Management of REM Sleep Behavior Disorder:
An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment

Introduction: The purpose of this systematic review is to provide supporting evidence for a clinical practice guideline for the management of rapid eye movement (REM) sleep behavior disorder in adults.

Methods: The American Academy of Sleep Medicine commissioned a task force (TF) 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. 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.

Results: The literature search resulted in 4,690 studies; 148 studies provided data suitable for statistical analyses; evidence for forty-five interventions is presented. The TF provided a detailed summary of the evidence along with the quality 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

INTRODUCTION

This systematic review is intended to provide supporting evidence for the accompanying clinical practice guideline on the management of REM sleep behavior disorder and update the evidence review conducted for the previously published American Academy of Sleep Medicine (AASM) best practice guide.

BACKGROUND

Rapid Eye Movement (REM) sleep is characterized by vivid dream mentation in the setting of near complete paralysis through brainstem-induced skeletal muscle atonia. REM sleep facilitates the maturation of a brain’s circuits, most pronounced during early development, and REM sleep motor paralysis confers motor quiescence despite the activation of emotional salient, complex, and often violent, memory traces.

REM paralysis is the end result of an elegant, but 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 consist of shouting, thrashing, punching and kicking. These more pronounced behaviors can result in injury to the patient or bedpartner.

RBD is common, with a 1% prevalence affecting approximately 80 million people worldwide and is most common (5%) among older adults. Injuries result when patients with vigorous limb movements hit a wall, window, object
or bed partner when reacting towards an imaginary threat. Uncontrolled falls out of bed are common as dreamers will suddenly arise and leap out of the 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. In addition, arousals out of REM sleep from sleep disordered breathing can result in dream enactment (pseudo RBD) and the kicking movements of 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 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 they 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, the 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 the patient’s wellbeing.

RBD is most often caused by alpha-synuclein neurodegeneration, characterized by abnormal accumulation of aggregates of alpha-synuclein protein in neurons which ultimately often leads to dementia with Lewy bodies (DLB) and Parkinson’s disease (PD). 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.

Thus, RBD most often represents a prodromal syndrome, manifesting as dream enactment prior to the phenoconversion into DLB, 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 disfunction, 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 RBD subjects indicated a 74% phenoconversion rate to a neurodegenerative disorder within 12 years.

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, brainstem tumors; neurogenetic disorders such as spinocerebellar ataxia type 3, as well as paraneoplastic neurological disorders and autoimmune diseases. Among patients <50 years of age, antidepressants are the most common etiology of RBD, particularly the serotonergic antidepressant medications resulting in serotonergic RBD (5-HT RBD). Serotonin inhibits REM sleep and it has been assumed that by augmenting serotonergic activity these exogenous agents induce RBD. However, recent investigations have noted other subtle neurodegenerative findings such as constipation and hyposmia among patients with medication-associated RBD. 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 the RBD later in life.

RBD classification is based upon presumed etiology. When occurring in the absence of an identifiable neurological syndrome such as DLB, PD, or narcolepsy, dream enactment with polysomnographic (PSG) confirmation of REM sleep without atonia (RSWA) has been termed idiopathic RBD. Idiopathic RBD has historically been used, until recently, despite the high likelihood that patients have α-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. 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. 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 for later neurodegeneration.

RBD presents a unique window of opportunity by which one may alter or prevent the natural history and inevitable course of phenoconversion. Ongoing investigations are establishing protocols for the development of clinical trials to test neuroprotective therapies. 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, 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.

Dream enactment behaviors may be dramatic, life threatening, and often terrifying to patients and bed partners, highlighting the critical need to effectively and efficiently establish a diagnosis of RBD and provide definite management. Since its original description in 1986, investigators have attempted to identify efficacious RBD treatments. 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 American Academy of Sleep Medicine (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. 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 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, 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 RBD patients.
METHODOLOGY

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 (COI), 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 conflicts of interest are listed in the Disclosures section.

PICO Questions

PICO (Patient, Intervention, Comparison, and Outcomes) 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 (BOD) 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 to no treatment, should be recommended for clinical practice. Input from stakeholders (patients, caregivers, and healthcare 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 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.

Table 1 – PICO Questions

<table>
<thead>
<tr>
<th></th>
<th>POPULATION: Patients* diagnosed with isolated RBD</th>
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<tbody>
<tr>
<td></td>
<td>INTERVENTION: Clonazepam, melatonin, paroxetine, pramipexole, ramelteon, rivastigmine, sodium oxybate, yi-gan san, ACTH, agomelatine, bed alarm, carbamazepine, clomipramine, desipramine, donepezil, escitalopram, haloperidol, lamotrigine, phenobarbital, quetiapine, sertraline, triazolam, vortioxetine, zopiclone</td>
</tr>
<tr>
<td></td>
<td>COMPARISON: Placebo; other intervention; no treatment</td>
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<tr>
<td></td>
<td>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</td>
</tr>
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</table>
cognitive impairment**; treatment-related worsening in gait stability**; treatment-related worsening in symptoms of depression or anxiety**

### 2 POPULATION: Patients diagnosed with secondary RBD due to medical condition (including neurological diseases; dementia; stroke; sleep disorders; Dementia with Lewy bodies (DLB); multiple systems atrophy (MSA); Parkinson 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: 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: older adults, older adults with OSA on CPAP, older 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 dissociatus.

**These outcomes are considered side-effects of the interventions.

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**Table 2 – Outcomes by PICO Question**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Isolated RBD</th>
<th>Secondary RBD due to medical condition</th>
<th>Drug-induced RBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of significant bed partner sleep disruption</td>
<td>√*</td>
<td>√*</td>
<td>√*</td>
</tr>
<tr>
<td>Frequency and/or intensity of dream enactment episodes</td>
<td>√*</td>
<td>√*</td>
<td>√*</td>
</tr>
<tr>
<td>Treatment-related worsening in sedation or cognitive impairment</td>
<td>√*</td>
<td>√*</td>
<td>√*</td>
</tr>
<tr>
<td>Outcome</td>
<td>Clinical Significance Threshold*</td>
<td>Expected change</td>
<td></td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Frequency of significant bed partner sleep disruption</td>
<td></td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>1.5 points or 65% of patients reporting change</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>Frequency and/or intensity of dream enactment episodes</td>
<td></td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>Simple motor behaviors (PSG – during REM sleep)</td>
<td>33% (10% for placebo studies) or</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>Complex motor behaviors (PSG – during REM sleep)</td>
<td>33% (10% for placebo studies) or</td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>1.5 points or 65% of patients reporting change</td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>RBDQ (Factor 2 score)</td>
<td>10% or 50% of patients reporting change</td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>Treatment-related worsening in sedation or cognitive impairment</td>
<td></td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>2 points or 10% of patients reporting change</td>
<td>Decline</td>
<td></td>
</tr>
<tr>
<td>KESS</td>
<td>2 points or 10% of patients reporting change</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>3 points or 10% of patients reporting change</td>
<td>Decline</td>
<td></td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>10% or 33% of patients reporting change</td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>MFQ</td>
<td>1 point or 10% of patients reporting change</td>
<td>Decline</td>
<td></td>
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<tr>
<td>Treatment-related worsening in gait stability</td>
<td>10% of patients reporting change</td>
<td>Decline</td>
<td></td>
</tr>
<tr>
<td>Treatment-related worsening in symptoms of depression or anxiety</td>
<td></td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>NPI</td>
<td>4 points or 20% of patients reporting change</td>
<td>Decline</td>
<td></td>
</tr>
</tbody>
</table>

*Critical outcomes
<table>
<thead>
<tr>
<th><strong>Frequency and/or intensity of unpleasant dreams and nightmares</strong></th>
<th><strong>Change in REM motor tone – tonic and/or phasic</strong></th>
<th><strong>Quality of life</strong></th>
<th><strong>Sleep quality</strong></th>
<th><strong>Daytime motor function</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>RBD frequency</td>
<td></td>
<td>SF-36 (physical score)</td>
<td>RBDQ (total score)</td>
<td>UPDRS (Part III score)</td>
</tr>
<tr>
<td>RBD intensity</td>
<td></td>
<td>SF-36 (mental score)</td>
<td>PSQI</td>
<td></td>
</tr>
<tr>
<td>RBD episodes per week or month</td>
<td></td>
<td>UPDRS (total score)</td>
<td></td>
<td></td>
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<tr>
<td>RBDQ (Factor 1 score)</td>
<td></td>
<td>Schwab and England</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33% (10% for placebo studies) or 50% of patients reporting change</td>
<td>10% or 50% of patients reporting change</td>
<td>10% or 50% of patients reporting change</td>
<td>2.3 points or 50% of patients reporting change</td>
</tr>
</tbody>
</table>
|                                                               | 33% (10% for placebo studies) or 50% of patients reporting change | 10% or 40% of patients reporting change | 10% or 50% of patients reporting change | 2.3 points or 50% of patients reporting change | Decrease Improvement
|                                                               | 33% (10% for placebo studies) or 50% of patients reporting change | 10% or 40% of patients reporting change | 10% or 50% of patients reporting change | 2.3 points or 50% of patients reporting change | Decrease Improvement
|                                                               | 33% (10% for placebo studies) or 50% of patients reporting change | 10% or 40% of patients reporting change | 10% or 50% of patients reporting change | 2.3 points or 50% of patients reporting change | Decrease Improvement
|                                                               | 33% (10% for placebo studies) or 50% of patients reporting change | 10% or 40% of patients reporting change | 10% or 50% of patients reporting change | 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; RBDQ – RBD Questionnaire (includes Korean, Japanese, and Hong Kong versions); ESS – Epworth Sleepiness Scale; KESS – Korean Epworth Sleepiness Scale; MMSE – Mini-Mental State Examination; MFQ – Mayo Fluctuation Questionnaire; NPI – Neuropsychiatric Inventory; RWA % – REM sleep without atonia; SF-36 – Short form questionnaire (36 item); UPDRS – Unified Parkinson’s Disease Rating Scale; PSQI – Pittsburgh Sleep Quality Index

**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 PubMed 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 PubMed 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 PubMed 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 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 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 two 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.

**Figure 1 – Evidence Base Flow Diagram**

- Studies identified through PubMed and Embase
  - Search 1 (PubMed): 1966 to December 2018 (1,924)
  - Search 2 (Embase): 1966 to June 2019 (1,702)
  - Search 3 (PubMed/Embase): December 2018 to February 2020 (717)
- 4,690 studies screened for inclusion/exclusion criteria
- 4,542 studies excluded.
  - **Reason for exclusion:**
    a. Wrong publication type (book/book chapters, conference abstracts, dissertations, editorials, letters to the editor, methodological and review papers)
    b. Animal research
    c. Patients in study were not diagnosed with RBD
    d. Patients in study did not undergo RBD treatment
    e. Study did not report on any of the outcomes of interest
    f. Non-English publication
- 107 studies identified through pearl, or "spot check"
- 148 studies included in review

**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 randomized control trials. 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 non-randomized trials were also compared.
These are presented in a table format in the supplemental material. Data from crossover trials were treated as parallel groups. Some studies had data presented in the form of median and interquartile range (IQR). These were converted into data expressed as means and standard deviation (SD).\textsuperscript{17, 18} If outcome data were not presented in the format necessary for statistical analysis (i.e., mean, SD, 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 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 to the clinical significance threshold (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 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 two patient representatives were educated on the AASM’s guideline development process and 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 which were FDA-approved and/or available for use in the U.S. 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 U.S., the TF would still present the data in the supplemental material, but they would not apply the GRADE process. The TF considered the following four GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below:\textsuperscript{19, 20}

1. **Quality 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\textsuperscript{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 four-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 ISOLATED RBD**

The aims of the current literature review and data were focused on addressing the management of isolated (previously referred to as idiopathic) RBD. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. For those interventions that had supporting evidence from a total of at least 3 patients with isolated RBD across all studies and are FDA-approved and/or available for use in the U.S., the GRADE process was applied and the evidence summary is accompanied by a discussion of the quality 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

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\textsuperscript{16, 21-69} which examined the effect of clonazepam on 1,003 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or elderly (mean age of 65 years) men (84% male). The observational studies included retrospective and prospective cohort, cross-sectional, case-control, case series and case report designs.

The tables are provided in Tables S1-S2, S4-S7 in the supplemental material. The summary of findings table is provided in Table S8 in the supplemental material. 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\textsuperscript{43} evaluated the effect of clonazepam on the frequency and/or intensity of dream enactment episodes using the Modified RBD Questionnaire 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 quality of evidence was low due to risk of bias associated with observational studies (Table S8).

Two retrospective observational studies\textsuperscript{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 0.5-1 mg, and the findings did not reach a level of clinical significance (Table S1). The quality of evidence was low due to risk of bias associated with observational studies (Table S8).

Forty-four observational studies\textsuperscript{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 3 months to 6 years). These studies showed improvement in RBD symptoms in 87% of their patients, which was clinically significant (Table S2). The quality 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\textsuperscript{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 1.5 points for 39 patients, respectively (Table S4). These reductions were not clinically significant. The quality 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\textsuperscript{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 quality 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\(^4\) evaluated the effect of clonazepam on the frequency and/or intensity of unpleasant dreams and nightmares using the modified RBD questionnaire tool (Table S6). The study reported a clinically significant 31.7% pre-post improvement on 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 quality 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\(^3\) evaluated the effect of clonazepam (0.5-2 mg) on the REM atonia index (RAI). The RAI is measured by chin and limb EMG and reflects the percentage of average amplitudes \(= 1 \mu V\) divided by the sum of percentages of average amplitudes \(> 2 \mu V\) (conducted at a follow-up duration which ranged from 2.6 to 2.8 years). These findings showed a pre-post increase in RAI (indicating decreased amount of REM sleep without atonia i.e., 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 quality 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 quality of evidence**

The TF determined that the overall quality 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 quality 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.

**Resource Use**

The TF concluded that there was a large savings in resource use for clonazepam, given its relatively small cost compared to the potential high cost of potentially severe life-threatening injury due to dream enactment during sleep. Per the NADAC database, the unit cost of 1 mg and 2 mg tablets ranged from $0.03-$0.05.\(^7\) Medication cost to any given patient is uncertain and determined by payer coverage, copayments, and deductibles.
**Patients’ Values and Preferences**

The TF, with the assistance of patient representatives, determined there was probably no important uncertainty or variability in how much people value the main study outcomes and that the majority of patients would most likely prefer the use clonazepam when compared to no treatment when dream enactment of their isolated RBD is potentially injurious. This is based on the TF’s determination that the undesirable effects are relatively small and that the balance of benefits versus harms strongly favors the use of clonazepam in low doses.

**Melatonin**

Our review of the literature identified 2 randomized, double-blind, placebo-controlled trials (RCT)\(^{71, 72}\) 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 on 303 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or elderly (mean age of 64 years) men (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 in Figures S1-S19 and Tables S10-S27 in the supplemental material. Summary of findings tables are provided in Tables S28-S29 in the supplemental material. 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 of percent mean change in dream enactment episodes per week for the melatonin group (2 mg dose) compared to the placebo group (Table S12, Figure S2). At a 6 mg dose, the melatonin group showed a 2.5% increase of percent mean change in dream enactment episodes per week compared to the placebo group (Table S13, Figure S4). This study also used the Korean RBD questionnaire tool, recording a 9.5% reduction in the behavioral factor score (e.g., burden/severity of nocturnal behaviors) for the 2 mg melatonin group compared to the placebo group (Table S12, Figure S3), and a clinically significant 18.4% reduction for the 6 mg melatonin group compared to the placebo group (Table S13, Figure S5). For the 6 mg dose, the 2.5% increase in DEB frequency in the melatonin group compared to placebo was presumably counteracted by the 18.4% reduction in DEB severity. The quality of life 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 CGI score for the melatonin group compared to the placebo group (Table S11). This change was not clinically significant. The quality of life 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\textsuperscript{76} evaluated the effect of immediate-release melatonin (3-6 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 quality of life 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\textsuperscript{21, 30, 34, 47, 49, 72-74} 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 53\% of their patients, which was clinically significant (Table S15). The quality of evidence was low due to risk of bias associated with observational studies (Table S28).

One observational cohort study\textsuperscript{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 quality of evidence was low due to risk of bias associated with observational studies (Table S29).

Two observational studies\textsuperscript{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 quality of life 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\textsuperscript{71} evaluated the effect of prolonged-release melatonin on daytime sleepiness using the Epworth Sleepiness Scale (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 to the placebo group (Table S17, Figure S7).

Neither of these changes were clinically significant. The quality of life 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\textsuperscript{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\textsuperscript{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\textsuperscript{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 8 months. The third study\textsuperscript{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 (6-15 mg), which was clinically significant. The quality 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 outcomes: daytime motor function.

**Frequency and/or intensity of unpleasant dreams and nightmares**

One RCT\textsuperscript{71} evaluated the effect of prolonged-release melatonin on the frequency and/or intensity of unpleasant dreams and nightmares using the Korean RBD questionnaire tool (follow-up duration was 4 weeks). The study recorded a 11.1\% increase of percent mean change in the dream-related factor score for the 2 mg melatonin group compared to the placebo group (Table S19, Figure S8), and a 0.3\% increase for the 6 mg melatonin group compared to the placebo group (Table S20, Figure S9). Neither of these increases were clinically significant. The quality of
life 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 REM sleep without atonia (RSWA) after 4 weeks of treatment, showing a 3.8% reduction of mean change for the melatonin group compared to the placebo group. This study also reported on phasic EMG %, showing a 1.5% reduction of mean change for the melatonin group compared to the placebo group (Table S22). The quality 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 RSWA, 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 quality 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 non-significant 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 quality 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 16.6% to 6% (10.4% reduction) for 15 patients (follow-up duration not reported) (Table S21). The quality 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 percentage of patients who demonstrated improvement in RSWA in response to prolonged-release melatonin (follow-up duration was 6 months). Neither of its two patients showed a reduced RSWA following treatment of melatonin (2 mg) (Table S23). The quality 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 Short Form (SF-36, version 2) Questionnaire. The study recorded a clinically significant 11.4% increase (indicating improved physical functioning) of percent mean change in SF-36 physical component score for the 2 mg melatonin group compared to the placebo group (Table S24, Figure S12), and a 6.9% increase for the 6 mg melatonin group compared to the placebo group (Table S25, Figure S14). The study also recorded a 2.9% reduction of percent mean change in SF-36 mental component score for the 2 mg melatonin group compared to the placebo group (Table S24, Figure S13), and a 3.2% increase for the 6 mg melatonin group compared to the placebo group (Table S25, Figure S15). The quality 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 RBD Questionnaire tools (follow-up duration was 4 weeks). The PSQI score showed a non-significant 2.8% reduction for the 2 mg melatonin group compared to the placebo group (Table S26, Figure S16), and a clinically significant 33.5% reduction for the 6 mg melatonin group compared to the placebo group (Table S27, Figure S18). The Korean RBD Questionnaire total score showed a non-significant 3.8% reduction for the 2 mg melatonin group compared to the placebo group (Table S26, Figure S17), and a clinically significant 13.4% reduction for the 6 mg melatonin group compared to the placebo group (Table S27, Figure S19). The quality 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 quality of evidence

The TF determined that the overall quality 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 quality 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 was insufficient data to favor 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 were 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 to 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, co-pays, 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 and that the vast majority of patients would most likely use melatonin when compared to 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 versus 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 U.S. 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 which examined the effect of pramipexole on 87 adult patients with isolated RBD. Participants in these studies were primarily middle-aged or elderly (mean age of 67 years) men (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 in Table S30-S34 in the supplemental material. Summary of findings tables are provided in Tables S35-S36 in the supplemental material. 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\(^7^9, ^8^0\) 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\(^8^0\) 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/day). The second study\(^7^9\) 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/day). This study also illustrated a 23.9% mean reduction in complex motor behaviors during REM sleep. The quality 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\(^8^1\) compared the effect of pramipexole (mean dose 0.21±0.09 mg/day) to that of clonazepam (mean dose 0.6±0.3mg/day) 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 to the clonazepam group (n=15). The quality 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\(^4^9, ^5^3, ^6^7, ^7^9, ^8^2\) 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 quality 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 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. 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\(^8^1\) compared the effect of pramipexole (mean dose 0.21±0.09 mg/day) to that of clonazepam (mean dose 0.6±0.3mg/day) on RSWA% after 3 months of treatment (Table S33). This study reported a 5.3% reduction in RSWA % in the pramipexole group (n=50) compared to the clonazepam group (n=15). The quality 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\(^7^9, ^8^0\) 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\(^7^9\) 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/day). The other study\(^8^0\) 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/day). The quality 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 quality of evidence**

While pramipexole was historically advocated for the management of disrupted sleep in the setting of RBD, the TF determined that the overall quality of evidence for pramipexole to treat isolated RBD was very low based on the critical outcomes reported in the literature and downgrading of the quality 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 hangover (5.1%) and gastrointestinal symptoms (3.1%). TF also raised concerns in light of the attributed negative impulsive behaviors 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 to 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-$0.06. Medication cost to any given patient is uncertain and determined by payer coverage, co-pays, 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 and that the majority of patients would most likely select pramipexole when compared to no treatment for their dream enactment behaviors. 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 randomized, single-blind, placebo-controlled, cross-over trial 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 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 elderly (mean age of 63 years).

The figures and tables are provided in Figure S20 and Tables S37-S38 in the supplemental material. The summary of findings table is provided in Table S39 in the supplemental material. 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 of percent mean change in dream enactment episodes per month for the rivastigmine arm compared to the placebo arm (Table S37, Figure S20). The quality 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 quality 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 quality of evidence**

The TF determined that the overall quality of evidence for rivastigmine to treat isolated RBD was moderate based on the critical outcomes reported in the literature and downgrading of the quality 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, co-pays, 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 and that the majority of patients would most likely use rivastigmine when compared to 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 versus harms favors the use of rivastigmine.

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

Paroxetine

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

The table is provided in Table S40 in the supplemental material. The summary of findings table is provided in Table S41 in the supplemental material. 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 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. 5 patients improved from a severe RBD rating to moderate, and 11 patients improved from severe to mild (Table S40). The quality 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 quality of evidence

The TF determined that the overall quality of evidence for paroxetine to treat isolated RBD was very low based on the critical outcomes reported in the literature, and downgrading of the quality 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 two 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. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patients’ Values and Preferences**

The TF, with the assistance of patient representatives, determined there was probably no important uncertainty or variability in how much people value the main study outcomes, and that the majority of patients would most likely not use paroxetine when compared to no treatment for their isolated RBD. This is based primarily upon uncertain efficacy and safety.

**Ramelteon**

Our review of the literature identified 1 observational, open label trial 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 elderly (mean age of 69 years) men (70% male).

The tables are provided in Table S42-S43 in the supplemental material. The summary of findings table is provided in Table S44 in the supplemental material. 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 evaluated the effect of ramelteon on the frequency and intensity of dream enactment episodes using the Visual Analog Scale (VAS) according to family, and the intensity of dream enactment episodes using the RBD Severity Scale (RBDSS) 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 VAS, there was an 87.5%, increase (worsening)
of percent mean change in RBDSS motor events, and a pre-post 16.7% increase (worsening) of percent mean change in RBDSS vocalization events (Table S42). The quality 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 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. 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\textsuperscript{86} evaluated the effect of ramelteon on REM sleep without atonia, showing a 5.5% increase of 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 of mean change, respectively (Table S43). The quality 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 quality of evidence**

The TF determined that the overall quality 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 VAS and RBDSS 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 one 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 other RBD treatments. Per the NADAC (National Average Drug Acquisition Cost) database, the unit cost of an 8 mg tablet was $3.53.\textsuperscript{70} Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 and that the majority of patients would most likely not use ramelteon when compared to 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\textsuperscript{49, 87, 88} which examined the effect of sodium oxybate in adult patients with treatment-resistant isolated RBD. The first study\textsuperscript{87} assessed sodium oxybate in three patients...
at a dose of 4.5 g. The second study\(^9\) assessed sodium oxybate in two patients at a dose of 4.5g (in a single dose) and 3g (in two doses) nightly. The third study\(^8\) assessed sodium oxybate in one patient at a dose that started at 3 g, and was increased to 4.5 g after one week. Participants in these studies were primarily middle-aged or elderly (mean age of 66 years) and composed of all men. The observational studies included case series and case report designs.

The table is provided in Table S45 in the supplemental material. The summary of findings table is provided in Table S46 in the supplemental material. 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\(^9\) reported on the percentage of patients who demonstrated improvement in RBD symptoms in response to sodium oxybate (follow-up duration ranged from 3 to 8 years). A second case series study\(^9\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to sodium oxybate (follow-up duration ranged from 2.5 to several years). This study showed that Clinical Global Impressions-Improvement scale scores improved significantly for both patients. A case report\(^8\) reported on a patient whose RBD symptoms resolved within two weeks of treatment with sodium oxybate, and remained well controlled after a 12-month follow-up (Table S45). The quality 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 quality of evidence**

The TF determined that the overall quality 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 quality 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 one 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, co-pays, 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 and that the majority of patients would most likely use sodium oxybate when compared to 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 to placebo for RBD.

Yi-Gan San
Our review of the literature identified four observational studies\(^53, 60, 89, 90\) which 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 2.5-5.0 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 one patient at an unknown dose. The fourth study\(^60\) was a case series study that assessed yi-gan san in one patient at a dose of 7.5 g/day. Participants in these studies were primarily middle-aged or elderly (mean age of 70 years) men (81% male). The observational studies included retrospective cohort, case-control, and case series designs. The tables are provided in Table S47-S48 in the supplemental material. 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 quality of evidence was low due to risk of bias associated with observational studies (Table S49). A second study\(^90\) reported an improvement in RBDQ-JP Factor 2 score in 11 patients treated with yi-gan san (Table S47). The quality 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 one patient (Table S48). A fourth study\(^60\) showed full suppression of RBD symptoms for one patient with isolated RBD, when yi-gan san (7.5 g/day) was combined with clonazepam (0.5 mg/day) (Table S48). The quality 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 quality of evidence**

The TF determined that the overall quality 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 one 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 small cost compared to 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, co-pays, 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 and that the majority of patients would most likely use yi-gan san when compared to no treatment for their isolated RBD. This is based on the TF’s determination that the balance of benefits versus 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.

**The following interventions are those for which the GRADE process was not applied based on the exclusion criteria of having less than 3 patients or medications not available for use in the U.S. These interventions are listed in alphabetical order:**

**Adrenocorticotropic Hormone**

Our review of the literature identified 1 case report study which examined the effect of adrenocorticotropic hormone (ACTH) on a young adult female patient with isolated RBD. This case report assessed ACTH in one patient at a dose of 40 units i.v. for 5 days. A table is provided in Table S50 in the supplemental material. 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 report\textsuperscript{91} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to ACTH (follow-up duration was 4 years) (Table S50). This study showed a progressive reduction in frequency of RBD episodes, from 5-7 episodes per week to 1-2 episodes per week after 5 months. All RBD episodes disappeared completely after 8 months, and yearly follow-up PSGs disclosed normal sleep structure and normal REM sleep.

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.

Agomelatine

Our review of the literature identified 1 observational study\textsuperscript{92} which examined the effect of agomelatine on adult patients with isolated RBD. This study assessed agomelatine in 3 elderly patients (2 male, 1 female) at doses ranging from 25-50 mg.

The tables are provided in Tables S51-S52 in the supplemental material. 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\textsuperscript{92} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to agomelatine (follow-up duration was 6 months). This study showed improvement in frequency and severity of RBD episodes in all 3 patients (100%), which was clinically significant (Table S51).

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. 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.

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Change in REM motor tone – tonic and/or phasic

One case series study\(^92\) evaluated the effect of agomelatine on the REM atonia density, showing a clinically significant pre-post improvement of 8.0% (follow-up duration was 6 months). This study also showed a clinically significant pre-post improvement of 8.0% for tonic EMG %, and a pre-post improvement of 0.7% for phasic EMG %, which was not clinically significant (Table S52).

Bed Alarm

Our review of the literature identified 1 observational study\(^91\) which examined the effect of a bed alarm in two elderly female patients with treatment-resistant isolated RBD.

The tables are provided in Tables S53-S54 in the supplemental material. 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\(^93\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to a bed alarm system (follow-up duration ranged from 6 to 36 months). This study reported that 2 patients with isolated RBD showed improvement in sleep-related injury events and RBD symptoms (Table S53).

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: 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 case series study\(^93\) reported on the percentage of patients who demonstrated partial or complete improvement in sleep quality in response to a bed alarm system (follow-up duration ranged from 6 to 36 months). This study reported a 21% reduction in Hong Kong RBD Questionnaire total score, which was clinically significant (Table S54).

Carbamazepine

Our review of the literature identified one observational study\(^94\) which examined the effect of carbamazepine in an elderly male patient with isolated RBD.

A table is provided in Table S55 in the supplemental material. 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 report\(^4\) reported on one patient who demonstrated partial improvement in RBD symptoms in response to carbamazepine. This study showed that after 14 months of treatment with carbamazepine (100 mg), dream enactment behavior was greatly improved in the patient (Table S55).

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.

Clomipramine

Our review of the literature identified 1 observational study\(^24\) which examined the effect of clomipramine on an elderly male patient with isolated RBD.

A table is provided in Table S56 in the supplemental material. 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 report\(^24\) reported on the percentage of patients who demonstrated partial improvement in RBD symptoms in response to clomipramine (follow-up duration was 2 years). This study showed no significant improvement in one patient’s RBD symptoms following treatment with clomipramine (100 mg) (Table S56).

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.
Desipramine
Our review of the literature identified one observational study\textsuperscript{16} which examined the effect of desipramine on two elderly male patients with isolated RBD.

The table is provided in Table S57 in the supplemental material. 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\textsuperscript{16} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to desipramine (follow-up duration ranged from 15 months to 4 years). This study showed that treatment with desipramine (up to 250 mg) resulted in significant improvement in RBD symptoms for 1 of 2 patients (50%), which was clinically significant, but lasted only 3 weeks (Table S57).

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.

Donepezil
Our review of the literature identified 1 observational study\textsuperscript{95} which examined the effect of donepezil on adult patients with isolated RBD. This study assessed donepezil in 2 male patients (ages 29 and 56) at a dose ranging from 5-15 mg.

The table is provided in Table S58 in the supplemental material. 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\textsuperscript{95} reported partial improvement in RBD symptoms in response to donepezil (follow-up duration was 1 year). This case series study reported a subjective decrease in frequency of dream enactment behaviors in 2 patients (Table S58).
**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.

**Escitalopram**

Our review of the literature identified 1 case report study\(^48\) which examined the effect of escitalopram on an elderly male patient with isolated RBD. This case report assessed escitalopram in one patient at a dose of 10 mg/day. The table is provided in Table S59 in the supplemental material. 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 report\(^48\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to escitalopram (follow-up duration was not reported). This study showed a reduction in the frequency, duration and intensity of RBD episodes following treatment with escitalopram (10 mg/day) and clonazepam (0.5 mg/day) (Table S59).

**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.

**Haloperidol**

Our review of the literature identified 1 observational study\(^61\) which examined the effect of haloperidol in an elderly male patient with isolated RBD.

The table is provided in Table S60 in the supplemental material. 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 reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to haloperidol (follow-up duration was not reported). This study showed that haloperidol (5 mg/day) failed to improve one patient’s violent behavior during sleep (Table S60).

**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.

**Lamotrigine**

Our review of the literature identified 1 case report which examined the effect of lamotrigine in an elderly male patient with isolated RBD. This study assessed lamotrigine in one patient at a starting dose of 25 mg/day, up to a maximum of 100 mg/day.

The table is provided in Table S61 in the supplemental material. 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 report reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to lamotrigine. This study showed that there were no appreciable changes in frequency or intensity of RBD symptoms in a patient following treatment with lamotrigine for 2 months, although once treatment stopped the frequency and intensity of vivid dreams increased (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.

**Phenobarbital**

Our review of the literature identified 1 observational study which examined the effect of phenobarbital on two elderly male patients with isolated RBD. This study assessed phenobarbital in the two patients at a dose of 100 mg/day.
The table is provided in Table S62 in the supplemental material. 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\(^4\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to phenobarbital (follow-up duration was 12 months). This study showed no improvement in the frequency and intensity of RBD symptoms for either of its patients (Table S62).

**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.

**Quetiapine**

Our review of the literature identified one observational study\(^6\) which examined the effect of quetiapine on two elderly patients (1 male, 1 female) with isolated RBD.

The table is provided in Table S63 in the supplemental material. 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\(^6\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to quetiapine (follow-up duration was not reported). This study showed that quetiapine (25 mg/day) failed to improve RBD symptoms in two patients (Table S63).

**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.
Sertraline

Our review of the literature identified one case report study\textsuperscript{25} which examined the effect of sertraline on an elderly male patient with isolated RBD.

The table is provided in Table S64 in the supplemental material. 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 report\textsuperscript{25} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to sertraline (follow-up duration was 3 years). This study showed a reduction in frequency and intensity of RBD symptoms in one patient treated with sertraline (150 mg), which lasted for a few months before worsening of symptoms (Table S64).

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.

Triazolam

Our review of the literature identified one observational study\textsuperscript{52} which examined the effect of triazolam on adult patients with isolated RBD.

The table is provided in Table S65 in the supplemental material. 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\textsuperscript{52} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to triazolam (follow-up duration was not reported). This study showed complete resolution of RBD symptoms for one patient, and uncertain results in another patient (Table S65).
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.

Vortioxetine

Our review of the literature identified one case report study\textsuperscript{97} which examined the effect of vortioxetine on an elderly female patient with isolated RBD. This case report assessed vortioxetine in one patient at a dose of 10 mg/day.

The table is provided in Table S66 in the supplemental material. 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 report\textsuperscript{97} reported on a patient who demonstrated partial or complete improvement in RBD symptoms in response to vortioxetine (follow-up duration was 15 months). This study showed a significant clinical improvement in CGI-S score, from 5 points to 1 point. After 15 months of treatment, the CGI-S score remained at 1 (Table S66).

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.

Zopiclone

Our review of the literature identified 1 observational study\textsuperscript{22} which examined the effect of racemic zopiclone on adult patients with isolated RBD. This study assessed zopiclone in 11 patients at doses ranging from 3.75-7.5 mg. Participants in this study were primarily middle-aged or elderly (mean age of 66 years) men (97% male).

The table is provided in Table S67 in the supplemental material. 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 reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to zopiclone (follow-up duration was 20 months). This study showed improvement in RBD symptoms for 8 of their 11 patients (73%), which was clinically significant (Table S6).

**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.

**MANAGEMENT OF SECONDARY RBD DUE TO MEDICAL CONDITION**

The aims of the current literature review and data were focused on addressing the management of secondary RBD due to a medical condition. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. For those interventions that had supporting evidence from a total of at least 3 patients with secondary RBD due to medical condition across all studies and are FDA-approved and/or available for use in the U.S., the GRADE process was applied and the evidence summary is accompanied by a discussion of the quality 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.

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

**Clonazepam**

Our review of the literature identified one randomized, double-blind, placebo-controlled trial (RCT) 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 which examined the effect of clonazepam on 679 adult patients with secondary RBD due to a medical conditions, including PD and DLB. Participants in these studies were primarily middle-aged or elderly (mean age of 57 years) men (79% male). The observational studies included retrospective and prospective cohort, case-control, case series and case report designs.

The figures and tables are provided in Figures S21-S24 and Tables S68-S71, S73-S77 in the supplemental material. The summary of findings table is provided in Table S78 in the supplemental material. 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.
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\(^98\) evaluated the effect of clonazepam on frequency of significant bed partner sleep disruption using the Clinical Global Impression-Improvement scale (CGI-I). The mean difference in CGI-I post-treatment score (4-week follow-up) between the clonazepam and placebo groups was -0.5, which was not clinically significant (Table S70, Figure S21). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S78).

One case report\(^105\) reported a significant reduction in frequency of significant bed partner sleep disruption in one patient after one week of treatment with clonazepam (Table S69). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S78).

**Frequency and/or intensity of dream enactment episodes**

One RCT\(^98\) evaluated the effect of clonazepam on frequency and/or intensity of dream enactment episodes using the Clinical Global Impression-Improvement scale (CGI-I). The mean difference in CGI-I post-treatment score (4-week follow-up) between the clonazepam and placebo groups was -0.5, which was not clinically significant (Table S70, Figure S22). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S78).

37 observational studies\(^16, 21, 22, 37, 40, 42, 44, 47, 52, 54-59, 61, 99-119\) 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 S71). The quality of evidence was low due to risk of bias associated with observational studies (Table S78).

**Treatment-related worsening in sedation or cognitive impairment**

One RCT\(^98\) 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 an improved difference of 4.1 points lower KESS in the clonazepam group compared to the placebo group (Table S73, Figure S23). The quality of evidence was high (Table S78).

Ten observational studies\(^22, 52, 58, 99, 101, 103, 107, 113, 116, 120\) 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 S74). The quality of evidence was low due to risk of bias associated with observational studies (Table S78).

**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\(^111\) evaluated the effect of clonazepam (1-2 mg/day) on phasic and tonic EMG % for one 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 S75), and in tonic EMG activities during REM sleep.
(from 40.0% to 3.7%) (Table S76). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S78).

**Daytime motor function**

One RCT\(^8\) 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 to the placebo group. This difference was not clinically significant (Table S77). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S78).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 quality 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 small cost compared to 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-$0.05.\(^7\) Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patients’ Values and Preferences**

The TF, with the assistance of patient representatives, determined there was probably no important uncertainty or variability in how much people value the main study outcomes and that the majority of patients would most likely use clonazepam when compared to no treatment when dream enactment of their secondary RBD is potentially injurious. This is based on the TF’s determination that the undesirable effects are relatively small and that the balance of benefits versus 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\textsuperscript{121-124} which examined the effect of deep brain stimulation on 64 adult patients with secondary RBD due to a medical condition. Participants in these studies were primarily middle-aged or elderly (mean age of 62 years) men (65% male). The observational studies included open-label trial, prospective cohort, cross-sectional, and case report designs.

The tables are provided in Tables S80-S86 in the supplemental material. The summary of findings table is provided in Table S87 in the supplemental material. 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\textsuperscript{121, 122, 124} reported on the percentage of patients with PD which 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 S80). The first study\textsuperscript{121} showed an increase in dream enactment after DBS for one patient. In the second study,\textsuperscript{122} the occurrence of RBD was unchanged in regard to subjective complaints and videographical assessments in all 50 patients reported. The third study\textsuperscript{124} showed no improvement in any of the 8 patients that reported RBD symptoms. The quality of evidence was low due to risk of bias associated with observational studies (Table S87).

**Treatment-related worsening in sedation or cognitive impairment**

Two observational studies\textsuperscript{122, 123} reported on changes in Epworth Sleepiness Scale (ESS) scores for patients with PD (follow-up duration ranged from 4 to 7.7 months) (Table S81). The first study\textsuperscript{122} 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\textsuperscript{123} was a cohort study that reported a clinically significant pre-post reduction in mean ESS score of 3.2 points for 5 patients. The quality 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 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**

Two observational studies\textsuperscript{122, 124} evaluated the effect of deep brain stimulation on REM motor tone (follow-up duration ranged from 6 to 7.7 months) (Table S82). One study\textsuperscript{122} showed a 2.4% reduction in REM sleep without atonia for 40 patients with PD. The other study\textsuperscript{124} showed a clinically significant 20.6% reduction in phasic EMG % for 11 patients with PD. The quality 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 S87).

One case series study\textsuperscript{121} reported on the percentage of patients who demonstrated partial or complete improvement in REM motor tone (follow-up duration ranged from 1 to 13 years). This study of patients with PD and parasomnia overlap disorder showed significant improvement in tonic EMG % for 2 of 3 patients (Table S83), and in phasic
EMG% for 1 of 3 patients (Table S84). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S87).

**Sleep quality**

One observational study\(^ {124}\) evaluated the effect of deep brain stimulation on sleep quality using the Pittsburgh Sleep Quality Index (follow-up duration was 6 months). This cohort study\(^ {124}\) showed a clinically significant 9.4 point pre-post reduction of Pittsburgh Sleep Quality Index for 11 patients with PD (Table S85). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S87).

**Daytime motor function**

Two observational studies\(^ {122, 123}\) evaluated the effect of deep brain stimulation on daytime motor function using various tools (follow-up duration ranged from 4 to 7.7 months) (Table S86). One open-label study\(^ {122}\) showed a clinically significant 9.5 point pre-post reduction of UPDRS (Part III) score for 50 patients with PD. A second study\(^ {123}\) showed a clinically significant 26.5 point pre-post reduction of UPDRS (Part III) score for 5 patients with PD. The quality of evidence was low due to risk of bias associated with observational studies (Table S87).

**Overall quality of evidence**

The TF determined that the overall quality 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 was reported in two 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 and that the vast majority of patients would most likely not use deep brain stimulation when compared to 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 randomized, double-blind, placebo-controlled trials (RCT)\(^ {72, 125}\) and 11 observational studies\(^ {21, 22, 47, 74, 76, 99, 109, 126-129}\) (2 on prolonged-release and 9 on immediate-release melatonin) which examined the effect of melatonin on secondary RBD due to a medical condition. Participants in these studies were
primarily middle-aged or elderly (mean age of 61 years) men (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 in Figures S25-S29 and Tables S88-S91, S93-S94 in the supplemental material. The summary of findings tables are provided in Tables S95-S96 in the supplemental material. 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\(^ {125}\) 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 of percent mean change in RBD events per week for the 15-patient melatonin group (4 mg dose) compared to the 15-patient placebo group, and a 30.8% increase in percent mean change in RBD nights per week for the melatonin group compared to placebo (Table S90, Figure S26). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S96).

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 to the placebo group (Table S88, Figure S25). This change was not clinically significant. The quality of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (Table S95).

Two observational studies\(^ {22,128}\) 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 S91). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S96).

One retrospective observational study\(^ {76}\) evaluated the effect of immediate-release melatonin (3-6 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 S89). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S95).

Eight observational studies\(^ {21,47,74,99,109,126,127,129}\) 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 42 days to 38 months). These studies showed improvement in RBD symptoms in 76% of their patients, which was clinically significant (Table S91). The quality of evidence was low due to risk of bias associated with observational studies (Table S95).

**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. 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\textsuperscript{72} evaluated the effect of immediate-release melatonin on REM sleep without atonia (RSWA) after 4 weeks of treatment, showing a 3.8% reduction for the melatonin group compared to the placebo group (Table S93, Figure S28). This study also reported on phasic EMG %, showing a 1.5% reduction of mean change for the melatonin group compared to the placebo group (Table S93, Figure S29). The quality of evidence was moderate due to imprecision associated with a small sample size (Table S95).

Two observational studies\textsuperscript{74, 76} evaluated the effect of immediate-release melatonin on the percentage of REM sleep without atonia, showing significant RSWA decrease from 32% to 11% (21% reduction) and RSWA decrease from 47% to 1.4% (45.6% reduction) pre-post treatment for 6 patients (6 weeks) and 26 patients (4 months), respectively (Table S94). The quality of evidence was very low due to imprecision associated with a small sample size (Table S95).

One observational study\textsuperscript{74} evaluated the effect of immediate-release melatonin on phasic EMG %, showing a non-significant pre-post treatment increase from 29% to 32% for 6 patients (follow-up duration was 6 weeks) (Table S94). The quality 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 S95).

Overall quality of evidence

The TF determined that the overall quality 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 quality 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 two observational studies limiting the generalizability of these results with no improvement versus 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 small cost compared to 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, co-pays, 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 and that the vast majority of patients would most likely use melatonin when compared to 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 versus 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 randomized, single-blind, placebo-controlled, cross-over trial\textsuperscript{130} which examined the effect of rivastigmine on 11 elderly patients (11 male, 1 female) with secondary RBD due to PD who were refractory to melatonin (up to 5 mg) and clonazepam (up to 2 mg). This RCT assessed rivastigmine 4.6 mg/day patch in 12 patients versus placebo with intervening washout period. The figures and tables are provided in Figure S30 and Tables S97-S98 in the supplemental material. The summary of findings table is provided in Table S99 in the supplemental material. 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\textsuperscript{130} 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 of percent mean change in dream enactment episodes per week for the rivastigmine group compared to when patients were in the placebo arm (Table S97, Figure S30). 2/12 patients dropped out due to orthostatic hypotension and asthenia. The quality of evidence was moderate due to imprecision associated with a small sample size and a wide 95% confidence interval that crossed the CST (Table S99).

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. 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\textsuperscript{130} evaluated the effect of rivastigmine on RSWA features (follow-up duration was 3 weeks). This study showed that for a subset of 4 patients, RSWA features were not modified when compared with baseline (Table S98). The quality of evidence was moderate due to imprecision associated with a small sample size (Table S99).
Overall quality of evidence

The TF determined that the overall quality 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 quality 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 2/12 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, co-pays, 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 and that the majority of patients would most likely use rivastigmine when compared to no treatment for their secondary RBD due to a medical condition. This is based on the TF’s determination that the balance of benefits versus harms favors the use of rivastigmine.

The following interventions are those for which the task force 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 randomized, single-blind, placebo-controlled, cross-over trial131 and one observational study132 which 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 elderly male patients. The figures and tables are provided in Figures S31-S38 and Tables S100-S105 in the supplemental material. The summary of findings table is provided in Table S106 in the supplemental material. 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\(^1\) 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 of percent mean change in RBD nights per week for the 17 patients in the cannabidiol group compared to the 16 patients in the placebo group (Table S10, Figures S31-S32). Neither of these changes were clinically significant. The quality of evidence for the RBD frequency was moderate due to imprecision. The quality of evidence for CGI-I was high (Table S10).

One case series study\(^2\) reported on the percentage of patients with PD which demonstrated partial or complete improvement in RBD symptoms in response to cannabidiol (follow-up duration was 6 weeks). This study showed a substantial reduction in the frequency of RBD symptoms in all four patients, which was clinically significant (Table S10). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S10).

**Treatment-related worsening in sedation or cognitive impairment**

One RCT\(^1\) 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 of mean change in ESS score for the cannabidiol group compared to the placebo group (Table S102, Figure S33). This change was not clinically significant. The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S10).

**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\(^1\) 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 of percent mean change in phasic RWA index for the cannabidiol group compared to the placebo group, and a 2.9% reduction of percent mean change in tonic RWA index for the cannabidiol group compared to the placebo group (Table S102, Figures S34-S35). Neither of these changes were clinically significant. The quality of evidence for the RBD frequency was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S10).

**Sleep quality**

One RCT\(^1\) evaluated the effect of cannabidiol on sleep quality (follow-up duration was 12 weeks). This study showed a 0.46 point reduction of mean change in PSQI score for the cannabidiol group compared to the placebo group, which was not clinically significant (Table S104, Figure S36). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S10).

**Daytime motor function**

One RCT\(^1\) evaluated the effect of cannabidiol on daytime motor function (follow-up duration was 12 weeks). This study showed a 0.05 point reduction of percent mean change in UPDRS-III (off) score for the cannabidiol group
compared to the placebo group (Table S105, Figures S37), and a clinically significant 7.16 point reduction of mean change in UPDRS-III (on) score for the cannabidiol group compared to the placebo group (Table S105, Figure S38). The quality of evidence was moderate due to imprecision associated with a wide 95% confidence interval that crossed the CST (Table S106).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 concluded that the balance between the desirable and undesirable effects is likely in favor of 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 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, co-pays, 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 and that the majority of patients would most likely not use cannabidiol when compared to no treatment for their secondary RBD due to 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\(^60, 133-136\) which 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 elderly (mean age of 67 years), and an even mix of men and women (54% female).

The tables are provided in Tables S107-S111 in the supplemental material. The summary of findings table is provided in Table S112 in the supplemental material. 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\(^{134, 136}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to carbidopa-levodopa (follow-up duration not reported). The first study\(^{134}\) 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\(^{136}\) reported improvement in RBD symptoms for all 3 patients with PD after starting treatment with carbidopa-levodopa (Table S107). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S112).

**Treatment-related worsening in sedation or cognitive impairment**

One observational study\(^{135}\) evaluated the effect of carbidopa-levodopa-entacapone on the treatment-related worsening in sedation or cognitive impairment for 39 patients with PD using the Epworth Sleepiness Scale (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 S108). The quality of evidence was low due to risk of bias associated with observational studies (Table S112).

**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\(^{133}\) 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 twitch, and a clinically significant 4.28 pre-post increase in tonic motor activity (Table S109). The quality 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 S112).

**Quality of life**

One observational study\(^{135}\) 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) (mean follow-up duration was 24.7 ± 2.4 weeks). 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 S110). The quality of evidence was low due to risk of bias associated with observational studies (Table S112).

**Daytime motor function**

One observational study\(^{135}\) evaluated the effect of carbidopa-levodopa-entacapone on daytime motor function for 39 patients with PD using the UPDRS and Schwab and England disability scale (SE-ADL) (mean follow-up duration was 24.7 ± 2.4 weeks). This open-label study reported a clinically significant 3.4 point pre-post reduction in UPDRS-III score (Table S111). The quality of evidence was low due to risk of bias associated with observational studies (Table S112).
**Overall quality of evidence**
The TF determined that the overall quality 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 quality 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 one 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 25-100 mg tablets was $0.10.70 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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, and that the majority of patients would most likely use carbidopa-levodopa when compared to no treatment for their secondary RBD due to a medical condition.

**Donepezil**
Our review of the literature identified 5 observational studies95, 112, 120, 137, 138 which examined the effect of donepezil on 10 adult patients with secondary RBD due to a medical condition. These studies assessed donepezil at dose ranging from 5-15 mg in patients with DLB outside of 1 who developed RBD symptoms after craniopharyngioma resection. Participants in these studies were primarily middle-aged or elderly (mean age of 73 years), and an even mix of men and women (54% male). The tables are provided in Table S113-S117 in the supplemental material. The summary of findings table is provided in Table S118 in the supplemental material. 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 studies95, 112, 120, 137, 138 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 S113). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S118).

**Treatment-related change in sedation or cognitive impairment**

One observational study\(^1\) reported on positive treatment-related change in cognitive impairment for patients with DLB and sleep disturbance in response to donepezil as measured on Mini-Mental State Exam score, Letter Fluency score, and reduction in Mayo Fluctuations Scale score; however, it was unclear how many of these patients had RBD (Table S114). The quality 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 S118).

One case report\(^2\) 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 Exam score in the patient (Table S115). The quality 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 S118).

**Treatment-related worsening in symptoms of depression or anxiety**

One observational study\(^3\) reported on the treatment-related worsening in symptoms of depression or anxiety for patients with DLB in response to donepezil (Table S116). This open-label trial showed a clinically significant 11.4 point improvement in Neuro-psychiatric Inventory score. It was unclear how many of these patients also had RBD. The quality 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 S118).

**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: 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\(^4\) 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 Pittsburgh Sleep Quality Index (from 12 to 9) (Table S117). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S118).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 quality 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\textsuperscript{137} (unclear number with RBD) and consisted of nausea, anorexia, abdominal discomfort, cerebral infarction, 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.\textsuperscript{70} Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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, but 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.

**IV Immunoglobulin**

Our review of the literature identified 3 observational studies\textsuperscript{139-141} which examined the effect of IV immunoglobulin on 8 adult patients with secondary RBD due to a medical condition. The tables are provided in Tables S119-S121 in the supplemental material. The summary of findings table is provided in Table S122 in the supplemental material. 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\textsuperscript{139-141} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to IV immunoglobulin (follow-up duration ranged from 3 to 86 months) (Table S119). Two of the studies\textsuperscript{139, 141} showed improvement of RBD symptoms in all of their patients (Baiardi 2015 was a case report of one elderly male patient with Morvan Syndrome; Vale 2016 reported data on 2 female patients with paraneoplastic cerebellar degeneration). The third study\textsuperscript{140} was a case series study that showed complete resolution of RBD symptoms after 62-86 months in 3 of 5 elderly male patients with limbic encephalitis. The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S122).

**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. 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\(^{140}\) reported on the percentage of patients who demonstrated partial or complete improvement in REM motor tone (follow-up duration ranged from 62 to 86 months). This study showed clinically significant improvement in tonic EMG % and phasic EMG% for two of the six patients that had polysomnography before and after treatment (Table S120). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S122).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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, co-pays, 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 and that there was variability among the different subgroups in whether patients would use IV immunoglobulin when compared to no treatment for their secondary RBD due to a medical condition. Patients suffering from only RBD or from 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\(^{142}\) which examined the effect of light therapy on 83 elderly patients (65% male) with PD. This study had limited application to the CPG as there were no clear or standardized outcomes measures for RBD, only a composite RBD severity score. The table is provided in Table S123 in the supplemental material. The summary of findings table is provided in Table S124 in the supplemental material. 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 reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to light therapy (Table S123). 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 42-60 months). The quality of evidence was low due to risk of bias associated with observational studies (Table S124).

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 quality of evidence**

The TF determined that the overall quality 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 to 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 and that the majority of patients would most likely use light therapy when compared to 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 randomized, double-blind, placebo-controlled trial\(^\text{143}\) which examined the effect of memantine on elderly 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 in Figures S39-S41 and Tables S125-S127 in the supplemental material. The summary of findings table is provided in Table S128 in the supplemental material. 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 randomized, double-blind, placebo-controlled trial\(^\text{143}\) reported on the treatment-related worsening in sedation in response to memantine using the Epworth Sleepiness Scale (follow-up duration was 24 weeks). This study showed a 0.4 point increase in mean change for the memantine group compared to the placebo group, which was not clinically significant (Table S125, Figure S39). The quality of evidence was moderate due to imprecision associated a wide 95% confidence interval that crossed the CST (Table S128).

*Treatment-related worsening in symptoms of depression or anxiety*

One randomized, double-blind, placebo-controlled trial\(^\text{143}\) reported on symptoms of depression or anxiety in response to memantine using the Neuro-psychiatric Inventory score (follow-up duration was 24 weeks). This study showed a 0.1 point reduction in mean change for the memantine group compared to the placebo group, which was not clinically significant (Table S126, Figure S40). The quality of evidence was moderate due to imprecision associated a wide 95% confidence interval that crossed the CST (Table S128).

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: 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 randomized, double-blind, placebo-controlled trial\(^\text{143}\) reported on daytime motor function in response to memantine using the UPDRS (Part III). This study showed a 0.3 point increase (1.8\%) in mean change for the memantine group compared to the placebo group, which was not clinically significant (Table S127, Figure S41). The quality of evidence was moderate due to imprecision associated a wide 95% confidence interval that crossed the CST (Table S128).
Overall quality of evidence
The TF determined that the overall quality 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 quality 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 neuro-psychiatric inventory (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, one 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 small cost compared to the potential cost of injury due to dream enactment during sleep. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 and that the majority of patients with DLB or dementias associated with PD would most likely use memantine when compared to no treatment for their physical activity during secondary RBD due to medical condition.

Positive Airway Pressure (PAP) Therapy
Our review of the literature identified 3 observational studies\textsuperscript{25, 144, 40} which examined the effect of PAP therapy on 29 adult patients with RBD comorbid to OSA. Participants in these studies were primarily middle-aged or elderly (mean age of 58 years) men (93% male).
The table is provided in Table S129 in the supplemental material. The summary of findings table is provided in Table S130 in the supplemental material. 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\textsuperscript{25, 144, 40} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to PAP therapy (Table S129). One case report\textsuperscript{25} showed improvement in its patient’s sleep pattern when treated with PAP therapy for 3 years. A second cohort study\textsuperscript{144} reported improvement in RBD symptoms for 11 of 27 patients treated with CPAP therapy. One cross-sectional cohort study\textsuperscript{40} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to PAP therapy (follow-up duration was not reported). This study showed one patient’s RBD symptoms being well controlled with a combined treatment of CPAP therapy and clonazepam (0.5-1 mg).
The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S130).

**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 quality of evidence**

The TF determined that the overall quality of evidence for PAP therapy to treat RBD was very low based on the critical outcomes reported in the literature and downgrading of the quality 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 PAP therapy or no treatment for the treatment of isolated RBD, depending on whether obstructive sleep apnea (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 there was probably no important uncertainty or variability in how much people value the main study outcomes, and that there was variability on whether patients would use PAP therapy when compared to 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 which 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 elderly (mean age of 67 years) men (86% male).

The tables are provided in Tables S131-S133 in the supplemental material. The summary of findings table is provided in Table S134 in the supplemental material. 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\(^8\) reported on the percentage of patients with PD which demonstrated partial or complete improvement in nocturnal motor activity in response to pramipexole (mean dose 0.89±0.31 mg). This study showed improvement in intensity of RBD symptoms for 6 of 9 patients, and improvement in frequency of RBD symptoms for 8 of 9 patients (follow-up duration ranged from 4 to 25 months) (Table S131). The quality 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**
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\(^1\) 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 a 11.7% pre-post increase in Schwab and England disability scale score (Table S132). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S134).

**Daytime motor function**
One observational cohort study\(^1\) 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 S133). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S134).

**Overall quality of evidence**
The TF determined that the overall quality 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 quality 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 two clinical trials. Only one study\(^8\) had a positive result, and its findings were based upon subjective impression from patient and bed partners. Further, it is likely that pramipexole decreased ancillary nocturnal motor activity, periodic limb movements (PLMs) 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\(^1\) that included a follow up PSG and did not demonstrate in 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 hangover (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 was negligible costs and savings in resource use for pramipexole, given its relatively small cost compared to 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 medical condition. Per the NADAC database, the unit cost of 0.5 mg and 1 mg tablets ranged from $0.05-$0.06. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 and there was variability among the different subgroups in whether patients would use pramipexole when compared to 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 for the treatment of RBD with ramelteon in 38 adult patients with secondary RBD due to a medical condition. The first study was a case report that assessed ramelteon (8 mg) in one elderly male patient with DLB. The second study was an open label trial that assessed ramelteon (8 mg) in 35 elderly patients (18 female, 17 male) with PD. The third study was a case series study that assessed ramelteon (8 mg) in 2 elderly patients (1 male, 1 female), one with PD and one with multiple system atrophy (MSA).

The tables are provided in Tables S135-S141 in the supplemental material. The summary of findings table is provided in Table S142 in the supplemental material. 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 case report reported partial improvement in the frequency of dream enactment episodes in one patient with DLB treated with ramelteon and clonazepam. One observational, open label trial evaluated the effect of ramelteon on the frequency and/or intensity of dream enactment episodes on 35 patients with PD using the Japanese RBD Questionnaire (RBDQ-JP). This study reported a clinically significant 42% reduction of RBDQ-JP score following treatment with ramelteon for 12 weeks (Table S135). The quality of evidence was low due to risk of bias associated with observational studies (Table S142).

In addition, one case series study reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to ramelteon. The two patients in this case series study showed clinically significant improvement in RBDQ-JP scores after three years of treatment with ramelteon (Table S136). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S142).
**Treatment-related worsening in sedation or cognitive impairment**

One case report\(^{103}\) evaluated the effect of ramelteon on the treatment-related worsening in cognitive impairment. This study showed no change in Mini-Mental State Exam score and a 1-point decline in Montreal Cognitive Assessment score following treatment with ramelteon and clonazepam (follow-up duration was 1 year) (Table S138). One observational, open label trial\(^{147}\) 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 Exam score, which was not clinically significant (Table S137). The quality of evidence was low due to risk of bias associated with observational studies (Table S142).

**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\(^{146}\) reported on improvement in REM sleep without atonia (RSWA) based on chin EMG in response to ramelteon (follow-up duration was 3 years). The two patients in this study showed a reduction in RSWA from 8.5% to 3.5% and 10.9% to 3.9%, respectively (Table S139). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S142).

**Sleep quality**

One observational, open label trial\(^{147}\) reported on sleep quality in response to ramelteon (follow-up duration was 12 weeks). This study showed a 0.6 point improvement in Pittsburgh Sleep Quality Index, which was not clinically significant (Table S140). The quality of evidence was low due to risk of bias associated with observational studies (Table S142).

**Daytime motor function**

One observational, open label trial\(^{147}\) 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 S141). The quality 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 quality of evidence**

The TF determined that the overall quality 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 two patients by Nomura et al. 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 to other treatments, as there is more evidence of its efficacy in treating patients with secondary RBD due to a medical condition. 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, co-pays, 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 and that the majority of patients would most likely use ramelteon when compared to 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 to immediate-release melatonin by patients as opposed to no treatment.

Rotigotine
Our review of the literature identified 1 observational study for the treatment of RBD with rotigotine transdermal patch in 11 elderly 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 in Tables S143-S147 in the supplemental material. The summary of findings table is provided in Table S148 in the supplemental material. 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 evaluated the effect of rotigotine on the frequency and/or intensity of dream enactment episodes for patients with PD using the Hong Kong RBD Questionnaire (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 S143). The quality 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 S148).

Treatment-related worsening in sedation or cognitive impairment
One observational study evaluated the effect of rotigotine on the treatment-related worsening in sedation for patients with PD using the Epworth Sleepiness Scale (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 S144). The quality 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 S148).

**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\(^1\) evaluated the effect of rotigotine on the frequency and/or intensity of unpleasant dreams and nightmares for patients with PD using the Hong Kong RBD Questionnaire (RBDQ-HK), Factor 1 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 S145). The quality 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 S148).

**Change in REM motor tone – tonic and/or phasic**

One observational study\(^1\) 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 S146). The quality 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 S148).

**Daytime motor function**

One observational study\(^1\) 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 S147). The quality 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 S148).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 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 to 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.\textsuperscript{70} Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 and that there was variability among the different subgroups in whether patients would use rotigotine when compared to 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\textsuperscript{106, 149, 150} which 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 2.5-8 g nightly. The table is provided in Table S149 in the supplemental material. The summary of findings table is provided in Table S153 in the supplemental material. 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\textsuperscript{106, 149, 150} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to sodium oxybate (follow-up duration ranged from 2 to 6 months). All of these studies showed improvement in RBD symptoms for all their patients, and complete resolution in the two cases of RBD related to PD (Table S149). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S153).

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 quality of evidence
The TF determined that the overall quality 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 quality 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 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 one 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 MSA, 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, i.e., 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, co-pays, 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 but that there was variability among the different subgroups (RBD associated with PD, DLB, and MSA) in whether patients would use sodium oxybate when compared to 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\(^\text{60, 151}\) which examined the effect of yi-gan san on 13 adult patients with secondary RBD due to a medical condition. The first study\(^\text{60}\) assessed yi-gan san in 2 patients at doses ranging from 2.5-7.5 g/day, while the second study\(^\text{151}\) assessed yi-gan san in 11 patients at a dose of 7.5 g/day. Participants in these studies were primarily middle-aged or elderly (mean age of 76 years) men (67% male). The tables are provided in Tables S155-S157 in the supplemental material. The summary of findings table is provided in Table S158 in the supplemental material. 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\(^\text{60}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to yi-gan san (follow-up duration was not reported). This study showed full suppression of RBD symptoms for two patients (one with bradykinesia, one with postural instability) when yi-gan san (7.5 g/day) was combined with clonazepam (0.5 mg/day) thus limiting confidence of attributing resolution of
RBD symptoms specifically to yi-gan san (Table S155). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S158). One cohort study\textsuperscript{151} 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 Neuropsychiatric Inventory (NPI) night-time behavior disturbance, from 5.9±2.1 to 2.5±1.8, following treatment with yi-gan san (7.5 g/day). This difference was not clinically significant (Table S156). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S158).

**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: 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\textsuperscript{151} 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 S157). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S158).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 two 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 yokukansankachimiphange, this new derivative of yi-gan san, that was reported in the Manabe 2020 study. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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, and that there was variability among the different subgroups in whether patients would use yi-gan san when compared to 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.
The following interventions are those for which the GRADE process was not applied based on the exclusion criteria of having less than 3 patients or medications not available for use in the U.S. These interventions are listed in alphabetical order.

**Bed Alarm**

Our review of the literature identified 1 observational study\(^{93}\) which examined the effect of a bed alarm in adult patients with treatment-resistant secondary RBD due to a medical condition. This study assessed the effect of a bed alarm system on four patients, two of which were elderly male patients diagnosed with PD. The tables are provided in Table S159-S160 in the supplemental material. 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*

This study\(^{93}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to a bed alarm system (follow-up duration ranged from 6 to 36 months). This case series study reported that 2 patients with PD showed improvement in sleep-related injury events and RBD symptoms (Table S159).

**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: 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*

This observational study\(^{93}\) reported on the percentage of patients who demonstrated partial or complete improvement in sleep quality in response to a bed alarm system (follow-up duration ranged from 6 to 36 months). This case series study reported a mean 20% reduction in Hong Kong RBD Questionnaire total score for the 2 patients, which was clinically significant (Table S160).

**Buspirone**

Our review of the literature identified 1 case report study\(^{129}\) which examined the effect of buspirone on adult patients with secondary RBD due to a medical condition. The table is provided in Table S161 in the supplemental material. 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 report\textsuperscript{129} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to buspirone (15 mg TID). This study showed improvement in the frequency of dream enactment behavior for a 47-year-old male patient with multiple peripheral mononeuropathies (follow-up duration was 38 months) (Table S161).

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.

Clozapine

Our review of the literature identified 1 observational study\textsuperscript{52} which examined the effect of clozapine on adult patients with secondary RBD due to a medical condition. The table is provided in Table S163 in the supplemental material. 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\textsuperscript{52} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to clozapine (follow-up duration was not reported). This study showed complete resolution of RBD symptoms in one patient and partial resolution of RBD symptoms in another with treatment with clozapine (Table S163).

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.
**Desipramine**

Our review of the literature identified one observational study which examined the effect of desipramine on 1 adult patient with secondary RBD due to a medical condition. The table is provided in Table S164 in the supplemental material. 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 reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to desipramine (Table S164). This case series study showed that treatment with desipramine (50 mg nightly) resulted in immediate suppression of vigorous sleep behaviors and restoration of diurnal alertness of one elderly male patient with dementia, although at a 12-month follow-up, “he still frequently vocalized and had minor limb twitching in his sleep.”

**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.

**Haloperidol**

Our review of the literature identified 1 observational study which examined the effect of haloperidol in a 76-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S165 in the supplemental material. 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 reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to haloperidol (follow-up duration was not reported). This study showed that haloperidol failed to improve one cancerous patient’s violent behavior during sleep (Table S165).
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.

Levetiracetam

Our review of the literature identified 1 observational study\textsuperscript{152} which examined the effect of levetiracetam in a 65-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S167 in the supplemental material. 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 report\textsuperscript{152} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to levetiracetam (follow-up duration was not reported). This study showed that for a patient with DLB treated with levetiracetam (1000 mg b.i.d.), nocturnal episodes decreased from 6 to 3 episodes per month with diminished severity (Table S167).

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.

Levodopa

Our review of the literature identified 1 observational study\textsuperscript{120} which examined the effect of levodopa on an elderly male patient with secondary RBD due to a medical condition. The tables are provided in Tables S168-S169 in the supplemental material. 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.
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 report study\(^{120}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to levodopa. This case report showed improvement in RBD symptoms for its patient with DLB after treatment with levodopa for 1 year (100-500 mg) (Table S168).

**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. 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 report study\(^{120}\) reported on a patient with DLB which demonstrated REM sleep without atonia (RSWA) % in response to levodopa (100-500 mg). This study showed a total lack of muscle atonia during REM sleep (worsening in REM motor tone) as reported in the post-treatment PSG following treatment with levodopa for 1 year (Table S169).

**Methotrexate**

Our review of the literature identified 1 case report study\(^ {153}\) which examined the effect of methotrexate in a 30-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S170 in the supplemental material. 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 report\(^ {153}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to methotrexate (dose of 3 g/m\(^2\), follow-up duration was 6 months). This study showed that the occurrence of nocturnal motor and verbal behaviors in a brainstem lymphoma patient was reduced from one to two times per week to only one to two times per month after chemotherapy treatment (Table S170).

**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.
**Nelotanserin**

Our review of the literature identified 1 randomized, double-blind, placebo-controlled trial (RCT)\(^{154}\) which examined the effect of nelotanserin in 34 elderly patients (29 male, 5 female) with PD or DLB. No outcomes were reported for frequency of significant bed partner sleep disruption, frequency and/or intensity of unpleasant dreams and nightmares, treatment-related worsening in sedation or cognitive impairment, treatment-related worsening in gait stability, treatment-related worsening in symptoms of depression or anxiety, change in REM motor tone – tonic and/or phasic, quality of life, sleep quality, and daytime motor function. The figures and tables are provided in Figures S42-S43 and Table S171 in the supplemental material. 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\(^{154}\) evaluated the effect of nelotanserin on frequency and/or intensity of dream enactment episodes. The mean difference in simple/major and complex RBD events/10 min between the nelotanserin and placebo groups was 1.5 events/10 min lower (Table S171, Figure S42). The mean difference in simple minor, simple/major and complex RBD events/10 min between the nelotanserin and placebo groups was 6.12 events/10 min lower (Table S171, Figure S43).

**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.

**Olanzapine**

Our review of the literature identified one case report study\(^{110}\) which examined the effect of olanzapine in a 78-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S172 in the supplemental material. 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 report study\(^{110}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to olanzapine (follow-up duration was not reported). This study showed that a patient with dementia was treated with olanzapine (10 mg/day) and clonazepam (1 mg/day), which resulted in reduced disruptive daytime and nighttime behavior (Table S172).

**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.

**Plasma Exchange**

Our review of the literature identified 1 observational study\(^{139}\) which examined the effect of plasma exchange on an elderly male patient with secondary RBD due to a medical condition. The table is provided in Table S173 in the supplemental material. 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 report\(^{139}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to plasma exchange (follow-up duration was 3 months). This study showed no improvement in RBD symptoms for a patient with Morvan Syndrome following three plasma exchange sessions (Table S173).

**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.

**Quetiapine**

Our review of the literature identified 1 observational study\(^{61}\) which examined the effect of quetiapine on two elderly adult patients (1 male, 1 female) with secondary RBD due to a medical condition. The tables are provided in Table S174 in the supplemental material. 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\textsuperscript{61} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to quetiapine (follow-up duration was not reported). This study showed that quetiapine failed to improve RBD symptoms in two patients with gastric carcinoma (Table S174).

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.

Temazepam
Our review of the literature identified 1 observational study\textsuperscript{134} which examined the effect of temazepam on a 51-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S175 in the supplemental material. 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 report\textsuperscript{134} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to temazepam (follow-up duration was not reported). This study showed improvement in RBD symptoms for its patient with Machado-Joseph disease following a combination of temazepam and carbidopa-levodopa (Table S175).

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.

Tiapride
Our review of the literature identified one observational study\textsuperscript{155} which examined the effect of tiapride on 6 elderly patients (5 males, 1 female) with DLB. The tables are provided in Tables S176-S177 in the supplemental material. 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\textsuperscript{155} reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to tiapride. This case series study showed that treatment with tiapride (50-150 mg) resulted in a reduction in intensity and severity of motor and vocal enactments during sleep for 5 of 6 patients (follow-up duration was 12 weeks) (Table S176).

**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. None of the studies identified in our literature review reported data for the following important outcomes: change in REM motor tone – tonic and/or phasic, quality of life, sleep quality, or daytime motor function.

*Frequency and/or intensity of unpleasant dreams and nightmares*

One observational study\textsuperscript{155} reported on the percentage of patients who demonstrated partial or complete improvement in frequency and/or intensity of unpleasant dreams and nightmares in response to tiapride. This case series study showed that treatment with tiapride (50-150 mg) resulted in a reduction in frequency of bad dreams for 5 of 6 patients (follow-up duration was 12 weeks) (Table S177).

**Triazolam**

Our review of the literature identified one observational study\textsuperscript{52} which examined the effect of triazolam on 2 adult patients with secondary RBD due to a medical condition. The table is provided in Table S178 in the supplemental material. 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\(^5\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to triazolam (follow-up duration was not reported). This study showed complete resolution of RBD symptoms for one patient, and uncertain results in another patient (Table S178).

**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.

**Zonisamide**

Our review of the literature identified 1 observational study\(^1\) which examined the effect of zonisamide on a 71-year-old male patient with PD.

The table is provided in Table S179 in the supplemental material. 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 report\(^2\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to zonisamide (25 mg/day). This study showed a resolution in the patient’s aggressive and violent dream enact behavior after treatment with zonisamide (follow-up duration was 7 months) (Table S179).

**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.

**Zopiclone**

Our review of the literature identified 1 observational study\(^3\) which examined the effect of zopiclone on adult patients with secondary RBD due to a medical condition. This study assessed zopiclone in 11 patients at doses ranging from 3.75-7.5 mg. Participants in this study were primarily middle-aged or elderly (mean age of 66 years) men (97% male).

The table is provided in Table S180 in the supplemental material. A summary of the evidence for each outcome is provided below.

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\(^1\) Refer to the original document for details.

\(^2\) Refer to the original document for details.

\(^3\) Refer to the original document for details.
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\(^{22}\) reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to zopiclone (follow-up duration was 20 months). This study showed improvement in RBD symptoms for 8 of their 11 patients (73%), which was clinically significant (Table S180).

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.

MANAGEMENT OF DRUG-INDUCED RBD

The aims of the current literature review and data were focused on addressing the management of drug-induced RBD. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. For those interventions that had supporting evidence from a total of at least 3 patients with drug-induced RBD across all studies and are FDA-approved and/or available for use in the U.S., the GRADE process was applied and the evidence summary is accompanied by a discussion of the quality 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.\(^1\)

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\(^{157-161}\) which examined the effect of drug discontinuation on 8 adult patients diagnosed with drug-induced RBD. Participants in these studies were primarily middle-aged or elderly (mean age of 60 years) men (88% male).

The tables are provided in Tables S181-S182 in the supplemental material. The summary of findings table is provided in Table S183 in the supplemental material. A summary of the evidence for each outcome is provided below.
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 studies157–161 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 five studies showed improvement in RBD symptoms for all of their patients following discontinuation of fluoxetine, bisoprolol, selegiline, fluoxetine/paroxetine, and venlafaxine respectively (Table S181). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S183).

**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. 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 studies157, 158 reported on the percentage of patients who demonstrated partial or complete improvement in RSWA in response to drug discontinuation (follow-up duration ranged from 2 to 6 months). One case report showed improvement in REM atonia for a patient after discontinuation of fluoxetine. The other case series study reported on restored REM atonia for one of its two patients after discontinuation of bisoprolol (Table S182). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S183).

**Overall quality of evidence**

The TF determined that the overall quality 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 quality 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 co-morbid 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, and that 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 task force 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, ¹⁰⁴, ¹¹⁴, ¹¹⁶, ¹⁶⁰, ¹⁶², ¹⁶³ which examined the effect of clonazepam on 225 adult patients with drug-induced RBD. Participants in these studies were primarily middle-aged or elderly (mean age of 62 years) men (83% male).

The tables are provided in Tables S184-S185 in the supplemental material. The summary of findings table is provided in Table S186 in the supplemental material. 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
14 observational studies ²⁷, ⁴⁰, ⁴⁴, ⁵⁵-⁵⁷, ⁵⁹, ⁶¹, ¹⁰⁴, ¹¹⁴, ¹¹⁶, ¹⁶⁰, ¹⁶², ¹⁶³ 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 S184). The quality of evidence was low due to risk of bias associated with observational studies (Table S186).

Treatment-related worsening in sedation or cognitive impairment
Three observational studies ²⁷, ⁵⁹, ¹¹⁶ 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 2.5 years). These studies showed an adverse effect in sedation or cognitive impairment in 36% of their patients, which was clinically significant (Table S185). The quality of evidence was low due to risk of bias associated with observational studies (Table S186).
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 quality of evidence

The TF determined that the overall quality 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-$0.05.70 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

Patients’ Values and Preferences

The TF, with the assistance of patient representatives, determined there was probably no important uncertainty or variability in how much people value the main study outcomes and that the majority of patients would most likely use clonazepam when compared to no treatment when dream enactment of their drug-induced RBD is potentially injurious. 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 ISOLATED RBD IN PEDIATRIC POPULATIONS

The aims of the current literature review and data were focused on addressing the treatment of RBD in pediatric populations. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. For those interventions that had supporting evidence from a total of at least 3 patients with isolated RBD across all studies and are FDA-approved and/or available for use in the U.S., the GRADE process was applied and the evidence summary is accompanied by a discussion of the quality 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
The following interventions are those for which the task force deemed there was insufficient evidence to make a recommendation in the accompanying clinical practice guideline. These interventions are listed in alphabetical order.

Clonazepam

Our review of the literature identified 1 observational study\textsuperscript{164} which examined the effect of clonazepam on 4 pediatric patients with isolated RBD.

The table is provided in Table S3 in the supplemental material. The summary of findings table is provided in Table S9 in the supplemental material. 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.

\textit{Frequency and/or intensity of dream enactment episodes}

One retrospective observational study\textsuperscript{164} 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 quality 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 quality of evidence

The TF determined that the overall quality 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 quality 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 one 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 judgement 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-$0.05. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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, and that there was variability on whether pediatric patients, guided by their parents, would use clonazepam when compared to 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.

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**MANAGEMENT OF SECONDARY RBD DUE TO MEDICAL CONDITION IN PEDIATRIC POPULATIONS**

The aims of the current literature review and data were focused on addressing the treatment of secondary RBD due to a medical condition in pediatric populations. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. For those interventions that had supporting evidence from a total of at least 3 patients with secondary RBD due to medical condition across all studies, and are FDA-approved and/or available for use in the U.S., the GRADE process was applied and the evidence summary is accompanied by a discussion of the quality 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

The following interventions are those for which the task force 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\(^{164-166}\) which 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 in Table S72 in the supplemental material. The summary of findings table is provided in Table S79 in the supplemental material. 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\(^{164-166}\) 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 S72). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S79).

**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 quality of evidence**

The TF determined that the overall quality 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 quality 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 judgement 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-$0.05.\(^{70}\) Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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, and that there was variability on whether pediatric patients, guided by their parents, would use clonazepam when compared to no treatment for their secondary 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.
Sodium Oxybate

Our review of the literature identified 1 observational study\textsuperscript{167} which examined the effect of sodium oxybate on 19 pediatric patients (10 males, 9 females) with narcolepsy.

The tables are provided in Tables S150-S152 in the supplemental material. The summary of findings table is provided in Table S154 in the supplemental material. 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\textsuperscript{167} 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 S150). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size.

Treatment-related worsening in sedation or cognitive impairment

One observational cohort study\textsuperscript{167} evaluated the effect of sodium oxybate on the treatment-related worsening in sedation or cognitive impairment in 19 pediatric patients using the Epworth Sleepiness Scale (ESS) (follow-up duration was 3 months). This study reported a clinically significant 6.53 point pre-post reduction in ESS score (Table S151). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S154).

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. 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\textsuperscript{167} 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 S152). The quality of evidence was very low due to risk of bias associated with observational studies and imprecision associated with a small sample size (Table S154).
Overall quality of evidence

The TF determined that the overall quality 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 quality 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, co-pays, 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 but that there was variability among the different subgroups (RBD associated with narcolepsy versus RBD associated with other medical disorders) in whether patients would use sodium oxybate when compared to 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.

The following interventions are those for which the GRADE process was not applied based on the exclusion criteria of having less than 3 patients or medications not available for use in the U.S. These interventions are listed in alphabetical order.

Carbamazepine

Our review of the literature identified 1 observational study which examined the effect of carbamazepine in a pediatric male patient with secondary RBD due to a medical condition.

The table is provided in Table S162 in the supplemental material. 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 reported on the percentage of pediatric patients who demonstrated partial or complete improvement in RBD symptoms in response to carbamazepine. This case series study showed that for a patient with autism initially treated with clonazepam, RBD symptoms improved only after treatment with carbamazepine (0.25-0.5 mg) (Table S162).

**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.

**Hypnotherapy**

Our review of the literature identified 1 observational study which examined the effect of hypnotherapy, combined with clonazepam, in a 16-year-old male patient with secondary RBD due to a medical condition. The table is provided in Table S166 in the supplemental material. 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 report reported on the percentage of patients who demonstrated partial or complete improvement in RBD symptoms in response to hypnotherapy (follow-up duration was 5.5 years). This study showed that RBD symptoms in a patient with parasomnia overlap disorder occurred only rarely following treatment of clonazepam and hypnotherapy (Table S166).

**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.

**Melatonin**

Our review of the literature identified 1 observational study which examined the effect of melatonin on 2 pediatric patients with secondary RBD due to a medical condition.
The table is provided in Table S92 in the supplemental material. 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 reported on the percentage of pediatric patients who demonstrated partial or complete improvement in RBD symptoms in response to melatonin (follow-up duration ranged from 3-6 months). Two male patients in this study were treated with melatonin (3-5 mg), and both showed improved sleep and RBD symptoms (Table S92).

### 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.

### DISCUSSION & FUTURE DIRECTIONS

The management of RBD, a common, distressing condition, is based upon limited evidence. Since 2010, when the American Academy of Sleep Medicine published a Best Practice Guide for the treatment of RBD, the literature on RBD management has grown. Over three 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 investigations that prioritize high quality controlled clinical trials. 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, identified 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 go undiagnosed. 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 bedpartners 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 elderly adults. Importantly, the cost of PSF is frequently prohibitive and testing is not universally accessible.

Obstructive sleep apnea is a common condition that frequently co-exists with RBD. At the time of diagnosis, it is often uncertain whether obstructive events during REM sleep are producing pseudo-RBD or whether the two diagnoses are independent. 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 a 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 positive airway pressure therapy trial on REM sleep.

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 isolate RBD have autonomic dysfunction manifesting as urinary urgency, erectile dysfunction, sweating abnormalities, and postural orthostasis, as well as quantitative abnormalities in the vocal characteristics of speech. 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. 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. Even among individuals with isolated RBD who did not clearly phenoconvert before death, brainstem lesions of Lewy body type pathology have been demonstrated on post-mortem examination.

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 SSRI (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 upon 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 Unified Parkinson’s Disease Rating Scale (UPDRS) II and III. These insights suggest that in individuals already burdened by early alpha-synuclein pathology, SSRI 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 a substantial improvement compared to 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, rather relying on patient or clinician impression. Patients’ logs of parasomnia activity can provide more granular, quantitative data, but often focus upon a patient’s report of RBD frequency without measure of intensity. Aggregate measures of RBD severity such as the clinical global impression scale (CGI), although meant to capture multiple aspects of RBD severity, lack precision.

After an era of exclusively uncontrolled studies, seven placebo-controlled trials were conducted since 2010,71, 83, 98, 125, 130, 131, 154 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 employing uncontrolled retrospective and prospective open-label designs.

Another challenge is due to the recall/awareness bias, inherent to the nature of RBD, a condition which occurs during patients’, and often bedpartners’ 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 (Shin et al 2019).

Finally, there was substantial lack of data in women. RBD is underdiagnosed in women. Prior investigations reported nearly all (>90%) of RBD subjects were men,55, 173 However, more recent investigations have demonstrated approximately 1/3rd of RBD subjects are women.5, 174 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.

Explicit statement: We recommend the development and execution of large, multicenter, well-designed, prospective clinical trials.
The 2010 guidelines for 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 two new drugs received conditional recommendation: low dose transdermal rivastigmine and low dose pramipexole. Paradoxically, the two treatments suggested by the TF in 2010, melatonin and clonazepam, failed to show superiority against placebo in recent controlled studies. While these studies were carefully considered and debated, ultimately the TF proceeded to give continued conditional recommendations for these treatments based upon the limitations of the negative studies as well as prior investigations and decades of clinical observation that their risk: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-D 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 event) but qualitative (intensity/dangerousness of event) description of RBD episodes should be routinely employed. When bed partners are present, their sleep and wellbeing should also be reported, including measures on sleep quality, safety, and QOL.

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 vary 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 different pathophysiology at different stages of disease. Second, tolerance to drug interventions, especially to sedatives and CNS depressants, varies between disease subtypes (isolated RBD, secondary RBD, 5-HT RBD) and reduces with aging and advanced disease. Therefore, drug trials should be designed, if possible, to use flexible dosing. Further, there may also be gender 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 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.

REFERENCES


Anderson KN, Shneerson JM. Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. (1550-9389 (Print)).


76. Lin C-M. Melatonin and REM Behavior Disorder. *Journal of Sleep Disorders & Therapy*. 2013;02(03).


