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REM Sleep Behaviour Disorder in Older Individuals: Epidemiology, Pathophysiology, and Management

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder that predominantly affects older adults, in which patients appear to be enacting their dreams while in REM sleep. The behaviors are typically violent, in association with violent dream content, so serious harm can be done to the patient or the bed-partner. The estimated prevalence in adults is 0.4–0.5%, but the frequency is much higher in certain neurodegenerative diseases, especially Parkinson's disease, Dementia with Lewy bodies, and multiple systems atrophy. RBD can occur in the absence of diagnosed neurologic diseases (the “idiopathic” form), although patients with this form of RBD may have subtle neurologic abnormalities and often ultimately develop a neurodegenerative disorder. Animal models and cases of RBD developing after brainstem lesions (pontine tegmentum, medulla) have led to the understanding that RBD is caused by a lack of normal REM muscle atonia and a lack of normal suppression of locomotor generators during REM. Clonazepam is used as first-line therapy for RBD and melatonin for second-line therapy, although evidence for both of these interventions comes from uncontrolled case series. Because the risk of injury to the patient or the bed-partner is high, interventions to improve the safety of the sleep environment are also often necessary. This review describes the epidemiology, pathophysiology, and treatment of RBD.

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a sleep disorder in which patients appear to physically act out dreams during REM sleep. The behaviours may be simple or complex, including talking, singing, shouting, grabbing, strangulating, and jumping from the bed. The majority of enacted dreams have violent content and associated violent behaviors, although non-violent behaviours can also occur[1]. Because of the violent nature of the actions, the potential for serious self-harm or bed-partner harm is high[2]. Despite the aggressive and violent content of dreams, however, RBD patients are not aggressive during the day[3]. First formally reported in the literature in 1986, the original case series highlighted the clinical features now recognized to be characteristic: violent dream enactment in elderly men, who frequently have underlying neurologic diseases[4] (see Table 1). This review, based on a literature search of the terms `REM behavior disorder' and `REM sleep behavior disorder' in PubMed (limited to publications in English), will review the epidemiology, pathophysiology, and treatment of RBD.

Epidemiology

Population-based estimates of RBD prevalence are 0.38% (among people aged 70 years or above in Hong Kong) to 0.5% (among non-institutionalized adults in the United Kingdom) [5–6]. There is a strong male predominance for RBD, with large case series reporting 82–88%

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of RBD patients being male[7–9], and a recent review of 126 articles on RBD yielding a pooled male frequency of 73%[10]. When RBD co-exists with narcolepsy, this male predominance is not as pronounced[10]. Women with RBD are no less likely to have violent dream content [7], but may have more dreams in which they are the victim[10]. Women may have a later age of both onset and diagnosis[7].

Symptoms typically begin in the sixth or seventh decade of life, although the range of symptom onset is broad, with onset as young as age 15 reported[11]. There frequently is a 4–5 year lag between symptom onset and diagnosis[7–9,12]. Sleep disruption, whether measured subjectively or objectively, is common in RBD[8–9,12]

Diagnosis

The diagnostic criteria for RBD include a history of potentially harmful behaviours in sleep or documented behaviours in REM sleep during polysomnography (PSG), as well as the presence of abnormal muscle tone during REM sleep during PSG[13]. Recall of dream content associated with the behaviors, while helpful in suggesting a diagnosis of RBD and usually present (see Table 1), is not a universal finding nor necessary for the diagnosis[14]. Clinical clues to the diagnosis include a tendency for behaviors to occur in the latter third of the night (when REM sleep is concentrated), a lack of behavior during the first hour of sleep (when REM sleep is not expected to occur), a tendency for eyes to be closed during the event, a typical lack of getting out of bed to walk, and a change in the semiology of events based on dream content (as opposed to stereotyped behaviors seen in nocturnal epilepsy)[14–16]. Bedpartners are useful in reporting the appearance, frequency, and timing of behaviors. Several screening questionnaires have been developed for use in RBD in languages including English, German [17], Japanese[18] (based on[17]), and Chinese[19]. These have been based on ICSD and ICSD-2 scoring criteria and have high sensitivity (82–96%) and moderate to high specificity (56–97%). Bedpartner input on these questionnaires was encouraged during the development process, and thus should also be used when applying these scales. Scores generated by patients plus their bedpartners were higher than those generated by patients alone[19].

Polysomnography, including surface electromyography (EMG) of the chin, arms, and legs, is mandatory for diagnosis[13]. As measured by EMG during PSG, healthy subjects demonstrate atonia during REM sleep; patients with RBD demonstrate increases in either sustained (tonic) or burst-like (phasic) muscle tone. Women may have higher density of EMG activity in the arms compared to men (who have higher density in the legs)[10], thus it is important to monitor both arm and leg EMG during diagnostic testing. Although dream-enactment behaviours may not occur every night in all patients, a single night of video-PSG is sufficient for the diagnosis in the majority of cases[20] and increased phasic EMG activity may be useful to differentiate patients with RBD from elderly controls in the proper clinical context[21]. In addition to demonstrating the lack of REM atonia and potentially capturing dream-enactment behaviours during REM sleep, the PSG is helpful in excluding severe obstructive sleep apnea (OSA). Severe OSA can cause symptoms that are otherwise suggestive of RBD, known as “pseudo-RBD”, that resolves with treatment for OSA[22]. The PSG is also helpful in excluding nocturnal seizures and parasomnias arising from non-REM sleep (such as somnambulism), as the distinction between RBD and these entities cannot always be made on purely clinical grounds.

It should also be noted that the description of “acting out dreams” implies a direction of causality that has yet to be proven, that is, that the specific dream content produces the particular action. As has been pointed out by other authors[23–24], it is also plausible that RBD entails “dreaming out actions”, or that it is abnormal body movements that are triggered during REM and that specific dream content is then created around those actions.

RBD Co-morbidities

RBD is characterized as idiopathic (IRBD) if it occurs in the absence of another neurologic disease. Patients with IRBD by definition have no diagnosed co-morbid neurologic disease, yet this group of patients may not be neurologically normal. Several studies have found subtle cognitive abnormalities in this group of patients in domains of visuospatial function, verbal memory, attention, and executive functioning[25–29]. One study found a frequency of diagnosable mild cognitive impairment (MCI) of 50% in patients with IRBD versus 8% of healthy, similarly-aged controls[30]. Subtle motor deficits may also be seen, including rigidity, mild tremor, and mild postural instability[31]. Olfactory and color vision impairment are present in idiopathic RBD[32–33].

Autonomic nervous system (ANS) abnormalities have also been demonstrated in IRB, including a lack of cardiac response to the transition from non-REM to REM sleep[34] and impairments in cardiac adrenergic function as measured by ^{123}I-MIBG uptake[35–38]. Presynaptic striatal dopamine transporters (as shown by SPECT)[39–40] and midbrain dopaminergic neurons (via PET)[41] are decreased in IRBD relative to control subjects. Cerebral perfusion abnormalities may be seen in RBD, with perfusion increases in the pons, putamen, and right hippocampus and decreases in the frontal and temporoparietal regions [42].

A number of `secondary' forms of RBD have been described, but the most robust associations are with narcolepsy in the young[11,43–44] and with neurodegenerative diseases in the elderly. Whether idiopathic or secondary, the clinical features of RBD tend to be similar[45] although the strong male predominance that is seen in most forms of RBD is not as marked when RBD occurs in the multiple systems atrophy (MSA)[8].

RBD associated with to Parkinson's disease (PD-RBD) is a common secondary form of RBD. The frequency of RBD in PD patients has been estimated to range from 15 to 59%[46–49] depending on method of diagnosis. PD patients with RBD are older, more likely to be male [46,48–49], sleepier[46], more likely to experience orthostatic hypotension[50], and less likely to have tremor-predominant PD[31,51] than PD patients without RBD. Daily dosages of dopaminergic medications have been shown to be related to likelihood of having PD-RBD in some[49,52], but not other[53], studies. Patients with PD-RBD also appear to have worsened cognition compared to patients with PD lacking RBD, especially in dimensions of episodic verbal memory, executive functions, and visuospatial processing [53–54]. One study found that 73% of PD-RBD patients met diagnostic criteria for mild cognitive impairment (MCI), compared to only 11% of PD patients without RBD [30]. In addition to these cognitive deficits, patients with PD-RBD may be at greater risk for developing another common PD complication, hallucinations, over an eight year period[55]. Although often suspected to be a persistent disease, one prospective study of PD-RBD found that one third of PD patients with RBD at baseline no longer demonstrated RBD four years later[49]. Although patients with PD have motor deficits during wakefulness, motor function appears normal or improved during episodes of RBD, even though patients are more likely to use the more disabled side of the body during RBD events[56].

In patients with dementia and RBD, the most common form of dementia appears to be Dementia with Lewy Bodies (DLB). Thirty-four of 37 patients with dementia and RBD in one series met criteria for clinically possible or probable DLB[57]. Another group confirmed a tendency for patients with RBD and dementia to exhibit a neuropsychological profile consistent with DLB; the absence of fluctuations and hallucinations (typical features of DLB) in these patients led the authors to speculate that RBD may be an early sign of DLB[58]. The male predominance seen in IRBD and PD-RBD is also apparent in patients with dementia and RBD[57]. Two

published cases of clinically-diagnosed idiopathic RBD for which autopsy results were available both were found to have pathology consistent with Lewy Body disease[59–60]. In contrast to DLB, Alzheimer's disease (AD) does not appear to be commonly associated with RBD. In a series of 15 AD patients, none had clinical symptoms of RBD, although one met PSG criteria and three additional had evidence of abnormal muscle tone during REM on PSG [61].

Multiple systems atrophy (MSA), another neurodegenerative disease, is also strongly associated with RBD, with 70–100% of MSA patients demonstrating symptoms of RBD and 90–100% showing PSG evidence of RBD[62–63]. These diseases (PD, DLB, MSA) share a common pathology of alpha-synuclein deposition, which have also been seen on autopsy in a patient with IRBD[60]. Despite this, RBD in no longer widely considered to be a disease solely of synuclein pathology[14,23], in part because RBD has also been seen in neurodegenerative diseases that have other underlying pathology. In progressive supranuclear palsy (PSP), a parkinsonian condition related to tau pathology rather than synuclein, 2 (13%) of a series of 15 patients had RBD and the group as a whole had similar rates of RWA as the idiopathic PD controls[64]. Six of 10 patients with parkinsonism due to *PARKIN* mutations (a condition in which synuclein aggregates are infrequently found in autopsy specimens) were found to have abnormal behaviors during REM sleep; a clinical history consistent with RBD was present 5 of these 6 patients[65]. In guadeloupean parkinsonism, a PSP-like parkinsonian condition shown in a few patients to be a tauopathy, 7 (78%) of 9 patients had clinical and PSG evidence for RBD[66]. RBD symptoms (not PSG-confirmed) have been reported in one pathologically-confirmed case of corticobasal ganglionic degeneration (CBD) (out of a series of 11 CBD patients)[67]. Thus RBD can be seen in association with a wide range of neurodegenerative diseases, most commonly PD, DLB, and MSA.

Several other clinical conditions which are common in the elderly may also be associated with RBD. Focal lesions (e.g., ischemic stroke) involving the REM-control areas of the brainstem have been associated with the onset of RBD in a number of case reports and series[68–76]. In several of these cases, the onset of RBD was temporally related to the onset of other focal neurologic symptoms and signs referable to the pons, suggesting that the lesion was also the cause of the RBD. In one case, the argument for causality was made even stronger by the fact that removal of the lesion (a neurinoma causing external compression of the pons) resulted in a resolution of RBD[70]. Vascular involvement of the medulla has also been reported to result in RBD[77]. The elderly are also at increased risk of epilepsy[78], and there also appears to be an association between epilepsy and RBD. Twelve percent of epilepsy patients older than 60 years were confirmed to have RBD by PSG[79]. The direction of this association is not clear, however, as RBD predated epilepsy in half the patients and epilepsy preceded RBD in the other half in this series. Another study by the same investigative group found interictal epileptiform discharges in 26.4% of RBD patients (whose mean age was 66.7), although whether this represents a true association or is just reflective of the fact that RBD is a disease of elderly patients, who are also at increased risk of interictal epileptiform discharges, is not known[80].

Other less-common neurologic syndromes have also been shown to be associated with RBD. Limbic encephalitis, either due to voltage-gated potassium channel antibodies in a small series [81] or due to non-antibody-mediated aseptic encephalitis in a single case[82], has been associated with RBD. In over half of the patients with voltage-gated potassium channel antibodies, RBD resolved after successful immunotherapy. Patients with Chiari malformations (type I or II)[83], Huntington's disease[84], spinocerebellar ataxia type 3[85–86], and autism [87] all appear to have frequencies of RBD that are higher than would be expected based on population rates.

Risk of developing neurodegenerative disease in idiopathic RBD

The frequent co-occurrence of RBD and neurodegenerative disease, often beginning as RBD symptoms prior to symptoms of the neurodegenerative disease, and the presence of subtle neurological deficits in patients with "idiopathic" RBD has led to the hypothesis that RBD is an early marker of neurodegeneration. Experience in several large clinical series of IRBD patients supports this view. In a series of 29 men with idiopathic RBD (all 50 years old or older), 38% developed a parkinsonian disorder by a mean follow up of 3.7 years[88]. A retrospective review of 44 patients with IRBD (89% male, mean age 74 years) found that 45% had developed some form of neurodegenerative disease at a mean follow up of 5 years from diagnosis, of which PD, DLB, and MCI were the most common[26]. Using a more stringent definition (which excluded MCI and mild parkinsonian signs in the absence of symptoms) on the largest series of IRBD patients to date, Postuma and colleagues found a 17.7% 5 year risk of parkinsonism or dementia. This risk increased to 40.6% at 10 years and 52.4% at 12 years [89]. Thus, in patients presenting with idiopathic RBD, especially males older than 50, there is a clear increase in risk for neurodegenerative disease. Given the agreement among multiple studies and magnitude of increased risk, it is reasonable to counsel patients and their spouses, when appropriate, about this risk. This knowledge could potentially help with financial and other planning for subsequent years. Additionally, as patient access to medical information increases via internet and other technology, many patients will learn about this increase in risk from non-physician sources; physicians may have a responsibility to explain the significance of this information to patients rather than putting patients into a situation where they must discover and interpret these data on their own. However, as neuroprotective or disease-modifying therapies are not yet available for these neurodegenerative diseases, knowledge of risk may bring significant distress without translating into action. When such neuroprotective therapies become available, the development of idiopathic RBD may be a critical marker signaling the need for initiation of such therapy.

The significance of "subclinical" RBD, defined as increased EMG activity or simple behaviors on PSG in the absence of clinical behaviors, is less clear. Subjects with subclinical RBD have been shown to have reduced striatal dopamine transporters compared to controls, on a spectrum with patients with IRBD and PD[39], suggesting that it may represent a stage in the progression toward parkinsonian conditions. Some authors have suggested that subjects found incidentally to have subclinical RBD undergo neurologic screening and that their treating physicians be notified of their potential risk for disease progression[90]

Pathophysiology

Prior to the description of human RBD in the medical literature, a similar phenomenon of motor behaviours during REM sleep was described in cats after experimental lesions of the bilateral pontine tegmentum[91]. This and subsequent animal studies have informed our understanding of normal and pathologically-altered atonia during REM sleep. Both the generation of atonia and the suppression of locomotor activity are thought to be present in normal REM sleep, and the absence of these features to result in RBD[91]. In cats, pontine nuclei (locus coeruleus, pedunculopontine, laterodorsal tegmental) project to the medullary reticular formation, which in turn projects to the spinal cord to inhibit spinal motor neurons. Experimental lesions of these brainstem areas in cats can result in features of what appears behaviourally equivalent to human RBD. Anatomy of brainstem nuclei varies somewhat between species, and the exact nuclei involved in suppression of behaviour during REM sleep have not been conclusively identified in humans[24]. Cases of RBD developing after pontine and medullary lesions suggest, however, that similar anatomic mechanisms are at play in humans. The locomotor generators presumed to be disinhibited during RBD have not yet be clearly identified in humans[24], although these generators co-localize with the atonia centers in the pons in dogs[91], so this

may also prove to be the case in human RBD. Lesions of regions that project to brainstem areas involved in REM sleep (limbic system, anterior thalamus, posterior hypothalamus) have also been seen in patients with RBD, suggesting that upstream dysregulation of these brainstem nuclei can also result in RBD[14].

The frequent co-occurrence of RBD and PD, the prototypic disorder of dopamine loss, has led to speculation that RBD could be a hypo-dopaminergic disorder. In keeping with this, patients with IRBD have measures of presynaptic dopamine transporter binding within the basal ganglia that are intermediate between those of normal controls and patients with PD[92]. Similarly, PET imaging shows reduced numbers of striatal dopaminergic terminals (a marker of dopaminergic neurons in the midbrain) in IRBD patients versus healthy controls[93]. However, the finding of decreased dopamine in patients with IRBD, who are at high risk of developing a neurodegenerative disease of the dopamine system, may be a marker of this impending neurodegeneration rather than the cause of the IRBD[14]. Further, it is clear that not all PD patients develop RBD. RBD is not consistently responsive to dopaminergic medications, nor are there reports of antipsychotic medications inducing RBD[14]. Thus dopaminergic dysfunction is unlikely the only or major pathology underlying RBD.

Perhaps the most conspicuously unexplained feature of RBD is the striking male predominance. Models of brainstem neurodegeneration do not, as yet, account for this difference. Investigations have shown that testosterone levels in male PD patients do not correlate with the presence of RBD[94], and sex hormone levels in patients with IRBD are no different than those of controls[95]. Alternately, it has been proposed that non-hormonal gender difference may underlie this phenomenon. Women could be hypothesized to be more likely to have milder RBD, less aggressive dreams, more embarrassment about their symptoms, or less observant bed-partners, all of which could make them less likely to seek medical evaluation [14]. Because the RBD literature is based almost exclusively on clinical populations, this could result in the apparent gender difference. These explanations, however, do not then account for the lack of a gender difference in those patients with RBD coexisting with narcolepsy.

Drug-induced RBD

Commonly-used medications may induce or unmask latent RBD (Table 2). Antidepressants are the class of medication most commonly implicated in altering muscle control during REM and causing RBD. Fluoxetine was reported to induce RBD in a 31 year old man with obsessive-compulsive disorder, and RBD was persistently present (clinically and polysomnographically) 19 months after discontinuation of this medication[96]. The persistence of disease after discontinuation of fluoxetine suggests that perhaps fluoxetine unmasked a latent predisposition to RBD rather than causing RBD directly, although this remains speculative. Review of EMG in 41 additional patients taking fluoxetine revealed increased muscle tone in REM in 15%, higher than would be expected in the unmedicated population (and higher than the rate in patients taking tricyclic antidepressants, in which it was seen in 4%)[96]. In a group of patients on serotonergic antidepressants (mostly selective serotonin reuptake inhibitors (SSRIs) but a serotonin-norepinephrine reuptake inhibitor in one patient) without clinical symptoms of RBD, increased rates of increased muscle tone during REM were seen compared to controls[97]. The most compelling data for a relationship comes from two series in which RBD started with the introduction of antidepressant medication and resolved after discontinuation, which has been shown in patients with IRBD as well as secondary forms[11,98]. The serotonergic action of the medications, acting either at the level of the pons or on the spinal cord directly, is thought to be responsible for the generation of REM atonia and RBD in these series[97] Buproprion, a dopaminergic/noradrenergic antidepressant, has been shown in two patients to be associated with a lack of atonia in REM (without frank RBD)[97]. However, as it has not been reported

to induce RBD and because of its non-serotonergic mechanism of action, it is considered by some authors to be the first-line antidepressant for patients with both depression and RBD.

When used in patients with narcolepsy, nortriptyline and imipramine have been reported to worsen pre-existing RBD in individual patients[44]. Clomipramine, another tricyclic antidepressant, has been reported to cause “severe hyperactivity” during REM sleep consistent with RBD (reported prior to the formal description of RBD)[99], and to decrease atonia during REM sleep[100]. A case-control study of patients with idiopathic RBD found that RBD patients had more psychiatric disease than controls, but antidepressant use (predominantly SSRIs) was only correlated with RBD in the younger, not older, subset of patients. This may support the contention that antidepressants can cause (or unmask) RBD, but might alternatively suggest that the association between RBD and antidepressants is driven by an association between RBD and psychiatric disease[101].

Other substances that preliminarily have been implicated in the development of RBD in case reports or small case series are selegiline (in three PD patients)[102], atenolol[11], bisoprolol [103], intravenous tramadol[98], caffeine[104] and chocolate[105].

Pharmacologic management of RBD

There are no published, double-blind, controlled, randomized trials of therapy for RBD[24, 106], and available therapies are `off-label' uses of medications approved for other indications. Treatment is purely symptomatic, and is generally recommended when there is significant risk of injury, troublesome dream content, or severe sleep disruption for the patient or bed-partner [14]. Based on large case series and clinical experience, the benzodiazepine clonazepam is considered first line treatment. Several large case series (totaling over 250 patients) using clonazepam in patients with IRBD and secondary forms of RBD and have found remarkably similar response rates of 87–90%, where response is defined as partial or complete resolution of symptoms[7–9,12]. In some patients (55% in one series), behaviours completely resolve on therapy[8]. Doses range from 0.25 to 4.0 mg at bedtime, with dosages between 0.5 mg and 2.0 mg being most commonly used. Long term use of clonazepam for RBD (and other sleep disorders) does not appear to be associated with a significant risk of tolerance and rates of benzodiazepine abuse or relapse of substance abuse disorders are reasonably low (~2% each) in this population[7,107]. Side effects such as excessive daytime sleepiness, confusion, and cognitive impairment may be seen in up to 58% of patients, resulting in medication discontinuation in up to one third[108], although lower rates have also been reported[107]. The presence of sleep apnea, dementia, or a high baseline risk of falling are relative contraindications to the use of clonazepam[109]. Because clonazepam suppresses abnormal behaviors without restoring REM atonia, it is suspected that clonazepam acts to inhibit the locomotor generator during REM[110]

When clonazepam is contraindicated, not successful or not tolerated, melatonin may be used as a second-line agent. This recommendation is based on the results of three small case series of patients with idiopathic and secondary forms of RBD (totaling 35 patients, with a minority of patients on combination melatonin and clonazepam therapy). Response rates ranged from 71–83%[111–113]. Side effects were mentioned in one series, and most commonly were morning sleepiness (13%) and morning headaches (13%), with any side effect occurring in 36%[113]. Doses ranged from 3 mg (the starting dose in all three series) to 12 mg, taken 30 minutes prior to bedtime. In the United States, melatonin is not regulated by the Food and Drug Administration, so pill contents may not be standardized. Melatonin is not available over-the-counter or by prescription in several countries. Unlike clonazepam, melatonin does restore REM atonia[112]. It has been proposed that melatonin may normalize the circadian timing of

REM sleep and thus decrease RBD behaviors[112], but the mechanism of action of melatonin in RBD remains unknown.

Other agents may be considered when clonazepam and melatonin are ineffective or contraindicated, although evidence supporting their use is very limited. Donepezil, an acetylcholinesterase inhibitor, has been used in two small series of RBD patients. At doses of 10–15 mg per night, donepezil reduced the frequency and severity of RBD events in 4 of the 6 patients[114–115]. Peer-reviewed data showing a lack of effect are not available, although Boeve et al have reported anecdotally that among 50 patients with DLB and RBD who were treated with donepezil, none experienced significant benefit[113]. Zopiclone (3.75–7.5 mg) was effective in controlling RBD symptoms in 8 of 11 patients, with side effects (nausea or rash) in two patients[108]. Rivastigmine, another acetylcholinesterase inhibitor, was evaluated in an open label fashion in 8 patients with DLB, four of whom had clinical symptoms consistent with RBD but who were not evaluated by polysomnography for formal classification; all 4 patients had improvement in their sleep disturbance on rivastigmine, although this was not the primary endpoint of the study nor confirmed in a standardized way, so results must be interpreted with caution[116].

Conflicting data exist regarding the efficacy of the dopamine agonist pramipexole. It has been shown to be effective in the majority of patients (63–89%) with IRBD or RBD associated with MCI or mild PD in two small series comparing pre- and post-treatment subjective reports [117–118]. More recently, a prospective series of patients with PD and RBD found no differences in behaviours on video-PSG or subjective reports when pramipexole was added to a stable levodopa regimen[119]. Levodopa shows similarly mixed results when used in PD-RBD. Levodopa has anecdotally been reported to decrease the frequency and/or severity of RBD events in a few patients with PD or DLB[120–121]. However, a systematic study of 70 PD patients found that those with RBD tend to use higher doses of levodopa than those without RBD in the setting of similar disease severity[52], suggesting that at a minimum, levodopa is unlikely to have a significant treatment benefit for RBD. Thus, while dopaminergic medications may be used to treat a major RBD co-morbidity, their usefulness for the symptoms of RBD must be questioned.

Single case reports suggest possible utility of sodium oxybate (which is effective for the related phenomenon of cataplexy in patients with narcolepsy)[122], carbamazepine[123], desipramine [4] (although this is somewhat difficult to reconcile with reports of tricyclic antidepressants worsening RBD), and clonidine[124].

Non-pharmacologic treatment of RBD

Because of the high risk of both self-injury and bed-partner injury in RBD[8], preventive measures to improve the safety of the sleep environment are recommended to patients and spouses[109]. These may include the use of a hospital-style bed with padded and raised side-rails, removal of sharp, heavy, or dangerous items from the immediate sleeping area, and the bed-partner choosing to sleep in another bed.

Conclusions

RBD is a potentially dangerous sleep disorder that disproportionately affects the elderly, especially elderly men. It may be seen in a variety of neurologic conditions, most commonly neurodegenerative diseases of alpha-synuclein pathology such as Parkinson's disease, Lewy Body Dementia, and multiple systems atrophy. RBD may predate the onset of neurodegeneration by several years, with estimates of the five-year risk of developing a neurodegenerative condition after onset of RBD ranging from 18 to 45%. Dysfunction of brainstem regions implicated in the generation of REM atonia and suppression of locomotor

generators is thought to underlie RBD pathophysiology. Treatments for RBD are based on observational data and clinical experience rather than randomized clinical trials, and constitute off-label use of medications designed for other indications. Clonazepam is the first-line therapy, and appears to have some benefit in the majority of cases. If clonazepam is not effective, not tolerated, or contraindicated, melatonin can then be considered. Third line agents consist of medications supported by conflicting case series or single case reports. Non-pharmacologic treatments focused on ensuring nocturnal safety of the patient and bed-partner are also important.

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Table 1

Characteristics of RBD in large case series

	Schenck 1993[9]	Sforza 1997[12]	Olson 2000[8]	Wing 2008[125]
Number of patients	96	52	93	82
% male	87.5%	--	87%	82%
Mean (SD) age of onset	52.4 (16.9)	Duration of disease prior to diagnosis: 4.3 (0.9) in idiopathic; 4.9(0.6) with secondary forms	60.9 (36–84)	62.1 (12.9)
Mean (SD) age at diagnosis	58.3 (17.4)	66.2 (2.1) for idiopathic form; 59.9 (1.2) for those associated with neurologic disease	64.4 (37–85)	67.4 (10.0)
Percent with a history of sleep-related injury	79.2%		32% (injury to self) 16% injury to bedpartner)	80.8%
Percent with sleep disruption	20.8%	Some degree of sleep disruption present in 100%. Average (SD) sleep efficiency 66.4 (4.4) in idiopathic RBD, 52.4 (2.6) in secondary	70% (self report)	--
Frequency of dream enacting behaviors	87.5%		93%	98%
Comorbid neurologic diagnoses	47.9% (composed of degenerative disorders in 23%, narcolepsy in 14%, other in 11%)	75%	57% (47% PD, 13% dementia, 26% MSA, 8% narcolepsy, 2% PSP, 2% brainstem stroke)	19.5%
Comorbid or lifetime history of psychiatric disorders	9.4%	--	25.8% (lifetime history)	33% (lifetime history)
Response to clonazepam	Total 90.0% (79.1% complete, 11.1% partial)	90%	87% (of the 38 people for whom information was available); 55% complete, 32% partial	87% of 71 pts

Table 2

Medications reported to induce RBD or lack of normal muscle atonia during REM sleep

Class	Medication	RBD or abnormal muscle tone on PSG
SSRI antidepressant	Fluoxetine Paroxetine	Both
SNRI antidepressant	Venlafaxine Mirtazepine	Both
Tricyclic antidepressant	Nortriptyline Imipramine Clomipramine	Worsening of pre-existing RBD or “hyperactivity” in REM
Monoamine oxidase inhibitor	Selegiline	
Beta-blocker	Atenolol Bisoprolol	Both
Opioid (with serotonin reuptake inhibition properties)	Tramadol	Witnessed behaviors presumed by medical observer to be RBD

Table 3

Treatment of RBD

	Medication	Dosage/Timing	Side Effects
First line	Clonazepam	0.25–4.0 mg nightly, with dosages 0.5–2.0 most commonly used	Sedation, confusion
Second line	Melatonin	3 mg starting dose, titrated to 12 mg as needed. Taken 30 minutes before bedtime	Morning sleepiness, morning headaches
Other (medications with conflicting reports of efficacy or those supported by only single case reports)	Pramipexole, levodopa, sodium oxybate, zopiclone, carbamazepine desipramine, clonidine, donepezil, rivastigmine		

Safety measures to protect the patient and bed-partner (i.e., modifications to the sleep environment) should always be considered, whether or not medication is implemented.