REM Sleep Behavior Disorder

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Carlos H. Schenck

> …he was thrusting his sword in all directions, speaking out loud as if he were actually fighting a giant. And the strange thing was that he did not have his eyes open, because he was asleep and dreaming that he was battling the giant… He had stabbed the wine skins so many times, believing that he was stabbing the giant, that the entire room was filled with wine…. [1]

Personal Experiences with Rapid Eye Movement Sleep Behavior Disorder in Patients and Spouses

Although rapid eye movement (REM) sleep behavior disorder (RBD), featuring its quintessential violent dream-enacting behaviors, was described in the world literature by Cervantes as early as 1605, it was not until 1986–1987 that RBD was formally identified and named [2, 3]. RBD was included in the international classification of sleep disorders (ICSD) in 1990, with diagnostic criteria being established, and with updates in the ICSD-2 in 2005 [4] and in the ICSD-3 in 2014. RBD emerges during loss of the mammalian generalized skeletal muscle atonia of REM sleep, a pathological state known as REM without atonia (RWA).

The index patient aptly described his RBD as "violent moving nightmares" [2]. The report of his case illustrated many common features of RBD: "Patient 1. A 67-year-old dextral man was referred because of violent behavior during sleep…. He had slept uneventfully through adolescence in a small room with three brothers. But on his wedding night, his wife was 'scared with surprise' over his sleep talking, groaning, tooth grinding, and minor body movements. This persisted without consequence for 41 years until one night, 4 years before referral, when he experienced the first 'physically moving dream' several hours after sleep onset; he found himself out of bed attempting to carry out a dream. This episode signaled the onset of an increasingly frequent and progressively severe sleep disorder; he would punch and kick his wife, fall out of bed, stagger about the room, crash into objects, and injure himself. These harmful behaviors, most prominent every tenth night, typically appeared several hours after sleep onset and never within the first hour… he quickly became alert with each awakening. In search of sound sleep, his wife began to sleep in another room 2 years before referral. They remain happily married, believing that these nocturnal behaviors are out of his control and discordant with his waking personality."

"An example of a recurring RBD dream consisted of his delivering a speech and emphasizing certain points with his right hand from which he awakened sitting up with right arm outstretched and fingers pointing in a manner consistent with the dream action. Another time 'I was on a motorcycle going down the highway when another motorcyclist comes up alongside me and tries to ram me with his motorcycle. Well, I decided I'm going to kick his motorcycle away and at that point my wife woke me up and said, 'What in heavens are you doing to me?', because I was kicking the hell out of her'." Both of these episodes exemplify an "isomorphism" between the dream action and the enacted behaviors (e.g., kicking)."

His most vivid and violent dream, which prompted referral, was described in a National Geographic magazine article, "What Is This Thing Called Sleep?," Dec. 1987, p. 787: "The crowd roared as running back Donald Dorff, age 67, took the pitch from his quarterback and accelerated smoothly across the artificial turf. As Dorff braked and pivoted to cut back over tackle, a huge defensive lineman loomed in his path. One hundred twenty pounds of pluck, Dorff did not hesitate. But let the retired grocery merchandiser from Golden Valley, Minnesota, tell it: 'There was a 280-pound tackle waiting for me, so I decided to give him my shoulder. When I came

C. H. Schenck (✉)
Minnesota Regional Sleep Disorders Center, Minneapolis, USA
e-mail: schen010@umn.edu

Department of Psychiatry, Hennepin County Medical Center, Minneapolis, USA

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

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to, I was on the floor in my bedroom. I had smashed into the dresser and knocked everything off it and broke the mirror and just made one heck of a mess. It was 1:30 a.m.'"

Patient #4 in the original series of RBD patients [2] had a notorious deer-hunting dream-enacting episode, in which he nearly strangled his wife to death in bed, that was described as "Hunting Deer Under the Blanket" (Stern magazine, Germany, March 24, 1988), and as "The Man Who Mistook His Wife For A Deer" (New York Times Sunday magazine cover story, February 2, 2003). "Mel Abel's eyes brim with tears when he tells how criminally close he came to harming his wife, Harriet. He was struggling with a deer whose head he was trying to snap when he discovered he was actually home in bed with his hands on Harriet's head and chin. Harriet woke him up, hollering, 'Mel, what in the world are you trying to do?'" (p. 36). "I started to cry and I said, 'Oh my God, am I glad you woke me up!' Another minute, you know, and I give a snap, and it might have broke her neck [5] (p. 51)." Figure 45.1 shows his desperate, often ineffective and at times harmful, self-remedy for control of the RBD.

Table 45.1 lists descriptions of sleeping and living with RBD by a group of 26 patients and their spouses that signal the dangers of sleeping with RBD [5]. Extreme force can be generated in RBD that rapidly produces life-threatening situations. The wives were convinced that their husbands were fully asleep while having prominent, excessive body movements throughout the night: "He is sleeping and his body is in motion" (p. 132). The assumption often expressed by patients and spouses was that RBD was caused by work stress that would resolve with retirement turned out to be false, much to their chagrin. Another common assumption was that RBD was "part of getting old" and "it simply became routine," [5] (p. 125); these couples became resigned to live with this new late-life "normality"—until they heard about RBD and its successful therapy, usually from media reports.

Fig 45.1 Patient #4 from the original reported series of RBD cases in 1986 [2] demonstrates a "home remedy" he resorted to using in desperation to prevent himself from leaping or falling out of bed and injuring himself. He wore a belt around his pajamas and then tied a rope around the belt on one end while tying the other end of the rope around the headboard of the bed. He engaged in this bedtime tethering ritual every night for 5 years before finding out about RBD in a news report and then presenting for evaluation at the sleep center

Historical Background of RBD: 1966–1985

Various polysomnography (PSG) and clinical aspects of human RBD were described since 1966 by investigators from Europe, Japan, and North America, almost exclusively in neurologic settings, as reviewed [2, 6, 7]. Two groups of pioneering investigators should be recognized [6]: (i) Passouant et al. from France in 1972 first identified a dissociated state of REM sleep with tonic muscle activity induced by tricyclic antidepressant medication. (ii) Tachibana et al. from Japan in 1975 named "stage 1-REM sleep" as a peculiar sleep stage characterized by muscle tone during an REM sleep-like state that emerged during acute psychoses related to alcohol and meprobamate abuse. Also, clomipramine therapy of cataplexy in a group of patients with narcolepsy commonly produced RWA in a study from 1976 by Guilleminault et al. [8]. Elements of both acute and chronic RBD manifesting with "oneirism" were represented in the early literature, along with RWA without clinical correlates: Delirium Tremens (DTs) and other sedative and narcotic withdrawal states, anticholinergic use, spinocerebellar and other brainstem neurodegenerative disorders; the "REM rebound and REM intrusion" theories were proposed and discussed in many of these early reports. The 1986 report in SLEEP firmly established that RBD is a distinct parasomnia, which occurs during unequivocal REM sleep, and which can be idiopathic or symptomatic of a neurologic disorder [2]. Although there is a variable loss of the customary, generalized muscle paralysis of REM sleep, all other major features of REM sleep remain intact in RBD, such as REM latency, REM percent of total sleep time, number of REM periods, and REM/nonrapid eye movement (NREM) cycling. PSG monitoring of these patients established that RBD did not emerge from a "stage-1 REM sleep" that was separate from REM sleep, nor did RBD emerge from a poorly defined variant of REM sleep, or from an unknown or "peculiar" stage of sleep, or during "delirious" awakenings from sleep—all of which had been mentioned in the literature. The 1986 SLEEP report also called attention to generalized motor dyscontrol across REM and NREM sleep, manifesting as increased muscle tone and/or excessive phasic muscle twitching in REM sleep, along with periodic limb movements and excessive nonperiodic limb twitching in NREM sleep [2]. A lengthy prodrome in

Table 45.1 RBD behaviors causing imminent danger: patient and spouse comments[a]

A. Comments by RBD Patients	
1	"It seems that I am extra strong when I am sleeping." (p. 142)
2	"I ran right smack into the wall, an animal was chasing me. I think it was a big black dog." (p. 157)
3	"And the last time that happened, I didn't remember the dream because I knocked myself out." (p. 149)
4	"I thought I was wrestling someone and I had her by the head." (p. 136)
5	"Pounding through the curlers into her head." (p. 157)
6	"What scares me is what a catastrophe that would be to wake up and find that I had broken her neck." (p. 137)
7	"I have hit her in the back too, and she has had a couple of (vertebral) disc operations." (p. 143)
8	"One night I woke up as I was beating the hell out of her pillow…that's when I realized that I had a problem." (p. 106)
9	"Just recently, I rammed into her pelvis with my head…during a dream." (p. 93)
B. Comments by the Wives	
1	"It's amazing. You should see the energy behind that activity, oh, it's unreal."(p. 107)
2	"He literally just kind of flew out of bed and landed on the floor with tremendous strength" (p. 53)
3	"It almost seems like a force picks him up." (p. 130)
4	"His legs go so fast, just like he's running" (p. 155)
5	"It is his kicking, violent kicking, his feet are just like giant hammers when they hit you over and over again." (p. 73)
6	"I felt that kick on the ankle for two months afterwards." (p. 82)
7	"That's the reason we got the waterbed—because he was wrecking his hands on the wooden bed." (p. 111)
8	"Oh, yes, there were always bloody sheets." (p. 105)
9	"Roaring like a wounded wild animal: he roared, he crouched, he punched." (p. 75)
10	"I told him I'd have one devil of a time explaining how I got a broken arm in bed with both of us asleep." (p. 126)
11	"What happens to people like my husband who don't get diagnosed? Do they kill their wives in these experiences, do we know?" (p. 139)

[a] From [5] a book based on audio-recorded interviews of a series of older male patients with RBD and their wives from the Minnesota Regional Sleep Disorders Center, with signed permission by the patients and spouses

RBD was also described; a characteristic dream disturbance was identified; and a successful treatment with bedtime clonazepam was empirically discovered.

Animal Models of RBD

An experimental animal model of RBD was first reported in 1965 by Jouvet and Delorme from the Claude Bernard University in Lyons, France [6, 9], which was produced by brainstem lesions in the peri-locus ceruleus area that released a spectrum of "oneiric" behaviors during REM sleep (called paradoxical sleep and active sleep by basic scientists). These oneiric behaviors in cats closely match the repertoire of RBD behaviors in humans. Research on animal models of RBD (that now include cats, rats (brainstem lesion models), and mice (transgenic mouse model with impaired GABA and glycine transmission) [6, 9–11] and on the neuroanatomy and neurochemistry subserving REM-atonia and the phasic motor system in REM sleep has progressed considerably in recent years.

Ramaligam et al. [12] summarize research from the past five decades on the neural circuitry regulating REM-atonia, and identify REM-active glutamatergic neurons in the pontine sublaterodorsal (SLD) nucleus as being a critical area, as descending projections from the SLD activate neurons in the ventromedial medulla (VMM), from where inhibitory descending projections to the spinal cord ultimately produce the REM atonia. Damage to the SLD appears critical for triggering RBD in humans, based on neuropathological findings in humans with neurodegenerative disorders. Luppi et al. focus on the potential roles of brainstem glutamate, GABA, and glycine dysfunction in the pathophysiology of RBD, and propose alternative explanations for RBD apart from SLD damage [13]. A new study by Hsieh et al. [14] found that yet another brainstem region may be implicated in human RBD, involving GABA-B receptor mechanisms in the external cortex of the inferior colliculus. Therefore, REM sleep has an intrinsically programmed, brain-generated, active motor-inhibitory system, and not a passive withdrawal of motor activity. The atonia of REM sleep is briefly interrupted by excitatory inputs which produce the REMs and the muscle jerks and twitches characteristic of REM sleep.

All categories of behaviors found in human RBD are mirrored in an experimental animal model of RBD produced by pontine tegmental lesions [6, 9]. The pathophysiology of human RBD is presumed to correspond to the findings from an animal model of RBD in regard to interruption of the REM-atonia pathways and/or disinhibition of brainstem motor pattern generators.

Finally, naturally occurring, congenital, and adult-onset RBD in cats and dogs has been reported, with effective

Table 45.2 Early historical milestones in RBD[a]

1986–1987	Formal description, naming, and treatment of RBD [2, 3]
1989	RBD in the differential diagnosis of sleep-related injury [15]
1990	Forensic aspects of RBD [16]
1991	Status dissociatus [17]
1992	Medication-induced RBD [18]
1992	Narcolepsy-RBD [19]
1996	Delayed emergence of parkinsonism in RBD [20]
1996	Association of RBD with specific HLA haplotypes [21]
1997	Parasomnia overlap disorder [22]

[a] From the Minnesota Regional Sleep Disorders Center, Minneapolis, Minnesota, USA

therapies being identified (as reviewed [5, p. 415–6], [6]). This reflects an intriguing animal–human reciprocity, as the experimental animal model of RBD facilitated the understanding of human RBD and its effective therapy with clonazepam, which in turn facilitated awareness of naturally occurring RBD in dogs and cats and use of effective therapy with clonazepam.

Early Historical Milestones of RBD: 1986–1997

Among the ten patients in the original series, five had diverse neurologic disorders etiologically linked with RBD, and five were idiopathic [2, 3]. As a larger group of idiopathic RBD (iRBD) patients was gathered and followed longitudinally at our center, a surprisingly strong and specific association with eventual parkinsonism and dementia became apparent [20, 23], which has spurred a major, growing, multinational research effort [24, 25], including the formation of the International RBD Study Group (IRBD-SG) [10]. Many other important clinical associations with RBD have been identified, such as the strong link with narcolepsy [19, 26]. RBD is situated at a strategic crossroad of sleep medicine, neurology, and the neurosciences. The literature on RBD has continued to grow exponentially in breadth and depth [27]. RBD publications have now exceeded 100 per year. The "RBD odyssey" [28] exemplifies the strong cross-linkage between the basic science underlying REM sleep and the clinical features of RBD, and the close correspondences between animal models of RBD and clinical RBD. Table 45.2 presents early RBD historical milestones [2, 3, 20, 19, 15–18, 21, 22], with elaboration below.

Clinical and PSG Findings in RBD

There are two essential diagnostic hallmarks of RBD, involving clinical and PSG components [4]. The clinical component involves either (i) a history of abnormal sleep-related behaviors that are often dream-enacting behaviors, and/or emerge during the second half of the sleep cycle when REM sleep predominates compared to the first half of the sleep cycle, and/or (ii) abnormal REM sleep behaviors documented during video-PSG in a sleep laboratory, which are often manifestations of dream enactment. It is important to note that the diagnosis of RBD does not require dream enactment [4], since about 30% of reported RBD cases in the world literature do not have dream enactment (usually in patients with neurodegenerative disorders, including dementia), as reviewed [29]. The PSG hallmark of RBD consists of electromyographic (EMG) abnormalities during REM sleep, referred to as "loss of REM-atonia," or "RWA," featuring increased muscle tone and/or increased phasic muscle twitching [4]. Figures 45.2, 45.3, 45.4a, b depict examples of PSG findings in RBD.

RBD represents how one of the defining features of mammalian REM sleep, viz. generalized skeletal muscle atonia—"REM-atonia"—can be partially or completely eliminated, resulting in a major clinical disorder. RBD is the only parasomnia in the ICSD-2 [4] and ICSD-3 that requires PSG confirmation. There are three reasons for this requirement: first, the core EMG abnormalities of RBD are present every night (given a sufficient amount of REM sleep); second, RBD is not the only dream-enacting disorder in adults, and so objective confirmation is highly desirable; third, given the strong probability of future parkinsonism in males $\geq$50 years of age initially diagnosed with idiopathic RBD, it is imperative to diagnose RBD objectively so that affected males (and their families) can be properly informed and be encouraged to plan for the future accordingly.

Some patients almost exclusively have arm and hand behaviors during REM sleep, indicating the need for both upper and lower extremity EMG monitoring in fully evaluating for RBD. Some patients preserve most of their REM-atonia, but have excessive EMG twitching during REM sleep. Autonomic nervous system activation (viz. tachycardia) is uncommon during REM sleep motor activation in RBD, in contrast to the disorders of arousal. Periodic limb movements (PLMs) during NREM and REM sleep are very common with RBD, and may disturb the sleep of the bed partner. These PLMs are rarely associated with electroencephalogram (EEG) signs of arousal. Increased percentages of slow-wave sleep and increased delta power in RBD have been found in controlled and uncontrolled studies, but this can be a highly variable

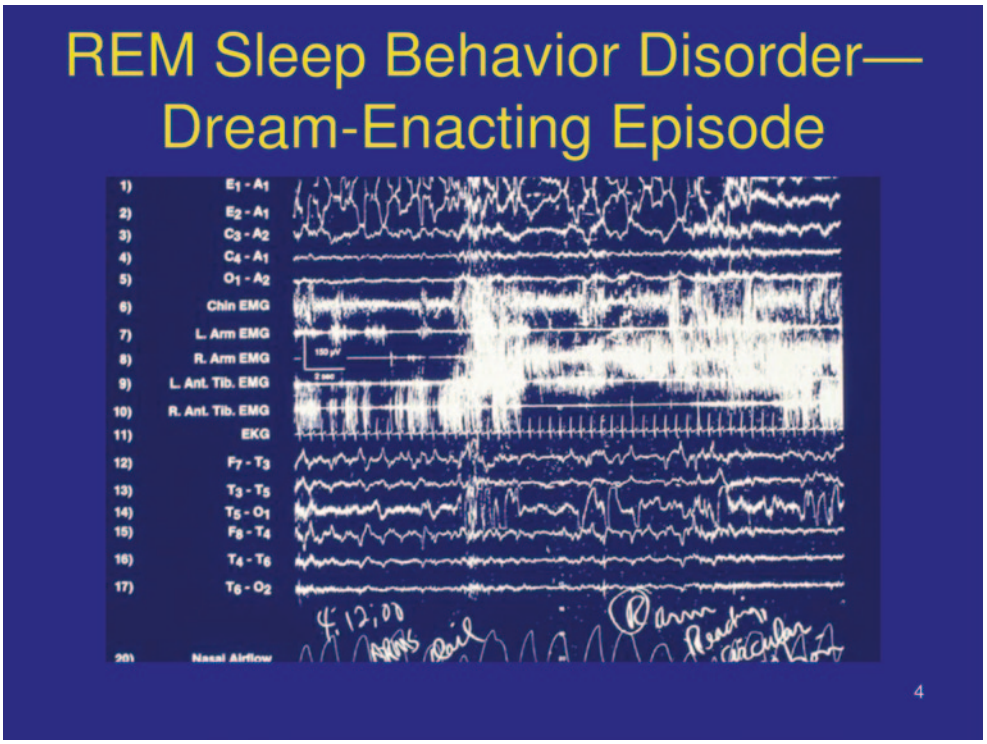

Fig 45.2 Dream-enacting episode during REM sleep in a 62-year-old man with RBD. As the sleep technologist noted the episode on the PSG tracing, the man was dreaming that he was on a boat on Lake Superior, by Duluth, Minnesota. The boat was rocking violently in the water, and he was on the main deck urgently reaching for the handrail with his right hand in circular motions to grab hold of the handrail and stabilize himself—and avoid being thrown down into the hold of the ship where menacing skeletons were beckoning at him. When he woke up, he instantly became alert and oriented, and relayed the dream to the technologist, who acknowledged that the observed behavior closely matched the dream sequence, an example of "isomorphism."There is complete obliteration of "REM-atonia" in this tracing, with continuous increase of chin muscle tone, and tremendous phasic EMG activation of the chin and both upper and lower extremities. Despite the intense, generalized phasic motor activation and concomitant behavioral release, the EKG rate remains constant, without acceleration, which is typical of RBD and in sharp contrast to the disorders of arousal from slow-wave sleep.

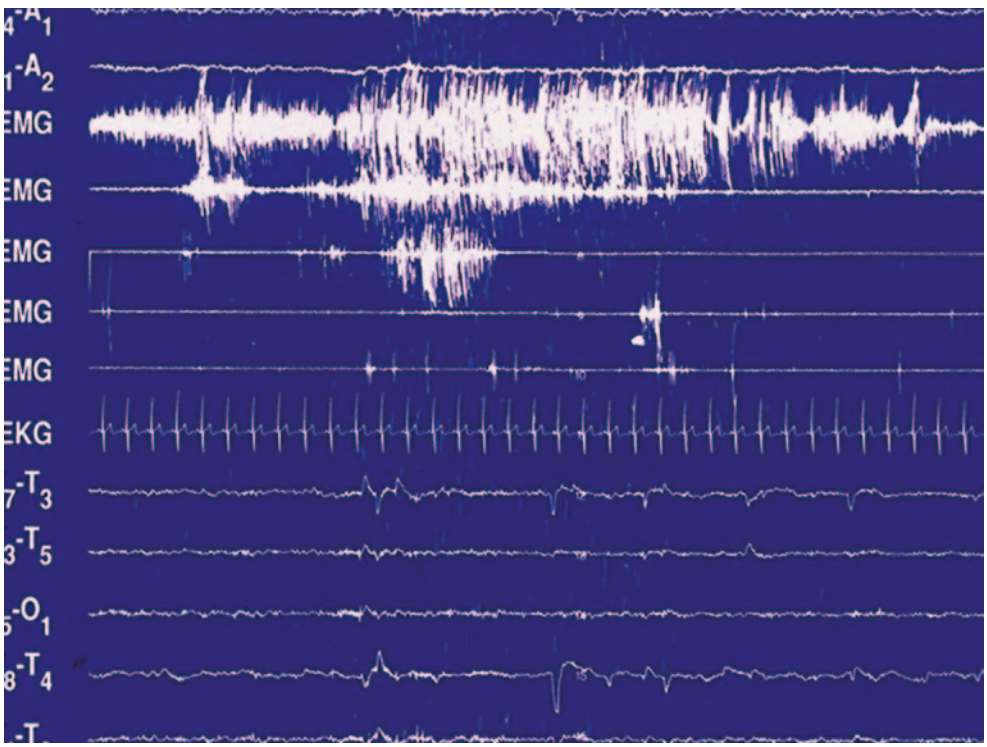

Fig 45.3 Same-patient and same-night PSG as in Fig. 45.2. This tracing during REM sleep shows REMs in the top two channels, nearly complete loss of REM-atonia, with brief restoration of normal REM-atonia in the chin EMG towards the end of the tracing. The upper extremities show robust phasic EMG twitching, in sharp contrast to the virtual lack of phasic EMG activity in the lower extremities, thus calling attention to the recommended EMG montage in evaluating for RBD that should include bilateral upper extremity EMG monitoring, besides lower extremity and chin EMG monitoring

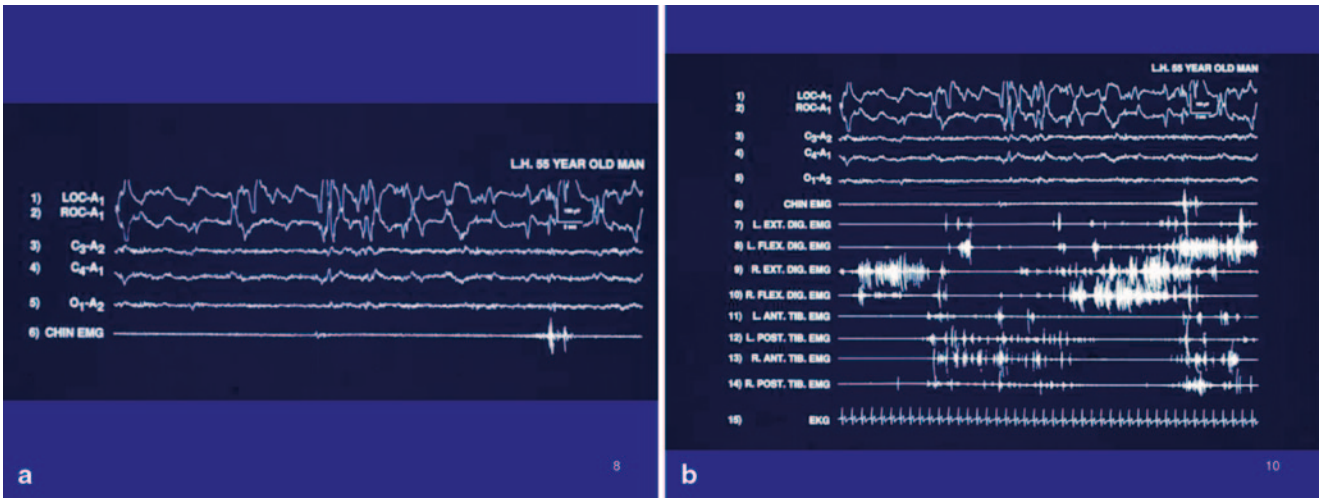

Fig 45.4 **a** PSG tracing of RBD, with REMs, an activated EEG, and continuously preserved REM-atonia, with normal, brief phasic twitching of the chin EMG **b** Expanded montage. Note the excessive phasic EMG twitching of opposing flexor and extensor muscles in both the upper and lower extremities, in the context of preserved REM-atonia shown by the chin EMG. This exemplifies the need for an expanded EMG montage in the evaluation of RBD. Also, the phasic coactivation of opposing muscle groups, viz. right flexor and right extensor digitorum muscles (robust in this tracing), is a common finding during REM sleep in RBD, which ordinarily is not present in wakefulness, since it would be completely dysfunctional (usually there is reciprocal inhibition of an opposing muscle group when one muscle group is activated for a functional purpose). This tracing exemplifies a subtype of motor dyscontrol in RBD in which there is excessive extremity phasic EMG twitching with preserved background atonia shown in the chin EMG

finding in RBD, depending on the clinical population. Sleep architecture and the customary cycling among REM and NREM sleep stages are usually preserved in RBD, although some patients show a shift toward N1 sleep (particularly in neurodegenerative disorders).

There has been an advance over time from the qualitative determination of RWA to a more rigorous, quantitative determination of RWA, to assist with the diagnosis of RBD. The most current evidence-based objective data provide the following guidelines for detecting RWA and guidelines for their interpretation supporting the diagnosis of RBD:

1. RWA is supported by the PSG findings of either: (i) tonic chin EMG activity in ≥30% of REM sleep; or (ii) phasic chin EMG activity in ≥15% REM sleep, scored in 20 s epochs [30].
2. Any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in ≥27% of REM sleep, scored in 30 s epochs [31].
3. Automated quantification methods have been developed for generating the "REM sleep atonia index" with scores ranging from 0 (complete loss of REM-atonia) to 1 (complete preservation of REM-atonia); cut-score for RSWA is atonia index <0.9 [32].

As demonstrated by RBD, REM-atonia serves an important protective function, as it allows the dreaming human or other mammal to engage in a full spectrum of physically active dreams while being simultaneously paralyzed and thus unable to actually move while having active dreams. A person with RBD moves with eyes closed and with complete unawareness of the actual surroundings—a highly vulnerable state for the dreamer [5, 15, 16]. The clinical manifestation of RBD is usually (but not necessarily) dream-enacting behavior. Injury to oneself or bed partner is common in RBD. Typically, at the end of an episode, the individual awakens quickly, becomes rapidly alert, and reports a dream with a coherent story, with the dream action corresponding to the observed sleep behaviors. This phenomenon is called "isomorphism" with examples provided in the previous section. After awakenings from RBD episodes, behavior and social interactions are appropriate, mitigating against either an NREM sleep phenomenon, delirious state, or an ictal phenomenon.

Sleep and dream-related behaviors reported by history and documented during video PSG include both violent and (less commonly) nonviolent and even pleasant behaviors [6, 33]: talking, smiling, laughing, singing, whistling, shouting, swearing profanities, crying, chewing, gesturing, reaching, grabbing, arm flailing, clapping, slapping, punching, kicking, sitting up, looking around, leaping from bed, crawling, running, dancing, and searching for a treasure or other objects. Walking, however, is quite uncommon with RBD, and leaving the room is especially rare, and probably accidental. Rarely there can be smoking a fictive cigarette; masturbation-like behavior; pelvic thrusting; and mimics of eating, drinking, urinating, and defecating. Since the person is attending to the dream action with eyes closed, and not attending to the actual environment with eyes open, this is a

major reason for the high rate of injury in RBD, besides the aggressive and violent behaviors.

Sleep talking with RBD runs the spectrum from short and garbled to long-winded and clearly articulated speech. Angry speech with shouting and profanity, and also humorous speech with laughter, can emerge.

One recent study found that of 14 RBD patients with repeated laughing during REM sleep documented by video-PSG, 9 were clinically depressed during the daytime, indicating a state-dependent dissociation between waking versus REM sleep emotional expression in RBD [34].

As RBD occurs during REM sleep, it usually appears at least 90 min after sleep onset, unless there is a coexisting narcolepsy, in that case RBD can emerge shortly after sleep onset during a sleep-onset REM period (SOREMP). Although irregular jerking of the limbs may occur nightly (comprising the "minimal RBD syndrome"), the major behavioral episodes appear intermittently with a frequency minimum of usually once every 1–2 weeks up to a maximum of four times nightly on ten consecutive nights [5, 6].

Chronic RBD may be preceded by a lengthy prodrome (in one series it was 25%) consisting of prominent limb and body movements during sleep and new-onset sleep talking [35]. RBD is usually a chronic progressive disorder, with increasing complexity, intensity, and frequency of expressed behaviors. Spontaneous remissions are very rare. RBD, however, may subside considerably during the later stages of an underlying neurodegenerative disorder. Although the prevalence of RBD is not known, surveys have estimated a prevalence of 0.38–0.5% [4]. The prevalence of RBD in older adults is probably considerably higher [36].

Most patients with RBD who present for clinical evaluation complain of sleep injury and rarely of sleep disruption. Daytime tiredness or sleepiness is uncommon, unless narcolepsy is also present, or there is coexisting obstructive sleep apnea (OSA). There is typically no history of irritable, aggressive, or violent behavior during the day. One study of consecutive referrals to a sleep center found that the majority of patients diagnosed with RBD reported symptoms on specific questioning only, underlining the importance of eliciting a comprehensive history for the diagnosis of RBD [37].

Documented injuries to the patient and bed partner resulting from RBD include: bruises; subdural hematomas; lacerations (including arteries, nerves, tendons); fractures (including high cervical fractures); dislocations, sprains, abrasions, rug burns; tooth chipping; scalp injury from hair pulling. The published cases of RBD (as of 2010 [38]), associated with potentially lethal behaviors include: choking/headlock ($n=22$–24), diving from bed ($n=10$), defenestration ($n=7$), and punching a pregnant bed partner ($n=2$). The potential for injury to self or bed partner raises important and challenging clinical issues (such as in ICU settings [39, 40]) and forensic medicine issues [16], including "parasomnia pseudo-suicide" [41] and inadvertent murder; guidelines have been developed to assist experts in forensic parasomnia cases [16, 42].

There has only been one reported case of marital separation or divorce related to RBD, in a recently married young adult with narcolepsy-RBD [43], this probably reflects the many decades of marriage prior to the onset of typical RBD, and so the wives of men with RBD understand that the violent dream-enacting behaviors are completely discordant from the usual pleasant-waking personality [5]. Nevertheless, RBD can pose serious risks to a marriage. A recently married, young adult Taiwanese woman with RBD attempted suicide because her husband would not sleep with her at night, since he complained that her RBD disrupted his sleep excessively and compromised his work productivity [44]. Fortunately, once her RBD was diagnosed and effectively treated with clonazepam, the husband resumed sleeping in their conjugal bed, and their marriage was preserved.

Finally, there is an acute form of RBD that emerges during intense REM sleep rebound states, such as during withdrawal from alcohol and sedative–hypnotic agents, with certain medication use, drug intoxication, or relapsing multiple sclerosis [45].

RBD and Dreaming

In typical RBD affecting middle-aged and older men, the enacted dreams are often vivid and action-filled with unpleasant ("nightmarish") scenarios involving confrontation, aggression, and violence with unfamiliar people and animals, and the dreamer is rarely the instigator. In fact, the dreamer is often defending his wife in a dream while actually beating her in bed. There can also be culture-specific sports dreams, such as American football, Irish rugby, or Canadian ice hockey. Some patients experience recurrent dreams (with enactment) with presumed vestibular activation, involving spinning objects or angular motion with acceleration (e.g., a car speeding down a steep hill); other patients experience atonia suddenly intruding into their dream-enacting episodes, and fall down while dreaming of suddenly becoming stuck in mud or trapped in deep snow.

The abnormal dreams of RBD typically emerge in tandem with the release of dream-enacting behaviors, and over time, they can progress and intensify in tandem, and ultimately both of these basic components of RBD usually resolve in tandem with clonazepam therapy [6]. This link suggests a mutual pathophysiology of behavioral and dream dyscontrol in RBD (with "isomorphism" in dream-enactment, as described in the first section). There is a focus on brainstem motor pattern generators, as extracted from Hobson and McCarley's "activation-synthesis model" of dream generation [46]. Also, temporary or sustained relapse of abnormal

dreaming and RBD behaviors often emerge in tandem (such as when a patient forgets to bring clonazepam on a trip), which also suggests a mutual pathophysiology.

A controlled study found that untreated men with RBD had more aggressive (and less sexual) dreams than controls, but did not have any increased tendency for aggressiveness in their waking lives [47]. A more recent study has challenged the universality of this finding in RBD [48], but most patients in a latter study were being treated with clonazepam, a highly effective therapy of both the disordered behaviors and disturbed dreaming in RBD, thus raising serious questions about the validity of the study [49, 50].

Atypical dream-enacting behaviors in RBD have been reported in a group of patients from three countries [51]: (i) retaliation dreams, related to prior verbal/physical abuse (USA); (ii) culture-specific dreams, involving Samurai warrior combat (Japan); (iii) religion-specific dreams (Taiwan). These cases encourage further search for atypical dream enactment in RBD, including across cultures.

Predisposing and Precipitating Factors

The major predisposing factors are male gender, age 50 years or older, and an underlying neurological disorder, particularly parkinsonism, multiple system atrophy (MSA), dementia with Lewy bodies (DLB), narcolepsy, and stroke [6, 45]. A recent, multicenter case-control study of environmental risk factors of RBD found that smoking, head injury, pesticide exposure, and farming were significant risk factors [52, 53]. An increasingly recognized precipitating factor involves medication-induced RBD, particularly the antidepressants venlafaxine, serotonin-specific reuptake inhibitors (SSRIs), mirtazapine, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), but not bupropion, trazodone, or nefazadone [45]. Beta blockers (bisoprolol, atenolol), anticholinesterase inhibitors, and selegiline can also trigger RBD, along with excess use of caffeine and chocolate. Psychiatric disorders involving depression (that require antidepressant pharmacotherapy) may comprise a predisposing factor, particularly in adults under 50 years of age [54, 55]; in fact, the Lam and Wing group in Hong Kong proposed that there is a "complex relationship of RBD, depression, and antidepressant usage" and discussed this topic from a variety of emerging data-based perspectives [56–58]. Also, RBD may be associated with some cases of post-traumatic stress disorder [45].

The overwhelming male predominance in RBD begs the question of hormonal influences, as suggested in male-aggression studies in both animals and humans. However, serum sex hormone levels are normal in idiopathic RBD or in RBD associated with Parkinson's disease (PD) [59, 60]. Another possible explanation for the male predominance is sex differences in brain development and aging.

Narcolepsy-RBD

RBD can be strongly linked with narcolepsy (almost always narcolepsy-cataplexy [NC]), as another form of REM sleep motor-behavioral dyscontrol, and may also be precipitated or worsened by the pharmacologic treatment of cataplexy with TCAs, SSRIs, and venlafaxine [19, 26, 45], but not with sodium oxybate therapy. The demographics (age and sex) of RBD in narcolepsy conform to those of narcolepsy (i.e., younger adults, and nonmale predominant), indicating that RBD in these patients is yet another manifestation of state boundary dyscontrol (primarily REM sleep-wakefulness boundaries) seen in narcolepsy [26]. RBD associated with narcolepsy is now considered to be a distinct phenotype of RBD, characterized by lack of gender predominance, less complex and more elementary movements in REM sleep, less violent behavior in REM sleep, earlier age of onset, and hypocretin deficiency (that is typical of NC, and not found in RBD [26]). In children, RBD can sometimes emerge months before the appearance of classic symptoms of NC. RBD is present in over half of patients with narcolepsy, and may be a presenting symptom in narcolepsy, including childhood narcolepsy. It is intriguing to note the pathological reverse images in motor dyscontrol involved with cataplexy, with sudden atonia during wakefulness precipitated by emotional triggers, and with RBD, with increased muscle tone and behavioral release associated with emotionally charged dreams during REM sleep. Also, a case of presumed RBD arising from cataplexy and wakeful dreaming has been reported [61].

Other reported etiologic associations of RBD with neurologic disorders include ischemic or hemorrhagic cerebrovascular disease, multiple sclerosis, Guillain–Barré syndrome, brainstem neoplasms (including cerebellopontine angle tumors), Machado–Joseph disease (spinocerebellar ataxia type 3), mitochondrial encephalo-myopathy, normal pressure hydrocephalus, Tourette's syndrome, group A xeroderma, autism, oneiric dementia, etc. [45].

Association of RBD with Specific Human Leukocyte Antigen Haplotypes

RBD, like narcolepsy, is a prominent disorder of REM sleep and REM sleep motor dysregulation. Narcolepsy has a very strong association with human leukocyte antigen (HLA) class II genes, with the DQB1*0602 (DQw1 group) allele being expressed in nearly all cases. Our center performed a study of HLA class II antigen phenotyping in a group of 25 Caucasian

males who had RBD but not narcolepsy: 84% ($N=21$) were DQw1 (DQB1*0506) positive (and 28% ($N=7$) were DR2-positive); DQB1*0501 ($N=9$) and DQB1*0602 ($N=7$) were the most common phenotypes [21]. The 84% DQw1 rate in RBD was significantly greater ($p=.015$) than the 56% DQw1 rate found in a local Caucasian comparison group ($N=66$), and was greater than the 39–66% DQw1 rates in 12 published Caucasian groups ($N=40$–418 per group). In contrast to the nearly 100% DQw1–DR2 linkage in narcolepsy, only 28% of RBD patients in this report were DR2-positive. The strong dissociation between DQw1 and DR2 in RBD can be contrasted with the very strong DQw1–DR2 association in narcolepsy. Narcolepsy and RBD, therefore, have strikingly convergent (DQw1) and divergent (DR2) HLA findings.

These data raise the question of whether RBD is, in part, an autoimmune disorder, analogous to NC that is presumed to be an autoimmune disorder [26]. The question of an autoimmune basis of RBD has been reinforced by the documented series of cases of RBD emerging in tandem with autoimmune limbic encephalitis, and with a shared therapeutic response to autoimmune therapy [62].

RBD in Children and Adolescents

RBD is uncommon in childhood and adolescence, and idiopathic RBD in children is especially rare, and when present, it can be an initial manifestation of NC lasting for months before the frank emergence of NC. RBD in this age group is most commonly found in association with NC or is psychotropic medication-induced (as therapy of cataplexy or depression/anxiety), related to brainstem tumor, or to a variety of rare conditions [6, 63]. Therapy with clonazepam is often effective, as with adults. There can be some atypical features, such as a predominant complaint of "scary dreams" that could delay diagnosis. Developmental considerations in juvenile RBD have been discussed [6].

Younger Versus Older Adult-Onset RBD

Classic RBD is a male-predominant disorder that usually emerges after the age of 50 and that usually signals the future emergence of parkinsonism/dementia [23]. However, any age group, from early childhood to 88 years of age, can be affected by RBD [6, 64]. RBD emerging in adults before 50 years of age is now recognized to comprise a subgroup of RBD patients with different demographics and associated features, including greater gender parity and increased rates of idiopathic cases, parasomnia overlap disorder (POD) cases, narcolepsy cases, antidepressant medication use, and possibly autoimmune diseases [65]. Also, the clinical presentation of RBD in younger adults differs from that in older adults in being less aggressive and violent on the basis of greater female representation and narcolepsy representation that manifest with more mild RBD behaviors. Otherwise, RBD associated with neurologic disorders and other symptomatic forms of RBD are as male-predominant as idiopathic RBD, with the exception of narcolepsy, as already described.

Parasomnia Overlap Disorder

POD is a variant of RBD that consists of RBD combined with a disorder of arousal (confusional arousals, sleepwalking, and sleep terrors) [4, 6, 22, 66], although it is now known to also consist of RBD combined with sleep-related eating disorder, sexsomnia, or rhythmic movement disorder [66]. Diagnostic criteria for both RBD and a disorder or disorders of arousal, or for both RBD and one of the other disorders just mentioned, must be met [4]. POD is male-predominant but less so than RBD. Most cases begin during childhood or adolescence. Virtually all age groups can be affected. It can be idiopathic or symptomatic of a broad set of disorders, including narcolepsy, multiple sclerosis, brain tumor (and therapy), rhombencephalitis (right pontine tegmentum/medullary lesion), brain trauma, congenital Mobius syndrome, Machado–Joseph disease, indeterminate neurologic disorder, nocturnal paroxysmal atrial fibrillation, various psychiatric disorders and their pharmacotherapies, and substance-abuse disorders and abstinence states, and the other conditions described in a recent update of POD [22, 66].

These cases demonstrate motor-behavioral dyscontrol extending across NREM and REM sleep, in addition to the usual findings in RBD of increased PLMs and nonperiodic limb movements during NREM sleep. These cases also suggest a possible unifying hypothesis for disorders of arousal and RBD: the primary underlying feature is motor disinhibition during sleep—when it predominately occurs during NREM sleep, it manifests as a disorder of arousal; and when it predominately occurs during REM sleep, it manifests as RBD—with the POD occupying an intermediate or mixed position, with features of both. Furthermore, developmental considerations may play a crucial role with a postulated evolution in POD, with the NREM parasomnia component predominating during earlier life stage, with a shift toward RBD predominance during middle and later life stages. In the original reported series of 33 patients [22], the mean age of parasomnia onset was 15 years (range: 1–66); and 70% ($N=23$) were males. An idiopathic subgroup ($N=22$) had a significantly earlier mean age of parasomnia onset (9 years; range: 1–28) than a symptomatic subgroup ($N=11$; 27 years; range: 5–66).

Status Dissociatus

> …When I have seen the hungry Ocean gain
> Advantage on the Kingdom of the shore,
> And the firm soil win of the watery main,
> Increasing store with loss, and loss with store; When I have seen such interchange of state, Or state itself confounded to decay….
> (excerpt from a Shakespeare Sonnet)

Status dissociatus (SD) is classified as a subtype of RBD that manifests as an extreme form of state dissociation without identifiable sleep stages, but with sleep- and dream-related behaviors that closely resemble RBD [4, 17]. SD represents a major breakdown of the PSG markers for REM sleep, NREM sleep, and wakefulness, with admixtures of these states being present, but with conventional sleep stages not being identifiable during PSG monitoring. There is abnormal behavioral release that can be associated with disturbed dreaming that closely resembles RBD. Not uncommonly, however, the individual thinks he is awake when observers presume he is asleep and attempting to act out a dream, or vice versa. An underlying neurologic or medical condition is virtually always present; reported cases can be classified as follows [66]: (i) proteopathies (synucleinopathies: PD, MSA, DLB; tauopathies: frontotemporal dementia; prion protein: fatal familial insomnia; ataxin: spinocerebellar ataxia); (ii) anoxic (cardiogenic CNS anoxia); (iii) lesional; (iv) autoimmune (Morvan's syndrome, Guillain–Barré syndrome, voltage-gated potassium channel autoimmune encephalitis), (v) infectious (brainstem involvement of HIV infection), (vi) mixed disorders/pharmacotherapy/ alcohol abuse NC and its pharmacotherapy; OSA/NC, and its pharmacotherapy; chronic severe alcohol abuse and acute withdrawal (delirium tremens); (vii) Mulvihill–Smith syndrome; (viii) Harlequin syndrome.

RBD and Neurodegenerative Disorders

As stated previously, a full range of neurologic disorders, including neurodegenerative disorders, can be etiologically linked with the onset of RBD, and most likely reflects the neuroanatomical location of the lesion that disrupts the brainstem nuclei and/or pathways subserving REM-atonia and the customary inhibition of motor-behavioral patterns during REM sleep [29, 67]. However, a selective and very strong association of RBD with the alpha-synuclein neurodegenerative disorders (PD, MSA, DLB) is now recognized. This area of clinical medicine and scientific research (both clinical and basic) is the subject of intense multidisciplinary research on a global scale, with an exponential growth of publications, and has culminated in the formation of the IRBD-SG [10]. RBD can precede, emerge concurrently with, or develop after the emergence of an alpha synucleinopathy [68].The synucleinopathies comprise a set of neurodegenerative disorders that share a common pathologic lesion composed of aggregates of insoluble alpha-synuclein protein in selectively vulnerable populations of neurons and glial cells. These pathologic aggregates appear to be closely linked to the onset and progression of clinical symptoms and the degeneration of affected brain regions in neurodegenerative disorders [69].

Delayed emergence of a neurodegenerative disorder, often more than a decade after the onset of idiopathic RBD, is very common in men who are 50 years of age and older [20, 24, 25]. One recently reported series from our center found an eventual conversion rate from iRBD to parkinsonism/dementia of 81 %, with a mean interval of 14 years from the onset and range extending to 29 years [23]. These data comprise a 16-year extension of previously published data indicating a 38 % rate of eventual emergence of parkinsonism in our series of male RBD patients. Identical findings, with an 82 % conversion rate, were recently reported by the Barcelona group of Iranzo et al. [70]. Furthermore, a retrospective study found that the interval from onset of iRBD to parkinsonism can extend up to 50 years [71]. Conversely, RBD is present in >90 % of the reported cases of MSA, and in approximately 50 % of the reported cases of PD and DLB, as reviewed [29, 69, 72, 73].

Combined animal and human studies have identified physiological and anatomical links between RBD and neurodegenerative disorders, leading to the proposal that neurodegeneration can begin in either the rostroventral midbrain or the ventral mesopontine junction and progressively extend to the rostral or caudal part of the brainstem, as reviewed [68, 74]. When the lesion starts in the ventral mesopontine region, RBD will develop first, but when the lesion initially involves the rostroventral midbrain, PD will be the initial manifestation. Also, midbrain degeneration may produce RBD and PD simultaneously, with support of this scenario coming from the lack of PLMs in NREM sleep in rats with lesions to the subceruleus region [75]. Perhaps mild damage produces RBD, and severe damage produces PD.

The link between PD and RBD is supported by the fact that impaired olfactory and color discrimination is common to both [76]. Also, the presence of cognitive deficits and slowing in the waking EEG in idiopathic RBD share common features with DLB disease [77]. Interestingly, there is a striking male predominance in patients with PD who display REM sleep behavior disorder [29, 69], although somewhat less than the male predominance found in idiopathic RBD. Additionally, two studies found that PD patients with RBD mostly had the nontremor subtype of PD [78, 79]. Also, RBD precedes PD only if PD starts after age 50 years [78].

Neuroimaging studies indicate dopaminergic abnormalities in RBD that are less severe forms of the same abnormalities found in PD. Single-photon emission computerized

tomography (SPECT) and positron emission tomography (PET) studies have found reduced striatal dopamine transporters, and decreased striatal dopaminergic innervations [80–83]. PET and SPECT studies have revealed decreased nigrostriatal dopaminergic projections in patients with MSA and RBD, as reviewed [69]. Impaired cortical activation as determined by EEG spectral analysis in patients with idiopathic RBD supports the relationship between RBD and neurodegenerative disorders [76, 84]. An increasing number of brain-based tests across many dimensions in iRBD patients have consistently revealed abnormal findings in RBD that are commonly seen in PD. Therefore, the brains of iRBD patients closely resemble the brains of PD patients despite the absence of clinical PD signs and symptoms. In this regard, it is notable and not surprising that the only two brain postmortem cases published to date on iRBD found extensive Lewy body pathology in the brainstem [85, 86]. In fact, iRBD is now being called "cryptogenic RBD" [87] because of the seeming inevitability of the eventual emergence of parkinsonism or dementia in middle-aged and older adults. iRBD is also considered to be the first manifestation of Lewy body disease (LBD), and there are compelling reasons to support this position [68].

Another important set of findings indicates that the presence of RBD in PD confers increased morbidity across virtually all dimensions tested, compared to PD without RBD, including higher Hoehn and Yahr stages, more falls, more fluctuations, more visual hallucinations, greater cognitive decline, greater psychiatric morbidity, and greater life burden [69, 72]. On the other hand, movements and speech in patients with RBD-PD and with RBD-MSA improve substantially during REM sleep compared to wakefulness, as carefully documented in two studies [88, 89]. There was restoration of normal motor control in REM sleep, in sharp contrast to the compromised movements and speech in wakefulness from these extrapyramidal disorders. In REM sleep, the movements became faster, smoother, stronger, with normalized facial expressions, and speech became louder and better articulated. The rate of these improvements was higher in PD than in MSA. Clearly, during REM sleep in PD and MSA, the extrapyramidal system is bypassed, thus facilitating the normalization of movements and speech. This is a striking example of how within a distinctly abnormal motor-behavioral state, i.e., RBD (produced by the abnormal wakeful motor state of PD or MSA), there can be substantial normalization of motor-behavioral functions in movements, facial expression, and speech.

A large, multicenter postmortem brain autopsy study of RBD has recently been published [90]. Of the 172 cases, 83% were men, with mean ± SD age of RBD onset of 62 ± 14 years (range 20–93). RBD preceded the onset of cognitive impairment, parkinsonism and/or autonomic dysfunction in 51% of patients by 10 ± 12 (range 1–61) years. The predominant neuropathologic diagnoses were LBD (n = 77), combined LBD and Alzheimer's Disease (n = 59), and MSA (n = 19). Among the neurodegenerative disorders associated with RBD (n = 170), 160 (94%) were synucleinopathies. The RBD-synucleinopathy association was particularly high when RBD preceded the onset of other neurodegenerative syndrome features. The pathophysiology of RBD in neurodegenerative diseases has been examined comprehensively [91].

Differential Diagnosis

RBD is one of several disorders that can manifest as complex, injurious, and violent sleep-related and dream-related behaviors in adults, and it is one of various disorders that can disrupt the sleep of children [6, 15, 45]. Table 45.3 lists the main differential diagnoses. In general, RBD involves attempted enactment of altered dreams, and rapid awakening from an episode that usually occurs 2 h or more after sleep onset. In contrast, sleepwalking and sleep terror episodes often emerge within 2 hours after sleep onset, are not usually associated with rapid alertness, and are rarely associated with dreaming in children. Adults can have associated dreaming, but it is usually more fragmentary and limited than RBD dreams. "OSA pseudo-RBD" presents with severe OSA/hypopnea-induced arousals with dream enactment, together with loud snoring and daytime sleepiness, and responds to continuous positive airway pressure (CPAP) therapy [92]. Sleep-related seizures usually present with repetitive, stereotypical behaviors, with or without associated dreaming. Sleep-related dissociative disorders can present with dreaming during the abnormal nocturnal behaviors, but the "dreaming" represents dissociated memories of past abuse occurring during wakefulness. Malingering should always be considered in the differential diagnosis of RBD and other parasomnias [93].

Table 45.3 Differential diagnosis of dream-enacting behaviors in adults

1	REM sleep behavior disorder
2	Sleepwalking and sleep terrors
3	Obstructive Sleep Apnea ("OSA Pseudo-RBD")
4	Nocturnal seizures
5	Sleep-related dissociative disorders
6	Malingering

Treatment of RBD

Maximizing the safety of the sleeping environment is imperative. Clonazepam is the established primary pharmacotherapy of RBD in most cases, with a typical dose of 0.25–2.0 mg at bedtime, and is usually well tolerated [35, 94–96]. A number of large case series totaling >250 RBD patients have reported a response rate to clonazepam therapy of 87–90% [6]. Clonazepam is not usually associated with dosage tolerance (habituation effect), despite years of nightly therapy [43, 95], as shown in Table 45.4. The mechanism of action appears to be suppression of the excessive phasic motor-behavioral activity rather than restoration of REM-atonia [94, 97].

A recent PSG study of RBD found no objective effects of clonazepam on REM sleep parameters, and an analysis of NREM sleep parameters found beneficial effects from clonazepam in these RBD patients [98, 99]. To date, there have been no double blind, controlled, randomized trials of clonazepam (or other) therapy of RBD. The therapies of RBD have been reviewed [100–102]. The American Academy of Sleep Medicine has recently published best practice guidelines for the treatment of RBD [103].

A recognized [103], co-first-line therapy of RBD is bedtime melatonin at robust pharmacologic doses ranging from 3 to 15 mg. The mechanism of action appears to be partial restoration of REM-atonia [102].

Tertiary pharmacotherapies of RBD include pramipexole, acetylcholinesterase inhibitors (which can also trigger RBD), desipramine/ imipramine (TCAs that can also trigger or aggravate RBD), paroxetine (in Japanese patients), monoamine oxidase inhibitors, clonidine, carbamazepine, gabapentin, zopiclone, temazepam, and sodium oxybate. The finding that paroxetine, an SSRI that can trigger or aggravate RBD in Caucasians, was effective in controlling RBD in Japanese patients [60, 61, 104] raises questions about racially mediated, divergent pharmacologic responses in RBD. Also, the herbal preparation *Yi-Gan San,* approved for treating insomnia in Japan, was reported to be effective in RBD in three cases from Japan [105]. Immunosuppressive therapy induced complete resolution of RBD in tandem with remission of autoimmune limbic encephalitis in three patients with potassium channel antibody-associated limbic encephalitis [62].

Table 45.4 Long-term nightly clonazepam therapy of RBD without dosage tolerance [90]

Paired *t*-test (N-49)	
1	Initial nightly dose: 0.63 ± 0.40 mg
2	Latest follow-up dose: 0.97 ± 0.89 mg
3	Paired *t*-test: no significant difference
4	Duration of treatment: 3.7 ± 2.3 years

The International RBD Study Group

The IRBD-SG was formed in 2007 and legally incorporated in Marburg, Germany, in 2009. It is comprised of an international team of leading basic science and clinical RBD researchers from 13 countries representing Europe, North America, and Asia [10]. The IRBD-SG has held eight symposia by September 2014 in Germany, Canada, Japan, France, and Spain and Finland. Objectives of the IRBD-SG are the promotion of international scientific research in the field of RBD and related fields (such as PD), and the optimization of medical care for patients by improving diagnostic and therapeutic measures. Given the relatively low number of patients with RBD identified at individual RBD research centers, a major focus of the IRBD-SG is to facilitate multicenter studies. One multicenter study identified familial RBD [106]. Also, there is an urgent need to test promising neuroprotective agents in controlled studies of high-risk groups of patients for imminent parkinsonism/dementia (i.e., within 5 years). such groups have been identified, consisting of iRBD patients with either decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity [82], or iRBD patients with olfaction and color vision impairment [107]. An overarching aim of the IRBD-SG is to enhance professional and public awareness of the field of RBD and associated fields, and to foster cooperation among physicians, scientists, and patients along with their family members.

Conclusions

RBD is an "experiment of Nature" that reveals a spectrum of brain mechanisms of motor dyscontrol and other disturbed functions in REM and NREM sleep, and its relation to neurologic disorders, antidepressant medications, and many other areas of neuroscience and clinical (sleep) medicine. RBD also provides a compelling example of the important and pervasive phenomenon of state dissociation [17, 108–111].

Finally, RBD was depicted in Disney animated films long before the formal identification of RBD in humans in 1986 [112]. In *Cinderella* (1950), a dog had nightmares with dream enactment, and three additional dogs with presumed RBD appeared in *Lady and the Tramp* (1955), *The Fox and the Hound* (1981), and in the short film *Pluto's Judgment Day* (1935). These dogs were elderly males who would pant, whine, snuffle, howl, laugh, paddle, kick, and propel themselves while dreaming that they were chasing someone or running away. Moreover, in *Lady and the Tramp*, the dog was also losing his sense of smell and his memory, two prominent associated features of human RBD, and very frequent findings in PD. The Disney screenwriters were clearly astute observers of sleep and its disorders, including RBD. To quote Walt Disney, "Sometimes we can recognize our-

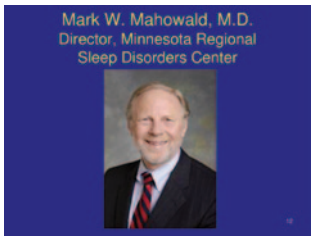

Fig 45.5 Mark W. Mahowald, M.D., director of the Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, Minnesota, USA, from 1986 to 2010

selves in animals. That's what makes them so interesting." Disney's words also conveyed scientific prescience.

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