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# REM Sleep Behavior Disorder and Other REM Parasomnias

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## ABSTRACT

**OBJECTIVE:** This article reviews rapid eye movement (REM) sleep behavior disorder (RBD) and other REM sleep parasomnias, particularly recurrent isolated sleep paralysis and nightmare disorder.

**LATEST DEVELOPMENTS:** People with RBD have dream enactment behaviors that can be distressing and cause injuries to themselves or a bed partner. Diagnosis of RBD still requires video polysomnography but new evaluative techniques are emerging. Automatic scoring of REM sleep without atonia, the polysomnographic RBD feature, has led to clearer diagnostic cutoff values. Isolated RBD is strongly linked with neurodegenerative disorders, particularly  $\alpha$ -synucleinopathies, with a median latency to neurodegenerative disease diagnosis of 8 years. Mounting imaging, electrophysiologic, and pathologic evidence supports neurodegenerative changes in patients with isolated RBD. Safety precautions should be reviewed with patients to reduce the risk of injury. Clonazepam and melatonin are first-line agents for RBD symptoms, and rivastigmine appears to be beneficial for RBD in people with mild cognitive impairment. For nightmare disorder, image rehearsal therapy is effective and can be delivered through online platforms.

**ESSENTIAL POINTS:** While RBD symptoms can often be managed, patients with isolated RBD should be monitored for signs and symptoms of impending neurodegenerative disease. Individuals who wish to know about the associated risk should be counseled accordingly to allow planning and involvement in research if they choose. Exercise may have some neuroprotective effects, although no treatment has been shown to modify the neurodegenerative risk.

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## INTRODUCTION

Several parasomnias arise in rapid eye movement (REM) sleep. These include REM sleep behavior disorder (RBD), sleep paralysis, and nightmares, which can occur in isolation or in association with various disorders.

## RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Sleep is behaviorally characterized by motor quiescence. While people dream in REM sleep the body has little to no movement. This paralysis, which spares

extraocular muscles and the diaphragm, is a protective mechanism that has presumably evolved to keep people safe from injuries. When this protective system malfunctions, the dreams can manifest with behaviors; this is known as RBD. Symptoms of RBD were noted in people with Parkinson disease in James Parkinson's essay,<sup>1</sup> and the disorder was identified and named RBD in 1986 by Carlos Schenck and Mark Mahowald.<sup>2</sup> Soon thereafter a strong association was discovered between isolated RBD and the development of neurologic diseases, particularly  $\alpha$ -synucleinopathies such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.<sup>3</sup> This finding of prodromal  $\alpha$ -synucleinopathy has motivated research aimed at understanding the pathophysiologic links between RBD and neurodegeneration, the prediction of neurodegeneration risk, biomarker identification, and preparation to test potential neuroprotective strategies to delay or prevent the development of neurodegenerative disease.

### Clinical Features

REM sleep is characterized by rapid eye movements, a desynchronized mixed alpha and theta EEG background rhythm, and muscle atonia. In addition, REM sleep is typically associated with dreaming. Dysfunction of the underlying neurophysiology of REM sleep, particularly of the mechanisms that control the REM atonia, results in increased motor activity and manifests with dream enactment behaviors.

The *International Classification of Sleep Disorders, Third Edition, Text Revision (ICSD-3-TR)* diagnostic criteria for RBD are shown in **TABLE 5-1**.<sup>4</sup> All criteria must be present to make a diagnosis of definite RBD.<sup>4</sup> Patients must have dream enactment behaviors by history or video polysomnography and REM sleep without atonia (RWA), a polysomnographic finding of increased motor activity during REM sleep. When the history is typical for RBD but video polysomnography is not obtained or limited (eg, due to lack of REM sleep during the study), this clinical entity may be called probable RBD.

A detailed history is essential to characterize a patient's symptoms of RBD, including dreams or nightmares, motor activity, and injuries. Symptom onset often predates the time of presentation by many years. Most people with RBD recall at least some unpleasant dreams. The types of dreams described are often

### ICSD-3-TR Diagnostic Criteria for REM Sleep Behavior Disorder<sup>a</sup>

**TABLE 5-1**

*International Classification of Sleep Disorders, Third Edition, Text Revision diagnostic criteria A through D must be met for a rapid eye movement (REM) sleep behavior disorder diagnosis:*

- A** Repeated episodes of sleep-related vocalization or complex motor behaviors
- B** These behaviors are documented by polysomnography to occur during REM sleep or, based on the clinical history of dream enactment, are presumed to occur during REM sleep
- C** Polysomnographic recording demonstrates REM sleep without atonia
- D** The disturbance is not better explained by another current sleep disorder or mental disorder

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persecutory, with the patient defending oneself, being chased by an assailant or animal, or arguing with someone. Less distressing dreams can also be action-packed (eg, playing sports) or calm and enjoyable (eg, playing cards).<sup>5</sup>

Various dream enactment behaviors that have been described include talking, screaming, punching, kicking, throttling, or jumping out of bed ([VIDEO 5-1](#)). While these types of behaviors are more commonly reported by patients and bed partners, especially when they are injurious, patients often have simple or noninjurious behaviors that are not observed or reported. Reported event frequency can vary widely, from less than once monthly to even daily, and can vary throughout the course of the disorder. As many as 44% of patients are unaware of the behaviors, so collateral history or recordings are important to estimate the frequency of all dream enactment events, not only those that lead to injury or fall.<sup>5</sup> Furthermore, one study reported that in 11% of patients, RBD symptoms were not volunteered but were elicited with specific questioning.<sup>5</sup> Of note, major or more injurious behaviors, which are more likely to be reported, constitute only a small fraction of the total event number when mild events are taken into account.<sup>6</sup>

A major concern about dream enactment behavior is the risk of injury to patients and their bed partners. Affected individuals may punch or kick the wall or jump out of bed, which can lead to bruises or hip or head injuries. Injuries have been reported in 32% to 76% of patients and 17% to 64% of bed partners.<sup>6</sup> Because of the risk to the bed partner, the patient and bed partner often either put a barrier between them in the bed or sleep in separate beds.

Mood disruption, including depression and anxiety symptoms, are more common in people with RBD compared with controls.<sup>7</sup> In addition, several antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can exacerbate RBD symptoms, so appropriate treatment options need to be carefully considered in patients with RBD.

Several features in the history distinguish RBD from non-REM parasomnias. Non-REM parasomnia events are more common in the first half of the sleep period (particularly during the first hour), and during the event the eyes are often open and the person can respond to the environment, albeit inappropriately. The non-REM parasomnia sleepwalking can include moving away from the bed or out of the room. Attempts to wake a person while sleepwalking can cause them to have an inappropriate or aggressive response. In contrast, dream enactment in RBD can happen across the night but tends to occur in the last half of the sleep period, which is usually richer in REM sleep. People with narcolepsy, who have frequent REM sleep intrusions during wake and sleep, can have dream enactment events at any time in the sleep period. RBD events are related to the internal dream mentation; a patient's eyes are typically closed during these events and they have no awareness of the environment. The lack of atonia is intermittent, and patients may sit up briefly or jump out of bed but do not step out of bed. Patients can wake up easily from RBD behaviors by themselves or from interacting with an observer. While the types of behaviors seen in RBD and non-REM parasomnias appear distinct, these historical details may not be available, and polysomnography can help distinguish these features. When both types of parasomnias co-occur, this is called parasomnia overlap disorder.<sup>4</sup>

## Polysomnography Features

In addition to the detection of RWA, as detailed below, video polysomnography is important to evaluate for other sleep disorders such as sleep-disordered breathing, periodic limb movements of sleep, or other non-REM motor events, particularly in people with neurodegenerative disease.<sup>8</sup> Periodic limb movements of sleep are present in about one-half of patients with RBD, more so in those with neurodegenerative disease,<sup>9</sup> and sleep apnea is seen in about one-quarter of people with neurodegenerative disease.<sup>5</sup>

Dream enactment behaviors can be observed on video polysomnography but are not always present during the sleep study. Most events are simple jerks, and less commonly are complex behaviors followed by major and violent movements. Violent movements occur less than 1% of the time. Upper limb movements are more common than leg or head movements.<sup>6</sup>

RWA is the core polysomnographic feature of RBD (**FIGURE 5-1**) and is required for diagnosis.<sup>4</sup> The American Academy of Sleep Medicine Scoring Manual defines visual scoring of RWA on an epoch of REM sleep based on the presence of tonic (sustained) or phasic (transient) EMG muscle activity.<sup>10</sup> For phasic muscle activity, a 30-second epoch is divided into ten 3-second mini-epochs, and RWA is present if at least 50% of the mini-epochs have bursts of activity (0.1 to 5.0 seconds in duration, at least double the baseline EMG amplitude). The scoring of RWA during any epoch is done based on the presence of any of the following: excessive tonic chin EMG activity ( $\geq 50\%$  of the epoch), excessive phasic chin or limb EMG activity ( $\geq 50\%$  of the mini-epochs), or if 50% or more of the mini-epochs have either tonic or phasic chin or limb EMG activity. Upper limb EMG may also be used, utilizing either the flexor digitorum superficialis or extensor digitorum communis. While specific criteria exist for scoring a single epoch as having RWA, neither the American Academy of Sleep Medicine Scoring Manual nor the *ICSD-3-TR* defines how many epochs are needed to establish that a patient has RWA for the diagnosis of RBD. However, RWA for RBD diagnosis should not be made based on the presence of only a single epoch with RWA.

Other validated visual scoring methods include the “Montreal” method by Lapierre and Montplaisir, the Sleep Innsbruck Barcelona (SINBAR) criteria, and the Mayo criteria.<sup>11</sup> All sets of criteria rely on a combination of phasic and tonic EMG activity, with slight differences in duration criteria for phasic EMG elevation. The SINBAR criteria include bilateral flexor digitorum superficialis EMG, while the others rely on chin and tibialis anterior EMG electrodes. Upper limb EMG does appear to be important given that movements are more common in arms than legs<sup>6</sup> and chin EMG may have artifacts from sleep apnea.<sup>12</sup> Based on the SINBAR criteria, a cutoff of 32% of REM sleep with RWA using chin and flexor digitorum superficialis EMG was optimal for a diagnosis of RBD.<sup>13</sup> The International RBD Study Group also recommended guidelines on video polysomnography technical settings, REM sleep scoring, RWA scoring, audio and video analyses, and RWA thresholds for RBD diagnosis.<sup>12</sup>

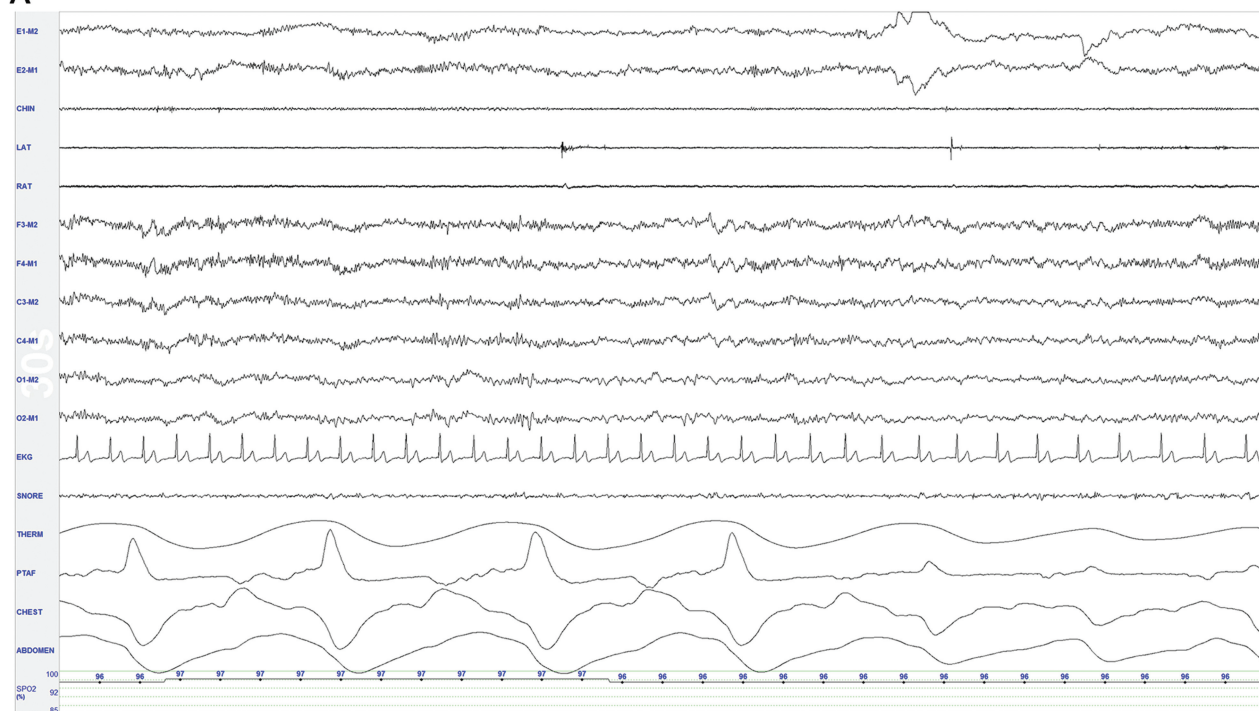
Several automated scoring methods have been developed,<sup>14,15</sup> although it remains unclear if one method is more optimal than another. Currently, their use is mainly limited to research, and they are not widely used in clinical practice.<sup>15</sup> The most widely reported method is the REM atonia index, which is a proportion calculated using automated analysis and ranges from 0 to 1, with higher values indicating more atonia (a REM atonia index score of 1 indicates complete atonia).

## KEY POINTS

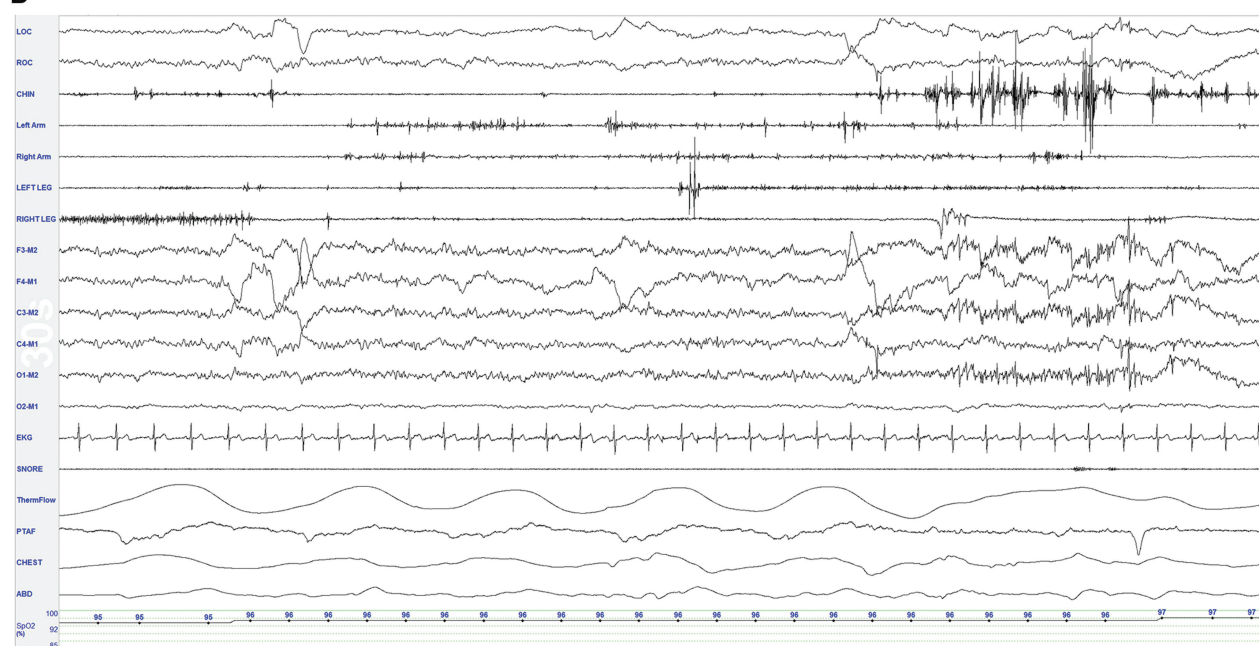
- Diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) requires historical or video polysomnographic evidence of dream enactment behaviors and REM sleep without atonia.
- Dream enactment behaviors in RBD can include punching, kicking, or falling from the bed, which can cause injuries to the patient and bed partner.
- Dream enactment in RBD can happen across the night but tends to occur in the last half of the sleep period, which is usually richer in REM sleep.
- Polysomnography is important to evaluate for RBD mimics, such as sleep apnea or periodic limb movements of sleep.



A



B



**FIGURE 5-1**

Polysomnograms showing rapid eye movement (REM) sleep with and without atonia. **A**, 30-second epoch of normal REM sleep. Channel names are on the left side. Note the low EMG tone in the CHIN and limb (left anterior tibialis [LAT], right anterior tibialis [RAT]) EMG electrodes. **B**, 30-second epoch of stage REM sleep in a patient with REM sleep behavior disorder. Note the increased motor activity throughout the epoch with some tonic activity in the right leg electrode and phasic activity in the chin and left and right arm electrodes.

A REM atonia index score less than 0.8 is considered abnormal; this cutoff has been validated in isolated RBD and RBD associated with Parkinson disease and correlates well with visual RWA scoring methods. Automated RWA scoring methods still require human supervision for REM sleep scoring and artifact exclusion.

Video polysomnography is necessary for the diagnosis of RBD, although the sensitivity of the test is not perfect. Reasons include night-to-night variability in the occurrence of RBD events and RWA, lack of REM sleep during the night of the study, or artifacts that obscure the detection of RWA. In cases with no observed REM sleep on the video polysomnogram, severe obstructive sleep apnea, which can mimic RBD, is common and should be addressed prior to reevaluation. Sleep disruptions and unpleasant dreams due to sleep apnea-related arousals can be very similar to those of RBD.<sup>16</sup> In addition,  $\alpha$ -synucleinopathies can also result in a lack of REM sleep.<sup>17</sup>

### Questionnaires

Given the time and financial cost of video polysomnography, several questionnaires and scales have been developed and validated against polysomnography.<sup>18</sup> Questionnaires intended for diagnostic purposes have limitations due to recall bias; up to 44% do not recall RBD behaviors in sleep, and collateral history may not be available.<sup>5</sup> Furthermore, these questionnaires cannot distinguish RBD from RBD mimics. Other scales are intended to monitor RBD severity longitudinally. The RBD Screening Questionnaire is a self-administered scale that measures the presence or absence of RBD symptoms over one's lifetime.<sup>18</sup> This scale is validated in the sleep clinic population and can be used for screening or diagnosis but not disease monitoring. The Mayo Sleep Questionnaire has a screening question that, if positive, triggers five additional questions and is validated for RBD screening in patients with neurodegenerative disease but not isolated RBD.<sup>18</sup> The Innsbruck RBD Inventory is a five-question survey validated in a sleep center that distinguishes RBD from other disorders and can be used for screening or diagnosis.<sup>19</sup> The RBD Questionnaire-Hong Kong evaluates behavior and dream frequencies and can be used for disease monitoring.<sup>18</sup> However, it cannot differentiate between subtypes of RBD (isolated or secondary) or RBD from non-REM parasomnia; of note, this scale has not been validated in English. The RBD Single-Question Screen is a single-question survey that assesses for any history of dream enactment behaviors.<sup>18</sup> The simple design is meant for screening the general population with minimal questionnaire burden but was validated in a sleep clinic population, not the general population.<sup>18</sup>

The recognized limitations of questionnaires and video polysomnography highlight the need for more practical diagnostic and surveillance techniques. Wrist actigraphy may be useful with high sensitivity and moderate to high specificity, but only with expert review.<sup>20</sup> Other automated analyses using minimal sensor recordings with electrooculogram and overnight EMG have shown moderate agreement for sleep staging and high agreement for RBD detection compared with visual scoring on video polysomnography.<sup>14</sup>

### Epidemiology

Isolated RBD typically starts in the fifth or sixth decade of life with a mean age of estimated onset of 63 years and a mean age at diagnosis of 68 years.<sup>5</sup> RBD due to

### KEY POINT

● Questionnaires can aid in RBD screening but have high false-positive rates compared to polysomnography-confirmed RBD diagnosis.

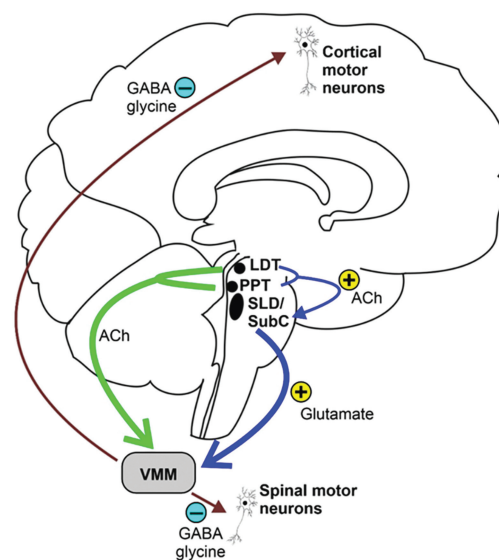
narcolepsy, however, often starts at a younger age. In those over 50 years old, RBD is more common in men but may be underreported in women. One cohort with video polysomnography–confirmed RBD was 82% male.<sup>21</sup> Men and women under 50 years old are affected equally.<sup>22</sup> Risk factors for RBD have varied among studies but are shared with those linked to the development of  $\alpha$ -synucleinopathies, including pesticide exposure, smoking, and head injury.<sup>22</sup>

Several studies have examined the prevalence of isolated RBD with varying results, possibly due to methodologic differences. The prevalence of video polysomnography–confirmed (definite) RBD is 0.68% (range 0.29% to 1.15%), while studies of probable RBD report a much higher prevalence of 5.65%. The discrepancy between definite and probable RBD prevalence likely results from the high false-positive rate seen with the questionnaires; this lack of accuracy can be mitigated by follow-up clinical evaluation or a telephone interview.<sup>23</sup>

Gene studies demonstrate that variants in glucocerebrosidase (*GBA*) confer an increased risk of isolated RBD and Parkinson disease. *GBA* mutations are seen more commonly in people with isolated RBD (9.5%) compared with those without RBD (4.1%). The more severe the variant, the greater the association between isolated RBD and Parkinson disease and the earlier the age of Parkinson disease development.<sup>24</sup> Other implicated genes include synuclein genes and genes related to circadian rhythm regulation.<sup>25</sup>

### Pathophysiology

Much of the understanding of REM sleep neurocircuitry comes from animal studies, clinical pathologic correlations, and radiographic studies.<sup>11</sup> The anatomical structures that control REM sleep involve mutually inhibiting REM-on and REM-off brainstem nuclei (FIGURE 5-2<sup>11</sup>). In the REM-on state, glutamatergic neurons in the sublateral dorsal nucleus or subcoeruleus send descending projections to the nucleus raphe magnus along with the ventral alpha gigantocellular and lateral paragigantocellular reticular nuclei of the ventromedial medulla. These second-order neurons send descending  $\gamma$ -aminobutyric acid–mediated (GABA-ergic) and glycinergic inhibitory projections to the spinal motor neurons, which results in motor atonia. In addition, cholinergic and noncholinergic neurons in the sublateral dorsal nucleus,



**FIGURE 5-2**

Neuroanatomical control of rapid eye movement (REM) atonia. The REM-on neurons of the sublateral dorsal nucleus or subcoeruleus (SLD/SubC, *thick blue arrow*), laterodorsal tegmentum (LDT), and pedunculopontine tegmentum (PPT, *thick green and thin blue arrows*) activate the ventromedial medulla (VMM) to inhibit motor activity (*thin maroon arrow*).

ACh = acetylcholine; GABA =  $\gamma$ -aminobutyric acid.

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laterodorsal tegmentum, and pedunculopontine tegmentum and glutamatergic neurons in the reticular formation send projections to the thalamus and hypothalamus, which may contribute to the cortical activation noted during REM sleep. In the REM-off state, the ventrolateral periaqueductal gray and lateral pontine tegmentum inhibit the sublaterodorsal nucleus and subcoeruleus.<sup>11</sup>

Lesions caused by  $\alpha$ -synuclein deposition, stroke, demyelination, and other causes can directly disrupt the sublaterodorsal nucleus, which subsequently can interfere with REM sleep and the mechanisms that preserve REM atonia. The result of this cascade is the clinical manifestation of RBD. Antidepressant medications may induce RBD via disrupted inhibition of REM-on neurons (which control motor atonia in the nondisease state).

Narcolepsy-related RBD may have a separate underlying mechanism. The main pathology in narcolepsy type 1 is the loss of orexinergic neurons in the lateral hypothalamus, which results in sleep/wake instability and disruption of the REM-on/REM-off switch. This instability allows for REM intrusions into wakefulness, with clinical manifestations such as hypnagogic and hypnopompic hallucinations, sleep paralysis, and cataplexy. The sleep-wake instability seen in narcolepsy type 1 also destabilizes REM sleep, which may explain RBD that occurs in people with narcolepsy.

### Types of RBD

RBD can be classified into different types based on the associated cause: isolated RBD, secondary RBD, and drug-induced RBD.

**ISOLATED RBD.** RBD that occurs in the absence of an identified cause is termed *isolated* RBD, previously called *idiopathic* RBD. Since most people with isolated RBD eventually develop a neurodegenerative disease, the term *isolated* is favored over *idiopathic*. Isolated RBD is the type that portends a high long-term risk of neurodegenerative disease, as detailed below (**CASE 5-1**).

**SECONDARY RBD.** Secondary RBD refers to RBD in the presence of an associated disorder such as neurodegenerative disease, narcolepsy, focal lesions, and other comorbidities (**TABLE 5-2**). When a person with isolated RBD develops a neurodegenerative disease, the subtype changes from isolated RBD to secondary RBD.

The most common cause of secondary RBD is neurodegenerative disease, particularly the  $\alpha$ -synucleinopathies: dementia with Lewy Bodies, Parkinson disease, and multiple system atrophy. The prevalence of RBD is very high among those with an  $\alpha$ -synucleinopathy, with RBD prevalence rates of 30% to 50% in people with Parkinson disease and more than 70% in people with dementia with Lewy bodies or multiple system atrophy.<sup>22</sup>

RBD symptoms can change over the course of the neurodegenerative disease. Dream enactment can remain stable or even decrease, but RWA appears to increase with the progression of Parkinson disease and dementia with Lewy bodies.<sup>26</sup> RBD symptoms can start after Parkinson disease onset, with RBD prevalence increasing from 25% to 52% over the course of Parkinson disease.<sup>26</sup>

In people with known neurodegenerative disease, the presence of RBD predicts worse motor and cognitive function. In those with Parkinson disease, probable RBD is associated with worse motor scores, longer Parkinson disease

### KEY POINTS

- RBD is more common in men among people 50 years old or older but can affect men and women equally in those younger than 50 years old.
- Antidepressant medications may induce RBD via disrupted inhibition of REM-on neurons (which control motor atonia in the nondisease state).
- RBD can start after the onset of neurodegenerative disease or can be comorbid with other disorders, such as narcolepsy.
- In people with known neurodegenerative disease, the presence of RBD predicts worse motor and cognitive function.



duration, more cognitive dysfunction, worse olfaction and constipation, and more gait and balance dysfunction.<sup>27,28</sup>

RBD secondary to narcolepsy comprises 10% to 15% of people with secondary RBD overall and 38% in those younger than 50 years old.<sup>29</sup> RBD symptoms are seen in 41.4% of people with narcolepsy type 1 and 13.2% of people with narcolepsy type 2, and RBD is more common in people with narcolepsy type 1 and narcolepsy type 2 who take antidepressants.<sup>30</sup> The events seen in RBD

## CASE 5-1

A 59-year-old man presented to the clinic with a 2-year history of moving in his sleep. He had various vivid dreams of being chased by a tiger, attacked by a robber, and having to jump away from an oncoming car. His spouse observed him acting out his dreams three times per week, during which he appeared to be running in the bed, punching, or jumping out of the bed. In the context of this behavior, he had unknowingly hit his spouse twice, both without injuries. The patient once bruised his wrist when he fell out of bed. The events mainly occurred later in the night; his eyes were closed and he could be easily awakened. He sometimes remembered the content of his dreams. He had no other medical history and took no medications. His neurologic examination was normal. In-laboratory polysomnography done with additional forearm EMG leads showed increased muscle activity in the chin, arms, and legs. Some simple movements and occasional punching were seen during rapid eye movement (REM) sleep. His apnea-hypopnea index score was 2 events per hour, and his periodic limb movement index score was 10 events per hour.

The patient was diagnosed with isolated REM sleep behavior disorder (RBD). Safety precautions were discussed, and the patient was advised to pad nearby furniture, place cushions on the floor or install a bed rail, and remove firearms from the bedroom. Clonazepam 0.25 mg nightly was initiated. When asked, the patient indicated that he wanted to know about future health risks associated with isolated RBD. The clinician discussed the risk of neurodegenerative disease over the next several years along with a plan for longitudinal monitoring. After 1 month of clonazepam use, the patient reported only one interval RBD event and no daytime sleepiness. Over 8 years of follow-up, the patient developed a tremor and difficulty fastening buttons. Resting tremor, slight shuffling gait, asymmetric bradykinesia, and rigidity were seen on examination. The patient was diagnosed with Parkinson disease and a dopamine agonist was initiated with improvement in symptoms.

## COMMENT

This case highlights a common presentation of isolated RBD, which can be the harbinger symptom prior to the development of a neurodegenerative disease such as Parkinson disease. RBD events typically respond well to clonazepam. In people with RBD and comorbid obstructive sleep apnea, treatment of sleep-disordered breathing is important to determine its contribution to RBD symptoms.

secondary to narcolepsy are more evenly distributed throughout the sleep period compared with the events noted in the setting of isolated RBD, which are more frequent in the second half of the sleep period.<sup>31</sup> The electrophysiologic measurement of the REM atonia index in those with RBD and narcolepsy is lower than in controls but still higher than in those with isolated RBD.<sup>29</sup>

Other neurologic diseases that are uncommon causes of RBD include multiple sclerosis, stroke, tumors, Wilson disease, Huntington disease, autoimmune disorders such as anti-IgLON5, contactin-associated protein-like 2, and leucine-rich glioma-inactivated 1 antibody diseases, and amyotrophic lateral sclerosis.<sup>32,33</sup> Posttraumatic stress disorder (PTSD) is also linked to RBD. RBD occurs in 15% of veterans with PTSD,<sup>34</sup> and RWA is more prominent in people who have PTSD with RBD compared with those who have PTSD without RBD but is less prominent than in isolated RBD. However, in one study the individuals with PTSD-related RBD were all on antidepressants, which may have influenced the amount of RWA observed.<sup>35</sup>

The pathophysiologic links between PTSD and RBD remain unclear. There may be neurochemical and physiologic changes that are not associated with  $\alpha$ -synucleinopathies. For example, prolonged stress in animal models can lead to depletion of norepinephrine and neuronal loss in the locus ceruleus.<sup>34</sup> However, it is also possible that this neurotransmitter depletion causes an unmasking of isolated RBD.<sup>36</sup>

RBD in children and young adults is typically secondary to another disorder such as narcolepsy or a neurodevelopmental disorder such as autism.<sup>37</sup> Pediatric RBD can also be due to other symptomatic disorders such as epilepsy, attention deficit hyperactivity disorder, and tumors.<sup>37</sup>

**DRUG-INDUCED RBD.** Some medications can induce or worsen RBD. The most common agents are antidepressants, particularly SSRIs, SNRIs, and tricyclic antidepressants. One group found that 12.2% of people on antidepressants who underwent polysomnography (excluding those with an  $\alpha$ -synucleinopathy, narcolepsy, and progressive supranuclear palsy) had RWA; 48% of that subgroup met diagnostic criteria for RBD.<sup>38</sup> Mirtazapine and monoamine oxidase inhibitors (MAOIs) can also increase REM motor activity,<sup>39</sup> but bupropion does not.<sup>40</sup> Still, most patients on antidepressants do not develop RBD. While the association between antidepressants and RBD raises questions about antidepressants unmasking latent RBD, this relationship is still controversial due to limited data and the fact that depression may be a prodromal symptom of  $\alpha$ -synucleinopathies.<sup>21</sup>

Treatment of drug-induced RBD can be challenging. Antidepressant discontinuation or switching to bupropion can help clarify whether the patient has isolated RBD or drug-induced RBD, but it may take several months for symptoms to resolve. Furthermore, antidepressant discontinuation can worsen the underlying mood disorder. Although bupropion can help with depressive symptoms, it does not have a major anxiolytic effect.

Clinicians and patients should discuss the risk-benefit ratio of adjusting antidepressant medications. If antidepressant dose adjustment is considered, the clinician should coordinate care with a psychiatrist, plan the antidepressant taper or cross-titration with bupropion as appropriate, and monitor for worsened mood dysfunction. If the antidepressant cannot be tapered or switched, then symptomatic management should proceed as it would for

## KEY POINTS

- Events seen in RBD secondary to narcolepsy are more evenly distributed throughout the sleep period compared with the events noted in the setting of isolated RBD, which are more frequent in the second half of the sleep period.

- The most common causes of drug-induced RBD are antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Symptoms can take several months to resolve after drug discontinuation.

isolated RBD. If the clinician is unable to confirm the diagnosis of drug-induced RBD via antidepressant discontinuation, they should longitudinally monitor the patient for signs and symptoms of neurodegenerative disease.

Beta-blockers, particularly propranolol, have also been reported to induce RBD symptoms. The mechanism is unclear, but it may involve binding to serotonin receptors or effects on melatonin production.<sup>41</sup> It remains unclear if beta-blocker-associated RBD unmasks latent RBD.

**ISOLATED RWA.** Cases of isolated RWA without dream enactment symptoms have been reported. Some have termed this prodromal RBD, as a precursor stage to

TABLE 5-2

Disorders Associated with Rapid Eye Movement Sleep Behavior Disorder

Neurodegenerative disease

- ◆ Parkinson disease<sup>a</sup>
- ◆ Dementia with Lewy bodies<sup>a</sup>
- ◆ Multiple system atrophy<sup>a</sup>
- ◆ Mild cognitive impairment<sup>a</sup>
- ◆ Huntington's disease
- ◆ Spinocerebellar ataxia types 2 and 3
- ◆ Amyotrophic lateral sclerosis
- ◆ Pure autonomic failure
- ◆ Alzheimer disease
- ◆ Progressive supranuclear palsy
- ◆ Frontotemporal dementia
- ◆ Corticobasal syndrome
- ◆ Neurodegeneration with brain iron accumulation
- ◆ Prion disease

Autoimmune and paraneoplastic disorders

- ◆ Narcolepsy<sup>a</sup>
- ◆ Anti-IgLON5 disease
- ◆ Anti-LGI1 disease
- ◆ Anti-CASPR2 disease
- ◆ Anti-NMDA receptor encephalitis
- ◆ Anti-Ma1 and anti-Ma2 encephalitis

Metabolic disease

- ◆ Wilson disease

CONTINUED ON PAGE 1103

isolated RBD.<sup>42</sup> Since this is a new concept, validated measures for isolated REM sleep without atonia do not exist.<sup>12</sup>

### Association With Neurodegenerative Disease

The association between RBD and the development of neurodegenerative disease has been recognized for the past three decades.<sup>3</sup> Phenoconversion refers to the point at which a patient in a prodromal state, such as isolated RBD, is diagnosed with a neurodegenerative disease. It should be noted that neurodegeneration is a continuous process, and those with isolated RBD will often have some evidence of neurodegeneration below the clinical threshold for parkinsonism or cognitive impairment.

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CONTINUED FROM PAGE 1102

#### Psychiatric disorders

- ◆ Posttraumatic stress disorder<sup>a</sup>

#### Developmental disorders

- ◆ Chiari malformation
- ◆ 22q11.2 deletion syndrome
- ◆ Autism spectrum disorder
- ◆ Attention deficit hyperactivity disorder
- ◆ Smith-Magenis syndrome
- ◆ Mobius syndrome

#### Focal lesions

- ◆ Pontine tumors
- ◆ Demyelinating plaques from multiple sclerosis
- ◆ Pontine ischemia
- ◆ Pontine cavernous malformation

#### Other neurologic disorders

- ◆ Essential tremor
- ◆ Myotonic dystrophy
- ◆ Tourette syndrome
- ◆ Autosomal dominant leukodystrophy
- ◆ Traumatic brain injury

#### Medications

- ◆ Selective serotonin reuptake inhibitors (SSRIs)<sup>a</sup>
- ◆ Serotonin-norepinephrine reuptake inhibitors (SNRIs)<sup>a</sup>
- ◆ Tricyclic antidepressants
- ◆ Beta-blockers

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CASPR2 = contactin-associated proteinlike 2; IgLON5 = immunoglobulinlike cell adhesion molecule 5; LGII = leucine-rich glioma inactivated protein 1; NMDA = *N*-methyl-D-aspartate.

<sup>a</sup> Most common causes.



Among neurologic diseases, RBD is particularly linked to synuclein pathology. Among 172 patients who underwent autopsy, 94% had an  $\alpha$ -synucleinopathy, including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. Alzheimer disease was less common and when present was often associated with dementia with Lewy bodies copathology. Progressive supranuclear palsy, an atypical parkinsonian disorder associated with tau protein inclusions, was seen in only 2 out of 172 cases (CASE 5-2).<sup>43</sup>

## CASE 5-2

A 75-year-old woman presented with episodes of screaming and falling out of bed during sleep. The patient had been diagnosed 2 years prior with dementia with Lewy bodies. While awake, she occasionally had visual hallucinations of people, but these hallucinations were not frightening or bothersome. She needed help with daily activities including cooking, cleaning, and finances. Over the past 1 year, she screamed in the night twice per week. Her caregiver had observed her sometimes punching the bed or in the air. She once fell out of bed in her sleep and bruised her hip. The movements occurred in the last half of the sleep period. Her caregiver could wake her easily during events. She did not remember any dreams. She could get confused at night and sometimes needed to be reoriented. She did not get up and walk around the house except for using the bathroom for nocturia once nightly. She occasionally snored. She took amlodipine for hypertension and donepezil for dementia.

On examination, she had a body mass index of 24 kg/m<sup>2</sup>, abnormal clock drawing, and mild parkinsonism. The option of a diagnostic in-laboratory polysomnogram was discussed, but the caregiver worried that the patient may get more confused and agitated in the sleep laboratory. Due to this concern, a home sleep apnea test was done and showed an apnea-hypopnea index score of 3 events per hour and no evidence of obstructive sleep apnea. A diagnosis of probable rapid eye movement sleep behavior disorder (RBD) was made. Melatonin 3 mg nightly was recommended and titrated to 6 mg for persistent events. On follow-up 1 month later, the caregiver reported a 75% improvement in RBD events and screaming. The patient had no medication side effects, with no worsening of daytime sleepiness and balance.

### COMMENT

Diagnosis and management of RBD can be challenging in people with dementia. While in-laboratory polysomnography is necessary for the diagnosis of RBD, patients with dementia may not tolerate the study in an unfamiliar environment with a myriad of electrodes. In the context of dementia with Lewy bodies, the patient's presenting symptoms were consistent with RBD; however, given the history of snoring and hypertension, it was important to evaluate for obstructive sleep apnea as it can mimic or worsen RBD. Although clonazepam can be effective for RBD, this medication may worsen cognitive function and balance in people with dementia with Lewy bodies.

The phenoconversion rate among studies slightly varies by cohort. The median time to phenoconversion is about 8 years after RBD diagnosis,<sup>21</sup> with a phenoconversion rate of 33% by 5 years follow-up and 60% to 73% by 10 years.<sup>21,44</sup> The longer the duration of follow-up, the higher the total phenoconversion rate, as high as 96% by 14 years.<sup>44</sup> One cohort study reported an annual phenoconversion rate of 8.3%, although this rate may not be linear.<sup>6</sup> People with isolated RBD may have evidence of neurodegeneration, including decreased dopamine transporter tracer binding on single-photon emission computed tomography (SPECT) imaging<sup>45</sup> and substantia nigra hyperechogenicity on transcranial sonography (particularly when mild motor symptoms are present).<sup>46</sup>

Since the recognition that RBD is an  $\alpha$ -synucleinopathy prodrome, many biomarkers have been identified to predict phenoconversion. Clinical biomarkers include male sex, frequency and duration of active dream enactment behaviors, cognitive dysfunction, hyposmia, constipation, depression, hypersomnia, motor dysfunction, age, erectile dysfunction, color vision abnormalities, and orthostatic hypotension.<sup>6,21</sup>

Imaging biomarkers include reduced dopamine transporter binding<sup>6,21</sup> and substantia nigra hyperechogenicity.<sup>46</sup> Higher free water on diffusion tensor imaging was seen in isolated RBD but it is unclear if this finding predicts phenoconversion.<sup>47</sup>

Electrophysiologic markers include shorter sleep duration, higher frequency of periodic limb movements in sleep associated with arousals, diffuse electroencephalographic slowing during wakefulness, and higher delta power and lower alpha power in central and occipital regions in REM sleep.<sup>48</sup> Mixed data exist on whether RWA predicts phenoconversion.<sup>9,21</sup>

Pathologic markers include  $\alpha$ -synuclein deposits in the enteric nervous system, salivary glands, and skin. Nasal mucosa  $\alpha$ -synuclein has low sensitivity but is very specific and may be more helpful in those with olfactory dysfunction to determine if the hyposmia is prodromal or due to another cause such as smoking or head trauma. The presence of  $\alpha$ -synuclein in the CSF can be detected in 85% to 90% of isolated RBD cases but only in up to 10% of controls.<sup>49,50</sup>

Attempts have been made to determine which combination of these many potential risk predictors best predicts phenoconversion.<sup>51</sup> The strongest individual risk factors are video polysomnography–confirmed RBD, dopamine transporter imaging abnormality, and orthostatic hypotension. The strongest predictive combination of a limited set of risk factors is dopamine transporter imaging abnormality, constipation, and age older than 70 years,<sup>52</sup> although another study suggested that abnormal dopamine transporter imaging, olfactory loss, orthostatic hypotension, and motor dysfunction are the strongest predictors.<sup>53</sup>

## Management

Management of RBD includes patient education, suppressing dream enactment events and implementing safety precautions to reduce the risk of injury, treating nightmares, and, in the case of isolated RBD, counseling on the risk of neurodegeneration.<sup>54</sup> Violent dreams associated with RBD can cause distress and concern for the patient and family. Education about the lack of correlation between dream enactment behaviors and the patient's personality and the typical characteristics of RBD can provide insight and reassurance for the patient and family.

## KEY POINTS

- People with isolated RBD have a high lifetime risk of neurodegenerative disease, particularly  $\alpha$ -synucleinopathies; about one-half of those with RBD will develop a neurodegenerative disease over 8 years of follow-up after RBD diagnosis.

- Factors that predict an increased risk of phenoconversion in isolated RBD include abnormal dopamine transporter and substantia nigra imaging, pathologic markers, and autonomic, motor, and cognitive dysfunction.

Safety precautions should always be reviewed to lower injury risk to the patient and their bed partner.<sup>54</sup> Each of these environmental adjustments may lower the risk of injury to the patient: pad or remove nearby furniture; remove nearby sharp objects, weapons, or other potentially injurious objects; add a bedrail; or lower the mattress. Bed partners often sleep in another bed by the time of clinical presentation; for those in the same bed, sleeping apart or the addition of a barrier may be recommended. In people with refractory RBD, a pressurized bed alarm can be used to wake patients if significant movement occurs.<sup>55</sup>

If the patient takes an antidepressant that can worsen RBD symptoms, a risk-benefit consideration is needed to decide whether to taper or switch the medication, with the knowledge that the symptoms may take weeks to months to improve. Coexisting sleep apnea should also be treated as this can mimic or worsen RBD symptoms.<sup>16</sup> If RBD symptoms dramatically improve with sleep apnea management, repeat polysomnography on treatment can be considered to see if the RWA also improved, although the long-term clinical implications of this finding are uncertain.

Pharmacotherapy should be based on the frequency and intensity of RBD events, prior injuries sustained due to the behavior, the presence of nightmares, and patient preference. Several medications have been studied, with the most data available on clonazepam and melatonin.<sup>54</sup> The choice of medication will also depend on the subtype of RBD and the patient's comorbidities (eg, dementia, sleep apnea). Several limitations influence the selection of optimal medication therapy or the benefits of monotherapy versus combination therapy. Many studies were retrospective or open-label trials, although randomized clinical trials exist for some medications. The outcome measures for RBD improvement have also varied significantly across studies, which limits comparability.<sup>32</sup> Most studies used questionnaires or self-reporting; since patients are not always aware of the events, such measures are not fully reliable. Polysomnography is an objective measure but is costly and one night of observation may not reflect the full extent of the behaviors. More objective measures are needed, particularly in the home setting, to help guide treatment decisions.

Clonazepam was one of the first medications used to treat RBD. Its use stemmed from its ability to control other types of movements during sleep and waking states. Several observational studies demonstrated its ability to suppress dream enactment behavior in isolated RBD and secondary RBD.<sup>5,56</sup> While its mechanism in improving RBD is unclear, it may work through enhanced GABA-ergic and glycinergic inhibition of spinal motor neurons.<sup>57</sup> Clonazepam may improve some phasic movements but does not appear to improve overall RWA, simple motor movements, or vocalizations, suggesting other mechanisms may be involved in major motor event suppression, such as through altering dream content.<sup>58,59</sup>

Clonazepam is dosed 0.25 mg to 4 mg 30 to 60 minutes before bedtime. Interestingly, tolerance does not appear to occur with long-term use of clonazepam for RBD.<sup>60</sup> The main side effects include daytime somnolence, confusion, and gait imbalance, which may be of particular concern in those with neurodegenerative disease.

Melatonin, a hormone involved in circadian regulation, is secreted at night in dim light conditions. Its mechanism in RBD has been elusive, although one hypothesis includes restoration of the circadian system.<sup>61</sup> Several retrospective studies and a few clinical trials studied immediate-release melatonin along with a few studies on sustained-release melatonin. Most

studies have shown improvement in dream enactment behavior frequency and intensity with immediate-release melatonin<sup>32</sup>; however, a recent trial using sustained-release melatonin did not show improvement in dream enactment behavior.<sup>62</sup> The data on melatonin's effect on RWA have not been consistent.

Melatonin is typically dosed between 3 mg and 12 mg nightly, with most patients responding to 6 mg to 9 mg nightly. Potential side effects include headaches and nightmares, and some patients report daytime sleepiness. In the United States, melatonin is a nutraceutical and is available over the counter. The lack of standardization in manufacturing and the variety of melatonin preparations (eg, tablet, capsule, chewable, gummy) can be a challenge and source of confusion for patients.

Cholinesterase inhibitors, such as rivastigmine and donepezil, are often used for cognitive symptoms in people with dementia with Lewy bodies or Parkinson disease. Two randomized crossover trials using rivastigmine 4.6 mg daily showed improvement in RBD symptoms in those with comorbid Parkinson disease<sup>63</sup> or mild cognitive impairment.<sup>64</sup> Much less data are available for donepezil, and those that currently exist show mixed results.<sup>65</sup> The potential mechanism may involve increased cholinergic transmission, which may potentiate REM atonia.

Several other treatments have been examined for RBD symptoms.

Observational studies on pramipexole have reported improvements in dream enactment behaviors in people with isolated RBD.<sup>32</sup> Sodium oxybate also appears beneficial for RBD symptoms and may improve REM atonia in adults and children with narcolepsy.<sup>66,67</sup> A recent clinical trial of sodium oxybate in treatment-resistant RBD (isolated and associated with Parkinson disease) showed improvements in RBD event frequency within the treatment group; however, possibly due to a strong placebo effect, no differences were seen between the sodium oxybate and placebo groups.<sup>68</sup> Recently, safinamide over 3 months in a crossover study improved RBD in Parkinson disease patients.<sup>69</sup>

To date, no medications have been proven to modify the disease course in people with neurodegenerative  $\alpha$ -synucleinopathies. Important factors in these negative results may be a lack of biomarkers sensitive to change and testing too late in the disease course. Such trials in patients with isolated RBD are difficult given the long latency to phenoconversion. A study aimed at reducing the risk of phenoconversion by 50% over 2 years of therapy would require 142 to 366 patients per arm.<sup>21</sup> While enrollment of people at higher risk of phenoconversion can reduce the study duration, the findings may not be generalizable to those without such risk factors, and the extent of neurodegeneration may still be too great to alter the course of and response to treatment. Therefore, it is vital to identify and validate neurodegeneration biomarkers that are sensitive to changes in isolated RBD. To better understand the disease, determine such biomarkers, and prepare for these trials, it is important to inform people with isolated RBD as appropriate about the risk of neurodegeneration and opportunities to participate in clinical research if they so choose. In the meantime, exercise should be recommended for patients with isolated RBD given that some evidence shows that exercise confers neuroprotection and is beneficial for general health.<sup>32</sup>

### Risk Disclosure

Disclosure of the risk of neurodegeneration to people with isolated RBD is a potential source of controversy. The reasons for the controversy are a

### KEY POINTS

- Reviewing safety precautions with patients (eg, pad or remove nearby furniture, remove potentially injurious objects, add a bedrail to reduce risk of injury) is critical to reducing the risk of injury from dream enactment behavior.

- Clonazepam and melatonin are the first-line agents to suppress dream enactment behaviors. Treatment choice requires consideration of the RBD subtype and comorbidities, such as dementia.



lack of consensus on disclosure methodology, the variable and often long latency to phenoconversion, a lack of disease-modifying therapies, and that RBD symptoms may not be the patient's presenting complaint.<sup>70</sup>

Several ethical principles need to be balanced when considering risk disclosure: beneficence, nonmaleficence, and autonomy. Beneficence requires that clinicians act in the best interest of the patient, to allow the patient to prepare for the future and consider potential risk-reduction strategies. Nonmaleficence requires that clinicians "do no harm"; disclosure about the high risk of neurodegenerative disease, even if years away, can lead to anxiety. When a disease-modifying strategy is available, beneficence and nonmaleficence are aligned; however, in the case of isolated RBD, they may not be. The principle of autonomy affirms that patients have a right to know about their health and prepare for the future. It also asserts that patients have a right to not know, as some patients may not want to be concerned with a potential disease that may never develop.

Two general approaches exist for disclosure about the risk of phenoconversion to neurodegenerative disease: full disclosure and watchful waiting. The benefits of full disclosure include respect for the patient's right to know, inclusion of patients in decision making about their health, facilitation of early neurodegenerative disease monitoring, and ability of patients and families to discuss future care planning, life goals, and finances, and participate in clinical research. The risks of full disclosure include potential anxiety and hopelessness when there is long phenoconversion latency and no available disease-modifying therapy. However, information about the association between isolated RBD and neurodegeneration is available on the internet; if the clinician withholds disclosure and the patient reads about this association on their own, trust in the patient-clinician relationship may be damaged.<sup>71</sup> Watchful waiting entails monitoring without risk discussion but allowing for such discussion if the patient later wishes.

A patient-centered approach to risk disclosure has been published. Patients should be provided with the option to learn about the risk of phenoconversion to neurodegenerative disease. If the patient does not wish to be informed, the clinician can offer to discuss it at another time. If the patient does want to be informed, the patient should indicate the extent of

TABLE 5-3

**ICSD-3-TR Diagnostic Criteria for Recurrent Isolated Sleep Paralysis<sup>a</sup>**

*International Classification of Sleep Disorders, Third Edition, Text Revision criteria A through D must be met for a recurrent isolated sleep paralysis diagnosis:*

- A** A recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep
- B** Each episode lasts seconds to a few minutes
- C** The episodes cause clinically significant distress, including bedtime anxiety or fear of sleep
- D** The disturbance is not better explained by another sleep disorder (especially narcolepsy), medical disorder, mental disorder, or medication or substance use

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information desired. When possible, individualized risk stratification should be pursued.<sup>70</sup>

## RECURRENT ISOLATED SLEEP PARALYSIS

Sleep paralysis is a phenomenon that can occur in healthy people or in association with disorders and has garnered much cultural curiosity.

### Clinical Historical Features and Diagnosis

Sleep paralysis is a phenomenon of waking from sleep unable to move the trunk or limbs for seconds to a few minutes until it resolves spontaneously or in response to an external stimulus. The diaphragm is spared but accessory respiratory muscles are not, which can lead to a sensation of a weight on one's chest. Sleep paralysis can be associated with visual, auditory, or tactile hallucinations or a feeling of a presence in the room.<sup>72</sup> Sleep paralysis has taken on various cultural meanings and has been expressed in several works of art such as Henry Fuseli's *The Nightmare* in 1781.

Sleep paralysis occurs in the transition between REM sleep and waking. Polysomnographic studies show an intrusion of EEG alpha activity into REM sleep, followed by an arousal and persistence of REM atonia into wakefulness. Those with sleep paralysis have no difference in REM macrostructure or fragmentation but do have higher bifrontal EEG beta activity in REM sleep.<sup>73</sup> Episodes may even occur during a sleep-onset REM period.

Sleep paralysis occurs in at least 7.6% of the population,<sup>72</sup> and 15% to 40% of people younger than 30 years old experience it at least once.<sup>4</sup> Sleep paralysis itself is benign and is not a common reason for people to seek medical care. When sleep paralysis is recurrent, the most common cause is narcolepsy. However, it may occur in an isolated form and cause clinical distress, a disorder known as recurrent isolated sleep paralysis.

### Causes and Associations

Sleep paralysis can be triggered by sleep deprivation, jet lag, shift work, and supine sleep, and is more common in those with PTSD.<sup>74,75</sup>

The diagnosis of recurrent isolated sleep paralysis is established by the patient's history (TABLE 5-3<sup>4</sup>), and there is no specific frequency threshold.<sup>4</sup> Still, polysomnography should be considered if the clinician suspects another condition such as sleep apnea, narcolepsy, or sleep-related seizure. The differential diagnosis also includes sleep terrors, nightmare disorder, lucid dreaming, RBD, and hypokalemic periodic paralysis.

### Management

Sleep paralysis is self-limiting and does not typically impact daytime function, so patient education and reassurance are the mainstays of recurrent isolated sleep paralysis management. Identifying triggers, maintaining good sleep hygiene and a consistent sleep schedule, and routinely sleeping at least 7 hours each night can help mitigate recurrent isolated sleep paralysis. Because events are more likely to occur when supine, positional therapy to prevent supine sleep may be helpful. The bed partner, if present, should be instructed to touch the patient if they hear soft vocalizations in the morning hours before full awakening.<sup>74</sup> Medications are rarely needed. Available data on pharmacologic therapy for sleep paralysis are based on studies of people with narcolepsy. Tricyclic or other

## KEY POINTS

- Patients should be offered information on the potential health risks of RBD, and if desired more specific information on the risk of neurodegeneration should be provided.
- Recurrent isolated sleep paralysis involves repeated episodes of sleep paralysis that cause distress and are not associated with another underlying disorder such as narcolepsy.
- Sleep paralysis can be triggered by sleep deprivation, jet lag, shift work, and supine sleep, and is more common in those with posttraumatic stress disorder.

antidepressants for sleep paralysis and cognitive behavioral therapy for insomnia for coping strategies may be helpful.<sup>74</sup>

NIGHTMARES AND NIGHTMARE DISORDER

While nightmares are common and occur sporadically in healthy people, they can also become recurrent and distressing as part of a disorder, such as nightmare disorder or PTSD. Nightmares can significantly impact sleep and quality of life and can respond to pharmacologic and cognitive behavioral therapies.

Clinical Features and Diagnosis

Nightmares are disturbing, frightening dreams that usually involve threats to self or others. Sporadic nightmares are common and do not typically present clinically. With nightmare disorder, one experiences recurrent and extended nightmares that cause distress or functional impairment (TABLE 5-4).<sup>4</sup> While no frequency criterion is required for diagnosis, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* specifies severity based on nightmare frequency (mild: less than one episode per week; moderate: at least one episode per week but less than nightly; severe: episodes nightly).<sup>76</sup>

Nightmares are strongly linked to psychiatric disorders. Symptoms of anxiety and depression are both commonly associated with nightmares, which can worsen mood disruption.<sup>77</sup> Nightmares are seen in 66.7% of people with PTSD and are common among combat veterans.<sup>74,78</sup> In fact, persistent reexperience of the traumatic event is part of the diagnostic criteria of PTSD.<sup>76</sup> Nightmare disorder can also be idiopathic.

TABLE 5-4

ICSD-3-TR Diagnostic Criteria for Nightmare Disorder<sup>a</sup>

International Classification of Sleep Disorders, Third Edition, Text Revision criteria A through C must be met for a nightmare disorder diagnosis:

- A Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity
- B On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert
- C The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:
  - 1 Mood disturbance (eg, persistence of nightmare affect, anxiety, dysphoria)
  - 2 Sleep resistance (eg, bedtime anxiety, fear of sleep/subsequent nightmares)
  - 3 Negative impact on caregiver or family functioning (eg, nighttime disruption)
  - 4 Behavioral problems (eg, bedtime avoidance, fear of the dark)
  - 5 Daytime sleepiness
  - 6 Fatigue or low energy
  - 7 Impaired occupational or educational function
  - 8 Impaired interpersonal or social function

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The evaluation of nightmares requires a detailed sleep history, with characterization of the dreams and their frequency. PTSD-related nightmares are more aligned with the trauma and involve more arousals and feelings of helplessness.<sup>79</sup> Other elements to query include psychiatric and trauma history, suicidal ideation and attempts, medication use, and substance use.<sup>80</sup> RBD symptoms are also common in those with PTSD.<sup>34</sup> Risk factors for nightmares include migraine, bronchitis, asthma, beta-blocker or SSRI use, and alcohol withdrawal.<sup>74</sup> Polysomnography can be helpful if comorbid sleep apnea, RBD, or narcolepsy is suspected.

Nightmares occur sporadically in 22% of adults and frequently in 3% to 4% of adults.<sup>74</sup> In those with psychiatric disease, nightmare prevalence ranges from 37% in those with mood disorders to 67% in those with PTSD. Nightmares are more common in women and are associated with higher rates of insomnia, daytime sleepiness, fatigue, impaired concentration, anxiety, depression, and poor academic performance. While general prevalence studies did not separate nightmares from nightmare disorder, the latter is thought to occur in 2% to 6% of adults.<sup>77</sup> In children, the prevalence of nightmares at least once weekly is 19%.<sup>80</sup>

The pathogenesis of nightmares is thought to involve elevated hyperarousal and impaired fear extinction.<sup>79</sup> Nightmares may act as a conditioning stimulus, which results in sleep avoidance behaviors. Polysomnographic findings in young adults with nightmares include more awakenings, an increase in the EEG alpha rhythm spectral power, and more non-REM to REM transitions.<sup>74</sup>

## Management

Prazosin 1 mg to 15 mg nightly is the first-line pharmacologic treatment for nightmare disorder and PTSD-associated nightmares. Prazosin, an  $\alpha_1$ -adrenergic receptor antagonist, has been repeatedly shown to benefit people with PTSD who experience nightmares. The medicine was previously recommended by published guidelines,<sup>81</sup> but a recent large multicenter study failed to show improvement in PTSD-related nightmares, which resulted in a downgraded recommendation.<sup>82</sup> However, a recent meta-analysis that included the negative trial still supports the use of prazosin.<sup>83</sup> Orthostatic hypotension is a prominent side effect of prazosin.

Other medications studied for the treatment of nightmare disorder include nabilone (a synthetic cannabinoid), topiramate, and gabapentin. Clonazepam and venlafaxine do not appear to improve nightmares, and there are recommendations against their use in the treatment of nightmare disorder.<sup>82</sup>

Several types of nonpharmacologic therapies can be used for the treatment of nightmare disorder. Cognitive behavioral therapy generally addresses the negative thoughts, emotions, and maladaptive behaviors that may occur in conjunction with nightmare disorder. Image rehearsal therapy is specifically recommended for the treatment of nightmare disorder.<sup>82</sup> Image rehearsal therapy attempts to alter the content of nightmares by exposure to the nightmare content and rehearsal during the day to replace the nightmare with a positive script. The intentional change and its rehearsal appears to decrease the activation of fear circuitry. Several trials have shown the efficacy of image rehearsal therapy in people with PTSD and non-PTSD nightmares, and the benefits can be sustained for years. Image rehearsal therapy can be combined with other cognitive behavioral therapy strategies and can be provided with limited face-to-face contact or with online programs.<sup>79</sup> Exposure, relaxation, and rescripting

## KEY POINTS

- Management of recurrent isolated sleep paralysis may include reassurance, behavioral strategies, positional therapy, and tricyclic or other antidepressants.

- Nightmares are distressing, frightening dreams that involve threats to self or others. In nightmare disorder, one has recurrent nightmares that result in distress or functional impairment.

- Nightmares are common in people with posttraumatic stress disorder and tend to be related to the traumatic incident.

- Management of nightmare disorder includes cognitive behavioral therapy, particularly image rehearsal therapy, and medications such as prazosin.



therapy, a type of image rehearsal therapy delivered over 3 weeks, provides additional sleep hygiene education, progressive muscle relaxation, and trauma exposure with rescripting of the nightmares.<sup>82</sup> Other nonpharmacologic options include lucid dreaming, sleep dynamic therapy, and systematic desensitization.

## CONCLUSION

RBD is a REM sleep parasomnia in which people may have vivid dreams or nightmares and manifest dream enactment behaviors that can disrupt sleep and cause injuries to people and their bed partners. Polysomnography remains necessary for diagnosis to confirm the presence of RWA and exclude RBD mimics. The implementation of safety precautions to reduce injury and judicious medication use to suppress dream enactment behavior are important management strategies. While RBD is often seen in those with neurodegenerative diseases, particularly  $\alpha$ -synucleinopathies, it can also occur as a prodromal marker seen many years prior to neurodegenerative disease onset. As prodromal biomarkers become better understood, future disease-modifying agents may reduce the risk of, or even prevent, the development of neurodegenerative disease. Recurrent isolated sleep paralysis is an uncommon parasomnia that is self-limited but can be controlled if symptoms cause distress. Finally, nightmare disorder can be idiopathic but is often seen in people with PTSD. Nightmare disorder treatment is best managed with image rehearsal therapy but medications such as prazosin can be beneficial.

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## VIDEO LEGEND

### VIDEO 5-1 REM SLEEP BEHAVIOR DISORDER

A 60-year-old man with isolated rapid eye movement (REM) sleep behavior disorder showing arm and body movements and vocalizations during REM sleep.

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