

# Clinical Overview of REM Sleep Behavior Disorder

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## Abstract

### Keywords

- ▶ sleep
- ▶ rapid eye movement sleep
- ▶ REM sleep without atonia
- ▶ REM sleep behavior disorder
- ▶ dream enactment behavior
- ▶ parasomnia
- ▶ Parkinson's disorders
- ▶ synucleinopathy
- ▶ neurodegenerative disease

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia during REM sleep that allows motor responses to dream content. Patients display patterns of unusual, complex, and even violent motor activities. There is a high risk for harm to the patients or their bedpartners. REM sleep behavior disorder is more likely to occur in synucleinopathies such as Parkinson's disease, Lewy body dementia, and multiple system atrophy and may precede clinical manifestations by decades. In secondary RBD, brainstem centers involved in muscle atonia during REM are disrupted. These conditions include multiple sclerosis, cerebral vascular accidents, and brainstem tumors. The acute onset of RBD may associate with the use of antidepressants and acute withdrawal from alcohol. The diagnosis of RBD should be confirmed by polysomnography utilizing multiple-limb electromyography and synchronized digital video monitoring and demonstrate elevation of muscle tone during REM sleep along with dream enactment behavior. The differential diagnosis includes sleepwalking, nocturnal seizures, sleep apnea, and periodic limb movement disorder. Management focuses on maximizing safety, use of clonazepam/melatonin, and discussion of prognosis with patients.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia that occurs during REM sleep, and was first described by Schenck et al in 1986.<sup>1</sup> The condition was initially found in cats following lesion experiments in the vicinity of the perilocus coeruleus back in the 1960s,<sup>2</sup> and was later described in humans two decades later by Dr. Schenck.<sup>1</sup>

Parasomnias are undesirable behaviors that occur in the transition from sleep to wakefulness. The episodes may include motor, verbal, or sensory experiences, but in RBD, the spells generally manifest as abnormal dream enactment of dream activity, often resulting in screaming, yelling, shouting, kicking, and punching behaviors generally in response to the patient's effort to protect themselves against a supposed intruder during the dream experience. Patients

with RBD characteristically display abnormal and recurrent nocturnal dream enactment behavior (DEB), occurring in the latter part of the night at a frequency that is highly variable from a few times per year to several times per month, to weekly or even nightly episodes.

On polysomnography, one observes loss of skeletal muscle tone in the chin and/or the upper or lower extremities corresponding to the dream experiences during stage-REM sleep. The dream content that is enacted is characteristically violent or aggressive, such that the patient may harm not only themselves but their bed partners as well. It is often this aspect of the behavior that brings this condition to medical attention. Paradoxically, patients with RBD may not experience the sleep difficulties per se, while it is the bed partner

who is likely to experience disrupted sleep that can result in hypersomnia.

The *International Classification of Sleep Disorders, Third Edition (ICSD- 3)* defines RBD as presenting with injurious behaviors.<sup>3</sup> This behavior also should not be attributable to another medical disorder, psychiatric condition, sleep disorder, or neurologic disorder such as seizures. Patients typically present with altered dream mentation causing nightmares and active physical behavior during dreaming,<sup>4</sup> along with abnormal augmentation of muscle tone during the episodes.

## Epidemiology

The prevalence of RBD in the population is suggested to range from 0.38 to 2.01%, but is much higher in neurodegenerative diseases, particularly the alpha ( $\alpha$ ) synucleinopathies.<sup>5</sup>

## Natural History

Rapid eye movement sleep behavior disorder may precede the emergence of various synucleinopathies by as much as a decade, such that its presence may herald the future emergence of neurodegenerative diseases.<sup>6-9</sup> In fact, RBD is considered one of the most specific predictors of the future risk of development of conditions such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).<sup>4,5</sup> In this article, we will review the clinical and unique polysomnographic signature markers of RBD, the established clinical criteria for the diagnosis of RBD, proposed pathophysiologic mechanism, and discuss conservative and pharmacological treatment options based on a recent position paper.

## Classification

Rapid eye movement sleep behavior disorder may be divided into two distinct phenotypes. The term "*idiopathic RBD*" (iRBD) refers to RBD that occurs in the absence of another other identifiable neurologic disorder (e.g., dementia). The term "*secondary or symptomatic RBD*" (sRBD) refers to RBD occurring in the context of another identifiable neurologic disorder (e.g., neurodegenerative disease).

However, a growing body of evidence that suggests that iRBD may actually represent an evolving neurodegenerative disorder in a significant number of affected individuals, and "cryptogenic" may be more appropriately applied in these individuals.<sup>6-10</sup> This is supported by the pathophysiological finding of Lewy bodies identified at autopsy in presumptive cases of iRBD in individuals who have not yet expressed symptoms of dementia.<sup>11,12</sup> Symptomatic RBD may be related to RBD in the context of another neurologic condition, such as narcolepsy, neurodegenerative disorders, another sleep disorder, or even medications including drug-withdrawal states.<sup>13</sup> The term "toxic" RBD has been coined to describe the emergence of RBD spells in relation to medications, particularly antidepressants and substances of use or abuse.

## Demographic Features

The demographics of RBD include a typical age of onset between 40 to 70 years, with a range from 15 to 80 years. Those individuals who develop RBD before age 50 appear to have different demographic characteristics, including an equal female: male gender predilection, higher rates of iRBD and parasomnia overlap syndrome (a combination of a none REM and REM parasomnia), comorbid narcolepsy, higher rates of antidepressant medication use, and possibly autoimmune diseases.<sup>5,10,14-16</sup> Above age 50, one observes a higher male gender predilection of RBD and<sup>17</sup> association with neurodegenerative conditions such as PD (82%), DLB (82%), and MSA (64%).<sup>18</sup>

## Clinical Semiology

Episodes of RBD consist of the enactment of action-filled dreams where patients believe that they are being attacked, confronted, or chased such that they are at risk of imminent harm. The dream enactment semiology may be violent and involve threatening imagery of intruders or animals (usually serpents, reptiles, or biting insects). At the end of the dream sequence, the patient awakens abruptly, and may be able to report the dream content that parallels the observed sleep behaviors and corresponds to the dream mentation.<sup>19</sup>

## Differential Diagnosis

Rapid eye movement sleep behavior disorder should be distinguished from other conditions in which vivid dreams and dream enactment may occur in the absence of RBD. These include conditions such as posttraumatic stress disorder (PTSD), severe obstructive sleep apnea, and nocturnal frontal lobe epilepsy.<sup>10</sup> In addition, abnormal sleep behaviors and unpleasant dreams simulating RBD symptomatology ("pseudo-RBD") may occur in patients with severe PLMS or OSA. In these cases, videopolysomnography (vPSG) has been used to effectively rule out RBD, and instead identify prominent PLMS followed by arousals containing abnormal behaviors.<sup>20</sup>

Dream enactment behavior is not specific to RBD and may also be observed in other parasomnias such as disorders of arousal (DOA), particularly sleep terrors (with recollection of negative, life-threatening images) and sleep walking (somnambulism), although ambulation and other forms of displacement from bed are extremely uncommon in RBD.<sup>19</sup> In these other parasomnia conditions, the sleeper is typically abruptly and momentarily confused upon awakening.<sup>19</sup> Dream enactment behavior may also occur after the use of certain drugs or alcohol, or the withdrawal from these substances.<sup>5</sup>

Rapid eye movement sleep behavior disorder by itself does not tend to cause the sleeper to be fatigued or excessively tired during the day. However, patients with RBD may have a higher risk for the co-occurrence of other conditions that may produce these symptoms, such as sleep apnea, periodic limb movement disorder, or narcolepsy.<sup>20-22</sup> It is, therefore, very important to differentiate these alternative causes of DEB from RBD through obtaining a careful and

detailed medical and psychiatric history, and consideration of use of vPSG utilizing expanded electromyographic (EMG) and electroencephalic (EEG) montages.

## Diagnostic Features

During nocturnal polysomnography studies, patients with RBD demonstrate loss of the EMG muscle atonia (REM sleep without atonia [RSWA]), which characterizes REM sleep. Rapid eye movement sleep behavior disorder is instead associated with enhanced transient and phasic skeletal muscle activity,<sup>23</sup> and may be seen as either sustained muscle activity during stage-REM sleep on the chin EMG, or excessive transient muscle activity (phasic muscle twitches) in either the chin or limb EMG during REM sleep.<sup>13</sup> Patients with RBD thus may enact violent and highly disruptive dream behaviors during stage-REM sleep in the absence of muscle atonia that may expose the patient and (and the bed partner) to significant levels of injury.<sup>19</sup>

Sleep-related behavioral manifestations may range from mild activities such as talking, laughing, shouting, swearing, gesturing, and grabbing, to more dramatic injurious behaviors consisting of flailing of extremities, punching, kicking, and sitting up or actually leaping out of bed unknowingly into another object and experiencing traumatic injuries in the process.<sup>2</sup> Rapid eye movement sleep behavior disorder has the potential to be associated with a relatively high rate

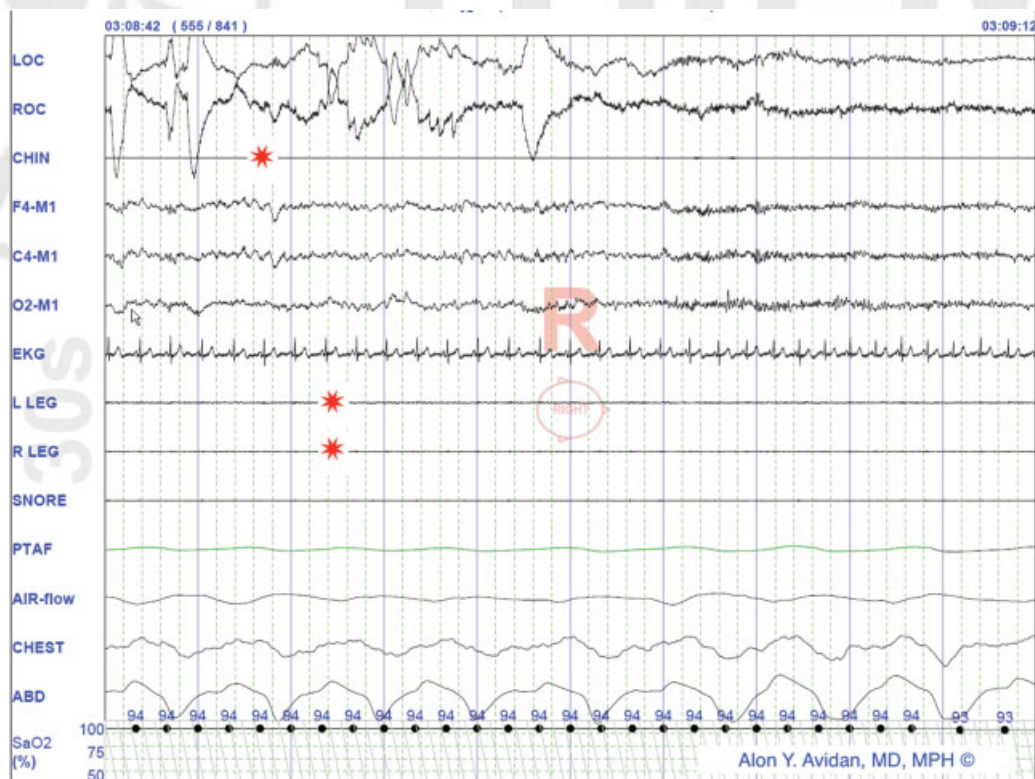
of sleep-related injury, with estimates between 33%<sup>24</sup> and 65%<sup>25</sup> in RBD patients that have reported self-injury or bed-partner injury. Episodes tend to worsen with time, and though early episodes may involve mild behaviors, later episodes may involve more intense behaviors that may result in more serious injuries such as bruises, abrasions, lacerations, subdural hematomas, and cervical spine fractures.<sup>13</sup> ▶Fig. 1 and ▶Fig. 2 illustrate normal REM sleep and abnormal REM sleep from a patient with RBD collected from the UCLA Sleep Disorders Center to illustrate normal REM-related muscle atonia (▶Fig. 1) and motor augmentation during RBD (▶Fig. 2) for contrast purposes.

## Specific Polysomnographic Diagnostic Criteria for RBD

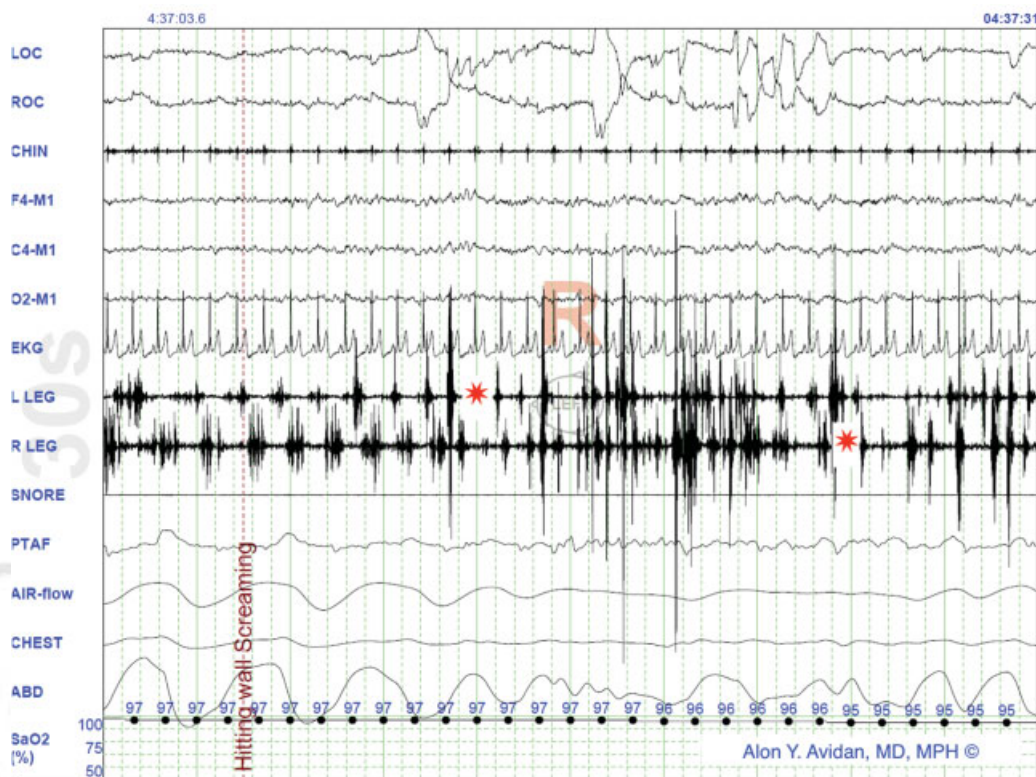
The diagnosis of definite RBD is based on the formal diagnostic criteria derived from the third edition of the *International Classification of Sleep Disorders* (2014).<sup>26</sup> The diagnosis of definite RBD must meet several distinct criteria simultaneously.

First, repeated episodes of sleep-related vocalizations and/or complex motor behaviors must be present, which may be detected on a single-night vPSG. In addition, upon awakening, the individual should be awake, alert, coherent, and able to relate the details of the dream without confusion.

The presence of RSWA (as defined by the American Academy of Sleep Medicine's *International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual*) must be



**Fig. 1** A 30-s polysomnogram out of normal rapid eye movement sleep depicting normal expression of muscle atonia in the chin and limbs (noted by the stars). Channels are as follows: LOC and ROC, electro-oculogram, left, and right outer canthus; CHIN, chin electromyogram, electroencephalogram (right frontal, central, and occipital referred to left mastoid- F4-M1, C4-M1, O2-M1); electrocardiogram (EKG) channel, right and left limb EMG (R & L LEG); snore channel (SNOR), PTAF, air-flow channel, respiratory effort (CHEST & ABD); oxygen saturation (SaO<sub>2</sub>). (Copyright to Alon Y. Avidan, MD, MPH)



**Fig. 2** A 30-s polysomnography epoch for a patient with rapid eye movement sleep behavior disorder (RBD). The polysomnogram shows rapid eye movement (REM) sleep without atonia, manifest by increased muscle activity during REM sleep depicted by the red stars corresponding by the arousal out of REM sleep associated with increased motor activity along with the annotation by the sleep technologist earlier in the epoch of a spell where the patient was witnessed to be “hitting the wall screaming.” The International Classification of Sleep Disorders III Diagnostic Criteria for RBD includes the following: (1) PGS abnormality—elevated electromyography tone during REM sleep in either submental or limb leads. (2) Either a history of dream enactment behavior or observation of abnormal REM sleep behavior during the PSG. (3) Absence of electroencephalography epileptiform activity during REM sleep. (4) The disturbance is not explained by another sleep/medical/neurologic/mental disorder, and is not related to medication/substance use. (Copyright to Alon Y. Avidan, MD, MPH)

demonstrated on PSG in addition to at least one of the following: (1) sleep-related injurious, potentially injurious, or disruptive behaviors by history; or (2) abnormal stage-REM behavior documented during PSG, including isomorphism (acting out of dreams). These manifestations must correlate with simultaneously occurring dream mentation that leads to DEB. Further, there must be absent EEG epileptiform activity during REM sleep, unless RBD can be clearly distinguished from any concurrent REM-related sleep seizure disorder. Finally, the sleep disorder should not be better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.<sup>3</sup>

Polysomnography with synchronous video monitoring should be considered in every patient in which dream enactment behavior (DEB) is suspected, and the dreams are viewed as unpleasant where the potential for injury is high for either the patient or the bed partner. It is important to distinguish RBD from other conditions in which DEB is present, without a diagnosis of RBD, such as in moderate to severe OSA, sleep walking or nocturnal seizures.<sup>20</sup>

In situations where PSG cannot be performed (for logistical or technical reasons), or when it is performed, but little or no stage-REM sleep periods are captured, or when the EMG tone during REM sleep is equivocally elevated, the term

“probable RBD” has been advocated. In these circumstances, the patients should display the typical history of recurrent DEB associated with dreams involve a threatening theme (e.g., chasing or attacking). Confidence in this “probable” diagnosis is heightened when there are no other confounding variables present in the history, such as a history of loud, disruptive snoring, observed apneic periods, or anatomical narrowing of the oropharynx to suggest a tendency toward OSA, or other conditions such as nocturnal seizures or sleepwalking.<sup>10</sup>

Rapid eye movement sleep without muscle atonia is the most important phenotype based on PSG finding. However, when formal polysomnography is not available or cannot be obtained, one can employ several well-validated questionnaires to improve the diagnostic probability of a RBD diagnosis, to facilitate time-sensitive assessment, to enhance the diagnostic accuracy, and to allow for monitoring of disease progress of RBD.<sup>27</sup> At our Sleep Disorders Center, we employ the Mayo Sleep Questionnaire (MSQ), which asks bed partners of patients with the suspected condition if they have ever seen the patient appear to “act out his/her dreams” while sleeping (i.e., punching or flailing arms in the air, shouting, or screaming).<sup>28</sup> The MSQ yielded a sensitivity of 100% and specificity (SP) of 95% for the diagnosis of RBD.

## Prognosis

Rapid eye movement sleep behavior disorder has been noted to be highly associated with the future development of various  $\alpha$ -synucleinopathies, particularly Parkinson's disease, DLB, and MSA, with an estimated rate of conversion of nearly 50% within 5 years.<sup>13,19,23</sup> Published observational studies have suggested that when patients with iRBD are followed longitudinally, the estimated 5-year risk of emergence of neurodegenerative disease was 17.7%, the 10-year risk was 40.6%, and the 12-year risk was 52.4%.<sup>8</sup> When patients with presumptive RBD were followed longitudinally, 38 to 65% of patients developed a synucleinopathy between 10 to ~30 years after RBD presentation, including PD, DLB, and MSA.<sup>9,13,29</sup>

Mild cognitive impairment (MCI) may also be seen with RBD, but with less frequency than is observed with the synucleinopathy conditions.<sup>29</sup> It has been suggested those individuals with RBD plus MCI may reflect evolving Lewy body disease, and further that the MCI subtypes characterized by maximal involvement in the attentional/executive and visuospatial domains would be more likely to reflect evolving brainstem and cerebral Lewy body disease.<sup>30</sup>

The noted association between the RBD and DLB has been demonstrated in case series suggesting that >90% of patients with RBD and dementia met formal criteria for DLB,<sup>25</sup> with RBD now being recognized as one of the suggestive features of DLB.<sup>31</sup>

Rapid eye movement sleep behavior disorder has also been reported in 70% of patients with MSA,<sup>32</sup> 40% of patients with DLB,<sup>32</sup> and 15<sup>24,33</sup> to 33%<sup>34</sup> of patients with PD. Rapid eye movement sleep behavior disorder has been reported in several members of kindreds with a *parkin* gene mutation,<sup>35</sup> and Lewy body disease pathology has been reported in different large kindreds with *parkin* mutations.<sup>36</sup> In contrast to the synucleinopathies, rare reports in the literature have shown RBD in association with some tauopathies (e.g., Alzheimer's disease, progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]), with a more-questionable causative association.<sup>37,38</sup>

In one study, patients with a neuropsychological profile consistent with probable AD were found to be indistinguishable from those with probable DLB,<sup>8</sup> thus suggesting that some cases of RBD associated with AD may in fact have underlying Lewy body disease pathology. This is also suggested by studies showing RBD in association with dementia, but not visual hallucinations or parkinsonism, likely reflecting underlying Lewy body disease pathology in the clinical context of conditions such as Alzheimer's dementia.<sup>39</sup>

Normal sleep consists of a series of REM dream episodes that occur about every 1.5 to 2 hours each night. This means that an RBD episode tends to first appear at ~1.5 hours after falling asleep. Episodes may continue to cycle and occur multiple times throughout the night until awakening the following morning. Active RBD episodes may appear as frequently as 4 times per night. Conversely, they may occur as rarely as once a week or month. Typically, normal stage-REM sleep is characterized by REMs, minimal to no EMG

tone, and mixed  $\alpha$ -to- $\theta$  brain-wave activity on electroencephalography (EEG). In contrast, the electrophysiological finding in patients with RBD is RSWA. Often, simultaneous vPSG recording is needed to fully evaluate patients with suspected RBD so that vocalizations and limb movements may be viewed in the context of the PSG data. When vocalizations and/or limb movements emerge during stage-REM sleep without associated epileptiform activity on the EEG, the diagnosis of RBD may be established.<sup>10</sup>

Rapid eye movement sleep behavior disorder is a critically important REM sleep parasomnia seen in older people. A characteristic feature of RBD is intermittent loss of REM sleep-related muscle hypotonia or atonia and the appearance of various abnormal quasi-dream enactment motor activities during sleep. The patient experiences violent dream-enacting behavior during REM sleep, often causing self-injury or injury to their bed partner.<sup>40</sup> Some patients have been known to construct specific restraints to prevent themselves from acting out their violent dream and sustaining injury as illustrated in **Fig. 3**.

One recent study from Spain demonstrates a "dose response" relationship between the onset of RBD to the development of a neurodegenerative syndrome, where the time of iRBD diagnosis to neurodegenerative disorder



**Fig. 3** A set of handcuffs constructed by a 65-year-old man with a history of dream enactment episodes to prevent himself from moving and hurting himself and his wife. The nocturnal episodes became extremely dangerous in the last few months before presentation to the UCLA Sleep Disorders Center. (Copyright retained by Alon Y. Avidan, MD, MPH)

phenoconversion was 33.1% at 5 years, 75.7% at 10 years, and 90.9% at 14 years, with a median conversion time of 7.5 years.<sup>41</sup> Data from another cohort reveal a similar trend, with a 5-year risk of neurodegenerative disease of 17.7%, 10-year risk of 40.6%, and 12-year risk of 52.4%.<sup>8</sup>

A follow-up by the group that initially discovered RBD as a sleep diagnosis, recently revealed that often following a prolonged dormant interval, the majority of patients initially diagnosed with iRBD eventually developed a parkinsonian disorder or dementia, where the specificity of iRBD converting to parkinsonism/dementia is striking.<sup>42</sup> The authors note that RBD is an important resource—with clinical and research implications—in the converging disciplines of neurology, sleep medicine, and neuroscience, highlighting the importance of conducting future prospective research evaluating putative neuroprotective agents to slow down and delay the progression to parkinsonism.<sup>42</sup>

The International Rapid Eye Movement Sleep Behavior Disorder Study Group (IRBD-SG) has recently published that whereas iRBD patients are ideal candidates for neuroprotective studies, to date, there are no agents with proven evidence of either disease-modification or neuroprotective properties in PD.<sup>43</sup> Nevertheless, the IRBD-SG provides an important platform for international collaboration to develop collaborative studies on RBD reviewing the role of environmental risk factors for iRBD, and candidate active treatment studies for both symptomatic and neuroprotective therapy.<sup>43</sup>

### Pathophysiology

An understanding of the pathophysiological loss of muscle atonia and the emergence of active motor movement during stage-REM sleep is critical to gaining insight into the factors that underlie the clinical manifestations of RBD. The normal loss of muscle tone that occurs during stage-REM sleep has been proposed to occur due to two mechanisms, one passive and one active.<sup>11</sup> In the “flip-flop switch model,”<sup>44</sup> transitions from non-REM to REM sleep are regulated by the “REM-on” and “REM-off” switches through reciprocal relationships.<sup>44</sup>

Experimentally, similar behavior has been noted after bilateral perilocus coeruleus lesions in cats, and current putative neuroanatomical explanations implicate the glutamatergic pontine sublateralodorsal nucleus as the key factor for RBD.<sup>4</sup>

Normally during stage-REM sleep, large-amplitude movements do not occur because uninhibited REM-on cells in the brainstem, with caudally directed neuronal tracts, lead to atonia.<sup>45,46</sup> Critical brainstem structures that are involved in mediating RBD in animal models include the REM-off region, consisting of the ventrolateral part of the periaqueductal gray matter (vlPAG) and lateral pontine tegmentum (LPT); and the REM-on region, consisting of the precoeruleus (PC) and sublateralodorsal nucleus (SLD), as well as the extended part of the ventrolateral preoptic nucleus (eVLPO), locus coeruleus (LC), laterodorsal tegmental nucleus (LDTN), pedunculopontine nucleus (PPN), and raphe nucleus (RN).<sup>10</sup> In cats, the REM-on neurons are thought to project rostrally to

induce the EEG changes and alterations of consciousness, and caudally to produce the suppression of muscle tone and autonomic changes characteristic of stage-REM sleep.<sup>47</sup> The REM-off region, involving the vlPAG and the LPT, causes inactivation of neurons in these regions that induces an obvious increase in paradoxical sleep. In humans, the specific nuclei or the precise neuronal networks remain less clear.<sup>5</sup>

Studies derived from cat and rat models suggest that there are two motor systems involved in the maintenance of normal stage-REM sleep. The first is involved in generating muscle atonia, and the second is involved in suppressing locomotor activity.<sup>48,49</sup> Spinal motor nerve inhibition has been suggested to occur by way of the medullary magnocellular reticular formation (MCRF), an inhibitory nucleus known to suppress anterior horn cell activity via projections of the ventrolateral reticulospinal tract (VLST). The pontine nuclei described are known to be influenced by REM and non-REM sleep circuits. Additional midbrain and forebrain structures also contribute to this circuitry, including areas such as the substantia nigra (SN), hypothalamus, thalamus, basal forebrain, and frontal cortex.

The brainstem region that appears to be particularly important in the pathophysiology of RBD, based largely on lesion studies in cats, include the MCRF, locus coeruleus/subcoeruleus complex, PPN, LDTN, and possibly the SN. Lesions in the MCRF release tonic inhibition on spinal motoneurons, leading to RSWA, but this was felt to possibly be reflective of destroying important fiber tracts with lesions. Lesions in the coeruleus/subcoeruleus complex cause RSWA, and the size of the lesion was felt to determine whether simple or complex behaviors were elicited.<sup>50</sup> There is controversy as to whether a lesion in the PPN causes RSWA.<sup>51</sup> Several lines of evidence now suggest that neurons involved in the REM-on system, are located in the subcoeruleus region and are important in the association between stage-REM sleep and EMG atonia.<sup>44,47</sup> From animal studies, it has been hypothesized that in RBD, degeneration of the subcoeruleus area disrupts descending tracts that would otherwise lead to atonia/paresis, thus releasing the motor system to produce the violent behaviors during stage-REM sleep dream-enactment behaviors.<sup>45</sup>

Although the substantia nigra and the dopaminergic system have been suggested to play a role in the REM sleep system, dopaminergic dysfunction itself does not seem to be strongly implicated in RBD pathophysiology.<sup>10</sup> In a study of 11 members of a pallidopontonigral degeneration kindred, this kindred lacked the historical, electrophysiological, and behavioral manifestations of RBD, thus providing evidence that RBD is rare in the sporadic and familial tauopathies. This further suggests that differences exist in the frequencies of RBD associated with synucleinopathies compared with the tauopathies, and further implies a selective vulnerability of brainstem circuits in synucleinopathies.<sup>52</sup>

In humans, the model is proposed to be similar, with the SLD as the major structure responsible for REM sleep.<sup>53,54</sup> Recently proposed models for the human brain suggest that the SLD or a similar nucleus, with projections to spinal interneurons (i.e., the “direct route”), is the final common

pathway that causes active inhibition of skeletal muscle activity in REM sleep. The “indirect pathway” has been demonstrated by SLD lesions causing reduced excitation of the MCRF, which in turn causes a net reduced inhibition of spinal motoneurons (either directly or via spinal interneurons). It is uncertain if direct lesioning of the MCRF in humans is sufficient to cause RBD in humans.<sup>10,11</sup>

Further, locomotor generators, which are suggested to project to the spinal motoneurons, either directly or indirectly via other brainstem nuclei, have yet to be fully characterized. There are believed to be supratentorial influences on both the locomotor generators and the processes involved in muscle atonia. In principle, other processes could also affect the locomotor drive and/or muscle atonia, such as primary sleep disorders (e.g., OSA), structural lesions in the brainstem from vascular events or mass lesions, neurodegenerative diseases, medications, recreational drugs, and head trauma, among other possibilities.<sup>10</sup> Culebras and Moore<sup>55</sup> reported on structural magnetic resonance imaging changes (T2 signal changes) in six patients with RBD, suggesting that vascular changes in the brainstem could disrupt REM sleep networks and result in clinical manifestations of RBD. However, this finding has not been corroborated in the majority of patients with RBD; therefore, it is likely reflective of one mechanism by which RBD may clinically manifest.<sup>25,56</sup>

Some molecular mechanisms that have been proposed to underlie RBD are dysregulation of the metabolism of hypocretin (orexin). Hypocretin is an important molecule modulating stage-REM sleep, and dysregulation of it could induce abnormal stage-REM sleep. In 2010, Knudsen et al showed that cerebrospinal fluid hypocretin-1 deficiency was independently associated with RBD in patients with narcolepsy.<sup>57</sup> In DLB, there was a study in 2010 demonstrating reduced neocortical hypocretin-immunoreactivity correlated with hypersomnolence and  $\alpha$ -synuclein levels, suggesting the involvement of hypocretin in sleep disorders in DLB.<sup>58</sup> Studies have also reported significant (50%) selective loss of hypocretin (Hcrt) in postmortem hypothalami of patients with PD.<sup>59,60</sup> However, the exact role of hypocretin in stage-REM sleep regulation needs to be further clarified.

### Treatment

The neurobiology of stage-REM and the characteristic features of REM atonia form the basis for understanding the factors that aggravate and predispose to the clinical manifestations of RBD. From there emerges an understanding of potential pharmacological strategies and other interventional and management techniques for RBD.

There are potential roles for both behavioral- and medication-based therapeutics. There is also an accumulating body of evidence to help guide the implementation of these interventions and their potential impact on factors such as the incidence of falls and injury, as well as effects on PSG findings, among other factors.<sup>61</sup> Drugs that stimulate the serotonin system (e.g., fluoxetine, venlafaxine, and paroxetine) and those that block acetylcholine transmission (e.g., tricyclics such as clomipramine) may induce RBD and RSWA. This may occur because they block normal sleep-related

hypotonia (serotonergic drugs) or normal RSWA (anticholinergic drugs).<sup>5</sup> It is uncertain if antidepressant-associated RBD reflects a side effect related to the use of these medications, or a marker of a prodromal neurodegenerative disease. It has also been suggested that antidepressants may unmask an earlier presentation of RBD due to a latent neurodegenerative condition.<sup>5,62</sup> Nightmares, which are considered a REM-related parasomnia have been suggested to worsen with the use of selective serotonin reuptake inhibitors (SSRIs). Although antidepressants have been shown to suppress REM sleep (by PSG), they also worsen RBD. This apparent paradox seems to suggest that although there is REM sleep suppression by SSRIs, enhanced brain arousal may be associated with aminergic stimulation leading to a greater expression of RBD. An alternative hypothesis is that late-night cholinergic rebound after serotonergic REM sleep suppression earlier in the night may result in reports of greater dream intensity. Patient reports of worsened nightmares with SSRIs are difficult to study, given the complex relationship of depression-related REM enhancement, drug-related REM sleep suppression, depression-related dream suppression, and recovery-related dream enhancement. Further research is needed to elucidate the mechanisms governing these interconnected systems.<sup>5,62</sup>

The pharmaceutical treatment of RBD is aimed at reducing the frequency and severity of DEB, abnormal vocalizations, and the unpleasant dream mentation.<sup>10</sup> The behavioral treatments for RBD are aimed at reducing potential injury to the patients and their bed partners through simple measures, such as moving sharp objects/edges out the room, placing a soft cushion or mattress on the floor adjacent to the bed, and placing a bedrail or other protective barrier on the side of the bed to prevent exit/falls. All of these behavioral interventions have been shown to be variably effective.<sup>5</sup>

Current pharmaceutical treatments for RBD are given in **Table 1**. Therapies for RBD are largely based on observational data and clinical anecdotal experience rather than larger randomized clinical trials. Clonazepam (0.25–2 mg before bedtime) appears to suppress the behavioral symptoms of RBD by reducing phasic REM muscle activity in patients with RBD, but it does not restore the normal stage-REM sleep muscle atonia. Side effects include daytime somnolence, cognitive compromise, and aggravation of OSA. For the patients who are most likely to have RBD, ones who are older might have elements of dementia already, such that adding a medication that can further impair memory, such as clonazepam, is not ideal. Approximately 10% of individuals have little to no therapeutic response to clonazepam.<sup>37</sup> Melatonin is another therapeutic option. In contrast to clonazepam, however, melatonin has a unique advantage in that it restores REM-related muscle atonia by diminishing RSWA, suggesting that it may have a more direct effect on the mechanisms that maintain normal stage-REM sleep.

The proposed mechanism supporting melatonin's activity against RBD remains elusive, but several theories have been suggested to help explain this mechanism of action including modulation of GABAergic inhibition, a direct impact on REM

**Table 1** Management options of rapid eye movement sleep behavior disorder (RBD)

Agent	Dose	Comment	Level of recommendation
Safety	NA	Universal parasomnia therapy. Removal of sharp objects from bedroom area, protecting sharp furniture, maximizing safety. Limitation: None	Recommended
Clonazepam	0.25–4.0 mg nightly, usual recommended dose = 0.5–2.0 mg 30 min before bedtime	Clonazepam will not restore muscle atonia, but will improve aggressive behaviors. Limitation: Sedation due to long half-life, respiratory depression, potential risk for falls given that RBD patients are older.	Suggested
Melatonin	3–12 mg nightly	Will improve/restore abnormal muscle atonia. Sustained dose melatonin may have an advantage. The melatonin agonist ramelteon has consistent formulation, which may be advantageous, but cost is downside. Limitation: Variable formulation, not well studied, but more data are emerging recently.	Suggested
Pramipexole	0.125 mg starting dose with effective dose ranging from 0.5–1.5 mg nightly		May be considered
Paroxetine	10–40 mg		May be considered
Donepezil	10–15 mg		May be considered
Rivastigmine	4.5–6 mg 2x/d		May be considered
Temazepam	10 mg		May be considered
Alprazolam	1–3 mg		May be considered
Yi-gan san	2.5 g 3x/d		May be considered
Desipramine	50 mg nightly		May be considered
Carbamazepine	500–1500 mg daily		May be considered
Sodium oxybate	Unknown		May be considered

Source: Aurora RN, Zak RS, Maganti RK, Auerbach SH, Casey KR, Chowdhuri S, Karipott A, Ramar K, Kristo DA, Morgenthaler TI. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med* 2010;6(1):85–95.

sleep atonia, stabilizing circadian rhythmicity, and improving sleep efficiency<sup>63–67</sup>

Melatonin dosed 3 to 12 mg at bedtime should be considered as the first-line therapy, followed by clonazepam 0.25 to 2.0 mg at bedtime if initial melatonin is judged ineffective or intolerable. However, neither agent is likely to completely stop dream-enactment behaviors, so choosing a moderate target dosage of melatonin 6 mg or clonazepam 0.5 mg, or the highest tolerable dosage that reduces attack frequency and avoids adverse effects from overtreatment, is currently the most reasonable strategy.<sup>10</sup> Melatonin 3 to 9 mg has also been tested many times openly, as well as in one much smaller study with a double-blind design.<sup>10</sup> Large multicenter, double-blind, placebo-controlled studies with well-defined outcomes are needed. Pramipexole in dosages of 0.125 to 1.5 mg has been reported to improve clinical manifestations of RBD, but efficacy studies show contradictory results.<sup>13</sup> Paroxetine and L-dopa have little evidence to support their use as treatments in RBD, and some studies

have suggested that these medications may even exacerbate RBD.<sup>13</sup> The use of anticholinergic medications (e.g., rivastigmine) is limited, but they may have a role in treating patients who also suffer from a coexisting neurodegenerative condition (i.e., a synucleinopathy).<sup>68</sup> Recent multicenter open trials have suggested that ramelteon may be helpful in the treatment of sRBD. Ramelteon is a melatonin receptor agonist at the MT1 and MT2 receptors, and is thought to function similarly to melatonin. This treatment has been shown to decrease the possibility of falling, and has been proposed to have some neuroprotective effects, like what has been shown with melatonin. Melatonin has been suggested to protect L-dopa from autoxidation in the striatum.<sup>69,70</sup> In one reported case, a 75-year-old woman with MSA and RBD was given 8 mg of ramelteon per day. The PSG showed a decrease in the percentage of RSWA from 8% to 3.5%, with associated improvement in RBD symptomatology during treatment.<sup>70</sup> In a second reported case, a 58-year-old man was diagnosed with PD with RBD. He was treated with 8 mg ramelteon per



day before going to sleep. Polysomnography revealed a decrease in RSWA from 10.9% to 3.9%, and his experience of vivid dreams and DES improved.<sup>70</sup> Large-scale clinical trials will need to occur to further assess the efficacy and safety of long-term usage.<sup>69,70</sup>

## Conclusion

Rapid eye movement sleep behavior disorder is a fascinating parasomnia, which may serve as a putative biomarker for emerging neurodegeneration. Patients with RBD may be divided into two groups: those with early age of onset (< 50 years) and those with later age of onset ( $\geq 50$  years). The most frequently associated comorbid condition in patients under the age of 50 years with RBD is narcolepsy, but in patients who are  $\geq 50$  years, it was RBD in the context of a neurodegenerative synucleinopathy. Published observational studies have suggested that when patients with RBD are followed longitudinally, the estimated 5-year risk of emergence of neurodegenerative disease was 17.7%, the 10-year risk was 40.6%, and the 12-year risk was 52.4%.<sup>7</sup> However, older patients who present with RBD are probably more likely to present with phenoconversion toward the  $\alpha$ -synucleinopathies. Traditional therapeutic mainstays with relatively robust retrospective evidence include melatonin and clonazepam, which appear to be equally effective, although melatonin is more tolerable. Third-line agents include pramipexole, paroxetine, and acetylcholinesterase inhibitors, among other choices. More recently, there has been interest in the melatonin-receptor agonist, ramelteon, but further studies are needed to prove efficacy. Behavioral interventions aimed at preventing injury in patients and their bed partners may also help to minimize injury during RBD.

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