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SPECIAL ARTICLES

Management of REM sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline

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Introduction: This guideline establishes clinical practice recommendations for the management of rapid eye movement sleep behavior disorder (RBD) in adults.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths based on a systematic review of the literature and an assessment of the evidence using Grading of Recommendations, Assessment, Development and Evaluation methodology. The task force provided a summary of the relevant literature and the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final recommendations.

Good Practice Statement: The following good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with RBD: It is critically important to help patients maintain a safe sleeping environment to prevent potentially injurious nocturnal behaviors. In particular, the removal of bedside weapons, or objects that could inflict injury if thrown or wielded against a bed partner, is of paramount importance. Sharp furniture like nightstands should be moved away or their edges and headboard should be padded. To reduce the risk of injurious falls, a soft carpet, rug, or mat should be placed next to the bed. Patients with severe, uncontrolled RBD should be recommended to sleep separately from their partners, or at the minimum, to place a pillow between themselves and their partners.

Recommendations: The following recommendations, with medications listed in alphabetical order, are a guide for clinicians in choosing a specific treatment for RBD in adults. Each recommendation statement is assigned a strength ("strong" or "conditional"). A "strong" recommendation (ie, "We recommend … ") is one that clinicians should follow under most circumstances. A "conditional" recommendation (ie, "We suggest … ") is one that requires that the clinician use clinical knowledge and experience and strongly consider the patient's values and preferences to determine the best course of action.

Adult patients with isolated RBD

1. The AASM suggests that clinicians use clonazepam (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)
2. * The AASM suggests that clinicians use immediate-release melatonin (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)
3. * The AASM suggests that clinicians use pramipexole (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)
4. The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the treatment of isolated RBD in adults with mild cognitive impairment. (CONDITIONAL)

Adult patients with secondary RBD due to medical condition

5. * The AASM suggests that clinicians use clonazepam (vs no treatment) for the treatment of secondary RBD due to medical condition in adults. (CONDITIONAL)
6. * The AASM suggests that clinicians use immediate-release melatonin (vs no treatment) for the treatment of secondary RBD due to medical condition in adults. (CONDITIONAL)
7. The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the treatment of secondary RBD due to medical condition (Parkinson disease) in adults. (CONDITIONAL)
8. * The AASM suggests that clinicians **not** use deep brain stimulation (DBS; vs no treatment) for the treatment of secondary RBD due to medical condition in adults. (CONDITIONAL)

Adult patients with drug-induced RBD

9. * The AASM suggests that clinicians use drug discontinuation (vs drug continuation) for the treatment of drug-induced RBD in adults. (CONDITIONAL)

* The Recommendations section of this paper includes remarks that provide additional context to guide clinicians with implementation of this recommendation.

Keywords: REM sleep, REM sleep behavior disorder, parasomnia, dream enactment, sleep disorder, narcolepsy, Parkinson disease, dementia with Lewy bodies

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INTRODUCTION

This clinical practice guideline updates the previously published American Academy of Sleep Medicine (AASM) Best Practice Guide on the treatment of rapid eye movement (REM) sleep behavior disorder[1] and reflects the current recommendations of the AASM.

Under normal physiological conditions, REM sleep is characterized by dream mentation combined with skeletal paralysis. This REM sleep atonia is lost in REM sleep behavior disorder (RBD), resulting in individuals acting out their dreams with potentially violent and injurious behaviors. RBD can have significant consequences on quality of life, including the risk of injury to patients and bed partners.

In 2010, the AASM published a best practice guide for the treatment of RBD.[1] Without placebo-controlled studies for guidance, a consensus was formed based upon case series and small uncontrolled clinical trials. Since 2010, several clinical trials have been conducted regarding the management of RBD among patients with isolated (or idiopathic) RBD, RBD secondary to a medical disorder (most commonly the alpha-synuclein pathologies of dementia with Lewy bodies [DLB], Parkinson disease [PD], and multiple system atrophy), and drug-induced/exacerbated RBD (most commonly selective serotonin reuptake inhibitors). This expansion of the literature on RBD management substantially informed the task force in crafting the clinical practice guideline.

This guideline, in conjunction with the accompanying systematic review,[2] provides a comprehensive update of the available evidence and a synthesis of clinical practice recommendations for the treatment of RBD.

It is intended to optimize patient-centric care by informing clinicians who care for patients with RBD. This clinical practice guideline provides practice recommendations for the management of RBD by identifying treatments that are most effective in specific circumstances (isolated RBD, secondary RBD, drug-induced/exacerbated RBD). However, we recognize that patients often do not segregate neatly across these conditions. Further, a significant degree of overlap frequently occurs, patients may move from one category to another, and appropriate treatments may change or emerge over time. Finally, this guideline provides advice for the counseling and disclosure of neurodegenerative risk for patients with RBD.

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the Grading of Recommendations, Assessment, Development and Evaluation process. The recommendations reflect only those interventions for which there was sufficient evidence to make a recommendation. Interventions for which literature was reviewed but it was determined that insufficient evidence existed to make a recommendation are discussed in the systematic review.[2] "Insufficient evidence" to determine the effectiveness of a particular intervention does not mean that the intervention does not provide benefit but rather that evidence is lacking to guide decision-making. Additional research is needed to determine the effectiveness of these interventions.

METHODS

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in RBD. These clinicians were required to disclose all potential conflicts of interest, per the AASM's conflicts of interest policy, before being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's conflicts of interest policy, TF members with a level 1 conflict were not allowed to participate. TF members with a level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

The TF conducted a systematic review of the published scientific literature, focusing on patient-oriented, clinically relevant outcomes. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material of the accompanying systematic review.[2] The purpose of the review was to determine whether the interventions provided clinically significant improvements in relevant outcomes relative to no treatment. The TF then developed clinical practice recommendations according to the Grading of Recommendations, Assessment, Development and Evaluation process.[3,4] The TF assessed the following 4 components to determine the direction and strength of a recommendation: (1) certainty of evidence, (2) balance of beneficial and harmful effects, (3) patient values and preferences, and (4) resource use. Details of these assessments can be found in the accompanying systematic review.[2] Taking these major factors into consideration, each recommendation statement was assigned a strength ("strong" or "conditional"). Additional information is provided in the form of "Remarks" immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and to guide clinicians in the implementation of the recommendations in daily practice.

This clinical practice guideline reflects the evidence and state of knowledge at the time of the last literature search. Scoping literature searches are performed on all published AASM clinical practice guidelines on an annual basis to review new evidence. Based on this review, updates may be made if there are significant changes in areas such as the available interventions, outcomes of interest (or values placed on outcomes), or evidence of the existing benefits and harms.

GOOD PRACTICE STATEMENT

The following good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with RBD.

It is critically important to help patients maintain a safe sleeping environment to prevent potentially injurious nocturnal behaviors. In particular, the removal of bedside weapons, or objects that could inflict injury if thrown or

wielded against a bed partner, is of paramount importance. Sharp furniture like nightstands should be moved away or their edges and headboard should be padded. To reduce the risk of injurious falls, a soft carpet, rug, or mat should be placed next to the bed. Patients with severe, uncontrolled RBD should be recommended to sleep separately from their partners, or at the minimum, to place a pillow between themselves and their partners.

RECOMMENDATIONS

The recommendations in this guideline were formulated to meet the needs of most patients in most situations. A "strong" recommendation is one that clinicians should follow for almost all patients (ie, something that might qualify as a quality measure). A "conditional" recommendation reflects a lower degree of certainty in the appropriateness of the patient care strategy for all patients. It requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources. The AASM expects this guideline to have an impact on professional behavior, patient outcomes, and—possibly—health care costs.

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the Grading of Recommendations, Assessment, Development and Evaluation process. The implications of the strength of recommendations for guideline users are summarized in **Table 1**. **Table 2** summarizes the recommendations for interventions in adult populations.

Table 1—Implications of strong and conditional recommendations for users of American Academy of Sleep Medicine clinical practice guidelines.

Strong recommendation "We recommend …"	Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.
Conditional recommendation "We suggest …"	Most patients should receive the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine whether the suggested course of action is clinically appropriate and consistent with their values and preferences.

The ultimate judgment regarding the suitability of any specific recommendation must be made by the clinician and the patient.

The task force identified studies reporting evidence for clonazepam, melatonin, and sodium oxybate in the treatment of pediatric patients. However, there was insufficient and inconclusive evidence to make specific treatment recommendations for isolated RBD, secondary RBD due to a medical condition, and drug-induced RBD in pediatric populations.

RECOMMENDATIONS FOR ADULT POPULATIONS

The following are recommendations for the treatment of adults with isolated RBD, secondary RBD due to a medical condition, and drug-induced RBD. Remarks are provided to guide clinicians in the implementation of these recommendations.

Isolated RBD

Recommendations with sufficient evidence for specific interventions for the treatment of isolated RBD in adults are presented below. However, there was insufficient and inconclusive evidence to make recommendations for prolonged-release melatonin, ramelteon, sodium oxybate, paroxetine, and yi-gan san. In addition, zopiclone and agomelatine are not available or approved by the U.S. Food & Drug Administration for use in the United States, so no recommendations for these interventions were made. A summary of the evidence for each intervention can be found in the accompanying systematic review.[2]

Recommendation 1: The AASM suggests that clinicians use clonazepam (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)

Remarks: The age of the patient should be considered in the use and dosing of clonazepam as older patients may be more sensitive to sedating side effects of clonazepam and take longer to metabolize and eliminate the benzodiazepine.

The TF assessed whether clonazepam was effective for the treatment of isolated RBD in adults based on improvements in the frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. The TF identified 50 observational studies assessing the efficacy of clonazepam in patients with isolated RBD. These studies demonstrated clinically significant improvements in the behavioral factor RBD Questionnaire score.

The overall certainty of evidence was low due to the risk of bias associated with observational studies. Across all included studies reporting the use of clonazepam (irrespective of the indication), commonly reported adverse events included daytime sleepiness, dizziness, cognitive impairment, and postural instability. Based on their clinical expertise, the members of the TF determined that the benefits of clonazepam use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of clonazepam. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment. The majority of patients would most likely use clonazepam compared to no treatment for their isolated RBD.

Recommendation 2: The AASM suggests that clinicians use immediate-release melatonin (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)

Table 2—Summary of recommended interventions in adult populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*		
		RBD Symptoms	RBDQ Score† (behavioral)	RBD Frequency‡
Isolated RBD				
Clonazepam	Conditional for	✓	✓	
Melatonin (immediate-release)	Conditional for	✓		✓
Pramipexole	Conditional for	✓		✓
Rivastigmine	Conditional for			✓
Secondary RBD due to medical condition				
Clonazepam	Conditional for	✓		
Melatonin (immediate-release)	Conditional for	✓		✓
Rivastigmine	Conditional for			✓
DBS	Conditional against	X		
Drug-induced RBD				
Drug discontinuation	Conditional for	✓		

*✓ = critical outcomes showing clinically significant improvement. X = critical outcomes not showing clinically significant improvement. Blank cells = no reported data for this critical outcome. †RBDQ = RBD Questionnaire (includes Korean, Japanese, and Hong Kong versions). ‡RBD frequency = the rate of RBD symptoms over a period of time. DBS = deep brain stimulation, RBD = rapid eye movement sleep behavior disorder.

Remarks: As melatonin is not regulated by the U.S. Food & Drug Administration in the United States and several other jurisdictions, different formulations could potentially lead to varying efficacy between different melatonin brands. Melatonin labeled with the U.S. Pharmacopeia Verification Mark have been confirmed to contain the amounts of melatonin stated on the label and may provide the most consistent dosing among currently available melatonin treatment options.

The TF assessed whether immediate-release melatonin was effective for the treatment of isolated RBD in adults based on improvements in the frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. The TF identified 1 randomized controlled trial and 9 observational studies that assessed the efficacy of immediate-release melatonin in patients with isolated RBD. These studies demonstrated clinically significant improvements in RBD dream enactment and vocalization episode frequency.

The overall certainty of evidence was low due to imprecision and the risk of bias associated with observational studies. Across all included studies reporting the use of immediate-release melatonin (irrespective of the indication), commonly reported adverse events included daytime sleepiness, headache, trouble thinking, and nausea. Based on their clinical expertise, the TF members determined that the benefits of immediate-release melatonin use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was strongly in favor of immediate-release melatonin. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment during sleep. The vast majority of patients would most likely use immediate-release melatonin compared to no treatment for their isolated RBD.

Recommendation 3: The AASM suggests that clinicians use pramipexole (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)

Remarks: Pramipexole appears to be most effective among patients with RBD with elevated periodic limb movements noted on polysomnography (PSG), suggesting that its efficacy may be secondary to addressing ancillary motor activity.

The TF assessed whether pramipexole was effective for the treatment of isolated RBD in adults based on improvements in the frequency and/or intensity of dream enactment episodes. The TF identified 7 observational studies assessing the efficacy of pramipexole in patients with isolated RBD. These studies demonstrated clinically significant improvements in RBD frequency and simple/complex motor behavior frequency.

The overall certainty of evidence was very low due to imprecision and the risk of bias associated with observational studies. Across all included studies reporting the use of pramipexole (irrespective of the indication), commonly reported adverse events included next-day hangover, gastrointestinal symptoms, and negative impulsive behavior. In addition, the use of daily pramipexole in individuals with restless legs syndrome (RLS) can result in the augmentation of RLS symptoms over time. The TF determined that the benefits of pramipexole use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of pramipexole. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment during sleep. The majority of patients would most likely use pramipexole compared to no treatment for their isolated RBD.

Recommendation 4: The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the

treatment of isolated RBD in adults with mild cognitive impairment (MCI). (CONDITIONAL)

The TF assessed whether rivastigmine was effective for the treatment of isolated RBD in adults based on improvements in the frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. The TF identified 1 randomized controlled trial assessing the efficacy of transdermal rivastigmine in patients with RBD and mild cognitive impairment and who were refractory to conventional therapy. This study demonstrated clinically significant improvements in RBD frequency.

The overall certainty of evidence was moderate due to imprecision. Across all included studies reporting the use of rivastigmine (irrespective of the indication), the most common adverse events leading to withdrawal were hypotension and asthenia; other commonly reported adverse events included daytime sleepiness and nausea. Based on their clinical expertise, the members of the TF determined that the benefits of rivastigmine use in patients with mild cognitive impairment outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of rivastigmine. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment during sleep. The majority of patients with RBD with MCI would most likely use rivastigmine compared to no treatment for their isolated RBD.

Secondary RBD due to medical condition

Recommendations with sufficient evidence for specific interventions for the treatment of secondary RBD due to a medical condition in adults are presented below. Alpha-synuclein pathologic neurologic disorders, in particular DLB and PD, are the most common associated conditions with RBD and as such were the most common associated conditions reported by studies that were reviewed by the TF. The TF considered separate recommendations for individual disorders; however, treatment data were lacking for specific conditions as most studies aggregated patient populations. There was insufficient and inconclusive evidence to make recommendations for prolonged-release melatonin, ramelteon, pramipexole, rotigotine, carbidopa-levodopa, sodium oxybate, positive airway pressure therapy, donepezil, yi-gan san, memantine, intravenous immunoglobulin, cannabidiol, and light therapy among individuals with RBD due to a medical condition. In addition, zopiclone, tiapride, and nelotanserin are not available or approved by the U.S. Food & Drug Administration for use in the United States, so no recommendations for these interventions were made. A summary of the evidence for each intervention can be found in the accompanying systematic review.[2]

Recommendation 5: The AASM suggests that clinicians use clonazepam (vs no treatment) for the treatment of secondary RBD due to a medical condition in adults. (CONDITIONAL)

Remarks: The nature of the patients' medical condition, their age, and their risk for clonazepam-induced sedation and imbalance should be considered in the use and dosing of clonazepam. Older patients may be more sensitive to sedating side effects of clonazepam and take longer to metabolize and eliminate the benzodiazepine.

The TF assessed clonazepam as a treatment of secondary RBD due to a medical condition in adults based on improvements in the frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. The TF identified 1 randomized controlled trial and 38 observational studies assessing the efficacy of clonazepam in patients with secondary RBD due to a medical condition, most commonly PD but also DLB. These studies demonstrated clinically significant improvements in RBD symptoms.

The overall certainty of evidence was low due to the risk of bias associated with observational studies. Across all studies reporting the use of clonazepam (irrespective of the indication), commonly reported adverse events included daytime sleepiness, dizziness, and postural instability. Based on their clinical expertise, the TF members determined that the benefits of clonazepam use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of clonazepam. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment. The majority of patients would most likely use clonazepam compared to no treatment for their secondary RBD due to a medical condition.

Recommendation 6: The AASM suggests that clinicians use immediate-release melatonin (vs no treatment) for the treatment of secondary RBD due to a medical condition in adults. (CONDITIONAL)

Remarks: As melatonin is not regulated by the U.S. Food & Drug Administration in the United States and several other jurisdictions, different formulations could potentially lead to varying efficacy between different melatonin brands. Melatonin labeled with the U.S. Pharmacopeia Verification Mark have been confirmed to contain the amounts of melatonin stated on the label and may provide the most consistent dosing among currently available melatonin treatment options.

The TF assessed whether immediate-release melatonin was effective for the treatment of secondary RBD due to a medical condition in adults based on improvements in the frequency and/or intensity of dream enactment episodes. The TF identified 1 randomized controlled trial and 9 observational studies assessing the efficacy of immediate-release melatonin in patients with secondary RBD due to a medical condition, most commonly PD. These studies demonstrated clinically significant improvements in RBD dream-acting and vocalization episode frequency.

The overall certainty of evidence was low due to imprecision and the risk of bias associated with observational studies. Across all studies reporting the use of immediate-release melatonin (irrespective of the indication), commonly reported adverse events included daytime sleepiness, headache, trouble thinking, and nausea. Based on their clinical expertise, the members of the TF determined that the benefits of immediate-release melatonin use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of immediate-release melatonin. The costs of the medication are relatively small compared to the potential high cost of injury due to dream enactment during sleep. The vast majority of

patients would most likely use immediate-release melatonin compared to no treatment for their secondary RBD due to a medical condition.

Recommendation 7: The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the treatment of secondary RBD due to a medical condition (PD) in adults. (CONDITIONAL)

The TF assessed whether rivastigmine was effective for the treatment of secondary RBD due to a medical condition in adults based on improvements in the frequency and/or intensity of dream enactment episodes. The TF identified 1 randomized controlled trial testing transdermal rivastigmine assessing the efficacy of rivastigmine in patients with secondary RBD due to a medical condition, in this case PD. This study demonstrated clinically significant improvements in RBD episode frequency.

The overall certainty of evidence was moderate due to imprecision. Across all studies reporting the use of rivastigmine (irrespective of the indication), adverse events leading to withdrawal were hypotension and asthenia; other commonly reported adverse events included daytime sleepiness and nausea. Based on their clinical expertise, the TF members determined that the benefits of transdermal rivastigmine use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects was in favor of rivastigmine. The costs of the medication may be higher than those of clonazepam or melatonin; however, they are relatively small compared to the potential high cost of injury due to dream enactment during sleep. The majority of patients would most likely use rivastigmine compared to no treatment for their secondary RBD due to a medical condition (PD).

Recommendation 8: The AASM suggests that clinicians not use DBS (vs no treatment) for the treatment of secondary RBD due to a medical condition in adults. (CONDITIONAL)

Remarks: This recommendation is based solely on the effects of DBS on secondary REM sleep behavior disorder. It does not apply to the use of DBS in the treatment of motor symptoms of PD.

The TF assessed DBS as a treatment of secondary RBD due to a medical condition in adults based on improvements in the frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. The TF identified 4 observational studies assessing the efficacy of DBS in patients with secondary RBD due to a medical condition. These studies demonstrated no clinically significant improvements in RBD symptoms.

The overall certainty of evidence was low due to the risk of bias associated with observational studies. Across all studies reporting the use of DBS (irrespective of the indication), increased periodic limb movements were reported in 2 patients. Other commonly reported adverse events included depression, memory impairment, seizures, anxiety, agitation, confusion, dizziness, abnormal movements, pain at implant site, paresthesias, and hardware complications. Based on their clinical expertise, the members of the TF determined that the risks and adverse events of DBS use in patients outweighed the benefits and that the balance between the desirable and undesirable effects was in favor of no treatment. The costs of DBS surgery are high. The vast majority of patients would most likely not use DBS for their secondary RBD due to a medical condition.

Drug-induced RBD

Recommendations with sufficient evidence for specific interventions for the treatment of drug-induced RBD in adults are presented below. There was insufficient and inconclusive evidence to make a recommendation for clonazepam. A summary of the evidence for each intervention can be found in the accompanying systematic review.[2]

Recommendation 9: The AASM suggests that clinicians use drug discontinuation (vs drug continuation) for the treatment of drug-induced RBD in adults. (CONDITIONAL)

Remarks: Careful consideration should be given to the severity of comorbid conditions for which the inciting drug is taken and the consequences of eliminating treatment before drug discontinuation for drug-induced RBD in adults.

The TF assessed whether drug discontinuation was effective for the treatment of drug-induced RBD in adults based on improvements in the frequency and/or intensity of dream enactment episodes. The TF identified 5 observational studies assessing the efficacy of drug discontinuation in patients with drug-induced RBD. These studies demonstrated clinically significant improvements in RBD symptoms, and no comorbid disorders were reported to have worsened when the inciting drug agent was discontinued.

The overall certainty of evidence was very low due to imprecision and the risk of bias associated with observational studies. The TF determined that the harmful effects of drug discontinuation may vary, based on the potential secondary effects that could be unmasked when discontinuing the drug, especially certain antidepressants. The TF concluded that the balance between the desirable and undesirable effects of stopping drug therapy may vary depending on the medication being discontinued and the type of patient population being treated. As a result, the TF concluded that the difference in resource use between drug discontinuation and no treatment may vary, due to the associated costs involved with the withdrawal of the inciting agent. In addition, the TF determined that there was variability on whether patients would use drug discontinuation for their drug-induced RBD, depending on the type of drug that was being discontinued and the specific clinical scenario for the patient.

DISCUSSION

The behaviors of RBD widely vary from night to night and over time in the same individual and between patients. Contrary to the classic descriptions of RBD necessarily causing complex, dangerous dream-enactment episodes, the majority of movements in RBD are discrete and seemingly benign and may thus remain unnoticed for months to years. These movements are small twitches and brief jerks primarily affecting the extremities, occurring every few seconds to every few minutes, and they may not be related to specific dream contents. However,

complex and potentially dangerous behaviors related to dream enactment can occur at any time on a given night or during the course of the disorder, which can be distressing and difficult to explain to bed partners, family, and clinicians. It is not unusual for patients with RBD to wonder whether they may be dealing with a psychological condition. On the contrary, research has shown that RBD manifestations and the dream mentation that patients may recall are largely independent of the individual's daytime personality.[5] For individuals without RBD, bizarre dream mentation is masked by the REM sleep atonia. Notably, RBD is common, afflicting 80 million patients worldwide, with age being the greatest risk factor. Community survey data suggest that approximately 1 in 20 older individuals may have RBD.[6,7]

Helping patients to understand the nature of REM sleep and how dream enactment can be unleashed is a critical first step. Insight helps patients address the distress that can occur on awakening from a dream enactment episode and explain the nature of their condition to concerned family members, maintain treatment strategies even when dangerous dream enactment is sporadic, and adhere to long-term neurologic disease monitoring.

Sleeping safely is challenging in RBD, as any patient can intermittently have violent episodes of dream enactment. It is important to secure the bedroom environment to reduce the risk of injury to the patient or bed partner, such as lowering the bed mattress, padding the corners of the furniture, installing window protection, and keeping a barrier between the patient and bed partner in the bed or having the bed partner sleep in a separate bed. Seemingly benign objects, such as bedside lamps, can be weaponized during dream enactment as patients may swing or hurl them across the bedroom. Of paramount importance is the removal of loaded firearms and in particular handguns, as they can be discharged during a dream enactment episode. When violent dream enactment persists despite these interventions or in situations with a high risk for injury, pharmacotherapy can be considered (see **Table 2** [summary of recommended interventions]).

Isolated RBD

Patients with isolated RBD have an emergence of dream enactment, along with a PSG-documented elevation in REM sleep motor tone, in the absence of a clear underlying disorder or inciting substance or medication. Patients with isolated RBD tend to be older than individuals with drug-induced RBD or narcolepsy and younger than individuals with DLB or PD.[8–10]

Because the natural history of RBD is typically relentless and lifelong, patients with isolated RBD can be expected to require treatment for years to decades.

We are making conditional recommendations for the use of 4 agents in the treatment of isolated RBD: clonazepam, immediate-release melatonin, pramipexole, and rivastigmine. Head-to-head studies comparing their effectiveness have not been performed; thus, customizing therapy for patients is based upon each agent's unique mechanism of action and therapeutic profile and a patient's comorbidities.

As a long-acting benzodiazepine, clonazepam promotes GABAergic inhibition by increasing the frequency of chloride channel opening. It has been the most commonly prescribed medication for RBD since its efficacy was described in the original 1986 report characterizing RBD.[11] Clonazepam reduces dream enactment, with only minimal reduction in REM sleep motor tone on PSG. Most patients initially respond well to low doses (0.25–1.0 mg) administered at bedtime. Higher doses may be considered in the absence of response if well tolerated. It is considered a controlled substance by most governmental regulating bodies and typically restricted to prescription only. Some patients may be hesitant to start clonazepam due to the negative stigma of benzodiazepines. Clonazepam is listed on the American Geriatrics Society Beers Criteria list of potentially inappropriate medications in older adults.[12]

Melatonin binds to the M1 and M2 receptors, suppressing REM sleep motor tone and renormalizing other circadian features of REM sleep. Under normal physiological conditions, the duration of REM sleep episodes and the frequency of rapid eye movements (REMs index) increase over the sleep period. Both of these findings are lost in RBD as patients show no such evolution of REM sleep duration or REMs index. These circadian markers of REM sleep desynchrony along with the REM sleep motor activity and dream enactment are improved with exogenous melatonin in patients with RBD. Consistent with melatonin's treatment of known circadian rhythm disorders, such as delayed sleep phase syndrome and jet lag, improvements in symptoms persist for several days after melatonin is discontinued but then gradually reemerge over the next several weeks.[13] The starting dose of immediate-release melatonin (prolonged-release melatonin had insufficient evidence to make a recommendation) in isolated RBD is usually 3 mg taken at bedtime. The dose may be titrated up to address dream enactment in 3-mg increments to 15 mg; data on higher dosing are not available. Melatonin is considered a dietary supplement and is available over the counter in the United States and Canada. However, as supplements are subject to fewer governmental regulations and scrutiny, melatonin's bioavailability and content may be less consistent across formulations, although the U.S. Pharmacopeia Verification Mark indicates that a supplement has been verified to contain the stated dose on the package label. Melatonin requires a prescription in the European Union and the United Kingdom.

Combination therapy using clonazepam and melatonin is common in clinical practice if response to monotherapy is inadequate. While there was enough evidence to make recommendations for clonazepam and melatonin monotherapies, there is a paucity of data examining combination therapies.

Pramipexole is a dopaminergic agonist typically used to treat the motor symptoms of PD, RLS, and periodic limb movement disorder. Its mechanism of efficacy in RBD is uncertain because RBD is not caused by dopaminergic dysfunction. Note that patients with RBD who respond to pramipexole often have increased periodic limb movements on PSG; thus, it is possible that pramipexole helps reduce ancillary motor activity. Conversely, pramipexole may reduce dream enactment by treating an underlying sleep-fragmenting condition, periodic limb movement disorder.[14] Dosing typically starts at 0.125 mg administered orally at bedtime and can be increased, slowly, to 2.0 mg nightly.

Adverse effects of dopaminergic agonists include nausea, orthostasis, headache, daytime sleepiness, impulse control disorder, and augmentation (treatment-induced worsening of RLS symptoms). Its use is restricted by most governmental regulating bodies to prescription only.

Rivastigmine is an acetylcholinesterase inhibitor that increases cholinergic effects by blocking the enzymatic degradation of acetylcholine. It has been shown to decrease the frequency of dream enactment in adults with MCI and treatment-resistant RBD.[15] Rivastigmine is typically administered by transdermal patch. Dosing typically starts at 4.6 mg applied every 24 hours and can increase to 13.3 mg daily. Although rivastigmine can reduce RBD symptoms associated with MCI, its efficacy in isolated RBD without MCI is still unknown. Adverse effects of rivastigmine include skin irritation, nausea, vomiting, headache, and bradycardia. Its use is restricted by most governmental regulating bodies to prescription only.

It may be expected that a patient's required dose for efficacy and the avoidance of disabling side effects will decrease over time as a function of age-related changes in drug metabolism or progression of neurologic disease. For example, a patient taking 1.0 mg of oral clonazepam at age 55 years may experience more substantial sedation at age 70 years, requiring a decrease to 0.5 mg. Notably, because patients with isolated RBD are at high risk for the development of neurodegenerative disorders, most commonly DLB or PD, they require careful monitoring for cognitive, motor, and autonomic deficits (see section below, "Prognosis and Counseling"). As patients with isolated RBD progress, they will often demonstrate subtle, cryptic signs that do not meet criteria for parkinsonism or cognitive impairment but nonetheless complicate medication management.[16,17] For example, a small degree of postural instability on examination may be unnoticed by the patient during the day but when combined with a sedating agent can lead to falls when taking a few steps to the bathroom at night.

We recognize that medication costs are often substantial and especially relevant in the setting of isolated RBD where treatment is expected to be long-term. The costs of these agents vary dramatically. Immediate-release melatonin and clonazepam are typically relatively inexpensive, with increasing costs for pramipexole and rivastigmine.

Secondary RBD due to a medical condition

Patients with secondary RBD have an emergence of dream enactment, along with PSG-documented elevation in REM sleep motor tone, in the presence of a clear underlying disorder, most commonly either an alpha-synuclein disorder such as DLB/PD or in the setting of type 1 narcolepsy (a disorder of orexin deficiency). Secondary RBD in the setting of DLB/PD is more likely to occur in older patients (> 50 years old), while those with narcolepsy are more likely to present as young adults and adolescents.[16,17]

We are making conditional recommendations for the use of 3 agents in the treatment of secondary RBD: clonazepam, immediate-release melatonin, and rivastigmine. While each agent met a threshold for clinical significance, their comparable effectiveness is uncertain without head-to-head clinical trials.

When choosing a medication, clinicians should consider the patient's underlying disease and attendant symptoms, because patients with neurodegenerative disorders frequently experience other symptoms affecting motor function, cognitive domains, and the autonomic system (eg, orthostatic hypotension) along with sleep (insomnia, nocturnal episodes of confusion or hallucinations, RLS) and daytime alertness.

Concerning side effects of clonazepam include morning sedation, gait imbalance/falls, depression, and cognitive disturbances, specifically delirium and amnesia. Clonazepam can also exacerbate sleep-disordered breathing. Among patients with secondary RBD and DLB, PD, or other neurodegenerative disease, clonazepam is often used in lower doses, starting at 0.25 mg. However, progressive cognitive decline combined with age-related impairments in drug metabolism often leads to gradual intolerance. In addition, the stigma of benzodiazepines may lead to a hesitancy to start clonazepam. Clonazepam is listed on the American Geriatrics Society Beers Criteria list of potentially inappropriate medications in older adults.[12]

Melatonin is an intriguing option for older patients (> 50 years old) and those with neurodegenerative disease because it is only mildly sedating. Other side effects include vivid dreams and sleep fragmentation, which only rarely result in discontinuation. Dosing of immediate-release melatonin to address dream enactment in secondary RBD is similar to that in isolated RBD, starting with 3 mg and increasing by 3-mg increments to 15 mg.

Rivastigmine, an acetylcholinesterase inhibitor, is commonly employed in the treatment of DLB and PD dementia. The most notable side effects include site reaction, gastrointestinal symptoms of nausea and diarrhea, bradycardia, and, based on the reviewed evidence in secondary RBD, possible excessive daytime sleepiness in this patient population. Considering its indication among patients with dementia, rivastigmine may be an appropriate choice for patients with RBD and cognitive impairment refractory to other treatments.

We also chose to make a conditional recommendation against the use of DBS in the treatment of secondary RBD. DBS of the subthalamic and globus pallidus interna nuclei is commonly employed to improve motor symptoms in patients with PD. Targeting these regions has not demonstrated improved control of dream enactment among patients with PD with RBD.

Note that several treatments we reviewed were aimed at treating an underlying disease often associated with RBD. These included sodium oxybate for narcolepsy (in children and adults) and intravenous immunoglobulin for autoimmune encephalopathy. While these therapies did not meet the threshold for recommendation therapy in this clinical practice guideline, they may be considered under the appropriate clinical context rather than solely for RBD.

Drug-induced/exacerbated RBD

Patients with drug-induced/exacerbated RBD (5-hydroxytryptamine or 5-HT RBD) have an emergence of dream enactment, along with PSG-documented elevation in REM sleep motor tone, after starting or increasing a dose of medication, most commonly a serotonergic antidepressant, such as a selective serotonin reuptake inhibitor.[8] Patients with 5-HT RBD are typically young

adults. Along with narcolepsy, drug-induced/exacerbated RBD is the most common etiology for RBD in patients younger than age 50 years.[9]

We are making a conditional recommendation for drug discontinuation in drug-induced/exacerbated RBD if it is safe to do so. Decreasing or discontinuing a selective serotonin reuptake inhibitor may improve, but often does not fully eliminate, a patient's dream enactment, and it may take several months for improvement. In patients in whom dream enactment persists after discontinuing the exacerbating agent, we recommend diagnosing the patients with either isolated RBD or secondary RBD (if there is a clear underlying disorder) and treating accordingly. Among patients with 5-HT RBD taking serotonergic antidepressants who still require antidepressant therapy, many do well on an agent with a lower serotonergic profile such as bupropion.[18] Changes to antidepressant therapy should be carefully discussed with the prescribing provider. Notably, no studies investigated the time between initiation of the inciting agent and the emergence of RBD manifestations. It may be expected that RBD would emerge within a generally short time frame after initiation of an inciting agent (ie, weeks or months, not years). The risks and benefits of discontinuing a drug known to induce RBD that has been taken uneventfully for a prolonged period of time should be carefully assessed.

Establishing expectations

Bed partners and family members should know that among patients with RBD, even those on medical treatment, some degree of dream enactment and vocalization is often inevitable. Unfortunately, these behaviors can disrupt the sleep of bed partners, and sleep talking can quickly escalate to shouting expletives. However, as long as dream enactment is noninjurious, escalating pharmacotherapy is usually unwarranted because more aggressive or sedating pharmacotherapy is often futile and dangerous, increasing the risk of nighttime falls and daytime sleepiness. It is difficult to predict future sleep-related injury; therefore, ongoing monitoring is crucial to assess the severity of dream enactment and treatment efficacy and to explore whether bed partners should be sleeping separately.

Prognosis and counseling

One of modern medicine's most profound challenges is to help patients adapt to the ever-expanding discovery of preclinical and prodromal syndromes. The discovery that RBD is linked to neurodegenerative diseases can be anguishing for patients and families. We believe clinicians should, if the patient desires, tactfully and expeditiously discuss the relationship and provide the patient with a customized risk assessment.

Ancillary, nonsleep symptoms linked to alpha-synuclein pathology, such as hyposmia (difficulty smelling), slowed bowel motility, and orthostasis, are historical clues helpful for stratifying patient risk. When these chronic symptoms coexist with RBD, they are strong predictors of phenoconversion in less than 5 years. Conversely, the absence of these symptoms, along with the presence of a serotonergic antidepressant (5-HT RBD), is associated with a lower risk of developing a neurodegenerative disorder in the next 5 years.[19]

Prognostic counseling for those with isolated RBD is important; however, disclosure of neurodegeneration risk presents ethical dilemmas. Disclosure may help patients plan for the future, have follow-up monitoring for phenoconversion, and participate in research. However, given the current lack of neuroprotective treatments to slow or halt disease progression, disclosure may result in anxiety, depression, and even suicidality for a disease that may take years to manifest and may not occur in the patient's lifetime. On the other hand, not providing disclosure risk may harm the provider–patient relationship, as patients may discover the relationship through other sources such as an internet search. Providers need to balance the ethical principles of autonomy (the patient's right to know or not know), beneficence (acting in the patient's best interest), and nonmaleficence (provider's responsibility to do no harm). While there are limited data on provider practice and attitudes on disclosure, there are no data on patient attitudes in isolated RBD to guide the disclosure process. Pending such guidance, we present 2 general approaches below, based upon the TF's unanimous consensus: patient-centered risk disclosure and watchful waiting.

After a diagnosis has been made, the provider should explore the patient's knowledge about isolated RBD and ask the patient about any desire to know its relationship to other conditions. Depending on how much the patient wants to know, the provider can then discuss the neurodegenerative diseases, their courses and treatments, risk stratification, and life planning, and then establish a follow-up plan to monitor for phenoconversion.

The benefits of this approach include giving the patient time for advanced-care planning, arranging care, and retirement planning. In addition, many patients with RBD appreciate the opportunity to participate in clinical research and are empowered by contributing to the scientific search for the cure for PD (and related disorders). Sleep clinicians can facilitate research by providing patients with RBD with contact information for RBD research groups such as the North American Prodromal Synucleinopathy consortium (https://www.naps-rbd.org/), the Parkinson's Progression Markers Initiative (https://www.ppmi-info.org/), and the International RBD Study Group (https://www.irbdsg.com/).

The watchful waiting approach, with a temporary delay in disclosure, may be appropriate in some situations, such as in the setting of severe, active psychiatric illness. This approach should be engaged in on a case-by-case, patient-centered basis, with the provider readdressing the topic at subsequent visits. Ultimately, clinicians need a framework to consider the ethical implications of caring for patients with prodromal neurodegenerative disease. As a model, we suggest the American Academy of Neurology's position statement, "Ethical Considerations in Dementia Diagnosis and Care."[20]

Ultimately, clinicians can help patients view their disorder with a degree of cautious, useful optimism. After an adjustment process, the vast majority of patients with RBD handle their new prognosis well. Many patients find motivation to pursue healthy lifestyle modifications, in particular aerobic exercise, which preliminary investigations have suggested may be neuroprotective.[21] Finally, a diagnosis of RBD itself can be a catalyst for patients to embrace life's joys and have a newfound appreciation for brain function.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
DBS, deep brain stimulation
DLB, dementia with Lewy bodies
MCI, mild cognitive impairment
PD, Parkinson disease
PSG, polysomnography
RBD, rapid eye movement sleep behavior disorder
REM, rapid eye movement
RLS, restless legs syndrome
TF, task force
5-HT RBD, 5-hydroxytryptamine (serotonergic) RBD

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