

Considering REM Sleep Behavior Disorder in the Management of Parkinson's Disease

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Abstract: Rapid eye movement (REM) sleep behavior disorder (RBD) is the result of the loss of physiological inhibition of muscle tone during REM sleep, characterized by dream-enacting behavior and widely recognized as a prodromal manifestation of alpha-synucleinopathies. Indeed, patients with isolated RBD (iRBD) have an extremely high estimated risk to develop a neurodegenerative disease after a long follow up. Nevertheless, in comparison with PD patients without RBD (PDnoRBD), the occurrence of RBD in the context of PD (PDRBD) seems to identify a unique, more malignant phenotype, characterized by a more severe burden of disease in terms of both motor and non-motor symptoms and increased risk for cognitive decline. However, while some medications (eg, melatonin, clonazepam, etc.) and non-pharmacological options have been found to have some therapeutic benefits on RBD there is no available treatment able to modify the disease course or, at least, slow down the neurodegenerative process underlying phenoconversion. In this scenario, the long prodromal phase may allow an early therapeutic window and, therefore, the identification of multimodal biomarkers of disease onset and progression is becoming increasingly crucial. To date, several clinical (motor, cognitive, olfactory, visual, and autonomic features) neurophysiological, neuroimaging, biological (biofluids or tissue biopsy), and genetic biomarkers have been identified and proposed, also in combination, as possible diagnostic or prognostic markers, along with a potential role for some of them as outcome measures and index of treatment response. In this review, we provide an insight into the present knowledge on both existing and future biomarkers of iRBD and highlight the difference with PDRBD and PDnoRBD, including currently available treatment options.

Keywords: Parkinson's disease, REM sleep behavior disorder, synucleinopathy, biomarkers, neurodegeneration

RBD in Neurodegenerative Disease, a Window into Prodromal Parkinson's Disease

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior and loss of physiological muscle atonia during REM sleep (REM sleep without atonia, RSWA).^{1,2}

Concerning RBD pathophysiology, studies mainly based on animal models seem to indicate the neurodegeneration of SLD glutamatergic and/or medullo-pontin GABA/glycinergic neurons as the cause of RBD.³

RBD may be isolated (iRBD) when non associated to other neurological diseases⁴ reaching a prevalence of about 0.5–1% in the general population over 60 years.^{5,6} RBD is also widely recognized as a prodromal manifestation of alpha-synucleinopathies, it is present when the neurodegeneration progress has already started but cardinal symptoms of the disease have not yet manifested.

In fact, about 90% of patients with iRBD at 15 years of follow-up receive a clinical diagnosis of alpha-synucleinopathy, namely Lewy Body Dementia (DLB) in about 45%, Parkinson's disease (PD) in 45%, and multiple system atrophy (MSA) in 5%.^{7,8}

Additionally, RBD associated with PD (PDRBD) seems to identify a malignant phenotype characterized with a more severe burden of disease in terms of motor and non-motor symptoms, and increased risk for cognitive decline, compared to PD patients without RBD (PDnoRBD).⁹

Managing of RBD includes pharmacological interventions (Clonazepam, Melatonin), bedroom interventions aimed to mitigate the risk of injuries improving the safety of both the patient and the bed-partner, in order to reduce dream-enacting behaviors, associated nightmares and consequent injuries, and to improve the quality of life. Moreover, in managing RBD it is important to inform the patient about the association between RBD and neurodegenerative disorders and scheduling follow-up neurological examinations in order to early recognize any sign of synucleinopathies.^{2,8}

Up to now, neuroprotective and disease-modifying therapy are not available, in order to arrest or slow down the neurodegenerative process of alphasynucleinopathy. RBD population represents an ideal candidate to neuroprotective or disease-modifying clinical trial. Thus, the identification of multimodal biomarkers, both diagnostic and prognostic, of neurodegeneration is crucial. In this review, we provide an insight into the present knowledge on both existing and future biomarkers of iRBD and highlight the difference with PDRBD and PDnoRBD, including currently available treatment options.

Parkinson's Disease Associated with RBD a New Phenotype Within the Spectrum of Alpha-Synucleinopathies

Although Parkinson's disease was initially considered a single entity, soon biological and instrumental evidence reflecting the heterogeneity of possible clinical trajectories, allowed the delineation of phenotypes that not only are guiding the search for the underlying pathological mechanisms of the disease, but can predict its course and which will become increasingly crucial once targeted therapeutic options become available.¹⁰ The concept of RBD heralding synucleinopathies was introduced in 1996,¹¹ but only in recent decades RBD and non-motor symptoms has been accorded the importance they deserve. Many years have elapsed since Braak postulated his famous hypothesis according to which the key lesions of the pathology begin to develop long before the onset of cardinal somato-motor symptoms of the disease, with an ascending and predictable topographical sequence.^{12,13} The first structures to be affected would be located in this model at the level of the medulla oblongata and pons, which may associate not only, as postulated by the author, with the onset of non-motor symptoms such as hyposmia and autonomic dysfunction, but structures critical for the preservation of physiological atonia during REM sleep.¹² Subsequently, involvement of the substantia nigra and other nuclear grays of the midbrain and forebrain would occur and then end at stages 5–6 with involvement of the neocortex.¹⁴ Regarding pathogenesis of PD, one of the most famous theories is the dual-hit hypothesis: a pathogenic agent spreading in a prion-like manner, leading to the accumulation of misfolded alpha-synuclein aggregates, would have access to the brain through the olfactory bulb and the dorsal motor nucleus of the vagus (DMV).^{15,16} Although a large proportion of studies seem to confirm the validity of Braak's model in most cases, it is also true that incidental PD may show pathological aggregates in substantia nigra or elsewhere in the brain with no implication of the dorsal motor nucleus of the vagus.^{17,18} These observations implying heterogeneity in the sites of origin from which alphasynucleinopathy progresses actually accord with the recent identification of two phenotypes, in contrast for their different spreading patterns: a brain-first (top-down) where the pathology originates in the central nervous system,⁹ and a body-first (bottom-up) type in which a-synuclein pathology initially arises in the enteric or peripheral autonomic nervous system.¹⁹ Premotor RBD is in this model a key clinical indicator of a body-first phenotype, in fact, the pons is involved before the substantia nigra in a bottom-up model; however, since late top-down involvement cannot be excluded, it is only iRBD that can be used as an early and distinctive biomarker of this phenotype.^{20,21} Moreover, the nigrostriatal dopamine system is widely preserved in many iRBD cases,¹⁹ whereas enteric phosphorylated α -synuclein histopathology (PASH) was found more frequent in a RBD subgroup of patients compared to PD patients without RBD.²² However, PDRBD patients also appear to display a more severe cerebral pathological involvement, reflecting a possible broader and heavier diffusion of alpha synucleinopathy in these subjects.^{19,23} To demonstrate the validity of the dichotomous brain first or gut first model, Horsager et al have investigated de novo PD patients with and without RBD through multimodal imaging studies and compared the results with those obtained in iRBD patients.²⁰

Pre-motor RBD Parkinson's disease and iRBD groups showed significantly reduced 11C-colonic donepezil and cardiac MIBG signal, mildly decreased locus coeruleus neuromelanin signal and colonic changes like an augmented colon volume and transit time, providing major support for the body-first disease subtype identification.^{20,24} The alpha-Synuclein Origin site and Connectome (SOC) model, proposed by Borghammer could be considered to some extent an evolution of the Brain-first/Body-first.²⁵ According to this theory, the anatomical point of origin of alpha-synucleinopathy spread and the density of ipsilateral connections dominating intra-cerebral propagation appear to be a potential explanation for the asymmetric involvement at the hemispheric level in CNS-first patients, whereas in the bottom-up model the differences in neuropathological diffusion in the two hemispheres are more subtle.²⁵ In addition to the asymmetry in motor symptoms it is also suggested by the author that the greater prevalence and severity in cognitive involvement in body-first patients is due to the fact that at the time of diagnosis of parkinsonism in this subgroup the alpha-synucleinopathy is already widely spread bilaterally in the brainstem and hemispheric regions, and presenting the aforementioned with a much more protracted prodromal phase.²⁵ Indeed, brain atrophy seems to be already present in de novo PDRBD, which as we have seen appears to be a body-first type hallmark, and there seems to be a stronger correlation between volume reduction of thalamus, hippocampus, and putamen in particular and a severer cognitive impairment.²⁶ Most early subtyping systems were based on age at onset and tremor versus akinetic-rigid predominance in general, on variables that were selected a priori, whereas, in order to improve the reliability and reproducibility of the identified phenotypes, more recent studies are adopting a hypothesis-free data-driven approach, giving increasing importance to non-motor symptoms such as RBD.^{9,10,27} Regardless, the dominant motor phenotype of tremor has always been found to have a more favorable prognosis than the postural instability and gait disturbance (PIGD) phenotype,⁹ and, in general, the dominant non-tremor subtypes have always been associated with a wider range of nonmotor symptoms, with early predominance of autonomies and later cognitive impairment as the most common nonmotor issues.

Fereshtehnejad et al, analyzing a comprehensive array of motor and nonmotor features in PD patients were able to identify three clinical subtypes: "mild motor-predominant", "intermediate" and "diffuse malignant".^{9,28} Interestingly, the most discriminating features were mild cognitive impairment, orthostatic hypotension, and RBD. Patients with the diffuse malignant subtype presented not only with a severer dopaminergic deficit on SPECT and atrophy in disease-specific brain networks²⁹ but also displayed an Alzheimer's disease-like CSF profile and faster progression of cognitive, motor, and other nonmotor domains.⁹

Finally, PDRBD may mark a unique, more malignant subtype of alphasynucleinopathy, with different neuropathological and genetic background and independent risk factor profile,³⁰ which, however, given the long prodromal phase could ensure the identification of an early therapeutic window once disease-modifying treatments are identified.

REM Sleep Behavior Disorder and Biomarkers for Phenoconversion Prediction

Patients with iRBD have an estimated risk to develop a neurodegenerative disease (such as PD, MSA and LBD) up to 90% after a long follow up: 44.8% after 6 years, and from 67.5%³⁰ to 81% after 10 years.³¹

This means that diagnosis of RBD offers a unique clue to individuate a cohort of patients that can be eligible for neuroprotective and disease modifying drug trials or therapy in the future.

In order to do so it is crucial to understand which features are associated with phenoconversion and with faster neurodegeneration, consequently during the last years, many longitudinal studies focused on the individuation of potential biomarkers of disease progression.³²

Ideally, a good biomarker must have a good sensitivity and specificity, must be easily available and be useful both as a marker for progression and also as a marker for therapy response in neuroprotective therapy trials.³³

To date, several clinical (motor symptoms, cognition, olfactive symptoms, visive function, autonomic function) neurophysiological, neuroimaging, biological (biofluids or tissue biopsy) and genetic biomarkers have been individuated. They can be classified accordingly to the purpose they serve as diagnostic biomarkers (to confirm diagnosis of alpha-synucleinopathy), prognostic biomarkers, (to predict phenoconversion), monitoring or therapy responsive (to monitor neurodegenerative progression and possible effect of therapies) and combined biomarkers.³³

Table 1 summarizes the biomarkers of neurodegeneration in iRBD.

Table I Biomarkers of Neurodegeneration in Isolated REM Sleep Behavior Disorder (iRBD)

Clinical	Motor function	<ul style="list-style-type: none"> • Early alterations on UPDRSIII scale • Early alteration of gait, balance and bradikinesia
	Smell	<ul style="list-style-type: none"> • Early presence of Hyposmia and altered smell test
	Visual function	<ul style="list-style-type: none"> • Altered color discrimination, stereopsis and retinal thinning at OCT
	Autonomic function	<ul style="list-style-type: none"> • Decreased Heart rate variability • Presence of urinary dysfunction • Presence of sexual dysfunction • Ortostatic hypotension
Biological	Blood test	<ul style="list-style-type: none"> • Alpha-synuclein in neuronal circulating exosomes, • Research of neurofilaments in serum • Circulating micro-RNA
	CSF	<ul style="list-style-type: none"> • Elevated misfolded with RT-QuIC
	Tissue Biopsy	<ul style="list-style-type: none"> • Presence α-synuclein in colon mucosae, salivary glands and skin
Neuroimaging	¹²³ I-FP-CIT SPECT	<ul style="list-style-type: none"> • Nigrostriatal dopamine impairment • Decreased dopamine uptake in striatum and putamen
	Glucose metabolism SPECT and PET	<ul style="list-style-type: none"> • Abnormal/increased metabolic activity in hippocampus
	Structural MRI	<ul style="list-style-type: none"> • Deep gray matter and cortical gray matter degeneration
	f-MRI	<ul style="list-style-type: none"> • Altered connectivity in basal ganglia, in cortico-striatal and cortico-cortical networks
Genetics		<ul style="list-style-type: none"> • GBA variants • SNCA • TMEM175

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; OCT, Optical coherence tomography; RT-QuIC, real-time quaking-induced conversion.

Clinical Biomarkers

Motor function can be altered in iRBD patients, in a large multicenter study, Unified Parkinson's disease Rating Scale (UPDRS) and quantitative motor test demonstrated to be powerful predictive factor of phenoconversion with an HR of 3.16 (95% CI 1.86–5.37),³⁴ moreover, UPDRS-III motor score may be altered starting from 6.5 years before diagnosis.³⁵

More recently assessment of motor function with wearable devices or computer detection algorithms was used in several studies, allowing an objective evaluation of gait,³⁶ balance,³⁷ eye movements,³⁸ and bradykinesia.³⁹

All these cross sectional studies showed promising results in the detection of alterations that can be used as biomarkers for phenoconversion, with sensitivity and specificity up to 80%;³³ these systems are relatively easy to use and low cost and can be used at patient's home,^{36,37} however further studies on larger population are needed for the validation of their use in clinical practice.

Hyposmia is recognized together with RBD a prodromal symptom of PD,⁴⁰ with 67% of patients with RBD presenting with this symptom.³⁴

The presence of hyposmia or anosmia is considered a low term risk factor for the development of alpha-synucleinopathy in iRBD patients,^{41,42} but smell test did not show any changes in time, therefore this symptom should be used as a prognostic marker at the moment of RBD diagnosis, but not as a monitoring biomarker in clinical intervention trials.⁴¹

Visual impairment, another common finding in alpha-synucleinopathies, can also be present in patients with iRBD in different forms, ranging from altered color discrimination,⁴³ stereopsis⁴⁴ and retinal thinning,⁴⁵ suggesting that color vision test and optical coherence tomography (OCT) may be used as potential diagnostic and prognostic markers.³³

Finally, another clinical feature that can be used as biomarker for phenoconversion is autonomic dysfunction, symptoms such as orthostatic hypotension, sexual and urinary dysfunction and constipation⁴⁶ are present in up to 94%

patients with RBD.⁴⁷ Moreover, autonomic dysfunction is one of the cardinal nonmotor symptoms of PD and in patients with iRBD can appear several years before the diagnosis of alpha-synucleinopathy.⁴⁷

Different studies reported a reduced heart rate variability (HRV) in iRBD patients,⁴⁸ which also correlated with quantified tonic RSWA,^{49,50} however there is not a clear difference between patients who converted to a neurodegenerative disorder and those who did not.⁴⁸

Even though longitudinal studies are still needed in order to have a standardization and clear cut-off values, performing a clinical assessment of motor, autonomic, olfactory and visual function is easy and low cost and is fundamental during baseline and follow-up visits of iRBD patients to predict and detect early signs of alpha-synucleinopathies

Neuroimaging

The use of neuroimaging in PD has greatly developed in the last decade, mostly with the purpose to detect early impairment of nigrostriatal dopaminergic circuit and dopamine transport alteration in the basal ganglia circuit with the use of PET and SPECT imaging.³³

The most studied is ¹²³I-FP-CIT SPECT for the assessment of dopamine transporter: many patients with iRBD have nigrostriatal dopamine impairment;⁵¹ decreased dopamine uptake in striatum and putamen demonstrated to predict phenoconversion with strong sensitivity and specificity,^{52–54} especially when combined to clinical biomarkers such as autonomic impairment.⁵⁵

The use of ¹²³I-FP-CIT SPECT is a powerful biomarker for phenoconversion and can also serve as a prognostic marker for neuroprotective therapy trials.⁵⁶

Other PET and SPECT techniques for the study of glucose metabolism and perfusion demonstrated abnormal metabolic activity, especially in hippocampus,⁵⁷ in RBD patients who converted to PD.⁵⁸ Serial follow up imaging demonstrated an increase in time of PD related pattern expression, making it a potential marker for prediction of short term phenoconversion.

Although these promising results, SPECT and PET are not available in all centers and expose the patient to radiation, therefore MRI has been considered as an alternative: structural studies demonstrated a reduction in deep gray matter and cortical gray matter degeneration in patients with RBD, along with changes in white matter typically found in neurodegenerative disorders.⁵⁹

Functional MRI studies (f-MRI) showed altered connectivity not only within basal ganglia, but also in cortico-striatal and cortico-cortical networks.⁶⁰

Biological

A more feasible and low cost alternative to imaging studies, may be biomarkers obtained from blood; however, research of alpha-synuclein in neuronal circulating exosomes, research of neurofilaments in serum and circulating micro RNA have only shown encouraging results and their validity as biomarker is yet to be confirmed.³³

A novel approach is the detection of alpha synuclein in neuronal extracellular vesicles, which are vesicles released from CNS cells that can transport and spread proteins, including pathological ones, they pass the blood brain barrier and spread the neuropathological proteins.⁶¹ Pathological soluble alpha-synuclein in neuronal extracellular vesicles is significantly higher in patients with PD compared to controls, this novel approach is promising and will need further validation.⁶²

In many patients with iRBD abnormal deposits of α -synuclein have been documented in olfactory mucosa,⁶³ in peripheral organs (skin, colon and salivary glands)⁶⁴ and misfolded α -synuclein has also been detected in the cerebral spinal fluid (CSF).⁶⁵

Recently, detection in CSF of pathologically misfolded α -synuclein with the use of Real-time quaking-induced conversion (RT-QuIC) showed very promising results with a sensitivity and specificity of 90% in patients with iRBD, and its positivity was associated with an increased risk of phenoconversion.⁶⁵ The same technique applied to swabs from olfactory mucosa, less invasive than lumbar puncture, showed a 90% specificity but lower sensitivity.⁶³

Quantification of α -synuclein in tissue research has emerged as an interesting biomarker, also providing information on its deposition spread over time. Studies on samples from colon mucosae, salivary glands and skin using antibodies targeting phosphorylated α -syn showed good sensitivity and specificity in iRBD patients, with skin biopsy coming up as the most promising technique.⁶⁴

Genetics

Several gene mutation related to Parkinson disease and other synucleinopathies have been discovered during the last 40 years, detection of gene mutations associated to PD in patients with RBD can represent a biomarker for phenoconversion prediction.

GBA, the gene encoding for Glucocerebrosidase, is more frequently mutated in patients with PDRBD than in patient with PDnoRBD.⁶⁶ Frequency of GBA mutation in iRBD was higher than in control population and associated with a risk of conversion to PD and DLB,^{67,68} and was also more frequent in patients with iRBD compared to PD patients with unknown RBD status.

Other genes potentially involved in neurodegeneration progress are SNCA variants⁶⁹ and TMEM175.⁷⁰

RBD as a Cognitive Decline Risk Factor

Several studies have shown impairment in different cognitive domains, including memory, attention, executive functions and visuospatial abilities, in RBD patients, both idiopathic and associated with PD.^{71–73} Likewise, presence of mild cognitive impairment (MCI) and reduced cognitive performances seem to predict the phenoconversion of iRBD patients into a neurodegenerative disease.^{32,71} Moreover, MCI and/or impaired attention and executive functions might predict conversion to dementia prior to parkinsonism in iRBD patients.^{34,74}

Up to 50% of iRBD and 73% of PDRBD show MCI, in particular, RBD in PD was associated with a more impaired cognitive performances compared to PDnoRBD patients and to healthy controls (HC).^{73,75} RSWA, the neurophysiological hallmark of RBD, have been correlated with reduced cognitive performances, namely attention, executive functions, episodic verbal and learning memory, verbal fluency and visuospatial abilities, in PDRBD compared to PDnoRBD and HC.⁷³ Furthermore, higher RSWA can discriminate probable synucleinopathy from probable non-synucleinopathy in older adults with cognitive impairment, including in those with no clinical symptoms of dream enactment.⁷⁶

MRI cortical thinning in the left anterior temporal cortex has been correlated with cognitive impairment in iRBD patients with MCI, and more precisely, reduced attention and executive function has been associated with thinning of the frontal cortex, reduced verbal learning with thinning in left temporal cortex and visuospatial abilities has been correlated with thinning of the fronto-temporal cortex in iRBD patients.^{33,77} Moreover, atrophy in the basal ganglia, thalamus, amygdala and frontotemporal grey and white matter might predict cognitive decline in both iRBD and PD, by means of MRI using partial least squares.⁷⁸ More recently, iRBD patients with MCI have shown a widespread pattern of local alteration and volume atrophy in both cortical and subcortical regions compared to iRBD without MCI and controls.⁷⁹

RBD is an heterogeneous clinical and neurophysiological entity, up to 50% of iRBD patients will develop DLB and the remainder will convert to a parkinsonism (PD>MSA).^{80,81} Thus, it is crucial to phenotype iRBD patients in dementia-first and parkinsonism-first converters. Presence of MCI, both amnesic and non-amnesic, in iRBD seems to be a key risk factor to dementia-first phenoconversion.⁸² Recently, cognitive impairment has been considered as a prodromal marker of alphasynucleinopathy and has been incorporated in the last updated research criteria for prodromal PD.⁸³ Different evidences suggest that RBD together with hyposmia and reduced dopamine transporter binding, prodromal signs of PD, might be associated with worse cognitive performances compared with subjects without any or with only one of these prodromal signs.^{75,84} Moreover, PD associated with RBD has been identified as a diffuse-malignant phenotype characterized by a heavier burden of disease in terms of motor and non-motor symptoms, namely cognitive decline and dysautonomia and a more rapid progression compared to the other two PD phenotype, “mild motor predominant” and “intermediate”.^{9,29} Also, the diffuse-malignant PDRBD phenotype has shown more atrophy in substantia nigra-connected areas, more dopaminergic deficit on SPECT and reduced amyloid- β in CSF compared to the others.⁹ Thus, RBD might be associated with a more widespread neurodegenerative process involving cortical-subcortical-mesolimbic networks. Further longitudinal studies are needed in order to intercept iRBD patients at risk to

develop cognitive decline, a specific population that might be included in future clinical trials for disease-modifying therapy for alpha-synucleinopathies and clinical trials for therapies targeting cognition in PD.

Neurophysiological Biomarkers of Neurodegeneration in RBD

Electroencephalography (EEG)

iRBD subjects showed some EEG changes which have been demonstrated also in those with PD and DLB, including diffuse slowing in wakefulness EEG recordings, though this was particularly evident on posterior brain regions.⁸⁵ Notably, the cortical slowdown was related to cognitive impairment, thus hypothesizing a correlation between electrophysiological and neuropsychological features. Moreover, higher absolute delta and theta power from all cortical areas allowed to identify those patients at greater risk of short-term conversion into synucleinopathies.⁸⁶

Both macro- and microstructure sleep alterations derived from EEG have been suggested as electrophysiological indexes, although prospective studies have not been performed yet. Only an earlier study found that quantification of RSWA, in particular the baseline high tonic chin EMG activity, may detect a greater risk of progression into PD.⁸⁵ A more recent study with high-density EEG showed that, unlike RBD patients, good sleepers displayed a decreased beta power during phasic with respect to tonic REM sleep. Furthermore, RBD individuals showed a lower SWA decline from early to late non-REM sleep, as well as decreased overnight modifications in the slow-wave amplitude distribution.⁸⁷ As such, because of the lack of suppression of the beta rhythms during phasic REM sleep, RBD subjects would show an increase in cortical arousal, thus likely favoring the presence of REM behavioral episodes.

A further report demonstrated, during REM sleep, the increase of instability of EEG microstructure in de novo iRBD subjects,⁸⁸ with power EEG spectrum frequency lower than 15 Hz indicating a reduced REM-related decrease than in controls and an increased beta band, which might correlate with persistent muscular activation. Of note, clonazepam partially recovered the power of frequencies lower than 15 Hz; also, the increased EEG power instability was remarkably reduced by this treatment.

Based on the same rationale, clonazepam might be effective also for PDRBD, as clinically highlighted by recent randomized double-blind clinical trials and systematic reviews/meta-analysis.^{89–93} Considering these objective findings, indeed, clonazepam may act by reducing the negative effects from the supratentorial network rather than acting directly on the infratentorial pathology of RBD.⁸⁸ However, its efficacy at EEG level has been demonstrated only in a mouse model of RBD, and not yet in patients with PDRBD.⁹⁴ Therefore, we recommend continuing the studies to reveal whether there is not only a subjective but also an objective improvement in these patients as well.

The investigation on the cyclic alternating pattern (CAP) has been conducted as well.⁹⁵ A previous study observed an increase of slow EEG transients (A1 CAP subtypes) and a decrease of fast EEG events (A2 and A3 CAP subtypes) in drug-naïve iRBD individuals.⁸⁹ In this report, long-term intake of clonazepam improved the stability of non-REM sleep and EEG transients duration. Different results come from another study, ie, a global increased CAP, particularly due to the A2 and A3 subtypes; conversely, the A1 subtype decreased in RBD.⁹⁶ Lastly, another investigation in iRBD showed a decrease of global CAP measures, mostly due to a decreased A1 CAP subtype.⁹⁷ Taken together, the impact of non-REM sleep instability on RBD is still inconclusive.

In addition, the density of sleep spindles was found to be altered in RBD patients, with a decreased fast but increased slow spindles, that was viewed as a possible marker predictive of a neurodegenerative disorder.⁹⁸ A further report revealed a diffuse decreased spindle density both in iRBD patients and in those with PDRBD, thus proposing it as a supportive diagnostic tool.⁹⁹

Recently, it should be mentioned an advanced EEG-based study in which the analysis method reported theta-band bursts and decreased alpha-band burst during the eye-closed wakefulness, which may predict the progression into DLB or PD.¹⁰⁰ Very recently, EEG power analyses showed a significant lower alpha and higher delta power in iRBD phenotypic converters during the phasic REM state, which was more evident over the occipital and central cortical areas, with respect to those patients who remained disease-free.¹⁰¹ Significant higher slow-to-fast ratio during the phasic state was noted more diffusely in iRBD converters than in non-converters. The further analysis of slowing ratio during phasic REM sleep from occipital regions resulted in a remarkable area under the curve, whereas the subjective RBD severity did not

have any predictive value. The authors concluded that EEG slowing (especially when generalized during the phasic period), rather than subjective RBD severity, may be promising in predicting phenoconversion.¹⁰¹

Motor Evoked Potentials (MEPs)

MEPs to transcranial magnetic stimulation (TMS) have been tested in sleep disorders to evaluate and non-invasively modulate cortical excitation, neuroplasticity, and brain connectivity.^{102–105}

The first TMS study in RBD¹⁰⁶ found an impaired short-latency afferent inhibition, which supported the cholinergic dysfunction in those patients developing cognitive decline; this was further supported in RBD patients in the context of PD.¹⁰⁷ As such, cholinergic dysfunction may substantially contribute to non-motor aspects of PD as well, raising also the hypothesis that RBD increased the risk of cognitive changes in PD.

The second study found that iRBD patients exhibited an electrocortical profile similar to that observed in PD.¹⁰⁸ Moreover, intracortical disinhibition was related to muscular tone change, which supports the model of retrograde influence of the brainstem to the cortex.¹⁰⁹ Therefore, an altered control in RBD, which would arise from the brainstem and ascend to the cortex, may determine both a reduced atonia during REM sleep and an imbalanced cortical disinhibition and hypofacilitation, favoring the former.¹⁰⁸

Recently, a direct comparison between iRBD and PDRBD revealed that both patient groups had a significantly decreased intracortical facilitation compared to healthy controls, thus sharing the involvement of glutamatergic transmission.¹¹⁰ Finally, another report has recently compared PD without and with RBD: an enhancement of GABA-mediated and a reduction of glutamine-mediated activity was found in PDRBD only, thus suggesting a distinctive physiopathological processes in these subjects.¹¹¹

To date, no study has applied repetitive TMS in RBD or PDRBD.¹¹²

Vestibular Evoked Myogenic Potentials (VEMPs) and Other Brainstem Responses

Ocular (oVEMP), masseter (mVEMP), and cervical (cVEMP) VEMPs can provide an extensive evaluation of whole-length brainstem functioning, also allowing the detection of subtle changes in radiologically or clinically “mute” areas.¹¹³

De Natale et al¹¹⁴ reported for the first time a significant alteration of VEMPs in iRBD subjects, especially for oVEMP and mVEMP, thus suggesting that synaptic and neuronal derangement was particularly evident in the upper areas of the brainstem, a finding which is in accordance with current physiopathology of RBD in PD.¹¹⁵ Moreover, the correlation between VEMP and RSWA may precede the progression from iRBD to neurodegeneration, whereas changes at the dopamine transporter scan would indicated a later stage.¹¹⁶

Very recently, PD patients with RBD showed bilateral delays in cVEMP and oVEMP peak latencies with respect to PDnoRBD, whereas cVEMP features were also higher in PDRBD than in iRBD group.¹¹⁷ Although follow-up studies are needed, this indicates that brainstem neurophysiology might reflect different disease involvement and that VEMPs can vary based on the occurrence of RBD in PD, even in its early stages.

Both PD and RBD subjects exhibited altered blink and pupil behavior with respect to healthy controls.¹¹⁸ Notably, since measures of RBD saccade were similar to those found in normal individuals, blink and pupil brain regions might be affected before those underlying saccadic control, thus making them potential prodromal markers of PD.¹¹⁹ Moreover, blink reflex parameters in PD did not relate to cognition or RBD.¹²⁰

Recently, the pedunculopontine nucleus in dream-enacting motor behavior has been assessed through the prepulse modulation (PPM). PPM was altered in both RSWA and iRBD patients, while auditory startle reflex was increased in iRBD only, suggesting the presence of both differences and similarities in RSWA and iRBD pathophysiology.¹²¹

Other Neurophysiological Investigations

Vegetative tests indicate that severity of autonomic dysfunction in iRBD seems to be intermediate between PD and normal values.¹²² Overall, orthostatic hypotension and RBD produced both combined and individual detrimental consequences on disability in alpha-synucleinopathy, possibly reflecting a “malignant subtype” of PD, along with postural instability and early cognitive decline. The involvement of selected noradrenergic and cholinergic brainstem nuclei may be among the proposed underlying pathomechanisms.¹²³

Cortico-muscular coherence (CMC) is the functional correlate of connectivity between the primary motor cortex (as indexed by magnetoencephalography or EEG) and contralateral muscles during isometric activity.¹¹⁸ Under normal condition, CMC significantly lowers during REM sleep with respect to wakefulness; conversely, in RBD, CMC during the REM sleep was found to be higher than in controls, thus hypothesizing that cortical locomotor drive was enhanced during REM sleep in this disorder.¹²⁴ These findings have been recently confirmed and extended by an independent study in which muscle atonia index, CMC, and cortico-cortical coherence revealed specific findings both in PDRBD and in iRBD groups.¹²⁵

Lastly, some studies assessed psychophysiological parameters, eg, through the active and passive oddball P300 paradigm.¹²⁶ In iRBD, no difference was noted between patients and matched controls, at least at early-middle stages of the disease. Since cognitive alterations have been reported in RBD,^{127,128} event-related potentials using a cognitive task have been also tested. An occipital positive wave (P2) was found in PDRBD subjects, whereas it was nearly absent in healthy individuals. Of note, PDnoRBD were similar to controls, thus indicating that RBD may worsen the cortical dysfunction in PD.¹²⁹

It should be acknowledged that, despite a number of available markers derived from different neurophysiological techniques, not all of them seem to have a diagnostic value or a clear prognostic role in the monitoring of disease progression or response to therapy. This may be due, at least in part, to the limited sample size included in most studies and some aspects of study design themselves (eg, drug-naïve vs de novo patients, adequate comparisons, technical/procedural variability, magnitude of the results, etc.).³³ Therefore, a combined use of neurophysiological and other, multidimensional, biomarkers, will be needed, especially in the case of RBD subtyping and differential diagnosis.^{130,131} For instance, using solid neurophysiological features, such as RSWA, in combination with other types of biomarkers might have a relevant role in the identification and characterization of RBD as a prodromal form of PD.¹³² Nevertheless, longitudinal studies are required to verify whether the neurophysiological abnormalities detected at the early stages of RBD by EEG, TMS, VEMP, and other techniques correlate with clinical progression of RBD.

Table 2 summarizes main findings obtained from different neurophysiological techniques in patients with isolated REM sleep behavior disorder (iRBD), Parkinson's disease with RBD (PDRBD), and Parkinson's disease without RBD (PDnoRBD). Figure 1 summarizes the neurophysiological findings in iRBD, PDRBD and PDnoRBD population.

Parkinson's Disease RBD Phenotype: Pharmacological Management

While many medications have been found to have some therapeutic effects on RBD, the overall effects of treatment are still unsatisfactory.

Clonazepam, a long-acting sedative benzodiazepine, is the first option to treat RBD,¹³³ however, its mechanism of action is still unclear and the proof of its efficacy for RBD relies on many observational studies, mainly retrospective cohorts and case-series.¹³⁴ Furthermore, most studies used small samples and did not contain quantitative measurements.

Clonazepam can dramatically decrease the phasic EMG activity on polysomnography, while there is insufficient evidence of reduction in the objective or subjective severity of RBD. It has been shown that Clonazepam can reduce phasic twitching in RBD without re-establish REM sleep muscle atonia.⁸⁹

A recent randomized placebo-controlled trial was conducted in order to determine the efficacy and safety of clonazepam for the treatment of probable RBD (pRBD) in patients with PD.

The primary outcome was the Clinical Global Impressions Improvement score at week four. No significant difference in scores between the clonazepam and placebo groups was detected. The conclusions of this study must be interpreted cautiously. In fact, the authors recruited pRBD patients without VPSG confirmation.⁹⁰

Very few studies have examined the effects of clonazepam on polysomnographic parameters. It has been previously reported in iRBD patients that 0.5 to 1 mg per day of clonazepam significantly improved the percentage of stage 2 sleep compared to baseline.^{135,136}

However, clonazepam can worsen cognitive impairment and sleep apnea and it should be used cautiously in patients with these symptoms.¹¹

Table 2 Main Findings Obtained from Different Neurophysiological Techniques in Patients with Isolated REM Sleep Behavior Disorder (iRBD), Parkinson's Disease with RBD (PDRBD), and Parkinson's Disease Without RBD (PDnoRBD)

Technique	iRBD	PDRBD	PDnoRBD
Electroencephalography (EEG)	Diffuse EEG slowing, more in occipital; higher delta and theta power, theta-band bursts; decreased alpha-band burst Lack of suppression of beta rhythms during phasic REM (increased cortical arousal) Increased EEG instability during REM Decreased fast, but increased slow, sleep spindles, or global density, during eye-closed wakefulness	Higher theta power; slowing of occipital frequency correlated with cognitive decline Global decrease in spindle density Higher delta and lower alpha power, more in central and occipital regions during phasic REM EEG slowing, especially during the phasic period, may predict phenoconversion rather than subjective RBD severity	No or mild/unspecific slowing
Motor evoked potentials (MEPs)	Reduced short-latency afferent inhibition, supporting cholinergic and cognitive dysfunction MEP disinhibition and hypofacilitation; correlation between disinhibition and muscle tone alteration	Reduced short-latency afferent inhibition, supporting cholinergic and cognitive dysfunction Increased MEP inhibition and decreased facilitation (GABAergic and glutaminergic change)	Lack of MEP intracortical facilitation, suggesting a more severe impairment of glutaminergic transmission than in PDRBD
Vestibular evoked myogenic potentials (VEMPs): masseter (mVEMP), ocular (oVEMP), and cervical (cVEMP) VEMPs	Severe alteration of mVEMP and oVEMP, implying the involvement of upper brainstem areas; correlation between REM sleep without atonia (RSWA) and VEMP	Delayed cVEMP and oVEMP compared to PDnoRBD; cVEMP scored higher in PDRBD than iRBD Phasic RSWA correlated with cVEMP; tonic RSWA with left oVEMP	No significant delay in cVEMP and oVEMP, bilaterally, compared to PDRBD
Other brainstem responses	Pupil and blink areas impacted before saccadic control (PD prodromes?) Abnormal prepulse modulation and auditory startle reflex	Altered pupil and blink behavior Blink reflex parameters did not relate to RBD	Startle reflex hyporeactivity
Vegetative tests	Dysfunction of intermediate severity between controls and PD	Autonomic dysfunction, often more severe than in PDnoRBD	Autonomic dysfunction, often less severe than in PDRBD
Cortico-muscular coherence (CMC)	Higher during REM sleep than controls (increased cortical locomotor drive)	Distinctive features of muscle atonia index, CMC, and cortico-cortical coherence	No comparison available between PDRBD and PDnoRBD
Event-related potentials	No difference compared to controls, at least at the early-middle stages	Occipital positive wave, nearly absent in controls.	No difference compared to PDRBD and controls

Melatonin is recommended as a safe complementary treatment option for patients with RBD. Melatonin and clonazepam were found to be effective in reducing the symptoms of RBD, but melatonin was better tolerated with fewer adverse reactions and greater reduction in injury.¹³⁷

Few studies are available on the therapeutic effects of melatonin on RBD. Melatonin is a hormone secreted by the pineal gland in a circadian pattern, influenced by dark environments with levels peaking during the middle of the night.¹³⁴

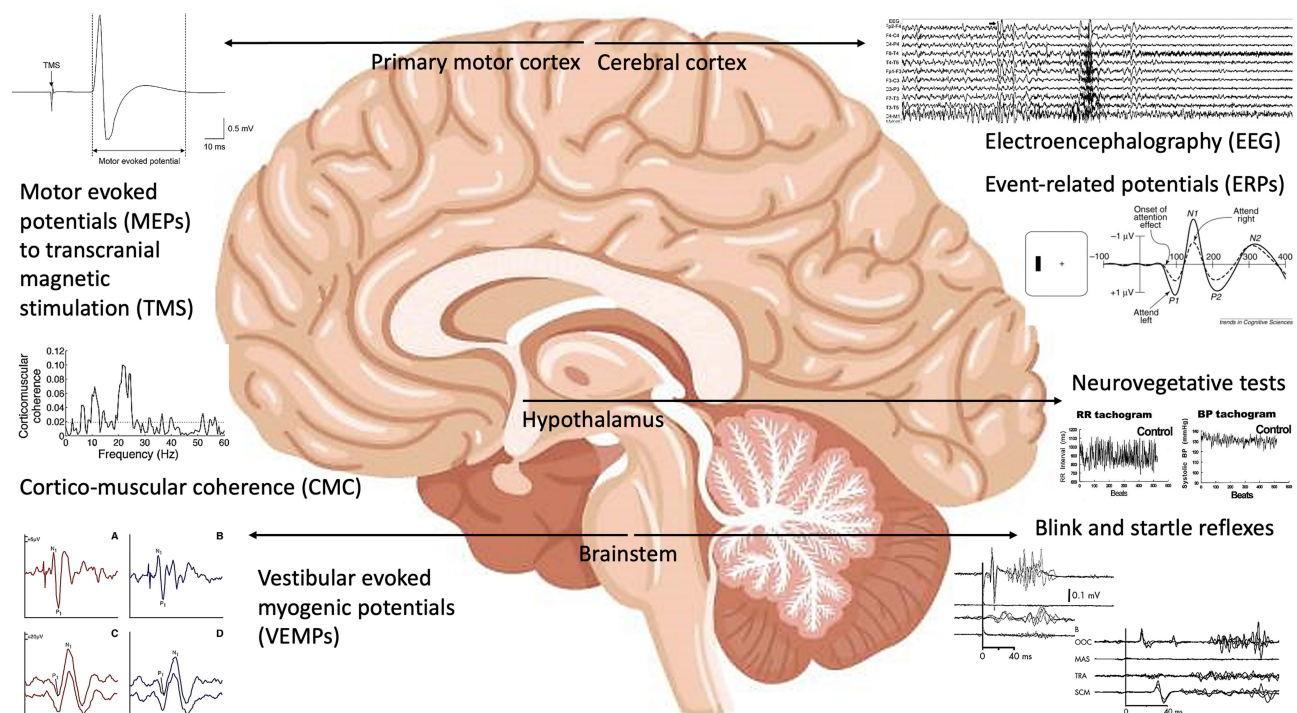


Figure 1 Neurophysiological findings in RBD population: Overview of the main electrophysiological techniques that have provided insights on the neurophysiological basis of RBD. Cortical activity is explored with conventional electroencephalography (EEG) and event-related potentials (ERPs). Cortico-muscular coherence (CMC) relates to the synchrony in the neural activity of brain's cortical areas and muscles, thus allowing to study the neural control of movement. Motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) specifically probe the excitation state of the primary motor cortex. Neurovegetative tests can be applied to functionally assess the hypothalamus, a key region for the central control of the autonomic nervous system. Finally, vestibular evoked myogenic potentials (VEMPs), as well as blink and startle reflexes, are suitable tools to evaluate the brainstem excitability.

Some studies have shown that 3 to 12 mg per day of melatonin can reduce RBD-related injuries with little side effects, though the numbers of RBD events has not decreased.^{134,137–140}

Evidence suggests that melatonin improves RBD by reducing the tonic EMG activity during REM sleep, the inhibition of gamma-aminobutyric acid, the stabilization of the circadian rhythm, the increased striatal bioavailability of L-dopa and modulation of skeletal muscles.¹⁴⁰

A recent randomized double-blind placebo-controlled trial was conducted to evaluate the efficacy of 4 mg slow-release melatonin in 30 patients with PD and RBD. The primary outcome was the difference in the total number of RBD events as assessed by the weekly CIRUS-RBD Questionnaire (item - 4). The trial shows that melatonin 4 mg per day did not have a large effect on the reduction of RBD in PD patients, but it is still unknown if other doses are ineffective.¹⁴¹

Ramelteon is an agonist of melatonin receptors that has a positive impact on idiopathic and secondary RBD. Recently, two studies have shown that Ramelteon improve clinical RBD symptoms and decrease RWA in two patients for which conventional therapies were contraindicated.^{142,143} Kashiwara et al showed that ramelteon improve nighttime sleep and PD motor performances according to UPDRS Part III scores.¹⁴²

Randomized controlled studies of dopaminergic agonists for RBD in PD are still missing. Available uncontrolled studies, including those using newer dopaminergic agonists, are considered inconclusive.¹³⁴

Dusek et al evaluated the impact of slow-release and immediate-release ropinirole on PD-related sleep disorders, including RBD. A total of 33 PD patients initially receiving immediate release ropinirole, followed by five to thirteen weeks of prolonged release ropinirole were investigated. The secondary outcome was to investigate the effects of slow-release versus immediate-release ropinirole on RBD symptoms assessed by RBDSQ. There was no statistically significant improvement in RBDSQ scores and RSWA.¹⁴⁴

An open-label study was conducted to assess the effect of rotigotine on RBD in PD patients PDRBD patients. Subjects were treated for approximately 28 weeks at increasing doses from 2 to 16 mg/24 h according to parkinsonism

response and tolerance. Patients were evaluated before and after treatment using the PSG, RBDSS, PDSS-2 and the REM sleep behavior disorder questionnaire-Hong Kong (RBDQ-HK) scales. At the end of the treatment, the PDSS-2, the overall RBDQ-HK scale scores decreased significantly. However, there were no objective changes in the motor variables assessed by PSG (percentage of RSWA) or RBDS.¹⁴⁵

Pramipexole affects REM sleep by increasing REM sleep latency and reducing total REM sleep time.¹⁴⁶ In patients with idiopathic RBD, pramipexole significantly decreased the frequency and severity of RBD symptoms and remained effective for 25 months.¹⁴⁷ In contrast, PD patients with RBD did not have any benefit.¹⁴⁸

In a prospective study, 11 PDRBD patients on levodopa monotherapy were treated with pramipexole. The effects on RBD were evaluated before and 3 months after stable pramipexole therapy through patient and bed partner interviews and blind assessment of video-polysomnography (VPSG) measures.¹³⁴ Before and 3 months after stable pramipexole therapy, effects on RBD were assessed through patients and bed-partners interviews and VPSG measures.

No significant changes in severity and frequency of RBD related motor and vocal behavior as well as frequency of unpleasant dreams were reported by patients and bed-partners. The VPSG analyses showed no difference in sleep measures related to RBD and the severity of abnormal behavior revealed by the videotape.¹⁴⁸

Currently rotigotine is the only dopaminergic agonist that has led to an improvement in the RBD symptoms in PD patients. That improvement appears to be due by improved nocturnal motor symptoms.¹⁴⁹

Donepezil and rivastigmine can also be considered for treating patients with RBD, particularly in patients with cognitive impairment.¹⁵⁰

The cholinesterase inhibitor rivastigmine has been used as a substitute treatment to melatonin and clonazepam. We found only one crossover double-blind study on the efficacy of rivastigmine in reducing the frequency of RBD episodes in PD.¹⁵⁰

Rivastigmine was administered through a transdermal patch (4.6 mg/24 hours) for 3 weeks to non demented PDRBD patients that were refractory to melatonin and clonazepam.

Rivastigmine has demonstrated a beneficial effect on the reduction of RBD events and the improvement of subjective night sleep, proving to be a viable alternative in the control of RBD in patients resistant to conventional therapies. Unfortunately, the sample size was too small to reach definitive conclusions.

These preliminary data should be evaluated cautiously, as cases of RBD induced by acetylcholinesterase inhibitors have been reported.

Interestingly, a reduction in the frequency of refractory RBD episodes have been reported in subjects with mild cognitive impairment, who participated in a placebo-controlled, cross-over pilot trial of Rivastigmine.¹⁵¹

Moreover, the donepezil, another acetylcholinesterase inhibitor, has shown an effectiveness in improving RBD symptoms.¹⁵²

Memantine may reduce the dream enactment frequency and the total REM sleep time.

A randomized controlled and multicenter study was conducted in order to assess the effectiveness of memantine on sleep disorders, including RBD in PD patients with dementia or DLB patients.¹³⁴ After 24 weeks of treatment, subjects who received memantine significantly improved restlessness during sleep when compared to placebo. Nevertheless, the absence of PSG, both at the screening stage and at the follow-up, compromised the reliability of these results. Indeed, the RBD was assessed through a single question "Is the patient physically active during sleep?".¹⁵³

In a pilot study the use of cannabidiol (CBD) in PDRBD patients at doses ranging from 75 to 300 mg for six weeks, caused a reduction of up to 80% in the frequency of the nocturnal behaviors assessed through the sleep diary.¹⁵⁴

Other drugs such as zopiclone (doses ranging from 3.75 to 7.5 mg) and sodium oxybate (doses ranging from 3 to 9 g) are also effective in RBD therapy, but their effectiveness has not been demonstrated in PD.¹⁵⁵

Some case reports indicate that 10 mg daily of temazepam may be effective in treating RBD symptoms.¹⁵⁵

There are also cases or small series that show the possible effectiveness of carbamazepine¹⁵⁶ and gabapentin¹⁵⁷ on RBD symptoms.

Antipsychotic drugs like quetiapine and clozapine have also been shown to be effective in patients with iRBD. However, there are no robust reports about their impact on RBD in PD.¹⁵⁸

In a recent randomized, double-blind placebo-controlled crossover trial, the 5-hydroxytryptophan (a precursor of serotonin) increased the overall percentage of REM sleep stage without a related increase of RBD episodes. Moreover, the self-reported RBD frequency and severity were improved during 5-hydroxytryptophan treatment.¹⁵⁹

The therapeutic effects of the Yi-Gan San, an herbal with gabaergic and serotonergic properties, has been described in iRBD.¹⁶⁰

As evidenced by previous studies, there have been major limitations in subjective quantification of RBD symptoms. In a recent observational cohort study a newly developed RBD symptom severity scale (Ikelos-RS) has been used in a large group of patients with iRBD.¹⁶¹

Moreover, a self-administered modified RBDQ scale (the timeframe of the scale were modified into the past 3-month period) has proven to be a sensitive tool for monitoring treatment progress over a brief period of time.¹³⁵ Table 3 summarizes the pharmacological treatment of RBD in PD patients.

Parkinson's Disease RBD Phenotype: Non-Pharmacological Management

RBD patients, both isolated and associated with PD, are at risk of injuries, to themselves or to bedpartner, related to complex-motor dream-enacting behaviors.

Table 3 Pharmacological Treatments of RBD in PD Patients

	Reccomended Dose	Benefits	Side Effects
Clonazepam	0.5–2 mg	Decrease RBD events; improve subjective nocturnal sleep; reduce phasic EMG activity	Morning sedation; falls; worsening of OSA(Obstructive Sleep Apnea); diurnal drowsiness.
Melatonin	3–12 mg	Reduce injuries associated with RBD; improve subjective night sleep	Light headache; daytime sleepiness; fatigue.
Ramelteon	8 mg	Decrease RBD episodes; improve subjective nighttime sleep; improve PD motor performances	Daytime sleepiness; aggravation of constipation; nausea; dizziness; delirium.
Rotigotine	2–16 mg	Decrease RBD events (no changes in percentage of RWA); improve PD motor and non-motor symptom; helps reduce pain.	Localized reactions; dyskinesia; headache; dizziness; diurnal drowsiness; tiredness; nausea.
Rivastigmine (patch)	4.6 mg/24 hours	Decrease RBD episodes; improve subjective nighttime sleep	Cholinergic adverse effects
Memantine	20 mg	Reduction of RBD events; improvement in cognitive functioning	Bradycardia; nausea
Cannabidiol	75–300 mg	Reduction of RBD-related events	No side effects.
5-hydroxytryptophan	50 mg–150 mg	Improvement of self-reported RBD frequency and severity	No side effects.
Gabapentin	300–800 mg	Reduction of RBD events	No side effects
Carbamazepine	300–800 mg	Improvement of RBD symptoms	No side effects
Zopiclone	3.75–7.5 mg	Reduction of RBD events	No side effects
Sodium oxybate	3–9 g	Long-term clinical improvement of RBD symptoms	No side effects
Temazepam	10 mg daily	Reduction of RBD events	No side effects
Yi-Gan San	2.5 g 3 times daily	Complete or significant improvement of RBD symptoms	No side effects.

Sleep protection measures are warranted to minimize the risk of injury to the patient and bedpartner. In order to improve the security of the bedroom, protective strategies such as the placement of mattresses on the ground or the securing of windows should be considered.¹⁶²

Regular physical exercise is advisable in patients with PD and sleep disorders. In a recent meta-analysis has been found that exercise had a significant positive effect on subjective sleep quality in people with PD.¹⁶³ Furthermore, it has been shown that intensive exercise may play a protective role through direct modulation of the accumulation of multiple proteins associated with neurodegenerative process. Since RBD is an early occurrence of a neurodegenerative disease caused by pathologic aggregates of α -synuclein, it would make sense to examine the potential neuroprotective effects of exercise with RBD patients.¹⁶⁴

A reduced prevalence of prodromal features associated with PD in patients who were more physically active has been described in a recent study. PD subjects who maintained a high level of physical activity during follow-up were less susceptible to be affected by RBD symptoms.¹⁶⁵

The benefits of multidisciplinary intensive rehabilitation treatment (MIRT) on sleep disorders in PD have been highlighted.¹⁴⁰ Specifically, the rehabilitation treatment included a wide range of aerobic exercises combined with relaxation techniques, stretching exercises, stability exercises focused on balance and gait.¹⁶⁶ However, research on exercise aimed at improving sleep disorders, including RBD, is still limited. Whereby the exercise modality, frequency, duration and intensity needed for sleep optimization are not known.¹⁶⁷

Patients with RBD have a low arousal threshold of REM sleep. A reduction in RBD symptoms and sleep-related injuries was reported in four patients with RBD through the use of customized bed alarms with a familiar voice to deliver a soothing message at the beginning of dream enactment behaviors (level III of evidence).¹⁶⁸

Many lines of evidence have demonstrated that deep brain stimulation (DBS) can ameliorate sleep quality in patients with PD.¹⁶⁹ Some studies shown that DBS of the PPN may modulate some non-motor functions, including REM sleep, mood, arousal and sleep-wake cycle.^{170,171} However, some studies suggest that PPN-DBS could contribute to worsening RBD in PD patients.¹⁷²

Conclusion

RBD offers a precious insight for the management of PD: not only its presence allows to individuate a population at risk of developing the disease, but also when the disease is conlabeled it's connected to a more aggressive phenotype for both motor and non-motor symptoms, especially cognitive impairment.

This can guide the physician to a more tailored treatment and follow up of PD patients, focusing on early intervention for the prevention and management of cognitive impairment.

Finally, iRBD is a unique cohort of patients ready to access to future trials of neuroprotective and disease modifying therapy.

Future research should focus on the creation of combination models and stratification of biomarkers in order to have easily accessible and reliable tools to select patients at risk of phenoconversion or to individuate early signs of cognitive impairment.

Final Remarks

- iRBD has an estimated risk to develop a neurodegenerative disease up to 90%, thus representing an ideal condition for testing new neuroprotective and disease-modifying drug.
- RBD seems to be a key clinical indicator of a body-first/diffuse-malignant phenotype, characterized by a more widespread neurodegenerative process and worse motor and non-motor symptoms of PD.
- RSWA, the neurophysiological hallmark of RBD, correlates with worse cognitive performances and MCI, and/or impaired attention and executive functions might predict early conversion to dementia.
- Some medications and non-pharmacological options have been found to have some therapeutic effects on RBD, although their overall impact is still unsatisfactory and, therefore, new evidence-based approaches are needed.

- Several clinical, neurophysiological, neuroimaging, biological, and genetic biomarkers have been individuated, although a consensus on the identification of one or more biomarkers to be translated in clinical practice is still lacking.

Disclosure

The authors report no conflicts of interest in this work.

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