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REVIEW ARTICLES

Management of REM sleep behavior disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment

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This systematic review provides supporting evidence for a clinical practice guideline for the management of rapid eye movement (REM) sleep behavior disorder in adults and children. The American Academy of Sleep Medicine commissioned a task force of 7 experts in sleep medicine. A systematic review was conducted to identify randomized controlled trials and observational studies that addressed interventions for the management of REM sleep behavior disorder in adults and children. Statistical analyses were performed to determine the clinical significance of critical and important outcomes. Finally, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence for making recommendations. The literature search identified 4,690 studies; 148 studies provided data suitable for statistical analyses; evidence for 45 interventions is presented. The task force provided a detailed summary of the evidence assessing the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.

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

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INTRODUCTION

This systematic review is intended to provide supporting evidence for the accompanying clinical practice guideline[1] on the management of rapid eye movement (REM) sleep behavior disorder and update the evidence review conducted for the previously published American Academy of Sleep Medicine (AASM) Best Practice Guide.[2]

BACKGROUND

REM sleep is characterized by vivid dream mentation in the setting of near-complete skeletal muscle paralysis, sparing the diaphragm and extraocular muscles through brainstem-induced skeletal muscle atonia. REM sleep facilitates the maturation of brain circuits, especially during early development, and REM sleep motor paralysis confers motor quiescence despite the activation of emotional salient, complex, and often violent, memory traces.[3,4]

REM paralysis is the end result of an intricate and vulnerable pathway, primarily localized in the dorsal pons and medulla, with descending inhibitory tone on the spinal motoneurons. When pathology disrupts these brainstem pathways, descending motor signals are no longer blocked and patients enact dreams, resulting in REM sleep behavior disorder (RBD). RBD behaviors, consistent with the spectrum of dream mentation, range from simple hand gestures to aggressive and violent dream enactment semiology with episodes that may consist of shouting, thrashing, punching, and kicking. These more-pronounced behaviors can result in injury to the patient or bed partner.[3,4]

RBD is a parasomnia characterized by increased muscle tone in REM sleep accompanied by abnormal limb movements, vocalizations, and dreams. Loss of skeletal atonia normally present in REM sleep permits an individual with RBD to talk and move when dreaming. Vocalizations, jerks, and complex motor behaviors occur during REM sleep, often associated with REM sleep dream content. The clinical presentation ranges from unnoticed sleep disruption to severe injuries to patients/bed partners.

RBD is common, with a 1% prevalence affecting approximately 80 million people worldwide, and is most common (5%) among older adults.[5,6] Injuries result when patients with vigorous limb movements hit a wall, window, object, or bed partner when reacting toward an imaginary threat. Falls out of bed are common, as dreamers will suddenly arise and leap out from bed.

Complex motor behaviors during sleep are not unique to RBD and must be differentiated from non-REM (NREM) parasomnias, such as sleepwalking and sleep terrors.[3,4] In addition,

arousals out of REM sleep from sleep-disordered breathing can result in dream enactment (pseudo-RBD) and periodic limb movements can also mimic RBD. Finally, sleep-related epilepsy can manifest with recurrent, abnormal complex nocturnal motor activity and behaviors. As REM sleep occurs predominantly during the second half of the night, RBD events usually arise in the final hours of the sleep period, often immediately prior to patients awakening for the day. REM sleep is characterized by a low threshold for arousal, accounting for the observation that patients with RBD typically orient quickly after an episode and are usually able to provide a detailed and elaborate narrative of the dream content that correlates with the witnessed behaviors. For example, a patient may be described by a bed partner as shouting and kicking vigorously. When awoken the patient may say they were trying to stomp on a poisonous snake that was trying to bite them. This is in contrast to disorders of arousal that emanate out of deep NREM sleep, where patients are often confused, difficult to arouse, and amnestic to the event. Paradoxically, the disruption of REM motor tone does not appear to culminate in clear daytime dysfunction, except for traumatic injuries, as patients with RBD typically do not describe excessive daytime sleepiness or insomnia. Rather, insomnia or daytime sleepiness is reported by bed partners, whose sleep is often fragmented and unrefreshing as they may lay awake anxious about their safety and for their partner's well-being.

RBD is most often caused by alpha-synuclein neurodegeneration, characterized by abnormal accumulation of aggregates of alpha-synuclein protein in neurons. Early in the course of these disorders, the pathology may originate in the enteric plexus of the gut (leading to constipation) where, over several years, it slowly ascends rostrally through the vagus nerve and later through the brainstem to the dopamine-producing basal ganglia and, ultimately, the cerebral cortex. Lurching neuron to neuron, alpha-synuclein pathology relentlessly spreads through REM sleep generators in the pons, disabling the protective mechanism promoting REM skeletal muscle atonia.[3,7]

Thus, RBD most often represents a prodromal syndrome, manifesting as dream enactment prior to the phenoconversion into dementia with Lewy bodies (DLB), Parkinson's disease (PD), or other neurodegenerative disorder. Most people with RBD phenoconvert slowly over years and sometimes decades as patients slowly evolve from subtle symptoms of anosmia (loss of sense of smell), constipation, orthostasis, and dream enactment to motor symptoms and cognitive dysfunction, once the alpha-synuclein pathology reaches the rostral brainstem and cerebral cortex. Ultimately, most people with RBD develop a neurodegenerative disorder. A recent investigation of over 1,200 individuals with RBD indicated a 74% phenoconversion rate to a neurodegenerative disorder within 12 years.[8]

While neurodegeneration is the most common etiology, RBD may be encountered in the setting of other neurological disturbances. These include orexin deficiency in the setting of narcolepsy type 1; discrete pontine lesions impacting the REM generators such as stroke, demyelinating disease in multiple sclerosis, and brainstem tumors; neurogenetic disorders such as spinocerebellar ataxia type 3; as well as paraneoplastic neurological disorders and autoimmune diseases.[3,4] Among patients < 50 years of age, antidepressants are the most common etiology of RBD, particularly the serotonergic antidepressant medications resulting in serotonergic RBD (5-hydroxytryptamine or 5-HT RBD).[9,10] Serotonin inhibits REM sleep and it has been assumed that, by augmenting serotonergic activity, these exogenous agents induce RBD. However, recent studies have found other subtle neurodegenerative findings such as constipation and hyposmia among patients with medication-associated RBD.[11] This important finding suggests that increased serotonergic activity does not induce RBD per se but more likely unmasks it early in a patient who would otherwise develop a synucleinopathy later in life.

RBD classification is based on presumed etiology. When occurring in the absence of an identifiable neurological syndrome such as DLB, PD, or narcolepsy, dream enactment with polysomnography (PSG) confirmation of REM sleep without atonia (RWA) has been termed idiopathic RBD. Idiopathic RBD has historically been used until recently, despite the high likelihood that patients have alpha-synuclein degeneration of REM brainstem circuits and will later develop more clinically fulminant pathology. As idiopathic implies an uncertain etiology, a more accurate term currently used among RBD investigators is isolated RBD, when RBD occurs in the absence of a clear neurological syndrome.[12,13] To be consistent with the evolving nomenclature, we will use the term isolated RBD but recognize that, for many of the studies reviewed, isolated RBD referred to idiopathic RBD.

Patients whose RBD dream enactment occurs in the setting of a neurodegenerative disorder, narcolepsy, or less commonly, with focal brainstem lesions, such as strokes, have been classified as having secondary (and occasionally symptomatic) RBD due to a medical condition.[4] Onset of RBD with temporal association or exacerbation with the initiation of a medication is classified as drug-induced RBD, despite the previously mentioned concerns that these patients, in particular those with 5-HT RBD, appear to have an increased risk of later neurodegeneration.

RBD presents a unique window of opportunity by which one may alter the natural history and prevent the course to phenoconversion. Ongoing investigations are establishing protocols for the development of clinical trials to test neuroprotective therapies.[14,15] As no therapy has yet been clearly demonstrated to alter disease course, this guideline is specifically focused on symptomatic management of disruptive dream enactment behavior (DEB), aimed at minimizing the frequency and severity of injurious nocturnal behaviors, and impact on quality of life. It is hoped that, prior to the next Clinical Practice Guideline, innovative disease-modifying therapies will emerge with the prospect of delaying, preventing, or reversing parkinsonian and other neurodegenerative disorders.

DEBs can be dramatic, life threatening, and often terrifying to patients and bed partners, highlighting the critical need to establish a diagnosis of RBD and provide definitive management. Since its original description in 1986, investigators have attempted to identify effective RBD treatments.[16] Early therapies included benzodiazepines, antidepressants, and antiseizure agents. The majority of early treatment data were case series or small, uncontrolled clinical trials. In 2010, the AASM published a Best Practice Guide for the treatment of RBD and concluded that optimizing safety intervention was supported by the highest recommended evidence ("level A"). This was followed

by suggested evidence for clonazepam and melatonin (level B), with lower quality data.[2] However, in the last 10 years a number of studies, including placebo-controlled investigations, have contributed substantially to the existing RBD literature, catalyzing the AASM to assemble a task force (TF) to augment the RBD management armamentarium for clinicians and their patients.

In addition to reducing the frequency and severity of disruptive dream enactment, sleep clinicians are encouraged to disclose to patients with RBD the risk of impending neurodegenerative syndromes. Patient autonomy includes respect for a patient's right to know, or if they so choose, the right not to know, their risk of future disease. Because of this, the TF elected to also explore best practices regarding the disclosure of high-risk syndromes among patients with RBD.

METHODS

Expert task force

The AASM commissioned a TF of sleep medicine clinicians with expertise in RBD. The TF was required to disclose all potential conflicts of interest (COIs), per the AASM's COI policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's COI 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 COIs are listed in the Disclosures section.

Patient, Intervention, Comparison, and Outcomes (PICO) questions

Patient, Intervention, Comparison, and Outcomes (PICO) questions were developed based on a review of the existing AASM Best Practice Guide on the treatment of RBD and an examination of systematic reviews, meta-analyses, and guidelines published for adult and pediatric populations. The AASM Board of Directors approved the final list of PICO questions presented in **Table 1** before the literature searches were performed.

In addition, the TF identified a list of patient-oriented, clinically relevant outcomes to determine whether the various interventions, compared with no treatment, should be recommended for clinical practice. Input from stakeholders (patients, caregivers, and health care providers) was also taken into consideration. The TF rated the relative importance of each outcome to determine which outcomes were critical for decision making. A summary of the outcomes by PICO is presented in **Table 2**.

The TF set a clinical significance threshold (CST) for tools of interest for each outcome to determine whether the mean

Table 1—PICO questions.

1	Population: Adult* and pediatric patients diagnosed with isolated RBD Intervention: Clonazepam, melatonin, paroxetine, pramipexole, ramelteon, rivastigmine, sodium oxybate, yi-gan san, adrenocorticotropic hormone, agomelatine, bed alarm, carbamazepine, clomipramine, desipramine, donepezil, escitalopram, haloperidol, lamotrigine, phenobarbital, quetiapine, sertraline, triazolam, vortioxetine, zopiclone Comparison: Placebo; other intervention; no treatment Outcome: Frequency of significant bed partner sleep disruption; frequency of dream enactment episodes; frequency and/or intensity of unpleasant dreams and nightmares; change in REM motor tone (tonic and/or phasic); quality of life; sleep quality; daytime motor function; treatment-related worsening in sedation or cognitive impairment**; treatment-related worsening in gait stability**; treatment-related worsening in symptoms of depression or anxiety**
2	Population: Adult and pediatric patients diagnosed with secondary RBD due to medical condition (including neurological diseases, dementia, stroke, sleep disorders, DLB, MSA, Parkinson's disease, narcolepsy) Intervention: Cannabidiol, carbidopa-levodopa, clonazepam, deep brain stimulation, donepezil, IV immunoglobulin, light therapy, melatonin, memantine, pramipexole, ramelteon, rivastigmine, rotigotine, sodium oxybate, yi-gan san, bed alarm, buspirone, carbamazepine, clozapine, desipramine, haloperidol, hypnotherapy, levetiracetam, levodopa, methotrexate, nelotanserin, olanzapine, plasma exchange, PAP therapy, quetiapine, temazepam, tiapride, triazolam, zonisamide, zopiclone Comparison: Placebo; other intervention; no treatment Outcome: Frequency of significant bed partner sleep disruption; frequency of dream enactment episodes; frequency and/or intensity of unpleasant dreams and nightmares; change in REM motor tone (tonic and/or phasic); quality of life; sleep quality; daytime motor function; treatment-related worsening in sedation or cognitive impairment**; treatment-related worsening in gait stability**; treatment-related worsening in symptoms of depression or anxiety**
3	Population: Adult and pediatric patients diagnosed with drug-induced RBD (antidepressants such as paroxetine, fluoxetine, imipramine, venlafaxine, mirtazapine; beta-blockers) Intervention: Clonazepam, drug discontinuation Comparison: Placebo, other intervention, or no treatment Outcome: Frequency of significant bed partner sleep disruption; frequency of dream enactment episodes; frequency and/or intensity of unpleasant dreams and nightmares; change in REM motor tone (tonic and/or phasic); quality of life; sleep quality; daytime motor function; treatment-related worsening in sedation or cognitive impairment**; treatment-related worsening in gait stability**; treatment-related worsening in symptoms of depression or anxiety**

*This PICO population includes the following special categories: adults with OSA on CPAP, adults with untreated OSA & risk of falls, adults with depression and RBD, pregnancy, adults with PTSD + RBD, patients with RBD in risky occupations (law enforcement shift workers), parasomnia overlap, status dissociates. **These outcomes are considered side-effects of the interventions. CPAP = continuous positive airway pressure, DLB = dementia with Lewy bodies, IV = intravenous, MSA = multiple systems atrophy, OSA = obstructive sleep apnea, PAP = positive airway pressure, PICO = Population, Intervention, Comparison, Outcome, PTSD = post-traumatic stress disorder, RBD = rapid eye movement sleep behavior disorder, REM = rapid eye movement.

Table 2—Outcomes by PICO question.

Outcomes	Adult and Pediatric Patient Populations		
	Isolated RBD	Secondary RBD due to Medical Condition	Drug-induced RBD
Frequency of significant bed partner sleep disruption	√*	√*	√*
Frequency and/or intensity of dream enactment episodes	√*	√*	√*
Treatment-related worsening in sedation or cognitive impairment	√*	√*	√*
Treatment-related worsening in gait stability	√*	√*	√*
Treatment-related worsening in symptoms of depression or anxiety	√*	√*	√*
Frequency and/or intensity of unpleasant dreams and nightmares	√	√	√
Change in REM motor tone—tonic and/or phasic	√	√	√
Quality of life	√	√	√
Sleep quality	√	√	√
Daytime motor function	√	√	√

*Critical outcomes. PICO = Population, Intervention, Comparison, Outcome, RBD = rapid eye movement sleep behavior disorder, REM = rapid eye movement.

changes in the outcomes assessed were clinically significant based on their clinical expertise, other AASM guidelines, and available literature. The CST was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. A summary of the CSTs for the clinical outcome measures is presented in **Table 3**. Where no clearly established threshold values could be determined, CSTs were determined based on consensus in conjunction with TF literature review of commonly used thresholds for the various tools, gathering input from other sleep specialists, clinical judgment, and experience.

Literature searches, evidence review, and data extraction

The TF performed an extensive review of the scientific literature to retrieve articles that addressed the PICO questions. Separate literature searches were performed by the AASM research staff for each PICO question using the and Embase databases. Articles that met inclusion criteria but did not report outcomes of interest were rejected from the final evidence base. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material. Randomized controlled trials (RCTs) and observational studies that were cited in the prior AASM practice parameters were included for data analysis only if they met the current inclusion criteria.

The initial search of using the systematic review methods filter was performed in December 2018. A second literature search of Embase was performed in June 2019. A third literature search of and Embase was performed in February 2020 to identify studies that were published since the second literature search to update the body of evidence for the review. The TF reviewed previously published guidelines, systematic reviews, and meta-analyses to pearl, or "spot check," for references that may have been missed during the prior searches. The TF identified a total of 4,690 articles (including 107 studies identified through pearling/spot checking) that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material and summarized in **Figure 1**. All abstracts were reviewed for inclusion/exclusion criteria by 2 TF members. Any discrepancies between the reviewers were discussed and resolved by the Chair. A total of 148 studies were determined to be suitable for meta-analysis and/or grading.

Statistical and meta-analysis and interpretation of clinical significance

Meta-analyses were performed on outcomes of interest, when possible, for each PICO question. Comparisons of various interventions to no treatment were performed using data obtained from RCTs. The pooled results for each continuous outcome measure are expressed as the mean difference between the intervention and comparator. Data from baseline and last-treatment time points from nonrandomized trials were also compared. These are presented in a table format in the supplemental material (**Tables S1–S186**). Data from crossover trials were treated as parallel groups. Some studies had data presented in the form of median and interquartile range. These were converted into data expressed as means and standard deviation.[17,18] If outcome data were not presented in the format necessary for statistical analysis (ie, mean, standard deviation, and sample size), then the data were reported as a percentage of patients reporting an improvement (or worsening) in a particular outcome, and presented qualitatively in a table format in the supplemental material. Some studies combined patient groups, such as individuals with isolated RBD along with those who had RBD due to a medical disorder, most commonly PD. Care was taken to identify and separate individuals and individual treatment responses across these groups.

Meta-analyses and pre-post analyses were performed using Review Manager 5.3 software (The Cochrane Collaboration, London, United Kingdom) by pooling data across studies for

Table 3—Summary of clinical significance thresholds for critical and important outcome measures.

Outcome Tool	Clinical Significance Threshold*	Expected Change
Frequency of significant bed partner sleep disruption		
CGI-I	1.5 points OR 65% of patients reporting change	Decrease Improvement
Frequency and/or intensity of dream enactment episodes		
Simple motor behaviors (PSG—during REM sleep)	33% (10% for placebo studies) OR 50% of patients reporting change	Decrease Improvement
Complex motor behaviors (PSG—during REM sleep)	33% (10% for placebo studies) OR 50% of patients reporting change	Decrease Improvement
CGI-I	1.5 points OR 65% of patients reporting change	Decrease Improvement
RBDQ (Factor 2 score)	10% OR 50% of patients reporting change	Decrease Improvement
Treatment-related worsening in sedation or cognitive impairment		
ESS	2 points OR 10% of patients reporting change	Increase Decline
KESS	2 points OR 10% of patients reporting change	Increase Decline
MMSE	3 points OR 10% of patients reporting change	Decrease Decline
Letter Fluency	10% OR 33% of patients reporting change	Decrease Decline
MFQ	1 point OR 10% of patients reporting change	Increase Decline
Treatment-related worsening in gait stability	10% of patients reporting change	Decline
Treatment-related worsening in symptoms of depression or anxiety		
NPI	4 points OR 20% of patients reporting change	Increase Decline
Frequency and/or intensity of unpleasant dreams and nightmares		
RBD frequency	33% (10% for placebo studies) OR 50% of patients reporting change	Decrease Improvement
RBD intensity	33% (10% for placebo studies) OR 50% of patients reporting change	Decrease Improvement
RBD episodes per week or month	33% (10% for placebo studies) OR 50% of patients reporting change	Decrease Improvement
RBDQ (Factor 1 score)	10% OR 50% of patients reporting change	Decrease Improvement
Change in REM motor tone—tonic and/or phasic		
Phasic EMG%	10% OR 50% of patients with change in REM motor tone	Decrease Improvement
Tonic EMG%	10% OR 50% of patients with change in REM motor tone	Decrease Improvement
REM Atonia Index	10% OR 50% of patients with change in REM motor tone	Increase Improvement
Quality of life		
SF-36 (physical score)	10% OR 50% of patients reporting change	Increase Improvement
SF-36 (mental score)	10% OR 40% of patients reporting change	Increase Improvement
UPDRS (total score)	4.1 points OR 50% of patients reporting change	Decrease Improvement
Schwab and England	20% OR 60% of patients reporting change	Increase Improvement

(continued on following page)

Table 3—Summary of clinical significance thresholds for critical and important outcome measures. (*Continued*)

Outcome Tool	Clinical Significance Threshold*	Expected Change
CGI-I	1.5 points OR 50% of patients reporting change	Decrease Improvement
Sleep quality		
RBDQ (total score)	10% OR 50% of patients reporting change	Decrease Improvement
PSQI	3 points OR 50% of patients reporting change	Decrease Improvement
Daytime motor function		
UPDRS (Part III score)	2.3 points OR 50% of patients reporting change	Decrease Improvement

*The clinical significance thresholds apply to the comparison of post-treatment effects between intervention and placebo as well as a pre-post treatment difference. CGI-I = Clinical Global Impressions–Improvement Scale, EMG = electromyography, ESS = Epworth Sleepiness Scale, KESS = Korean Epworth Sleepiness Scale, MFQ = Mayo Fluctuation Questionnaire, MMSE = Mini-Mental State Examination, NPI = Neuro-psychiatric Inventory, PSQI = Pittsburgh Sleep Quality Index, RBD = rapid eye movement sleep behavior disorder, RBDQ = RBD Questionnaire (includes Korean, Japanese, and Hong Kong versions), REM = rapid eye movement, RWA = REM sleep without atonia, SF-36 = Short-Form Questionnaire (36-item), UPDRS = Unified Parkinson's Disease Rating Scale.

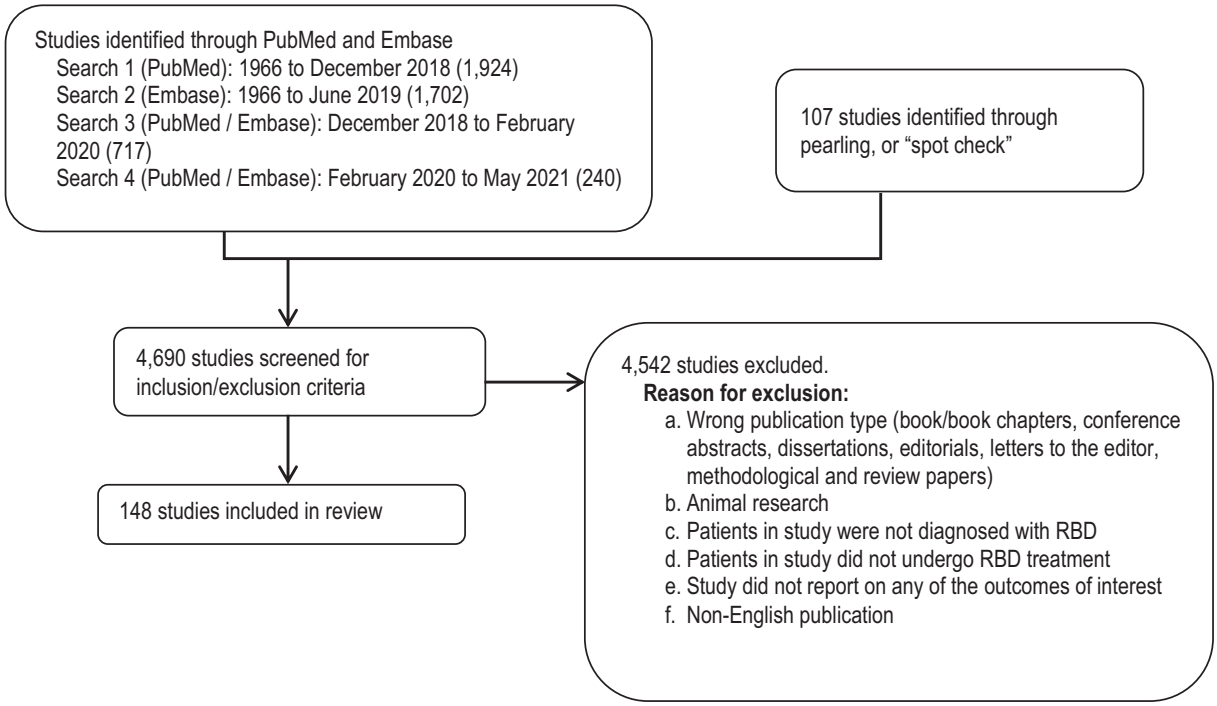
each outcome measure. All analyses were performed using a random-effects model. Interpretation of clinical significance for the outcomes of interest was conducted by comparing the mean difference in effect of each treatment approach with the CST (see **Table 3**). There was insufficient evidence to perform meta-analyses for some outcome measures. For some interventions, none of the accepted publications provided data that could be used for statistical analysis.

For adverse events, all data presented in the accepted papers were used for statistical and meta-analysis. Whenever possible, meta-analyses were performed by pooling data across studies for each outcome and adverse event.

Patient representatives

Two patient stakeholders who provided input on the PICO outcomes were invited by the TF to provide their feedback on

Figure 1—Evidence-base flow diagram.



RBD = rapid eye movement sleep behavior disorder.

patient values and preferences for the interventions. These patient representatives were well-informed patient advocates who were previously involved in RBD clinical studies and research workgroups. Prior to their involvement, the 2 patient representatives were educated on the AASM's guideline development process and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) concepts.

GRADE assessment for developing recommendations

The evidence was assessed according to the GRADE process for the purposes of making clinical practice recommendations. The TF decided to only apply the GRADE process for those interventions that were Food and Drug Administration (FDA)–approved and/or available for use in the United States and had supporting evidence from a total of at least 3 patients for a particular PICO (isolated RBD, secondary RBD due to medical condition, or drug-induced RBD). If an intervention did not have the minimum of 3 patients or was not FDA-approved and/or available for use in the United States, the TF would still present the data in the supplemental material but they would not apply the GRADE process. The TF considered the following 4 GRADE domains: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below[19,20]:

1. Certainty of evidence: Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (small sample size of < 30 patients or 95% confidence interval crosses the CST), inconsistency (I^2 cutoff of 50%), indirectness (study population), and risk of publication bias (funding sources), the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical patients with RBD would see. The overall quality of the evidence was based on outcomes that the TF deemed critical for decision making, relying on RCT data when available.
2. Benefits vs harms: Based on the meta-analysis (if data were available), analysis of any harms/side effects reported within the included literature, and the clinical expertise of the TF, the TF determined if the beneficial outcomes of the intervention outweighed any harmful side effects.
3. Patient values and preferences: Based on the clinical expertise of the TF members, feedback from the patient representatives, and any data published on the topic relevant to patient preferences, the TF determined if patient values and preferences would be generally consistent across the majority of patients, and if patients would use the intervention based on the relative harms and benefits identified.
4. Resource use: Based on the clinical expertise of the TF members, the TF determined if accessibility and costs associated with each treatment approach compared favorably to comparator treatments. Information on both costs to patients and to the health care system were considered.

A summary of each GRADE domain is provided after the detailed evidence review for each PICO question.

Public comment and final approval

Drafts of the systematic review and accompanying guideline were made available for public comment for a 4-week period on the AASM website. AASM members, the general public, and other relevant stakeholders were invited to provide feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility of comments. The public comments and revised documents were submitted to the AASM Board of Directors who subsequently approved the final documents for publication.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

MANAGEMENT OF RBD IN ADULT POPULATIONS

The aims of the current literature review and data were focused on addressing the management of isolated (previously referred to as idiopathic) RBD, secondary RBD due to a medical condition, and drug-induced RBD. Below are detailed summaries of the evidence for adult populations for those interventions that had supporting evidence from a total of at least 3 patients with RBD across all studies and are FDA-approved and/or available for use in the United States. The GRADE process was applied, which describes the certainty of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the accompanying clinical practice guideline.[1]

Isolated RBD

The following interventions are those for which recommendations were made in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 50 observational studies[16,21–69] which examined the effect of clonazepam on 993 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or older men (mean age of 65 years; 84% male). The observational studies included retrospective and prospective cohort, cross-sectional, case-control, case series, and case report designs.

The tables are provided as **Table S1, Table S2**, and **Tables S4–S7** in the supplemental material. The summary of findings table is provided as **Table S8**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One observational prospective cohort study[43] evaluated the effect of clonazepam on the frequency and/or intensity of dream enactment episodes using the modified RBD questionnaire (RBDQ) tool (**Table S1**). The study reported a clinically significant 37.1% pre-post improvement in the mean behavioral factor score of 39 patients treated with clonazepam (mean dose of 0.98 ± 0.63 mg). The mean follow-up duration was 28.8 ± 13.3 months (range: 3–60 months). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S8**).

Two retrospective observational studies[31,32] evaluated the effect of clonazepam on the frequency of dream enactment episodes using the modified RBD severity scale tool (follow-up duration ranged from a mean of 2.6 to 2.8 years). These studies assessed clonazepam at a dose ranging from 0.5 to 1 mg, and the findings did not reach a level of clinical significance (**Table S1**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S8**).

Forty-four observational studies[16,21–30,34–42,44–59,61,63–69] reported on the percentage of patients who demonstrated a qualitative, partial or complete, improvement in RBD symptoms in response to clonazepam (follow-up duration ranged from 10 days to 6 years). These studies showed improvement in RBD symptoms in 87% of their patients, which was clinically significant (**Table S2**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S8**).

Treatment-related worsening in sedation or cognitive impairment: Two observational studies[32,43] reported on changes in sleepiness scores using the Epworth Sleepiness Scale (ESS) tool (follow-up duration ranged from 2.4 to 2.8 years). These studies reported pre-post mean reductions in ESS of 0.2 points for 15 patients and 2.0 points for 39 patients, respectively (**Table S4**). These reductions were not clinically significant. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S8**).

Nine observational studies[22,27,30,51,52,59,60,62,66] reported on the percentage of patients who demonstrated a qualitative worsening in sedation or cognitive impairment in response to clonazepam (follow-up duration ranged from 6 months to 5 years). These studies showed an adverse effect in sedation or cognitive impairment in 20% of their patients, which was clinically significant (**Table S5**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S8**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: frequency and/or intensity of unpleasant dreams and nightmares and change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: quality of life, sleep quality, or daytime motor function.

Frequency and/or intensity of unpleasant dreams and nightmares: One observational prospective cohort study[43] evaluated the effect of clonazepam on the frequency and/or intensity of unpleasant dreams and nightmares using the modified RBDQ tool (**Table S6**). The study reported a clinically significant 31.7% pre-post improvement in the mean dream-related factor score in 39 patients treated with clonazepam (mean dose of 0.98 ± 0.63 mg). The mean follow-up duration was 28.8 ± 13.3 months (range: 3–60 months). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S8**).

Change in REM motor tone—tonic and/or phasic: Three retrospective observational studies[31–33] evaluated the effect of clonazepam (0.5–2 mg) on the REM atonia index, a measure of REM motor inactivity (conducted at a follow-up duration that ranged from 2.6 to 2.8 years). These findings showed a pre-post increase in REM atonia index (indicating decreased amount of REM sleep without atonia—ie, a marker of increasing RBD) of 1.8% for 13 patients, 0.1% for 15 patients, and 5.0% for 14 patients, respectively (**Table S7**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S8**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for clonazepam to treat isolated RBD was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and worsening in sedation or cognitive impairment.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is in favor of clonazepam. The use of clonazepam demonstrated moderate improvements in RBDQ behavioral score and RBD symptoms in patients with isolated RBD.

In the single RCT included in the systematic review that reported on the use of clonazepam, commonly reported adverse events included daytime sleepiness (21.1%), dizziness (15.8%), and postural instability (5.3%). Commonly reported adverse events across all observational studies on the use of clonazepam included excessive daytime sleepiness (19.6%), unsteadiness (16.1%), and dizziness (7.5%). The TF determined that the harmful effects of clonazepam are small.

While the overall certainty of evidence for efficacy was low, the value and relative safety of clonazepam at low doses have been reported in RBD studies over nearly 40 years.

Resource use: The TF concluded that there was a large savings in resource use for clonazepam, given its relatively small cost compared with the potential high cost of potentially severe life-threatening injury due to dream enactment during sleep. Per the National Average Drug Acquisition Cost (NADAC) database, the unit cost of 1-mg and 2-mg tablets ranged from $0.03 to $0.05.[70] Medication cost to any given patient is uncertain and determined by payer coverage, copayments, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use clonazepam when compared with no treatment for their isolated RBD. This is based on the TF's determination that the undesirable effects are relatively small and that the balance of benefits vs harms strongly favors the use of clonazepam in low doses.

Melatonin

Our review of the literature identified 2 double-blind, placebo-controlled RCTs[71,72] for the treatment of RBD with melatonin in adult patients diagnosed with isolated RBD. The first RCT[71] assessed prolonged-release (sustained-release, timed-release, extended-release) melatonin in 7 patients vs 9 patients in a placebo group, at doses of 2 mg and 6 mg. The second RCT[72] assessed immediate-release melatonin in 8 patients vs 8 patients in a placebo group, at a dose of 3 mg. In addition, the TF identified 12 observational studies[21,22,30,34,47,49,73–78] (3 on timed prolonged-release and 9 on immediate-release melatonin), which examined the effect of melatonin in 303 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or older men (mean age of 64 years; 78% male). The observational studies included open-label trial, retrospective and prospective cohort, cross-sectional, case-control, case series, and case report designs.

The figures and tables are provided as **Figures S1–S19** and **Tables S10–S27**. Summary of findings tables are provided as **Table S28** and **Table S29**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One RCT[71] evaluated the effect of prolonged-release melatonin on the frequency of dream enactment episodes (follow-up duration was 4 weeks). This study showed a clinically significant 18.7% reduction in percentage mean change in dream enactment episodes per week for the melatonin group (2-mg dose) compared with the placebo group (**Table S12**, **Figure S2**). At a 6-mg dose, the melatonin group showed a 2.5% increase in percentage mean change in dream enactment episodes per week compared with the placebo group (**Table S13**, **Figure S4**). This study also used the Korean RBDQ tool, recording a 9.5% reduction in the behavioral factor score (eg, burden/severity of nocturnal behaviors) for the 2-mg melatonin group compared with the placebo group (**Table S12**, **Figure S3**), and a clinically significant 18.4% reduction for the 6-mg melatonin group compared with the placebo group (**Table S13**, **Figure S5**). For the 6-mg dose, the 2.5% increase in DEB frequency in the melatonin group compared with placebo was presumably counteracted by the 18.4% reduction in DEB severity. The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Another RCT[72] evaluated the effect of immediate-release melatonin (3 mg) on the frequency of dream enactment episodes (follow-up duration was 4 weeks). This study showed a 1.2-point decrease in mean Clinical Global Impressions (CGI) score for the melatonin group compared with the placebo group (**Table S11**). This change was not clinically significant. The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S28**).

One retrospective observational study[76] evaluated the effect of immediate-release melatonin (6 mg) on the frequency of dream enactment episodes in 26 patients (follow-up duration was 4 months). This study showed a clinically significant 88.8% reduction in dream enactment episodes per week and a clinically significant 93.5% reduction in vocalization episodes (**Table S10**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S28**).

Eight observational studies[21,30,34,47,49,73,74,78] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to immediate-release melatonin (follow-up duration ranged from 6 weeks to 6 years). These studies showed improvement in RBD symptoms in 66% of their patients, which was clinically significant (**Table S15**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S28**).

One observational cohort study[75] evaluated the effect of prolonged-release melatonin (2 mg) on the frequency of dream enactment episodes in 209 patients (follow-up duration was 4 weeks). This study showed a clinically significant 59.0% reduction in Ikelos-RS score after treatment, from 6.1 points to 2.5 points (**Table S14**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S29**).

Two observational studies[22,77] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to prolonged-release melatonin (follow-up duration ranged from 6 to 20 months). Both studies showed improvement in RBD symptoms in all 6 of their patients, which was clinically significant (**Table S15**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S29**).

Treatment-related worsening in sedation or cognitive impairment: One RCT[71] evaluated the effect of prolonged-release melatonin on daytime sleepiness using the ESS questionnaire (follow-up duration was 4 weeks). This study showed no change in mean ESS score for the melatonin group (2-mg dose) (**Table S16**, **Figure S6**). At a 6-mg dose, the study showed equal reductions in sleep propensity in the melatonin group, compared with the placebo group (**Table S17**, **Figure S7**). Neither of these changes was clinically significant. The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Three observational studies[30,47,73] reported on the percentage of patients who demonstrated worsening in sedation in response to immediate-release melatonin (**Table S18**). The first study[30] showed an adverse effect of morning sedation in 1 of its 8 patients following treatment with melatonin (1.9–9 mg), which was clinically significant by TF criteria. The second study[73] was a case report that showed an improvement in daytime alertness and cognitive performance for its patient treated with 3 mg of melatonin for 5 months. The third study[47] was a cohort study that reported sleepiness in 56% of patients (14/25) after an average of 27.4 ± 24 months of melatonin treatment (6–25 mg), which was clinically significant. The certainty of evidence was low due to risk of bias associated with observational studies (**Table S28**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, and sleep quality. None of the studies identified in our literature review reported data for the following important outcome: daytime motor function.

Frequency and/or intensity of unpleasant dreams and nightmares: One RCT[71] evaluated the effect of prolonged-release melatonin on the frequency and/or intensity of unpleasant dreams and nightmares using the Korean RBDQ tool (follow-up duration was 4 weeks). The study recorded a 11.1% increase in percentage mean change in the dream-related factor score for the 2-mg melatonin group compared with the placebo group (**Table S19**, **Figure S8**) and a 0.3% increase for the 6-mg melatonin group compared with the placebo group (**Table S20**, **Figure S9**). Neither of these increases was clinically significant. The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Change in REM motor tone—tonic and/or phasic: One RCT[72] evaluated the effect of immediate-release melatonin on RWA after 4 weeks of treatment, showing a 3.8% reduction in mean change for the melatonin group compared with the placebo group. This study also reported on phasic electromyography (EMG) percentage, showing a 1.5% reduction in mean change for the melatonin group compared with the placebo group (**Table S22**). The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S28**).

Two observational studies[74,76] evaluated the effect of immediate-release melatonin on RWA, showing a decrease from 32% to 11% (21% reduction) and from 47% to 1.4% (45.6% reduction) pre-post treatment for 6 patients (6 weeks) and 26 patients (4 months), respectively (**Table S21**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S28**).

Two observational studies[74,78] evaluated the effect of immediate-release melatonin on phasic EMG%, showing a nonsignificant pre-post treatment increase from 29% to 32% (3% increase) for 6 patients (6 weeks) and a clinically significant reduction from 51.7% to 7.6% (44.1% reduction) for 15 patients, respectively (**Table S21**). The certainty of evidence was very low due to imprecision (**Table S28**).

One observational study[78] evaluated the effect of immediate-release melatonin on tonic EMG%, showing a clinically significant pre-post reduction from 16.4% to 6% (10.4% reduction) for 15 patients (follow-up duration not reported) (**Table S21**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S28**).

One observational case series study[77] reported on the effect of prolonged-release melatonin on RWA in 2 patients (follow-up duration was 6 months). Neither of its 2 patients showed a reduced RWA following treatment of melatonin (2 mg) (**Table S23**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Quality of life: One RCT[71] evaluated the effect of prolonged-release melatonin on quality of life using the 36-item Short Form Questionnaire (SF-36, version 2). The study recorded a clinically significant 11.4% increase (indicating improved physical functioning) in percentage mean change in the SF-36 physical component score for the 2-mg melatonin group compared with the placebo group (**Table S24**, **Figure S12**) and a 6.9% increase for the 6-mg melatonin group compared with the placebo group (**Table S25**, **Figure S14**). The study also recorded a 2.9% reduction in percentage mean change in SF-36 mental component score for the 2-mg melatonin group compared with the placebo group (**Table S24**, **Figure S13**) and a 3.2% increase for the 6-mg melatonin group compared with the placebo group (**Table S25**, **Figure S15**). The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Sleep quality: One RCT[71] evaluated the effect of prolonged-release melatonin on sleep quality using the Pittsburgh Sleep Quality Index (PSQI) and Korean RBDQ tools (follow-up duration was 4 weeks). The PSQI score showed a nonsignificant 0.1-point reduction for the 2-mg melatonin group compared with the placebo group (**Table S26**, **Figure S16**), and a nonsignificant 1.8-point reduction for the 6-mg melatonin group compared with the placebo group (**Table S27**, **Figure S18**). The Korean RBDQ total score showed a nonsignificant 3.8% reduction for the

2-mg melatonin group compared with the placebo group (**Table S26**, **Figure S17**) and a clinically significant 13.4% reduction for the 6-mg melatonin group compared with the placebo group (**Table S27**, **Figure S19**). The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S29**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for melatonin to treat isolated RBD was low for both immediate-release melatonin and prolonged-release melatonin, based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30 and a wide 95% confidence interval that crossed the CST).

Clinical thresholds were met for the critical outcomes of decreasing frequency and/or intensity of dream enactment episodes and without a worsening in sedation and/or cognitive impairment. These findings were noted among individuals taking immediate-release melatonin and, to a lesser degree, prolonged-release melatonin.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is in favor of immediate-release melatonin, but there were insufficient data to favor prolonged-release melatonin due to the conflicting and largely negative results of the 1 RCT evaluating prolonged-release melatonin. The use of immediate-release melatonin demonstrated moderate improvements in RBD dream-acting and vocalization episodes per month and RBD symptoms in patients with isolated RBD. The use of prolonged-release melatonin demonstrated small improvements in RBDQ behavioral score and RBD symptoms in patients with isolated RBD.

Across all RCTs included in the systematic review that reported on the use of melatonin, commonly reported adverse events included headache (6.3%) and nausea (6.3%). Commonly reported adverse events across all observational studies on the use of melatonin included excessive daytime sleepiness (25.0%), headache (14.3%), and trouble thinking (12.0%). While there was a relatively high percentage of side effects, based on extensive clinical experience the TF determined that the harmful effects of melatonin are trivial.

Resource use: The TF concluded that there was a large savings in resource use for melatonin, given its relatively small cost compared with the potential high cost of severe injury due to dream enactment during sleep. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The vast majority of patients who require treatment for dream enactment would most likely use melatonin when compared with no treatment for their isolated RBD. This is based on the TF's determination that the undesirable effects are trivial and that the balance of benefits vs harms favors the use of melatonin. There may be some providers and patients, however, who are concerned with the lack of FDA regulation for melatonin. Melatonin labels with the US Pharmacopeia (USP) Verification Mark have been confirmed to contain the amounts of melatonin stated on the label and may provide the most consistent dosing among melatonin treatment options.

Pramipexole

Our review of the literature identified 7 observational studies[49,53,67,79–82] that examined the effect of pramipexole on 87 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or older men (mean age of 67 years; 79% male). The observational studies included open-label trial, retrospective cohort, cross-sectional, case-control, case series, and case report designs.

The tables are provided as **Tables S30–S34**. Summary of findings tables are provided as **Table S35** and **Table S36**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Two observational studies[79,80] evaluated the effect of pramipexole on the frequency and/or intensity of dream enactment episodes (follow-up duration ranged from 4.5 to 9.1 months) (**Table S30**). The first study[80] was an open-label trial that reported a clinically significant 60.7% mean reduction in RBD episodes per week for 15 patients treated with pramipexole (mean dose 0.21 ± 0.09 mg/d). The second study[79] was a case series study that showed a clinically significant 54.0% mean reduction in simple motor behaviors during REM sleep for 8 patients treated with pramipexole (mean dose 0.78 ± 0.25 mg/d). This study also illustrated a 23.9% mean reduction in complex motor behaviors during REM sleep. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S35**).

One retrospective observational study[81] compared the effect of pramipexole (mean dose 0.21 ± 0.09 mg/d) with that of clonazepam (mean dose 0.6 ± 0.3 mg/d) on the frequency of dream enactment episodes per week (follow-up duration was 3 months) (**Table S31**). This study reported a 27.3% reduction in RBD episodes per week in the pramipexole group (n = 50) compared with the clonazepam group (n = 15). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S36**).

Five observational studies[49,53,67,79,82] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to pramipexole (follow-up duration ranged from 4.5 months to 6 years). These studies showed improvement in RBD symptoms in 82% of their

patients, which was clinically significant (**Table S32**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S35**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One retrospective observational study[81] compared the effect of pramipexole (mean dose 0.21 ± 0.09 mg/d) with that of clonazepam (mean dose 0.6 ± 0.3 mg/d) on RWA% after 3 months of treatment (**Table S33**). This study reported a 5.3% reduction in RWA% in the pramipexole group (n = 50) compared with the clonazepam group (n = 15). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S36**).

Two observational studies[79,80] evaluated the effect of pramipexole on the change in REM motor tone (follow-up duration ranged from 4.5 to 9.1 months) (**Table S34**). The first study[79] reported on a 0.2% increase in phasic EMG% and a 9.6% reduction in REM atonia, for 8 patients treated with pramipexole (mean dose 0.78 ± 0.25 mg/d). The other study[80] showed a 3.6% pre-post reduction in phasic EMG% and a 1.4% reduction in tonic EMG% for 15 patients treated with pramipexole (mean dose 0.21 ± 0.09 mg/d). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S35**).

Overall certainty of evidence: While pramipexole was historically advocated for the management of disrupted sleep in the setting of RBD, the TF determined that the overall certainty of evidence for pramipexole to treat isolated RBD was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence due to imprecision (small sample size of n < 30 and wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of pramipexole. The use of pramipexole demonstrated moderate improvements in RBD episodes per week, the number of simple and complex motor behaviors, and RBD symptoms in patients with isolated RBD.

Across all observational studies included in the systematic review that reported on the use of pramipexole, commonly reported adverse events included next-day sedation (5.1%) and gastrointestinal symptoms (3.1%). The TF also raised concerns in light of the attributed impulse-control disorders associated with dopamine agonist agents, although the TF recognized that the harmful effects of pramipexole are small at the relatively low dose of this agent when used in the management of RBD.

Resource use: The TF concluded that there was a moderate savings in resource use for pramipexole, given its relatively low cost compared with the burden and cost of injury in the setting of injurious dream enactment behaviors Per the NADAC database, the unit cost of 0.5-mg and 1-mg tablets ranged from $0.05 to $0.06.[70] Medication cost to any given patient is uncertain and determined by payer coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use pramipexole when compared with no treatment for their isolated RBD. This is based on the TF's determination that the benefit on dream enactment outweighed potential undesirable effects. Patients with a psychiatric history of impulse-control behavior (and those with compulsive tendencies), however, are not good candidates for this medication.

Rivastigmine

Our review of the literature identified 1 single-blind, placebo-controlled, crossover RCT,[83] which examined the effect of rivastigmine on adult patients with isolated RBD (although with concomitant mild cognitive impairment) who were refractory to melatonin (up to 5 mg) and clonazepam (up to 2 mg). This RCT assessed a rivastigmine patch of 4.6 mg/day in 25 patients vs placebo after a 7-day washout period. The majority of the patients were male (17/25), and they were primarily middle-aged or older (mean age of 63 years).

The figures and tables are provided as **Figure S20** and **Table S37** and **Table S38**. The summary of findings table is provided as **Table S39**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One RCT[83] evaluated the effect of rivastigmine on the frequency of dream enactment episodes (follow-up duration was 30 days). This study showed a clinically significant 44.7% reduction in percentage mean change in dream enactment episodes per month for the rivastigmine arm compared with the placebo arm (**Table S37**, **Figure S20**). The certainty of evidence was moderate due to imprecision associated with a small

sample size and a wide 95% confidence interval that crossed the CST (**Table S39**).

Treatment-related worsening in sedation or cognitive impairment: One RCT[83] reported on the percentage of patients who demonstrated worsening in sedation or cognitive impairment in response to rivastigmine (follow-up duration was 30 days). This study showed that 40% of their patients (10/25) experienced daytime sleepiness following treatment, which was clinically significant (**Table S38**). The certainty of evidence was moderate due to imprecision associated with a small sample size (**Table S39**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for rivastigmine to treat isolated RBD was moderate based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30 and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of rivastigmine. The use of rivastigmine demonstrated moderate improvements in RBD episodes per month in patients with isolated RBD.

In the RCT included in the systematic review that reported on the use of rivastigmine in patients with isolated RBD, adverse events did not lead to withdrawal. Commonly reported adverse events include daytime sleepiness (10/25 patients, 40.0%) and mild self-limiting nausea (20.0%). The TF determined that the harmful effects of rivastigmine are small for patients with isolated RBD.

Resource use: The TF concluded that there was a moderate savings in resource use for rivastigmine, despite its relatively greater costs than other RBD treatments, due to the potential cost of injury due to dream enactment during sleep. Per the NADAC database, the unit cost of a rivastigmine patch ranged from $4.19 to $4.27.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use rivastigmine when compared with no treatment for their isolated RBD. This is based on the TF's determination that the undesirable effects are small and that the balance of benefits vs harms favors the use of rivastigmine.

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Paroxetine

Our review of the literature identified 1 observational cohort study[84] that examined the effect of paroxetine on adult patients with isolated RBD. This study assessed paroxetine in 19 patients at doses ranging from 10 to 40 mg. Participants in this study were primarily middle-aged or older men (mean age of 65 years; 79% male). In addition, numerous other studies of selective serotonin reuptake inhibitors have reported that these agents, and paroxetine in particular, exacerbate RBD.[85]

The table is provided as **Table S40**. The summary of findings table is provided as **Table S41**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One observational cohort study[84] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to paroxetine (follow-up duration was not reported). This study showed improvement in RBD symptoms for 16 of 19 patients (84%), which was clinically significant. Five patients improved from a severe RBD rating to moderate, and 11 patients improved from severe to mild (**Table S40**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S41**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for paroxetine to treat isolated RBD was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored paroxetine or no treatment. The use of paroxetine

demonstrated improvements in RBD symptoms in patients with isolated RBD, but based on the TF's clinical experience, there is too much uncertainty to make a judgment on the balance of benefits and harms.

In the observational study included in the systematic review that reported on the use of paroxetine, commonly reported adverse events included nausea (5.3%), dizziness (5.3%), and diarrhea (5.3%). Administration of paroxetine was discontinued in 2 patients due to dizziness and diarrhea, respectively. The TF determined that the harmful effects of paroxetine are small, based on their clinical experience.

Resource use: The TF was unable to conclude how large the difference in resource use was between paroxetine and no treatment, due to the uncertainty of the balance between its desirable and undesirable effects. Per the NADAC database, the unit cost of 10-mg and 30-mg tablets was $0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely not use paroxetine when compared with no treatment for their isolated RBD. This is based primarily on uncertain efficacy and safety.

Ramelteon

Our review of the literature identified 1 observational, open-label trial[86] for the treatment of RBD with ramelteon in adult patients diagnosed with isolated RBD. This study assessed ramelteon in 10 patients at a dose of 8 mg. Participants in this study were primarily middle-aged or older men (mean age of 69 years; 70% male).

The tables are provided as **Table S42** and **Table S43**. The summary of findings table is provided as **Table S44**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One observational, open-label trial[86] evaluated the effect of ramelteon on the frequency and intensity of dream enactment episodes using the Visual Analog Scale according to family and the intensity of dream enactment episodes using the RBD Severity Scale tool, which is based on video analysis of single-night PSG (mean follow-up duration was 8.3 ± 6.8 weeks). The study failed to show significant improvement. While there was a reported pre-post 42% reduction (improvement) on the Visual Analog Scale, there was an 87.5% increase (worsening) of percentage mean change in RBD Severity Scale motor events, and a pre-post 16.7% increase (worsening) in percentage mean change in RBD Severity Scale vocalization events (**Table S42**). The certainty of evidence was very low due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S44**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One observational, open-label trial[86] evaluated the effect of ramelteon on REM sleep without atonia, showing a 5.5% increase in mean change (mean follow-up duration was 8.3 ± 6.8 weeks). This study also reported on phasic EMG% and tonic EMG%, showing a 4.6% and 0.9% increase in mean change, respectively (**Table S43**). The certainty of evidence was very low due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S44**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for ramelteon to treat isolated RBD could not be determined due to the inadequate outcome tools used in the only study testing ramelteon in isolated RBD (the Visual Analog Scale and RBD Severity Scale not being validated tools to evaluate RBD clinical outcomes).

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects did not favor either ramelteon or no treatment. The TF determined that the beneficial effects of ramelteon are trivial, based on the limited evidence from only 1 observational study with no critical outcome data.

Across all observational studies included in the systematic review that reported on the use of ramelteon, commonly reported adverse events included rash (8.3%) and dizziness (8.3%). The TF determined that the harmful effects of ramelteon are trivial.

Resource use: The TF concluded that there were moderate costs in resource use for ramelteon, as out-of-pocket costs are greater than for other RBD treatments. Per the NADAC database, the unit cost of an 8-mg tablet was $3.53.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely not use ramelteon when compared with no treatment for their isolated RBD. This was based on the TF's determination that the balance of benefits and harms did not favor either

ramelteon or comparison and that the costs of ramelteon are greater than other RBD treatments.

Sodium oxybate

Our review of the literature identified 3 observational studies[49,87,88] that examined the effect of sodium oxybate in adult patients with treatment-resistant isolated RBD. The first study[87] assessed sodium oxybate in 3 patients at a dose of 4.5 g. The second study[49] assessed sodium oxybate in 2 patients at a dose of 4.5 g (in a single dose) and 3 g (in 2 doses) nightly. The third study[88] assessed sodium oxybate in 1 patient at a dose that started at 3 g and was increased to 4.5 g after 1 week. Participants in these studies were primarily middle-aged or older (mean age of 66 years) and composed of all men. The observational studies included case series and case report designs.

The table is provided as **Table S45**. The summary of findings table is provided as **Table S46**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One case series study[87] reported on 3 patients who demonstrated an improvement in RBD symptoms and a significant decrease in nocturnal violent episodes in response to sodium oxybate (follow-up duration ranged from 3 to 8 years). A second case series study[49] reported on the 2 patients who showed significant improvement in CGI-Improvement (CGI-I) scale scores in response to sodium oxybate (follow-up duration ranged from 2.5 to several years). A case report[88] reported on a patient whose RBD symptoms resolved within 2 weeks of treatment with sodium oxybate and remained well controlled after a 12-month follow-up (**Table S45**). The certainty of evidence was very low due to imprecision associated with a small sample size (**Table S46**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for sodium oxybate to treat isolated RBD was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate. The use of sodium oxybate demonstrated large improvements in CGI-I score and RBD symptoms in patients with isolated RBD.

Across all observational studies included in the systematic review that reported on the use of sodium oxybate in patients with isolated RBD, there was a report of constipation in 1 patient. The TF could not conclude how large the magnitude of harmful effects would be for sodium oxybate based on its unknown cardiovascular and cognitive risks on the older patients.

Resource use: The TF concluded that there were large costs in resource use for sodium oxybate, as out-of-pocket costs would be prohibitive. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use sodium oxybate when compared with no treatment for their isolated RBD. However, the symptomatic benefits of sodium oxybate treatment appeared to primarily stem from treating sleep fragmentation and not necessarily resolving dream enactment. Thus, given the high cost and very limited low grade data indicating efficacy, the TF believed that many patients would not prefer it compared with placebo for RBD.

Yi-gan san

Our review of the literature identified 4 observational studies[53,60,89,90] that examined the effect of yi-gan san on adult patients with isolated RBD. The first study[89] was a retrospective study that assessed yi-gan san in 36 patients at a dose ranging from 2.5 to 5.0 g/day. The second study[90] was a retrospective study that assessed yi-gan san in 11 patients at a dose of 3.0 g/day. The third study[53] was a case-control study that assessed yi-gan san in 1 patient at an unknown dose. The fourth study[60] was a case series study that assessed yi-gan san in 1 patient at a dose of 7.5 g/day. Participants in these studies were primarily middle-aged or older men (mean age of 70 years; 81% male). The observational studies included retrospective cohort, case-control, and case series designs.

The tables are provided as **Table S47** and **Table S48**. The summary of findings table is provided as **Table S49**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related

worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Four observational studies[53,60,89,90] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to yi-gan san (follow-up duration ranged from 1 month to 77 months). One retrospective study[89] reported a CGI-I mean improvement of 1.7 points in 36 patients treated with yi-gan san (**Table S47**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S49**).

A second study[90] reported an improvement in the Japanese RBDQ (RBDQ-JP) Factor 2 score in 11 patients treated with yi-gan san (**Table S47**). The certainty of evidence was very low due to imprecision associated with a small sample size (**Table S49**).

Another study[53] reported a reduction in RBD symptom frequency for 1 patient (**Table S48**). A fourth study[60] showed full suppression of RBD symptoms for 1 patient with isolated RBD when yi-gan san (7.5 g/d) was combined with clonazepam (0.25 mg/d) (**Table S48**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S49**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for yi-gan san to treat isolated RBD was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of yi-gan san. The use of yi-gan san demonstrated improvements in CGI-I score, RBDQ-JP Factor 2 score, and RBD symptoms in patients with isolated RBD.

Across all observational studies included in the systematic review that reported on the use of yi-gan san in patients with isolated RBD, there was a report of mild gastric distress in 1 patient. Although the evidence has shown no significant side effects, the TF could not conclude how large the magnitude of harmful effects would be for yi-gan san, due to uncertainty with its long-term and variable harmful effects, lack of clinical experience, and multiple formulations of yi-gan san available.

Resource use: The TF concluded that there was a moderate savings in resource use for yi-gan san, given its relatively low cost compared with the potential high cost of injury due to dream enactment during sleep. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use yi-gan san when compared with no treatment for their isolated RBD. This is based on the TF's determination that the balance of benefits vs harms favors the use of yi-gan san. There may be some patients, however, who are concerned with the lack of FDA regulation for yi-gan san.

Secondary RBD due to a medical condition

The following interventions are those for which recommendations were made in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 1 double-blind, placebo-controlled RCT[91] for the treatment of RBD with clonazepam in 19 adult patients diagnosed with RBD and PD. This study assessed clonazepam in 19 patients vs 20 patients in a placebo group, at a dose of 0.5 mg. In addition, the TF identified 38 observational studies[16,21,22,37,40,42,44,47,52,54–59,61,92–113] that examined the effect of clonazepam on 663 adult patients with secondary RBD due to a medical condition, including PD and DLB. Participants in these studies were primarily middle-aged or older men (mean age of 58 years; 79% male). The observational studies included retrospective and prospective cohort, case-control, case series, and case report designs.

The figures and tables are provided as **Figures S21–S24** and **Tables S50–S53** and **Tables S55-S59**. The summary of findings table is provided as **Table S60**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency of significant bed partner sleep disruption, frequency and/or intensity of dream enactment episodes, and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: treatment-related worsening in gait stability or treatment-related worsening in symptoms of depression or anxiety.

Frequency of significant bed partner sleep disruption: One RCT[91] evaluated the effect of clonazepam on the frequency of significant bed partner sleep disruption using the CGI-I scale. The mean difference in CGI-I post-treatment score (4-week follow-up) between the clonazepam and placebo groups was –0.48, which was not clinically significant (**Table S50**, **Figure S21**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S60**).

One case report[98] reported a significant reduction in the frequency of significant bed partner sleep disruption in 1 patient after 1 week of treatment with clonazepam (**Table S51**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S60**).

Frequency and/or intensity of dream enactment episodes: One RCT[91] evaluated the effect of clonazepam on frequency and/or intensity of dream enactment episodes using the CGI-I scale. The mean difference in CGI-I post-treatment score (4-week follow-up) between the clonazepam and placebo groups was –0.48, which was not clinically significant (**Table S52**, **Figure S22**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S60**).

Thirty-seven observational studies[16,21,22,37,40,42,44,47,52,54–59,61,92–112] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to clonazepam (follow-up duration ranged from 1 week to 6 years). These studies showed improvement in RBD symptoms in 87% of their patients, which was clinically significant (**Table S53**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S60**).

Treatment-related worsening in sedation or cognitive impairment: One RCT[91] evaluated the effect of clonazepam on excessive daytime sleepiness using the Korean Epworth Sleepiness Scale (KESS) tool (follow-up duration was 4 weeks). This study showed that the mean change in KESS score for the clonazepam group was 4.1 points lower than the mean change in KESS score for the placebo group (**Table S55**, **Figure S23**). The certainty of evidence was high (**Table S60**).

Ten observational studies[22,52,58,92,94,96,100,106,109,113] reported on the percentage of patients who demonstrated worsening in sedation or cognitive impairment in response to clonazepam (follow-up duration ranged from 9 months to 6 years). These studies showed an adverse effect in sedation or cognitive impairment in 28% of their patients, which was clinically significant (**Table S56**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S60**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone (tonic and/or phasic) and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, or sleep quality.

Change in REM motor tone—tonic and/or phasic: One case report[104] evaluated the effect of clonazepam (1–2 mg/d) on phasic and tonic EMG% for 1 patient with hyperekplexia (follow-up duration was not reported). This study reported an improvement in phasic EMG activities during REM sleep (from 40.6% to 11.2%) (**Table S57**) and in tonic EMG activities during REM sleep (from 40.0% to 3.7%) (**Table S58**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S60**).

Daytime motor function: One RCT[91] evaluated the effect of clonazepam on daytime motor function using the Unified Parkinson's Disease Rating Scale (UPDRS) tool (follow-up duration was 4 weeks). This study showed a mean difference of 0.5 points lower UPDRS Part III score in the clonazepam group compared with the placebo group. This difference was not clinically significant (**Table S59**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S60**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for clonazepam to treat secondary RBD due to a medical condition was low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision associated with a small sample size ($n < 30$) and a wide 95% confidence interval that crossed the CST. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and worsening in sedation or cognitive impairment.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of clonazepam. The use of clonazepam demonstrated improvements in KESS score and RBD symptoms in patients with secondary RBD due to a medical condition.

In the single RCT included in the systematic review that reported on the use of clonazepam, commonly reported adverse events included daytime sleepiness (21.1%), dizziness (15.8%), and postural instability (5.3%). Commonly reported adverse events across all observational studies on the use of clonazepam included excessive daytime sleepiness (19.6%), unsteadiness (16.1%), and dizziness (7.5%). The TF determined that the harmful effects of clonazepam are small.

While the overall certainty of evidence for efficacy was low the value and relative safety of clonazepam at low doses has been reported in RBD studies over nearly 40 years, there was a substantial concern by the TF that harms may be expected to progressively increase over time among individuals with neurodegenerative disease.

Resource use: The TF concluded that there was a moderate savings in resource use for clonazepam, given its relatively low cost compared with the potential high cost of potentially severe life-threatening injury due to dream enactment during sleep, but also considering the higher risk of adverse effects in the neurodegenerative disorder population. Per the NADAC database, the unit cost of 1-mg and 2-mg tablets ranged from $0.03 to $0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would

most likely use clonazepam when compared with no treatment for their secondary RBD due to a medical condition. This is based on the TF's determination that the undesirable effects are relatively small and that the balance of benefits vs harms favors the use of clonazepam in low doses, although there is concern for confusion as an adverse effect for patients with a neurodegenerative disorder.

Deep-brain stimulation

Our review of the literature identified 4 observational studies[114–117] that examined the effect of deep-brain stimulation on 66 adult patients with secondary RBD due to a medical condition. Participants in these studies were primarily middle-aged or older men (mean age of 62 years; 61% male). The observational studies included open-label trial, prospective cohort, cross-sectional, and case report designs.

The tables are provided as **Tables S62–S68**. The summary of findings table is provided as **Table S69**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Three observational studies[114,115,117] reported on the percentage of patients with PD that demonstrated partial or complete improvement in RBD symptoms in response to deep-brain stimulation (follow-up duration ranged from 6 months to 1 year) (**Table S62**). The first study[114] showed an increase in dream enactment after deep-brain stimulation for 2 of 3 patients. In the second study,[115] the occurrence of RBD was unchanged with regard to subjective complaints and videographical assessments in all 50 patients reported. The third study[117] showed no improvement in any of the 8 patients who reported RBD symptoms. The certainty of evidence was low due to risk of bias associated with observational studies (**Table S69**).

Treatment-related worsening in sedation or cognitive impairment: Two observational studies[115,116] reported on changes in ESS scores for patients with PD (follow-up duration ranged from 3 to 7.7 months) (**Table S63**). The first study[115] was an open-label trial that showed a clinically significant pre-post reduction in mean ESS score of 2.0 points for 50 patients. The second study[116] was a cohort study that reported a clinically significant pre-post reduction in mean ESS score of 3.2 points for 5 patients. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S69**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone (tonic and/or phasic), sleep quality, and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares or quality of life.

Change in REM motor tone—tonic and/or phasic: Two observational studies[115,117] evaluated the effect of deep-brain stimulation on REM motor tone (follow-up duration ranged from 6 to 7.7 months) (**Table S64**). One study[115] showed a 2.4% reduction in REM sleep without atonia for 40 patients with PD. The other study[117] showed a clinically significant 20.6% reduction in phasic EMG% for 11 patients with PD. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S69**).

One case series study[114] reported on 3 patients with PD and parasomnia overlap disorder who demonstrated improvement in REM motor tone (follow-up duration ranged from 1 to 13 years). This study showed significant improvement in tonic EMG% for 2 of 3 patients (**Table S65**) and in phasic EMG% for 1 of 3 patients (**Table S66**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S69**).

Sleep quality: One observational study[117] evaluated the effect of deep-brain stimulation on sleep quality using the PSQI (follow-up duration was 6 months). This cohort study[117] showed a clinically significant 9.4-point pre-post reduction of PSQI for 11 patients with PD (**Table S67**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S69**).

Daytime motor function: Two observational studies[115,116] evaluated the effect of deep-brain stimulation on daytime motor function using various tools (follow-up duration ranged from 3 to 7.7 months) (**Table S68**). One open-label study[115] showed a clinically significant 9.5-point pre-post reduction in UPDRS (Part III) score for 50 patients with PD. A second study[116] showed a clinically significant 26.5-point pre-post reduction in UPDRS (Part III) score for 5 patients with PD. The certainty of evidence was low due to risk of bias associated with observational studies (**Table S69**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for deep-brain stimulation to treat secondary RBD due to a medical condition was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of no treatment specifically for RBD outcomes without comment on such balance for the relevant outcomes for the underlying neurological disorder. The use of deep-brain stimulation

demonstrated improvement in ESS score but no improvement in RBD symptoms in patients with secondary RBD due to a medical condition.

Across the observational studies included in the systematic review that reported on the use of deep-brain stimulation, increased periodic limb movements were reported in 2 patients. Commonly reported adverse events include depression, memory impairment, seizures, anxiety, agitation, confusion, dizziness, abnormal movements, pain at implant site, paresthesias, and hardware complications. The TF determined that the harmful effects of deep-brain stimulation are small, based on the typical risks associated with surgery and placement of the leads.

Resource use: The TF concluded that there was a large cost in resource use for deep-brain stimulation, as equipment, hospital, and follow-up costs would be prohibitive if considering RBD as an indication.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The vast majority of patients who require treatment for dream enactment would most likely not use deep-brain stimulation when compared with no treatment for their secondary RBD due to a medical condition. Most patients would prefer a pharmacological treatment rather than accept the risks of a surgical procedure.

Melatonin

Our review of the literature identified 2 double-blind, placebo-controlled RCTs[72,118] and 11 observational studies[21,22,47,74,76,92,102,119–122] (2 on prolonged-release and 9 on immediate-release melatonin) that examined the effect of melatonin on secondary RBD due to a medical condition. Participants in these studies were primarily middle-aged or older men (mean age of 61 years; 78% male). The observational studies included open-label trial, retrospective and prospective cohort, case-control, case series, and case report designs.

The figures and tables are provided as **Figures S25–S29** and **Tables S70–S75**. The summary of findings tables are provided as **Table S76** and **Table S77**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One RCT[118] evaluated the effect of prolonged-release melatonin on the frequency of dream enactment episodes (follow-up duration was 8 weeks). This study showed an 32.9% increase in percentage mean change in RBD events per week for the 15-patient melatonin group (4-mg dose) compared with the 15-patient placebo group and a 30.8% increase in percentage mean change in RBD nights per week for the melatonin group compared with placebo (**Table S72**, **Figure S26** and **Figure S27**). These differences reflect the difference in RBD events per week and RBD nights per week between prolonged-release melatonin and placebo. While these outcomes both decreased with each treatment, there were no significant differences between treatment group, with placebo showing a greater reduction in each outcome compared with prolonged release melatonin. The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S77**).

A second RCT[72] assessed immediate-release melatonin in 8 patients vs 8 patients in a placebo group, at a dose of 3 mg (follow-up duration was 4 weeks). This study showed a 1.2-point decrease in mean CGI score for the melatonin group compared with the placebo group (**Table S70**, **Figure S25**). This change was not clinically significant. The certainty of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S76**).

Two observational studies[22,121] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to prolonged-release melatonin (follow-up duration ranged from 20 to 31 months). Both studies showed improvement in RBD symptoms in all 3 of their patients, which was clinically significant (**Table S73**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S77**).

One retrospective observational study[76] evaluated the effect of immediate-release melatonin (6 mg) on the frequency of dream enactment episodes for 26 patients with RBD and PD (follow-up duration was 4 months). This study showed a clinically significant 88.8% reduction in dream-acting episodes per week and a clinically significant 93.5% reduction in vocalization episodes (**Table S71**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S76**).

Eight observational studies[21,47,74,92,102,119,120,122] reported on the percentage of patients who had demonstrated partial or complete improvement in RBD symptoms in response to immediate-release melatonin (follow-up duration ranged from 6 weeks to 38 months). These studies showed improvement in RBD symptoms in 76% of their patients, which was clinically significant (**Table S73**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S76**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams

and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One RCT[72] evaluated the effect of immediate-release melatonin on RWA after 4 weeks of treatment, showing a 3.8% reduction for the melatonin group compared with the placebo group (**Table S74**, **Figure S28**). This study also reported on phasic EMG%, showing a 1.5% reduction in mean change for the melatonin group compared with the placebo group (**Table S74**, **Figure S29**). The certainty of evidence was moderate due to imprecision associated with a small sample size (**Table S76**).

Two observational studies[74,76] evaluated the effect of immediate-release melatonin on the percentage of RWA, showing a significant RWA decrease from 32% to 11% (21% reduction) and RWA decrease from 47% to 1.4% (45.6% reduction) pre-post treatment for 6 patients (6 weeks) and 26 patients (4 months), respectively (**Table S75**). The certainty of evidence was very low due to imprecision associated with a small sample size (**Table S76**).

One observational study[74] evaluated the effect of immediate-release melatonin on phasic EMG%, showing a nonsignificant pre-post treatment increase from 29% to 32% for 6 patients (follow-up duration was 6 weeks) (**Table S75**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S76**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for melatonin to treat secondary RBD due to a medical condition was low for immediate-release melatonin and moderate for prolonged-release melatonin, based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision associated with a small sample size ($n < 30$) and a wide 95% confidence interval that crossed the CST. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and worsening in sedation or cognitive impairment for immediate-release melatonin but were not met for prolonged-release melatonin.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of immediate-release melatonin over no treatment and did not favor prolonged-release melatonin or no treatment. The use of immediate-release melatonin demonstrated moderate improvements in RBD dream-acting and vocalization episodes per month and RBD symptoms in patients with secondary RBD due to a medical condition. The use of prolonged-release melatonin demonstrated improvements in RBD symptoms in patients with secondary RBD due to a medical condition, but this was based on only 3 patients from 2 observational studies, limiting the generalizability of these results with no improvement vs placebo in a small RCT.

Across all RCTs included in the systematic review that reported on the use of melatonin, commonly reported adverse events included headache (6.3%) and nausea (6.3%). Commonly reported adverse events across all observational studies on the use of melatonin included excessive daytime sleepiness (25.0%), headache (14.3%), and trouble thinking (12.0%). Given extensive clinical experience with melatonin, the TF determined that the harmful effects of immediate-release melatonin are trivial and the harmful effects of prolonged-release melatonin are small.

Resource use: The TF concluded that there was a large savings in resource use for melatonin, given its relatively low cost compared with the potential high cost of injury due to dream enactment during sleep. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The vast majority of patients who require treatment for dream enactment would most likely use melatonin when compared with no treatment for their secondary RBD due to a medical condition. This is based on the TF's determination that the undesirable effects are trivial and that the balance of benefits vs harms favors the use of immediate-release melatonin. There may be some providers and patients, however, who are concerned with the lack of FDA regulation for melatonin.

Rivastigmine

Our review of the literature identified 1 single-blind, placebo-controlled, crossover RCT[123] that examined the effect of rivastigmine on 12 older patients (11 male, 1 female; mean age of 67 years) with secondary RBD due to PD who were refractory to melatonin (up to 5 mg) and clonazepam (up to 2 mg). This RCT assessed a 4.6-mg/d rivastigmine patch in 12 patients vs placebo with an intervening washout period.

The figures and tables are provided as **Figure S30** and **Table S78** and **Table S79**. The summary of findings table is provided as **Table S80**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One RCT[123] evaluated the effect of rivastigmine on the frequency of dream enactment episodes (follow-up duration was 3 weeks). This study showed a clinically significant 45.4% reduction in percentage mean change in dream enactment episodes per week for the rivastigmine group compared with when patients were in the placebo arm (**Table S78**, **Figure S30**). Two of 12 patients dropped out due to orthostatic hypotension and asthenia. The certainty of evidence was moderate due to

imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S80**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One RCT[123] evaluated the effect of rivastigmine on RWA features (follow-up duration was 3 weeks). This study showed that, for a subset of 4 patients, RWA features were not modified when compared with baseline (**Table S79**). The certainty of evidence was moderate due to imprecision associated with a small sample size (**Table S80**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for rivastigmine to treat secondary RBD due to a medical condition was moderate based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30 and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of rivastigmine. The use of rivastigmine demonstrated moderate improvements in RBD episodes per week and RBD symptoms in patients with secondary RBD due to a medical condition.

In the RCT included in the systematic review that reported on the use of rivastigmine in patients with secondary RBD due to a medical condition, adverse events leading to withdrawal occurred in 2 of 12 patients with PD and consisted of orthostatic hypotension and asthenia. Other commonly reported adverse events included daytime sleepiness (66.7%) and nausea (33.3%). The TF determined that the harmful effects of rivastigmine are moderate for patients with secondary RBD due to a medical condition.

Resource use: The TF concluded that there was a moderate savings in resource use for rivastigmine, despite its relatively greater costs than other RBD treatments, due to the potential cost of injury due to dream enactment during sleep. Per the NADAC database, the unit cost of a rivastigmine patch ranged from $4.19 to $4.27.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use rivastigmine when compared with no treatment for their secondary RBD due to a medical condition. This is based on the TF's determination that the balance of benefits vs harms favors the use of rivastigmine.

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Cannabidiol

Our review of the literature identified 1 single-blind, placebo-controlled, crossover RCT[124] and 1 observational study[125] that examined the effect of cannabidiol (75–300 mg) on adult patients with secondary RBD due to a medical condition. Participants in the observational study were 4 older male patients.

The figures and tables are provided as **Figures S31–S38** and **Tables S81–S86**. The summary of findings table is provided as **Table S87**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One RCT[124] evaluated the effect of cannabidiol on the frequency of dream enactment episodes (follow-up duration was 12 weeks). This study showed a 9.0% increase in percentage mean change in RBD nights per week for the 17 patients in the cannabidiol group compared with the 16 patients in the placebo group, and a 0.12 increase in mean change in CGI-I score for the cannabidiol group compared with the placebo group (**Table S81**, **Figure S31**, **Figure S32**). Neither of these changes was clinically significant. The certainty of evidence for the RBD frequency was moderate due to imprecision. The certainty of evidence for CGI-I was high (**Table S87**).

One case series study[125] showed a substantial reduction in the frequency of RBD symptoms in response to cannabidiol in all 4 patients (follow-up duration was 6 weeks), which was clinically significant (**Table S82**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S87**).

Treatment-related worsening in sedation or cognitive impairment: One RCT[124] evaluated the effect of cannabidiol on the treatment-related worsening in sedation or cognitive impairment (follow-up duration was 12 weeks). This study showed a 1.83-point reduction in mean change in ESS score for the cannabidiol group compared with the placebo group (**Table S83**, **Figure S33**). This change was not clinically significant. The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S87**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone (tonic and/or phasic), sleep quality, and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares or quality of life.

Change in REM motor tone—tonic and/or phasic: One RCT[124] evaluated the effect of cannabidiol on the change in REM motor tone—tonic and/or phasic (follow-up duration was 12 weeks). This study showed a 1.3% reduction in percentage mean change in phasic RWA index for the cannabidiol group compared with the placebo group and a 2.9% reduction in percentage mean change in tonic RWA index for the cannabidiol group compared with the placebo group (**Table S84**, **Figure S34** and **Figure S35**). Neither of these changes was clinically significant. The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S87**).

Sleep quality: One RCT[124] evaluated the effect of cannabidiol on sleep quality (follow-up duration was 12 weeks). This study showed a 0.46-point reduction in mean change in PSQI score for the cannabidiol group compared with the placebo group, which was not clinically significant (**Table S85**, **Figure S36**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S87**).

Daytime motor function: One RCT[124] evaluated the effect of cannabidiol on daytime motor function (follow-up duration was 12 weeks). This study showed a 0.05-point reduction in percentage mean change in UPDRS-III (off) score for the cannabidiol group compared with the placebo group (**Table S86**, **Figure S37**) and a clinically significant 7.16-point reduction in mean change in UPDRS-III (on) score for the cannabidiol group compared with the placebo group (**Table S86**, **Figure S38**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S87**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for cannabidiol to treat secondary RBD due to medical condition was low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$ and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes in the observational study but not in the RCT.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored cannabidiol or no treatment. The use of cannabidiol demonstrated small improvements in RBD symptoms in patients with secondary RBD due to a medical condition.

In the observational study included in the systematic review that reported on the use of cannabidiol, no adverse events were reported. The TF was unable to determine how large the harmful effects of cannabidiol were based on the limited available evidence on adverse effects in patients with secondary RBD due to a medical condition.

Resource use: The TF concluded that the difference in resource use between cannabidiol and no treatment varied, depending on its availability in different regions. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely not use cannabidiol when compared with no treatment for their secondary RBD due to a medical condition. Some patients may also be concerned with the stigma associated with taking cannabidiol.

Carbidopa-levodopa

Our review of the literature identified 4 observational studies[126–129] that examined the effect of carbidopa-levodopa on 48 adult patients with secondary RBD due to a medical condition. Participants in these studies were primarily middle-aged or older (mean age of 67 years) and with an even mix of men and women (54% female).

The tables are provided as **Tables S88–S92**. The summary of findings table is provided as **Table S93**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Two observational studies[127,129] reported on 4 patients who demonstrated improvement in RBD symptoms in response to carbidopa-levodopa (follow-up duration not reported). The first study[127] was a case report that showed improvement in RBD symptoms for its patient with Machado-Joseph disease following treatment with carbidopa-levodopa and temazepam. The second study[129] reported improvement in RBD symptoms for all 3 patients with PD after starting treatment with carbidopa-levodopa (**Table S88**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S93**).

Treatment-related worsening in sedation or cognitive impairment: One observational study[128] evaluated the effect of carbidopa-levodopa-entacapone on the treatment-related worsening in sedation or cognitive impairment for 39 patients with PD using the ESS (follow-up duration was 3 months). This open-label

trial reported a clinically significant 3.9-point pre-post increase in ESS score (**Table S89**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S93**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone (tonic and/or phasic), quality of life, and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares or sleep quality.

Change in REM motor tone—tonic and/or phasic: One observational study[126] evaluated the effect of carbidopa-levodopa on change in REM motor tone for patients with PD (mean follow-up duration was 184.4 ± 52.2 days). This case-control study reported a clinically significant 5.34 pre-post increase in phasic EMG twitches and a clinically significant 4.28 pre-post increase in tonic motor activity (**Table S90**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S93**).

Quality of life: One observational study[128] evaluated the effect of carbidopa-levodopa-entacapone on quality of life for 39 patients with PD using the UPDRS and Schwab and England disability scale (SE-ADL) (follow-up duration was 3 months). This open-label study reported a clinically significant 5.2-point pre-post reduction in UPDRS total score and a 0.6-point pre-post reduction in SE-ADL score (**Table S91**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S93**).

Daytime motor function: One observational study[128] evaluated the effect of carbidopa-levodopa-entacapone on daytime motor function for 39 patients with PD using the UPDRS and SE-ADL (follow-up duration was 3 months). This open-label study reported a clinically significant 3.4-point pre-post reduction in UPDRS-III score (**Table S92**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S93**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for carbidopa-levodopa to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$ and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored carbidopa-levodopa or no treatment. The use of carbidopa-levodopa demonstrated improvements in RBD symptoms in patients with secondary RBD due to a medical condition, but this was from case reports of only 4 patients, with 1 patient being treated with a combination of carbidopa-levodopa and temazepam.

Across all observational studies included in the systematic review that reported on the use of carbidopa-levodopa, no significant adverse events were reported besides sleepiness. The TF determined that the harmful effects of carbidopa-levodopa would vary depending on the type of secondary RBD being treated.

Resource use: The TF was unable to conclude how large the difference in resource use was between carbidopa-levodopa and no treatment due to the uncertainty of the balance between its desirable and undesirable effects. Per the NADAC database, the unit cost of 25- to 100-mg tablets was $0.10.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use carbidopa-levodopa when compared with no treatment for their secondary RBD due to a medical condition.

Donepezil

Our review of the literature identified 5 observational studies[105,113,130–132] that examined the effect of donepezil on 10 adult patients with secondary RBD due to a medical condition. These studies assessed donepezil at doses ranging from 3 to 10 mg in patients with DLB, with the exception of 1 patient who developed RBD symptoms after craniopharyngioma resection. Participants in these studies were primarily middle-aged or older (mean age of 73 years), and with an even mix of men and women (54% male).

The tables are provided as **Tables S94–S98**. The summary of findings table is provided as **Table S99**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes, treatment-related worsening in sedation or cognitive impairment, and treatment-related worsening in symptoms of depression or anxiety. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: Five observational studies[105,113,130–132] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to donepezil (follow-up duration ranged from 23 days to 1 year). These studies showed improvement in RBD symptoms in 50% of their patients, which was clinically significant (**Table S94**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S99**).

Treatment-related change in sedation or cognitive impairment: One observational study[130] reported on positive treatment-related change in cognitive impairment for patients with DLB and sleep disturbance in response to donepezil as measured on the Mini-Mental State Examination score, Letter Fluency score, and reduction in Mayo Fluctuations Scale score; however, it was unclear how many of these patients had RBD (**Table S95**). These findings are not unexpected based on the agent and not necessarily thought to be due to improvement in RBD. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S99**).

One case report[131] reported on the effect of donepezil on cognitive impairment in a patient with DLB (follow-up duration was 23 days). This study showed a 4-point improvement in Mini-Mental State Examination score in the patient (**Table S96**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S99**).

Treatment-related worsening in symptoms of depression or anxiety: One observational study[130] reported on the treatment-related worsening in symptoms of depression or anxiety for patients with DLB in response to donepezil (**Table S97**). This open-label trial showed a clinically significant 11.4-point improvement in Neuro-psychiatric Inventory (NPI) score. It was unclear how many of these patients also had RBD. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S99**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: sleep quality. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, or daytime motor function.

Sleep quality: One observational study[131] reported on the effect of donepezil on sleep quality in a patient with DLB (follow-up duration was 23 days). This case report reported a clinically significant 3-point reduction in the PSQI (from 12 to 9) (**Table S98**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S99**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for donepezil to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$ and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment in 3 of 5 observational studies.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored donepezil or no treatment. The use of donepezil demonstrated improvements in RBD symptoms as well as potentially measures of cognition in patients with secondary RBD due to a medical condition; however, the TF was unable to make a recommendation due to the very low certainty of evidence combined with a high withdrawal rate.

Across all observational studies included in the systematic review that reported on the use of donepezil in patients with secondary RBD due to a medical condition, adverse events leading to withdrawal occurred in 8 patients[130] (unclear number with RBD) and consisted of nausea, anorexia, abdominal discomfort, cerebral infarction (presumed incidental), neuropsychiatric symptoms, and difficulty falling asleep. The TF determined that the harmful effects of donepezil are small based on their clinical experience in treating patients with PD and DLB.

Resource use: The TF was unable to conclude how large the difference in resource use was between donepezil and no treatment due to the uncertainty of the balance between its desirable and undesirable effects. Per the NADAC database, the unit cost of 5-mg and 10-mg tablets was $0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. It was uncertain if donepezil would be acceptable to patients for treatment of their secondary RBD due to a medical condition. This is mainly based on the uncertainty of the balance between its desirable and undesirable effects.

Intravenous immunoglobulin

Our review of the literature identified 3 observational studies[133–135] that examined the effect of intravenous (IV) immunoglobulin on 8 adult patients with secondary RBD due to a medical condition.

The tables are provided as **Tables S100–S102**. The summary of findings table is provided as **Table S103**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in symptoms of depression or anxiety, or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: Three observational studies[133–135] reported on 8 patients who

demonstrated improvement in RBD symptoms in response to IV immunoglobulin (follow-up duration ranged from 3 to 86 months) (**Table S100**). Two of the studies[133,135] showed improvement in RBD symptoms in all of their patients (Baiardi et al[133] was a case report of 1 older male patient with Morvan syndrome; Vale et al[135] reported data on 2 female patients with paraneoplastic cerebellar degeneration). The third study[134] was a case series study that showed complete resolution of RBD symptoms after 12–86 months in 3 of 5 older male patients with limbic encephalitis. The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S103**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One case series study[134] showed clinically significant improvement in tonic EMG% and phasic EMG% for 2 patients who had PSG before and after treatment with IV immunoglobulin (follow-up duration ranged from 62 to 86 months) (**Table S101** and **Table S102**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S103**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for IV immunoglobulin to treat secondary RBD due to a condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded the balance between the desirable and undesirable effects varied on whether it favored IV immunoglobulin or no treatment, depending on the secondary cause being treated. The use of IV immunoglobulin demonstrated moderate improvements in RBD symptoms in patients with secondary RBD due to a medical condition, specifically autoimmune and paraneoplastic etiologies.

Across all observational studies included in the systematic review that reported on the use of IV immunoglobulin, no adverse events were reported. Commonly reported adverse events include flushing, headache, malaise, fever, chills, fatigue, and lethargy, which are normally transient and mild. The TF determined that the harmful effects of IV immunoglobulin are small.

Resource use: The TF concluded that there were large costs in resource use for IV immunoglobulin, as out-of-pocket medication and hospital costs would be prohibitive if it is considered as a treatment for RBD and not for the primary disease of an autoimmune or paraneoplastic disorder. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups in whether patients would use IV immunoglobulin when compared with no treatment for their secondary RBD due to a medical condition. Patients who experience only RBD or with RBD not due to an autoimmune or paraneoplastic cause would likely not choose IV immunoglobulin as a treatment.

Light therapy

Our review of the literature identified 1 observational study[136] that examined the effect of light therapy on 83 older patients (65% male) with PD. This study had limited application to the clinical practice guideline as there were no clear or standardized outcomes measures for RBD, only a composite RBD severity score.

The table is provided as **Table S104**. The summary of findings table is provided as **Table S105**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One observational study[136] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to light therapy (**Table S104**). This retrospective study showed that treatment with light therapy (3000–4000 lux) resulted in a mean 54.5% reduction in RBD severity score, which was clinically significant (follow-up duration ranged from 42 to 60 months). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S105**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for light therapy to treat secondary RBD due to a medical condition was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of light therapy. The use of light therapy demonstrated moderate improvements in RBD severity score in patients with secondary RBD due to a medical condition.

In the observational study included in the systematic review that reported on the use of light therapy, no adverse events were reported. The TF determined that the harmful effects of light therapy are trivial based on their clinical experience with this type of intervention.

Resource use: The TF concluded that there was a moderate savings in resource use for light therapy, given its larger upfront costs but no monthly medication costs, compared with the potential high cost of injury due to dream enactment during sleep.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use light therapy when compared with no treatment for their secondary RBD due to a medical condition. This is mainly based on the TF's determination that the balance of benefits and harms favored light therapy over no treatment.

Memantine

Our review of the literature identified 1 double-blind, placebo-controlled RCT[137] that examined the effect of memantine on older patients (40 male, 17 female) with either DLB or PD on self-reported physical activity in sleep ascertained by the Stavanger Sleepiness Questionnaire. This study assessed memantine in 27 patients vs a placebo group of 30 patients using a 20-mg dose.

The figures and tables are provided as **Figures S39–S41** and **Tables S106–S108**. The summary of findings table is provided as **Table S109**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: treatment-related worsening in sedation or cognitive impairment and treatment-related worsening in symptoms of depression or anxiety. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, frequency and/or intensity of dream enactment episodes, or treatment-related worsening in gait stability.

Treatment-related worsening in sedation or cognitive impairment: One double-blind, placebo-controlled RCT[137] reported on the treatment-related worsening in sedation in response to memantine using the ESS (follow-up duration was 24 weeks). This study showed a 0.4-point increase in mean change for the memantine group compared with the placebo group, which was not clinically significant (**Table S106**, **Figure S39**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S109**).

Treatment-related worsening in symptoms of depression or anxiety: One double-blind, placebo-controlled RCT[137] reported on symptoms of depression or anxiety in response to memantine using the NPI score (follow-up duration was 24 weeks). This study showed a 0.1-point reduction in mean change for the memantine group compared with the placebo group, which was not clinically significant (**Table S107**, **Figure S40**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S109**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, or sleep quality.

Daytime motor function: One double-blind, placebo-controlled RCT[137] reported on daytime motor function in response to memantine using the UPDRS (Part III). This study showed a 0.2-point increase in mean change for the memantine group compared with the placebo group, which was not clinically significant (**Table S108**, **Figure S41**). The certainty of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (**Table S109**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for memantine to treat secondary RBD due to a medical condition was moderate based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (wide 95% confidence interval that crossed the CST).

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of no treatment. The use of memantine demonstrated only minimal improvement in NPI score in patients with secondary RBD due to a medical condition.

In the RCT included in the systematic review that reported on the use of memantine, 1 patient treated with memantine withdrew from the study due to adverse events, which were not specified. The TF determined that the harmful effects of memantine are small based on the TF's clinical experience with memantine in treating patients with dementia.

Resource use: The TF concluded that there was a moderate savings in resource use for memantine, given its relatively low cost compared with the potential cost of injury due to dream enactment during sleep. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of

patients with DLB or dementias associated with PD would most likely use memantine when compared with no treatment for their physical activity during secondary RBD due to a medical condition.

Positive airway pressure therapy

Our review of the literature identified 3 observational studies[25,40,138] that examined the effect of positive airway pressure (PAP) therapy on 29 adult patients with RBD comorbid to obstructive sleep apnea (OSA). Participants in these studies were primarily middle-aged or older men (mean age of 58 years; 93% male).

The table is provided as **Table S110**. The summary of findings table is provided as **Table S111**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Three observational studies[25,40,138] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to PAP therapy (**Table S110**). One case report[25] showed improvement in its patient's sleep pattern when treated with PAP therapy for 3 years. A cohort study[138] reported improvement in RBD symptoms for 11 of 27 patients treated with CPAP therapy. One cross-sectional cohort study[40] showed 1 patient's RBD symptoms being well controlled with a combined treatment of CPAP therapy and clonazepam (0.5–1 mg) (follow-up duration was 10 months). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S111**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for PAP therapy to treat RBD was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects varied on whether it favored PAP therapy or no treatment for the treatment of isolated RBD, depending on whether OSA is a comorbidity. The use of PAP therapy demonstrated improvements in RBD symptoms in patients with isolated RBD, but these patients were also being treated with clonazepam and/or melatonin, and there was no evidence reported on patients without OSA.

The TF determined that the harmful effects of PAP therapy are trivial based on their clinical experience with its well-known minimal side effects.

Resource use: The TF concluded that the difference in resource use between PAP therapy and no treatment varied due to the uncertainty of the balance between its desirable and undesirable effects.

Patients' values and preferences: The TF determined that there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability in whether patients would use PAP therapy when compared with no treatment for their RBD. This was mainly based on whether OSA was present as a comorbidity in the patient.

Pramipexole

Our review of the literature identified 2 observational studies[82,139] that examined the effect of pramipexole on 20 adult patients with secondary RBD due to a medical condition. Participants in these studies were primarily middle-aged or older men (mean age of 67 years; 86% male).

The tables are provided as **Tables S112–S114**. The summary of findings table is provided as **Table S115**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in symptoms of depression or anxiety, or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: One case series study[82] showed improvement in intensity of RBD symptoms in response to pramipexole (mean dose 0.89 ± 0.31 mg) for 6 of 9 patients with PD and improvement in frequency of RBD symptoms for 8 of 9 patients with PD (follow-up duration ranged from 4 to 25 months). A second cohort study[139] reported no changes in frequency and severity of motor and vocal RBD symptoms in 11 patients with PD after treatment with pramipexole (follow-up duration was 3 months) (**Table S112**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S115**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: quality of life and

daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), or sleep quality.

Quality of life: One observational cohort study[139] evaluated the effect of pramipexole (0.54 mg) on quality of life in 11 patients with PD (follow-up duration was 3 months). This study reported on a 11.7% pre-post increase in the Schwab and England disability scale score (**Table S113**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S115**).

Daytime motor function: One observational cohort study[139] evaluated the effect of pramipexole (0.54 mg) on daytime motor function in 11 patients with PD (follow-up duration was 3 months). This study reported a 7.8-point clinically significant reduction in UPDRS (Part III) score (**Table S114**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S115**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for pramipexole to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of $n < 30$). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects does not favor either pramipexole or no treatment. This conclusion was reached after balancing the results of 2 clinical trials. Only 1 study[82] had a positive result, and its findings were based on subjective impressions from patient and bed partners. Further, it is likely that pramipexole decreased ancillary nocturnal motor activity and periodic limb movements, and would explain, at least partially, an impression by patients and bed partners of lesser nocturnal motor activity. This conclusion is supported by the separate investigation[139] that included follow-up PSG and did not demonstrate REM motor activity. Across all observational studies included in the systematic review that reported on the use of pramipexole, commonly reported adverse events included next-day sedation (5.1%) and gastrointestinal symptoms (3.1%). The TF determined that the harmful effects of pramipexole are generally small but could be greater in patients with DLB.

Resource use: The TF concluded that there were negligible costs and savings in resource use for pramipexole, given its relatively low cost compared with the potential cost of injury due to dream enactment during sleep, but also considering the costs involved with monitoring and evaluating patients with secondary RBD due to a medical condition. Per the NADAC database, the unit cost of 0.5-mg and 1-mg tablets ranged from $0.05 to $0.06.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups in whether patients would use pramipexole when compared with no treatment for their secondary RBD due to a medical condition. Those patients with cognitive issues would likely not find pramipexole acceptable as a treatment.

Ramelteon

Our review of the literature identified 3 observational studies[96,140,141] for the treatment of RBD with ramelteon in 38 adult patients with secondary RBD due to a medical condition. The first study[96] was a case report that assessed ramelteon (8 mg) in 1 older male patient with DLB. The second study[141] was an open-label trial that assessed ramelteon (8 mg) in 35 older patients (18 female, 17 male) with PD. The third study[140] was a case series study that assessed ramelteon (8 mg) in 2 older patients (1 male, 1 female), 1 with PD and 1 with multiple system atrophy.

The tables are provided as **Tables S116–S122**. The summary of findings table is provided as **Table S123**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in symptoms of depression or anxiety, or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: One observational, open-label trial[141] evaluated the effect of ramelteon on the frequency and/or intensity of dream enactment episodes on 35 patients with PD using the RBDQ-JP. This study reported a clinically significant 46% reduction in RBDQ-JP score for the 24 patients who were diagnosed with probable RBD following treatment with ramelteon for 12 weeks (**Table S116**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S123**).

One case report[96] reported partial improvement in the frequency of dream enactment episodes in 1 patient with DLB treated with ramelteon and clonazepam. In addition, 1 case series study[140] showed clinically significant improvement in RBDQ-JP scores for 2 patients after 3 years of treatment with ramelteon (**Table S117**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S123**).

Treatment-related worsening in sedation or cognitive impairment: One observational, open-label trial[141] in 35 patients with PD reporting on the treatment-related worsening in cognitive impairment in response to ramelteon (follow-up duration was 12 weeks) showed a 0.7-point reduction in Mini-Mental State Examination score, which was not clinically significant

(**Table S118**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S123**).

One case report[96] evaluated the effect of ramelteon on the treatment-related worsening in cognitive impairment. This study showed no change in Mini-Mental State Examination score and a 1-point decline in Montreal Cognitive Assessment score following treatment with ramelteon and clonazepam (follow-up duration was 1 year) (**Table S119**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S123**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone (tonic and/or phasic), sleep quality, and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares or quality of life.

Change in REM motor tone—tonic and/or phasic: One case series study[140] reported on improvement in RWA based on chin EMG in response to ramelteon (follow-up duration was 3 years). The 2 patients in this study showed a reduction in RWA from 8.5% to 3.5% and 10.9% to 3.9%, respectively (**Table S120**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S123**).

Sleep quality: One observational, open-label trial[141] reported on sleep quality in response to ramelteon (follow-up duration was 12 weeks). This study showed a 0.6-point improvement in PSQI, which was not clinically significant (**Table S121**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S123**).

Daytime motor function: One observational, open-label trial[141] reported on daytime motor function in response to ramelteon (follow-up duration was 12 weeks). This study showed a 2.0-point improvement in UPDRS (Part III) score, which was not clinically significant (**Table S122**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S123**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for ramelteon to treat secondary RBD due to a medical condition was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes. Despite the size of the larger study including 35 patients, it was a multicenter open study without blinding or comparison intervention, and the magnitude of the placebo effect cannot be measured. In addition, it cannot be ascertained whether the RBD symptom reduction reported after 3 years of follow-up in 2 patients by Nomura et al[140] was due to ramelteon or to natural disease progression.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of ramelteon. The use of ramelteon demonstrated moderate improvements in RBDQ-JP score and RBD symptoms in patients with secondary RBD due to PD. The TF was concerned with the methodological approach and lack of RBD-specific outcomes.

Across all observational studies included in the systematic review that reported on the use of ramelteon, commonly reported adverse events included rash (8.3%) and dizziness (8.3%). The TF determined that the harmful effects of ramelteon are trivial.

Resource use: The TF concluded that there were moderate savings in resource use for ramelteon despite its greater out-of-pocket costs compared with other treatments, as there is more evidence of its efficacy in treating patients with secondary RBD due to a medical condition. Per the NADAC database, the unit cost of an 8-mg tablet was $3.53.[70] Cost, however, is a likely clear factor determining patient preference when contrasted to the comparable immediate-release melatonin. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients who require treatment for dream enactment would most likely use ramelteon when compared with no treatment for their secondary RBD due to a medical condition. This is mainly based on the TF's determination that the balance of benefits and harms favored ramelteon over no treatment. As ramelteon is a melatonin agonist, however, it is likely to be compared with immediate-release melatonin by patients as opposed to no treatment.

Rotigotine

Our review of the literature identified 1 observational study[142] for the treatment of RBD with a rotigotine transdermal patch in 11 older male patients with secondary RBD due to a medical condition. This open-label study assessed rotigotine in 11 patients with PD, at a mean dose of 12.36 ± 4.27 mg.

The tables are provided as **Tables S124–S128**. The summary of findings table is provided as **Table S129**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in symptoms of depression or anxiety, or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: One observational study[142] evaluated the effect of rotigotine on the frequency and/or intensity of dream enactment episodes for patients with PD using the Hong Kong RBDQ (RBDQ-HK)

Factor 2 score (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a 16.8% pre-post reduction in RBDQ-HK Factor 2 score, which was not clinically significant (**Table S124**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S129**).

Treatment-related worsening in sedation or cognitive impairment: One observational study[142] evaluated the effect of rotigotine on the treatment-related worsening in sedation for patients with PD using the ESS (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a clinically significant 2.0-point pre-post increase in ESS score (**Table S125**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S129**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes, but not critical, for decision making when determining whether to use this intervention: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), and daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: quality of life or sleep quality.

Frequency and/or intensity of unpleasant dreams and nightmares: One observational study[142] evaluated the effect of rotigotine on the frequency and/or intensity of unpleasant dreams and nightmares for patients with PD using the RBDQ-HK Factor 1 (dream-related) score (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a 15.9% pre-post reduction in RBDQ-HK Factor 1 score, which was not clinically significant (**Table S126**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S129**).

Change in REM motor tone—tonic and/or phasic: One observational study[142] evaluated the effect of rotigotine on change in REM motor tone for patients with PD (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a 2.0% pre-post reduction in phasic EMG% and a 1.4% pre-post reduction in tonic EMG%, which were both not clinically significant (**Table S127**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S129**).

Daytime motor function: One observational study[142] evaluated the effect of rotigotine on daytime motor function for patients with PD using the UPDRS, Part III (UPDRS-III), tool (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a clinically significant 4.0-point pre-post reduction in UPDRS-III score (**Table S128**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (**Table S129**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for rotigotine to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30 and a wide 95% confidence interval that crossed the CST). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects does not favor either rotigotine or no treatment. The use of rotigotine demonstrated small improvements in RBDQ-HK Factor 2 (behavioral) score in patients with secondary RBD due to a medical condition.

In the observational study included in the systematic review that reported on the use of rotigotine, commonly reported adverse events included application-site reaction (18.2%), nausea (9.1%), and somnolence (9.1%). The TF determined that the harmful effects of rotigotine are generally small, although they could be higher in patients with DLB.

Resource use: The TF concluded that there were moderate costs in resource use for rotigotine, given its prohibitive out-of-pocket costs compared with other treatments, but also considering the potential cost of injury due to dream enactment during sleep. Per the NADAC database, the unit cost of a 1-mg and 4-mg rotigotine patch ranged from $22.46 to $22.58.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups in whether patients would use rotigotine when compared with no treatment for their secondary RBD due to a medical condition. Those patients with cognitive issues would likely not find rotigotine acceptable as a treatment.

Sodium oxybate

Our review of the literature identified 3 observational studies[99,143,144] that examined the effect of sodium oxybate in 3 adult patients with treatment-resistant secondary RBD due to a medical condition. These case reports assessed sodium oxybate in male patients with either narcolepsy or PD, using doses ranging from 2.5 to 8 g nightly.

The table is provided as **Table S130**. The summary of findings table is provided as **Table S134**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of

significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Three case reports[99,143,144] showed improvement in RBD symptoms in response to sodium oxybate for all their patients and complete resolution in the 2 cases of RBD related to PD (**Table S130**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S134**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for sodium oxybate to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects varied on whether it favored sodium oxybate or no treatment, depending on the patient population being treated.

Across all observational studies included in the systematic review that reported on the use of sodium oxybate in patients with secondary RBD due to a medical condition, there was a report of constipation in 1 patient. However, the safety profile of sodium oxybate in patients experiencing neuropsychiatric symptoms, impairment in cognition, sundowning, or nocturnal episodes of confusion and wandering as seen in DLB, or significant balance difficulties/ataxia and urinary symptoms as seen in multiple system atrophy, is unknown.

In conclusion, the TF determined that the harmful effects of sodium oxybate may vary depending on each specific situation. Factors to consider in decision making should not be limited to RBD (ie, its severity and past treatment failures) but include the underlying condition and symptom burden specific to the patient.

Resource use: The TF concluded that there were large costs in resource use for sodium oxybate, as out-of-pocket costs may be prohibitive. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups (RBD associated with PD, DLB, and multiple system atrophy) in whether patients would use sodium oxybate when compared with no treatment for their secondary RBD due to a medical condition. This is in contrast to the case of patients with secondary RBD due to narcolepsy, a condition for which sodium oxybate is already established as standard of care and for which the benefits of the treatment are not limited to reduction in RBD symptoms.

Yi-gan san

Our review of the literature identified 2 observational studies[60,145] that examined the effect of yi-gan san on 13 adult patients with secondary RBD due to a medical condition. The first study[60] assessed yi-gan san in 2 patients at doses ranging from 2.5 to 7.5 g/day, while the second study[145] assessed yi-gan san in 11 patients at a dose of 7.5 g/day. Participants in these studies were primarily middle-aged or older men (mean age of 76 years; 67% male).

The tables are provided as **Tables S136–S138**. The summary of findings table is provided as **Table S139**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in symptoms of depression or anxiety, or treatment-related worsening in gait stability.

Frequency and/or intensity of dream enactment episodes: One case series study[60] showed full suppression of RBD symptoms for 2 patients (one with bradykinesia, one with postural instability) when yi-gan san (7.5 g/d) was combined with clonazepam (0.5 mg/d), thus limiting confidence of attributing resolution of RBD symptoms specifically to yi-gan san (**Table S136**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S139**).

One cohort study[145] reported on the effect of yi-gan san in 11 patients with DLB (follow-up duration of 4 weeks). This study showed an improvement in NPI nighttime behavior disturbance, from 5.9 ± 2.1 to 2.5 ± 1.8, following treatment with yi-gan san (7.5 g/d). This difference was not clinically significant (**Table S137**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S139**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: daytime motor function. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, or sleep quality.

Daytime motor function: One cohort study[145] evaluated the effect of yi-gan san on daytime motor function using the

UPDRS tool (follow-up duration was 4 weeks). This study showed a mean difference of 0.0 points in UPDRS Part III score. This difference was not clinically significant (**Table S138**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S139**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for yi-gan san to treat secondary RBD due to a medical condition was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcome of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored yi-gan san or no treatment based on the limited evidence from only 13 patients from the 2 observational studies. The TF could not conclude how large the magnitude of beneficial effects would be for yi-gan san.

Across all observational studies included in the systematic review that reported on the use of yi-gan san in patients with secondary RBD due to a medical condition, there were no serious adverse events reported. Although the evidence has shown no significant side effects, the TF could not conclude how large the magnitude of harmful effects would be for yi-gan san, due to uncertainty with its long-term and variable harmful effects, lack of clinical experience, and multiple formulations of yi-gan san available.

Resource use: The TF concluded that there was a moderate cost in resource use for yi-gan san, based on the more expensive costs related to yokukansankachimpihange, this new derivative of yi-gan san, that was reported in the Manabe 2020 study.[145] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined that there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups in whether patients would use yi-gan san when compared with no treatment for their secondary RBD due to a medical condition. This is based on the variability in yi-gan san's acceptability as a treatment in different countries.

Drug-induced RBD

The following interventions are those for which recommendations were made in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Drug discontinuation

Our review of the literature identified 5 observational studies[146–150] that examined the effect of drug discontinuation on 8 adult patients diagnosed with drug-induced RBD. Participants in these studies were primarily middle-aged or older men (mean age of 60 years; 88% male).

The tables are provided as **Table S140** and **Table S141**. The summary of findings table is provided as **Table S142**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Five observational studies[146–150] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to drug discontinuation (follow-up duration ranged from 2 months to 2 years). All 5 studies showed improvement in RBD symptoms for all of their patients following discontinuation of fluoxetine, bisoprolol, selegiline, fluoxetine/paroxetine, and methylphenidate/venlafaxine, respectively (**Table S140**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S142**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: Two observational studies[146,147] reported on the 3 patients who demonstrated improvement in RWA in response to drug discontinuation (follow-up duration ranged from 2 to 6 months). One case report[146] showed improvement in REM atonia for a patient after discontinuation of fluoxetine. The other case series study[147] reported on restored REM atonia for 1 of its 2 patients after discontinuation of bisoprolol (**Table S141**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S142**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for drug discontinuation to treat drug-induced RBD was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects varied on whether it favored drug discontinuation or no treatment, depending on the medication being discontinued and the type of patient population being treated. The use of drug discontinuation demonstrated large improvements in RBD symptoms in patients with drug-induced RBD.

In the observational studies included in the systematic review that reported on the use of drug discontinuation, no comorbid disorders were reported to have worsened when the inciting drug agent was discontinued. The TF determined that the harmful effects of drug discontinuation varied based on the potential secondary effects that could be unmasked when discontinuing the drug, especially certain antidepressants.

Resource use: The TF concluded that the difference in resource use between drug discontinuation and no treatment varied due to the uncertainty of the balance between its desirable and undesirable effects and the associated costs involved with the withdrawal of the inciting agent on comorbid conditions.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability on whether patients would use drug discontinuation for their drug-induced RBD, depending on the type of drug that is being discontinued and the specific clinical scenario for the patient.

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 14 observational studies[27,40,44,55–57,59,61,97,107,109,149,151,152] that examined the effect of clonazepam on 225 adult patients with drug-induced RBD. Participants in these studies were primarily middle-aged or older men (mean age of 62 years; 83% male).

The tables are provided as **Table S143** and **Table S144**. The summary of findings table is provided as **Table S145**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Fourteen observational studies[27,40,44,55–57,59,61,97,107,109,149,151,152] reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to clonazepam (follow-up duration ranged from 2 months to 6 years). These studies showed improvement in RBD symptoms in 89% of their patients, which was clinically significant (**Table S143**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S145**).

Treatment-related worsening in sedation or cognitive impairment: Three observational studies[27,59,109] reported on the percentage of patients who demonstrated worsening in sedation or cognitive impairment in response to clonazepam (follow-up duration ranged from 9 months to 3.7 years). These studies showed an adverse effect in sedation or cognitive impairment in 36% of their patients, which was clinically significant (**Table S144**). The certainty of evidence was low due to risk of bias associated with observational studies (**Table S145**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for clonazepam to treat drug-induced RBD was low based on the critical outcomes reported in the literature and due to risk of bias associated with observational studies. Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and worsening in sedation or cognitive impairment.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored clonazepam or no treatment. The use of clonazepam demonstrated improvements in RBD symptoms in patients with drug-induced RBD, but most of these observational studies involved mixed populations of patients with RBD and various comorbidities, making it difficult to determine the balance between benefits and harms in specific populations.

In the single RCT included in the systematic review that reported on the use of clonazepam, commonly reported adverse events included daytime sleepiness (21.1%), dizziness (15.8%), and postural instability (5.3%). Commonly reported adverse events across all observational studies on the use of clonazepam included excessive daytime sleepiness (19.6%), unsteadiness (16.1%), and dizziness (7.5%). The TF was unable to determine how large the harmful effects of clonazepam were due to mixed populations with various comorbidities in these studies.

Resource use: The TF was unable to conclude how large the difference in resource use was between clonazepam and no treatment due to the uncertainty of the balance between its desirable and undesirable effects. Per the NADAC database, the unit cost of 1-mg and 2-mg tablets ranged from $0.03 to $0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF, with the assistance of patient representatives, determined that there was probably no important uncertainty or variability in how much people value the main study outcomes. The majority of patients

who require treatment for dream enactment would most likely use clonazepam when compared with no treatment for their drug-induced RBD. This is mainly based on the TF's clinical experience with clonazepam in this type of patient with RBD, along with the experience of the patient representatives.

MANAGEMENT OF RBD IN PEDIATRIC POPULATIONS

The aims of the current literature review and data were focused on addressing the management of isolated (previously referred to as idiopathic) RBD, secondary RBD due to a medical condition, and drug-induced RBD. Below are detailed summaries of the evidence for pediatric populations that had supporting evidence from a total of at least 3 patients with RBD across all studies and are FDA-approved and/or available for use in the United States. The GRADE process was applied, which describes the certainty of evidence, balance of benefits and harms, patient values and preferences, and resource-use considerations that contributed to the development of the accompanying clinical practice guideline.[1]

Isolated RBD

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 1 observational study[153] that examined the effect of clonazepam on 4 pediatric patients with isolated RBD.

The table is provided as **Table S3**. The summary of findings table is provided as **Table S9**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One retrospective observational study[153] reported on the percentage of pediatric patients who demonstrated partial or complete improvement in RBD symptoms in response to clonazepam. All 4 patients in this study showed complete resolution of RBD symptoms following treatment with clonazepam (0.25 mg) (**Table S3**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S9**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for clonazepam to treat isolated RBD in pediatric patients was very low based on the critical outcomes reported in the literature, the low volume of studies, and downgrading the certainty of evidence because of imprecision (small sample size of $n < 30$). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF was unable to conclude whether the balance between the desirable and undesirable effects favored clonazepam or no treatment in pediatric patients. The use of clonazepam demonstrated large improvements in RBD symptoms in pediatric patients with isolated RBD, but this was based solely on 1 study with 4 patients.

In the single observational study included in the systematic review that reported on the use of clonazepam in pediatric patients with isolated RBD, no adverse events were reported. The TF could not make a judgment on the magnitude of undesirable effects in pediatric patients due to the limited available evidence.

Resource use: The TF was unable to conclude how large the difference in resource use was between clonazepam and no treatment due to the uncertainty of the balance between its desirable and undesirable effects in pediatric patients. Per the NADAC database, the unit cost of 1-mg and 2-mg tablets ranged from $0.03 to $0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability on whether pediatric patients, guided by their parents, would use clonazepam when compared with no treatment for their isolated RBD. This was mainly because of the TF's concern for potential abuse of clonazepam, a benzodiazepine, in older pediatric patients, hesitancy starting a pediatric patient on chronic, possibly life-long therapy, and due to the uncertain efficacy of this agent in pediatric populations.

Secondary RBD due to a medical condition

The following interventions are those for which the TF deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline.[1] These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 3 observational studies[153–155] that examined the effect of clonazepam on 15 pediatric patients with secondary RBD due to a medical condition.

The observational studies included retrospective cohort and case series designs.

The table is provided as **Table S54**. The summary of findings table is provided as **Table S61**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: Three observational studies[153–155] reported on the percentage of pediatric patients who demonstrated partial or complete improvement in RBD symptoms in response to clonazepam. These studies showed improvement in RBD symptoms in 80% of their patients, which was clinically significant (**Table S54**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S61**).

Important outcomes

None of the studies identified in our literature review reported data for any of the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, change in REM motor tone (tonic and/or phasic), quality of life, sleep quality, or daytime motor function.

Overall certainty of evidence: The TF determined that the overall certainty of evidence for clonazepam to treat secondary RBD in pediatric patients was very low based on the critical outcomes reported in the literature, the low volume of studies, and downgrading the certainty of evidence because of imprecision (small sample size of $n < 30$). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes.

Benefits vs harms: The TF concluded the balance between the desirable and undesirable effects varied on whether it favored clonazepam or no treatment, based on its different effects on the various subgroups within the secondary RBD pediatric patient population. The use of clonazepam demonstrated improvements in RBD symptoms in pediatric patients with secondary RBD.

In the single observational study included in the systematic review that reported on the use of clonazepam in pediatric patients with secondary RBD, no adverse events were reported. The TF could not make a judgment on the magnitude of undesirable effects in pediatric patients due to the limited available evidence.

Resource use: The TF was unable to conclude how large the difference in resource use was between clonazepam and no treatment due to the uncertainty of the balance between its desirable and undesirable effects in pediatric patients. Per the NADAC database, the unit cost of 1-mg and 2-mg tablets ranged from \$0.03 to \$0.05.[70] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability on whether pediatric patients, guided by their parents, would use clonazepam when compared with no treatment for their secondary RBD due to a medical condition. This was mainly because of the TF's concern for potential abuse of clonazepam, a benzodiazepine, in older pediatric patients, hesitancy starting a pediatric patient on chronic, possibly life-long therapy, and due to the uncertain efficacy of this agent in pediatric populations.

Sodium oxybate

Our review of the literature identified 1 observational study[156] that examined the effect of sodium oxybate on 19 pediatric patients (10 males, 9 females) with narcolepsy.

The tables are provided as **Tables S131–S133**. The summary of findings table is provided as **Table S135**. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision making when determining whether to use this intervention: frequency and/or intensity of dream enactment episodes and treatment-related worsening in sedation or cognitive impairment. None of the studies identified in our literature review reported data for the following critical outcomes: frequency of significant bed partner sleep disruption, treatment-related worsening in gait stability, or treatment-related worsening in symptoms of depression or anxiety.

Frequency and/or intensity of dream enactment episodes: One observational cohort study[156] evaluated the effect of sodium oxybate on the frequency and/or intensity of dream enactment episodes in 19 pediatric patients (follow-up duration was 3 months). This study reported a 0.0% mean reduction in simple motor behaviors during REM sleep and a clinically significant 66.6% mean reduction in complex motor behaviors during REM sleep (**Table S131**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S135**).

Treatment-related worsening in sedation or cognitive impairment: One observational cohort study[156] evaluated the effect of sodium oxybate on the treatment-related worsening in sedation or cognitive impairment in 19 pediatric patients using the ESS (follow-up duration was 3 months). This study reported a clinically significant 6.53-point pre-post reduction in ESS score (**Table S132**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S135**).

Important outcomes

The following outcome was determined by the TF to be an important outcome, but not critical, for decision making when determining whether to use this intervention: change in REM motor tone—tonic and/or phasic. None of the studies identified in our literature review reported data for the following important outcomes: frequency and/or intensity of unpleasant dreams and nightmares, quality of life, sleep quality, or daytime motor function.

Change in REM motor tone—tonic and/or phasic: One observational cohort study[156] evaluated the effect of sodium oxybate on the change in REM motor tone (tonic and/or phasic) in 19 pediatric patients using the REM atonia index (follow-up duration was 3 months). This study reported a clinically significant 13% pre-post increase in REM atonia index (**Table S133**). The certainty of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (**Table S135**).

Overall certainty of evidence: The TF determined that the overall certainty of evidence for sodium oxybate to treat secondary RBD in pediatric patients was very low based on the critical outcomes reported in the literature and downgrading of the certainty of evidence because of imprecision (small sample size of n < 30). Clinical thresholds were met for the critical outcomes of frequency and/or intensity of dream enactment episodes and the treatment-related worsening in sedation or cognitive impairment.

Benefits vs harms: The TF concluded that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate in pediatric patients. Across all observational studies included in the systematic review that reported on the use of sodium oxybate in pediatric patients, no harmful effects were reported.

Resource use: The TF concluded that there were moderate costs in resource use for sodium oxybate in pediatric patients, as out-of-pocket costs may be prohibitive, although some patients will be treated with sodium oxybate for narcolepsy symptoms beyond RBD. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patients' values and preferences: The TF determined there was probably no important uncertainty or variability in how much people value the main study outcomes. There was variability among the different subgroups (RBD associated with narcolepsy vs RBD associated with other medical disorders) in whether patients would use sodium oxybate when compared with no treatment for their secondary RBD due to a medical condition. This is in contrast to the case of patients with secondary RBD due to narcolepsy, a condition for which sodium oxybate is already established as standard of care and for which the benefits of the treatment are not limited to reduction in RBD symptoms.

OTHER INTERVENTIONS

The TF also identified studies reporting evidence for interventions where the GRADE process was not applied, based on the exclusion criteria of having less than 3 patients or not being available for use in the United States. These interventions are as follows: adrenocorticotropic hormone, agomelatine, bed alarm, buspirone, carbamazepine, clomipramine, clozapine, desipramine, escitalopram, haloperidol, hypnotherapy, lamotrigine, levetiracetam, levodopa, methotrexate, nelotanserin, olanzapine, phenobarbital, plasma exchange, quetiapine, sertraline, temazepam, tiapride, triazolam, vortioxetine, zonisamide, and zopiclone. The evidence summaries for these interventions can be found in the supplemental material (pages 73–107).

DISCUSSION AND FUTURE DIRECTIONS

The management of RBD, a common, distressing condition, is based on limited evidence. Since 2010, when the AASM published a Best Practice Guide for the treatment of RBD,[2] the literature on RBD management has grown. Over 3 years the TF for the Treatment of RBD considered nearly 4,000 studies, carefully extracting clinical management data on dozens of potential therapies. Numerous agents appeared promising but failed to pass grading for standards of clinical evidence. Current and future patients will benefit from high-quality, controlled clinical trials of interventions. At this time, diagnostic challenges persist and questions linger regarding the relevance of the framework for stratifying patients with RBD (isolated RBD, RBD secondary to a medical disorder, and drug induced/exacerbated RBD). In addition, considering the relationship between RBD and Lewy body disorders such as DLB and PD, clinicians need standards on best practices for disclosing neurodegenerative risk. Finally, RBD therapy studies have, until now, focused on symptomatic treatment and not, as we hope they will in the near future, on identifying disease-modifying agents with a potential to cure RBD, DLB, PD, and related disorders.

Diagnosis and ambiguous stratification

As a diagnosis requires a careful clinical history, examination, and sleep laboratory investigation, the vast majority of the estimated 80 million individuals worldwide with RBD remain undiagnosed.[4] The reasons for this include the following: lack of health care access, misattribution by clinicians of dream enactment to mental illness, patient embarrassment, cultural taboos regarding bedroom activities, fear that reporting violent behaviors will alert law enforcement, lack of bed partners to report nighttime behaviors, and mild dream enactment that goes unrecognized by patients and families. RBD can also be misdiagnosed and mistreated as another parasomnia, such as sleepwalking, sleep terrors, or sleep-related epilepsy, which increases in prevalence in older adults.[4] Importantly, the cost of PSG is frequently prohibitive and testing is not universally accessible.

OSA is a common condition that frequently coexists with RBD. At the time of diagnosis, it is often uncertain whether obstructive events during REM sleep are producing pseudo-RBD or whether the 2 diagnoses are independent.[3,4] Close scrutiny of the PSG recording and use of additional arm EMG leads can be helpful as patients with both OSA and RBD may have a clear persistence of increased REM motor activity in the absence of respiratory events. However, some patients with

OSA have such frequent respiratory events throughout REM sleep that a diagnosis of RBD cannot be established or excluded without observing the effects of a therapeutic trial, such as PAP therapy. When the diagnosis is uncertain, we recommend a repeat polysomnogram with treatment to confirm the presence, or absence, of REM motor activity.

Once an RBD diagnosis is established, patients do not often segregate neatly across the conditions reported in the Clinical Practice Guideline (isolated RBD, RBD secondary to medical disorder, and drug-induced/exacerbated RBD). Frequently, a significant degree of overlap occurs. Patients with isolated RBD often have early signs of Lewy body disease. Subliminal cognitive impairments (visual spatial and executive deficits) along with changes in motor function (alterations in gait, muscle tone, muscle activation patterns) have been well characterized in people with isolated RBD. Patients with isolated RBD have impaired color vision, difficulty with smell, as well as autonomic dysfunction manifesting as urinary urgency, erectile dysfunction, sweating abnormalities, and postural orthostasis. Further, recent investigations have demonstrated quantitative abnormalities in the vocal characteristics of speech.[8,157] Neuroimaging investigations demonstrate pontine lesions in regions that control REM sleep (coeruleus/subcoeruleus complex) and structural and functional brain network changes suggestive of compensatory neuroplasticity.[157–161] Ultimately, isolated RBD is highly predictive of the eventual progression to a neurodegenerative disorder, with 74% of individuals phenoconverting (typically to DLB or PD) over 12 years.[8] Even among individuals with isolated RBD who did not clearly phenoconvert before death, brainstem lesions of Lewy body type pathology have been demonstrated on postmortem examination.[157]

It also appears that many cases of drug-induced/exacerbated RBD may be related to Lewy body type neurodegenerative pathology. The emergence of dream enactment after starting an selective serotonin reuptake inhibitor (5-HT RBD) was previously assumed to be caused by a toxic effect on REM sleep circuitry. However, careful scrutiny of patients with 5-HT RBD reveals neurodegenerative findings, such as olfactory deficits and constipation, not explained by serotonergic mechanisms. In addition, there is further evidence to suggest that patients with 5-HT RBD are at an increased neurodegenerative risk based on the presence of other early indicators of neurodegeneration: impaired color vision and orthostatic blood pressures, erectile dysfunction, mild cognitive impairment, and subclinical motor deficits in the timed up-and-go, alternate tap test, Purdue Pegboard, and UPDRS II and III.[11] These insights suggest that, in individuals already burdened by early alpha-synuclein pathology, selective serotonin reuptake inhibitor antidepressants do not induce RBD but instead unmask RBD.

This, combined with the presence of many subtle parkinsonian motor and Lewy body type cognitive findings among patients with isolated RBD and the ultimate phenoconversion of most individuals with isolated RBD to a neurodegenerative disorder, suggests that nearly all cases of RBD may be later categorized as RBD secondary to a medical disorder. This has substantial implications on management and requires careful consideration of best long-term therapies as well as tactful prognosis counseling and risk assessment.

Need for rigor

Over the past decade, well-designed studies have markedly enhanced our understanding of RBD. In particular, investigations have characterized the natural history, epidemiology, environmental risk factors, and neuroimaging features of RBD. In addition, researchers have further refined the clinical and polysomnographic diagnostic criteria of RBD and astutely characterized ancillary cognitive, motor, and autonomic signs. It is now time for equally well-designed studies focusing on the therapeutic management of RBD.

While there has been a substantial improvement compared with 12 years ago, there were still too few interventions with randomized placebo-controlled data to review. The vast majority of reports were small case studies or case series across all subtypes: isolated RBD, RBD secondary to a medical condition, and drug-induced/exacerbated RBD.

Additional challenges include inadequate methods for assessing RBD severity. The majority of studies report outcomes without a predefined or well-characterized assessment tool, relying on patient or clinician impression. Patients' logs of parasomnia activity can provide more granular, quantitative data but often focus on a patient's report of RBD frequency without a measure of intensity. Aggregate measures of RBD severity, such as the CGI scale, although meant to capture multiple aspects of RBD severity, lack precision.

After an era of exclusively uncontrolled studies, 7 placebo-controlled trials have been conducted since 2010,[71,83,91,118,123,124,162] most of them revealing a significant placebo effect. This placebo effect is possibly more pronounced in parallel-arm study designs. This undermines the interpretability of the bulk of the literature using uncontrolled retrospective and prospective open-label designs.

Another challenge is due to the recall/awareness bias, inherent to the nature of RBD, a condition that occurs during patients', and often bed partners', sleep. Patients' reports of dream enactment alone are not sufficient, as their recollection is often poor. Bed partners are helpful but frequently not available or unaware of the severity if they sleep in a different room.

Given the variability of response and tolerance to drug interventions observed in patient populations with RBD, it may be expected that different patients would benefit or experience side effects under different treatment doses. While the optimal therapeutic dose for a drug such as melatonin is still debated, other drugs, like clonazepam, are observed to have a linear dose-response relationship in terms of both benefit and adverse effects. This may partly contribute to the overall absence of benefit observed in a heterogeneous study population receiving a fixed, predetermined dose.[91]

Finally, there was a substantial lack of data in women as well as other demographic subgroups. RBD is underdiagnosed in women. Prior investigations reported nearly all (> 90%) of individuals with RBD were men.[55,163] However, more recent investigations have demonstrated that approximately one-third of individuals with RBD are women.[6,164] This is most notable among RBD populations younger than 50 years, indicating that women may require longer lifelong therapeutic management, emphasizing the critical need to enhance female recruitment in clinical trials. Racial disparities, both in terms of diagnosis of

conditions and involvement in clinical studies, emphasize the need for further inclusion and research in these domains.

Explicit statement

We recommend the development and execution of large, multicenter, well-designed, prospective clinical trials.

Future directions

The 2010 guidelines for the management of RBD were almost exclusively based on uncontrolled studies, stressing the need for more rigorous designs. Despite a relative abundance of studies published since then, only 2 new drugs received conditional recommendation: low-dose transdermal rivastigmine and low-dose pramipexole. Paradoxically, the 2 treatments suggested by the TF in 2010, melatonin and clonazepam, failed to show superiority against placebo in recent controlled studies.[71,72,91,118] While these studies were carefully considered and debated, ultimately the TF proceeded to give continued conditional recommendations for these treatments based on the limitations of the negative studies as well as prior investigations and decades of clinical observation that their risk-to-benefit ratio remains favorable in most cases.

Today's disconnect between clinical practice and scientific evidence pleads for more, better-designed studies testing current and new therapies for RBD symptoms, and importantly, the great need to develop disease-modifying therapies that impede or reverse alpha-synuclein pathology.

Because of the variability of RBD manifestations from night-to-night and the inherent nature of RBD being a sleep-related phenomenon for patients and often for their partners, methods for objective monitoring of disease activity in the ambulatory setting should be developed. We encourage researchers to evaluate relevant technology such as motion detectors using wearables (wrist, headbands) and traditional infrared or 3-dimensional video- and audio-monitoring systems. Such methods could accelerate drug discovery, improve patient care, and maximize safety. Until such methods are validated and applied in drug trials, RBD logs jointly filled by patients and partners including not only quantitative (number of events) but qualitative (intensity/dangerousness of events) descriptions of RBD episodes should be routinely used. When bed partners are present, their sleep and well-being should also be reported, including measures on sleep quality, safety, and quality of life.

Although more research is needed to understand the natural history of RBD symptoms, PSG-based studies and clinical observation suggest that the *frequency* range of RBD episodes varies from night to night for the same individual and possibly from month to month. The interindividual variability of RBD *severity* is also important, ranging from infrequent, mild manifestations for some individuals, to nightly vigorous episodes of dream enactment for others. We argue that enrollment of patients with more *frequent* and more *severe* RBD is not just clinically meaningful but more likely to reveal the true benefit of an effective drug over placebo. However, the relative scarcity of participants willing to participate in drug trials has been a challenge. Crossover designs present the advantages of increasing power with smaller population samples and offering the active drug to all participants.

While designing trials that include various subpopulations including prodromal and advanced neurodegenerative diseases is conceptually valid, such an approach presents its own set of challenges. First, it is possible that therapies need to target a different pathophysiology at different stages of disease. Second, tolerability of drug interventions, especially to sedatives and central nervous system depressants, varies between disease subtypes (isolated RBD, secondary RBD, 5-HT RBD) and is reduced with aging and advanced disease, resulting in greater side effects. Therefore, drug trials should be designed, if possible, to use flexible dosing. Further, there may also be sex and ethnic differences with regard to treatment response that a flexible-dose vs fixed-dose protocol may be able to identify.

Well-designed, large-scale future RBD studies will need to be facilitated by collaborative efforts such as the North American Prodromal Synucleinopathy (NAPS) Consortium, the Parkinson's Progression Markers Initiative (PPMI), and the International RBD Study Group (IRBDSG). Both the NAPS Consortium and the IRBDSG are currently conducting research aimed at developing disease-modifying therapies. All practicing sleep clinicians can assist in the development of these neuroprotective therapies by referring patients with RBD to NAPS and IRBDSG at the following websites (https://www.naps-rbd.org/; https://www.irbdsg.com/). The ultimate goal of these investigations is to identify cures for RBD, DLB, and PD.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
CGI, Clinical Global Impressions
CGI-I, Clinical Global Impressions–Improvement
COI, conflict of interest
CST, clinical significance threshold
DEB, dream enactment behavior
DLB, dementia with Lewy bodies
EMG, electromyography
ESS, Epworth Sleepiness Scale
FDA, Food and Drug Administration
GRADE, Grading of Recommendations, Assessment, Development, and Evaluation
IV, intravenous
KESS, Korean Epworth Sleepiness Scale
NADAC, National Average Drug Acquisition Cost
NPI, Neuro-psychiatric Inventory
NREM, non–rapid eye movement
PD, Parkinson's disease
PICO, Patient, Intervention, Comparison, and Outcomes
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
RBD, rapid eye movement sleep behavior disorder
RBDQ, rapid eye movement sleep behavior disorder questionnaire
RBDQ-HK, Hong Kong rapid eye movement sleep behavior disorder questionnaire
RBDQ-JP, Japanese rapid eye movement sleep behavior disorder questionnaire
RCT, randomized controlled trial

REM, rapid eye movement
RWA, rapid eye movement sleep without atonia
SF-36, 36-item Short Form Questionnaire
TF, task force
UPDRS, Unified Parkinson's Disease Rating Scale
5-HT RBD, 5-hydroxytryptamine (serotonergic) RBD

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