

Orthostatic Hypotension and REM Sleep Behavior Disorder:

Impact on Clinical Outcomes in α -Synucleinopathies

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Keywords: α -synucleinopathies; orthostatic hypotension; RBD; cognition; falls; survival

Word Count: 2296

Figures: 2

Tables: 2

Supplementary Figures: 3

Supplementary Tables: 6

References: 138

Study funding: Nothing to report

ABSTRACT

Objective: Review the effect of orthostatic hypotension (OH) and rapid-eye-movement sleep behavioral disorder (RBD) on survival, cognitive impairment, and postural stability, and discuss pathogenic mechanisms involved in the association of these two common non-motor features with relevant clinical outcomes in α -synucleinopathies.

Methods: We searched PubMed (2007–2019) for human studies of OH and RBD evaluating cognitive impairment, postural instability, and survival in Parkinson disease, dementia with Lewy bodies, multiple system atrophy, and pure autonomic failure. Included studies were analyzed for design, key results, and limitations as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Findings: OH and RBD showed a positive association with cognitive impairment in Parkinson disease and dementia with Lewy bodies, conflicting association in pure autonomic failure, and no association in multiple system atrophy. OH was correlated with incident falls and postural instability in Parkinson disease and dementia with Lewy bodies but not in multiple system atrophy. The association between RBD and postural instability was inconclusive; positive in five studies, negative in seven. OH, but not RBD, correlated with reduced survival in Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. The combination of OH and RBD was associated with cognitive impairment and more rapid progression of postural instability.

Conclusions and Relevance: OH and RBD yielded individual and combined negative effects on disability in α -synucleinopathies, reflecting a “malignant” phenotype of Parkinson disease with early cognitive impairment and postural instability. Underlying mechanisms may include involvement of selected brainstem cholinergic and noradrenergic nuclei.

INTRODUCTION

Orthostatic hypotension (OH) and rapid-eye-movement sleep behavior disorder (RBD) are frequent non-motor sources of disability in α -synucleinopathies including Parkinson disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA) ¹⁻³. OH occurs in 20-50% in PD, 30-70% in DLB, 80% in MSA and, by definition, 100% in PAF². RBD has a prevalence of 30-50% in PD, 70-80% in DLB, and 80-90% in MSA. In addition, 70-90% of idiopathic RBD convert to alpha-synucleinopathies¹.

OH is defined as a blood pressure (BP) drop of at least 20/10 mmHg (systolic/diastolic) from supine to standing position, which results from cardiovascular dysfunction caused by the complex interplay between autonomic dysregulation in central (brainstem) and peripheral mechanisms, cardiac noradrenergic sympathetic denervation, peripheral norepinephrine deficiency, and arterial baroreflex failure, ultimately leading to impaired arterial vasoconstriction and reduced compensatory cardiac output in response to hypotension⁴. The clinical manifestations of OH are typically insidious, ranging from nonspecific symptoms such as dizziness, lightheadedness, and confusion, to potentially dramatic complications from syncope and falls⁵, with a 36% increased mortality risk among the elderly⁶.

RBD is a clinical disorder characterized by loss of the normal muscle atonia during the rapid eye movement (REM) phase of sleep, which results in impaired suppression of movement generators and complex dream enactment behaviors⁷. Although the RBD-generating pathogenic mechanisms remain unclear, several lines of evidence suggest a dysregulation of specific brainstem areas, in particular, the REM-activating pre-coeruleus and sub-laterodorsal regions and the REM-inhibitory periaqueductal grey matter and lateral pontine tegmentum⁸. Clinically, RBD represents not only a primary cause of sleep quality disruption, but also a major cause of secondary injuries due to punching, kicking, jumping, or other involuntary motor behaviors occurring during sleep⁹.

Studies investigating the phenotypic heterogeneity of PD have identified OH and RBD as risk factors for early development of postural instability and dementia¹⁰⁻¹⁵. However, the clinical and pathological association of these two non-motor symptoms has never been properly investigated in α -synucleinopathies. We sought to systematically analyze and discuss data accumulated in support of the individual and combined effects of OH and RBD on cognitive impairment, postural instability, and survival.

METHODS

Search Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁶. We searched PubMed for human studies published between January 2007 and February 2019 using combinations of the following terms: orthostatic hypotension, REM sleep behavior disorder, cognition, dementia, postural instability, survival, Parkinson, multiple system atrophy, pure autonomic failure, dementia with Lewy bodies. Qualifying studies were categorized as documenting the individual vs. combined effect of OH and RBD on at least one of the following endpoints: a) cognitive impairment, b) falls or postural instability, and c) survival. Imaging and pathological studies were included but analyzed separately. To limit potential confounders, we excluded studies reporting outcomes on patients treated with deep brain stimulation or infusion therapies. No restrictions were applied to gender, age, ethnicity, disease duration, disease severity, or language.

Selection of Studies and Quality Appraisal

Abstracts were independently reviewed for eligibility criteria by 2 investigators (A.M., J.A.T.). Quality appraisal and selection of pertinent full-text articles were conducted using the Wales Health Evidence Bulletin tools for cohort, case-control, and cross-sectional studies¹⁷.

Disagreements were settled by consensus among the authors. The reference lists of selected articles were additionally screened for additional pertinent studies.

Data Extraction

We used a standardized form to extract the following data from eligible studies: a) study population (PD, DLB, PAF, MSA), b) study design (longitudinal, cross-sectional, retrospective, pathologically-proven [e.g., autopsy] case-series), c) sample size, d) key results, e) measures of statistical association, and f) possible bias and study limitations.

The level of diagnostic accuracy for OH, RBD, cognitive impairment, and postural instability/falls was rated as follows:

Diagnosis of RBD. Level A: based on polysomnography; level B: based on RBD-specific validated questionnaires such as the REM Behavioral Screening Questionnaire (RBDSQ)¹⁸ or the Mayo Clinic RBD questionnaire¹⁹; level C: based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms such as the Non-Motor Symptoms Questionnaire (NMSQ)²⁰ or the Non-Motor Symptoms Scale (NMSS)²¹.

Diagnosis of OH. Level A: based on cardiovascular autonomic laboratory testing; level B: based on supine-to-standing blood pressure measurements in a clinical setting; level C: based on clinical questionnaires.

Diagnosis of Cognitive Impairment. Level A: based on the Movement Disorder Society (MDS) level II criteria for mild cognitive impairment (MCI)²² or dementia²³; level B: based on MDS level I criteria for MCI²² or dementia²³; level C: based on clinical diagnosis of cognitive impairment not supported by formal neuropsychological testing.

Diagnosis of Falls and Postural Instability. Level A: prospective assessment of the number of falls; level B: postural instability evaluated by validated clinical scales (i.e. Tinetti and Berg balance scales²⁴) or posturography²⁵; level C: postural instability at the “pull test”²⁶.

RESULTS

Out of the 2,601 records derived from the initial search strategy, 101 studies met full eligibility criteria and underwent data extraction: 41 focused on OH; 43 on RBD; 3 on both OH and RBD; and 14 on the association between OH and RBD (eFigures 1, 2, and 3 in the Supplement).

Individual Impact of OH on Clinical Outcomes

Cognition. Three longitudinal studies found a 2.8-3.3-fold increased risk of cognitive impairment in PD patients with OH^{10,27,28}, confirming the results from six cross-sectional studies in PD²⁹⁻³⁴ and one in PAF³⁵. Negative data were reported by four cross-sectional studies in PD³⁶⁻³⁹, three in MSA⁴⁰⁻⁴², and one in PAF⁴³ (eTable 1 in the Supplement).

Postural Stability and Falls. Six longitudinal⁴⁴⁻⁴⁹, one cross-sectional⁵⁰, and two autopsy^{51,52} studies found an association between OH and incident falls in PD. OH was associated with number of falls in PD and DLB⁵³, and with increased postural sway in PD⁵⁴. Negative data were reported in one longitudinal and two cross-sectional studies in PD⁵⁵⁻⁵⁷, one autopsy series in DLB⁵², and two autopsy series in MSA (eTable 2 in the Supplement)^{52,58}.

Survival. Two longitudinal studies and one autopsy cohort demonstrated an independent association between OH and reduced survival in PD^{51,59,60}, with a 10-year survival rate of 74% in PD patients with OH compared with 93% in PD patients without OH, 36% in MSA, and 87% in PAF⁵⁹ (Table 1). A reduced life-expectancy was also documented in DLB patients with OH⁶⁰, and a trend towards reduced survival in MSA with early autonomic dysfunction^{58,61,62}. Only one study did not find an association between OH and survival in PD⁶³.

Imaging and pathology. OH correlated with cerebral atrophy involving the insular cortex⁶⁴, as well as with cholinergic alterations³⁴, subcortical microbleeds⁶⁵, and white matter hyperintensities (WMH)^{66,67} in PD (eTable 3 in the Supplement and Figures 1-2). One study documented the association between OH and WMH in MSA⁶⁸, while two (one in PD and one in MSA) reported negative results^{30,41}. In DLB, OH was correlated with hypoperfusion in the occipital-parietal cortex⁶⁹ (eTable 3 in the Supplement).

Individual Impact of RBD on Clinical Outcomes

Cognition. Nine longitudinal studies reported an increased risk of cognitive impairment (OR= 2-49) in PD patients with RBD^{10,11,27,70-75}, confirming the results from twelve cross-sectional studies⁷⁶⁻⁸⁷. An autopsy series showed an association between RBD and more aggressive progression of dementia and hallucinations in DLB⁸⁸. Negative data were reported in one longitudinal⁸⁹ and seven cross-sectional studies in PD⁹⁰⁻⁹⁶, and one longitudinal study in DLB (eTable 4 in the Supplement)⁹⁷.

Postural Stability and Falls. One longitudinal⁴⁸ and four cross-sectional studies showed that RBD is associated with falls^{83,91,98} and postural instability⁹⁶ in PD, while two longitudinal and five cross-sectional studies, all based on clinical questionnaires^{81,93,95,99-102}, yielded negative results (eTable 5 in the Supplement).

Survival. A prospective population-based study found similar survival rates in PD patients with and without RBD after adjusting for age, age at onset, sex, and motor symptoms severity (Table 1)¹⁰³.

Imaging and pathology. RBD was associated with WMH^{104,105} and cerebral atrophy in the pedunculo-pontine nucleus, raphe, locus coeruleus/subcoeruleus^{77,79,106}, thalamus^{77,107}, medial

amygdala, prefrontal, posterior cingulate, and hippocampal cortex¹⁰⁸ in PD (eTable 6 in the Supplement; Figure 1). Functional and nuclear medicine studies found a correlation between RBD and reduced primary motor cortex activation on functional MRI^{109,110}, reduced cortical metabolism⁸⁰, and extensive noradrenergic⁷⁹, cholinergic^{98,111} denervation, with still inconclusive data on nigrostriatal denervation^{75,80}. Pathological data from two PD autopsy series documented an association between RBD and α -synuclein deposition in both cortical and subcortical regions^{112,113}. In DLB, there was an association between RBD and lower cortical metabolic activity¹¹⁴, greater nigrostriatal dopaminergic denervation¹¹⁵, and decreased amyloid or neurofibrillary tangles compared to α -synuclein pathology (increased DLB ratio)^{88,116,117} (eTable 6 in the Supplement).

Combined Impact of OH and RBD on Clinical Outcomes

The association between OH and RBD was examined in four longitudinal^{12–14,74}, nine cross-sectional studies^{79,81,83,93,95,118–121}, and one autopsy series in PD¹²². The OH-RBD cluster correlated with cognitive impairment and postural instability in a cohort of drug-naïve PD patients followed-up for a mean of 4.5 years¹⁴, and in analysis of the PPMI cohort^{12,122}, which also demonstrated an association between OH-RBD and greater cerebral atrophy, lower dopamine uptake, and lower β -amyloid levels in the cerebrospinal fluid (Table 2). In drug-naïve PD, a cross-sectional study ascertained an association between OH-RBD and cognitive impairment, nigrostriatal denervation, and electroencephalographic (EEG) alterations in the posterior cortical areas¹³.

DISCUSSION

There was robust evidence supporting an association for OH and RBD with cognitive impairment in PD and DLB, as well as a significant negative effect of OH on postural instability and survival. The combination of OH and RBD (“OH-RBD cluster”) was associated with a

malignant phenotype of PD characterized by more rapid progression of cognitive deficits and postural instability.

In PD, OH strongly correlated with reduced survival, as well as with an increased risk of dementia, falls and postural instability. RBD was associated with increased risk of dementia and, to a lower extent, gait and postural impairment. Associations were more evident in studies employing a tilt table for the diagnosis of OH and a polysomnography for the diagnosis of RBD, casting doubts on the accuracy of clinical questionnaires for the screening of orthostatic symptoms and sleep disorders¹²³. Similarly, we found that studies using screening measures of global cognition, such as the MMSE (Mini Mental State Examination) or Montreal cognitive assessment, frequently failed to find an association between RBD and OH or to predict the risk of incident dementia compared to those employing extensive neuropsychological testing^{27,124,125}.

Similar data were also found in other α -synucleinopathies. In DLB, OH correlated with cognitive deficits⁶⁹, and RBD with Lewy body cortical pathology^{116,88}. Also, idiopathic RBD showed higher risk of conversion to DLB than PD, possibly indicating an association between RBD and prodromal cognitive deficits^{126–129}. In MSA, we did not find any associations between OH or RBD and cognitive deficits. While these findings might reflect lesser cortical involvement in this specific α -synucleinopathy¹³⁰, the limited sample size of available studies should be taken into consideration due to the frequent finding of attentional, visual-spatial, and executive deficits in patients with MSA¹³¹. In PAF, conflicting results were reported on the cognitive effect of cerebral hypoperfusion^{35,43}.

Neuroimaging studies identified severe nigrostriatal denervation and electroencephalographic (EEG) alterations in the posterior cortical areas of PD patients with RBD and OH¹³, as well as an individual association of both conditions with cholinergic deficits^{34,98,111}. These data prove relevant when considering the pathological overlap in the anatomical and functional structures

associated with OH and RBD, which involve critical brainstem regions modulating the cholinergic, serotonergic, and noradrenergic pathways (Figures 1 and 2).

Neuropathological studies found an association between RBD and α -synuclein deposition in critical areas such as the locus coeruleus, raphe nuclei, paramammillary nuclei, amygdala, thalamus and entorhinal cortex. The same regions are involved in the central autonomic network that extends from cortical and diencephalic structures (insular cortex, anterior cingulate and amygdala) to the brainstem periaqueductal grey, ventrolateral medulla, medullary raphe, dorsal motor nucleus of vagus, nucleus ambiguus, and pontine micturition centre.²

OH, in particular, is associated with degeneration in the pedunculopontine cholinergic nucleus, noradrenergic periaqueductal gray neurons, rostral ventrolateral medulla, dorsolateral vagal motor nucleus, and nucleus ambiguus (Figure 1). All of these structures participate in a subcortical network projecting to the thalamic areas and to the posterior insular cortex, which receives and integrate inputs from visceral, thermal and pain receptors and connect with the anterior cingulate cortex, amygdala, and basal ganglia⁶⁴. While cholinergic and noradrenergic deficits due to the involvement of locus coeruleus, pontine reticular formation, and lower raphe are likely to be involved in cognitive impairment^{79,132}, mechanisms underlying the association between OH and falls remain unclear. It has been suggested that OH might cause falls due to orthostatic cortical hypoperfusion¹³³, neurodegeneration of critical areas responsible for both postural instability and cardiovascular dysautonomia³⁴, or a combination thereof¹³⁴.

Critically, the effect of peripheral hypotension and the frequently associated supine hypertension (SH) on the regulation of cerebrovascular perfusion remains to be clarified. A retrospective assessment of 204 subjects found that patients having PD with OH have a greater extent of deep and periventricular white matter lesions. However, the differential effect of OH and SH on white matter abnormalities remains unclear, as well as the impact of these two opposing haemodynamic conditions on cortical and subcortical areas involved in cognition and gait.

Pathogenic mechanisms associated with RBD involve an extensive network of micro-circuits within the brainstem, forebrain, and hypothalamus. In normal subjects, cholinergic inputs activate the subcoeruleus glutamatergic and gabaergic neurons, which promote REM sleep and muscle atonia¹³⁵. The locus coeruleus activity is also modulated by the dorsal paragigantocellular reticular medullar nucleus, hypothalamic melanin-concentrating hormone neurons, dorsal raphe, and periaqueductal gray matter (Figures 1-2)⁹. Pathologically-proven case series have shown an association between RBD and α -synuclein deposition in the locus coeruleus and other brainstem nuclei participating to the thalamic modulation of the cortical activity^{88,112,113,136}. In addition, independent reports found evidence of cholinergic dysfunctions in patients with RBD¹¹¹, as well as signs of involvement of the pedunculopontine nucleus, which is a critical node in the locomotor mesencephalic area modulating gait and balance¹³⁴.

Some limitations may affect the interpretation of our data. First, the studies assessing the combined effect of OH and RBD are relatively few. Second, the majority of studies focused on PD, with relatively limited data from other α -synucleinopathies. Third, substantial heterogeneity was detected in the inclusion criteria, as well as in the methodologies used to assess OH and RBD.

Also, the variable number of available studies for each α -synucleinopathy inevitably limited comparisons between different pathologies. While OH and RBD showed a positive association with cognitive impairment in PD and DLB, conflicting results were reported in PAF and no association in MSA. To what extent these data reflect fundamental differences in pathological mechanisms remains to be clarified.

CONCLUSIONS

Limitations notwithstanding, our systematic review highlights the importance of OH and RBD as markers of a distinctive subtype of α -synucleinopathies characterized by early cognitive impairment, pronounced postural instability, and reduced survival rate. These data support the

need for well-designed clinical and neuroimaging studies focusing on the management of non-dopaminergic symptoms^{124,137,138}, critical to inform the development of innovative cholinergic and noradrenergic agents for cognitive impairment and postural instability in α -synucleinopathies.

AUTHORS' CONTRIBUTION

Andrea Pilotto: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content.

Alberto Romagnolo: study concept and design, acquisition of data, drafting/revising the manuscript for content.

Jasmine A Tuazon: acquisition of data, revising the manuscript for content.

Joaquin Vizcarra: revising the manuscript for content.

Luca Marsili: acquisition of data, revising the manuscript for content.

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Jennifer R Molano: revising the manuscript for content.

Leonardo Lopiano: revising the manuscript for content.

Roberto Ceravolo: acquisition of data, revising the manuscript for content.

Mario Masellis: revising the manuscript for content.

Alberto Espay: study concept and design, revising the manuscript for content.

Alessandro Padovani: study concept and design, revising the manuscript for content.

Aristide Merola: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content.

POTENTIAL CONFLICT OF INTEREST

Andrea Pilotto received speaker honoraria from BioMarin Pharmaceutical, Chiesi Pharmaceuticals, Nutricia Pharmaceuticals, UCB Pharma and Zambon Pharmaceuticals. He received travel grants from AbbVie Pharmaceuticals, BioMarin Pharmaceutical, Nutricia Pharmaceuticals, Zambon Pharmaceuticals and the Italian movement disorder society.

Alberto Romagnolo received speaker honoraria from AbbVie and Chiesi Pharmaceuticals and travel grants from Medtronic, Lusofarmaco and UCB Pharma.

Jasmine A Tuazon has no financial conflicts to disclose.

Joaquin Vizcarra has no financial conflicts to disclose.

Luca Marsili has no financial conflicts to disclose.

Maurizio Zibetti received speaker honoraria from AbbVie, Medtronic, Zambon and UCB Pharma and received travel grants from AbbVie.

Michela Rosso has no financial conflicts to disclose.

Federico Rodriguez-Porcel has no financial conflicts to disclose.

Barbara Borroni has no financial conflicts to disclose.

Maria Cristina Rizzetti has no financial conflicts to disclose.

Carlo Rossi received speaker honoraria from Zambon and UCB Pharma and received travel grants from Zambon, UCB Pharma, Medtronic and Chiesi Pharmaceuticals.

Jennifer R Molano has received research support from Axovant. She is also an editorial board member for NEJM Journal Watch Neurology.

Leonardo Lopiano: received honoraria for lecturing and travel grants from Medtronic, UCB Pharma, and AbbVie.

Roberto Ceravolo received speaker honoraria from General Electric, AbbVie, UCB Pharma, Zambon. He received consulting fees from General Electric and Zambon and grant support from Ministry of Health (MINSAL).

Mario Masellis receives salary support from the Department of Medicine at Sunnybrook Health Sciences Centre and the University of Toronto, as well as the Sunnybrook Research Institute. He has received grants/research Support from: Parkinson Canada, Canadian Institutes of Health Research, Teva, Early Researcher Award - Ministry of Economic Development and Innovation, C5R, Weston Brain Institute, Ontario Brain Institute, Sunnybrook AFP Innovation Fund, Novartis, Washington University, Roche, Alzheimer's Drug Discovery Foundation (ADDF), Brain Canada, Heart and Stroke Foundation Centre for Stroke Recovery. He has received consulting Fees from UCB, Ionis, Novartis, and Arkuda Therapeutics, as well as royalties from Henry Stewart Talks Ltd.

Alberto Espay has received grant support from the NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, Adamas, Acadia, Acorda, Neuroderm, TEVA, Impax, Sunovion, Lundbeck, Osmotica Pharmaceutical, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, Sunovion, the American Academy of Neurology, and the Movement Disorders Society.

Alessandro Padovani received grant support from Ministry of Health (MINSAL) and Ministry of Education, Research and University (MIUR), from CARIPLO Foundation; personal compensation as a consultant/scientific advisory board member for Avanir, Lundbeck, Eli-Lilly, Neuraxpharma, Biogen, GE Health.

Aristide Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Cynapsus Therapeutics, Lundbeck, AbbVie, and Abbott. He has received grant support from Lundbeck and Abbott.

REFERENCES

1. Louis EKS, Boeve AR, Boeve BF. REVIEW REM Sleep Behavior Disorder in Parkinson's Disease and Other Synucleinopathies. *Mov Disord.* 2017;32(5):17-23. doi:10.1002/mds.27018.
2. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. *Mov Disord.* 2018; 33(3):349-358 doi:10.1002/mds.27186.
3. Goedert M, Jakes R, Grazia M, Neurosciences C, Building CA. The Synucleinopathies : Twenty Years On. *J Parkinsons Dis.* 2017;7(s1):S51-S69. doi:10.3233/JPD-179005.
4. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. *Neurobiol Dis.* 2012;46(3):572-580. doi:10.1016/j.nbd.2011.10.025.
5. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. *J Am Geriatr Soc.* 2011;59(3):383-389. doi:10.1111/j.1532-5415.2011.03317.x.
6. Angelousi A, Girerd N, Benetos A, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality. *J Hypertens.* 2014;32(8):1562-1571. doi:10.1097/HJH.0000000000000235.
7. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain.* 2007;130(Pt 11):2770-2788. doi:10.1093/brain/awm056.
8. Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - An update. *Nat Rev Neurol.* 2018;14(1):40-56. doi:10.1038/nrneurol.2017.157.
9. Boeve BF. REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci.* 2010;1184:15-54. doi:10.1111/j.1749-6632.2009.05115.x.
10. Anang JBM, Gagnon J-F, Bertrand J-A, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology.* 2014;83(14):1253-1260. doi:10.1212/WNL.0000000000000842.
11. Postuma RB, Bertrand J-A, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord.* 2012;27(6):720-726. doi:10.1002/mds.24939.
12. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: Biomarkers and longitudinal progression. *Brain.* 2017;140(7):1959-1976. doi:10.1093/brain/awx118.
13. Arnaldi D, De Carli F, Famà F, et al. Prediction of cognitive worsening in de novo Parkinson's disease: Clinical use of biomarkers. *Mov Disord.* 2017; 32(12):1738-1747 doi:10.1002/mds.27190.
14. Fereshtehnejad S-M, Romenets SR, Anang JBM, Latreille V, Gagnon J-F, Postuma RB. New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression A Prospective Cohort Comparison With Other Phenotypes. *JAMA Neurol.* 2015:1-11. doi:10.1001/jamaneurol.2015.0703.
15. Udow SJ, Robertson AD, Macintosh BJ, et al. ' Under pressure ' : is there a link between orthostatic hypotension and cognitive impairment in α -synucleinopathies ? *J Neurol Neurosurg Psychiatry.* 2016;(Mci):1311-1321. doi:10.1136/jnnp-2016-314123.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269, W64. <http://www.ncbi.nlm.nih.gov/pubmed/19622511>. Accessed

June 2, 2018.

17. Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol.* 2007;36(3):666-676. doi:10.1093/ije/dym018.
18. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. *Mov Disord.* 2007;22(16):2386-2393. doi:10.1002/mds.21740.
19. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep Med.* 2011;12(5):445-453. doi:10.1016/j.sleep.2010.12.009.
20. Rios Romenets S, Wolfson C, Galatas C, et al. Validation of the non-motor symptoms questionnaire (NMS-Quest). *Parkinsonism Relat Disord.* 2012;18(1):54-58. doi:10.1016/j.parkreldis.2011.08.013.
21. Martinez-Martin P, Rodriguez-Blazquez C, Abe K, et al. International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease. *Neurology.* 2009;73(19):1584-1591. doi:10.1212/WNL.0b013e3181c0d416.
22. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord.* 2012;27(3):349-356. doi:10.1002/mds.24893.
23. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord.* 2007;22(12):1689-707; quiz 1837. doi:10.1002/mds.21507.
24. Raïche M, Hébert R, Prince F, Corriveau H. Screening older adults at risk of falling with the Tinetti balance scale. *Lancet.* 2000;356(9234):1001-1002. doi:10.1016/S0140-6736(00)02695-7.
25. Rossi-Izquierdo M, Soto-Varela A, Ernst A, et al. What Could Posturography Tell Us About Balance Problems in Parkinson's Disease? *Otol Neurotol.* 2016;37(9):e326-e331. doi:10.1097/MAO.0000000000001120.
26. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Mov Disord* 2008;23(15):2129-2170 doi:10.1002/mds.22340.
27. Anang JBM, Nomura T, Romenets SR, Nakashima K, Gagnon JF, Postuma RB. Dementia Predictors in Parkinson Disease: A Validation Study. *J Parkinsons Dis.* 2017;7(1):159-162. doi:10.3233/JPD-160925.
28. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease, findings from a 5-year prospective study using the SCOPA-COG. *Park Relat Disord.* 2014;20(9):980-985. doi:10.1016/j.parkreldis.2014.06.006.
29. Centi J, Freeman R, Gibbons CH, Nearing S, Canova AO, Cronin-Golomb A. Effects of orthostatic hypotension on cognition in Parkinson disease. *Neurology.* 2017;88(1):17-24. doi:10.1212/WNL.0000000000003452.
30. Pilleri M, Facchini S, Gasparoli E, et al. Cognitive and MRI correlates of orthostatic hypotension in Parkinson's disease. *J Neurol.* 2013;260(1):253-259. doi:10.1007/s00415-012-6627-y.
31. Allcock LM, Kenny RA, Mosimann UP, et al. Orthostatic hypotension in Parkinson's disease : association with cognitive decline ? *Int J Geriatr Psychiatry.* 2006;21(8):778-783
32. Peralta C, Stampfer-Kountchev M, Karner E, et al. Orthostatic hypotension and attention in Parkinson's disease with and without dementia. *J Neural Transm.* 2007;114(5):585-588. doi:10.1007/s00702-006-0615-2.
33. Hohler AD, Zuzuárregui JP, Katz DI, et al. Differences in Motor and Cognitive Function in Patients With Parkinson's Disease With and Without Orthostatic Hypotension
Differences in Motor and Cognitive Function in Patients With Parkinson's Disease With

- and Without Orthostatic Hypotension. *Int J Neurosci*. 2012;122(5):233-236
doi:10.1080/00207454.2012.642038.
34. Kim J-S, Oh Y-S, Lee K-S, Kim Y-I, Yang D-W, Goldstein DS. Association of cognitive dysfunction with neurocirculatory abnormalities in early Parkinson disease. *Neurology*. 2012;79(13):1323-1331. doi:10.1212/WNL.0b013e31826c1acd.
 35. Guaraldi P, Poda R, Calandra-Buonaura G, et al. Cognitive Function in Peripheral Autonomic Disorders. *PLoS One*. 2014;9(1):e85020. doi:10.1371/journal.pone.0085020.
 36. Bae H, Lim J, Cheon S. Orthostatic Hypotension and Cognitive Impairment in De Novo Patients with Parkinson ' s Disease. *J Mov Disord*. 2014;7(2):102-104
 37. Allcock LM, Ulliyart K, Kenny RA, Burn DJ. Frequency of orthostatic hypotension in a community based cohort of patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75(10):1470-1471. doi:10.1136/jnnp.2003.029413.
 38. Idiaquez J, Benarroch EE, Milla P. Autonomic and Cognitive dysfunction in Parkinson ' s disease. *Clin Auton Res*. 2007;17(2):93-98 doi:10.1007/s10286-007-0410-7.
 39. Allcock L, Kenny R, Burn D. Clinical phenotype of subjects with Parkinson's disease and orthostatic hypotension: autonomic symptom and demographic comparison. *Mov Disord*. 2006;21:1851-1855.
 40. Kawamura K, Shimohata T, Nakayama H, Tomita M, Ozawa T, Nishizawa M. Factors influencing the cognitive function in patients with multiple system atrophy. *Mov Disord*. 2010;25(16):2891-2892. doi:10.1002/mds.23260.
 41. Lim TS, Lee PH, Kim HS, Yong SW. White matter hyperintensities in patients with multiple system atrophy. *J Neurol*. 2009;256(10):1663-1670. doi:10.1007/s00415-009-5176-5.
 42. Barcelos LB, Saad F, Giacominielli C, et al. Neuropsychological and clinical heterogeneity of cognitive impairment in patients with multiple system atrophy. *Clin Neurol Neurosurg*. 2018;164:121-126. doi:10.1016/j.clineuro.2017.10.039.
 43. Van Vliet P, Hilt AD, Thijs RD, Van Dijk JG. Effect of orthostatic hypotension on sustained attention in patients with autonomic failure. *J Neurol Neurosurg Psychiatry*. 2016;87(2):144-148. doi:10.1136/jnnp-2014-309824.
 44. Merola A, Romagnolo A, Rosso M, et al. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. *Mov Disord*. 2018;33(3):391-397. doi:10.1002/mds.27268.
 45. Rudzińska M, Bukowczan S, Stożek J, et al. Causes and consequences of falls in Parkinson disease patients in a prospective study. *Neurol Neurochir Pol*. 2013;47(5):423-430. doi:10.5114/ninp.2013.38222.
 46. Czarkowska H, Tutaj M, Rudzińska M, et al. Cardiac responses to orthostatic stress deteriorate in Parkinson disease patients who begin to fall. *Neurol Neurochir Pol*. 2010;44(4):339-349. doi:10.1016/S0028-3843(14)60293-0.
 47. Gray P, Hildebrand K. Fall risk factors in Parkinson's disease. *J Neurosci Nurs*. 2000;32(4):222-228. doi:32(4):222-8.
 48. Romagnolo A, Zibetti M, Merola A, et al. Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study. *J Neurol*. 2019;266(1):85-91. doi: 10.1007/s00415-018-9104-4
 49. Merola A, Sawyer RP, Artusi CA, et al. Orthostatic hypotension in Parkinson disease: Impact on health care utilization. *Park Relat Disord*. 2018;47:45-49. doi:10.1016/j.parkreldis.2017.11.344.
 50. Rascol O, Perez-Lloret S, Damier P, et al. Falls in ambulatory non-demented patients with Parkinson's disease. *J Neural Transm*. 2015;122(10):1447-1455. doi:10.1007/s00702-015-1396-2.
 51. De Pablo-fernandez E, Tur C, Revesz T, Lees AJ. Association of Autonomic Dysfunction With Disease Progression and Survival in Parkinson Disease. *JAMA Neurol*. 2017;74(8):970-976. doi:10.1001/jamaneurol.2017.1125.
 52. Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: A retrospective study. *J Neurol Neurosurg Psychiatry*. 2006;77(4):468-473.

- doi:10.1136/jnnp.2005.074070.
53. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: A prospective study in older people. *PLoS One*. 2009;4(5):1-8. doi:10.1371/journal.pone.0005521.
 54. Matinolli M, Korpelainen JT, Korpelainen R, Sotaniemi KA, Myllylä V V. Orthostatic hypotension, balance and falls in Parkinson's disease. *Mov Disord*. 2009;24(5):745-751. doi:10.1002/mds.22457.
 55. Michalowska M, Fiszler U, Krygowska-Wajs A, Owczarek K. Falls in Parkinson's disease. Causes and impact on patients' quality of life. *Funct Neurol*. 2005;20(4):163-168.
 56. Koller WC, Glatt S, Vetere-Overfield B, Hassanein R. Falls and Parkinson's disease 31. *ClinNeuropharmacol*. 1989;12(2):98-105.
 57. Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry*. 2002;72(6):721-725. <http://www.ncbi.nlm.nih.gov/pubmed/12023412>. Accessed May 20, 2018.
 58. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain*. 2008;131(Pt 5):1362-1372. doi:10.1093/brain/awn065.
 59. Goldstein DS, Holmes C, Sharabi Y, Wu T. Survival in synucleinopathies: A prospective cohort study. *Neurology*. 2015;85(18):1554-1561. doi:10.1212/WNL.0000000000002086.
 60. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. *PLoS One*. 2012;7(10):e45451. doi:10.1371/journal.pone.0045451.
 61. Tada M. Early Development of Autonomic Dysfunction May Predict Poor Prognosis in Patients With Multiple System Atrophy. *Arch Neurol*. 2007;64(2):256-260.
 62. Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. *Brain*. 2015;138(12):3623-3631. doi:10.1093/brain/awv274.
 63. Gray WK, Wood BH, Walker RW. Do autonomic function tests in people with Parkinson's disease predict survival rates at 7 years follow-up? *Mov Disord*. 2009;24(16):2432-2434 doi:10.1002/mds.22834.
 64. Papapetropoulos S, Mash DC. Insular pathology in Parkinson's disease patients with orthostatic hypotension. *Park Relat Disord*. 2007;13(5):308-311. doi:10.1016/j.parkreldis.2006.06.009.
 65. Yamashiro K, Tanaka R, Hoshino Y, Hatano T, Nishioka K, Hattori N. The prevalence and risk factors of cerebral microbleeds in patients with Parkinson's disease. *Park Relat Disord*. 2015;21(9):1076-1081. doi:10.1016/j.parkreldis.2015.06.019.
 66. Oh Y-S, Kim J-S, Lee K-S. Orthostatic and supine blood pressures are associated with white matter hyperintensities in Parkinson disease. *J Mov Disord*. 2013;6(2):23-27. doi:10.14802/jmd.13006.
 67. ten Harmsen BL, van Rumund A, Aerts MB, et al. Clinical correlates of cerebral white matter abnormalities in patients with Parkinson's disease. *Park Relat Disord*. 2018;49:28-33. doi:10.1016/j.parkreldis.2017.12.029.
 68. Umoto M, Miwa H, Ando R, Kajimoto Y, Kondo T. White matter hyperintensities in patients with multiple system atrophy. *Park Relat Disord*. 2012;18(1):17-20. doi:10.1016/j.parkreldis.2011.08.004.
 69. Robertson AD, Messner MA, Shirzadi Z, et al. Orthostatic hypotension, cerebral hypoperfusion, and visuospatial deficits in Lewy body disorders. *Park Relat Disord*. 2016;22:80-86. doi:10.1016/j.parkreldis.2015.11.019.
 70. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM, Free R. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease : a cohort study. *Lancet Neurol*. 2016;4422(16):1-10.

- doi:10.1016/S1474-4422(16)30328-3.
71. Mollenhauer B, Zimmermann J, Sixel-Döring F, et al. Monitoring of 30 marker candidates in early Parkinson disease as progression markers. *Neurology*. 2016;87(2):168-177. doi:10.1212/WNL.0000000000002651.
 72. Chahine LM, Xie SX, Simuni T, et al. Longitudinal changes in cognition in early Parkinson's disease patients with REM sleep behavior disorder. *Parkinsonism Relat Disord*. 2016;27:102-106. doi:10.1016/j.parkreldis.2016.03.006.
 73. Sinforiani E, Pacchetti C, Zangaglia R, Pasotti C, Manni R, Nappi G. REM behavior disorder, hallucinations and cognitive impairment in Parkinson's disease: A two-year follow up. *Mov Disord*. 2008;23(10):1441-1445. doi:10.1002/mds.22126.
 74. Nomura T, Inoue Y, Kagimura T, Nakashima K. Clinical significance of REM sleep behavior disorder in Parkinson's disease. *Sleep Med*. 2013;14(2):131-135. doi:10.1016/j.sleep.2012.10.011.
 75. Pagano G, De micco Ro, Yousaf T, Wilson H, Chandra A, Politis M. REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease. *Neurology*. 2018;91(10):e894-e905. doi:10.1212/wnl.00000000000006134.
 76. Vendette M, Gagnon J-F, Décary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*. 2007;69(19):1843-1849. doi:10.1212/01.wnl.0000278114.14096.74.
 77. Boucetta S, Salimi A, Dadar M, Jones BE, Collins DL, Dang-Vu TT. Structural Brain Alterations Associated with Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease. *Sci Rep*. 2016;6(February):1-11. doi:10.1038/srep26782.
 78. Gagnon J-F, Vendette M, Postuma RB, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. *Ann Neurol*. 2009;66(1):39-47. doi:10.1002/ana.21680.
 79. Sommerauer M, Fedorova TD, Hansen AK, et al. Evaluation of the noradrenergic system in Parkinson's disease: An 11 C-MeNER PET and neuromelanin MRI study. *Brain*. 2018;141(2):496-504. doi:10.1093/brain/awx348.
 80. Arnaldi D, Morbelli S, Brugnolo A, et al. Functional neuroimaging and clinical features of drug naive patients with de novo Parkinson's disease and probable RBD. *Park Relat Disord*. 2016;29:47-53. doi:10.1016/j.parkreldis.2016.05.031.
 81. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2014;85(5):560-566. doi:10.1136/jnnp-2013-306104.
 82. Marion MH, Qurashi M, Marshall G, Foster O. Is REM sleep Behaviour Disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? *J Neurol*. 2008;255(2):192-196. doi:10.1007/s00415-008-0629-9.
 83. Romenets SR, Gagnon J-F, Latreille V, et al. Rapid eye movement sleep behavior disorder and subtypes of Parkinson's disease. *Mov Disord*. 2012;27(8):996-1003. doi:10.1002/mds.25086.
 84. Sinforiani E, Zangaglia R, Manni R, et al. REM sleep behavior disorder, hallucinations, and cognitive impairment in Parkinson's disease. *Mov Disord*. 2006;21(4):462-466. doi:10.1002/mds.20719.
 85. Kang SH, Lee HM, Seo WK, Kim JH, Koh SB. The combined effect of REM sleep behavior disorder and hyposmia on cognition and motor phenotype in Parkinson's disease. *J Neurol Sci*. 2016;368:374-378. doi:10.1016/j.jns.2016.07.057.
 86. Jozwiak N, Postuma RB, Montplaisir J, et al. REM sleep behavior disorder and cognitive impairment in Parkinson's disease *Sleep*. 2017;40(8). doi: 10.1093/sleep/zsx101.
 87. Naismith S, Terpening Z, Shine J, Lewis S. Neuropsychological functioning in Parkinson's disease: differential relationships with self-reported sleep-wake disturbances. *Mov Disord* 2011 Jul;26(8)1537-41. 2011;26:1537-1541.

88. Dugger BN, Boeve BF, Murray ME, et al. Rapid eye movement sleep behavior disorder and subtypes in autopsy-confirmed dementia with Lewy bodies. *Mov Disord.* 2012;27(1):72-78. doi:10.1002/mds.24003.
89. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. *J Neurol Neurosurg Psychiatry.* 2008;79(4):387-391. doi:10.1136/jnnp.2007.116830.
90. Plomhause L, Dujardin K, Duhamel A, et al. Rapid eye movement sleep behavior disorder in treatment-naïve Parkinson disease patients. *Sleep Med.* 2013;14(10):1035-1037. doi:10.1016/j.sleep.2013.04.018.
91. Sixel-Doring F, Trautmann E, Mollenhauer B. Associated factors for REM sleep behavior disorder in Parkinson disease. *Neurology.* 2011;77:1048-1054. doi:10.1212/WNL.0b013e31822e560e.
92. Scullin MK, Fairley JA, Trotti LM, Goldstein FC, Factor SA, Bliwise DL. Sleep correlates of trait executive function and memory in Parkinson's disease. *J Parkinsons Dis.* 2015;5(1):49-54. doi:10.3233/JPD-140475.
93. Liu Y, Zhu X-Y, Zhang X-J, Kuo S-H, Ondo WG, Wu Y-C. Clinical features of Parkinson's disease with and without rapid eye movement sleep behavior disorder. *Transl Neurodegener.* 2017;6(1):35. doi:10.1186/s40035-017-0105-5.
94. Meral H, Aydemir T, Ozer F, et al. Relationship between visual hallucinations and REM sleep behavior disorder in patients with Parkinson's disease. *Clin Neurol Neurosurg.* 2007;109(10):862-867. doi:10.1016/j.clineuro.2007.08.010.
95. Yoritaka A, Ohizumi H, Tanaka S, Hattori N. Parkinson's disease with and without REM sleep behaviour disorder: Are there any clinical differences? *Eur Neurol.* 2009;61(3):164-170. doi:10.1159/000189269.
96. Lee JE, Kim KS, Shin H, Sohn YH. Parkinsonism and Related Disorders Factors related to clinically probable REM sleep behavior disorder in Parkinson disease q. *Park Relat Disord.* 2010;16(2):105-108. doi:10.1016/j.parkreldis.2009.08.005.
97. Chwiszczuk L, Breitung MH, Brønnick K, et al. REM sleep behavior disorder is not associated with a more rapid cognitive decline in mild dementia. *Front Neurol.* 2017;8(AUG):1-8. doi:10.3389/fneur.2017.00375.
98. Müller MLTM, Bohnen NI, Kotagal V, et al. Clinical markers for identifying cholinergic deficits in Parkinson's disease. *Mov Disord.* 2015;30(2):269-273. doi:10.1002/mds.26061.
99. Benninger DH, Michel J, Waldvogel D, et al. REM sleep behavior disorder is not linked to postural instability and gait dysfunction in Parkinson. *Mov Disord.* 2010;25(11):1597-1604. doi:10.1002/mds.23121.
100. Bugalho P, Viana-Baptista M. REM sleep behavior disorder and motor dysfunction in Parkinson's disease--a longitudinal study. *Parkinsonism Relat Disord.* 2013;19(12):1084-1087. doi:10.1016/j.parkreldis.2013.07.017.
101. Lavault S, Leu-Semenescu S, Tezenas Du Montcel S, Cochen De Cock V, Vidailhet M, Arnulf I. Does clinical rapid eye movement behavior disorder predict worse outcomes in Parkinson's disease? *J Neurol.* 2010;257(7):1154-1159. doi:10.1007/s00415-010-5482-y.
102. Suzuki K, Okuma Y, Uchiyama T, et al. Impact of sleep-related symptoms on clinical motor subtypes and disability in Parkinson's disease: A multicentre cross-sectional study. *J Neurol Neurosurg Psychiatry.* 2017;88(11):953-959. doi:10.1136/jnnp-2017-316136.
103. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease?: a prospective population-based long-term study. *Neurology.* 2010;75(14):1270-1276. doi:10.1212/WNL.0b013e3181f61311.
104. Ansari M, Rahmani F, Dolatshahi M, Pooyan A, Aarabi MH. Brain pathway differences between Parkinson's disease patients with and without REM sleep behavior disorder. *Sleep Breath.* 2017;21(1):155-161. doi:10.1007/s11325-016-1435-8.
105. Ford AH, Duncan GW, Firbank MJ, et al. Rapid eye movement sleep behavior disorder in

- Parkinson's disease: magnetic resonance imaging study. *Mov Disord*. 2013;28(6):832-836. doi:10.1002/mds.25367.
106. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. *Brain*. 2013;136(7):2120-2129. doi:10.1093/brain/awt152.
 107. Salsone M, Cerasa A, Arabia G, et al. Reduced thalamic volume in Parkinson disease with REM sleep behavior disorder: Volumetric study. *Park Relat Disord*. 2014;20(9):1004-1008. doi:10.1016/j.parkreldis.2014.06.012.
 108. Lim JS, Shin SA, Lee JY, Nam H, Lee JY, Kim YK. Neural substrates of rapid eye movement sleep behavior disorder in Parkinson's disease. *Park Relat Disord*. 2016;23:31-36. doi:10.1016/j.parkreldis.2015.11.027.
 109. Li D, Huang P, Zang Y, et al. Abnormal Baseline Brain Activity in Parkinson's Disease With and Without REM Sleep Behavior Disorder : A Resting-State Functional MRI Study. *J Magn Reson Imaging*. 2017;46(3):697-703 doi:10.1002/jmri.25571.
 110. Gallea C, Ewenczyk C, Degos B, et al. Pedunculopontine network dysfunction in Parkinson's disease with postural control and sleep disorders. *Mov Disord*. 2017;32(5):693-704. doi:10.1002/mds.26923.
 111. Kotagal V, Albin RL, Mueller ML, et al. Symptoms of Rapid Eye Movement Sleep Behavior Disorder are Associated with Cholinergic Denervation in Parkinson Disease Vikas. *Ann Neurol*. 2013;71(4):560-568. doi:10.1002/ana.22691.Symptoms.
 112. Postuma RB, Adler CH, Dugger BN, et al. REM sleep behavior disorder and neuropathology in Parkinson's disease. *Mov Disord*. 2015;30(10):1413-1417. doi:10.1002/mds.26347.
 113. Kalaitzakis ME, Gentleman SM, Pearce RKB. Disturbed sleep in Parkinson's disease: anatomical and pathological correlates. *Neuropathol Appl Neurobiol*. 2013;39(6):644-653. doi:10.1111/nan.12024.
 114. Iaccarino L, Marelli S, Iannaccone S, Magnani G, Ferini-Strambi L, Perani D. Severe Brain Metabolic Decreases Associated with REM Sleep Behavior Disorder in Dementia with Lewy Bodies. *J Alzheimer's Dis*. 2016;52(3):989-997. doi:10.3233/JAD-151000.
 115. Lamotte G, Morello R, Lebasnier A, et al. Influence of education on cognitive performance and dopamine transporter binding in dementia with Lewy bodies. *Clin Neurol Neurosurg*. 2016;146:138-143. doi:10.1016/j.clineuro.2016.05.009.
 116. Murray ME, Ferman TJ, Boeve BF, et al. MRI and pathology of REM sleep behavior disorder in dementia with Lewy bodies. *Neurology*. 2013;81(19):1681-1689. doi:10.1212/01.wnl.0000435299.57153.f0.
 117. Dugger BN, Murray ME, Boeve BF, et al. Neuropathological analysis of brainstem cholinergic and catecholaminergic nuclei in relation to rapid eye movement (REM) sleep behaviour disorder. *Neuropathol Appl Neurobiol*. 2012;38(2):142-152. doi:10.1111/j.1365-2990.2011.01203.x.
 118. Kim JS, Park HE, Oh YS, et al. Orthostatic hypotension and cardiac sympathetic denervation in Parkinson disease patients with REM sleep behavioral disorder. *J Neurol Sci*. 2016;362:59-63. doi:10.1016/j.jns.2016.01.020.
 119. Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir J. REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features. *J Neurol Neurosurg Psychiatry*. 2008;79(10):1117-1121. doi:10.1136/jnnp.2008.149195.
 120. Postuma RB, Montplaisir J, Lanfranchi P, et al. Cardiac autonomic denervation in Parkinson's disease is linked to REM sleep behavior disorder. *Mov Disord*. 2011;26(8):1529-1533. doi:10.1002/mds.23677.
 121. Nomura T, Inoue Y, Högl B, et al. Relationship between 123I-MIBG scintigrams and REM sleep behavior disorder in Parkinson's disease. *Park Relat Disord*. 2010;16(10):683-685. doi:10.1016/j.parkreldis.2010.08.011.

122. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of parkinson disease. *JAMA Neurol.* 2019 Jan 14. doi: 10.1001/jamaneurol.2018.4377. [Epub ahead of print]
123. Palma J-A, Gomez-Esteban JC, Norcliffe-Kaufmann L, et al. Orthostatic hypotension in Parkinson disease: how much you fall or how low you go? *Mov Disord.* 2015;30(5):639-645. doi:10.1002/mds.26079.
124. Goldman JG, Holden SK, Litvan I, McKeith I, Stebbins GT, Taylor JP. Evolution of diagnostic criteria and assessments for Parkinson's disease mild cognitive impairment. *Mov Disord.* 2018;33(4):503-510. doi:10.1002/mds.27323.
125. Pilotto A, Premi E, Caminiti SP, et al. Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson's disease. *Neurology.* 2018; 90(12):e1029-e1037.
126. Boeve BF, Silber MH, Ferman TJ, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med.* 2013;14(8):754-762. doi:10.1016/j.sleep.2012.10.015.
127. Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol.* 2013;12(5):443-453. doi:10.1016/S1474-4422(13)70056-5.
128. Fereshkenejad SM, Montplaisir JY, Pelletier A, Postuma, Gagnon JF, Berg D PR. Validation of the MDS Research Criteria for Prodromal Parkinson's disease: longitudinal assesment in a REM sleep behaviour disorder (RBD) cohort. *Mov Disord.* 2017;32(6):865-873. doi: 10.1002/mds.26989.
129. Pilotto A, Heinzel S, Suenkel U, et al. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. *Mov Disord.* 2017;32(7). doi:10.1002/mds.27035.
130. Koga S, Dickson DW. Recent advances in neuropathology , biomarkers and therapeutic approach of multiple system atrophy. *J Neurol Neurosurg Psychiatry.* 2018;89(2):175-184.
131. Stankovic I, Krismer F, Jesic A, et al. Cognitive Impairment in Multiple System Atrophy : A Position Statement by the Neuropsychology Task Force of the MDS Multiple System Atrophy (MODIMSA) Study Group. *Mov Disord.* 2014;29(7):857-867.
132. Del Tredici K, Braak H. Dysfunction of the locus coeruleus – norepinephrine system and related circuitry in Parkinson's disease-related dementia. *J Neurol Neurosurg Psychiatry.* 2013;84(7):774-783. doi:10.1136/jnnp-2011-301817.
133. McDonald C, Pearce M, Kerr SR, Newton J. A prospective study of the association between orthostatic hypotension and falls: definition matters. *Age Ageing.* 2016;46(3):439-445. doi:10.1093/ageing/afw227.
134. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L. Falls in Parkinson's disease: A complex and evolving picture. *Mov Disord.* 2017;32(11):1524-1536. doi:10.1002/mds.27195.
135. Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM Sleep at its Core - Circuits, Neurotransmitters, and Pathophysiology. *Front Neurol.* 2015;6(May):1-9. doi:10.3389/fneur.2015.00123.
136. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: The role of the thalamus. *Brain Res Bull.* 2009;78(2-3):69-74. doi:10.1016/j.brainresbull.2008.09.013.
137. Henderson EJ, Lord SR, Brodie MA, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised , double-blind , placebo-controlled , phase 2 trial. *Lancet Glob Heal.* 2016;4422(15):1-10. doi:10.1016/S1474-4422(15)00389-0.
138. Hauser RA, Heritier S, Rowse GJ, Hewitt LA, Isaacson SH. Droxidopa and reduced falls in a trial of Parkinson disease patients with neurogenic orthostatic hypotension. *Clin Neuropharmacol.* 2016;39(5):220-226. doi:10.1097/WNF.0000000000000168.

FIGURE LEGENDS

FIGURE 1. Structures associated with OH, RBD, cognitive impairment, and postural stability

OH-associated structures include the intermediolateral cell column (sympathetic), caudal and rostral ventrolateral medulla (sympathetic), tractus solitarius and nucleus ambiguus (parasympathetic), and paraventricular and supraoptic nuclei of the hypothalamus (production of oxytocin and ADH), anterior cingulate and insular cortex. RBD-associated structures include the magnocellularis nucleus of the medulla, pontine sublateral dorsal and dorsal raphe (serotonergic) nuclei, locus subcoeruleus (noradrenergic/sympathetic), and lateral pontine tegmentum, midbrain periaqueductal gray matter formation (GABAergic) and substantia nigra (dopaminergic), basal ganglia, hypothalamus, and motor cortex. Postural instability-associated structures include the pedunculopontine nucleus (glutamatergic/cholinergic) in the pontine tegmentum/midbrain, cerebellum, caudate nucleus (GABAergic), posterior thalamus, thalamic ventrolateral nucleus (GABAergic), and parieto-insular vestibular and prefrontal cortex. Cognitive-associated structures include the hippocampus, nucleus basalis of Meynert (cholinergic/parasympathetic), and the neocortex, especially prefrontal, temporo-parietal and occipital lobes.

Abbreviations. BG, basal ganglia; HT, hypothalamus; ILCC, intermediolateral cell column; LC, locus coeruleus; LSC, locus subcoeruleus; MCN, magnocellularis nucleus; OH, orthostatic hypotension; NBM, nucleus basalis of Meynert; PAG, periaqueductal gray matter; PPN, pedunculopontine nucleus; RBD, REM-sleep behavior disorders; RM, raphe medialis; SLD, sublateral dorsal nucleus; SN, substantia nigra; TS&A, tractus solitarius and ambiguus nuclei; VLM, caudal and rostral ventrolatero medulla; VTA, ventrosegmental area.

FIGURE 2. Functional Neurotransmission Pathways connected to the regions linking OH, RBD, Cognitive Impairment, and Postural Stability

Cholinergic pathways connect the pedunculopontine/lateral dorsal tegmental nuclei projections to thalamus and the nucleus basalis of Meynert with the neocortex. Dopaminergic pathways connect the substantia nigra in the ventral midbrain with the nigrostriatal system, and the ventro tegmental area to mesolimbic and mesocortical areas. Noradrenergic pathways connect the locus coeruleus with the cingulate and prefrontal cortex. Serotonergic pathways connect the raphe nuclei with the frontal cortex.

TABLES

Table 1. Association between OH and RBD and survival in α -synucleinopathies

Study	Study Design	Study Population	Diagnosis of OH	Diagnosis of RBD	Main Results
OH					
In support of an association					
De Pablo Fernandez et al. 2017	AS	PD (n= 100)	Level B	-	Association between OH, dysautonomia, and reduced survival rate
Stubendorf et al. 2016	L - 3 y	PDD (n= 14) DLB (n= 16)	Level B	-	Association between OH and reduced survival rate
Goldstein et al. 2015	L - 10 y	PD (n= 95) PAF (n= 26) MSA (n= 55)	Level B	-	Association between OH and reduced survival in PD; reduced survival rate in MSA compared to PD and PAF
Coon et al. 2015	R	MSA (n= 685)	Level A	-	Association between early autonomic dysfunction and reduced survival
Tada et al. 2007	AS	MSA (n= 49)	Level B	-	Association between early autonomic dysfunction and reduced survival
O' Sullivan et al. 2008	AS	MSA (n= 83)	Level A	-	Association between early autonomic dysfunction and reduced survival
Not in support of an association					
Gray et al. 2009	L - 7 y	PD (n= 109)	Level B	-	No association between OH and reduced survival
RBD					
Not in support of an association					
Forsaa et al. 2010	L - 20y	PD (n= 230)	-	Level C	No association between RBD and reduced survival rate

Abbreviations: AS, Autopsy Series; DLB, Dementia with Lewy Bodies; L, Longitudinal; MSA, Multiple System Atrophy; OH, Orthostatic Hypotension; PAF, Pure Autonomic Failure; PD, Parkinson Disease; PDD, Parkinson's disease dementia; R, retrospective; RBD, REM Sleep Behavioural Disorder; y, years

* **Diagnostic accuracy – OH:** level A: diagnosis based on cardiovascular autonomic testing; level B: diagnosis based on laying-to-standing blood pressure measurements in a clinical setting; level C: diagnosis based on clinical questionnaires

** **Diagnostic accuracy – RBD:** level A: diagnosis based on polysomnography; level B: diagnosis based on RBD-specific validated questionnaires; level C: diagnosis based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms

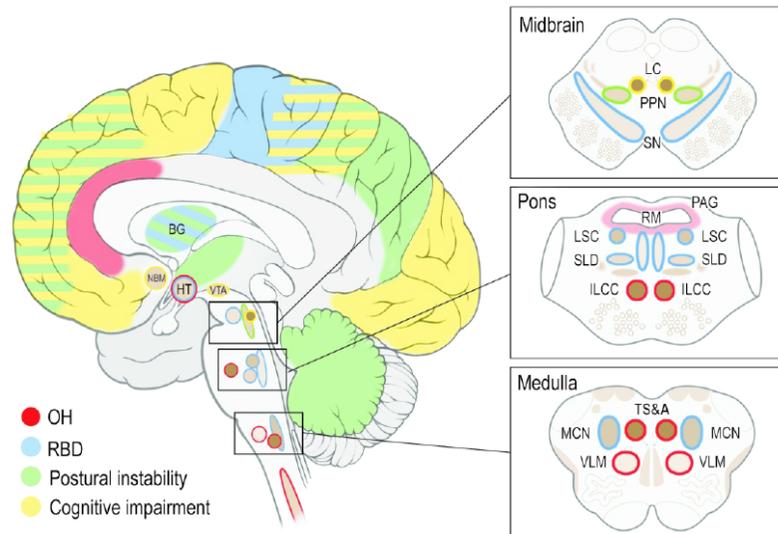
Table 2: Association between OH and RBD

Study	Study Design	Study Population	Diagnosis of OH	Diagnosis of RBD	Main Results
In support of an association					
Nomura et al. 2013	L - 2 y	PD (n= 82)	Level B	Level A	Association between RBD and OH
Postuma et al. 2011	CS	PD (n= 53)	Level A	Level A	Association between RBD and cardiac autonomic denervation
Sommerauer et al. 2018	CS	PD (n= 30)	Level A	Level A	Higher prevalence of OH in patients with versus without RBD
Kim et al. 2016	CS	PD (n= 94)	Level A	Level B	Association between RBD and OH
Postuma et al 2008	CS	PD (n= 36)	Level B	Level A	Association between RBD and OH
Nomura et al. 2010	CS	PD (n= 49)	Level B	Level A	Association between RBD and cardiac autonomic denervation
Romenets et al. 2012	CS	PD (n= 98)	Level B	Level A	Association between RBD and OH
Rolinski et al. 2014	CS	PD (n= 475)	Level B	Level B	Higher BP drop at the tilt-test in patients with versus without RBD
Liu et al 2017	CS	PD (n= 141)	Level C	Level B	Association between RBD and OH symptoms
Not in support of an association					
Yoritaka et al. 2009	CS	PD (n= 150)	Level C	Level B	No association between RBD and OH medication
CLUSTERS studies					
Fehrestenehjad et al. 2015	L - 5 y	PD (n= 76)	Level B	Level A	Worse motor, non-motor, and cognitive (NPS) symptoms progression in the OH-RBD cluster
Fehrestenehjad et al. 2017	L - 3 y	PD (n= 421)	Level B	Level B	Worse motor and cognitive (UPDRS-I, MoCA) symptoms progression and worse ADL progression (UPDRS-II) in the OH-RBD cluster
Arnaldi et al. 2017	L - 5 y	PD (n= 54)	Level B	Level B	Worse cognitive (NPS) symptoms progression in the OH-RBD cluster
De Pablo Fernandez et al. 2019	AS	PD (n=111)	Level C	Level B	Malignant phenotype associated with falls, inability to walk, dementia and shorter survival

Abbreviations: ADL, Activities of Daily Living; AS, Autopsy Series; BP, Blood Pressure; CS, cross-sectional; L, longitudinal; MoCA, Montreal Cognitive Assessment; NPS, Neuropsychological Testing; OH, Orthostatic Hypotension; PD; Parkinson Disease; RBD, Rem Sleep Behavioural Disorder; UPDRS-I, Unified Parkinson's Disease Rating Scale - section I; UPDRS-II, Unified Parkinson's Disease Rating Scale - section II; y, years

* **Diagnostic accuracy – OH:** level A: diagnosis based on cardiovascular autonomic testing; level B: diagnosis based on laying-to-standing blood pressure measurements in a clinical setting; level C: diagnosis based on clinical questionnaires

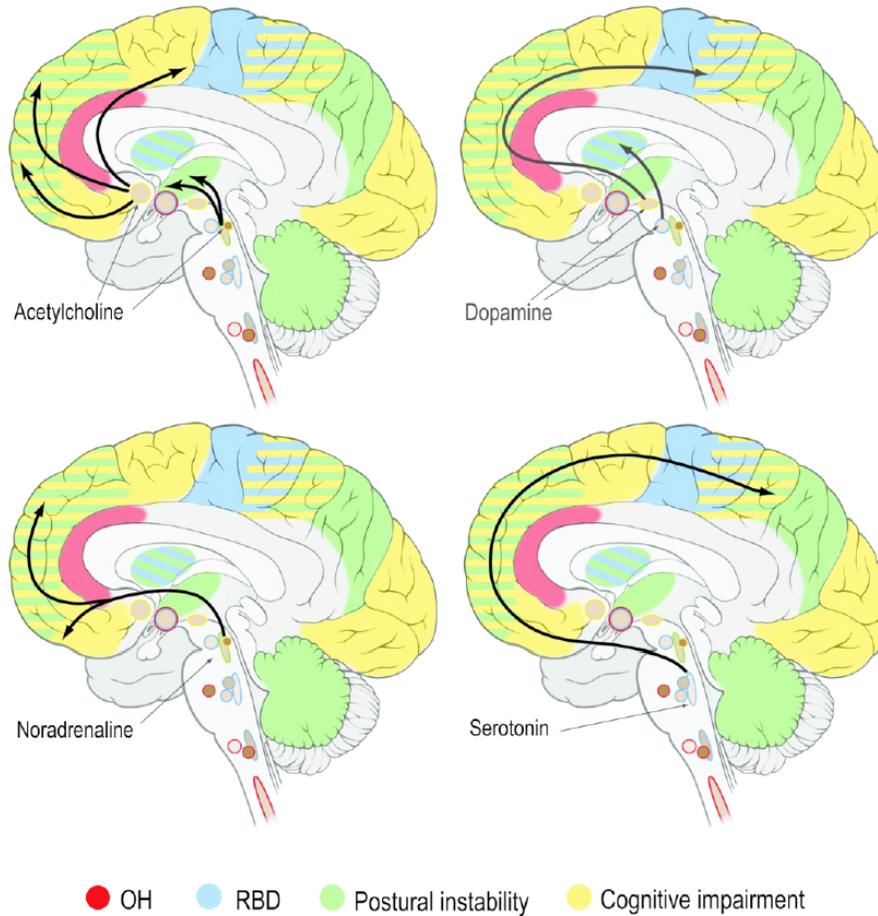
** **Diagnostic accuracy – RBD:** level A: diagnosis based on polysomnography; level B: diagnosis based on RBD-specific validated questionnaires; level C: diagnosis based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms



Structures associated with OH, RBD, cognitive impairment, and postural stability in PD and DLB

OH-associated structures include the intermediolateral cell column (sympathetic), caudal and rostral ventrolateral medulla (sympathetic), tractus solitarius and nucleus ambiguus (parasympathetic), and paraventricular and supraoptic nuclei of the hypothalamus (production of oxytocin and ADH), anterior cingulate and insular cortex. RBD-associated structures include the magnocellularis nucleus of the medulla, pontine sublateral dorsal and dorsal raphe (serotonergic) nuclei, locus subcoeruleus (noradrenergic/sympathetic), and lateral pontine tegmentum, midbrain periaqueductal gray matter formation (GABAergic) and substantia nigra (dopaminergic), basal ganglia, hypothalamus, and motor cortex. Postural instability-associated structures include the pedunculopontine nucleus (glutamatergic/cholinergic) in the pontine tegmentum/midbrain, cerebellum, caudate nucleus (GABAergic), posterior thalamus, thalamic ventrolateral nucleus (GABAergic), and parieto-insular vestibular and prefrontal cortex. Cognitive-associated structures include the hippocampus, nucleus basalis of Meynert (cholinergic/parasympathetic), and the neocortex, especially prefrontal, temporo-parietal and occipital lobes.

Abbreviations. ILCC, intermediolateral cell column; LC, locus coeruleus; LSC, locus subcoeruleus; MCN, magnocellularis nucleus; OH, orthostatic hypotension; NBM, nucleus basalis of Meynert; PAG, periaqueductal gray matter; PPN, pedunculopontine nucleus; RBD, REM-sleep behavior disorders; RM, raphe medialis; SLB, sublateral dorsal nucleus; SN, substantia nigra; TS&A, tractus solitarius and ambiguus nuclei; VLM, caudal and rostral ventrolateral medulla; VTM, ventro tegmental area.



Functional Neurotransmission Pathways connected to the regions linking OH, RBD, Cognitive Impairment, and Postural Stability

Serotonin pathways connect the raphe nuclei (1) with the frontal cortex. Dopamine pathways connect the substantia nigra (2) in the ventral midbrain with the nigrostriatal system, and the ventro tegmental area (3) to mesolimbic and mesocortical areas. Cholinergic pathways connect the pedunculopontine/lateral dorsal tegmental nuclei (4) projections to thalamus and the nucleus basalis of Meynert (5) with the neocortex.

Noradrenergic pathways connect the locus coeruleus (6) with the cingulate and prefrontal cortex.

Legends: - no association -/+ discussed association + association supported by 1-3 studies ++ association supported by 4-10 studies +++ strong association supported by more than 10 studies or different modalities (neuropathology, neurophysiology, imaging)