Management of a Patient with RBD

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23.1 Introduction

The spectrum of dream enactment in RBD ranges from benign hand movements to violent life-threatening behaviors. The primary management goal is to prevent sleep-related injury. Thus, educating a newly diagnosed patient and the bed partner about the potential dramatic adverse consequences is an important first step, as subsequent measures ranging from environmental modification to the treatment of comorbid sleep disorders and the pharmacotherapy of RBD will depend upon their adherence and follow-through.

If concerning dream enactment persists once ancillary sleep disorders are treated and RBD-inducing medications (primarily SSRIs and venlafaxine) are minimized or discontinued, then medication therapy is reasonable. The most commonly employed agents include clonazepam or melatonin taken orally at bedtime. However, clinicians should be aware that the evidence supporting these therapies is primarily based upon case series, small clinical trials, and expert consensus.

As RBD is often a prodromal syndrome of alpha-synuclein pathology, management should include monitoring for neurodegeneration. This includes careful clinical follow-up for subtle abnormalities of movement and cognition. Additionally, patients should be provided with a disease risk assessment and counseling for what is often a sobering discovery. Finally, interested patients should be offered the opportunity to participate in research, as an international network of RBD investigators is currently developing protocols for clinical trials of disease-modifying (neuroprotective) agents. For these RBD patients, enrollment in translational research can be empowering as they deal with the likely prospect of developing a neurodegenerative disorder.

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23.2 Environmental Safety

RBD can result in bruising, lacerations, and fractures to both patients and bed partners. Over 11% of RBD patients have had injuries requiring medical attention or hospitalization [1]. Severe neurological injury can result from epidural or subdural hematomas as well as cervical or other spinal fractures. Elderly RBD patients at high risk include those with osteoporosis or those on anticoagulant medications. Additionally, there is a long list of medical vulnerabilities that can lower the threshold for severe RBD-related injuries [2].

Thus environmental modification is a critical early intervention in all patients with RBD. Any potentially dangerous items that could be picked up, swung, or thrown should be removed. These can include such seemingly benign objects as an alarm clock or lamp. To inquire about the bedroom environment, a clinician can ask an open-ended question such as. "What are the items in your bedroom that could potentially injure you or your bed partner?"

Considering the widespread prevalence of firearms (over 300 million) in the United States [3], a special consideration needs to be made to screen for guns, particularly handguns, in the bedrooms of the United States. Given the potential fatal consequences of discharging a firearm during dream enactment, it is critically important that guns (and other weapons, such as knives) be removed from the bedroom.

In cases where patients have previously stood or exited the bed (both high-risk behaviors), strenuous efforts should be made to minimize potential injury. Options include sleeping bags or bed rails to prevent the patient from leaving the bed, removing the box spring and bedframe to sleep on a solitary mattress, or a pressure-sensitive bed alarm with a friendly voice recording directed to calm the patient during vigorous dream enactment [4].

Adherence to these interventions will vary and may require repeated discussions to convince a patient that these measures are necessary. It is important for patients to understand that even rare dream enactment behavior can result in potentially life-threatening injury [1].

23.3 Managing Ancillary Sleep Disorders

Under normal physiological conditions, REM sleep is characterized by vivid mentation combined with skeletal paralysis that prevents dream enactment. REM sleep fragmenting disorders can lead to RBD-like behaviors as abrupt cortical arousals suddenly unleash previously suppressed dream enactment. The three most common pathologies that mimic RBD are obstructive sleep apnea (OSA), severe periodic limb movement disorder, and orexin deficiency causing Narcolepsy type 1. Addressing these conditions can minimize potentially injurious behaviors.

OSA, a collapse of the upper airway during sleep, is most pronounced during REM sleep. Because of this phenomenon, many OSA patients will suddenly awaken from a dream, often with a gasp, while striking or lashing out. This is known as

"OSA pseudo-RBD" [5]. Dream mentation may include a theme of drowning or being choked by an assailant. In these cases, preventing upper airway collapse with either positive airway pressure, dental appliance, or upper airway surgery typically resolves the abnormal behaviors. When dream enactment persists despite effective OSA treatment, it is appropriate to pursue a repeat in-laboratory polysomnogram to evaluate for the persistence of REM motor activity, i.e., loss of REM atonia, despite the correction of sleep-disordered breathing.

Periodic limb movements (PLMs) are a recurrent triple-flexion (dorsiflexion of the foot, knee flexion, and hip flexion) response of the lower extremities. When correlated with non-restorative sleep, a patient is considered to have PLM disorder (PLMD) . Occasionally PLMs can be robust, even injurious, and thus mimic the motor activity of RBD, especially when there is simultaneous dream enactment. Furthermore, while the stereotyped motor activity of PLMs typically arises out of NREM sleep, it can persist into REM sleep. Distinct from RBD however, injurious PLM activity can be typically resolved, including control of dream-enacting behavior, with dopaminergic therapy [6].

These pseudo-RBD disorders, due to OSA and/or PLMD, are distinguished from RBD as their behavior is a REM-related motor event that arises during an arousal out of REM sleep, while RBD is a within-REM sleep motor and DEB disorder.

Narcolepsy is a disorder of sleep-state stability. It is caused by a deficiency of the neurotransmitter orexin, and affected individuals will experience sudden fluctuations between wake and sleep phenomena. Patients describe not only daytime sleepiness but also nighttime sleep fragmentation (unable to consolidate sleep), sleep-related hallucinations (REM mentation intruding into wakefulness), sleep paralysis (REM paralysis persisting into wakefulness), and cataplexy (intrusion of REM atonia triggered by an emotional stimulus). Approximately half of narcolepsy patients experience excessive REM sleep motor tone (intrusion of wakeful motor activity during REM sleep) [7–9]. Because of this, many patients with narcolepsy describe dream enactment, although patients are typically younger and the dream enactment less violent than in the idiopathic form of RBD [9]. Bedtime therapy with sleep-consolidating agents, such as clonazepam or sodium oxybate, has been anecdotally reported to be effective. However, further studies are clearly needed to better understand the optimal treatment of dream enactment in the setting of narcolepsy [10]. For further discussion of RBD in narcolepsy-cataplexy, please refer to Chap. 11.

23.4 Managing Medications That Induce (or Possibly Unmask) RBD

Dream enactment behaviors may arise after initiating neuropsychotropic medications, in particular the antidepressants such as the serotonin-specific reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, mirtazapine, tricyclics or tetracyclics, and monoamine oxidase inhibitors [11]. The exact triggering mechanism is uncertain, but the most likely candidate neurotransmitter is serotonin as the serotonin-producing raphe nucleus modifies REM sleep [12].

Drug-associated RBD is common and considering the widespread use of these medications may represent the most prevalent cause of dream enactment, particularly among the young (see Clinical Case 23.1). One study demonstrated increased REM motor activity in 10% of all depressed subjects who were started on sertraline, a SSRI [13].

When dream enactment clearly presents after a patient initiates an antidepressant, consider initiating a discussion with the treating psychiatrist (or other treating physician) about switching to a different agent, preferably one with a different mechanism of action. However taking into consideration the widespread use of serotonin-based agents, this is often challenging. One antidepressant, bupropion, is by consensus considered an antidepressant least likely to induce dream enactment. This is due to its unique mechanism of action, viz., norepinephrine-dopamine reuptake inhibition, lacking any serotonergic effect and the absence of any published case suggesting a link with RBD [12–14]. Additionally, a clinician should consider recommending, in clinically appropriate cases, the maximal use of non-pharmacological therapy, e.g., psychotherapy, for mental illness. Among cases of persistent dream enactment despite antidepressant dose reductions, switching antidepressants, or eliminating antidepressant medications, RBD pharmacotherapy could be started with either melatonin or clonazepam.

Of note, there is considerable debate as to whether antidepressants induce dream enactment directly through a toxic effect or whether they are merely unmasking dream enactment in an individual who would ultimately have developed RBD even in the absence of a serotonergic medication. Recent evidence suggests that patients with medication associated RBD also have other prodromal markers of neurodegeneration such as anosmia, constipation, and decreased brain dopamine on PET imaging [15, 16]. These findings imply that antidepressant medications are not causing RBD in isolation but instead identify individuals with early alpha-synuclein neuropathology. For further discussion of RBD and antidepressant medications, please refer to Chap. 10.

Clinical Case 23.1

A 32-year-old female presents with a 6-month history of nightly dream enactment. According to her bed partner, the patient's new sleep behaviors include shouting, thrashing, punching, and kicking. These behaviors are short-lived, lasting only a few seconds, and occur predominantly in the latter half of the night. Neither the patient nor bed partner has had a sleep-related injury.

These events began soon after starting fluoxetine to treat a mood disorder. She indicates that while fluoxetine did improve her mood, she would like to consider switching to another antidepressant medication.

She has no Parkinsonian motor symptoms, reports that her sense of smell is intact, but does indicate that she has struggled with constipation for most of her adult life.

The only other medication she takes is hormonal contraception.

Family history is significant only for cardiovascular disease, with no history of neurodegeneration.

Her neurological examination is normal, without resting tremor, bradykinesia, or cogwheel rigidity. Her gait appears normal with a good turn and arm swing. She walks without freezing. Objective olfactory testing was not performed.

In-laboratory video polysomnography demonstrated hand and finger movements during REM sleep suggestive of dream enactment (she appeared to be pointing). Transient REM motor activity was most prominent during the final period of REM sleep. No other sleep-related abnormality was identified.

She was diagnosed with medication-associated RBD and switched from fluoxetine to bupropion. Bupropion was well tolerated and controlled her mood disorder. Dream enactment also diminished, but did not fully resolve as she reported still having weekly episodes. Therefore, she was advised to start bedtime oral melatonin, which at 6 mg fully resolved the dream enactment behaviors.

23.5 Medication Therapy for RBD

If dream enactment behavior persists once ancillary sleep disorders have been treated and any putative offending medication minimized or withdrawn, it is reasonable to consider medication therapy for RBD, which is most appropriate in situations where there is a high risk of sleep-related injury. These cases include patients (or bed partners) with a history of osteoporosis, coagulopathy, anticoagulant use, etc., or who have been hospitalized or sought medical attention for a sleep-related injury. Even in the absence of previous sleep-related injury, concerning behavior that warrants more aggressive management includes either standing up or exiting the bed during dream enactment [17].

In the absence of potentially injurious behaviors and/or comorbidities that increase the risk for sleep-related injury, conservative observation (without pharmacotherapy), with environment safety measures, is reasonable as long as it is paired with clinical follow-up.

The most commonly prescribed[1] agents for the treatment of RBD are clonazepam and melatonin. While the vast majority of RBD reports suggest that either one

[1] For the purposes of this review, melatonin is considered a medical therapy despite being considered a nutritional supplement available over the counter in the United States. It is a biological compound with pharmacokinetic properties that has been demonstrated to be effective compared to placebo in sleep and circadian rhythm disorders. In addition, numerous countries in the European Union and Canada classify melatonin as a medication and require a prescription for its use.

or both of the agents in combination are reliably effective therapies, it is important for physicians, patients, and bed partners to be aware that the evidence supporting their efficacy is limited [18, 19]. Their use has emerged from published case reports, case series, small clinical trials, and expert consensus. Clearly further research in RBD therapy is needed, in particular large, randomized placebo-controlled trials. However, serious ethical issues are raised by the prospect of such studies, mainly involving RBD patients with injurious dream enactment who would be receiving a placebo, as discussed [20]. For further discussion of these and other RBD therapies, refer to Chaps. 24 and 25.

23.6 Monitoring for Neurodegeneration

By the time most RBD patients come to clinical attention, they have already developed other, often subtle, symptoms such as hyposmia and constipation [17]. It is the combination of findings that indicates a more diffuse neuropathology, and it helps a clinician confirm (as well as explain to the patient) that this sleep disorder is part of a larger and evolving neurological syndrome. Neuropsychological examination and other testing may reveal impairments in executive function, color identification, and/or visual-spatial tasks; however, these deficits often go undetected in routine clinical evaluations [12, 17].

As RBD is considered to be a prodrome of alpha-synuclein pathology, prospective long-term clinical follow-up is necessary. Once dream enactment behavior has been addressed, patients should meet with a clinician who can perform a detailed neurological evaluation at regular intervals, at least annually, to be screened for movement and cognitive deficits.

At each visit patients should be queried for bradykinesia and resting tremor. Common bradykinetic symptoms include taking longer to eat, dress, or walk through a store. However, patients may have limited insight and assume that their slowness is similar to their middle-aged or elderly peers. Because of this, a secondary observer, such as a family member or companion, can be a valuable resource when screening for bradykinesia. In regard to resting tremor, it should be noted that RBD is linked with the non-tremor predominant subtype of Parkinson's disease which is easily missed in the early stages [21, 22]. Further, even when the oscillations are present, they may go unrecognized, as a resting tremor is by definition not functionally limiting [17].

RBD predicts the development of freezing of gait (FOG), a disabling condition poorly treated with conventional dopamine-based Parkinson's disease therapies [22, 23]. FOG is characterized by transient episodes of absent forward movement during ambulation most commonly noted during gait initiation or turning. FOG can be screened with a single question, "Do your feet ever feel as if they are stuck to the floor?" FOG is important to identify as interventions, such as physical therapy and assistive devices (canes, walkers), can prevent falls. For further discussion of gait and postural disorders in RBD, please refer to Chap. 38.

Subsymptomatic Parkinsonism can often be elicited on examination. A clinician should scrutinize a patient's affectation, blink rate, speed of articulation, and motor tone (with distracting maneuvers in the opposite extremity to extract subtle cogwheel rigidity). Gait testing can detect arm swing asymmetry, bradykinetic strides, excessive steps per turn, and FOG. Postural instability is common in the non-tremor predominant subtype of Parkinson's disease and can be tested by sudden retropulsion that normally elicits a righting reflex. However, great care should be taken with this test as the full weight of a patient may suddenly fall back on the clinician (see Clinical Case 23.2). The Unified Parkinson's Disease Rating Scale provides quantified assessments of these examinations and is a useful tool in the prospective evaluation of RBD patients. Cognitive screening and monitoring can be conducted with the Montreal Cognitive Assessment [17].

Clinical Case 23.2

A 62-year-old male RBD patient presents with imbalance. He states that he has fallen on several occasions in the last year, and with a history of osteoporosis, he is concerned about traumatic fractures.

He was diagnosed with RBD 2 years prior after a 15-year history of dream enactment and a polysomnogram that confirmed excessive transient and tonic REM motor activity. His parasomnia has been under good control with 12 mg of melatonin along with bedroom modification. He was diagnosed with mild Parkinson's disease last year with bradykinesia and cogwheel rigidity that clearly improved with carbidopa/levodopa therapy.

When asked about gait freezing, he indicates that yes, he often gets "stuck" particularly in restaurants when he has to navigate his feet around chairs and tables.

On examination (2 h after taking carbidopa/levodopa), the patient has only mild bradykinesia and cogwheel rigidity in the right upper extremity. Tremor was not elicited on examination even with distracting maneuvers. Gait testing revealed subtle decreased arm swing on the right. However, when testing sudden retropulsion, the 100 kg patient had no reflexive righting response and fell backward onto the examiner who struggled but managed to catch him.

The patient and his family were educated on the nature of his imbalance and he was referred to physical therapy. Several Parkinson's disease medications were initiated but his gait freezing and postural instability persisted.

23.7 Counseling and Neuroprotection

RBD is a fearsome diagnosis for many patients. While medications can control dream enactment, the prospect of an impending neurodegenerative disease is a frightening and often overwhelming discovery. Physicians can help lessen the shock of the diagnosis by building rapport with empathy and education.

The greatest concerns for most patients are the prospect of impending disability and the unknown impact the disease may have upon family and finances. With a careful clinical evaluation, the physician can define a patient's risk profile and determine those who are likely to convert to Parkinson's disease (or related condition) in the midterm (within the next 5–10 years). In particular, hyposmia, constipation, impaired color vision, sleepiness, orthostatic hypotension, and subtle motor and/or cognitive dysfunction in the absence of antidepressant medications place RBD patients at high risk of converting to a diagnosable neurodegenerative disease. Stratification with these markers increases the risk of conversion by 200% [24]. Conversely, the absence of these findings suggests that a patient may be reassured that conversion is more likely remote.

RBD among younger adults, those less than 50 years of age, is most often due to either an RBD-associated medication or associated with narcolepsy. It is uncertain whether these individuals have the same risk for neurodegeneration as older RBD patients (see Sects. 23.3 and 23.4 above). It is suspected that their risk of conversion is lower; however it should be noted that parkinsonian disorders can emerge as late as half a century after the onset of RBD [25]. Thus, even young patients should be screened for other early features of neurodegeneration (anosmia, constipation) and carefully followed with serial neurological examinations.

Importantly, patients should be informed that the most common future disorder, Parkinson's disease, is a treatable condition, and a brief summary of what comprises PD and related disorders should be stated. Numerous medications, surgical procedures, and rehabilitative therapies can help patients maintain a high level of independent function that can last for many years. Additionally, patients and their families should also be advised to watch for symptoms of dementia with Lewy bodies. This disorder of progressive cognitive impairment is distinguished from Alzheimer's disease by a fluctuating course and visual hallucinations. Unfortunately, unlike PD, therapeutic options for DLB are limited. An important consideration in regard to what and how this topic should be communicated and discussed is the level of education and medical sophistication, and personality style, of the patient and spouse.

RBD patients often wonder about possible neuroprotective interventions. At the current time, there are no proven neuroprotective therapies in RBD. Aerobic exercise may be disease modifying in Parkinson's disease but results are mixed [26, 27]. However, considering the clear cardiovascular and mood benefits of exercise, it is reasonable to recommend a routine of aerobic activity (>30 min at least 3 times per week) in nearly all individuals. For a further discussion of neuroprotection and potential disease modification, please refer to Chap. 44.

As numerous scientific investigations are currently underway, RBD patients should be offered the opportunity to participate in clinical trials. Many patients describe a feeling of empowerment, even in the absence of a discovery that directly affects them, by participating in a process that benefits future generations. A multinational consortium of investigators, the International Rapid Eye Movement Sleep Behavior Disorder Study Group (IRBDSG), is a resource for patients interested enrolling in clinical trials [20]. An ultimate goal of the IRBDSG is to identify

disease-modifying therapies that could slow or halt the progression from iRBD to overt neurodegeneration or cure emergent Parkinson's disease and related disorders. For further discussion of the IRBDSG, please refer to Chap. 3.

Finally, RBD offers patients, and their physicians, a unique and valuable perspective. There should be enhanced appreciation for the intact brain function we have while we have it. Our ability to move, to think, and to feel spontaneously is a wondrous marvel, but ultimately these delights are transient. Because of this situation, a diagnosis of RBD presents an opportunity to initiate or accelerate activities (such as taking a foreign trip, climbing a mountain, hiking around national parks, etc.) often imagined but never adequately completed. Most importantly it is a reminder that we should express the appreciation and affection we have for those with whom we share our lives.

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