Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(2): 45114
https://doi.org/10.31083/JIN45114

Review

REM Sleep Behavior Disorder: Pathophysiology, Biomarkers, and Therapeutic Strategies

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Academic Editor: Luigi De Gennaro
Submitted: 18 July 2025 Revised: 2 September 2025 Accepted: 5 September 2025 Published: 13 February 2026

Abstract

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by the loss of muscle atonia during rapid eye movement sleep, leading individuals to physically act out their dreams, often resulting in injuries. This condition is linked to SubCoeruleus nucleus dysfunction (homologous to the sublaterodorsal tegmental nucleus in rodents) and related neural circuits. Despite its profound impact on patient safety and quality of life, the role of environmental and lifestyle factors in RBD pathogenesis remains underexplored. To bridge this gap, we conducted a review of observational and interventional studies published between 2000 and 2025, using PubMed, Web of Science databases, and ScienceDirect. After systematic screening, 129 studies were selected, covering pathophysiological mechanisms, biomarkers, diagnostic approaches, and therapeutic interventions. Emerging evidence suggests that early detection through biomarkers and neuroimaging, combined with targeted therapeutic interventions, may help delay or prevent progression to more severe neurodegenerative diseases. This review underscores significant advances in identifying RBD biomarkers and targeted interventions, while highlighting the critical need for future research on modifiable environmental and lifestyle risk factors to guide preventive strategies.

Keywords: REM sleep behavior disorder; neurodegenerative diseases; α-synucleinopathies; biomarkers; pathogenesis

1. Introduction

The human sleep cycle, a fundamental aspect of daily physiological rhythms, is conventionally divided into rapid eye movement (REM) and non-REM sleep. During REM sleep, the brain is remarkably active and often accompanied by vivid dreams, while the body experiences reduced muscle tone. This muscle atonia is crucial for REM sleep, and its disruption can result in dreaming-enacting behaviors such as vocalizations and twitches that mirror dream content, potentially resulting in REM sleep behavior disorder (RBD) [1–3].

RBD is categorized into idiopathic (iRBD) and secondary RBD (sRBD), with the latter being associated with neurological disorders or medications such as antidepressants. Globally, the prevalence of RBD in the general population ranges from 0.5% to 1.25%, while in older individuals, the rate doubles to approximately 2% [4]. Although the exact pathogenesis of RBD has not been fully elucidated, it is widely recognized that it primarily involves dysfunction in the pontine and midbrain regions of the brainstem. In addition, environmental risk factors (occupational hazards such as fine particulate matter in the air with a diameter of 2.5 µm or less (PM2.5), pesticides, or heavy metals) may also exacerbate neurodegenerative processes through mechanisms such as oxidative stress and neuroinflammation, which may promote the pathogenesis of RBD [5].

This review aims to provide an integrative overview of RBD pathophysiology, explore potential biomarkers for early detection, and discuss the latest therapeutic strategies to mitigate the impact on patients' quality of life.

2. Methods

For this narrative review, a comprehensive literature search was performed using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://webofscience.com), and ScienceDirect (https://www.sciencedirect.com/), for articles published between 2000 and 2025. Key search terms included "REM sleep behavior disorder", "pathogenesis", "biomarkers", and "therapeutic strategies". The selection focused on original research and review articles, emphasizing scholarly relevance. The authors examined the included papers for their relevance to the narrative review, resulting in the inclusion of 129 publications. Although earlier works (pre-2000) provide seminal observa-

tions on REM sleep atonia circuitry and parasomnia phenomenology, these foundational findings have since been summarized and expanded in more recent reviews. Consequently, limiting the reference search to 2000–2025 captures the consolidated evidence while avoiding redundancy.

3. Generation of Rapid Eye Movement Sleep

During REM sleep, cholinergic neurons in the pontine reticular formation and midbrain exhibit heightened activity [6]. Glutamatergic neurons in a small pontine nucleus located ventral to the laterodorsal tegmental nucleus (LDT) play a key role in muscle atonia. In rats, this nucleus is termed the sublaterodorsal tegmental nucleus (SLD), while in humans, it corresponds to the SubCoeruleus (SubC) nucleus [7]. In rats and mice, the absence of glutamatergic neurons or impairment of their neurotransmission in SLD leads to the loss of muscle atonia and the emergence of abnormal RBD-like behaviors during REM sleep [8,9]. Recent studies have demonstrated that SLD glutamatergic neurons play a critical role in maintaining muscle atonia during REM sleep [8,10]. Beyond atonia, these neurons are now also recognized as the key trigger of REM sleep themselves. Crucially, a pontine-medullary loop involving reciprocal connections between corticotropin-releasing hormone binding protein (CRHBP)-expressing glutamatergic neurons and Nos1-expressing neurons in the dorsomedial medulla (dorsal paragigantocellular nucleus/prepositus hypoglossal nucleus, DPGi/Pr) constitutes a core circuit for REM sleep induction and maintenance. Optogenetic activation of this loop potently initiates REM sleep, while its inhibition suppresses REM episodes [11]. In addition to the SLD (a REM-on region), the pontomesencephalic junction, the ventrolateral periaqueductal gray (vlPAG), the adjoining lateral pontine tegmentum (LPT), and the lateral hypothalamus (LH) contain numerous REM-off neurons that inhibit REM sleep [12]. The subset of "REM-off" γ-aminobutyric acid-ergic (GABAergic) neurons in the vlPAG/LPT inhibits REM-on neurons, thereby suppressing the transition from non-REM to REM sleep and shortening REM episode duration. When the activity of REM-off neurons in the vlPAG/LPT diminishes and is deactivated, this inhibition is lifted, allowing SLD glutamatergic activity to be restored, thereby initiating REM sleep [12–15].

The vlPAG/LPT GABAergic neurons also project to multiple other regions, including the LDT and locus coeruleus (LC), both of which are involved in regulating REM sleep. Notably, REM sleep inhibition has been observed following the activation of vlPAG/LPT GABAergic terminals in the LH [12]. Additionally, most orexin (Orx)-producing neurons in the LH inhibit REM sleep by activating vlPAG/LPT neurons, which suppress REM sleep initiation [13]. However, approximately 8% of these neurons may promote or stabilize REM sleep by directly influencing the SLD, thereby highlighting their dual regulatory role [13].

4. Pathology of RBD

The pathology of RBD is multifactorial, arising from dysregulation of brainstem nuclei that control REM sleep atonia, frequently associated with α-synucleinopathy, and occasionally with focal structural lesions. The following sections detail the neural circuit dysfunctions, protein aggregation mechanisms, and structural pathologies implicated in RBD.

4.1 Dysfunction of the REM Sleep Atonia Circuit

The fundamental mechanism of RBD involves the disruption of brainstem-to-spinal cord pathways that maintain muscle paralysis during REM sleep. Recent studies have shown that projections from glutamatergic neurons in the SubC nucleus (equivalent to the SLD in mice) to the ventromedial medulla (VMM) and spinal cord form the basis of REM sleep atonia in skeletal muscles [13]. Tracing studies have confirmed that glutamatergic neurons in the directly project to GABAergic and glycinergic (Gly) neurons in the VMM, inducing glycine-mediated spinal cord postsynaptic inhibition of motoneurons. Additionally, glutamatergic neurons in the SubC nucleus directly project to layer VII of the spinal cord, which contains GABAergic/glycinergic interneurons [14,16].

The specific loss or inactivation of GABAergic/Gly neurons in the VMM results in REM sleep without atonia, characterized by exaggerated phasic twitching and involuntary motor activity. Furthermore, experiments in mice have shown that the absence of glutamatergic neurons in the SLD or disrupted glutamatergic neurotransmission from SLD neurons can lead to REM sleep without atonia and dream-enacting behaviors [8,9,16]. Therefore, the core pathophysiological mechanism underlying RBD involves the disruption of the descending SLD-VMM-spinal cord pathway, leading to a failure of glycinergic/GABAergic inhibition of motor neurons during REM sleep. Neurodegeneration involving glutamatergic SubC nucleus and/or GABAergic/glycinergic medullary neurons may disrupt these inhibitory systems, ultimately compromising the ability to induce muscle relaxation during REM sleep [17]. Thus, the core pathophysiological mechanism underlying RBD involves the disruption of the descending SLD-VMM-spinal cord pathway, leading to a failure of glycinergic/GABAergic inhibition of motor neurons during REM sleep (Fig. 1).

4.2 Aggregation of α-synuclein

α-synuclein (α-syn) pathology is a major contributor to RBD, often preceding overt neurodegeneration and spreading through peripheral and brainstem pathways.

Peripheral α-syn accumulation may serve as an early site of pathology, with spread to the central nervous system (CNS) via neural and circulatory routes. Red blood cells (RBCs) serve as the primary source of peripheral α-syn, and recent pathological and imaging evidence suggest that

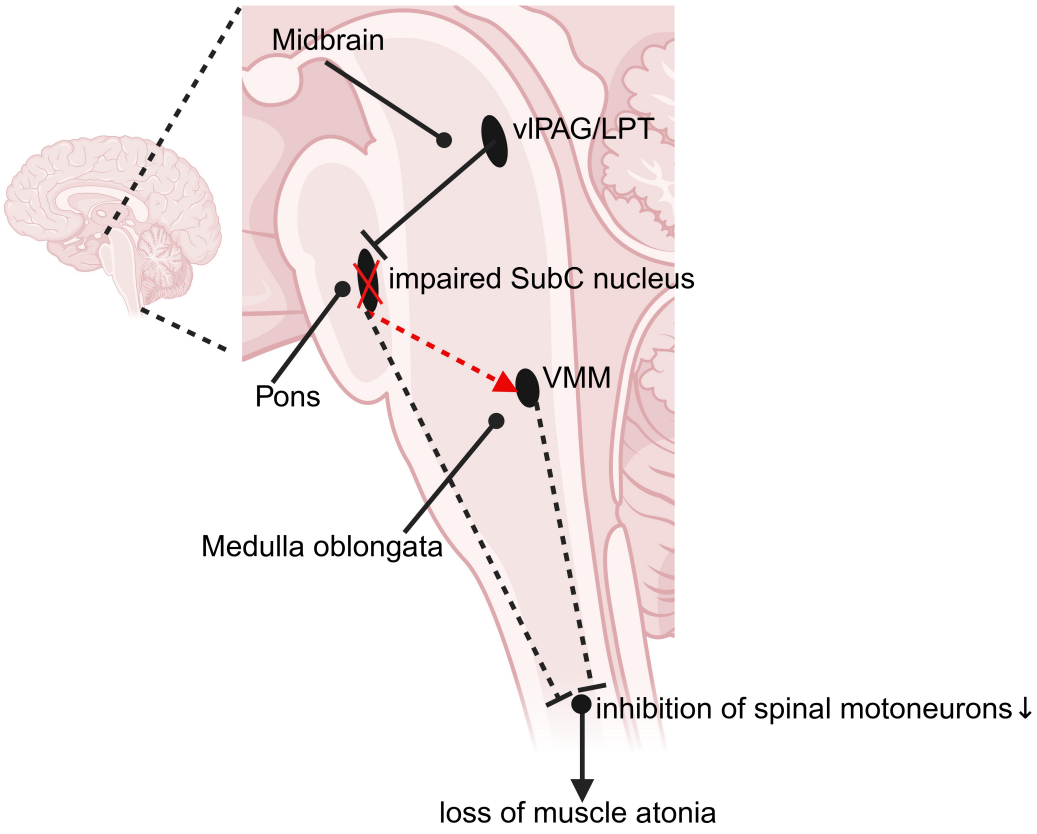

Fig. 1. Circuit dysfunction underlying RBD-like behavior disorder in the human brain. Loss or dysfunction of glutamatergic neurons in the SubC nucleus disrupts glutamatergic neurotransmission, failing to activate GABAergic and glycinergic neurons in the VMM. As a result, the inhibitory control over spinal motor neurons is compromised, leading to their aberrant activation and the subsequent loss of muscle atonia during REM sleep. LPT, lateral pontine tegmentum; RBD, rapid eye movement sleep behavior disorder; REM, rapid eye movement; SubC nucleus, SubCoeruleus nucleus; vlPAG, ventrolateral periaqueductal gray; VMM, ventromedial medulla. The black solid line represents functional inhibitory synapses. Red and black dashed lines indicate excitatory and inhibitory synaptic pathways with impaired or ineffective transmission, respectively. Black solid arrow: spinal motoneurons project to skeletal muscles. Created with biorender (https://www.biorender.com/); Agreement number: KD285OGHOM.

its initial aggregation may begin in peripheral organs before spreading to the brain. Impairment in peripheral clearance systems can contribute to inefficient α-syn removal and greater deposition. Peripheral α-syn released from RBCs may spread to the CNS in a prion-like manner from peripheral sites [18].

Gastrointestinal biopsies show that abnormal α-syn aggregation is detected in 24% of colon biopsy samples from patients with iRBD [19,20]. Enteroendocrine cells secrete α-syn, which may be taken up by presynaptic neurons of the sympathetic nerves in the lateral horn of the spinal cord and can then undergo retrograde transport to the brainstem or higher brain regions such as the thalamus or cerebral cortex. This process leads to the formation of α-syn aggregates [21]. α-syn pathology can also spread to the pelvic plexus, pelvic ganglia, and sacral parasympathetic nucleus, resulting in impaired rectal function [22]. Additionally, up to 82% of patients with iRBD tested positive for α-syn in a recent skin biopsy [23]. α-syn aggregates have been observed in approximately half of the submandibular and labial salivary gland samples from patients with iRBD [24,25]. The frequent involvement of the submandibular gland, submandibular ganglion, and salivatory nucleus suggests that an ascending craniofacial parasympathetic pathway may play a role in α-syn progression [22].

The precise causal link between α-syn pathology and RBD symptomatology is hypothesized to involve the targeted disruption of key brainstem nuclei governing REM sleep atonia. The injection of preformed α-syn protofibrils into the SLD induces degeneration of SLD neurons, leading to widespread dissemination of α-syn pathology accompanied by RBD-like behaviors in mice [13]. This suggests that α-syn accumulation in the SLD may contribute to RBD pathogenesis.

As neuropathological aggregates propagate rostrally through the brainstem, they ultimately infiltrate the SLD in rats (homologous to the SubCoeruleus, SubC, in humans), which is a core component of the REM sleep reg-

ulatory circuit [26]. This nucleus contains a population of glutamatergic "REM-on" neurons that, during normal REM sleep, become active and send excitatory projections to glycinergic/GABAergic premotor neurons in the ventral medulla and spinal cord. This excitatory drive is essential for inducing hyperpolarization and atonia in somatic motoneurons. The accumulation of α-syn pathology within the SLD/SubC and its connected circuitry, potentially through α-syn oligomer-mediated neuroimmune inflammation mechanisms, is proposed to impair the function of these critical glutamatergic neurons. This dysfunction disrupts the excitatory command to the medullary/spinal inhibitory interneurons, resulting in a failure to suppress motor activity during REM sleep and the characteristic dream-enactment behaviors of RBD [27].

In RBD patients, α-syn aggregates have been detected in the olfactory mucosa using assays such as real-time quinacrine-induced conversion (RT-QuIC), suggesting that α-syn pathology may originate in peripheral tissues like the nasal epithelium before spreading centrally [28]. These anomalies are closely linked to RBD and broader sleep disorders, suggesting that individuals exposed to PM2.5 air pollution may face an increased risk of developing RBD [29]. Collectively, these findings establish a strong link between RBD and widespread α-syn neuropathology.

In addition, several pathways have been identified to facilitate α-syn entry into the CNS, including olfactory, vagus, and blood-borne routes. α-syn spreads from the nasal cavity to the brain via two primary routes: (1) through the olfactory nerve to the olfactory bulb (OB), subsequently spreading to other brain regions, including the limbic system and possibly the temporal lobe; and (2) via nasal entry affecting the enteric nervous system, with α-syn propagating retrogradely along the vagus nerve to the dorsal motor nucleus of the vagus [22,30]. Beyond the vagal pathway, other routes of α-syn oligomers transport should not be overlooked. Complement receptor 1, a component of the peripheral blood system, promotes α-syn pathology by exacerbating its phosphorylation and aggregation *in vitro* through its transmembrane domain (CR1-TM) [31]. Additionally, high blood cholestanol levels can activate the asparagine endopeptidase, inducing α-syn fragmentation and aggregation [32]. Elevated plasma α-syn oligomers have been detected in patients with RBD, and α-syn is capable of crossing the blood-brain barrier [33]. Circulating α-syn in plasma may thus induce central nervous system pathology.

In summary, when α-syn propagation reaches key brainstem nuclei regulating REM sleep (particularly the SLD), it disrupts glutamatergic projections to inhibitory interneurons in the spinal cord. This impairs glycinergic/GABAergic neurotransmission required for muscle atonia during REM sleep, leading to pathological motor activation and RBD symptom manifestation.

4.3 Focal Ischemic, Inflammatory, Degenerative, or Demyelinating Lesions in the Brainstem, Cortical, and Subcortical Structures

Non-α-syn etiologies such as vascular, inflammatory, or demyelinating lesions in REM-regulating regions can also lead to RBD, underscoring the anatomical vulnerability of these pathways. The brainstem plays a crucial role in regulating REM sleep and muscle atonia. Lesions in the pontine and midbrain tegmentum, particularly within key REM-regulating nuclei, can disrupt normal REM sleep processes, contributing to RBD [34]. Dysfunction of pontine tegmental neurons can disrupt descending projections to spinal motor neurons, leading to the abnormal loss of muscle atonia during REM sleep [35].

In recent years, an increasing number of case reports have demonstrated that acute-onset RBD is closely associated with focal lesions in the pontine tegmentum caused by ischemia, tumors, hemorrhage, demyelination, or inflammation [36]. For example, lesions in the right pontine tegmentum cause RBD, characterized by the loss of muscle atonia during REM sleep and dream-enacting behaviors. In one case, a right pontine infarct led to RBD symptoms that were alleviated by clonazepam [37]. Similarly, ischemic stroke affecting the left rostrodorsal pons can disrupt the LC and LPT regions, interfering with REM sleep pathways and visual processing [38].

Acute encephalitis affecting the brainstem can also lead to inflammatory lesions in the dorsomedial pontine tegmentum characterized by inflammatory infiltration, neuronal loss, and gliosis. Patients with such lesions often develop RBD, supporting the hypothesis that inflammatory damage in this region can induce acute RBD [39]. Furthermore, in patients with multiple system atrophy associated with RBD, degeneration of the pedunculopontine (PPN) and laterodorsal tegmental nuclei results in the depletion of cholinergic neurons, which is considered a key pathological feature of RBD [40]. Similarly, demyelinating lesions in the dorsal pontine region can disrupt pathways that regulate skeletal muscle tone and movement suppression during REM sleep, resulting in the loss of muscle atonia [41].

Although less frequently implicated than in the brainstem, cortical lesions can also affect sleep regulation. Inflammatory demyelinating diseases, such as multiple sclerosis, can lead to lesions in white and grey matter, including regions involved in sleep control [42]. Degenerative changes in subcortical structures, such as the thalamus, putamen, and amygdala, have been observed in patients with RBD. These regions are involved in motor control and emotional regulation during sleep [43]. Neurodegeneration in brainstem nuclei such as the substantia nigra, PPN, and LC may disrupt REM sleep atonia mechanisms, contributing to abnormal motor activation and the hallmark dream-enactment behaviors of RBD [43].

In summary, RBD pathogenesis may result from structural impairments within critical neural networks span-

ning the brainstem nuclei and cortico-subcortical pathways. These neuroanatomical components, which are essential for mediating muscle atonia during REM sleep, can be compromised by various pathological mechanisms, including ischemic damage, inflammatory processes, neurodegenerative changes, and demyelinating disorders.

5. Diseases Associated With RBD

Longitudinal cohort studies indicate that a significant proportion (81%–91%) of patients with iRBD develop definitive neurodegenerative diseases or mild cognitive impairment within 14 years of follow-up [44]. RBD has been recognized as an early manifestation of several neurodegenerative diseases, particularly disorders associated with α-synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [45]. Additionally, emerging research has demonstrated that sleep disorders contribute to neurodegeneration, as prolonged sleep deprivation induces a proinflammatory response, which plays a critical role in disease progression [46].

5.1 Parkinson's Disease

During REM sleep, sleep disruption and neural inflammation may lead to an imbalance between the production and clearance of α-syn, promoting the formation of oligomers, amyloidogenic fibers, and ultimately Lewy bodies from soluble monomeric α-syn [47]. Furthermore, experimental findings have demonstrated that inoculation of α-syn fibrils in the gastrointestinal tract can induce pathological propagation to the brain and compromised peripheral clearance can lead to α-syn accumulation systemically [18]. Additionally, defects in the dopaminergic system have been observed in patients with iRBD, and brain imaging studies have identified abnormal dopamine transporter protein activity, which increases the risk of progression to PD in these patients [48]. Taken together, this evidence supports the conclusion that iRBD may contribute to PD development. This emphasizes the need for more in-depth studies on RBD and its relationship with neurodegenerative diseases to better understand their early biological hallmarks and identify potential targets for early intervention.

Body-first PD (RBD-positive at the onset of motor symptoms) and brain-first PD (RBD-negative at the onset of motor symptoms) have been distinguished using RBD as a clinical identifier [49]. In body-first PD, pathological α-syn initially originates in the enteric nervous system and gradually spreads to the autonomic and central nervous systems [50]. Emerging evidence indicates that α-syn propagation from the periphery (e.g., the gut) to the brain is a critical process associated with an increased risk of PD, as α-syn deposits have been found in peripheral tissues of patients with Lewy body diseases. Moreover, organs with extensive neural connections, like the gut, may serve as an initiation site for α-syn pathology [18]. In contrast, in brain-first PD, α-syn pathology often originates in regions such as OB or the amygdala, serving as a critical starting point for subsequent spread to other brain areas, including the substantia nigra pars compacta [50]. Neuroimaging studies suggest that substantial volume loss in the substantia nigra pars compacta can be detected even in early stages of PD (Hoehn and Yahr stage 1), supporting its involvement in early α-syn pathology, particularly in brain-first PD [51].

Patients with body-first PD typically exhibit more prominent autonomic symptoms, including upright hypotension and constipation, more frequent pathological aggregation of α-syn in peripheral tissues, and greater involvement of the brainstem and autonomic nervous system in imaging studies. These patients also show more symmetrical loss of striatal dopaminergic, more pronounced olfactory dysfunction, and even more distributed motor symptoms. By contrast, brain-first PD presents with opposing clinical and imaging features. Before the onset of motor symptoms, patients with brain-first PD show only mild cortical metabolic changes [19]. Most diffusion-based magnetic resonance imaging (MRI) studies confirm that patients with body-first PD have a higher degree of microstructural brainstem damage than patients with brain-first PD [52].

In investigating the progression of iRBD to PD, research identified common and distinct genetic factors for both disorders (Fig. 2). Genome-wide association studies have identified five genetic loci associated with RBD, primarily involving the autophagy-lysosome pathway [53]. A high proportion of patients with iRBD diagnosed via polysomnography carry pathogenic glucocerebrosidase (*GBA*) variants, providing strong evidence of a link between *GBA* genetic variants and RBD [54]. Mutations in the *GBA* gene impair lysosomal glucocerebrosidase activity, potentially disrupting lysosomal degradation and leading to α-syn accumulation [52]. Patients carrying pathogenic GBA variants typically exhibit traits of body-first PD [52]. Impaired synuclein alpha/α-syn (*SNCA*) catabolism further exacerbates toxic oligomer formation [55]. Although *SNCA* variant carriers are relatively evenly distributed between the two PD subtypes, patients with leucine-rich repeat kinase 2 (*LRRK2*) mutations predominantly exhibit brain-first PD features [52].

However, not all patients with PD develop RBD, as disease manifestation varies among individuals. The prevalence of RBD in patients with PD is approximately 40% [56]. Differences in affected brain regions and genetic factors may explain why some patients do not develop RBD [19,49,54]. Furthermore, disease subtypes and progression patterns influence RBD occurrence in PD [3,57]. Clinical heterogeneity suggests that PD comprises multiple subtypes, with some forms predominantly affecting motor pathways while sparing sleep regulation centres [57]. Additionally, symptom timelines vary; RBD may emerge before, during, or after the onset of motor symptoms, meaning some patients develop RBD later in the disease course [3].

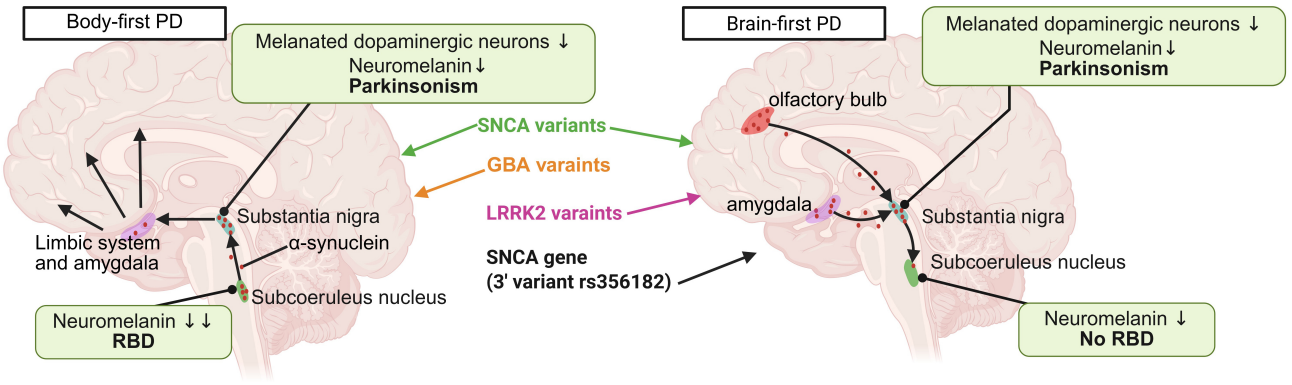

Fig. 2. The relationships between genetic variants and the subtypes of PD. PD primarily affects dopamine-producing neurons in the substantia nigra, but the involvement of other brain regions varies among individuals. RBD is linked to dysfunction in specific brainstem areas controlling muscle atonia during REM sleep, such as the SubCoeruleus nucleus and pontine tegmentum, and if these areas remain unaffected, RBD may not develop. GBA variants are more commonly associated with body-first PD, while LRRK2 variants are predominantly linked to brain-first PD, though some overlap exists. The SNCA variants are evenly distributed across the two PD subtypes. Notably, the *SNCA* gene (*3′ variant rs356182*), while linked to an increased PD risk, has been suggested to reduce the likelihood of RBD. Black arrows indicate the direction of spread of α-syn pathology inside the brain. GBA, glucocerebrosidase; LRRK2, Leucine-Rich Repeat Kinase 2; PD, Parkinson's disease; SCNA, Synuclein Alpha/α-syn; α-syn, α-synuclein. Created with biorender (https://www.biorender.com/); Agreement number: WM285OGIRW.

5.2 Dementia With Lewy Bodies

iRBD is considered an important pre-clinical indicator of PD and DLB. Long-term follow-up studies indicate that approximately 95% of patients with iRBD will eventually be diagnosed with DLB and PD, with each occurring at roughly equal rates (45%), while an additional 5% develop MSA [58,59]. DLB and PD are often discussed together because of their overlapping pathological features, both involving dopaminergic innervation loss in the nigrostriatal pathway, as observed on dopamine transporter imaging. However, patients with DLB exhibit a more uniform and symmetrical reduction in dopaminergic activity across the putamen and caudate nuclei. As PD progresses, the dopaminergic deficit becomes increasingly symmetric, making dopamine imaging patterns resemble those seen on DLB [60].

The association between DLB and iRBD primarily highlights marked cognitive decline, particularly in attention and executive function, as assessed by specific tests such as the Trail Making Test B and immediate recall in word lists. In contrast, iRBD-associated PD manifests as early impairments in a broader range of cognitive domains, including attention, executive function, memory, and visuospatial abilities [61]. Patients with DLB and RBD may exhibit a 'bottom-up' disease progression pattern, in which α-syn pathology initially affects the brainstem before spreading to cortical regions, resembling the trajectory observed in PD [62]. Variations in the 5′ region of the *SNCA* gene and mutations in the *GABA* gene may increase neuronal sensitivity to α-syn, thereby facilitating RBD progression to DLB by altering gene expression or splicing [63]. Variations in the 5′ region of the *SNCA* gene may increase neuronal sensitivity to α-syn, potentially influencing the progression from RBD to DLB through altered gene expression or splicing. Although dysfunction of GABAergic neurotransmission has been implicated in RBD, the role of specific GABA-related genetic mutations in disease progression remains to be clarified [64,65].

5.3 Multiple System Atrophy

MSA is a progressive neurodegenerative disorder characterized by a heterogeneous combination of autonomic failure, cerebellar syndrome, and Parkinsonian features that respond poorly to levodopa and pyramidal signs [66]. Patients presenting primarily with Parkinsonian features are classified as MSA-P, typically characterized by striatal degeneration, whereas individuals with predominant cerebellar ataxia are classified as MSA-C, commonly associated with olivopontocerebellar atrophy [67].

The development of RBD in MSA occurs when pathological changes affect the LDT, PPN, and LC [68]. Study indicates that RBD is highly prevalent in MSA, with up to 90% of patients experiencing RBD at some stage of the disease course. No significant difference in prevalence has been observed between MSA-P and MSA-C subtypes [69]. However, RBD preceding motor symptom onset tends to be more severe in patients with MSA-C than in patients with RBD developing later in the disease course [70].

The pre-RBD patients develop RBD before MSA, and MSA tends to initially present with autonomic dysfunction (e.g., orthostatic hypotension, urinary issues), rather than typical motor symptoms of Parkinsonism. These patients are more likely to develop stridor, pyramidal signs, and

Table 1. Molecular, genetic, imaging, and electrophysiological biomarkers for RBD.

Category	Biomarker	Method of detection	Key genetic variant/locus	Phenoconversion endpoint	Sensitivity (%)	Specificity (%)	Ref
Molecular	α-syn (CSF)	RT-QuIC	/	PD/DLB	90.4	90.0	[75]
	α-syn (Oral mucosa)	SAA	/	PD/DLB/MSA	63.6	90.3	[76]
	NfL	Simoa HD-1	/	PD/DLB/MSA	75.0	83.3	[73]
	Plasma p-Tau181/Aβ42:40 ratio	Elecsys® immunoassays, cobas® e 601 and e 801 analyzers	/	DLB	89.0	pTau181: 73.0 Aβ42:40: 63.0	[77]
Genetic	*SNCA-AS1*	GWAS + eQTLs colocalization	*rs3756059* (*SNCA 5′ region*)	PD/DLB/MSA	/	/	[64]
	sGBA	Genetic screening/Sequencing	$L_{444}P$, $c.8_4insG$, $IVS_2{+}_1G{>}A$, $V_{394}L$, $_{370}Rec$	Presence of RBD in PD patients	/	/	[74]
	MAPT	Genetic Genotyping	*rs12185268*	/	/	/	[78]
Imaging	DAT SBR-Putamen	DAT-SPECT Imaging	/	PD/DLB/MSA	86.0	83.0	[79]
	VMAT2 binding (SUVR) -Posterior Putamen	^{18}F-AV-133 VMAT2 PET imaging	/	PD	/	/	[80]
	PDRP Expression (Network Activity)- Pons	^{18}F-FDG PET or ECD SPECT	/	PD/DLB	/	/	[81]
	Free-water value- Posterior Substantia Nigra	dMRI; Free-water imaging	/	PD or other synucleinopathy	61.8	75.0	[82]
	Iron overloa- Nigrosome 1	QSM	/	PD/DLB	/	/	[83]
Electro-physiological	RWA (mentalis)	vPSG + EMG (mentalis)	/	PD/DLB	68.4	80.0	[84]
	alpha phase synchronization increased	HD-EEG during resting-state wakefulness	/	PD/DLB	/	/	[85]
	Probable napping episodes (during active period)	7-day actigraphy (Actiwatch Spectrum Plus)	/	PD/DLB/MSA	/	/	[86]

Notes: CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DAT, Dopamine Transporter; SBR, specific binding ratio; SPECT, Single-Photon Emission Computed Tomography; dMRI, diffusion magnetic resonance imaging; eQTLs, expression quantitative trait loci; ECD SPECT, ethylcysteinate dimer single-photon emission computed tomography; EMG, electromyography; ^{18}F-AV-133 VMAT2 PET, fluorine-18 AV-133 vesicular monoamine transporter 2 positron emission tomography; ^{18}F-FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography; GWAS, genome-wide association study; HD-EEG, high-eensity electroencephalography; $L_{444}P$, $c.8_4insG$, $IVS_2{+}_1G>A$, $V_{394}L$, and $_{370}Rec$ refer to mutations of *GBA* gene at different positions; *MAPT*, microtubule associated protein tau; MSA, multiple system atrophy; NfL, neurofilament light chain; PD, Parkinson's disease; PDRP, Parkinson disease–related covariance pattern; QSM, quantitative susceptibility mapping; RT-QuIC, real-time quinacrine -Induced conversion; RWA, REM sleep without atonia; SBR, specific binding ratios; SPECT, single photon emission CT; SUVR, standardized uptake value ratio; SAA, seed amplification assay; Simoa HD-1, single molecule array high-definition 1 analyzer; *SNCA-AS1*, SNCA Antisense RNA 1; *sGBA*, severe *GBA* mutation; VMAT2, vesicular monoamine transporter 2; vPSG, video-polysomnogram.

urinary dysfunction at an earlier stage, and tend to have a shorter overall disease duration [71]. The post-RBD patients develop RBD after the onset of MSA, typically following the emergence of autonomic or motor symptoms [71]. Compared with the post-RBD patients, the pre-RBD patients have a lower incidence of typical motor symptoms of Parkinsonism not only at disease onset but also throughout the disease course [71]. The *SNCA* gene encodes α-syn, a presynaptic protein involved in synaptic vesicle regulation and neurotransmitter release. Recent studies indicate that carrying *SNCA* gene is a shared genetic risk factor for RBD and MSA, while *GBA* mutations are strongly associated with RBD and PD, but less so with MSA [64,72].

6. Biomarker Detection and Targeted Therapy

Current understanding remains limited by the inability to predict or differentiate specific phenotypic transformations in individuals with iRBD. The duration of RBD varies considerably, with some patients progressing within months while others remain stable for decades [45]. Addressing this challenge requires targeted therapies leveraging biomarkers identified in prior studies. A summary of key candidate biomarkers categorized by their biological or clinical nature is provided in Table 1. (Ref. [64,73–86]). The following sections explore the most extensively researched markers in this context.

6.1 Alpha-synuclein

Alpha-syn plays a central role in RBD pathogenesis, and its aberrant aggregation is a key indicator of disease progression. Current therapeutic approaches increasingly focus on preventing the early stages of protein aggregation, particularly protofibril formation [87].

In vitro studies have demonstrated that 4-arylidene curcumin and bis-chalcone polyphenols effectively inhibit α-syn aggregation and promote the disaggregation of preformed fibrils [88,89]. Moreover, the combined application of polyphenolic acid hybrids and xanthones has shown efficacy in disaggregating existing α-syn oligomers, presenting promising avenues for early intervention [90].

Recent investigations into the gut microbiome suggest that oral administration of resveratrol-selenium peptide nanocomposites can modulate specific bacterial taxa, such as *Desulfovibrio*, potentially reducing α-syn aggregation and offering new therapeutic strategies [91]. Additionally, the small peptide Tat-βsyn-degron, which targets α-syn, has been shown to reduce its levels and aggregation, improving bradykinesia, tremor, balance, and coordination of patients [92].

The peripheral clearance mechanisms play an important role in α-syn homeostasis by removing it from the blood circulation, and impairment in peripheral clearance can lead to α-syn accumulation in peripheral sites, which may spread to the CNS via blood or neural pathways, contributing to neuronal damage and PD [18].

Accurate detection of α-syn aggregation is essential for predicting and diagnosing RBD and associated diseases. Notably, specific α-syn forms in plasma and cerebrospinal fluid (CSF) have been identified as diagnostic markers for PD and RBD [93]. Although positron emission tomography (PET) imaging offers potential for localizing and quantifying drug targets, monitoring therapeutic efficacy, and imaging at the molecular level, PET tracers require higher selectivity owing to the coexistence and co-localization of α-syn with amyloid-β and Tau fibers [94]. Additionally, RT-QuIC and the α-synuclein seeded amplification assay (αSyn-SAA) enable the detection of α-syn aggregation [95].

These advancements in understanding and detecting α-syn aggregation have not only improved the prediction of RBD progression but have also contributed to the development of novel therapeutic interventions.

6.2 Neurofilament Light Chain

Neurofilament light chain (NfL), a cytoskeletal protein predominantly expressed in large-calibre myelinated axons, has provided valuable insights into neuronal injury mechanisms. Its detection in CSF offers promising avenues for diagnosing and monitoring neurodegenerative disorders [96]. A recent study investigated the potential of plasma NfL levels and cardiac metaiodobenzylguanidine imaging as predictors of phenotypic transformation in patients with iRBD. Baseline plasma NfL levels were significantly elevated in patients with RBD and MSA. The sensitivity and specificity of NfL concentrations exceeding 21.3 pg/mL in predicting the transformation of iRBD to MSA were 100% and 94.3%, respectively. Thus, elevated plasma NfL levels are associated with conversion to MSA, whereas decreased cardiac metaiodobenzylguanidine uptake is indicative of conversion to Lewy body dementia [73,97].

Moreover, neither olfactory nociceptive sensitization nor a quantitative assessment of striatal dopamine uptake appears to reliably predict phenotypic transition, contradicting previous studies [98,99]. This challenges the conventional view of these biomarkers and underscores the need to refine and optimize existing biomarker combinations. Based on these findings, controlling plasma NfL levels may be a feasible therapeutic approach for RBD. For instance, nonsteroidal anti-inflammatory drugs have been shown to reduce NfL release following nerve injury. Similarly, neuroprotective agents such as butylphthalide, which mitigate oxidative stress and inflammation, may help lower NfL levels and slow disease progression.

As research advances, NfL has emerged as a key biomarker for predicting and monitoring various neurological disorders. Recent studies have emphasized several detection assays, including traditional enzyme-linked immunosorbent assay (ELISA), and single-molecule array (Simoa) technologies [100,101]. These techniques have not only improved the early diagnosis and monitoring of neuro-

logical disorders but have also enhanced our understanding of the role of NfL in neuropathology. Investigating NfL as a biomarker paves the way for early diagnosis and treatment of RBD while establishing a scientific foundation for understanding the interplay between sleep disorders and cognitive function.

6.3 Intensity of Muscle Activity During REM Sleep

In patients with iRBD, REM sleep without atonia (RWA) has been established as a reliable electrophysiological biomarker for predicting phenotypic conversion to synucleinopathy [102]. The current assessment protocol uses video-polysomnography (vPSG) combined with advanced computer algorithms to accurately calculate the percentage of submental muscles and bilateral upper limb muscles (flexor digitorum superficialis) containing excessive electromyography (EMG) activity, which has been rigorously developed and widely accepted by the international RBD research group [103]. Compared with single-channel monitoring, multi-channel monitoring can provide more comprehensive muscle activity information in the diagnosis of RBD, significantly improve the accuracy of diagnosis, and ensure accurate identification of RBD patients. Continuous advances in technology have further optimized the RWA analysis process. The introduction of deep learning algorithms enables RWA analysis to achieve a high degree of agreement with expert visual scoring, while significantly reducing the analysis time, which strongly promotes the widespread application of this technology in clinical practice [104,105]. In one study, 221 consecutive patients with clinically suspected RBD underwent DAT single photon emission CT (SPECT) and vPSG. vPSG confirmed 176 patients with RBD, and most RWA parameters were significantly correlated with Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT) ratios. Therefore, the range of RWA values is important to estimate whether patients are in the early, middle, or late prodromal phase of α-synucleinopathy, providing them with important information about the time before possible conversion [106]. In terms of clinical application, RWA is emerging as a key stratification tool in neuroprotective trials. A study has found that different types of RWA can be used as biomarkers for the transformation of iRBD into neurodegenerative diseases. The predictive value was highest when phasic and tonic RWA were present together [102]. Collectively, RWA quantification through standardized multimodal assessment provides a robust framework for stratifying phenoconversion risk and guiding early intervention in iRBD patients on the synucleinopathy continuum.

6.4 Genetic Markers: SNCA and GBA

In addition to the molecular and electrophysiological biomarkers discussed above, genetic factors play a crucial role in the pathogenesis and progression of RBD. Genome-wide association studies and single-gene mutation analyses have identified several genetic variants associated with synucleinopathies and increased risk of developing RBD. Notably, variants in the *SNCA* gene, which encodes alpha-synuclein, and the *GBA* gene, encoding glucocerebrosidase, are among the most well-established genetic markers.

The SNCA Antisense RNA 1 (*SNCA-AS1*) variant (*rs3756059*) has been implicated through genome-wide association study (GWAS) and colocalization analyses, highlighting the role of SNCA in RBD and its progression to PD, DLB, or MSA [64]. Similarly, GBA pathogenic variants (such as L444P, c.84insG, and others) are strongly associated with the presence of RBD in Parkinson's disease patients, further supporting the link between lysosomal dysfunction and alpha-synuclein aggregation [74]. These genetic biomarkers not only enhance our understanding of RBD etiology but also offer potential targets for personalized therapeutic strategies.

6.5 Others

Recent research trends show a shift from the traditional detection of RWA to the collaborative application of multi-dimensional indicators to improve the ability of early diagnosis and pathological mechanism analysis. At the REM sleep microarchitecture level, refined electroencephalography (EEG) oscillation analysis revealed the core features of brain stem-thalamo-cortical circuit dysregulation: proportion of phasic REM in iRBD patients is significantly increased, indicating excessive activation of the motor commands system, while the density of sawtooth waves and the abnormal correlation between sawtooth waves and ponto-geniculo-occipital waves in PD-RBD patients reflect the dysfunction of thalamo-cortical information integration. These findings confirm that REM sleep disorders in RBD not only involve muscle tone loss and dream behavior interpretation but also extend to specific electrophysiological characteristics [107]. Such microstructure parameters can be obtained by secondary mining of PSG data, which has high specificity and clinical practicability.

At the level of cortical degeneration, cortical mean diffusivity (cMD) derived from diffusion MRI, as a new imaging marker, is significantly more sensitive to neuronal microstructure damage than traditional cortical thickness measurement. A study has shown that the cMD values of PD-RBD patients are increased in the left superior temporal gyrus, superior frontal gyrus, precentral gyrus, precuneus, and the right middle frontal gyrus, postcentral gyrus, and paracentral lobule [108]. In addition, although prolonged REM latency is not a specific marker of α-synucleinopathy, its association with increased CSF tau/β-amyloid and decreased brain-derived neurotrophic factor suggests its predictive value for the pathology of RBD comorbid with Alzheimer's disease (AD) [109]. To overcome the limitations of a single marker, future studies can adopt multimodal integration strategies (such as combining

electrophysiological and imaging indicators). This research paradigm, from microscopic oscillation to macroscopic cortical diffusion, from local neural circuits to multi-system interaction, will provide a new path for the accurate classification of RBD and the early intervention of neurodegeneration.

7. Treatment of RBD

Symptomatic treatment for RBD is crucial for preventing sleep-related falls or injuries; however, only a limited number of patients with RBD seek medical attention. Current treatment guidelines include two main categories: non-pharmacological and pharmacological interventions. Non-pharmacological approaches primarily involve comprehensive environmental modification and safety counselling to reduce injury risk, which are the cornerstone of non-pharmacological management. Recommended measures involve placing mattresses on the floor or lowering the bed height, padding furniture edges, securing windows, and removing potential hazards (such as sharp objects and fragile items) before bedtime [110]. It is also advised to maintain a certain distance from the bed partner or even sleep in separate rooms for safety [111]. Beyond environmental adjustments, establishing good sleep hygiene is important. This includes maintaining a regular sleep schedule (adhering to fixed bedtimes and wake-up times), and avoiding napping, compensating for sleep, or lying in bed for extended periods while awake. Incorporating moderate physical activity, such as daily mindful movement exercises or aerobic exercise for about an hour, may also be beneficial for overall sleep quality [112]. For anxiety and psychological burden associated with RBD, relaxation techniques like progressive muscle relaxation (PMR) and mindfulness practices (e.g., breath watching and body scanning) can help patients relax and reduce excessive focus on symptoms. Although psychotherapy (e.g., cognitive behavioral therapy, CBT) has been explored, current evidence for its efficacy in reducing RBD symptoms remains limited [113].

A summary of pharmacological treatments is shown in Table 2 (Ref. [114–119]). Pharmacological treatment includes first-line agents such as clonazepam and melatonin, as well as additional agents, including pramipexole, ramelteon, rotigotine [3,120], and clonazepam, a benzodiazepine, enhances the activity of the inhibitory neurotransmitter GABA, leading to chloride influx, neuronal hyperpolarization, and inhibition of postsynaptic potentials. This process suppresses central nervous system activity, producing anticonvulsant, anxiolytic, and muscle relaxant properties. Clonazepam effectively reduces RBD symptoms by inhibiting electromyographic activity during REM sleep, with reported clinical efficacy rates up to 90% [114]. However, it may cause side effects, including falls and related injuries [121].

Melatonin is an endogenous hormone that regulates the sleep-wake cycle and modulates muscle tone during sleep by enhancing GABAergic inhibitory effects [122]. Experimental studies confirm its efficacy in reducing clinical behavioral manifestations and muscle tone during REM sleep. Moreover, melatonin has a more favorable safety and tolerability profile than does clonazepam [115]. Schaefer *et al*. [123] found that prolonged-release melatonin improved RBD symptoms coexisting with obstructive sleep apnea syndrome. However, neither clonazepam nor melatonin significantly alters sleep architecture [124].

Recent studies suggest that prazosin, an α1-adrenergic antagonist, may be effective in treating high doses of melatonin-resistant RBD, though no reduction in dream-enacting behaviors was observed. A potential synergistic effect of prazosin in combination with melatonin cannot be excluded [125]. Dopamine receptor agonists, such as pramipexole, ramelteon, and rotigotine, have also demonstrated efficacy in alleviating RBD symptoms. Existing studies hypothesize that these agents modulate the basal ganglia on the pudendal nucleus or are related to the degradation of the basal ganglia occurring in conjunction with damage to the pudendal nucleus [116]. Further research suggests that dopaminergic dysfunction may play a critical role in the pathophysiology of RBD [117].

Nonetheless, the role of dopamine agonists in ameliorating the symptoms of RBD remains controversial. Short- to medium-term randomized clinical trials involving small cohorts have reported variable efficacy for rivastigmine, memantine, 5-hydroxytryptophan, and the herbal medicine yokukansan. Additionally, the excitatory effects of selective serotonin reuptake inhibitors, such as paroxetine, on serotonin receptors may influence cortical functions related to mood and sleep regulation, although no direct experimental evidence supports their role in RBD treatment. However, previous studies suggest that paroxetine improves sleep quality and depressive symptoms in patients with comorbid sleep disorders [126]. Trazodone, a medication widely used for treating insomnia and other symptoms, has demonstrated sedative effects and potential benefits in improving early symptoms of attention deficit disorders, REM sleep abnormalities, concussion, and olfactory memory deficits [127]. Its role in modulating early tau pathology suggests it may slow disease progression. This highlights the need for further research into the interaction between RBD and tau proteins, particularly in validating the predictive role of tau proteins in phenotypic transitions [128]. Barrow and Vendrame [129] recently reported significant clinical improvement in three iRBD cases following trazodone treatment, reinforcing its potential therapeutic role. Further details on pharmacological treatments are summarized in Table 2.

It is noteworthy that although the aforementioned medications demonstrate efficacy in treating RBD, further research is needed to elucidate their mechanisms of action and optimize treatment regimens. Long-term, multicenter, randomized, placebo-controlled clinical trials are essential

Table 2. Pharmaceutical treatment of RBD.

Drug	Dose (mg/day)	Benefits	Side effects	Targeted patients	Ref
Clonazepam	0.25–2.00	Effective inhibition of neuronal excitability and muscle activities during REM sleep	Daytime excessive sedation, impotence, dyskinesia, confusion, memory loss, etc.	Patients with confirmed RBD, but it should be used with caution in those with concomitant dementia, gait disorders, or OSA	[114,117]
Melatonin	3.00–12.00	Improvements of sleep quality and regulation of circadian rhythms with neuroprotective effects	Morning headaches, daytime sleepiness, delusions and hallucinations	RBD patients with DLB, Parkinson's disease, and MSA	[115]
Pramipexole	<0.70	Reduction of the potential side effects of clonazepam in older adults or patients with RBD with sleep disordered breathing	Patients with DLB may experience hallucinations and delusions	Patients with RBD not diagnosed with neurodegenerative diseases	[116]
Rotigotine	Limited data	Significant improvements in morning motor function, sleep quality, and non-motor symptoms	No information available	PD patients with concomitant RBD	[116]
Paroxetine	10.00–40.00	Reduction of RBD symptoms by reducing REM sleep	Nausea, dizziness, diarrhea, thirst, etc.	Patients with RBD who have not yet developed neurodegenerative disease	[118]
Donepezil	10.00–15.00	Improvement of cognitive function	Seizures due to cholinergic effects	RBD patients with mild cognitive impairment, PD, or DLB	[119]
Alprazolam	1.00–3.00	Anxiolytic and sedative effects may be more effective in RBD patients with concomitant anxiety symptoms	No information available	Patients with RBD who have not yet developed neurodegenerative disease	[117]
Temazepam	10.00	Sedative and anti-anxiety effects	No information available	RBD patients with symptoms of insomnia	[117]
Desipramine	50.00	Effective inhibition of REM sleep	No information available	Secondary RBD	[117]

OSA, obstructive sleep apnea.

for evaluating symptomatic and preventive therapies. Additionally, patient-specific factors, such as comorbid sleep disorders (e.g., obstructive sleep apnea, restless legs syndrome), should be carefully considered to ensure timely intervention. Until RBD symptoms are effectively controlled, cohabitating partners may need to sleep in separate rooms for safety. Future studies should explore novel medications and innovative therapies to provide safer and more effective treatment options for patients with RBD.

8. Strengths and Limitations

We reviewed literature on RBD published between 2000 and 2025, providing an integrated overview of its pathophysiological mechanisms, biomarkers used for early detection, and therapeutic strategies. This comprehensive approach might deepen the understanding of RBD's intricate relationship with neurodegenerative disorders and underscores the importance of early intervention strategies. Special emphasis was placed on key biomarkers such as α-syn and NfL, which are essential for the early diagnosis and monitoring of RBD progression. Additionally, the review provided a thorough exploration of therapeutic interventions, including pharmacological (melatonin, clonazepam, and trazodone) and non-pharmacological methods, thus addressing critical aspects of clinical management. Despite these strengths, the review has some limitations. The literature search was restricted to studies published from the year 2000 onwards to focus on contemporary evidence, which may have excluded some earlier seminal works. In addition, it exclusively included literature published in English, potentially overlooking important contributions published in other languages. Moreover, the analysis was confined to PubMed and Web of Science databases, which might restrict the comprehensiveness and depth of the review. Future research should aim to incorporate additional databases and diverse data sources to mitigate these limitations.

9. Conclusions

RBD is increasingly recognized as a prodromal stage for neurodegenerative diseases, and (e.g., α-syn, NfL, and tau proteins) plasma and CSF biomarker assessment holds promise for early diagnosis. Technological advancements, such as RT-QuIC and Simoa, have further improved biomarker detection sensitivity. Nevertheless, these advances, including RT-QuIC, show particular promise for early RBD diagnosis and synucleinopathy detection.

Furthermore, this review emphasizes the need for future research to explore multimodal biomarker combinations—integrating neuroimaging, fluid biomarkers, and electrophysiological signals—to enhance diagnostic accuracy and prognosis. Clinical trials targeting environmental risk reduction, such as air pollution and occupational exposure interventions, should also be prioritized to assess their preventive potential.

Regarding pharmacotherapy, clonazepam and melatonin remain first-line treatments for RBD; however, treatment strategies must be individualized to account for disease complexity, comorbidities, and potential side effects. As research progresses, further exploration of therapeutic targets and biomarker-driven interventions will be crucial in refining management strategies for RBD.

Abbreviations

α-syn, α-synuclein; αSyn-SAA, α-synuclein seeded amplification assay; CR1-TM, Complement receptor 1 transmembrane domain; CSF, Cerebrospinal fluid; cMD, Cortical mean diffusivity; CNS, Central nervous system; DLB, Dementia with Lewy bodies; DAT, Dopamine transporter; DAT SBR, Dopamine transporter specific binding ratio; DAT-SPECT, Dopamine transporter single-photon emission computed tomography; dMRI, Diffusion magnetic resonance imaging; eQTLs, Expression quantitative trait loci; ECD SPECT, Ethylcysteinate dimer single-photon emission computed tomography; EMG, Electromyography; ELISA, Enzyme-Linked Immunosorbent Assay; ^{18}F-AV-133 VMAT2 PET, Fluorine-18 AV-133 vesicular monoamine transporter 2 positron emission tomography; ^{18}F-FDG PET, Fluorine-18 fluorodeoxyglucose positron emission tomography; GABAergic, γ-aminobutyric acid-ergic; GBA, Glucocerebrosidase; Gly, Glycinergic; iRBD, idiopathic RBD; GWAS, Genome-wide association study; HD-EEG, High-density electroencephalography; LC, Locus coeruleus; LDT, Laterodorsal tegmental nucleus; LH, Lateral hypothalamus; LPT, Lateral pontine tegmentum; MSA, Multiple system atrophy; LRRK2, Leucine-Rich Repeat Kinase 2; NfL, Neurofilament light chain; OB, Olfactory bulb; Orx, Orexin; OSA, Obstructive sleep apnea; PD, Parkinson's disease; PET, Positron emission tomography; PPN, Pedunculopontine; PDRP, Parkinson disease–related covariance pattern; QSM, Quantitative susceptibility mapping; RBCs, Red blood cells; RBD, REM Sleep Behavior Disorder; REM, Rapid eye movement; RT-QuIC, Real-time quinacrine-induced conversion; RWA, REM sleep without atonia; Simoa, Single-molecule array; SLD, Sublaterodorsal tegmental nucleus; sRBD, secondary RBD; SubC, SubCoeruleus; SPECT, Single photon emission CT; SBR, Specific binding ratios; SUVR, Standardized uptake value ratio; SAA, Seed amplification assay; Simoa HD-1, Single molecule array high-definition 1 analyzer; sGBA, Severe GBA mutation; VMM, Ventromedial medulla; vlPAG, Ventrolateral periaqueductal gray; vPSG, Video-polysomnography; VMAT2, Vesicular monoamine transporter 2.

Author Contributions

HZ: Conceptualization, Methodology, Investigation, Writing—Original Draft. SZ: Investigation, Data Curation, Validation, Writing—Original Draft. HC: Investiga-

tion, Data Curation, Writing—Review & Editing. YW: Visualization, Writing—Review & Editing. HG: Validation, Visualization. DY: Conceptualization, Supervision, Project Administration, Writing—Review & Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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