orthostatic blood pressure changes among older adults: the influence of meals. J Am Geriatr Soc 47:1332–1336
36. Jamnadas-Khoda J, Koshy S, Mathias CJ, Muthane UB, Ragothaman M, Dodaballapur SK (2009) Are current recommendations to diagnose orthostatic hypotension in Parkinson's disease satisfactory? Mov Disord 24:1747–1751
37. Low PA (2008) Prevalence of orthostatic hypotension. Clin Auton Res 18[Suppl 1]:8–13
38. Ricci F, De Caterina R, Fedorowski A (2015) Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol 66:848–860
39. Wu JS, Yang YC, Lu FH, Wu CH, Chang CJ (2008) Population-based study on the prevalence and correlates of orthostatic hypotension/hypertension and orthostatic dizziness. Hypertens Res 31:897–904
40. Zhu QO, Tan CS, Tan HL, Wong RG, Joshi CS, Cuttilan RA, Sng GK, Tan NC (2016) Orthostatic hypotension: prevalence and associated risk factors among the ambulatory elderly in an Asian population. Singap Med J 57:444–451
41. Pavy-Le Traon A, Amarenco G, Duerr S, Kaufmann H, Lahrmann H, Shaftman SR, Tison F, Wenning GK, Goetz CG, Poewe W, Sampaio C, Schrag A, Stebbins GT, Rascol O (2011) The movement disorders task force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension. Mov Disord 26:1985–1992