

Clinical Recognition and Neuropathological Mechanisms of REM Sleep Behavior Disorder as a Prodromal Marker of Parkinson's Disease

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Abstract

Rapid eye movement sleep behavior disorder (RBD) is a sleep disorder characterized by dream-enacting behaviors and loss of muscle atonia during REM sleep. It is currently recognized as a significant prodromal marker for α -synucleinopathy-related neurodegenerative diseases, particularly Parkinson's disease (PD) and dementia with Lewy bodies. This article comprehensively reviews clinical identification strategies for RBD as a prodromal marker of PD, potential neuropathological mechanisms, and recent advances in neuroimaging and biomarkers. Furthermore, it evaluates interventions targeting RBD and their clinical implications. By integrating the latest research findings, this paper aims to provide a systematic theoretical basis and clinical reference for the early identification, risk stratification, and development of neuroprotective strategies for PD.

Keywords

REM Sleep Behavior Disorder, Parkinson's Disease, Neuropathological Mechanisms, Biomarkers, Alpha-Synucleinopathy

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a type of parasomnia, with its fundamental pathophysiological mechanism lying in the loss of skeletal muscle atonia that normally accompanies rapid eye movement (REM) sleep. This allows patients to physically act out vivid dream content; these actions are often vigorous, such as punching or kicking, and may sometimes include aggressive behaviors.

Additionally, patients may exhibit involuntary movements of the face, perioral region, or limbs, which can pose safety risks to themselves or others [1]. Currently, polysomnography (PSG) is regarded as the gold standard for diagnosing RBD. This examination helps more accurately distinguish between patients with and without RBD by quantifying the percentage of REM sleep periods that meet the criteria for REM sleep without atonia (RWA) [2]. The neurophysiological basis of RWA is associated with dysfunction in brainstem nuclei responsible for regulating muscle relaxation during REM sleep, particularly structures such as the sublaterodorsal nucleus and the ventral tegmental area [3] [4]. In clinical practice, RBD must be clearly classified based on its etiology and associated conditions. Isolated RBD (iRBD) refers to a form of RBD occurring without any identifiable neurological disorder or known causative factor. Secondary RBD is caused by a specific underlying etiology. Furthermore, unlike the aforementioned two scenarios, some PD patients develop RBD (PD-RBD) during the disease course. This comorbid condition is widely regarded as a more aggressive clinical phenotype, characterized primarily by faster disease progression and a more severe burden of non-motor symptoms. These three categories have distinct diagnostic, prognostic, and therapeutic implications.

Although relatively rare in clinical practice, focal lesions of the brainstem (e.g., ischemic foci) may induce secondary RBD. This suggests that for cases with atypical clinical manifestations and no evidence of neurodegenerative diseases, the possibility of structural etiologies should be considered [3]. Furthermore, RBD is frequently comorbid with obstructive sleep apnea (OSA), and RWA may exert a protective effect on respiratory function in OSA patients by maintaining upper airway muscle tone; this phenomenon is termed the “respiratory RWA benefit” [5]. Studies indicate that patients with iRBD are highly likely to develop neurodegenerative diseases characterized by alpha-synuclein pathology within several years to over a decade after diagnosis, with PD being one of the primary outcomes [6]. In fact, iRBD is considered the most significant prodromal marker for alpha-synucleinopathies, including PD, dementia with Lewy bodies, and multiple system atrophy [7]. Long-term follow-up studies show that the conversion rate of iRBD patients to overt neurodegenerative diseases can exceed 96% over a 15-year period [8]. This extremely high conversion rate makes RBD a unique and valuable window for studying the preclinical stage of PD. A deep understanding of the clinical features and neuropathological changes in RBD holds significant scientific importance for elucidating the pathogenesis of PD, achieving ultra-early diagnosis, and developing disease-modifying therapies. From the perspective of neuropathological mechanisms, iRBD is essentially an early-stage alpha-synucleinopathy [9]. Pathological changes typically originate in the lower brainstem (such as the subcoeruleus nucleus), the region containing the key neural circuits controlling REM sleep muscle atonia; subsequently, the alpha-synuclein pathological process may spread rostrally along specific pathways, progressively involving brain regions such as the substantia nigra, limbic system, and cerebral cortex. Genetic analyses reveal that iRBD shares only partial genetic overlap with PD and dementia with

Lewy bodies, suggesting that iRBD patients may represent a specific subgroup [10]. Genome-wide association studies have identified multiple genetic loci associated with iRBD, among which the GBA1 pathway may play a central role. Furthermore, further analysis using genomic structural equation modeling indicates that iRBD not only possesses partially unique genetic characteristics but also exhibits partial genomic overlap with alpha-synucleinopathies, implying that its genetic architecture may lie within a continuous risk spectrum [8]. These findings provide a crucial theoretical basis for risk stratification and intervention at the earliest stages of the disease. This review focuses on the central theme of RBD serving as a precursor marker of PD across different clinical contexts, providing an in-depth exploration from five perspectives: clinical identification, neuropathological basis, neuroimaging and biochemical biomarkers, impact on disease progression, and implications for clinical management. By systematically synthesizing existing evidence, this review aims to establish a framework for the clinical identification and management of this critical prodromal syndrome and highlights its pivotal role in future neuroprotective therapeutic trials.

2. Clinical Identification of RBD and Epidemiological Evidence as a Precursor Marker

2.1. Clinical Diagnostic Criteria and Screening Tools

The diagnosis of REM sleep behavior disorder relies on video polysomnography, the core of which is the recording of excessive phasic or tonic electromyographic activity during REM sleep, that is, the absence of muscle atonia during REM sleep. Both the American Academy of Sleep Medicine and the International RBD Research Group have established detailed diagnostic criteria and technical guidelines, emphasizing the indispensable role of video polysomnography in detecting abnormal behaviors and quantifying RWA [11]. Video polysomnography not only confirms the presence of RWA but also aids in differentiating other conditions that may mimic RBD symptoms, such as obstructive sleep apnea, non-REM paroxysmal sleep disorder, nocturnal seizures, and periodic limb movement disorder. In clinical practice, quantitative assessment of RWA is crucial; sleep reports should specify the percentage of REM sleep episodes meeting RWA criteria to enable precise patient subtype classification [2]. As technology continues to advance, automated RWA quantification methods based on convolutional neural networks have been proven to effectively identify RBD patients and can be applied to front-line screening [12]. However, despite the broad application prospects demonstrated by automated methods, visual rating strategies, particularly protocols for assessing mentalis or flexor digitorum superficialis phasic activity, remain regarded as the gold standard in terms of diagnostic efficacy [13].

Questionnaire tools play a pivotal role in population screening and initial clinical evaluation. Tools such as the RBD screening questionnaire and single-question RBD screening assays are widely utilized. An epidemiological study conducted by Taeko Sasai-Sakuma *et al.* among Japanese elderly populations demon-

strated an iRBD prevalence rate of approximately 1.23% based on questionnaire screening [14]. However, the accuracy of questionnaires may be influenced by application contexts, such as subjects' awareness of their own RBD symptoms, underscoring the need for cautious interpretation of questionnaire-based screening results [15]. Studies have confirmed that individuals classified as "highly likely RBD" through questionnaire screening exhibit elevated prevalence rates among Parkinson's disease patients and correlate with more severe non-motor symptom burdens [16]. In the clinical identification of RBD, attention should be paid to differential diagnosis with other parasomnias, such as sleep terrors and sleepwalking, which are non-rapid eye movement (NREM) parasomnias [17]. These parasomnias may also be associated with an increased risk of Parkinson's disease, suggesting that dysregulation of arousal during sleep could be a broader manifestation of Parkinson's disease-related neurodegeneration [18]. Notably, in cases presenting with complex sleep disorder networks (where RBD coexists with other paradoxical sleep patterns like sleepwalking), the odds ratio for Parkinson's disease is significantly elevated, further highlighting the complexity of sleep disturbances as early indicators of neurodegenerative processes [19].

2.2. Risk and Predictive Factors for iRBD Transition to PD

Extensive research has confirmed that iRBD is the most prominent presymptomatic clinical marker for α -synucleinopathies such as Parkinson's disease, Lewy body dementia, and multiple system atrophy. Given that its phenotypic transition often occurs within ten years or even earlier before clinical diagnosis, iRBD provides a critical time window for early diagnosis and intervention. Over 90% of iRBD patients eventually progress to these neurodegenerative disorders, with the risk of transition increasing steadily as the disease duration extends [20]. Therefore, identifying predictive factors for the progression of iRBD to Parkinson's disease holds significant clinical importance. The longitudinal cohort study led by Monica Puligheddu systematically collected various biological markers to stratify the risk of phenoconversion in patients with iRBD, further emphasizing the important role of iRBD in the prodromal stage of neurodegenerative diseases [21].

The factors predicting progression to PD in iRBD patients exhibit multidimensional characteristics, collectively delineating a comprehensive clinical picture of the presymptomatic stage of PD. Among non-motor symptoms, olfactory dysfunction, autonomic nervous system abnormalities, and mild cognitive impairment (particularly visuospatial and executive function deficits) are frequently regarded as key prognostic indicators. Meanwhile, neuroimaging biomarkers, including molecular imaging of dopaminergic system decline in the substantia nigra and striatum (e.g., ^{18}F -AV-133 PET), can identify potential neurodegenerative changes in iRBD patients, thereby supporting the diagnosis of presymptomatic PD [22]. An eight-year longitudinal cohort study conducted by Gulcin Benbir-Senel *et al.* over a period of 8 years systematically observed 45 patients. The results revealed that in iRBD patients over the age of 60 who also presented with loss of

smell and constipation, the odds ratio for phenotypic conversion risk was significantly elevated, reaching 44.8. Additionally, the study identified a critical neurophysiological biomarker: a decrease in alpha power on electroencephalogram (EEG) in the occipital region during wakefulness and REM sleep, which showed a significant correlation with phenotypic conversion. This finding further underscores the potential value of neurophysiological biomarkers in predicting the risk of iRBD conversion [23]. Kuang B's systematic review further confirmed that when RBD is comorbid with other parasomnias (such as sleepwalking), the odds ratio for phenoconversion to Parkinson's disease is significantly elevated. This finding suggests that such complex patterns of sleep disorder comorbidity may serve as prodromal markers or risk biomarkers of neurodegenerative pathology [19]. The combined application of the aforementioned clinical features and relevant biomarkers provides a theoretical basis for conducting early neuroprotective treatment trials in high-risk populations such as those with iRBD, and establishes a foundation for patient stratification.

In clinical practice, accurately distinguishing iRBD associated with prodromal α -synucleinopathy from RBD caused by other etiologies or mimicking conditions is equally crucial for assessing an individual's risk of converting to PD. First, antidepressants—particularly selective serotonin reuptake inhibitors (SSRIs)—can induce or exacerbate RBD symptoms, which may improve or resolve after discontinuation or switching to medications with less impact on RBD; such patients generally have a lower risk of PD conversion than those with true iRBD. Second, a minority of RBD cases may result from focal brainstem lesions (e.g., stroke, tumor, or demyelinating disease), presenting acutely with other brainstem localizing signs, and neuroimaging is essential to exclude such structural lesions. Third, OSA is one of the most common mimickers of RBD, where the associated behaviors are typically closely linked to respiratory event-related arousals and are not accompanied by REM sleep without atonia; effective treatment of OSA can significantly improve these behaviors. Finally, non-REM (NREM) parasomnias (such as sleep terrors and sleepwalking) predominantly occur during the first third of the night in deep NREM sleep, involving simple and stereotyped behaviors without dream recall the next day, whereas RBD predominantly occurs during the latter third of the night in REM sleep, featuring complex behaviors with vivid and recallable dream content; video-polysomnography remains the gold standard for differentiation. Accurate differentiation of these conditions enables clinicians to identify patients with true high-risk iRBD driven by α -synuclein pathology, thereby avoiding the inappropriate inclusion of low-risk or reversible RBD patients in PD prodromal monitoring cohorts, allowing for more precise risk stratification and prognostic interpretation.

3. The Neuropathological and Neurochemical Basis of RBD

3.1. Lesions of Brainstem Nuclei and Pathology of α -Synuclein

The core pathological mechanism of RBD lies in the selective and early neuro-

degenerative changes occurring in specific nuclei within the brainstem that regulate muscle tone during REM sleep. Under normal conditions, these nuclei emit signals during REM sleep, mediated by inhibitory neurons in the pontine reticular formation and spinal cord, resulting in a state of muscle hypotonia. In the early stages of RBD, these nuclei first exhibit deposition of misfolded proteins such as Lewy bodies, leading to progressive neuronal loss and dysfunction [24]. This pathological damage disrupts the inhibitory pathways governing muscle tone during REM sleep, allowing dream content to be unrestrainedly released via motor pathways, thereby giving rise to dream-enacting behaviors. This pathological process typically precedes other motor or cognitive symptoms, making it a significant prodromal marker of PD. Notably, these pathological changes usually occur before the marked loss of dopaminergic neurons in the substantia nigra, providing a plausible neuropathological explanation for why RBD symptoms may manifest years or even decades earlier than the classic motor symptoms of Parkinson's disease. The α -synuclein pathology within these nuclei likely follows a specific neural pathway, spreading from the lower brainstem to higher brain regions (e.g., the substantia nigra and cerebral cortex), forming the basis for the progression of synucleosis. Neuroimaging evidence further supports that RBD involves multisystem neurodegenerative processes, with pathological changes extending beyond the brainstem to include the substantia nigra-striatal system, limbic system, and cortex [25]. Therefore, early involvement of brainstem nuclei, particularly the sublaterodorsal nucleus (SLD) and the giant reticular nucleus, leads to reduced output of inhibitory signals (such as glycine and GABA) to spinal motor neurons, impairing effective inhibition of muscle activity and thereby inducing dream-enacting behaviors during REM sleep. This mechanism elucidates the neuroanatomical basis of RBD as a prodromal sign of Parkinson's disease, with its pathological origin residing in a specific sleep-muscle tone regulatory network within the brainstem.

3.2. Dysregulation of the Neurotransmitter System: Beyond Dopamine

In addition to the classical dopamine system, early imbalances in other neurotransmitter systems also play a critical role in the pathophysiological processes of RBD, suggesting that the PD subtype associated with RBD involves broader and more early-stage multisystem neurochemical disturbances. In both RBD patients and PD patients with concomitant RBD, not only are functional alterations observed in the dopaminergic and cholinergic systems, but abnormalities in cerebral blood flow and glucose metabolism are also present. Notably, early involvement of the cholinergic system is particularly prominent, with degenerative changes in the basal nucleus of Meynert (nucleus basalis of Meynert, NBM) closely linked to cognitive decline in patients with idiopathic RBD. Degeneration of cholinergic neurons in this nucleus leads to a significant reduction in acetylcholine levels in the cerebral cortex (particularly in the prefrontal and hippocampal regions). As

acetylcholine is a key neurotransmitter regulating attention, learning, and memory, its deficiency directly impairs synaptic plasticity, thereby affecting information encoding and integration in neural networks. Concurrently, reduced cholinergic afference weakens the cortical inhibitory effects on the brainstem and limbic system, exacerbating neuroinflammation and oxidative stress, thereby collectively accelerating cognitive decline. Although the specific circuit mechanisms require further elucidation, cholinergic dysfunction is recognized as a pivotal link between RBD and subsequent cognitive impairment, constituting an early pathological basis [26]. Additionally, abnormalities in the glutamatergic system have garnered increasing attention. Du L *et al.* established a PD rat model through chronic tetrandrine treatment and found that the progressive degeneration of glutamatergic neurons in SLD is a key contributor to the onset of RBD symptoms [27]. This finding strongly suggests that an imbalance in glutamate signaling plays a pivotal role in the development of RBD symptoms. Although current research on changes in the availability of metabotropic glutamate receptor 5 (mGluR5) remains in its preliminary stages, animal experimental evidence robustly supports the critical role of glutamatergic neurotransmission in the pathological mechanisms of RBD. These extensive neurochemical alterations that extend beyond the dopamine system may constitute the biological basis for the more aggressive clinical phenotype characteristic of RBD-associated Parkinson's disease subtypes. Therefore, elucidating the mechanisms underlying these neurotransmitter system dysregulations holds significant translational medical value for developing multi-target intervention strategies targeting the prodromal stage of PD.

4. Advances in Neuroimaging and Biomarker Research

4.1. Structural and Functional Magnetic Resonance Imaging Findings

Magnetic resonance imaging (MRI) studies have revealed specific gray matter volume alterations in patients with PD-RBD. Wang *et al.*, combining voxel-based morphometry (VBM) with functional connectivity (FC) analysis, found that compared to PD patients without RBD, those with PD-RBD exhibited significantly reduced gray matter volume in the left middle temporal gyrus and bilateral cuneus—regions closely associated with dream processing and visuospatial functions, respectively—and these volumetric changes may be linked to RBD symptoms and cognitive impairment, while their FC analysis further uncovered a unique pattern of brain network reorganization in PD-RBD patients, characterized by enhanced functional connectivity between the left middle temporal gyrus and the right postcentral gyrus alongside weakened connectivity between the bilateral cuneus and the right middle frontal gyrus, suggesting an RBD-specific mechanism of network reorganization [28]. A separate VBM study by Donzuso *et al.* confirmed that both iRBD and PD-RBD patients exhibit gray matter alterations in multiple brain regions, including the frontal and temporal lobes, compared to healthy controls, indicating the involvement of cortical structures related to sleep cycle and

REM phase regulation and a potential common structural basis linking iRBD and PD [29]. Additionally, resting-state functional MRI (rs-fMRI) studies indicate functional abnormalities within the striato-cortical network in iRBD patients, particularly connectivity anomalies in the striato-frontal network that are closely associated with deficits in attention and executive function [30], collectively suggesting that RBD is closely associated with the disruption and reorganization of functional coupling between specific brain regions.

The Magnetic Resonance Parkinson Index (MRPI), as an imaging metric based on brainstem structural measurements, has demonstrated significant potential value in biomarker research for RBD. Although current literature has not directly investigated the quantitative assessment of MRPI, multiple studies have unequivocally highlighted the central role of brainstem structural abnormalities in the pathological mechanisms of RBD. Garcia-Gomar MG *et al.* employed high-field (7 Tesla) magnetic resonance imaging and found that in patients with iRBD, structural connectivity impairments were observed in several brainstem nuclei closely associated with REM sleep-related muscle tone loss, including the subthalamic nucleus and medullary reticular formation [31]. Nepozitek J's study further confirmed through quantitative magnetization mapping that iRBD patients exhibited significantly elevated magnetization values in bilateral substantia nigra, red nucleus, and ventral tegmental area; notably, the magnetization value in the substantia nigra region showed a positive correlation with the severity of REM sleep muscle tone loss, suggesting that increased iron deposition may mediate RBD symptoms [32]. Additionally, Nobileau A utilized neuro-melanin-sensitive MRI technology to observe reduced signal intensity in the locus coeruleus/subthalamic nucleus complex among patients with Parkinsonian syndromes (including Parkinson's disease with RBD, progressive supranuclear palsy, and multiple system atrophy) compared to healthy controls, with the presence of RBD correlating with lower signal intensity [33]. These structural and microstructural alterations in the brainstem demonstrate clear clinical significance, providing robust support for RBD as an imaging biomarker reflecting early brainstem involvement.

4.2. Molecular Imaging and Metabolic Patterns

Single-photon emission computed tomography imaging of dopamine transporters has confirmed that patients already exhibit loss of dopaminergic terminals in the striatum even during the iRBD phase, indicating a high risk of progression to overt Parkinson's disease [34]. However, increasing evidence suggests that the impact of RBD on cognitive functions (such as processing speed) in patients with PD may be independent of striatal dopamine levels, highlighting the importance of non-dopaminergic mechanisms in RBD-related symptoms. Research by De Micco R indicates that patients with PD and RBD exhibit altered functional connectivity within and between large-scale neurocognitive networks, including the default mode network, the frontoparietal network, and the salience network; these alterations emerge early in the disease course, even in the absence of overt cognitive

impairment [35]. These findings suggest that RBD-associated cognitive impairment involves complex cortical and subcortical network dysfunction, extending beyond mere striatal dopamine depletion.

Fluorodeoxyglucose positron emission tomography (FDG-PET) also holds critical value in revealing the unique brain metabolic patterns of RBD. Rus T's study demonstrated that the brain metabolic patterns defined in newly diagnosed PD patients with RBD can effectively predict the progression to overt neurodegenerative disease in iRBD patients. Moreover, compared to the classic PD-related metabolic patterns derived from long-term PD patients, these metabolic characteristics identified in early-stage PD with RBD exhibit stronger predictive power. This suggests that preclinical metabolic patterns possess distinct features and may more sensitively capture pathophysiological changes during the disease onset stage [36]. Yoon EJ's prospective cohort study further confirmed that in patients with iRBD, the subgroup with mild cognitive impairment exhibited relative hypometabolism in extensive brain regions, including the bilateral inferior parietal lobules, lateral and medial occipital cortices, and middle-inferior temporal cortices. More importantly, hypometabolism in the occipital pole, medial occipital lobe, and precuneus was significantly associated with a high risk of conversion to PD or dementia with Lewy bodies. These findings highlight the clinical potential of FDG-PET in identifying iRBD subgroups at high risk of conversion [37]. Thus, molecular imaging-based metabolic pattern analysis, particularly those specific patterns derived from preclinical patients, provides a powerful tool for pre-symptomatic risk stratification and early intervention.

5. The Impact of RBD on the Disease Progression and Phenotype of PD

PD accompanied by RBD is widely recognized as a more aggressive clinical phenotype, characterized by faster disease progression and a heavier burden of non-motor symptoms. In terms of motor symptoms, patients with this condition exhibit a significantly higher annual deterioration rate. A study by Pilotto A, which measured plasma neurofilament light chain (NfL) levels, found that PD patients with elevated NfL levels were associated with faster motor progression, with a markedly greater degree of deterioration over two years as measured by the Motor Impairment Association Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) scores compared to the NfL-normalized group [38]. This rapid decline in motor function is linked to a broader neuropathological basis, involving not only the substantia nigra-striatal dopamine pathway. A longitudinal dopamine transporter (DAT) imaging study of PD patients with probable RBD by Cao R *et al.* revealed that, compared to PD patients without RBD, those with RBD not only exhibited more severe striatal dopaminergic deficits at baseline but also showed faster DAT loss across all striatal subregions (including the caudate nucleus and putamen) during the four-year follow-up, with less pronounced interhemispheric asymmetry in the putamen, suggesting a more diffuse and symmetrical

pathological process [39]. The extensive nature of this pathology is directly reflected in more severe non-motor symptoms. Early RBD has been recognized as a robust predictor of a malignant non-motor phenotype. Patients with PD exhibiting early RBD demonstrate significantly higher incidences of cognitive impairment, apathy, hallucinations, depression, anxiety, impulse control disorders, and autonomic dysfunction [40]. Clinical classification studies based on motor and non-motor symptoms categorize PD into the predominantly mild motor type, intermediate type, and diffuse malignant type. Patients with the diffuse malignant type often present with features such as RBD and exhibit poorer quality-of-life scores. This phenotypic heterogeneity stems from earlier-onset and more extensive neuropathological changes involving multiple regions, including the brainstem, limbic system, and cortex, rather than solely the substantia nigra-striatal system [41]. Consequently, PD with RBD represents a “malignant” phenotype characterized by a distinct clinical trajectory and pathological basis.

6. Clinical Management Insights and Future Directions

6.1. Diagnostic Assessment and Risk Stratification Strategy

For middle-aged and elderly patients with newly diagnosed RBD, systematic neurological evaluation is the critical first step in identifying it as a prodromal sign of PD. Video polysomnography (vPSG) serves not only as a standard tool for diagnosing RBD and quantifying RWA but also as the gold diagnostic standard. A comprehensive evaluation should include detailed sleep history collection and neurological physical examination, as well as olfactory function testing, cognitive assessment, and emotional status screening. Research by Nigam M *et al.* revealed that patients with iRBD exhibit not only olfactory impairment but also frequent gustatory dysfunction, which occurs independently of olfactory deficits and demonstrates severity comparable to that seen in PD patients [42]. Cognitive assessment is equally vital; the Montreal Cognitive Assessment Scale (MoCA) has demonstrated excellent psychometric properties in iRBD patients, effectively identifying mild cognitive impairment (MCI) and predicting the risk of progression to Lewy body dementia (DLB). Furthermore, emotional disturbances are highly prevalent in iRBD and closely associated with REM-phase paroxysmal events, highlighting both the role of sleep in emotional regulation and its significant clinical implications in prodromal neurodegenerative processes.

To achieve precise risk stratification, it is essential to integrate multidimensional clinical features and biomarkers. Regarding clinical features, constipation is a common non-motor symptom in patients with iRBD; the severity of constipation assessed by the Constipation Assessment Scale-J (CAS-J) independently predicts the time to progression from iRBD to PD or DLB. In biomarker testing, seed amplification techniques for α -synuclein (α -syn), such as RT-QuIC, demonstrate high sensitivity and specificity in both cerebrospinal fluid and skin biopsies, effectively identifying α -syn pathology in iRBD patients, with positive results strongly correlated with supporting clinical features such as hyposmia and abnor-

mal dopamine transporter imaging [43]. Dopamine transporter single-photon emission computed tomography (DaT-SPECT) is one of the strongest risk factors for predicting iRBD progression. Additionally, fluorodeoxyglucose positron emission tomography (FDG-PET) studies have shown reduced metabolic levels across extensive brain regions associated with mild cognitive impairment in iRBD patients, particularly in the occipital and parietal lobes, which serves as an effective predictor of progression to PD/DLB. By integrating these clinical features, neuropsychological assessment results, humoral biomarkers, and neuroimaging data, personalized transformation risk prediction models can be developed, enabling precise stratification of the iRBD population and identifying high-risk individuals for early intervention trials.

6.2. Outlook on Therapeutic Intervention and Neuroprotective Trials

The core objective of symptomatic management for RBD is to ensure the safety of both the patient and their co-sleeping partner in the bedroom. Specific measures include removing sharp objects from the room, placing soft cushions on the floor, and installing bed rails. Regarding pharmacological interventions, according to a systematic review published by the American Academy of Sleep Medicine, clonazepam and melatonin are currently the primary drug options for managing RBD [44]. However, caution is advised when using clonazepam due to its potential adverse effects, such as daytime sleepiness, impaired cognitive function, and increased risk of falls. Melatonin, in addition to serving as a first-line symptomatic treatment, may exhibit cell-protective effects at high doses; however, its efficacy in delaying the progression of α -synucleinopathy requires further investigation. Exploration of novel therapeutic targets, such as metabotropic glutamate receptor 5 (mGluR5), is ongoing, but mature clinical applications are currently lacking. Notably, commonly used medications like levodopa may be associated with more vivid or disturbing dreams, while evidence regarding the impact of pramipexole on dream content remains limited. Therefore, treatment decisions must be individualized, and drug side effects should be closely monitored.

The key future direction for research lies in establishing the iRBD population as an ideal trial cohort for neuroprotective or disease-modifying therapies. Given that iRBD serves as the most specific prodromal marker of alpha-synucleinopathy, over 90% of iRBD patients progress to PD, DLB, or multiple system atrophy (MSA) within a decade. Intervention prior to the onset of irreversible motor symptoms holds promise for delaying or preventing PD progression, marking a new era of “prodromal intervention” in PD treatment. Currently, multiple clinical trials aimed at delaying iRBD progression are underway. To successfully advance such trials, precise patient stratification and rational biomarker selection are critical. For example, the combined use of attention/working memory cognitive assessments with DaT-SPECT imaging metrics can effectively identify high-risk patients, thereby optimizing clinical trial design [45]. Additionally, reproducible olfactory function

assessments, plasma glial fibrillary acidic protein (GFAP) levels, and neurofilament light chain (NfL) levels have been demonstrated to enhance risk stratification and predict progression to DLB [46] [47]. These advances lay the foundation for evaluating the efficacy of disease-modifying therapies targeting α -synuclein pathology (e.g., α -syn aggregation inhibitors, immunotherapies) or other pathogenic pathways (e.g., mitochondrial function, neuroinflammation) during the early stages, and also demonstrate broad prospects for ultimately altering the course of neurodegenerative diseases.

Certainly, several heterogeneity limitations must be considered when translating the aforementioned research findings into clinical practice. First, PSG scoring criteria vary across different sleep centers, and the quantification algorithms for RWA—such as proprietary software or manual scoring rules—remain inconsistent, making it difficult to standardize diagnostic thresholds. Second, the inclusion criteria, scanning parameters, and interpretation methods for imaging cohorts (e.g., DaT-SPECT, FDG-PET) differ significantly, limiting the comparability of results across studies. Finally, the reproducibility of biomarkers—particularly the detection protocols and positive cutoff thresholds for α -synuclein seed amplification assays in cerebrospinal fluid and skin biopsies—lacks large-scale multicenter validation, and their performance varies across ethnicities, ages, and patient comorbidities. These factors contribute substantially to the often overly optimistic nature of current translational claims. Future efforts should focus on establishing a unified evaluation framework through prospective, standardized multicenter cohorts (e.g., the International RBD Study Group) to enhance the robustness and clinical applicability of risk prediction models.

7. Summary and Outlook

In summary, as the most distinctive prodromal sign of PD, the core mechanism of RBD lies in the early invasion of α -synuclein pathology in brainstem nuclei, leading to the loss of normal inhibitory control over muscle tone during REM sleep. This discovery not only deepens our understanding of the pathological initiation stage of PD but, more critically, identifies a unique and more aggressive subpopulation of the disease. PD patients with comorbid RBD exhibit faster motor function deterioration, a heavier burden of non-motor symptoms, and more widespread neurotransmitter system disturbances—the scope of involvement extends beyond the classic dopaminergic pathways to include glutamatergic and cholinergic systems. This suggests that in clinical practice and research design, RBD should not be regarded merely as an isolated sleep disorder but rather as an early, active, and more destructive manifestation of systemic neurodegenerative processes. Currently, the combined application of multimodal neuroimaging techniques (e.g., assessments based on MRPI indices and specific brain metabolic patterns) with emerging biochemical biomarkers enables unprecedented precision in identifying high-risk individuals at the preclinical stage and predicting their progression toward overt Parkinson's disease. Such integrated strategies lay a solid

foundation for ultra-early intervention. Clinical management should adopt a dual approach: on one hand, controlling RBD symptoms and ensuring patient safety; on the other hand, conducting systematic evaluation and long-term dynamic monitoring of potential neurodegenerative changes. It is noteworthy that the population with idiopathic RBD provides an extremely valuable “golden window period” for evaluating disease-modifying therapies, which has become the most promising critical stage for halting or even reversing the progression of Parkinson’s disease.

Future research should focus on elucidating the specific α -synuclein pathological diffusion mechanisms driving RBD onset to identify the underlying causes of the more severe disease course in such patients. Concurrently, it is essential to identify and validate a combination of earlier biomarkers with enhanced sensitivity and specificity to optimize risk stratification and prognostic prediction. Ultimately, this will facilitate the development of effective neuroprotective strategies for the prodromal stage of PD, facilitating their transition from rigorous clinical trials to widespread clinical practice. The key to reconciling existing research perspectives lies in understanding the dialectical relationship between the high specificity of RBD as a prodromal marker of PD and the heterogeneity among its disease subtypes. Future studies should fully account for this heterogeneity, validate the generalizability of biomarkers through refined stratification strategies, and evaluate the differential efficacy of treatment regimens, thereby achieving genuine early diagnosis and precision intervention for PD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Barone, D.A. and Henchcliffe, C. (2018) Rapid Eye Movement Sleep Behavior Disorder and the Link to α -Synucleinopathies. *Clinical Neurophysiology*, **129**, 1551-1564. <https://doi.org/10.1016/j.clinph.2018.05.003>
- [2] Sobreira-Neto, M.A., Stelzer, F.G., Gitaí, L.L.G., Alves, R.C., Eckeli, A.L. and Schenck, C.H. (2023) REM Sleep Behavior Disorder: Update on Diagnosis and Management. *Arquivos de Neuro-Psiquiatria*, **81**, 1179-1194. <https://doi.org/10.1055/s-0043-1777111>
- [3] Biscarini, F., Montini, A., Antelmi, E., Vandi, S., Pizza, F. and Plazzi, G. (2022) REM Sleep Behavior Disorder with Predominant Nightmares in a Patient with Ischemic Pontine Lesions. *Journal of Clinical Sleep Medicine*, **18**, 945-948. <https://doi.org/10.5664/jcsm.9762>
- [4] Figorilli, M., Lanza, G., Congiu, P., Lecca, R., Casaglia, E., Mogavero, M.P., *et al.* (2021) Neurophysiological Aspects of REM Sleep Behavior Disorder (RBD): A Narrative Review. *Brain Sciences*, **11**, Article 1588. <https://doi.org/10.3390/brainsci11121588>
- [5] Giardino, D.L., Fasano, P. and Garay, A. (2021) The “Respiratory REM Sleep without Atonia Benefit” on Coexisting REM Sleep Behavior Disorder—Obstructive Sleep Apnea. *Sleep Science*, **14**, 181-185. <https://pubmed.ncbi.nlm.nih.gov/34381583/>

- [6] Howell, M.J. (2020) Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Parasomnias. *Continuum*, **26**, 929-945. <https://doi.org/10.1212/con.0000000000000896>
- [7] Hu, M.T. (2020) REM Sleep Behavior Disorder (RBD). *Neurobiology of Disease*, **143**, Article ID: 104996. <https://doi.org/10.1016/j.nbd.2020.104996>
- [8] Gaudio, A., Gotta, F., Ponti, C., Geroldi, A., La Barbera, A. and Mandich, P. (2025) GWAS by Subtraction to Disentangle RBD Genetic Background from α -Synucleinopathies. *International Journal of Molecular Sciences*, **26**, 3578. <https://doi.org/10.3390/ijms26083578>
- [9] Fereshtehnejad, S. (2026) Skin-Based α -Synuclein Deposits Detection across the Prodromal Continuum of Synucleinopathies: Updated Evidence and Perspectives. *Bio-molecules*, **16**, Article 376. <https://doi.org/10.3390/biom16030376>
- [10] Saini, P., Yu, E., Estiar, M.A., Krohn, L., Mufti, K., Rudakou, U., *et al.* (2025) Lack of Epistatic Interaction of *SNCA* with *APOE* in Synucleinopathies. *Brain Communications*, **7**, fcaf455. <https://doi.org/10.1093/braincomms/fcaf455>
- [11] Bergmann, M., Högl, B. and Stefani, A. (2024) Clinical Neurophysiology of REM Parasomnias: Diagnostic Aspects and Insights into Pathophysiology. *Clinical Neurophysiology Practice*, **9**, 53-62. <https://doi.org/10.1016/j.cnp.2023.10.003>
- [12] Mancini, R., Mattioli, P., Famà, F., Giorgetti, L., Calizzano, F., Nikolic, M., *et al.* (2024) Automatic Quantification of REM Sleep without Atonia Reliably Identifies Patients with REM Sleep Behavior Disorder: A Possible Screening Tool? *Neurological Sciences*, **45**, 4837-4846. <https://doi.org/10.1007/s10072-024-07532-6>
- [13] Byun, J., Yang, T., Sunwoo, J., Shin, W.C., Kwon, O. and Jung, K. (2022) Comparison of Rapid Eye Movement without Atonia Quantification Methods to Diagnose Rapid Eye Movement Sleep Behavior Disorder: A Systematic Review. *Sleep*, **45**, zsac150. <https://doi.org/10.1093/sleep/zsac150>
- [14] Sasai-Sakuma, T., Takeuchi, N., Asai, Y., Inoue, Y. and Inoue, Y. (2020) Prevalence and Clinical Characteristics of REM Sleep Behavior Disorder in Japanese Elderly People. *Sleep*, **43**, zsaa024. <https://doi.org/10.1093/sleep/zsaa024>
- [15] Röttgen, S., Doppler, C.E.J., Seger, A., Kalbe, E., Fink, G.R., Sommerauer, M., *et al.* (2025) Context-Dependency of the REM Sleep Behavior Disorder Screening Questionnaire—Clinical Utility under Scrutiny. *Parkinsonism & Related Disorders*, **130**, Article ID: 107211. <https://doi.org/10.1016/j.parkreldis.2024.107211>
- [16] Forbes, E., Tropea, T.F., Mantri, S., Xie, S.X. and Morley, J.F. (2021) Modifiable Comorbidities Associated with Cognitive Decline in Parkinson's Disease. *Movement Disorders Clinical Practice*, **8**, 254-263. <https://doi.org/10.1002/mdc3.13143>
- [17] Loddo, G., La Fauci, G., Vignatelli, L., Zenesini, C., Cilea, R., Mignani, F., *et al.* (2021) The Arousal Disorders Questionnaire: A New and Effective Screening Tool for Confusional Arousals, Sleepwalking and Sleep Terrors in Epilepsy and Sleep Disorders Units. *Sleep Medicine*, **80**, 279-285. <https://doi.org/10.1016/j.sleep.2021.01.037>
- [18] Irfan, M. and Schenck, C.H. (2025) Current Perspectives on Nonrapid Eye Movement Parasomnias. *Seminars in Neurology*, **45**, 358-367. <https://doi.org/10.1055/a-2565-3317>
- [19] Kuang, B., Li, D., Lobbezoo, F., de Vries, R., Hilgevoord, A., de Vries, N., *et al.* (2022) Associations between Sleep Bruxism and Other Sleep-Related Disorders in Adults: A Systematic Review. *Sleep Medicine*, **89**, 31-47. <https://doi.org/10.1016/j.sleep.2021.11.008>
- [20] Bruschi, G., Bortolin, E., Mazzeo, S., Bombaci, A., Pozzi, F.E., Agosta, F., *et al.* (2025)

- Tracking Prodromal α -Synucleinopathies: Novel Fluid- and Tissue-Based Biomarker Approaches for iRBD Phenoconversion. *Sleep*, **48**, zsaf174. <https://doi.org/10.1093/sleep/zsaf174>
- [21] Puligheddu, M., Figorilli, M., Antelmi, E., Arnaldi, D., Casaglia, E., d'Aloja, E., *et al.* (2022) Predictive Risk Factors of Phenoconversion in Idiopathic REM Sleep Behavior Disorder: The Italian Study "Farpresto". *Neurological Sciences*, **43**, 6919-6928. <https://doi.org/10.1007/s10072-022-06374-4>
- [22] Beauchamp, L.C., Villemagne, V.L., Finkelstein, D.I., Doré, V., Bush, A.I., Barnham, K.J., *et al.* (2020) Reduced Striatal Vesicular Monoamine Transporter 2 in REM Sleep Behavior Disorder: Imaging Prodromal Parkinsonism. *Scientific Reports*, **10**, Article No. 17631. <https://doi.org/10.1038/s41598-020-74495-x>
- [23] Benbir Senel, G., Albayrak, N., Yanik, I., Gokcen Polat, E., Schenck, C.H. and Karadeniz, D. (2024) Estratificación del riesgo de fenotipo conversión al parkinsonismo en pacientes con trastorno de conducta del sueño REM aislado. Estudio de seguimiento en un centro de Turquía. *Revista de Neurología*, **78**, 73-81. <https://doi.org/10.33588/rn.7803.2023181>
- [24] Stefani, A., Antelmi, E., Arnaldi, D., Arnulf, I., During, E., Högl, B., *et al.* (2025) From Mechanisms to Future Therapy: A Synopsis of Isolated REM Sleep Behavior Disorder as Early Synuclein-Related Disease. *Molecular Neurodegeneration*, **20**, Article No. 19. <https://doi.org/10.1186/s13024-025-00809-0>
- [25] Valli, M., Uribe, C., Mihaescu, A. and Strafella, A.P. (2022) Neuroimaging of Rapid Eye Movement Sleep Behavior Disorder and Its Relation to Parkinson's Disease. *Journal of Neuroscience Research*, **100**, 1815-1833. <https://doi.org/10.1002/jnr.25099>
- [26] Woo, K.A., Kim, H., Kim, R., Jin, B., Shin, J.H., Kim, S., *et al.* (2025) Cholinergic Degeneration and Early Cognitive Signs in Prodromal Lewy Body Dementia. *Alzheimer's & Dementia*, **21**, e14584. <https://doi.org/10.1002/alz.14584>
- [27] Du, L., Xu, L., Liang, T., Wing, Y., Ke, Y. and Yung, W. (2021) Progressive Pontine-Medullary Dysfunction Leads to REM Sleep Behavior Disorder Symptoms in a Chronic Model of Parkinson's Disease. *Nature and Science of Sleep*, **13**, 1723-1736. <https://doi.org/10.2147/nss.s328365>
- [28] Wang, F., Zhu, Z., Zhou, C., Zhu, Y., Zhu, Y., Liang, C., *et al.* (2024) MRI Brain Structural and Functional Networks Changes in Parkinson Disease with REM Sleep Behavior Disorders. *Frontiers in Aging Neuroscience*, **16**, Article 1364727. <https://doi.org/10.3389/fnagi.2024.1364727>
- [29] Donzuso, G., Cicero, C.E., Giuliano, L., Squillaci, R., Luca, A., Palmucci, S., *et al.* (2023) Neuroanatomical Findings in Isolated REM Sleep Behavior Disorder and Early Parkinson's Disease: A Voxel-Based Morphometry Study. *Brain Imaging and Behavior*, **18**, 83-91. <https://doi.org/10.1007/s11682-023-00815-0>
- [30] Zhang, H., Wang, S., Bai, Y., Zhang, J. and Chen, S. (2021) Abnormal Striatal-Cortical Networks Contribute to the Attention/Executive Function Deficits in Idiopathic REM Sleep Behavior Disorder: A Resting State Functional MRI Study. *Frontiers in Aging Neuroscience*, **13**, Article 690854. <https://doi.org/10.3389/fnagi.2021.690854>
- [31] García-Gomar, M.G., Videnovic, A., Singh, K., Stauder, M., Lewis, L.D., Wald, L.L., *et al.* (2021) Disruption of Brainstem Structural Connectivity in rem Sleep Behavior Disorder Using 7 Tesla magnetic Resonance Imaging. *Movement Disorders*, **37**, 847-853. <https://doi.org/10.1002/mds.28895>
- [32] Nepozitek, J., Varga, Z., Dostalova, S., Perinova, P., Keller, J., Robinson, S., *et al.* (2023) Magnetic Susceptibility Changes in the Brainstem Reflect REM Sleep without Atonia Severity in Isolated REM Sleep Behavior Disorder. *npj Parkinson's Disease*, **9**,

Article No. 112. <https://doi.org/10.1038/s41531-023-00557-2>

- [33] Nobileau, A., Gaurav, R., Chougar, L., Faucher, A., Valabrègue, R., Mangone, G., *et al.* (2023) neuromelanin-sensitive Magnetic Resonance Imaging Changes in the Locus Coeruleus/Subcoeruleus Complex in Patients with Typical and Atypical Parkinsonism. *Movement Disorders*, **38**, 479-484. <https://doi.org/10.1002/mds.29309>
- [34] Nishikawa, N. (2025) [Neurodegenerative Diseases and Isolated REM Sleep Behavior Disorder]. *Brain and Nerves*, **77**, 1101-1104. <https://pubmed.ncbi.nlm.nih.gov/41097922/>
- [35] De Micco, R., Piramide, N., Di Nardo, F., Siciliano, M., Cirillo, M., Russo, A., *et al.* (2022) Resting-state Network Connectivity Changes in Drug-Naive Parkinson's Disease Patients with Probable REM Sleep Behavior Disorder. *Journal of Neural Transmission*, **130**, 43-51. <https://doi.org/10.1007/s00702-022-02565-7>
- [36] Rus, T., Schindlbeck, K.A., Tang, C.C., Vo, A., Dhawan, V., Trošt, M., *et al.* (2022) Stereotyped Relationship between Motor and Cognitive Metabolic Networks in Parkinson's Disease. *Movement Disorders*, **37**, 2247-2256. <https://doi.org/10.1002/mds.29188>
- [37] Yoon, E.J., Lee, J., Kim, H., Yoo, D., Shin, J.H., Nam, H., *et al.* (2022) Brain Metabolism Related to Mild Cognitive Impairment and Phenoconversion in Patients with Isolated REM Sleep Behavior Disorder. *Neurology*, **98**, e2413-e2424. <https://doi.org/10.1212/wnl.0000000000200326>
- [38] Pilotto, A., Imarisio, A., Conforti, F., Scalvini, A., Masciocchi, S., Nocivelli, S., *et al.* (2021) Plasma NFL, Clinical Subtypes and Motor Progression in Parkinson's Disease. *Parkinsonism & Related Disorders*, **87**, 41-47. <https://doi.org/10.1016/j.parkreldis.2021.04.016>
- [39] Cao, R., Chen, X., Xie, C., Hu, P. and Wang, K. (2020) Serial Dopamine Transporter Imaging of Nigrostriatal Function in Parkinson's Disease with Probable REM Sleep Behavior Disorder. *Frontiers in Neuroscience*, **14**, Article 349. <https://doi.org/10.3389/fnins.2020.00349>
- [40] Martinez-Nunez, A.E., Hutchinson, H., Coutinho, P., Sarmento, F.P., Lavu, V.S., Yuan, Q., *et al.* (2025) Clinically Probable RBD Is an Early Predictor of Malignant Non-Motor Parkinson's Disease Phenotypes. *npj Parkinson's Disease*, **11**, Article No. 25. <https://doi.org/10.1038/s41531-025-00874-8>
- [41] Fan, Y., Zhang, M., Liang, X., Shen, B., Xu, Z., Li, S., *et al.* (2021) Determinants of Quality of Life in Parkinson's Disease: A Perspective of Novel Clinical Subtypes. *Annals of Clinical and Translational Neurology*, **8**, 2174-2183. <https://doi.org/10.1002/acn3.51475>
- [42] Nigam, M., Ayadi, I., Noiray, C., Branquino-Bras, A.C., Herraiez Sanchez, E., Leu-Semenescu, S., *et al.* (2021) Sweet or Bland Dreams? Taste Loss in Isolated REM-Sleep Behavior Disorder and Parkinson's Disease. *Movement Disorders*, **36**, 2431-2435. <https://doi.org/10.1002/mds.28692>
- [43] Iranzo, A., Mammanna, A., Muñoz-Lopetegui, A., Dellavalle, S., Mayà, G., Rossi, M., *et al.* (2023) Misfolded α -Synuclein Assessment in the Skin and CSF by RT-QuIC in Isolated REM Sleep Behavior Disorder. *Neurology*, **100**, e1944-e1954. <https://doi.org/10.1212/wnl.0000000000207147>
- [44] Howell, M., Avidan, A.Y., Foldvary-Schaefer, N., Malkani, R.G., During, E.H., Roland, J.P., *et al.* (2023) Management of REM Sleep Behavior Disorder: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *Journal of Clinical Sleep Medicine*, **19**, 769-810. <https://doi.org/10.5664/jcsm.10426>

- [45] Arnaldi, D., Mattioli, P., Famà, F., Girtler, N., Brugnolo, A., Pardini, M., *et al.* (2021) Stratification Tools for Disease-Modifying Trials in Prodromal Synucleinopathy. *Movement Disorders*, **37**, 52-61. <https://doi.org/10.1002/mds.28785>
- [46] Dall'Antonia, I., Nepožitek, J., Hlavnička, J., Ruzs, J., Peřinová, P., Dostálová, S., *et al.* (2025) Refining α -Synucleinopathy Risk in Isolated REM Sleep Behavior Disorder Patients Using Repeated Olfactory Testing. *Sleep Medicine*, **136**, Article ID: 106812. <https://doi.org/10.1016/j.sleep.2025.106812>
- [47] Delva, A., Zatti, C., Pelletier, A., Montplaisir, J., Gagnon, J., Kollmorgen, G., *et al.* (2025) Plasma Markers of Astrocytic and Axonal Integrity in Idiopathic/Isolated REM Sleep Behavior Disorder (iRBD) as Predictors of Dementia with Lewy Bodies. *Movement Disorders*, **40**, 2497-2503. <https://doi.org/10.1002/mds.70016>