Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia manifested by vivid, often frightening dreams associated with simple or complex motor behavior during REM sleep. Patients appear to “act out their dreams,” in which the exhibited behaviors mirror the content of the dreams. Management of RBD involves counseling about safety measures in the sleep environment; in those at risk for injury, clonazepam and/or melatonin is usually effective. In this article, the authors present a detailed review of the clinical and polysomnographic features, differential diagnosis, diagnostic criteria, management strategies, and pathophysiologic mechanisms of RBD. They then review the literature and their institutional experience of RBD associated with neurodegenerative disease, particularly Parkinson’s disease and dementia with Lewy bodies. The evolving data suggests that RBD may have clinical diagnostic and pathophysiologic significance in isolation and when associated with neurodegenerative disease. (J Geriatr Psychiatry Neurol 2004; 17:146-157)

**Keywords:** REM sleep behavior disorder; Parkinson’s disease; dementia with Lewy bodies; synuclein; synucleinopathy

Rapid eye movement sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep with prominent motor activity and dreaming. The evolving literature and our clinical experience suggest RBD may not simply represent an interesting parasomnia but rather reflects dysfunction in REM sleep control that has relevance for understanding certain neurodegenerative disorders. In this article, we will first review the clinical and polysomnographic features of RBD, differential diagnosis of RBD, criteria for diagnosis of RBD, management of RBD, and pathophysiologic underpinnings of RBD. We will then view RBD in the context of certain neurodegenerative disorders (this material is updated from our prior review published in 2003). Readers will perceive the window that RBD provides on understanding key features of REM sleep control as well as the clinical and pathophysiologic significance of REM sleep dyscontrol in neurodegenerative disorders.

**CLINICAL FEATURES OF REM SLEEP BEHAVIOR DISORDER**

The typical clinical features of RBD are listed in Table 1. About 90% of RBD patients are male. The age of onset is typically in the sixth or seventh decade, although symptoms may begin in the teens or beyond 80 years of age. Patients often vocalize and may scream or swear. Many spouses describe the violent behaviors and vocalizations being very different from the calm manner and speech patients usually exhibit during wakefulness. Movements may involve single limb jerks, but often complex behaviors are exhibited such as punching, pulling hair, running, jumping out of bed, and so on. Most patients view their dreams as nightmares, and the dream content often involves insects, animals, or people chasing or attacking them or their relatives or friends. Many patients are able to recount the content of their dreams upon being awakened at the time of the behavior, although those with significant dementia may not be able to describe their dreams. We encountered one patient with polysomnogram (PSG)-proven RBD who fell asleep as a passenger on a commercial flight and then exhibited punching and kicking behavior (who months later still recalled the dream fight-
ing animals in a cave); the behavior was interpreted as a seizure, and the pilot quickly landed the plane for emergency medical care. Some bed-partners have attempted to awaken patients during an episode, and their comments and gestures become interwoven into the dream, sometimes resulting in injury. These behaviors can lead to falling off or leaping from the bed, striking bedposts or nightstands, and injuries to patients and bed-partners can occur. Injuries that have been associated with RBD include lacerations, bruises, fractures, and subdural hematomas. Suicide and homicide have not been reported in association with RBD. Some patients have been known to tie themselves to bedposts or erect padded panels between themselves and bed-partners to minimize injury. Since most REM sleep occurs in the latter half of the sleep period, RBD tends to occur in the early morning hours, although some may begin exhibiting RBD shortly after falling asleep. As will be discussed later, RBD can occur in association with neurodegenerative disease, most often Parkinson’s disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA). In many cases, RBD begins years to decades before parkinsonism and/or dementia evolves. Our clinical experience also indicates that in many patients with RBD, particularly in those with coexisting PD, DLB, or MSA, the frequency and severity of dream enactment behavior gradually wanes as dementia and/or parkinsonism progresses.

DIFFERENTIAL DIAGNOSIS OF REM SLEEP BEHAVIOR DISORDER

The differential diagnosis of disruptive sleep behavior includes the non-REM parasomnias (somnambulism, night terrors, confusional arousals), nocturnal panic attacks, nocturnal seizures, nightmares, nocturnal wandering associated with dementia, and obstructive sleep apnea (OSA). The history usually allows differentiation of these disorders from RBD. Somnambulism and nocturnal wandering associated with dementia tend to be less violent, not associated with tormenting dreams, involve walking away from the bed rather than leaping or jumping, involve more purposeful activity with a rumaging quality. Also, somnambulism is associated with non-REM sleep (usually stage 3 or stage 4) and tends to occur in the first third of the night when most non-REM sleep occurs. Night terrors and confusional arousals also tend to occur early in the night, involve screaming or anxiety, include inconsistent or incoherent speech during or immediately following the behavior, and importantly, there is typically no recall of dream content after awakening. Nocturnal panic attacks involve extreme anxiety, tachycardia, diaphoresis, and immediate full awareness; dream enactment does not occur. Patients with nocturnal seizures tend to exhibit posturing or generalized tonic-clonic activity without associated dreams, may be incontinent, and are often somnolent or disoriented for minutes to hours following an episode. Patients with moderate to severe OSA can have features that may be identical to RBD; such patients have normal electromyographic (EMG) atonia during REM sleep on PSG, and their “RBD” can be abolished with nasal continuous positive airway pressure.

Eliciting a careful history often allows identification of the disorder, but when diagnostic clarification is necessary, particularly when the risk for injury is high or loud snoring and observed apnea suggestive of OSA is present, PSG with simultaneous video monitoring is warranted.

POLYSOMNOGRAPHIC FEATURES OF REM SLEEP BEHAVIOR DISORDER

On PSG, REM sleep is characterized by the following: rapid eye movements, minimal to no EMG tone, and mixed alpha and theta activity on electroencephalography (EEG) (Figure 1A). The characteristic electrophysiologic finding in patients with RBD is elevated EMG tone on the submental or limb EMG derivations, otherwise known as REM sleep without atonia (RSWA) (Figure 1B). This usually takes the form of a pathologic accentuation of normal phasic twitches, although sometimes EMG tone is tonically increased. Simultaneous video/PSG recording is essential for evaluating patients with suspected RBD, as vocalizations and limb movements can be captured and viewed concurrently with PSG data. When vocalizations and/or limb movements emerge out of REM sleep, without associated epileptiform activity on the EEG derivations (as in Figure 1B), the diagnosis of RBD is established. In our experience, violent and complex dream enactment behavior is encountered infrequently during single-night PSG recordings; rather, increased EMG tone during REM sleep and sparse limb jerks are the norm.

DIAGNOSTIC CRITERIA FOR REM SLEEP BEHAVIOR DISORDER

The International Classification of Sleep Disorders diagnostic criteria for RBD are shown in Table 2; these criteria are similar to the criteria proposed by Mahowald and
Schenck. As can be seen, RBD is characterized by both abnormal REM sleep behavior and abnormal REM sleep electromyography.

Clinicians must decide who to refer to a sleep medicine specialist for PSG, and also to which sleep disorder center for referral. We recommend evaluations with sleep medicine clinicians and PSG in patients who have one or more of the following features: young age (and thus long-term medical therapy may be necessary), dream enactment behavior is frequent and severe enough to raise concerns about patient and bed-partner injury, diagnosis cannot be surmised with confidence by history alone, or a history suggestive of OSA is elicited (ie, loud crescendo snoring, irregularities in snoring with snorts or gasps, observed apnea, daytime hypersomnolence). Determining the presence or absence of OSA is critical, as the drug of choice for RBD—clonazepam—can exacerbate untreated OSA. Untreated OSA increases the risk of cardiovascular and cerebrovascular morbidity and adversely affects cognitive functioning and quality of life.

If RBD may be helpful in establishing the precise diagnosis of patients with parkinsonism and/or dementia (as described below), PSG may be indicated in those clinical settings as well. Not all sleep disorder centers have staff with expertise in the evaluation of parasomnias, nor are all equipped with simultaneous video/PSG monitoring capabilities, thus referral to appropriate centers is necessary. Readers are encouraged to contact the American Academy of Sleep Medicine (www.aasmnet.org) for information regarding accredited sleep disorders centers in the United States. Information on organizations and centers outside the United States can be accessed at www.wfsrs.org (World Federation of Sleep Research Societies) and associated links.

Figure 1. Polysomnograms showing normal REM sleep (A) and rapid eye movement (REM) sleep without atonia—the electrophysiologic substrate for sleep behavior disorder (RBD) (B, next page). In A, note the absence of electromyographic (EMG) activity in the ocular (LOC-FPz and ROC-FPz derivations), submental (CHN-CH2), and limb (LLg-RLg, Larm-Rarm) derivations, whereas increased EMG tone is present in these derivations in B. Simultaneous video monitoring revealed that the patient yelled and punched in the latter part of B (arrows).
The goals of therapy are to minimize the abnormal behavior and unpleasant dreams, and particularly, minimize the potential for injury. All patients and their bed-partners should be counseled on simple steps to minimize injury, such as moving lamps, nightstands, and so on, away from the bed, and placing a mattress or cushion of some type on the floor adjacent to the bed (many patients use inexpensive foam rubber mattresses). Clonazepam has been the mainstay of medical therapy, usually effective at 0.25-0.5 mg/night, but doses above 1 mg nightly are necessary in some patients.3,7 Recent experience with melatonin shows that doses ranging from 3 to 12 mg/night can be effective either as monotherapy or in conjunction with clonazepam when either melatonin or clonazepam alone is ineffective.8-10 Other drugs reported to improve RBD include pramipexole,11 donepezil,12 levodopa,13 carbamazepine,14

Table 2. Diagnostic Criteria for REM Sleep Behavior Disorder (780.59)

A. Patient has a complaint of violent or injurious behavior during sleep
B. Limb or body movement is associated with dream mentation
C. At least one of the following occurs:
   1. Harmful or potentially harmful sleep behaviors
   2. Dreams appear to be “acted out”
   3. Sleep behaviors disrupt sleep continuity
D. Polysomnographic monitoring demonstrates at least one of the following electrophysiologic measures during rapid eye movement (REM) sleep:
   1. Excessive augmentation of chin electromyographic (EMG) tone
   2. Excessive chin or limb phasic EMG twitching, irrespective of chin EMG activity and one or more of the following clinical features during REM sleep:
      a. Excessive limb or body jerking
      b. Complex, vigorous, or violent behaviors
      c. Absence of epileptic activity in association with the disorder
E. The symptoms are not associated with mental disorders but may be associated with neurologic disorders
F. Other sleep disorders (eg, sleep terrors or sleepwalking) can be present but are not the cause of the behavior

triazolam, and clozapine. We have also seen quetiapine effective for managing RBD in many patients.

It is not clear why clonazepam, melatonin, and other agents improve RBD. Clonazepam reduces phasic activity in REM sleep, and although clonazepam clearly improves both unpleasant dreams and dream enactment behavior in most patients, REM sleep without atonia is still evident in those who undergo PSG while taking the drug. Melatonin has been shown to decrease the percentage of REM sleep epochs without muscle atonia and to decrease the number of stage shifts in REM sleep, suggesting it has a more direct mode of action on REM sleep pathophysiology, perhaps by restoring circadian modulation of REM sleep.

**PATHOPHYSIOLOGY OF REM SLEEP BEHAVIOR DISORDER**

The following discussion on RBD pathophysiology is updated from past references. Studies in the cat have shown that there are 2 systems involved in normal REM sleep: one for generating muscle atonia and one for suppressing locomotor activity (Figure 2A). Muscle atonia involves active inhibition by neurons in the nucleus reticularis magnocellularis (NRMC) in the medulla via the ventrolateral reticulospinal tract synapsing on the spinal motoneurons. NRMC neurons receive excitatory influences from the peri–locus ceruleus (peri-LC) region in the pons via the lateral tegmentoreticular tract. Neurons in the peri-LC region are thought to inhibit the cholinergic pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDTN) in the pons. The PPN is interconnected with the substantia nigra, hypothalamus, thalamus, basal forebrain, and frontal cortex. Locomotion involves pontine generators that have not been adequately characterized; the locomotor generator(s) likely receive input from supratentorial structures (particularly the forebrain and thalamus) and ultimately influence the spinal motoneurons. During REM sleep, phasic oculomotor and locomotor activity such as rapid eye movements and muscle twitches occur, but more elaborate motoric activity is directly or indirectly suppressed.

Several brainstem regions have been implicated in RBD pathophysiology, particularly the peri-LC region, PPN, and LDTN (Figure 2B). In the cat model, lesions in the peri-LC region cause REM sleep without atonia, but the site and extent of the lesion determines whether simple or complex behaviors are exhibited. There is debate whether lesions in the PPN are sufficient to cause RBD. Lesions in the ventral mesopontine junction (VMPJ) have recently been found to increase phasic REM sleep movements, suggesting this structure may be involved in RBD pathogenesis. Mahowald and Schenck suggested that increased phasic locomotor drive and/or loss of REM sleep atonia underlies the clinical expression of RBD. It should be noted, however, that some patients have PSG evidence of REM sleep without atonia yet have never exhibited dream enactment behavior. Thus, sufficient locomotor drive is likely necessary in the setting of REM sleep without atonia to result in clinical RBD.

In the first human RBD case ever reported where detailed brainstem analyses were performed, a marked reduction in the number of neurons in the locus caeruleus and marked increase in the number of neurons in the PPN and LDTN were found. The authors proposed that the increased activity in cholinergic neurons and/or decreased disinhibition of the PPN and LDTN by the reduced monoaminergic activity of the LC led to the expression of RBD. In a more recent analysis involving 4 patients with MSA, other investigators found depletion of choline acetyltransferase–containing neurons in the LDTN/PPN nuclei, and depletion of neuromelanin-containing locus caeruleus neurons, leading these authors to suggest that depletion of cholinergic REM—on neurons in the LDTN/PPN—neurons may underlie RBD in MSA patients.

The pathophysiologic underpinnings of human RBD are likely complex judging from the variable response of RBD to agents affecting cholinergic, dopaminergic, and serotoninergic networks. Any theory on pathophysiology must explain why clonazepam is most efficacious for RBD, yet elevated EMG tone during REM sleep still exists on PSG in those with excellent clinical response to the drug. Characterization of the pathophysiology of RBD is critical, as this knowledge may provide insights into the pathophysiology of certain neurodegenerative disorders (see below).

RBD has been described in dementing and parkinsonian disorders and was initially considered a nonspecific feature of neurodegenerative disease. However, the literature suggests that RBD has a predilection for some neurodegenerative conditions and not others. In the following sections, we will review data on those neurodegenerative disorders most commonly associated with RBD—PD, DLB, and MSA. We will also review emerging data that suggest RBD may have particular pathophysiologic and clinical relevance in the synucleinopathies. Finally, we will discuss the implications of narcolepsy-like features and RBD for future drug trials.

**RBD ASSOCIATED WITH PARKINSON’S DISEASE**

Schenck et al are credited as pioneering much of the work on RBD as a clinical entity, with the key PSG findings published in 1986 and 1987. A few of their initial patients had PD, and several PD patients with clinically suspected and PSG-confirmed RBD have since been reported.

Schenck et al identified 38% of 29 patients with idiopathic RBD who subsequently developed a parkinsonian disorder with a mean of 12.7 years after the onset of...
REM Sleep - Normal

REM Sleep - RBD

Figure 2. Schematic of neuroanatomic connections underlying normal rapid eye movement (REM) sleep (A) and sleep behavior disorder (RBD) (B). See text for details. Adapted from Reference 1, p 389. Reprinted with permission from Humana Press, Copyright 2003.

SN, substantia nigra; HT, hypothalamus; Thal, thalamus; BF, basal forebrain; PPN, pedunculopontine nucleus; LDT, laterodorsal tegmental; LC = locus ceruleus; NRMC = nucleus reticularis magnocellularis; VLRT, ventrolateral reticulospinal tract; AHC, anterior horn cell; EMG, electromyographic.
RBD, Schenck et al have continued to follow this cohort with initially idiopathic RBD, and 65% have now developed parkinsonism and/or dementia. Others have also noted the tendency for RBD to precede parkinsonism.

Comella et al examined the occurrence of RBD and sleep-related injury (SRI) in consecutively evaluated patients with PD. A structured questionnaire was used to determine the presence of RBD and SRI. Nine of 61 (15%) patients had responses suggesting RBD. SRI occurred more frequently in the group with RBD than in those with no RBD, and 66% of the patients with SRI had features suggesting RBD. The authors concluded that SRI in PD patients likely reflects RBD, and they suggested treatment such as clonazepam to minimize future SRI risk.

Rye et al reported a woman with juvenile PD whose clinical, PSG, and multiple sleep latency test (MSLT) findings indicated the presence of both RBD and a narcolepsy-like illness. Her monozygotic twin did not have evidence of any neurologic or sleep disorder. The authors suggest that the RBD and narcoleptic features were etiologically related to her PD, perhaps reflecting midbrain dopaminergic dysfunction.

Olson et al analyzed the demographic, clinical, and laboratory features and associated disorders in 93 consecutive patients with RBD. Twenty-five had PD, of whom 10 subsequently developed dementia. RBD preceded the development of PD in 13 cases by a median of 3 years. The frequency and severity of RBD waned with progression of PD in some of these cases, which contrasts with the observation that no cases have been noted to spontaneously improve.

Arnulf et al investigated the relationship between hallucinations and sleep disorders by performing PSG and MSLT studies in 10 patients with PD and visual hallucinations (PD+VH) and 10 PD patients without hallucinations (PD−VH). All patients were on levodopa therapy, and none was considered to have dementia. PSGs revealed RBD in all PD+VH cases and in 6 PD−VH cases. MSLT studies showed approximately half in each group had excessive daytime somnolence (mean initial sleep latency less than 10 minutes; normal is 10 or more minutes). One or more sleep onset REM periods occurred in 8 of the PD+VH patients compared to 2 of the PD−VH patients (2 or more sleep onset REM periods and mean initial sleep latencies below 10 minutes are characteristic of patients with narcolepsy). The drowsiest patients had sleep onset REM periods. Two patients reported hallucinations, and the hallucinations were immediately preceded by REM sleep. Delusions were also temporally associated with REM sleep. The authors concluded that visual hallucinations and delusions in patients with PD may reflect dream imagery, and they suggested that psychosis reflects a narcolepsy-like REM sleep disorder.

Using structured questionnaires and PSG, Gagnon et al investigated the frequency of RSWA and RBD in 33 consecutive patients with PD seen at their institution. They found that 19 (58%) of these 33 patients had RSWA on PSG, yet only 11 (33%) had a history of dream enactment behavior. They interpreted these findings as indicating that PSG revealed that the frequency of RBD was twice that suggested by history alone. The authors posed 2 possible hypotheses to explain these findings, which are not mutually exclusive: (1) the absence of dream enactment behavior on PSG could reflect the tendency of many patients with RBD to exhibit dream enactment behavior a few nights per week or month but not every night and/or (2) RSWA precedes the clinical expression of RBD in many patients with PD.

RBD ASSOCIATED WITH DEMENTIA WITH LEWY BODIES

We originally noted the association of RBD and DLB in 1995 and have been actively studying patients with this association since. RBD is regarded as a supportive feature for the diagnosis of DLB, although some now view RBD as a core diagnostic feature for DLB. Importantly, most of the patients described in these reports began experiencing RBD years, sometimes decades, before their cognitive symptoms evolved.

We initially identified 37 patients with degenerative dementia ± parkinsonism and RBD. Neuropsychological testing demonstrated impaired visual perceptual-organizational skills, constructional praxis, and verbal fluency. These findings suggested that the clinical and neuropsychometric features of the groups of patients with and without parkinsonism were similar, and we hypothesized that the underlying pathology in these patients was DLB.

We subsequently compared the neuropsychometric profile of 31 patients with RBD/dementia to 31 with autopsy-proven Alzheimer’s disease (AD) and found a striking double dissociation with worse impairment on measures of attention, visual perceptual-organization, and letter fluency for the RBD/dementia group, whereas the AD group showed significantly worse performance on confrontation naming and verbal memory. These findings suggested that patients with RBD and degenerative dementia demonstrate a significantly different pattern of cognitive performance from AD, and the dementia associated with RBD may represent DLB. Since RBD and cognitive decline may precede the onset of parkinsonism and hallucinations in DLB, we recently analyzed the neuropsychometric performance of patients with dementia and RBD who do not have parkinsonism or visual hallucinations. Our findings indicated that patients with dementia and RBD who do not have parkinsonism or visual hallucinations have a dementia syndrome that is neuropsychologically indistinguishable from that of probable DLB, and both groups differ significantly from AD. Therefore, even in the absence of visual hallucinations or parkinsonism, the presentation of dementia and RBD may nevertheless indicate underlying Lewy body disease.
CLINICOPATHOLOGIC FINDINGS IN PATIENTS WITH RBD

As of December 2003, 18 autopsied patients with RBD have been reported. The report of Uchiyama et al involved a patient with a 20-year history of RBD who had no cognitive or motor findings throughout his clinical course. At autopsy, Lewy bodies were identified particularly in the brainstem. Schenck et al reported a man with a 15-year history of RBD before dementia evolved, and autopsy initially showed AD pathology, but subsequently ubiquitin immunocytochemistry revealed limbic Lewy bodies. To date, we have identified 9 other dementia cases and all had Lewy body disease (LBD); coexisting AD pathology was present in 6, argyrophilic grain pathology was present in 3, andBinswanger’s pathology was present in 1 and multiple subcortical infarcts in 1. Another 3 patients were found to have MSA at autopsy. Turner et al described a case with a 17-year history of RBD before typical DLB features evolved. At autopsy, α-synuclein immunocytochemistry showed Lewy bodies in the substantia nigra, locus caeruleus, and primarily limbic cortex (mild Alzheimer changes were also present). The PD case reported by Arnulf et al had LBD. Since our report in 2003, we have identified 2 additional patients with LBD who have had LBD present at autopsy. Therefore, all 20 patients with RBD examined to date have had either Lewy body pathology or MSA at autopsy.

THE RBD-SYNUCLEINOPATHY ASSOCIATION

When associated with a neurodegenerative disorder, RBD appears to have a predilection for some disorders and not others. There are no published reports of RBD associated with pure AD (without coexisting Lewy bodies), Pick’s disease (Pick), frontotemporal dementia (FTD), progressive nonfluent aphasia (PNA), semantic dementia (SD), corticobasal degeneration (CBD), progressive subcortical gliosis (PSG), argyrophilic grain disease (AGD), or dementia lacking distinctive histopathology (DLDH). RBD has been reported in clinically suspected PSP, pure autonomic failure, and amyotrophic lateral sclerosis. REM sleep without atonia has been reported in single cases of CBD and PSP, but neither had clinical RBD features. There are a few recent reports on RBD associated with spinocerebellar atrophy type 3 (Machado-Joseph disease). As noted above, numerous cases of RBD have been reported in conjunction with MSA, PD, and DLB. Although frequency data on the presence of RSWA and RBD in the neurodegenerative disorders is based on relatively small numbers of patients thus far, the presence of each in MSA has been reported to be 90% to 95% for RSWA and 68% to 90% for RBD, and presence of each in PD is approximately 58% for RSWA and 33% for RBD. Our data suggest at least 50% of patients with DLB have RBD. Furthermore, as stated above, all patients with RBD who have undergone autopsy have had either Lewy body disease or MSA. Therefore, there is considerable evidence indicating RBD occurs in association with PD, DLB (both forms of LBD), and MSA, and rarely in other neurodegenerative disorders.

Recent immunocytochemical analyses have revealed that PD, DLB, and MSA share the similarity of α-synuclein positive intracellular inclusions. Specifically, the oligodendroglial cytoplasmic filamentous inclusions in MS and Lewy bodies and Lewy neurites in PD and DLB are composed of the protein α-synuclein, and these disorders can be collectively considered as “synucleinopathies.” In contrast, the neurofibrillary tangles of AD and the intracellular inclusions in Pick’s disease, PSP, CBD, PSG, and AGD are made of the microtubule-associated protein tau in a hyperphosphorylated state, and these disorders can be characterized as “tauopathies.”

A testable hypothesis that stems from the published literature is the following: RBD occurs with disproportionately greater frequency, or is relatively specific for, the synucleinopathies (eg, MSA, PD, DLB) compared to those disorders that are nonsynucleinopathies (eg, AD, Pick, PSG, CBD, AGD, and DLDH). Since the syndromes of mild cognitive impairment (MCI), FTD, PNA, and SD are typically manifestations of the nonsynucleinopathy disorders, one would also expect that RBD would be infrequent or absent in patients with these syndromes. We have performed 3 analyses to test this hypothesis.

In the first analysis, we compared the frequency of suspected and PSG-confirmed RBD among patients with the synucleinopathies MSA, PD, or DLB to the frequency among patients with the nonsynucleinopathies AD, FTD, CBD, PSP, MCI, primary progressive aphasia (PPA), and posterior cortical atrophy (PCA). The results indicated that patients with MSA, PD, or DLB were more likely to have probable and PSG-confirmed RBD compared to patients with the nonsynucleinopathies (probable RBD 77/120 = 64% vs 7/278 = 3%, P < .01; PSG-confirmed RBD 47/120 = 39% vs 1/278 = 1%, P < .01). In the second analysis, we reviewed the clinical records of 360 consecutive patients evaluated at Mayo Clinic Jacksonville for parkinsonism and/or cognitive impairment, and we found the frequency of probable RBD among patients with PD and DLB was far greater than the frequency of probable RBD among patients with AD and MCI (56% vs 2%, P < .01). In the final analysis, we reviewed the brain biopsy or postmortem autopsy diagnoses of 23 Mayo Clinic Rochester patients who had been clinically examined for possible RBD and a neurodegenerative disorder (this analysis includes 10 of the patients reported in the section Clinicopathologic Findings in RBD). Of the 23 autopsied patients who had been questioned about possible RBD, 10 were clinically diagnosed with RBD. The neuropathologic diagnoses in these 10 included LBD in 9 and MSA in 1. Of the other 13 cases, 12 did not have a history suggesting RBD, and the 1 case who did had normal EMG atonia.
during REM sleep plus obstructive sleep apnea on PSG and autopsy findings of PSP. Thus, the positive predictive values for RBD indicating a synucleinopathy exceeded 90% for each of these analyses.

In summary, the literature indicates that RBD is often associated with the synucleinopathies but rarely with the nonsynucleinopathies. Future clinicopathologic studies in patients with neurodegenerative disease, with and without RBD, will be necessary to test the hypothesis that in the setting of degenerative dementia and/or parkinsonism, the presence of RBD often reflects an underlying synucleinopathy.

BRAINSTEM ANATOMY OF RBD AND SYNUCLEINOPATHY PATHOLOGY

Dopaminergic dysfunction has been implicated in RBD pathophysiology based on anatomic, pharmacologic, and functional neuroimaging studies, yet there is no convincing evidence that dopaminergic dysfunction is the primary cause of RBD. A recent analysis using synuclein immunocytochemistry in incidental and symptomatic Parkinson’s disease cases reveals striking overlap between the presumed brainstem nuclei involved in RBD pathophysiology and PD pathophysiology. The findings in this report suggest a temporal sequence of synuclein pathology beginning in the medulla and eventually ascending to more rostral structures (Figure 3).

### BRAINSTEM ANATOMY OF RBD AND SYNUCLEINOPATHY PATHOLOGY

![Figure 3. Schematic of brainstem nuclei presumably involved in sleep behavior disorder (RBD) pathophysiology, and nuclei and cortical regions implicated in Lewy body disease pathophysiology according to Braak staging system.](image)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tr>
<td>Stage 1</td>
<td>Degeneration of dorsal IX/X motor nucleus and intermediate reticular zone, olfactory bulb</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Stage 1 pathology plus involvement of caudal raphe nuclei, nucleus reticularis magnocellularis (NRMC), and locus coeruleus (LC)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Stage 2 pathology plus involvement of substantia nigra (SN), tegmental pedunculopontine nucleus (PPN), amygdala (A), and magnocellular nuclei of the basal forebrain</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Stage 3 pathology plus involvement of the substantia nigra (SN), tegmental pedunculopontine nucleus (PPN), amygdala (A), and magnocellular nuclei of the basal forebrain</td>
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<tr>
<td>Stage 5</td>
<td>Stage 4 pathology plus involvement of the multimodal association neocortices (MAC)</td>
</tr>
<tr>
<td>Stage 6</td>
<td>Stage 5 pathology plus involvement of the unimodal association neocortices (UAC)</td>
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IMPLICATIONS OF NARCOLEPTIC-LIKE FEATURES IN PD/DLB AND OF RBD FOR FUTURE DRUG TRIALS

There is growing evidence of sleep-wake boundary dysfunction in PD and DLB similar to what occurs in narcolepsy. The hypersonolence and sleep attacks of narcolepsy are often attributed to the somnolence of REM sleep and non-REM sleep intruding into wakefulness. The hypnopompic and hypnagogic hallucinations in narcolepsy represent intrusions of the dream imagery of REM sleep into wakefulness. The intrusion of muscle atonia into wakefulness causes cataplexy and sleep paralysis. REM sleep behavior disorder involves the intrusion of active muscle tone into REM sleep, and many patients with nar-
colepsy have RBD. Thus, the maintenance of REM sleep-related phenomena in REM sleep, and of wake-related phenomena in wakefulness, is critical for humans to avoid experiencing symptoms characteristic of narcolepsy. The absence of narcoleptic symptomatology is due in part to normal functioning of hypocretin-1 in the brain. 85

The findings of Arnulf et al suggesting some features of PD with psychosis are narcoleptic-like in nature have several implications, many of which are acknowledged in their report.30 Daytime hypersomnolence may be intrinsic to Lewy body pathophysiology in some patients. Hypocretin-1—a protein critical for arousal—is often low or undetectable in the cerebrospinal fluid (CSF) of patients with narcolepsy.26 There is now evidence indicating low or undetectable hypocretin-1 levels in the CSF of some patients with PD,87 which further supports the “narcoleptic-like” features in LBD. The visual hallucinations associated with PD and DLB may reflect intrusions of dream imagery into wakefulness.1,30 Spells, drop attacks, and stroke-like spells occur in some patients with PD and DLB, and despite exhaustive diagnostic testing, no etiology is often found. Perhaps an emotional trigger (eg, fright from a perceived image while hallucinating) could cause a cataplectic event, thus explaining why diagnostic studies are unrevealing. These are intriguing possibilities that warrant further study.

From the treatment perspective, if hypersomnolence, visual hallucinations, and conceivably cataplexy-like spells represent narcoleptic-like phenomena, then the principles of management in patients with narcolepsy may have applicability to patients with PD and DLB. There may be a general reluctance to use psychostimulants in those who are already experiencing hallucinations and delusions, but if hallucinations and delusions represent features of REM sleep invading into wakefulness, psychostimulants may actually improve “psychotic” symptoms. We have already observed improvements in cognition, hypersomnolence, hallucinations, and delusions in some PD and DLB patients with modafinil or methylphenidate. When visual hallucinations occur primarily at night, drugs used for RBD such as clonazepam and melatonin may theoretically be helpful, and we have observed exactly this in some patients. Characterization of the sleep/wake abnormalities in patients with PD and DLB may therefore lead to more effective treatments for challenging clinical problems.

As noted above, RBD tends to precede the onset of parkinsonism or dementia in patients with MSA, PD, and DLB by years or decades.1-5,10,15,24,26,36,41,45,48,53,58-60,69,70 Almost 40% of patients with idiopathic RBD in one series were subsequently found to have developed a parkinsonian disorder,36 and continued follow-up of this cohort has shown approximately 65% have now developed parkinsonism and/or cognitive impairment.37 RBD preceded dementia and/or parkinsonism in 67% of another series.15 Therefore, idiopathic RBD may represent the harbinger of an evolving neurodegenerative disorder, which in many cases may be a synucleinopathy.15,55 Thus, if idiopathic RBD represents the earliest clinical manifestation of an evolving neurodegenerative disorder, the presence of RBD may be particularly relevant early in the course of a neurodegenerative disease when intervention may be most critical. Agents that may positively affect synucleinopathy pathophysiology could be instituted in patients with idiopathic RBD and potentially delay or prevent the development of cognitive impairment or parkinsonism. This is an exciting avenue for future drug therapy.

SUMMARY

While attention to features during the waking state has been successful in characterizing and treating patients with PD and DLB, this review substantiates the importance of studying sleep mechanisms and REM sleep dyscontrol in these disorders. The tendency for RBD to occur in the synucleinopathies and rarely in the nonsynucleinopathy disorders, and tendency for RBD to precede symptoms of dementia and parkinsonism, suggests that RBD may have clinical diagnostic and pathophysiologic significance in isolation and when associated with neurodegenerative disease.

References


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