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REM Sleep Behavior Disorder: Diagnosis, Clinical Implications, and Future Directions

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Abstract

Rapid eye movement sleep behavior disorder (RBD) is diagnosed by a clinical history of dream enactment accompanied by polysomnographic rapid eye movement sleep atonia loss (rapid eye movement sleep without atonia). Rapid eye movement sleep behavior disorder is strongly associated with neurodegenerative disease, especially synucleinopathies such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. A history of RBD may begin several years to decades before onset of any clear daytime symptoms of motor, cognitive, or autonomic impairments, suggesting that RBD is the presenting manifestation of a neurodegenerative process. Evidence that RBD is a synlucleinopathy includes the frequent presence of subtle prodromal neurodegenerative abnormalities including hyposmia, constipation, and orthostatic hypotension, as well as abnormalities on various neuroimaging, neurophysiological, and autonomic tests. Up to 90.9% of patients with idiopathic RBD ultimately develop a defined neurodegenerative disease over longitudinal follow-up, although the prognosis for younger patients and antidepressant-associated RBD is less clear. Patients with RBD should be treated with either melatonin 3 to 12 mg or clonazepam 0.5 to 2.0 mg to reduce injury potential. Prospective outcome and treatment studies of RBD are necessary to enable accurate prognosis and better evidence for symptomatic therapy and future neuroprotective strategies.

Rapid eye movement sleep behavior disorder (RBD) is diagnosed when dream enactment and complex motor behaviors occur during rapid eye movement (REM) sleep, accompanied by supportive evidence from loss of normal REM sleep muscle atonia known as REM sleep without atonia (RSWA) during polysomnography.[1] The prevalence of RBD has been estimated to be in the range of 0.5% to 2%,[2–4] yet larger population-based studies of probable dream enactment symptoms suggest that RBD is likely considerably more frequent and present in between 5% and 13% of older community-dwelling adults aged 60 to 99

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years.[5–8] Rapid eye movement sleep behavior disorder appears to be more common in men than women in older adults,[9–13] yet below the age of 50 years it is equally frequent in women and men.[14–17] Rapid eye movement sleep behavior disorder is 5-fold more likely to develop in patients receiving antidepressants and 10-fold more likely to develop in those with a psychiatric diagnosis.[15] Rapid eye movement sleep behavior disorder usually onsets in the fifth or sixth decade, although it may be seen in younger patients with antidepressant use, narcolepsy, autoimmunity, or developmental disorders.[15,18–21] Risk factors for RBD are similar to Parkinson disease (PD), including lower educational level, previous head injury, occupational pesticide exposure, and farming, yet some distinct risk factors have also been reported, including smoking, ischemic heart disease, and inhaled corticosteroids,[22,23] whereas caffeine use and smoking are not protective in RBD.

Rapid eye movement sleep behavior disorder is idiopathic when unassociated with neurological disorders or symptomatic when underlying causes such as autoimmune or inflammatory disorders, brain lesions, or provoking antidepressant medications are present.[10,12,15,18,21,23–32] In both idiopathic and symptomatic categories, RBD is strongly associated with neurodegenerative diseases, especially synucleinopathies including PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure.[1,10,12,24–28,31,33–41] Rapid eye movement sleep behavior disorder may manifest initially as an idiopathic prodromal state that occurs years to decades before the evolution of overt motor, cognitive, or autonomic impairments as the presenting manifestation of synucleinopathy. Dream enactment symptoms and idiopathic RBD diagnosis may be accompanied by other subtle prodromal features such as subjective cognitive symptoms without evidence of impairment on neuropsychological testing, asymptomatic cognitive or motor deficits, hyposmia, constipation, and orthostatic hypotension; many of these features are associated with a higher risk of pheno-conversion to a defined neurodegenerative disorder.[20,22,24,30,31,37,42–46]

We will review evidence of the strong association between RBD and synucleinopathies, especially PD, mild cognitive impairment (MCI), DLB, and MSA. We will also review diagnosis and differential diagnosis of RBD as well as its pathophysiology and treatment. The article begins with an illustrative case typical of an initially idiopathic RBD diagnosis, that progresses to PD.

ILLUSTRATIVE CASE

Mr F was a 52-year-old man with a history of depression and anxiety. Because of loud disruptive snoring and a 10-year history of excessive daytime sleepiness (Epworth Sleepiness Scale score, 14), he underwent polysomnography, which exhibited an apnea-hypopnea index of 82 per hour and an oxyhemoglobin saturation nadir of 79%, consistent with severe obstructive sleep apnea. Rapid eye movement sleep atonia loss was also noted (Figure 1), prompting further collateral history from his wife that revealed that the patient had also developed violent sleep behaviors of arm flailing movements beginning at the age of 30 years, escalating to nightly shouting or arm flailing movements over the past 5 years for which he had not previously sought medical attention. He had inadvertently struck his spouse on occasion. He received fluoxetine 20 mg daily, which had been initiated 1 month

before his polysomnogram. His family history was pertinent for parkinsonism and dementia in his mother, who had developed rest tremor in her 70s and died after the development of severe dementia in her 80s. Symptoms of hyposmia or constipation were absent.

Mr F's initial neurological examination results at the age of 52 years were normal, without any signs of parkinsonism or cognitive decline. He was treated with nasal continuous positive airway pressure for severe obstructive sleep apnea, and with faithful adherence to treatment he noted some improvement in sleep quality, but no further improvement in parasomnia behaviors or daytime sleepiness; so modafinil 200 mg twice daily was added with incomplete benefit for his tendency to doze off, and he still needed a daily 15- to 20-minute nap. Melatonin was then prescribed, and after raising the dose to 6 mg, dream-enactment behaviors ceased entirely.

He was seen annually without further change until the age of 56 years, when repeat neurological examination demonstrated an intermittent right upper extremity postural and rest tremor, increased tone, and reduction of right arm swing during gait assessment. Because of concern about whether the tremor was more consistent with essential or parkinsonian tremor, a subsequent dopamine transporter uptake scan revealed asymmetrical reduced uptake in the tail of the left putamen. A diagnosis of PD was made, and carbidopa-levodopa 25/100 mg thrice daily was prescribed, with improvement in his tremor. Dream enactment frequency had decreased substantially within the year and he had discontinued melatonin.

This case reports several typical and remarkable features about the clinical course of idiopathic RBD as it evolves to a defined neurodegenerative disease. In this case, RBD was detected and brought to clinical attention only because of recognition of marked REM sleep atonia loss (RSWA) during polysomnography that had been performed for another indication for sleep apnea suspicion. Such cases of RBD diagnosed incidentally are not uncommon at the time of polysomnography in sleep medicine practice, and isolated REM sleep atonia loss without dream enactment is relatively common in the general population.[47] A recent large idiopathic RBD case series from Barcelona has also similarly suggested that up to 44% of idiopathic RBD cases may be unaware of their sleep behaviors, suggesting that the diagnosis may be detected secondarily when patients present with other sleep problems.[13] In this case, prompt diagnosis and treatment with melatonin helped prevent injury and enabled surveillance and early detection and treatment of symptomatic parkinsonism that may improve function and quality of life, and hopefully one day, serial follow-up may enable application of neuroprotective therapy.

PATHOPHYSIOLOGY OF RBD

The mechanisms for RSWA and RBD currently remain poorly understood. Most insights into REM sleep atonia control and its abnormal loss have been drawn from animal lesion studies and functional models, which have shown that REM sleep regulation predominantly involves the key pontine centers including the predominantly glutamatergic subcoeruleus/sublateral dorsal nucleus, the noradrenergic locus coeruleus, the cholinergic pedunculopontine and laterodorsal tegmental nuclei, as well as the medullary magnocellular

reticular formation, with additional modulation by the hypothalamus, thalamus, substantia nigra, basal forebrain, limbic system, and frontal cortex.[48–50] The possibility of RBD was foreseen by the eminent neurophysiologist Michel Jouvet, who initially described that dorsal pontine lesions near the locus coeruleus caused REM sleep atonia loss and RSWA, anticipating the eventual recognition of RBD in humans by Dr Carlos Schenck and Dr Mark Mahowald and their team at Hennepin County Medical Center in Minnesota.[48–50] In rats, REM onset and offset is mediated by a complex reciprocal flip-flop circuit between the "REM-active" sublateral dorsal nucleus, pontine "REM-inactive" nuclei, and the inhibitory gamma-aminobutyric acid/galaninergic non-REM sleep "active" center in the basal forebrain ventrolateral preoptic nucleus, and it appears this mechanism for REM sleep duration and latency remains largely unaffected in REM sleep behavior disorder.[48,49,51–55] During REM sleep, excitatory sublateral dorsal/subcoeruleus nucleus glutamatergic neurons also activate spinal cord inhibitory interneurons to hyperpolarize and thereby inhibit the spinal motoneuron pool, causing REM sleep atonia, so sublateral dorsal/subcoeruleus nucleus lesions resulting from brain lesions in the dorsal pons cause REM sleep atonia loss and may cause clinical REM sleep behavior disorder (Figure 2).[29,56,57] Posterior hypothalamic hypocretin may also further stabilize the REM-active and REM-inactive centers and networks, and in the context of hypocretin deficiency as in narcolepsy type 1, RBD may also occur.[58]

The hypothesis of Braak, based on pathologic staging of Lewy body progression in PD, suggests that pathology begins in the medulla and pons, which could be associated with initial RSWA and RBD development in idiopathic RBD. Then as Lewy disease ascends to the substantia nigra, the motor expression of PD evolves, and eventually as Lewy disease progresses to the cortex, PD dementia unfolds.[56,59] In those who develop DLB, RBD typically begins many years before the onset of cognitive decline, with parkinsonism and other core features of DLB usually evolving sometime later. The onset of cognitive decline prior to parkinsonism in the DLB phenotype may be explained by the temporal sequence of evolution from RBD to DLB, such that the nigrostriatal system may be impacted in a less severe and/or later fashion than in the evolution of RBD to PD/PD dementia. Limbic and/or neocortical structures are impacted more severely and/or earlier in the DLB phenotype, thereby explaining the onset of cognitive decline prior to parkinsonism. However, not all RBD, PD, and DLB patients follow this typical ascending Braak model of progression, since RBD may also follow cognitive, motor, or autonomic symptoms in some patients. Rapid eye movement sleep behavior disorder is not universally seen in patients with all of the synucleinopathies, suggesting that topographic onset and progression varies considerably across individual patients. Finally, not all patients with RSWA are aware of symptoms of sleep disturbance, implying that either the neurophysiologic property of RSWA may dissociate from clinical dream enactment, or that patients' dream enactment behaviors may be subtle and remain subclinical and covert.

Lastly, genetic studies of RBD remain limited, but RBD has been associated with glucocerebrosidase sequence variation and PD-related genetic loci including the microtubule associated protein tau (*MAPT*) gene in genome-wide association studies,[41,60,61] and the leucine rich repeat kinase (*LRRK2*) mutation carriers with Parkinson disease.[41,62,63] It has been proposed that the variability in RBD expression in some genetic Parkinsonian disorders

may reflect heterogeneous neuropathological substrate with less marked involvement of the brainstem REM atonia control structures in *LRRK2* mutation carriers than in idiopathic PD.

DIAGNOSIS OF RBD

Diagnosis of RBD requires either a clinical history of sleep-related complex motor behaviors or REM sleep complex vocal or motor behaviors recorded during polysomnography, accompanied by RSWA.[1] Rapid eye movement sleep behavior disorder diagnosis also requires that the sleep disturbance is not better explained by another disorder, such as obstructive sleep apnea or an alternative non-rapid eye movement (NREM) sleep parasomnia. Idiopathic RBD is diagnosed when there is clinical sleep-related complex motor dream enactment behavior, without a clearly associated underlying pathology, such as PD or related synucleinopathies.[1] Even when idiopathic, RBD has a very strong association with PD and other synucleinopathies. Rapid eye movement sleep behavior disorder is considered symptomatic RBD when it occurs in direct association with previously diagnosed PD, DLB, or MSA, or when there is another known underlying pathology such as a brain lesion (Figure 2).[29,57,64]

Confirmatory collateral history from a bed partner is necessary, especially when the patient has cognitive impairment.[24,65] Dream content in RBD usually involves aggressive themes, like being chased or defense against attack by animals or people.[24,66–69] Screaming or shouting, arm flailing, punching, kicking, or running movements paralleling action-filled dream content is common, complicated by minor or serious injuries such as bruising, lacerations, fractures, and subdural hematomas.[12,70,71] Vivid dream recall and falls from bed have been associated with injury.[70]

Loss of REM sleep atonia, known as RSWA, is required for diagnosis, although probable RBD may be diagnosed on clinical grounds when a clear history of dream enactment—type behaviors is present. There are several well-validated RBD screening measures for the diagnosis of probable RBD when polysomnography is unavailable or when REM sleep is not captured during polysomnogram recording.[65,72–77] These various instruments include the REM Sleep Behavior Disorder Screening Questionnaire,[75] the Innsbruck REM Sleep Behavior Disorder Inventory,[76] the RBD-HK,[74] and the Mayo Sleep Questionnaire (MSQ).[65,72,77] The MSQ is an especially well-validated diagnostic tool for RBD screening in older patients with cognitive impairment and/or parkinsonism, administered to either the bed partner (informant version) or the patient (patient version) when a bed partner is not available. The REM Sleep Behavior Disorder Single-Question Screen is a similar patient-administered tool containing essentially the same core question regarding dream enactment.[73] The REM Sleep Behavior Disorder Single-Question Screen and MSQ have each shown reasonable sensitivity and specificity in comparison to polysomnography when it is unavailable or impractical, yet polysomnography remains essential to support a clinical diagnosis of RBD.

Rapid eye movement sleep without atonia may be identified either qualitatively in clinical practice or quantitatively defined by visual or automated methods for research purposes.[47,78–84] Rapid eye movement sleep without atonia is of 3 types: *phasic/transient* (short

muscle activity bursts), *tonic* (sustained increase in the muscle activity background voltage), or "*any*" (either phasic or tonic). Several quantitative methods are available as references for RBD diagnostic cutoffs for use in research or for difficult or questionable cases in clinical settings. Currently there is no consensus on the best standard for RSWA, although widely validated visual quantitative techniques include the Sleep Innsbruck Barcelona, Montreal, American Academy of Sleep Medicine, and Mayo visual scoring methods, and the automated REM atonia index.[76,78,79,83–85] The Sleep Innsbruck Barcelona submentalis (chin) combined with flexor digitorum superficialis phasic muscle activity is the most specific method as recommended by the American Academy of Sleep Medicine, although it is not yet widely used in most sleep laboratories.[1,47]

Rapid eye movement sleep without atonia may also be an incidental or isolated finding during polysomnography without clinical accompaniment. The significance and natural history of isolated RSWA has not been defined. In a recent study of motor events, phasic RSWA exceeded defined cutoffs for RBD in 25% of a community sample of people without symptoms or signs of dream enactment.[86] Isolated RSWA is most frequent in older men and is a common finding in patients receiving antidepressant medications.[21,87] Isolated RSWA has been associated with positive neurodegenerative biomarkers such as loss of smell or color vision[88] and has been associated with gait freezing and cognitive impairment in PD.[89,90] Rapid eye movement sleep without atonia amounts have also been shown to progress over time in patients with idiopathic RBD[91] and have been associated with a higher risk of phenoconversion to PD in idiopathic RBD.[92] Isolated RSWA may also phenoconvert to idiopathic RBD, as shown in a recent study, with 7% to 14% of patients developing clinical RBD during longitudinal follow-up.[88] Further research of isolated RSWA is necessary to clarify whether it could be a biomarker for an underlying synucleinopathy.

CLINICAL IMPLICATIONS OF RBD

Rapid eye movement sleep behavior disorder is strongly associated with synucleinopathy neurodegeneration. There are several lines of converging evidence substantiating that idiopathic RBD is a prodromal form of synucleinopathy, including longitudinal cohort outcome studies, neurodegenerative biomarker studies, and pathological evidence from both autopsy series and demonstration of extranigral α-synuclein pathology in living patients with RBD. One very recent large cross sectional study of 171 RBD patients found that 74% (95% CI 66, 80%) met Movement Disorders Society criteria for a diagnosis of prodromal Parkinson's disease.[41] Longitudinal cohort studies of patients with idiopathic RBD have shown consistent evidence for a strong association with eventual phenoconversion to a defined neurodegenerative disease, predominantly the synucleinopathy phenotypes of PD, nonamnestic MCI, DLB, and MSA (Figure 3).[10,11,28,31,93–97] Phenoconversion risk over 2 to 5 years is approximately 15% to 35%, and longitudinal follow-up between 12 and 25 years increases to 41% to 90.9%, although the risk of phenoconversion has substantial interindividual variability, sometimes occurring over 50 years after initial symptom onset.[10,11,20,28,31,84,95,97] In a general community sample of elderly individuals older than 70 years, probable RBD symptoms endorsement on the MSQ was associated with a ratio for phenoconversion to PD or MCI over three years of 2.2 (95% CI, 1.3-3.9).[5] Given the high lifetime risk for phenoconversion to overt synucleinopathy in patients with idiopathic RBD,

when and how best to counsel patients about this risk remains a current controversy and uncertain point in practice.[98]

Several clinical investigational studies have clearly shown that patients with idiopathic RBD have frequent symptoms or signs, indicating likely underlying synucleinopathy pathology, including hyposmia and constipation, orthostatic hypotension, and gait abnormalities, which have been associated with a higher risk of phenoconversion.[23,30,31,41,42,45,89,99–101] In addition, neuropsychological deficits of dysexecutive, attentional, visuoperceptual, and short-term memory impairments appear to progress over time,[38,44,96,102–107] and neurophysiological markers such as electroencephalographic slowing,[108–111] and neuroimaging studies have also demonstrated findings indicating likely underlying synucleinopathy pathology.

Neuroimaging has shown altered neuromelanin signal intensity in the locus coeruleus/subcoeruleus nucleus region,[29,57,112–115] and functional imaging studies, including dopamine transporter uptake, have found decreased nigrostriatal putamenal dopaminergic uptake in patients with idiopathic RBD[95,116–120] as well as decreased cortical thickness and diffuse resting state metabolic network dysfunction with similar patterns to PD.[121–123] Lastly, autopsy series of patients with RBD have found underlying synucleinopathy in 94% of patients,[25,97,124,125] and tissues from living patients with idiopathic RBD have exhibited abnormal α-synuclein immunoreactivity in peripheral tissues such as the submandibular gland[126] and colonic submucosal nerve fibers or ganglia.[127] Other neurodegenerative pathologies have been reported, sometimes intermingling with typical synucleinopathy pathology of Lewy bodies and neurites with neuronal loss, including Alzheimer disease pathology of amyloid beta and tau proteins, progressive supranuclear palsy, neuronal brain iron accumulation type 1, other neurodegenerative pathologies, or brain lesions. However, the implication from converging evidence from cohort outcome studies, clinical neurodegenerative biomarker studies, and pathological series is that in most cases, particularly in older adults with symptom onset after the age of 50 years, RBD is associated with underlying synucleinopathy pathology.

In younger patients with RBD symptom onset before the age of 50 years, prodromal synucleinopathy is still possible, but alternative nondegenerative causes should also be considered, such as narcolepsy, autoimmunity, and antidepressant-associated RBD. In narcolepsy type 1 (previously known as narcolepsy with cataplexy), REM sleep dream imagery (hypnogogic hallucinations) and atonia (cataplexy, sleep paralysis) intrude into wakefulness, and conversely, waking motor tone (RSWA) and complex motor behavior giving rise to RBD may also be seen.[128–130] Rapid eye movement sleep without atonia may occur with or without RBD, which may occur in 36% to 50% of those with narcolepsy.[129,131] Another cause of RBD in younger and some older patients is paraneoplastic or autoimmune disorders, such as the anti-voltage-gated potassium channel antibody complex syndrome (including the CASPR-2 and LGI-1 epitopes), IgLON5 disease, and brainstem lesions caused by inflammatory, neoplastic, or cerebrovascular disorders.[29,57,64,132–139] In addition, both RBD and RSWA have been strongly associated with antidepressant use, especially selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants, and it remains unclear whether this association is

mediated by reversible pharmacological effects or whether antidepressants are causing earlier expression of RSWA and RBD in predisposed individuals with covert synucleinopathy[15,16,21,30] in a manner analogous to drug-induced parkinsonism.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER TREATMENT

All patients with RBD should be counseled about bedroom safety principles to prevent injury or serious consequences, including lowering the mattress to the floor or safe-guarding against falls by placing mattresses or foam cushions on the floor, padding any sharp bedside furniture surfaces, and removing firearms from the bedroom environment. In some cases, advising separate bedrooms to prevent bed partner injury may be necessary. A bed alarm system that could reassure and alert the patient during RBD behaviors may be useful in some patients, especially if they also have sleep walking behaviors.[140] Comorbid obstructive sleep apnea treatment with nasal continuous positive airway pressure may also improve the frequency and severity of RBD behaviors.

The 2 main pharmacological treatments of RBD are melatonin and clonazepam.[141–147] Both have been shown to prevent injury and reduce the frequency and severity of RBD behaviors, with melatonin having fewer adverse effects and better tolerability than clonazepam.[142] Most adverse effects are dose related, such as the carryover of sedation to the next morning, headache, or daytime sleepiness, and these can often be improved by lowering the dose used. Melatonin is particularly desirable in symptomatic RBD treatment for patients with comorbid sleep apnea or memory problems, and the recommended starting dose is 3 mg, increased gradually to the range of 6 to 12 mg at bedtime, with the average effective dose being 6 mg. Melatonin has been shown to increase REM sleep atonia levels, thereby diminishing RSWA.[53,144,148] Clonazepam 0.25 to 2.0 mg at bedtime is also a useful treatment for RBD. However, clonazepam does not appear to reduce RSWA and may instead modulate dreaming or complex motor behaviors. Clonazepam may exacerbate comorbid obstructive sleep apnea and cognitive impairment, so it should be used with caution in elderly patients, especially those with PD, DLB, or MSA.[145,146] Adverse effects include sedation, sexual dysfunction, and imbalance. Other RBD treatments with reported benefit for RBD in small uncontrolled case series include pramipexole, donepezil, ramelteon, Yi-Gan San, and cannabinoids,[141,149,150] and further evidence basis for the use of all symptomatic treatment of RBD is greatly needed. Some medications such as the antidepressants mirtazapine, b-blockers, or tramadol may worsen the frequency and severity of RBD, and when possible should be either discontinued or reduced.[149] Patients should also be counseled to avoid alcohol abuse and withdrawal, which have been reported to precipitate RBD.

FUTURE DIRECTIONS

Considering the compelling evidence of RBD usually reflecting an underlying synucleinopathy, there is considerable interest among clinicians and investigators to plan for future therapeutic trials in the hope of modifying the course, delaying the onset, or preventing the development of the disabling manifestations of PD, DLB, and MSA. A schematic framework for such an effort is shown in Figure 4.

The basic tenet of this framework (Figure 4, A) is that most patients with idiopathic RBD will develop other features reflecting accumulating synucleinopathy pathology in the central and peripheral nervous system such that phenoconversion to a definable transitional state, and then to an overt synucleinopathy phenotype, will evolve over time. One would predict that most of those who are destined to develop a parkinsonism-predominant syndrome will develop mild parkinsonian signs (as well as other degrees of neurological/neuropsychiatric dysfunction) before meeting clinical criteria for PD; most of those destined to develop a dementia-predominant syndrome will develop MCI (as well as other degrees of neurological/neuropsychiatric dysfunction) before meeting clinical criteria for DLB; and most of those destined to develop an autonomic dysfunction-predominant syndrome will develop mild autonomic dysfunction (as well as other degrees of neurological/neuropsychiatric dysfunction) before meeting clinical criteria for MSA or a Lewy body disorder such as PD or DLB.[150–152] Additionally, some individuals do not develop either initial predominant phenotypic manifestations, or evolve along a clearly delineated motor, cognitive, or autonomic phenotypic pathway, and instead develop parkinsonism, dementia, and dysautonomia simultaneously in tandem. Among those with idiopathic RBD, predicting *when* phenoconversion will occur and *which phenotype* will evolve is not yet possible on the basis of available data. A comprehensive battery of clinical, neuropsychological, biofluid, neuroimaging, and electrophysiological measures performed at regular intervals (eg, every 1-3 years) involving a large number of patients with idiopathic RBD, as well as the application of outcome criteria developed by consensus panels and analytical models, will be required to develop clinical trial methodology to plan for future disease-modifying trials. Many envision the future to appear as shown in Figure 4, B, and liken the goals to be similar to previous and ongoing therapeutic trials in those with hypertension or hyperlipidemia in delaying the onset or preventing cardiovascular and cerebrovascular morbidity/mortality. With adequate research funding and infrastructure development for these efforts and the development of putative therapies for synucleinopathy pathophysiology, the future appears brighter to potentially affect the burden of synuclein-associated neurodegenerative disease.

CONCLUSION

Rapid eye movement sleep behavior disorder is diagnosed when patients present with a clinical history of complex motor dream enactment behaviors during REM sleep and exhibit REM sleep atonia loss (RSWA) on polysomnography. Both idiopathic RBD and symptomatic RBD are strongly associated with synucleinopathy neurodegenerative diseases, including PD, nonamnestic MCI, DLB, and MSA. Evidence suggests that RBD is likely to represent prodromal synucleinopathy, preceding overt motor, cognitive, or autonomic impairments by years to decades. Melatonin 3 to 12 mg or clonazepam 0.5 to 2.0 mg are the treatments of choice for RBD to reduce the potential for injury. Further evidence regarding the clinical course of RBD and its treatment are needed to clarify its rate of phenoconversion to overt synucleinopathy and to determine a defined time point at which neuroprotective therapies could be offered to prevent or delay more devastating motor, cognitive, and autonomic sequelae of synucleinopathy.

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Abbreviations and Acronyms

DLB	dementia with Lewy bodies
MCI	mild cognitive impairment
MSA	multiple system atrophy
MSQ	Mayo Sleep Questionnaire
PD	Parkinson disease
RBD	rapid eye movement sleep behavior disorder
REM	rapid eye movement
RSWA	rapid eye movement sleep without atonia

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Target Audience

The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need

General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives

On completion of this article, you should be able to (1) recognize rapid eye movement sleep behavior disorder, a potentially injurious parasomnia strongly associated with synucleinopathy neurodegeneration; (2) delineate idiopathic and symptomatic forms of rapid eye movement sleep behavior disorder; and (3) choose efficacious and tolerable treatments for rapid eye movement sleep behavior disorder.

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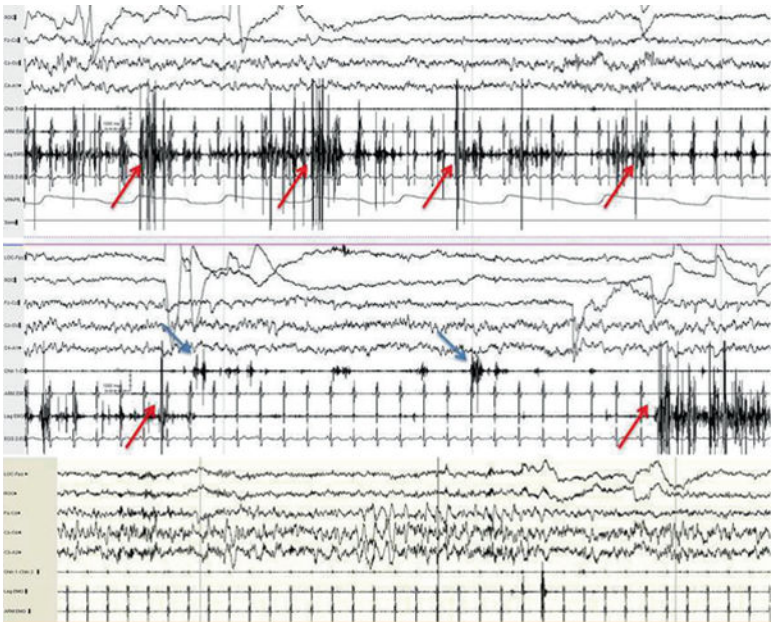

FIGURE 1.

Rapid eye movement (REM) sleep atonia loss, also known as REM sleep without atonia, in a 52-year-old man with REM sleep behavior disorder. Note that the predominant abnormality in the top epoch is excessive phasic/transient muscle activity confined to the anterior tibialis muscle (seventh channel, red arrows) and the middle epoch shows additional activations of abnormal phasic bursting in the submentalis muscle (blue arrows, sixth channel). By contrast, the bottom polysomnogram epoch shows normal REM atonia levels in the chin, leg, and arm muscles (in channels 6-8).

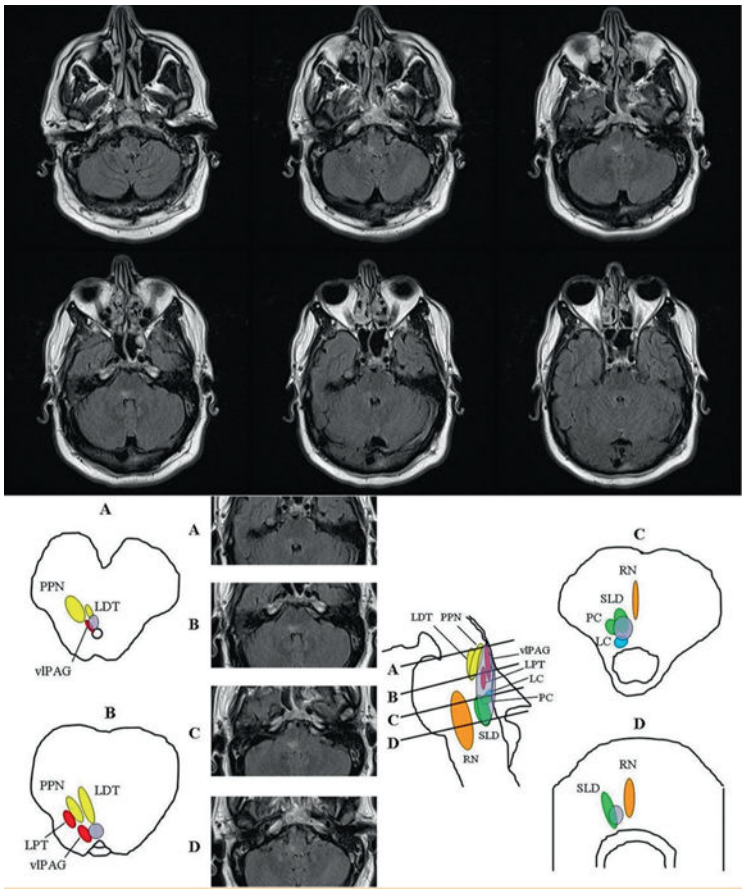

FIGURE 2.

Rapid eye movement (REM) sleep behavior disorder results from a lesion in the neuronal network regulating REM atonia in the dorsal medial pons. A 47-year-old man evolved mononeuritis multiplex with biopsy-proven vasculitis, followed by multiple cranial neuropathies involving the III, IV, VI, VII, IX, and X cranial nerves, and within weeks, he also began exhibiting complex motor behavior during sleep paralleling dream mentation of defense against attack during which he would punch, kick, flail his arms, or stand up in bed. Magnetic resonance imaging of the brain exhibited a hyperintense FLAIR signal abnormality in the dorsal pontomedullary region, neighboring the sublateral dorsal nucleus, which is the “REM-on” center governing REM sleep atonia. A lesion in this area leads to REM sleep atonia loss (REM sleep without atonia), a permissive state for dream enactment and REM sleep behavior disorder. Coronal fluid-attenuated inversion recovery (FLAIR) intensity MRI sections at the level of the medulla and pons show a discrete longitudinally extensive hyperintense lesion at the level of the dorsomedial pons extending rostrally to the right superior pons ventral to the superior cerebellar peduncle. The brainstem nuclei thought to be involved in REM sleep atonia regulation are shown on human brainstem templates. Letters for each template and corresponding MRI FLAIR sections selected from our case represent cross-sectional views through the brainstem as shown in the midsagittal figure, with sections representing (A) the pontomesencephalic junction, (B) the upper/mid pons, (C) the lower/mid pons, and (D) the pontomedullary junction. The approximate location of the lesion is shown in the superimposed pink oval. LC = locus ceruleus; LDT = laterodorsal

tegmental nucleus; LPT = lateral pontine tegmentum; PPN = pedunculopontine nucleus; RN = raphe nucleus; SLD = sublateral dorsal nucleus; vlPAG = ventrolateral part of the periaqueductal gray matter. Reproduced from *Neurology*,[29] with permission from Wolters Kluwer.

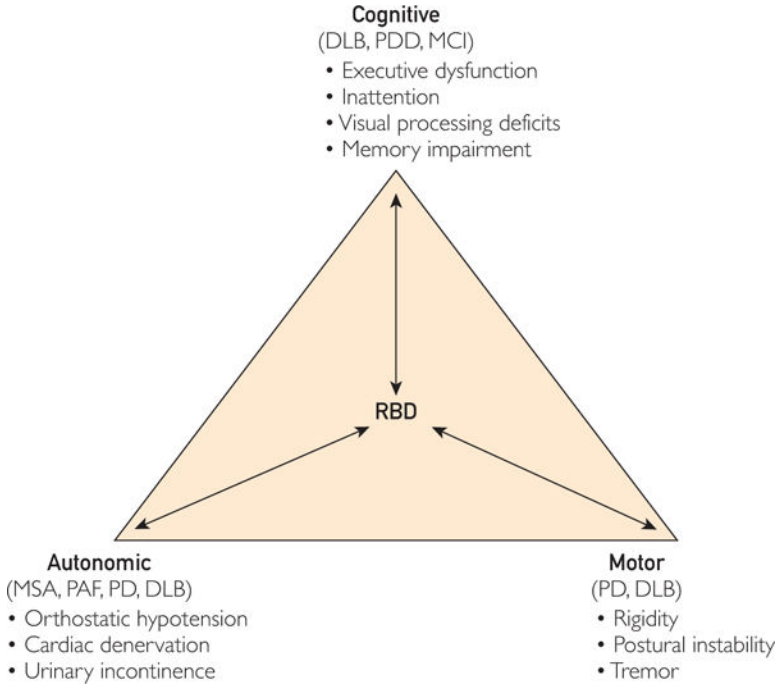

FIGURE 3.

Theoretical model of rapid eye movement sleep behavior disorder (RBD) and its relationship with different clinical manifestations of synucleinopathies. Idiopathic RBD may remain as an isolated syndrome with or without additional cognitive, autonomic, or motor "soft signs" that may or may not evolve toward more definitive, clinically overt, "full-blown" synucleinopathy subtypes of dementia with Lewy bodies (DLB), multiple system atrophy (MSA), Parkinson disease (PD), or PD with dementia (PDD). Patients with parkinsonism and dementia are considered to have PDD if cognitive decline occurs longer than 1 year after the emergence of parkinsonism and DLB if patients present with cognitive decline less than 1 year after the emergence of parkinsonism. Patients with PD and patients without RBD may represent different clinical phenotypes, given different and more severe motor signs, cognitive impairments, and autonomic signs in those with PD compared with those without PD. MCI = mild cognitive impairment; PAF = pure automatic failure. Reproduced from *Sleep Med*,[93] with permission from Elsevier, Inc.

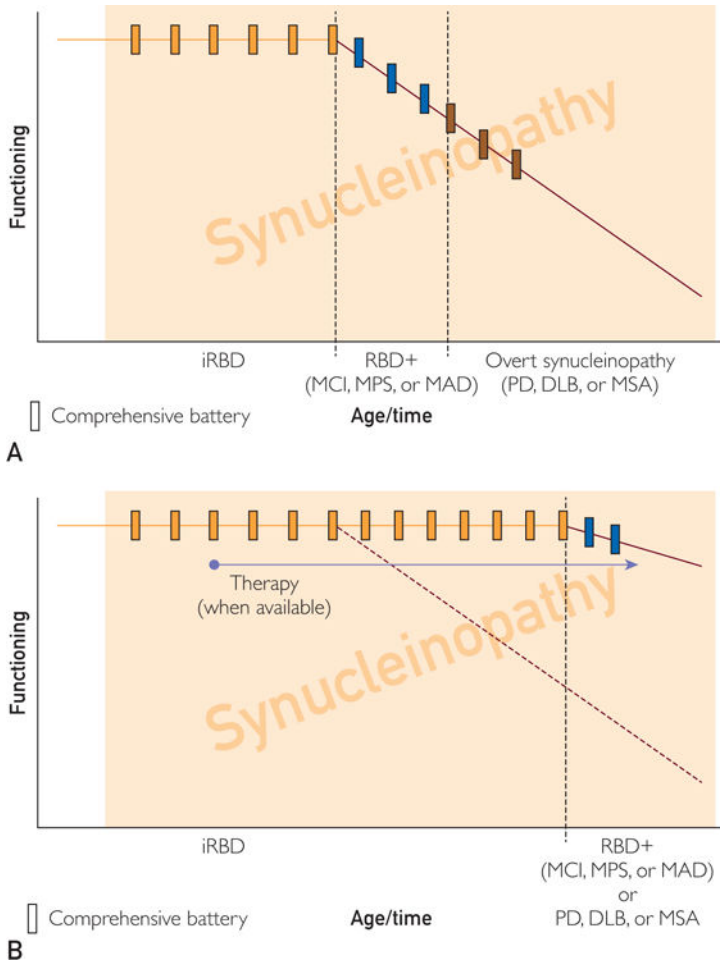

FIGURE 4.

Schematic framework for viewing natural history studies (A) and showing efficacy of disease-modifying therapies (B) in patients with RBD and/or other neurological symptoms and findings. See text for details. DLB = dementia with Lewy bodies; iRBD = idiopathic RBD (RBD without other neurological symptoms or signs); MAD = mild autonomic dysfunction (phase preceding overt MSA); MCI = mild cognitive impairment (phase preceding overt DLB); MPS = mild parkinsonian signs (phase preceding overt PD); MSA = multiple system atrophy; PD = Parkinson disease; RBD = rapid eye movement sleep behavior disorder