MAYO CLINIC

Importance of Rapid Eye Movement Sleep Behavior Disorder to the Primary Care Physician

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Learning Objectives: On completion of this article, you should be able to (1) recognize the clinical manifestations of rapid eye movement sleep behavior disorder, (2) describe the importance of early diagnosis and treatment of this disorder, and (3) identify which factors are associated with an increased rate of progression from rapid eye movement sleep behavior disorder to clinically overt neurodegenerative disease.

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Abstract

Sleep disorders and neurodegenerative diseases are commonly encountered in primary care. A common, but underdiagnosed sleep disorder, rapid eye movement sleep behavior disorder (RBD), is highly associated with Parkinson disease and related disorders. Rapid eye movement sleep behavior disorder is common. It is estimated to affect 0.5% of the general population and more than 7% of individuals older than 60 years; however, most cases go unrecognized. Rapid eye movement sleep behavior disorder presents as dream enactment, often with patients thrashing, punching, and kicking while they are sleeping. Physicians can quickly assess for the presence of RBD with high sensitivity and specificity by asking patients the question "Have you ever been told that you act out your dreams, for example by punching or flailing your arms in the air or screaming and shouting in your sleep?" Patients with RBD exhibit subtle signs of neurodegenerative disease, such as mild motor slowing, constipation, or changes in sense of smell. These signs and symptoms may predict development of a neurodegenerative disease within 3 years. Ultimately, most patients with RBD develop a neurodegenerative disease, highlighting the importance of serial neurological examinations to assess for the presence of parkinsonism and/or cognitive impairment and prognostic counseling for these patients. Rapid eye movement sleep behavior disorder is treatable with melatonin (3-6 mg before bed) or clonazepam (0.5-1 mg before bed) and may be the most common, reversible cause of sleep-related injury. Thus, it is important to identify patients at risk of RBD in a primary care setting so that bedroom safety can be addressed and treatment may be initiated.

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Sleep disorders are common in the general population and can lead to a marked impairment in daytime functioning and quality of life; however, they are often underdiagnosed.[1] Obstructive sleep apnea (OSA), insomnia, restless legs syndrome, and excessive daytime sleepiness are among the most commonly encountered sleep problems in the primary care setting.[2] Furthermore, primary care physicians are often tasked with the challenge of unraveling the complexities of abnormal motor behaviors during sleep, ranging from sleepwalking to nocturnal seizures and confusional arousals. However, an underdiagnosed sleep disorder, rapid eye movement (REM) sleep behavior disorder (RBD), is a potentially injurious parasomnia that should be considered in older patients presenting to the primary care physician complaining of abnormal activity during sleep.

Sleep is divided broadly into non—rapid eye movement (NREM) sleep and REM sleep, with unique nocturnal behaviors arising from NREM and REM sleep, respectively. Under normal physiological conditions, REM sleep is typified by active mentation (dreams) and skeletal muscle paralysis. Rapid eye movement sleep skeletal muscle atonia is critical to prevent dream enactment and promote a period of quiescence for REM sleep—related memory consolidation. Rapid eye movement sleep behavior disorder is characterized by dream enactment behavior (DEB) that emerges resulting from the loss of REM sleep without atonia. Although RBD was initially thought to be simply an intriguing nocturnal phenomenon, longitudinal studies of patients with RBD revealed high potential for injuries to patients with RBD and their bed partners as well as a concerning connection to parkinsonian neurodegenerative diseases that make this disorder important to be recognized by primary care physicians.

EPIDEMIOLOGY AND PHENOMENOLOGY OF RBD

Spontaneous RBD is traditionally considered to be a disorder of older adults, with large published case series reporting approximately an 80% male prevalence with the onset of disease most commonly in the fifth to sixth decade of life.[3-5] However, there is evidence to suggest that RBD in women is underrecognized, particularly in the young and in the setting of autoimmune conditions.[6,7] Furthermore, women have less violent and, therefore, less injurious DEB and thus are less likely to receive medical attention.[7] Another contributing factor to this discrepancy is likely due to the sex difference in life expectancy; elderly women are less likely to have bed partners than elderly men, leading to unwitnessed parasomnia behaviors. Rapid eye movement sleep behavior disorder typically presents in either the sixth or the seventh decade; however, when questioned specifically, many patients will report a long-standing history suggestive of DEB.[8] Population-based studies[9,10] estimate that 0.5% of the general population and 7.7% of individuals older than 60 years have probable RBD. However, most individuals with RBD go unrecognized or underreported. Patients and bed partners are often unsure how to broach the frequently taboo subject of out-of-control activities in the bedroom. Furthermore, physicians often interpret the behaviors as symptoms of an underlying mood disorder or conflict between spouses rather than a primary sleep disturbance.

Despite the seemingly disruptive nature of punching, flailing, and screaming during sleep, up to 44% of patients with RBD are unaware of their DEB. In addition, it is not uncommon to identify a history of RBD as a secondary symptom when evaluating a patient for other sleep problems such as OSA or insomnia.[3] Dream enactment behaviors can range from violent and complex behaviors, such as thrashing in bed, punching and kicking bed partners, and jumping out of windows, to simple activities of daily living such as playing the piano or washing dishes.[11] In fact, it is likely that the minority of patients with RBD involve impressive and obvious DEB whereas most DEB may be unobtrusive movements limited to the hands, otherwise known as *hand babbling*. The violent nature of RBD can often result in injury, with 55% to 96% of patients and/or bed partners reporting injury, highlighting the importance for timely recognition and treatment of this disorder.[12,13] Injuries range from bruises and scratches to the more severe: fractures of the cervical vertebrae and basilar skull, shoulder dislocations, or hematomas.[12]

SCREENING FOR RBD

Fortunately, it is easy to screen for RBD. Polysomnography (PSG) is the standard for a diagnosis of RBD; however, given the time- and resource-intensive nature of PSG, primary care clinicians can use survey methods to identify those with likely RBD.[14] The observations of a bed partner or someone who has witnessed the patient's sleep are invaluable, as the patients themselves, as noted above, are often unaware of their behaviors. In patients without a bed partner, clues suggesting possible RBD include vivid or terrifying dreams, falling out of bed, or unexplained nocturnal bruising. Rapid eye movement sleep behavior disorder can be accurately identified with the following screening question: "Have you ever been told that you act out your dreams (eg, punching or flailing arms in the air of screaming and shouting in your sleep?)."[14,p1] The Mayo Sleep Questionnaire[14] has been validated in a community sample with a sensitivity and specificity of 100% and 95%, respectively, and uses input from the patient's bed partner, which is important given the limited insight of patients into their sleep habits.

DIFFERENTIAL DIAGNOSIS

Not all nocturnal motor activity is RBD, and primary care physicians are often tasked with initially trying to distinguish between different parasomnias. Non–rapid eye movement parasomnias include confusional arousals, sleepwalking, and sleep terrors, whereas REM parasomnias mainly include RBD and nightmares. Although history may distinguish these disorders from RBD, PSG is often required for definitive diagnosis. Non–rapid eye movement parasomnias tend to present in youth, often during childhood, as compared with RBD. In addition, RBD episodes typically last less than 60 seconds and occur during the second half of the night with patients reporting vivid dream recall. Non–rapid eye movement parasomnias tend to emanate from the first half of the night and generally last about 5 to 10 minutes (longer if associated with sedative medication). Furthermore, patients with RBD are often alert and oriented and immediately recall vivid dream mentation as compared with NREM parasomnias, in which patients are often confused after arousal with little recollection.[15]

As in RBD, patients with parasomnias such as nightmares and sleep terrors will often vocalize during sleep. However, patients with nightmares do not have associated motor activity and night terrors occur without dream recall and typically occur in young children, a population in which RBD is incredibly rare. Nocturnal frontal lobe epilepsy can be confused with RBD; however, patients are often younger, present with stereotyped behaviors, and often have epileptiform activity on the electroencephalogram (Table 1).[15]

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER AND ITS ASSOCIATION WITH PSYCHIATRIC DISEASE

Rapid eye movement sleep behavior disorder cases among women are more likely to be younger (age, <50 years) and often occur in the setting of autoimmune disease or by using antidepressants.[5,6,16,17] Patients with a psychiatric disease history have a 10-fold increased risk of developing RBD, whereas antidepressant use increases the likelihood of RBD diagnosis 5-fold.[18] Depression is the most common psychiatric disorder associated with RBD; however, patients with posttraumatic stress disorder may also evolve DEB and increased REM sleep muscle tone after exposure to trauma.[16]

Rapid eye movement sleep behavior disorder has been reported to evolve in patients after the initiation of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). In addition, neurophysiological studies have shown abnormally increased muscle tone during REM sleep (without the development of dream enactment) in patients taking antidepressants as compared with healthy controls and psychiatric patients not taking antidepressants.[16] Although the pathogenesis of antidepressant-induced RBD remains unclear, it is not thought that antidepressants directly cause RBD and parkinsonism (see section Rapid Eye Movement Sleep Behavior Disorder as a Prodromal Neurodegenerative Disease).[16,17] Fortunately, antidepressant-induced RBD may decrease in severity with cessation of the medication or decrease in the dose. Bupropion may be less likely

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than SSRIs to cause RBD and may be trialed in patients with RBD who require mood disorder treatment.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER AS A PRODROMAL NEURODEGENERATIVE DISEASE

Longitudinal studies of patients with RBD have revealed a strong association with the future development of neurodegenerative disease, especially Parkinson disease (PD) and other related conditions such as dementia with Lewy bodies (DLB) and multiple system atrophy.[4,5,8] Rapid eye movement sleep behavior disorder has traditionally been separated into 2 categories: idiopathic (RBD without signs of neurodegenerative disease) or symptomatic/secondary (RBD associated with known neurodegenerative disease, narcolepsy, or medication). Nearly all patients with idiopathic RBD (81%-91%) will go on to develop α-synuclein–mediated disorders such as PD or DLB, especially if symptoms emerge after the age of 60 years, suggesting that idiopathic RBD is likely an early manifestation of a progressive neurodegenerative disorder.[19,20] However, the risk of neurodegenerative disease in young patients with RBD (ie, patients with RBD younger than 50 years), women with RBD, and those with antidepressant-induced RBD remains to be elucidated.

Although most patients with idiopathic RBD eventually progress to neurodegenerative disease, the prevalence of RBD varies among α-synuclein–mediated disorders: up to 50% in PD, up to 80% in DLB, and 80% to 95% in multiple system atrophy, suggesting that idiopathic RBD may be a unique form of disease.[4,5] Rapid eye movement sleep behavior disorder may also worsen the prognosis of PD, as patients with PD with RBD appear to have a more aggressive form of disease, with increased cognitive impairment, visual hallucinations, orthostatic hypotension, and more rapid motor decline as compared with patients with PD without RBD.[4] Furthermore, patients with PD with RBD are more likely to develop DLB or PD dementia than do patients with PD alone.[21]

Most importantly, for primary care physicians, patients with idiopathic RBD often manifest nonmotor signs of neurological dysfunction, such as orthostatic hypotension,

TABLE 1. Differential Diagnosis of RBD

Variable	RBD	Confusional arousals	Sleep walking	Parasomnia overlap disorder	Sleep terrors	Nocturnal frontal lobe epilepsy
Typical age range	Middle aged, elderly	Childhood, young adult	Childhood, young adult	Young adult	Preadolescence	Childhood, young adult
Sleep stage	REM	NREM	NREM	NREM/REM	NREM/REM	NREM
Time of behaviors	Second half of the sleep period	First half of the sleep period	First half of the sleep period	Throughout the night	First half of the sleep period	Throughout the night
Dream recall	++	–	–	+	–	–
Sleep-related injury	++	–	–/+	+	–	–/+
Duration	0-60 s	5-10 min	5-10 min (longer if associated with sedative medication)	0-10 min	5-20 min	3-5 min
Comorbid conditions	Parkinson disease and related disorders	OSA, sleep deprivation, sedative medication	RLS, OSA, sleep deprivation, sedative medication	Antidepressants	Sleep deprivation, OSA	Daytime epilepsy
Treatment	Melatonin, clonazepam	Correct underlying sleep disorder	Correct underlying sleep disorder	Correct underlying sleep disorder, clonazepam	Correct underlying sleep disorder	Antiepileptic medications at bedtime

OSA = obstructive sleep apnea; NREM = non–rapid eye movement; RBD = rapid eye movement sleep behavior disorder; REM = rapid eye movement; RLS = restless legs syndrome; ++ = strongly present; – = not present; + = sometimes present; +/– = may or may not be present.

constipation, hyposmia, and cognitive impairment, especially in the domains of attention and executive function, as compared with healthy controls.[4,5,9,22,23] In fact, these features may be present 10 to 20 years before the onset of clinically overt features of PD or DLB.[23] Patients with antidepressant-induced RBD also manifest these prodromal symptoms of neurodegenerative disease but have a longer duration from manifestation of RBD symptoms to clinically evident PD or DLB as compared with patients with RBD who were not taking antidepressants.[17] These findings can be used to predict which patients with RBD are more likely to develop PD in the near future. In particular, if a patient with RBD is older at the age of dream enactment onset; has difficulty with smell, color vision, constipation; and is not taking an antidepressant, they are highly likely to progress onto PD or a related condition in the next 3 years (Table 2).[22]

TREATMENT OF RBD

Rapid eye movement sleep behavior disorder is a readily treatable condition. The most important initial management strategies are environmental to protect the patient and the bed partner: removing objects that could pose a danger, especially firearms, but also nightstands, lamps, or sleeping separately until DEB are under control.[4] Sleeping bags can help prevent a patient from leaving the bed. Patients may place their mattress on the floor next to the bed to prevent from falling out of bed. Medications known to cause RBD, such as antidepressants (especially SSRIs), should be discontinued, if possible. As noted above, bupropion has not been strongly associated with the evolution of RBD and may be trialed in patients requiring treatment for depression. In addition, all patients with dream enactment history should be screened for OSA, which can mimic RBD. Patients often report a decrease in DEB frequency after treatment of their OSA.[24]

TABLE 2. Assessing Risk of Neurodegeneration in RBD[a,b]

Variable	Low risk (>3 y) of developing PD/DLB	High risk (<3 y) of developing PD/DLB
Age at diagnosis (y)	<65	>65
Smell	Normal	Abnormal
Color vision	Normal	Abnormal
Antidepressant use	Yes	No
Constipation	Absent	Present
Orthostasis	Absent	Present
Motor slowing	Absent	Present

[a]DLB = dementia with Lewy bodies; PD = Parkinson disease.
[b]Combining risk factors results in significantly higher risk compared to patients with single risk factor.

Some patients have mild RBD symptoms and, therefore, prefer not to be treated. Because the frequency of DEB does not appear to be predictive of injury, it could be argued that treatment, or at a minimum bedroom safety measures, should be initiated as soon as the RBD diagnosis is made.[12] The most commonly used medications for RBD are clonazepam and/or melatonin. In addition to a small clinical trial[4] for melatonin, there has been a paucity of placebo-controlled studies of RBD, and the consensus on management is based on a case series and this small clinical trial. Low doses of clonazepam (0.5-1 mg) at bedtime have been reported to be effective in reducing DEBs in up to 90% of cases; however, clonazepam may cause sedation and worsen underlying cognitive impairment, sleep apnea, and gait impairment.[3,4,12]

Melatonin has also been reported to be effective in reducing RBD symptoms and injury occurrence with a median effective dose of 6 mg at bedtime.[3,25] A recent retrospective analysis comparing clonazepam and melatonin reported that they were equally effective in reducing falls and injury in patients with RBD, with melatonin having considerably fewer adverse effects. In addition, melatonin was better tolerated in patients with comorbid neurodegenerative disease.[25] Other medications such as dopaminergic agonists (pramipexole) and acetylcholinesterase inhibitors (rivastigmine) have been trialed with variable success in patients with RBD and may be considered in treatment-refractory patients.[26]

WHEN TO REFER PATIENTS WITH RBD TO SPECIALTY CARE

As mentioned above, the frequency of DEB often decreases dramatically with a relatively low dose of melatonin or clonazepam. However, patients with persistent DEB requiring

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polytherapy or high doses of clonazepam or melatonin may benefit from referral to a sleep specialist for further management and PSG to rule out RBD mimics (confusional arousals and nocturnal seizures) or conditions that may worsen dream enactment (OSA). In addition, patients with an unclear history may benefit from referral to sleep specialist for PSG to rule out other parasomnias.

Patients with RBD with concern for motor dysfunction (slowing, tremor, shuffling gait, and postural instability) should be referred to a movement disorder specialist for a detailed neurological evaluation. Similarly, patients with concern for cognitive impairment may benefit from a behavioral neurology consult and neuropsychiatric evaluation. Neurology referral is important not only for symptomatic management (ie, levodopa for parkinsonism and acetylcholinesterase inhibitors for cognitive impairment) but also for enrollment in clinical trials of neuroprotective therapies and prognostic counseling for patients with RBD on risk of developing neurodegenerative disease.

CONCLUSION

Rapid eye movement sleep behavior disorder is a common and potentially injurious sleep disorder affecting primarily older adults and is likely underrecognized in the primary care setting. Primary care physicians can quickly and accurately screen for RBD during clinical interview by asking the question "Have you ever been told that you act out your dreams?" or by using a questionnaire (such as the Mayo Sleep Questionnaire) that the patient can complete during triage. Rapid eye movement sleep behavior disorder may be treated with clonazepam (0.5-1 mg) or melatonin (3-6 mg) at bedtime to help reduce risk of injury to the patients and their bed partners, although melatonin may be preferable given its similar efficacy and more favorable adverse-effect profile as compared with clonazepam. Rapid eye movement sleep behavior disorder can evolve after the initiation of antidepressants, especially SSRIs, and may remit with cessation of the medication or by using an alternative antidepressant such as bupropion. More importantly, given the emerging evidence that RBD is part of a spectrum of progressive neurodegenerative diseases, it is important that patients screening positive for RBD be questioned about antidepressant use, changes in sense of smell or bowel function, as well as be evaluated with serial neurological examinations and receive prognostic counseling and consideration for enrollment in future clinical trials of neuroprotective therapies.

Abbreviations and Acronyms: **DEB** = dream enactment behavior; **DLB** = dementia with Lewy bodies; **NREM** = non–rapid eye movement; **OSA** = obstructive sleep apnea; **PD** = Parkinson disease; **PSG** = polysomnography; **RBD** = rapid eye movement sleep behavior disorder; **REM** = rapid eye movement; **SSRI** = selective serotonin reuptake inhibitor

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