# Orthostatic Hypotension and REM Sleep Behavior Disorder:

# Impact on Clinical Outcomes in α-Synucleinopathies

Andrea Pilotto[1,2]*, MD; Alberto Romagnolo[3]*, MD; Jasmine A Tuazon[4,5], BA; Joaquin A Vizcarra[4], MD; Luca Marsili[4], MD, PhD; Maurizio Zibetti[3], MD, PhD; Michela Rosso[6], MD; Federico Rodriguez-Porcel[4,7], MD; Barbara Borroni[1], MD; Maria Cristina Rizzetti[2], MD, PhD; Carlo Rossi[8], MD; Darwin Vizcarra-Escobar[9], MD; Jennifer R Molano[10], MD; Leonardo Lopiano[3], MD, PhD; Roberto Ceravolo[11], MD; Mario Masellis[12], MD; Alberto J Espay[4], MD, MSc; Alessandro Padovani[1],MD, PhD; Aristide Merola[4], MD, PhD.

[1] Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[2] Parkinson's Disease Rehabilitation Centre, FERB ONLUS – S. Isidoro Hospital, Trescore Balneario (BG), Italy

[3] Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy

[4] Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

[5] The Ohio State University College of Medicine, Columbus, Ohio, USA

[6] Department of Neurology, The State University of New York (SUNY) Downstate Medical Center, Brooklyn, NY, USA.

[7] Department of Neurology, Medical University of South Carolina, Charleston, South Carolina, USA

[8] Unit of Neurology - "F. Lotti" Hospital - Pontedera - Pisa

[9] Hypnos, Instituto del Sueño; Clinica San Felipe; Faculty of Medicine, Universidad Peruana Cayetano Heredia. Lima, Peru

[10] Department of Neurology and Rehabilitation Medicine, The University of Cincinnati, Cincinnati, OH, USA.

[11] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[12] Department of Medicine (Neurology), University of Toronto; Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada

* The authors equally contributed to the work

**Corresponding Author:**
Aristide Merola, MD, PhD
Gardner Family Center for Parkinson's Disease and Movement Disorders,
Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA
Tel: +1 (513)558-1107
e-mail: merolaae@ucmail.uc.edu

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**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 PAF[2]. 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-synucleinopathies[1].

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 hypotension[4]. 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 falls[5], with a 36% increased mortality risk among the elderly[6].

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 behaviors[7]. 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 tegmentum[8]. 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 sleep[9].

Studies investigating the phenotypic heterogeneity of PD have identified OH and RBD as risk factors for early development of postural instability and dementia[10–15]. 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) guidelines[16]. 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 studies[17].

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 questionnaire[19]; 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 dementia[23]; level B: based on MDS level I criteria for MCI[22] or dementia[23]; 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 scales[24]) or posturography[25]; 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 PD[29–34] and one in PAF[35]. Negative data were reported by four cross-sectional studies in PD[36–39], three in MSA[40–42], and one in PAF[43] (eTable 1 in the Supplement).

*Postural Stability and Falls.* Six longitudinal[44–49], one cross-sectional[50], 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 DLB[53], and with increased postural sway in PD[54]. Negative data were reported in one longitudinal and two cross-sectional studies in PD[55–57], one autopsy series in DLB[52], 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 PAF[59] (Table 1). A reduced life-expectancy was also documented in DLB patients with OH[60], 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 PD[63].

*Imaging and pathology*. OH correlated with cerebral atrophy involving the insular cortex[64], as well as with cholinergic alterations[34], subcortical microbleeds[65], 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 MSA[68] , 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 cortex[69] (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 studies[76-87]. An autopsy series showed an association between RBD and more aggressive progression of dementia and hallucinations in DLB[88]. Negative data were reported in one longitudinal[89] and seven cross-sectional studies in PD[90–96], and one longitudinal study in DLB (eTable 4 in the Supplement)[97].

*Postural Stability and Falls*. One longitudinal[48] and four cross-sectional studies showed that RBD is associated with falls[83,91,98] and postural instability[96] 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 cortex[108] 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 metabolism[80], and extensive noradrenergic[79], 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 activity[114], greater nigrostriatal dopaminergic denervation[115], 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 PD[122]. 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 years[14], 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 areas [13].

## 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 disorders[123]. 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 deficits[69], 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-synucleinopathy[130], 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 MSA[131]. 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 OH[13], 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, serotoninergic, 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 ambiguous, and pontine micturition centre. [2]

OH, in particular, is associated with degeneration in the pedunculopontine cholinergic nucleus, noradrenergic periacqueductal gray neurons, rostral ventrolateral medulla, dorsolateral vagal motor nucleus, and nucleus ambiguous (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 ganglia[64]. 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 hypoperfusion[133], neurodegeneration of critical areas responsible for both postural instability and cardiovascular dysautonomia[34], or a combination thereof[134].

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 atonia[135]. The locus coeruleus activity is also modulated by the dorsal paragigantocellular reticular medullar nucleus, hypothalamic melanin-concentrating hormone neurons, dorsal raphe, and periacqueductal 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 RBD[111], as well as signs of involvement of the pedunculopontine nucleus, which is a critical node in the locomotor mesencephalic area modulating gait and balance[134].

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.
Maurizio Zibetti: acquisition of data, revising the manuscript for content.
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Federico Rodriguez-Porcel: acquisition of data, revising the manuscript for content.
Barbara Borroni: revising the manuscript for content.
Maria Cristina Rizzetti: revising the manuscript for content.
Carlo Rossi: revising the manuscript for content.
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.
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## 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 ambiguous (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, ventrotegmental 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 ventrotegmental area to mesolimbic and mesocortical areas. Noradrenergic pathways connect the locus coeruleus with the cingulate and prefrontal cortex. Serotoninergic 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)<br>DLB (n= 16) | Level B | - | Association between OH and reduced survival rate |
| Goldstein et al. 2015 | L - 10 y | PD (n= 95)<br>PAF (n= 26)<br>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

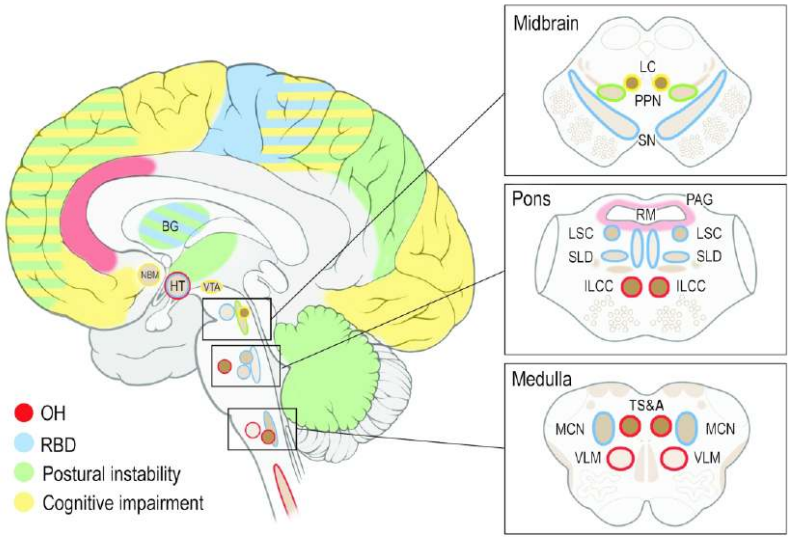
**Table 2: Association between OH and RBD**

| 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

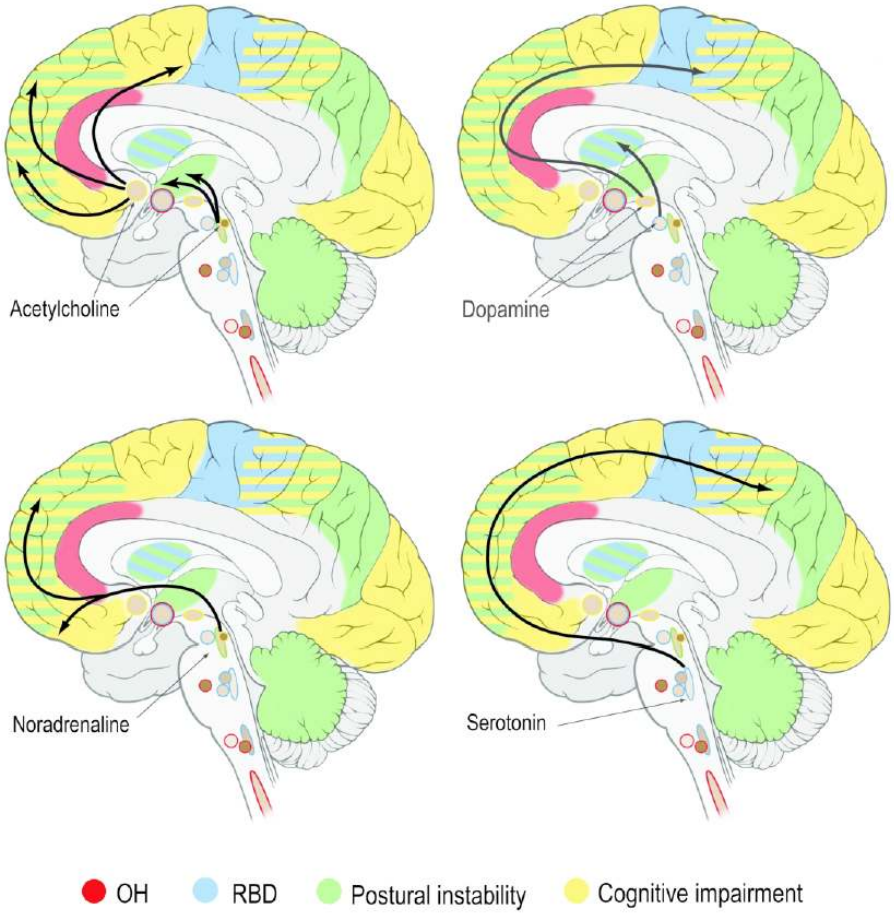
**** Diagnostic accuracy – RBD:** level A: diagnosis based on polysomnography; level B: diagnosis based on RBD-specific validated questionnaires; level C: diagnosis based on non-specific questionnaires assessing sleep disturbances and other non-motor symptoms




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 ambiguous (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 ventrolatero medulla; VTM, ventrotegmental 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 ventrotegmental 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)