Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD)

Standards of Practice Committee:

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Summary of Recommendations: Modifying the sleep environment is recommended for the treatment of patients with RBD who have sleep-related injury. Level A

Clonazepam is suggested for the treatment of RBD but should be used with caution in patients with dementia, gait disorders, or concomitant OSA. Its use should be monitored carefully over time as RBD appears to be a precursor to neurodegenerative disorders with dementia in some patients. Level B

Clonazepam is suggested to decrease the occurrence of sleep-related injury caused by RBD in patients for whom pharmacologic therapy is deemed necessary. It should be used in caution in patients with dementia, gait disorders, or concomitant OSA, and its use should be monitored carefully over time. Level B

Melatonin is suggested for the treatment of RBD with the advantage that there are few side effects. Level B

Pramipexole may be considered to treat RBD, but efficacy studies have shown contradictory results. There is little evidence to support the use of paroxetine or L-DOPA to treat RBD, and some studies have suggested that these drugs may actually induce or exacerbate RBD. There are limited data regarding the efficacy of acetylcholinesterase inhibitors, but they may be considered to treat RBD in patients with a concomitant synucleinopathy. Level C

The following medications may be considered for treatment of RBD, but evidence is very limited with only a few subjects having been studied for each medication: zopiclone, benzodiazepines other than clonazepam, Yi-Gan San, desipramine, clozapine, carbamazepine, and sodium oxybate. Level C

Keywords: REM sleep behavior disorder, synucleinopathy, clonazepam, melatonin, pramipexole, L-DOPA, acetylcholinesterase inhibitor, paroxetine, zopiclone, benzodiazepine, Yi-Gan San, desipramine, carbamazepine, clozapine, sodium oxybate, sleep-related injury

Citation: Aurora RN; Zak RS; Maganti RK; Auerbach SH; Casey KR; Chowdhuri S; Karippot A; Ramar K; Kristo DA; Morgenthaler TI. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med* 2010;6(1):85-95.

1. INTRODUCTION

REM sleep behavior disorder (RBD) was first defined in 1986.[1] Since then, a number of reviews but no evidence-based treatment recommendations have been published. To address this issue, the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) commissioned a task force to assess the literature on the treatment of RBD. The task force found that although the literature is voluminous, much of the data are low-level studies, mostly case series and case reports with no randomized controlled clinical trials. These studies were deemed insufficient to support the standards or guidelines of a practice parameter. Thus, the Board of Directors authorized the task force to draft a Best Practice Guide on the treatment of RBD based on a systematic review and compilation of recommended evaluation or management strategies.

2. METHODS

The Standards of Practice Committee of the AASM commissioned among its members 7 individuals to conduct this review and develop best practice principles. Work began in December 2007 to review and grade evidence in the peer-reviewed scientific literature regarding the treatment of RBD in adults. A search for articles on the medical treatment of RBD was conducted using the PubMed database, first in February 2008, and subsequently updated in June 2009, to include the most current literature. The key words for the searches were the following: [(RBD OR Rapid Eye Movement Sleep Disorder OR REM Sleep behavior disorder) AND (treatment OR medication OR drug therapy] as well as [Rapid eye movement behavior disorder AND evaluation AND (neurological diseases OR dementia OR stroke OR sleep disorders OR Lewy body dementia OR drug induced OR multiple systems atrophy OR narcolepsy OR Parkinson's OR synucleinopathies)]. Each search was run separately and findings were merged. When the search was limited to articles published in English and regarding human adults (age 19 years and older), a total of 315 articles was identified. Abstracts from these articles were reviewed to determine if they met inclusion criteria. The literature on medical treatment of RBD was noted to comprise mostly small case series. In order to be inclusive, latitude in

Table 1—Summary of PICO questions

Do patients with RBD demonstrate a clinical response to clonazepam compared with natural history or other medications?

Do patients with RBD demonstrate a clinical response to melatonin compared with natural history or other medications?

Do patients with RBD demonstrate a clinical response to dopaminergic medications compared with natural history or other medications?

Do patients with RBD demonstrate a clinical response to acetylcholinesterase inhibitors compared with natural history or other medications?

Do patients with RBD demonstrate a clinical response to other medications compared with natural history or those medications listed above?

Do patients with RBD benefit from modification to the sleep environment to prevent injury or falls?

Table 2—AASM classification of evidence (Adapted from Oxford Centre for Evidence-based Medicine[2])

Evidence Levels	Study Design
1	High quality randomized clinical trials with narrow confidence intervals
2	Low quality randomized clinical trials or high quality cohort studies
3	Case-control studies
4	Case series or poor case control studies or poor cohort studies or case reports

Table 3—Levels of Recommendation

Term	Level	Evidence Levels	Explanation
Recommended / Not recommended	A	1 or 2	Assessment supported by a substantial amount of high quality (Level 1 or 2) evidence and/or based on a consensus of clinical judgment
Suggested / Not Suggested	B	1 or 2 few studies / 3 or 4 many studies and expert consensus	Assessment supported by sparse high grade (Level 1 or 2) data or a substantial amount of low-grade (Level 3 or 4) data and/or clinical consensus by the task force
May be considered / Probably should not be considered	C	3 or 4	Assessment supported by low grade data without the volume to recommend more highly and likely subject to revision with further studies

disorder definition was allowed and no minimum number of subjects was applied. The articles had to address at least 1 of the "*PICO*" questions (acronym standing for Patient, Population or Problem, provided a specific Intervention or exposure, after which a defined Comparison is performed on specified Outcomes) that were decided upon ahead of the review process (see **Table 1**). The literature review and pearling (i.e., checking the reference sections of search results for articles otherwise missed) provided 42 articles for review and grading.

Evidence was graded according to the *Oxford Centre for Evidence-based Medicine Levels of Evidence* (**Table 2**).[2] All evidence grading was performed by independent review of the article by 2 members of the task force. Areas of disagreement were addressed by the task force until resolved. Recommendations were formulated based on the strength of clinical data and consensus attained via a modified RAND/UCLA Appropriateness Method.[3] The task force developed a ranking of recommendations for increased transparency. The nomenclature for the recommendations and levels of recommendation are listed in **Table 3**.

Recommendations were downgraded if there were significant risks involved in the treatment or upgraded if expert consensus determined it was warranted. The paper was reviewed by content experts in the area of REM sleep behavior disorder.

The Board of Directors of the AASM approved these recommendations. All members of the AASM Standards of Practice Committee and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject.

The Best Practice Guides endorse treatments based on review of the literature and with agreement by a consensus of the task force. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding propriety of any specific care must be made by the physician in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.

The AASM expects these recommendations to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. These assessments reflect the state of knowledge at the time of publication and will be reviewed, updated, and revised as new information becomes available.

3. BACKGROUND

3.1. Definition

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia, first described in cats[4] and later described in human beings by Schenck et al.[1] in 1986. RBD is typically characterized by abnormal or disruptive behaviors emerging during rapid eye movement (R) sleep having the potential to cause injury or sleep disruption such as talking, laughing, shouting, gesturing, grabbing, flailing arms, punching, kicking, and sitting up or leaping from bed.[5] Vigorous, violent episodes may occur rarely or up to several times nightly. Polysomnography (PSG) shows loss of normal electromyographic (EMG) atonia (REM sleep without atonia–RSWA) manifest as either or both sustained muscle activity during R sleep in the chin EMG and excessive transient muscle activity (phasic muscle twitches) in either the chin or limb EMG. RBD usually presents after the age of 50,[6] though any age group can be affected. There is predilection for male gender,[7] and prevalence estimates are 0.38%[8] to 0.5%[9] in the general population.

Patients with RBD are at risk for sleep-related injury (SRI). Between 33%[10] and 65%[11] of RBD patients have been reported to have had sleep related injury to self or bed partner. Common injuries included bruises, abrasions, lacerations, and, less commonly, subdural hematomas. Interestingly, in patients with RBD

who develop α-synucleinopathies, symptoms of RBD as well as sleep related injuries decline over time.[11]

RBD may be idiopathic or secondary. At this time, it is unknown if idiopathic RBD (IRBD) truly exists or if it is merely cryptogenic since Lewy bodies were demonstrated by autopsy in 2 cases of presumptive IRBD.[12,13] Secondary RBD can be related to neurodegenerative disorders, other neurologic disorders, sleep disorders or medications, including withdrawal states. RBD appears to be associated with the α-synucleinopathies.[14] Between 38% and 65% of patients with presumptive RBD followed longitudinally developed a synucleinopathy between 10 and 29 years after RBD presentation, mostly Parkinson disease (PD), but even more extensively dementia of Lewy body (DLB) type and multiple system atrophy (MSA).[15-17] Mild cognitive impairment also emerged but was less common.[16] Conversely, RBD has been found in 70%[18] of patients with MSA, 40%[18] of patients with DLB, and 15%[10,19] to 33%[20] of patients with PD. In 1 series,[11] 92% of patients with RBD and dementia met consensus-based criteria for DLB. RBD is now a suggestive feature for DLB.[21] There have also been rare reports of RBD in some of the tauopathies, such as Alzheimer disease, progressive supranuclear palsy, and corticobasal degeneration,[22] although a clear association has not been proven.

RBD may be secondary to other neurological disorders such as spinocerebellar ataxia,[23,24] limbic encephalitis,[25] brain tumors,[26] multiple sclerosis,[27] Guillaine-Barre,[1] and stroke.[28] RBD may be associated with other sleep disorders such as narcolepsy[29-31] and periodic limb movements of sleep.[32] Vigorous arousals in OSA can mimic RBD in clinical presentation; thus, some patients with severe OSA may present as if they have RBD. In these cases, PSG can clarify the diagnosis.[33] Finally, RBD can be associated with medication use and withdrawal. There are case reports of different antidepressant medications causing RBD (e.g., paroxetine,[34] fluoxetine and impipramine,[35] venlafaxine,[36] and mirtazapine[37]). A recent population study[38] showed an increased risk ratio of being on antidepressants for patients with early-onset RBD; furthermore, a study[39] evaluating the effect of SSRI medications on motor tone in R (which specifically excluded subjects with RBD) demonstrated that SSRI medications can induce RSWA. β-Blockers have also been noted to cause RBD.[40] RBD may be seen in association with R rebound states such as alcohol[40] and barbiturate withdrawal.[41]

3.2. Diagnosis

The minimal diagnostic criteria for RBD proposed by the International Classification of Sleep Disorders (ICSD)-2[42] are the following:

A) Presence of R sleep without atonia, defined as sustained or intermittent elevation of submental EMG tone or excessive phasic muscle activity in the limb EMG (**Appendix 1**)[43];

B) At least 1 of the following:
   1) Sleep related injurious or potentially injurious disruptive behaviors by history;
   2) Abnormal R behaviors documented on polysomnogram (PSG);

C) Absence of epileptiform activity during R sleep unless RBD can be clearly distinguished from any concurrent R sleep-related seizure disorder;

D) Sleep disturbance not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Of note, some papers used either ICSD or ICSD-revised edition criteria for the diagnosis of RBD. The evidence table denotes which criteria were used in each paper.

3.3. Neuropharmacology

The apparent efficacy of multiple families of medications for RBD may be related to the complexity of its pathogenesis. The neuropharmacology underlying RBD is inferred from animal studies, case reports of lesions, and physiologic neuroimaging data, which implicate serotonin, norepinephrine, hypocretin, acetylcholine, and dopamine in the development of RBD. Analyzing these data, Boeve et al.[13] proposed that the most likely neuroanatomic abnormality lies in the human equivalent of the sublaterodorsal nucleus (a glutamatergic nucleus in the rat pons) and the precoeruleus region or in the regions that modulate these R-on neurons in the rat. The R-on neurons are inhibited by the R-off neurons, which are *activated* by norepinephrine from the locus coeruleus, serotonin from the raphe nuclei, and hypocretin from the lateral hypothalamus. This suggests that norepinephrine[44] and serotonin[39,44] may inhibit R (as seen in reports of medication effects) and a deficiency of hypocretin may promote R (as seen in narcolepsy). Cholinergic neurons from the pedunculopontine and lateral dorsal tegmental nuclei in the pons *inhibit* the R-off cells as do GABA-ergic and galanin-ergic neurons from the ventrolateral preoptic nucleus in the forebrain, and, thus, acetylcholine promotes R. Thus, there are likely multiple different anatomical and neurochemical lesions that, either individually or in combination, can lead to clinical RBD. This may explain the efficacy of multiple families of medications.

Dopaminergic dysfunction may also play a role in the pathophysiology of RBD. Neurophysiologic imaging using SPECT scans has demonstrated a decreased number of striatal dopamine transporters in patients with RBD.[45,46] A study using PET showed decreased striatal binding in patients with RBD and a correlation between decreased striatal binding and the severity of increased muscle activity in patients with MSA who had clinical and PSG evidence of RBD.[47] Albin et al.[48] propose that the mechanism may be through the influence of the basal ganglia on the pedunculopontine nucleus (PPN) or that degeneration in the basal ganglia co-occurs with damage to the PPN.

Despite the data and theories presented above, there are instances of the same medication both causing[34] and treating[49,50] RBD. A possible explanation is dose-dependent activation of different receptor subtypes causing different degrees of inhibition of various components of R sleep.

3.4. Prognosis

Patients with RBD are at risk for developing cognitive impairment. Patients with IRBD with no other neurological disorder were found to have visuospatial and constructional abnormalities as well as altered visuospatial learning compared to age-matched controls.[51] In patients with PD, however, presence of RBD may help predict future cognitive impairment. In 1 study, patients with PD and RBD had multiple deficits, including verbal memory, executive function, visuospatial, and visuoperceptual processing compared to controls or patients

Table 4—Summary

Section	Treatment	Evidence Level (Number of studies)	Number of Subjects Treated	Number of Subjects Responding	Dose
4.1.1	Clonazepam	4 (22)	339	306[1]	Range: 0.25-4.0 mg qhs but usual recommended dose = 0.5-2.0 mg 30 minutes before bedtime
4.1.2	Melatonin	4 (6)	38	31	3 mg to 12 mg hs
4.1.3.1	Pramipexole	4 (3)	29	13	0.125 mg starting dose with effective dose ranging from 0.5 to 1.5 mg nightly for RBD (3 regimens in 2 papers: total dose 1 hour before bedtime; total dose at bedtime; divided doses—first dose in early evening and second dose at bedtime); for study looking at whether or not dosing pramipexole for PD would affect RBD, dose was 0.7 mg tid
4.1.3.2	Paroxetine	4 (3)	21	17[2]	10-40 mg
4.1.3.3	L-DOPA	4 (1)	3	3	Not stated for case series of efficacy[3]
4.1.3.4	Acetylcholinesterase inhibitors				
	Donepezil	4 (2)	6	4	10-15 mg
	Rivastigmine	4 (2)	10	10	4.5-6 mg bid; Diagnostic criteria not standard
4.1.4.1	Zopiclone	4 (2)	12	9	3.75 to 7.5 mg hs
4.1.4.2	Benzodiazepines				
	Temazepam	4 (2)	2	2	10 mg; Given with zopiclone--dose not stated
	Triazolam	4 (1)	2	1	Not stated
	Alprazolam	4 (3)	8	6[4]	Either 1-3 mg or not stated
4.1.4.3	Yi-Gan San	4 (1)	3	3[5]	2.5 gm tid with normal renal function
4.1.4.4	Desipramine	4 (1)	3	1	50 mg qhs (effective); 250 mg qhs (ineffective)
4.1.4.5	Clozapine	4 (2)	3	3	Not stated
4.1.4.6	Carbamazepine	4 (2)	5	5[6]	100 mg tid for one subject; 500 to 1500 mg qd for other subjects
4.1.4.7	Sodium oxybate	4 (1)	1	1	Not stated
4.2.1	Safe Sleep Environment	Anecdotal reports			
4.2.2	Clonazepam for SRI	4 (3)	105	> 80	0.25 mg to 2.0 mg hs

[1]57/308 were listed as partial responders; subjects were considered to have a partial response to clonazepam if either the authors designated the response that way or if they reported residual minor behaviors such as vocalizations or twitching with elimination of gross motor behaviors.
[2]only rarely with complete elimination of symptoms
[3]NB: a prospective study giving L-DOPA at the minimum dose that would control PD symptoms—mean 393.3 mg—noted the ONSET of RBD in 5/10 participants in under 1 year with statistically significant increase in R motor tone on PSG for the group as a whole.
[4]although up to 4 may have been treated either solely or additionally with carbamazepine
[5]1 with clonazepam in addition
[6]although up to 4 may have been treated either solely or additionally with alprazolam

with PD and no RBD on standardized neuropsychological testing.[52] Cognitive decline may coincide or precede the onset of RBD. One group reported that cognitive decline occurred in 94% of a sample of patients with RBD.[53] It is not clear from the studies whether the risk for dementia is limited to those who develop abnormal neurological findings or includes all patients presenting with cryptogenic RBD. Nonetheless, these studies suggest that a baseline neurological examination with particular attention to cognition and extrapyramidal signs is merited when a diagnosis of RBD is established. Patients without an established neurological diagnosis and their families should be counseled about the possibility of onset of a neurodegenerative disorder or dementia. Learning this information from readily available public media rather than from a well-informed health professional may cause needless distress.

3.5. Treatment Data

To date, there are no large randomized controlled trials of treatments for RBD. Small case series and case reports describe efficacy of a wide range of medications, most prominently clonazepam but also melatonin, pramipexole, acetylcholinesterase inhibitors, paroxetine, L-DOPA, zopiclone, temazepam, triazolam, alprazolam, Yi-Gan San, desipramine, carbamazepine, clozapine, and sodium oxybate. In addition, appropriate safety measures, including environmental modifications and medication, are addressed. The treatment data are summarized in **Table 4** and the evidence table is available in the online version at www.asasmnet.org/jcsm/.

Certain precautions should be taken when interpreting the results presented below. Many of the studies have subjects with DLB. Because DLB is characterized by symptom fluctuation, it

may be difficult to ascertain whether or not symptom improvement is a function of medication effect or natural history.

4. TREATMENT FOR RBD INVOLVES MEDICATION AND INJURY PREVENTION

4.1. The following medications are treatment options for RBD

4.1.1. Clonazepam is suggested for the treatment of RBD but should be used with caution in patients with dementia, gait disorders, or concomitant OSA. Its use should be monitored carefully over time as RBD appears to be a precursor to neurodegenerative disorders with dementia in some patients. Level B

The original case series describing RBD by Schenck et al. in 1986[1] reported that clonazepam successfully treated the vigorous behaviors during R sleep in 2 of the original 5 subjects (only 3 were treated and the third was successfully treated with desipramine). We identified 22 studies of the treatment of RBD using clonazepam. None of the studies exceeded Level 4 evidence. These include 16 case series[6-8,11,16,54-64] and 6 case reports.[65-70] A number of studies did not use PSG to diagnose RBD. A majority of the studies evaluated sleep clinic populations, whereas only 1 studied a community sample.[8] There were a total of 339 subjects, of whom 306 were noted to have complete (249) or partial (57) treatment response to clonazepam. These studies demonstrated substantial efficacy in patients with cryptogenic RBD[6,16] as well as secondary RBD (associated with such disorders as synucleinopathies,[7,15,71] narcolepsy,[29] and brainstem lesions[54,66,69]), parasomnia overlap syndrome,[60] and status dissociatus.[57] These data are consistent with the results from the Minnesota Regional Sleep Disorders Center, where clonazepam has been used to treat more than 200 patients with RBD with clinical efficacy in more than 80%.[72] Clonazepam was chosen because other initial therapies, which included R-suppressing tricyclic antidepressants, had failed and because of its efficacy in treating periodic limb movements of sleep (PLMS), which were noted to be present in some of the patients with RBD.[73]

Clonazepam is a long acting benzodiazepine with an elimination half-life of 30-40 hours that is rapidly absorbed after oral administration, with a bioavailability of 90%. Maximum plasma concentrations are reached within 1-4 hours after oral administration.[74] The recommended dose is 0.25 mg to 2.0 mg 30 minutes prior to bedtime, but doses as high as 4.0 mg were reported.[14] Studies have reported minimal dosage tolerance and medication abuse with clonazepam for management of RBD.[73,75] One study reported that women required higher dosing (1.4 ± 0.4 mg) than men (0.68 ± 0.4 mg) to control RBD symptoms.[73] Failure to take clonazepam has resulted in immediate RBD relapse, but rapid control was restored after resumption of treatment.[73] Dose escalation was reportedly rare,[73,76] but was noted in 1 study.[64] There was no significant difference in initial versus final mean dose (0.63 ± 0.4 vs. 0.97 ± 0.89 mg),[76] indicating absence of tolerance; withdrawal symptoms typically did not develop upon dose reduction or drug discontinuation.[64,76] However, many patients are unable

to substantially reduce their dose despite periodic attempts at gradual tapering without experiencing prompt reemergence of the primary sleep disorder.[76] In a series of intensive care unit (ICU) patients with RBD, failure to take clonazepam resulted in same-night relapse.[62] Follow-up has been reported for as long as 6 years.[15]

The mechanism of action of clonazepam is unknown. R sleep suppression is not involved nor is there normalization of R atonia.[56,73] Clonazepam may preferentially control phasic locomotor activity at the brainstem level without restoring atonia via a serotonergic effect.[56,73] It may also modify dream content in RBD.[73] An alternative proposed hypothesis suggests that dream generators are suppressed by clonazepam with inhibition of brainstem locomotor pattern generators.[73] The fact that it produces clinical improvement without an effect upon RSWA suggests that it acts preferentially upon the locomotor systems rather than those affecting R atonia.[77] A hierarchical response to clonazepam was suggested in decreasing order of control: vigorous/violent behaviors and loud vocalizations > complex non-vigorous behaviors > simple limb jerking and body movements > excessive EMG twitching in R sleep. PSG data in 8 patients while on clonazepam demonstrated no change in sleep architecture including R sleep.[73] The only case-control study[56] (Level 4) of 5 RBD patients (age 45-66 years) treated with 0.5 to 2 mg clonazepam did not note any change in sleep variables compared to 5 age-matched controls except for a significant reduction in eye movement density and phasic chin EMG density. Clonazepam suppressed PLMS significantly but did not restore R atonia.

Most studies reported minimal side effects, but a recent retrospective study noted that 58% of 36 patients on clonazepam for RBD had moderate or severe side effects resulting in discontinuation of the medication in 13 patients.[78] The most common side effects included sedation, particularly in the morning[7,73,76,79]; impotence[7,73]; early morning motor incoordination[7]; confusion[78]; and memory dysfunction,[76] with no instance of drug abuse.[73] Clonazepam at 0.5 to 1.0 mg can also be associated with the possible risk of developing or worsening sleep apnea.[80] There is also a risk of confusion and falls with clonazepam at 2.0 mg nightly, with the potential for a subdural hematoma.[11] Only a minority of patients in a Hong Kong Chinese population reported adverse effects, including intolerable daytime somnolence (5/71) and transient and reversible increase in liver enzyme (1/71).[64] These data suggest that clonazepam should be used with caution and oversight in patients with neurodegenerative disorders, obstructive sleep apnea, and underlying liver disease.

In conclusion, clonazepam has been effective in a number of Level 4 studies. However, there is a paucity of more robust data with most studies limited by selection bias of a sleep clinic sample, absence of long-term follow-up, and no comparison or control group. Prospective, controlled trials are needed to allow us to determine the efficacy of clonazepam in the treatment of RBD.

4.1.2. Melatonin is suggested for the treatment of RBD with the advantage that there are few side effects. Level B

The evidence for melatonin is less strong than for clonazepam. Nevertheless it is far stronger than for any of the subse-

quent agents; therefore, based on the evidence plus clinical consensus melatonin use is recommended at Level B. Melatonin 3-12 mg at bedtime has been shown to be effective in the treatment of RBD in Level 4 studies with relatively few subjects. Initially, melatonin was introduced to promote sleep,[81] but others have speculated that it may help with an underlying disorder of desynchronization.[82] This benefit has been reported in 1 case report,[81] 2 open-label prospective case series of patients with IRBD[82,83] and 2 retrospective case series.[78,84] Taken together, these reports include a total of 38 patients. Thirty-one were noted to experience improvement with melatonin,[78,81-84] 2 more experienced transient improvement,[84] and 1 seemed to worsen.[84] Follow-up as far as 25 months was reported.[84] Doses ranged from 3 mg[81] to 12 mg,[84] and 6 subjects were also taking clonazepam (one of these used gabapentin as well).[78,84] Successfully treated patients included those with synucleinopathies including DLB, PD and MSA[82,84], memory problems,[78,82,85] and sleep-disordered breathing.[78,85] Dose-related side effects included morning headache, morning sleepiness, and delusions/hallucinations.[84] PSG showed statistically significant decreases in number of R epochs without atonia[82,83] and in movement time in R.[82] This contrasts with the persistence of tonic muscle tone in R sleep seen with patients treated with clonazepam.[56]

4.1.3. Pramipexole may be considered to treat RBD but efficacy studies have shown contradictory results. There is little evidence to support the use of paroxetine or L-DOPA to treat RBD, and some studies have suggested that these drugs may actually induce or exacerbate RBD. There are limited data regarding the efficacy of acetylcholinesterase inhibitors, but they may be considered to treat RBD in patients with a concomitant synucleinopathy. Level C

4.1.3.1. Pramipexole

The relationship of RBD and PD, as well as the results of PET[48] and SPECT[45] scans suggesting dysfunction in the dopaminergic nigrostriatal systems of patients with IRBD, led some to consider dopaminergic agents in the treatment of RBD. Level 4 studies with pramipexole, a dopaminergic D_2 - D_3 receptor agonist, have produced mixed results. There are 2 published case series[86,87] examining the effectiveness of pramipexole in idiopathic and secondary RBD and a third[88] examining the role in patients already receiving therapy for previously diagnosed PD. There were a total of 29 subjects with and without synucleinopathies diagnosed at the time of the reports. Of these, 13 had a positive response,[86,87] with an additional 2 subjects having a brief transient response.[86] One study[88] of 11 subjects with PD demonstrated no benefit from pramipexole treatment on RBD symptoms, including blinded review of post treatment video. It should be noted that the pramipexole dose was titrated using general PD motor symptoms rather than RBD symptoms as an endpoint with a maximal dose of 0.7 mg three times a day. However, this was similar to the mean nightly dose used in the other 2 studies (0.78 and 0.89 mg).[86,87] Surprisingly, 1 study with pretreatment and treatment PSG, which demonstrated clinical efficacy, showed a statistically significant increase in tonic REM motor tone during treatment with a decrease in video-

taped simple, but not complex, motor behaviors.[86] The study in PD subjects that did not demonstrate clinical efficacy also did not show any statistically significant changes in R-related increases in muscle tone.[88]

Taken together, these few studies suggest the possibility that pramipexole may be helpful in some patients with RBD. If a benefit exists, it seems to be in patients who have not yet been diagnosed with neurodegenerative disease. Dopaminergic agonists may exacerbate symptoms of DLB, and since many patients with IRBD ultimately develop DLB, caution should be exercised with its use.

4.1.3.2. Paroxetine

Paroxetine is a selective serotonin reuptake inhibitor (SSRI). Case reports of SSRI-induced RBD[35,36] suggest that it might exacerbate RBD. A recent population study[38] showed an increased risk ratio of being on antidepressants (including paroxetine) for patients with early-onset RBD. Nonetheless, paroxetine was used in 1 Level 4 case series[50] of 19 subjects with cryptogenic RBD because of its ability to suppress R sleep. Sixteen of the 19 participants noted improvement in RBD symptoms, with 11 showing significant improvement but none having complete elimination of symptoms. Doses ranged from 10-40 mg at bedtime. Paroxetine was also noted to be efficacious in 1 case report[49] at a dose of 10 mg. Yet there is also a case report[34] of paroxetine causing RBD (the dose was 30 mg daily). Reported side effects included nausea, dizziness, diarrhea,[50] and thirst.[49] These data provide little support for the use of paroxetine in the treatment of RBD.

4.1.3.3. L-DOPA

There are limited Level 4 data demonstrating efficacy of L-DOPA in the treatment of RBD. However, there are additional low-grade data that imply that L-DOPA may promote RBD, although this conclusion cannot be definitively inferred. A small Level 4 case series[89] reported efficacy of L-DOPA in 3 RBD subjects with PD at unspecified doses. The postulated mechanism for efficacy was a reduction in R sleep.[89] In contrast, there are data[79] showing that patients with PD and RBD have had a greater exposure to L-DOPA than those with PD alone, suggesting that L-DOPA may not be efficacious. In addition, a Level 4 prospective case series showed the onset of RBD in under one year of administering L-DOPA in 5/15 L-DOPA naïve participants.[90] Furthermore, PSG showed a statistically significant increase in tonic and phasic chin EMG activity in the group as a whole. The authors do not speculate on how L-DOPA would trigger the onset of RBD. These data overall suggest a limited role for L-DOPA in the treatment of RBD at this time.

4.1.3.4. Acetylcholinesterase inhibitors

As described above, circuitry controlling R sleep involves multiple neurotransmitters, including acetylcholine. Thus, dysfunction of cholinergic nuclei or pathways are likely to be involved, even if they are only secondarily affected by dysfunction in modulating systems, such as those of the basal ganglia. Some authors have suggested that RBD may be due to a disruption in R-related cholinergic systems.[91] Despite the fact that cholinesterase inhibitors may be associated with sleep disruption, vivid dreams and sleep-related disruptive behaviors, they have also been con-

sidered for the treatment of RBD, possibly through enhancing cholinergic R-on neurons to normalize the R circuitry.[59,92] There were 2 papers[59,93] presenting 6 cases of treatment of RBD with donepezil—4 were associated with unspecified neurodegenerative disorders (and 1 had previously undergone resection of a craniopharyngioma) and 1 was "childhood onset". Four patients responded at doses between 10 mg and 15 mg,[59,93] and two patients failed to respond to donepezil at a dose of 10 mg.[59]

The data addressing efficacy of rivastigmine are compromised by the absence of the typical history of clearly acting out dreams, which may be a function of the difficulty obtaining clear subjective symptoms from patients with DLB. Instead, correlates such as nightmares, PLMS, vigorous movements during sleep, and confusion on wakening are used to suggest the presence of RBD in the DLB population. Two small case series[94,95] examined the efficacy of rivastigmine on multiple symptoms of DLB. Ten subjects were thought to have RBD, which was not documented by PSG data, and all 10 were reported to have improvement of nighttime symptoms with rivastigmine at doses ranging from 4.5 mg to 6 mg twice daily.

Unfortunately, most of the reported cases of the use of cholinesterase inhibitors included patients with the diagnosis of DLB. None of the studies addressed the issue of disease fluctuation making it difficult to determine with any degree of certainty whether or not improvements in clinical state are the result of treatment or represent the natural course of the disease, particularly in the absence of large numbers of subjects followed over a long period of time.[21]

4.1.4. The following medications may be considered for treatment of RBD, but evidence is very limited with only a few subjects having been studied for each medication: zopiclone, benzodiazepines other than clonazepam, Yi-Gan San, desipramine, clozapine, carbamazepine, and sodium oxybate. Level C

4.1.4.1. ZOPICLONE

One case series and 1 case report mention treatment of RBD with zopiclone.[29,78] The authors do not propose a specific mechanism other than to suggest that there may be a class-specific effect of GABA acting hypnotics on RBD.[78] In total, 9/12 subjects were effectively treated with zopiclone, of which 2 required an additional benzodiazepine agent. The dose ranged from 3.75 mg to 7.5 mg nightly. Side effects included rash and nausea.[78] Thus, there are positive but sparse Level 4 data supporting the use of zopiclone.

4.1.4.2. BENZODIAZEPINES OTHER THAN CLONAZEPAM: TEMAZEPAM, TRIAZOLAM, ALPRAZOLAM

The data on benzodiazepines other than clonazepam consists of Level 4 studies of generally 1 or 2 subjects. Efficacy was noted in 1 subject treated with temazepam alone (10 mg)[29] and one treated with temazepam in conjunction with zopiclone (dose not specified)[78]; 1 of 2 subjects given triazolam (dose not stated)[7]; and reference to success in 4 patients with parasomnia overlap syndrome given alprazolam (1-3 mg) and/or carbamazepine, so the exact efficacy of alprazolam is difficult to infer.[60] Another report of 2 patients treated with alprazolam failed to demonstrate clinical efficacy (initially effective at 0.5 mg but symptoms returned and were unresponsive to higher doses; for the other patient, the dose was not specified)[1] although 2 other patients did demonstrate a response to alprazolam at a dose of 1-3 mg.[76] The exact mechanism of action is unknown.

4.1.4.3. YI-GAN SAN, AN HERBAL MEDICATION

A Level 4 case series[96] of 3 subjects who were either intolerant of clonazepam or for whom clonazepam was contraindicated reported complete resolution of symptoms with Yi-Gan San, which consists of *Atractylodis Lanceae* rhizoma, Hoelen, Cnidii rhizoma, Angelicae radix, Bupleuri radix, Glycyrrhizae radix, and Uncariae ramulus et uncus. The authors propose that the efficacy demonstrated by Yi-Gan San may reflect the GABA-ergic and serotonergic (5-HT_2) properties of Angelicae radix. The dose of Yi-Gan San was 2.5 g before meals 3 times a day except in a patient with renal dysfunction, who was successfully treated with 1 evening dose of 2.5 g. One of the other subjects was also treated with a small dose of clonazepam (0.25 mg) in addition to the Yi-Gan San. Yi-Gan San did not result in any side effects in this study.

4.1.4.4. DESIPRAMINE

The original RBD case series[1] included 3 patients treated with desipramine because of its ability to suppress phasic and tonic components of R sleep, with sustained success in 1 of 3 patients. One patient had suppression of violent behaviors with persistence of minor behaviors (such as minor limb twitching and vocalizations) at a dose of 50 mg nightly; 1 patient had suppression of RBD symptoms for only 3 weeks, despite doses up to 250 mg nightly and eventually required treatment with clonazepam; and 1 patient was unable to tolerate desipramine.

4.1.4.5. CLOZAPINE

Three patients are reported[7,11] to have been treated with clozapine (dose not specified) who had both RBD and dementia, in 2 of whom clonazepam had failed. No presumed mechanism of action was mentioned. One patient had complete resolution of RBD symptoms, 1 had partial resolution, and 1 had reduced symptoms. Both of these were level 4 studies.

4.1.4.6. CARBAMAZEPINE

There is sparse Level 4 evidence consisting of 1 case report[97] and 1 small case series[60] (4 subjects) with minimal information suggesting that carbamazepine, perhaps in conjunction with alprazolam, may be effective in the treatment of RBD. The case report from Bamford[97] presents a patient with RBD who responded to carbamazepine at a dose of 100 mg three times a day. Carbamazepine was chosen at the time because of its ability to control aggressive behavior in psychiatric disorders (which was not present during the day in the patient) and resulted in an absence of violent behavior during the night, elimination of "crazy dreams," and a 75% improvement in jerking nocturnal movements. The case series[60] is of patients with parasomnia overlap syndrome, most of whom were treated with clonazepam, but there is mention that 4 subjects were treated with carbamazepine (500 to 1500 mg) and/or alprazolam who had full or substantial control of symptoms. Unfortunately, the exact dosing and the number of subjects on carbamazepine alone are not reported.

4.1.4.7. SODIUM OXYBATE

There is 1 case report within a recent case series (Level 4 evidence) citing efficacy of sodium oxybate, dose not specified, in a patient with RBD.[78]

4.2. The following are injury prevention techniques for patients with RBD

A striking aspect of RBD is the history of SRI. Injuries were a significant portion of the morbidity related to the disorder. The reported sleep clinic prevalence of SRI in diagnosed RBD patients ranged from 30% to 81%.[7,11,64,73] In a community sample of 1034 elderly surveyed in Hong Kong, 0.8% reported history of sleep-related injuries.[8] Types of injuries ranged from ecchymoses and lacerations to fractures and subdural hematomas,[11,62,64,73,75] with ecchymoses and lacerations being significantly more common than fractures.[62,64,73] RBD also carries an ongoing risk for injury to the bed partner.[11] In a series[7] of 92 patients, 64% of the bed partners (53/83) sustained punches, kicks, attempted strangulation, and assault with objects. RBD-related injuries may warrant ICU admission or may arise during ICU admissions for other medical reasons, such as stroke.[62] RBD is also a treatable cause of falls in the elderly.[68]

4.2.1. Modifying the sleep environment is suggested for the treatment of patients with RBD who have sleep-related injury. Level A

There was a strong consensus among task force members that non-pharmacologic measures, specifically maintaining a safe sleeping environment for both the patient and the bed partner, are paramount to injury prevention and should be enforced as an adjunct to therapeutic intervention.[8,98,99] Recommended measures include placing a mattress on the floor, padding corners of furniture, window protection, and removing potentially dangerous objects, such as guns or sharp objects, from the bedroom. In addition, it may be prudent for the bed partner to sleep in a different room until the RBD symptoms are controlled.

In 4 Level 4 case series for treatments, methods improvised by both patients and clinicians to prevent injuries were summarized. These provide the basis for current recommendations to prevent trauma related to nocturnal RBD-related behaviors. Self-protection measures adopted by the patients include placing a mattress on the floor,[8,64,73] sleeping in separate beds or separate rooms from bed partners,[64,73] barricades of pillows or plastic screens,[64,73] restraint devices (including sleeping bags and ropes, belts, or dog leashes attaching patients to their beds),[64,73] and padded waterbeds.[64,73] In a case series of RBD patients requiring ICU admissions,[62] patients were safeguarded from injury during their PSG studies by having padded rails on their beds, by removing potentially dangerous objects from their bedside, and by having a technician continuously observing them on a video monitor in an adjacent room during sleep. No active restraints were used as such devices were considered potentially dangerous if sudden twisting movements occurred. In the Mayo clinic series,[7] the authors advised institution of safety measures of the sleeping environment, including moving furniture away from the bed and sleeping on a mattress on the floor. Additionally, potentially danger-

ous objects should be removed from the bedroom, weapons (if any) should be stored and locked away safely outside the bedroom with the key entrusted to another person, the corners around the bed should be padded or cushioned, and window protection should be considered.[77,99]

Clinicians should emphasize the importance of maintaining a safe sleep environment to prevent potentially injurious nocturnal behaviors as an adjunct to treatment with medications during sleep or as the sole therapy when medications are not indicated. Given the nature of the problem, controlled studies will not be feasible; however longitudinal data collection in larger clinic and community based samples with measured outcomes are recommended.

4.2.2. Clonazepam is suggested to decrease the occurrence of sleep-related injury caused by RBD for whom pharmacologic therapy is deemed necessary. It should be used in caution in patients with dementia, gait disorders, or concomitant OSA, and its use should be monitored carefully over time. Level B

Clonazepam was effective in 2 Level 4 case series of SRI and RBD and 1 level 4 case series of SRI that had just 1 patient with RBD: 62/71 subjects in a case series from Hong Kong,[64] in "most" of 33 patients with RBD and SRI in an early report of the syndrome,[73] and in a patient admitted to the ICU with a C-2 fracture secondary to RBD (and in 11 other ICU patients who had RBD but were not admitted for injury from RBD).[62] Clonazepam at a dose of 0.25-2.0 mg 1 to 2 hours before bedtime was effective in preventing further injuries. The rate of SRI after treatment with clonazepam fell from 80.8% pre-treatment to 5.6% post-treatment in the Hong Kong series.[64]

5. CONCLUSION AND AREAS FOR FUTURE RESEARCH

The medical literature on the treatment of RBD lacks randomized, double-blind controlled or head-to-head clinical trials of pharmacologic therapy. The most abundant published data are on the use of clonazepam, a medication with significant side effects, particularly in those patients with concomitant dementia. Given that there is a significant likelihood of any patient with RBD developing a synucleinopathy, alternative medications that will not have adverse effects on cognition are needed for the treatment of this disorder. It may be advantageous to switch from benzodiazepine therapy to an alternative when symptoms such as dementia arise in the course of the disorder. Melatonin use is increasing as a first-line treatment for RBD and in patients with dementia and sleep apnea. A variety of other medications have been tried without much data supporting their use. With or without pharmacologic therapy, the physician should counsel the patient about ways to modify the sleep environment to ensure safety.

Future studies should focus on the effects of medications on critical outcomes of treatment: prevention of injury, improvement of sleep quality, reduction of adverse daytime effects and improvement of the PSG features of RBD such as RSWA. In addition, long-term efficacy and safety in medications other than clonazepam needs to be established. A central registry tracking treatment effects may also advance the field.

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ACKNOWLEDGMENT

SUBMISSION & CORRESPONDENCE INFORMATION

DISCLOSURE STATEMENT

The Standards of Practice Committee members have indicated no financial conflicts of interest.

Appendix 1[43]—Scoring PSG features of REM sleep behavior disorder (RBD): [recommended]

DEFINITIONS
Sustained muscle activity (tonic activity) in REM sleep: An epoch of REM sleep with at least 50% of the duration of the epoch having a chin EMG amplitude greater than the minimum amplitude than in NREM.

Excessive transient muscle activity (phasic activity) in REM sleep: In a 30-second epoch of REM sleep divided into 10 sequential 3 second mini-epochs, at least 5 (50%) of the mini-epochs contain bursts of transient muscle activity. In RBD, excessive transient muscle activity bursts are 0.1–5.0 seconds in duration and at least 4 times as high in amplitude as the background EMG activity.

Rule:
1. The polysomnographic characteristics of RBD are characterized by either or both of the following features:
   a. Sustained muscle activity in REM sleep in the chin EMG
   b. Excessive transient muscle activity during REM in the chin or limb EMG

Notes:
1. Time synchronized video PSG audio or a characteristic clinical history are necessary to make the diagnosis of RBD in addition to polysomnographic evidence of REM without atonia or excessive transient muscle activity in REM.
2. Transient muscle activity and occasional accompanying visible twitching of small muscle groups are a normal phenomenon seen in REM sleep (see IV. Adult. 7). When larger muscle groups are involved, this activity is not associated with large, overt muscular activity acting across large joints. When smaller muscle groups are involved, the movement often involves the distal muscles of the hands and face or the corners of the mouth. Transient muscle activity may be excessive in RBD.
3. The sustained muscle activity or the excessive transient muscle activity observed in REM sleep may be interrupted by superimposed (usually dream-enacting) behaviors of RBD.
4. In normal individuals there is an atonia seen in REM sleep in the chin and anterior tibialis EMG. In this state the baseline amplitude of the EMG signal decreases markedly. This atonia of REM sleep is lost to a considerable extent in RBD, with variable frequency, and as a result, the EMG baseline amplitude is often higher. In this situation, the EMG can be said to be in a tonic rather than atonic state.

RBD Evidence Table—Clonazepam

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated in Study	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
6	Chiu (1997)	1990 Mahowald and Schenck criteria	1.25 and 0.75 mg	Idiopathic RBD	2	2	Mixed	Unclear	Mixed	Case series	1 Male (74 y.o.) 1 Female (72 y.o.)	Case 1: her sleep problem improved, and she only had talking and infrequent yelling without any vigorous movements; Case 2: dramatic improvement in symptoms, with disappearance of abnormal movements during sleep.
7	Olson (2000)	Mahowald and Schenck 1994	0.25 to 1.5 mg before sleep	Neurological disorders in 57% of patients, mostly PD, dementia without parkinsonism, and multiple system atrophy	38 out of 57/93 had information available	33	High	Moderate (early morning sedation, early morning motor incoordination, impotence)	Weakly beneficial	Case series	87% M, Mean age=64.4 (37-85)	Clonazepam treatment of RBD was completely or partially successful in 87% of the patients who used the drug.
8	Chiu (2000)	1990 Mahowald and Schenck criteria	0.5 to 1 mg	2 idiopathic and one PD	3	3	High	Unclear	Strongly beneficial	Case series	2 Males (88 and 74 y.o.) 1 Female (81 y.o.)	All had good response with no further SRI after treatment as well as marked decrease in their sleeptalking, shouting, and limb movements.
11	Boeve (1998)	31/37 PSG-confirmed	Not stated	Patients with degenerative dementia and RBD symptoms	11/37	10	High	Unclear	Strongly beneficial	Case series	34 Males 3 Females Mean 70.2 y.o., Range 50-82	RBD responded to 10/11 patients for whom it was prescribed and follow-up information was available
16	Iranzo (2006)	ICSD-II	Mean dose 1.0 mg [SD 0.6]	Idiopathic RBD	36/44	35	High	Unclear	Strongly beneficial	Case series / retrospective chart review of natural history	89% M of cohort, mean age 74 years	35/36 were deemed successful.
54	Culebras (1989)	ICSD-II; Typical history confirmed by PSG demonstrating REM sleep without atonia	0.5 - 1.0 mg	MRI showed "multifocal signal intensity lesions suggestive of lacunar infarcts in perventricular regions (5 patients) and in dorsal pontomesencephalic areas (3 patients)" and normal in 1 patient	6	6	High	Unclear	Strongly beneficial	Case series	4/6 Males Range 64-74 y.o.	Disappearance of symptoms
55	Husain (2001)	ICSD-I	Not stated	Veterans with only RBD vs. those with RBD plus PTSD	8/27 (5/15 RBD+PTSD, 3/12 RBD)	5	Moderate	Unclear	Strongly beneficial	Case series	For 15 RBD+PTSD, mean age=55.2 (46-78), for 12 RBD, mean age=57.6 (35-72), all Males	In 2/3 patients with RBD, clonazepam was successful; in 3/5 patients with RBD + PTSD, clonazepam was successful

RBD Evidence Table—Clonazepam *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated in Study	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
56	Lapierre (1992)	ICSD-II	0.5-2 mg	4 patients, idiopathic RBD; one patient Arnold-Chiari type I malformation	5	5	Moderate	Low	Weakly beneficial	Case series	3 Males 2 Females Mean age 58.6; Range 44-65	Decreased REM density and phasic EMG activity;decreased PLMD
57	Mahowald (1991)	ICSD-II	Dosage not stated	Status dissociatus; 6 subjects—3 with narcolepsy, one with alcoholism in withdrawal, one with OPCA, and one status-post open heart surgery	5/6	5	High	Unclear	Strongly beneficial	Case series	60% Male Mean age 52 y.o.	Case 1: "appearance of conventional sleep patterns and nearly complete elimination of the motor/verbal activity during sleep" Case 2: "increased the percentage of identifiable stages 3/4 NREM sleep (19%), reduced twitches and jerks, and has resulted in significant clinical reduction of sleep-related motor/verbal activity" Case 3: not given clonazepam; Cases 4-6: "each clinically improved with clonazepam."
58	Manni (2005)	ICSD-R	0.5 to 1 mg/day	Patients whose idiopathic RBD preceded late-onset cryptogenic sleep-related tonic-clonic seizures by several years	2	2	High	Unclear	Strongly beneficial	Case series	2 Males (60 and 75 y.o.)	Clonazepam at 0.5 mg/day (Patient 2) and 1 mg/day (Patient 1) at bedtime resulted in reduced frequency and intensity of RBD episodes in both patients.
59	Massironi (2003)	ICSD-I	0.3-0.5 mg	Patients with DLB	3	2	Mixed	Unclear	Mixed	Case series	33.3% Males Mean age 74.7 y.o.	In two patients, clonazepam ameliorated RBD; in the third it did not (but donepezil was successful)
60	Schenck (1997)	PSG-confirmed RBD	0.25-4.0 mg	Parasomnia overlap disorder; 67% idiopathic and 33% symptomatic	13/20 for which outcome was available (33 in study)	13	High	Unclear	Strongly beneficial	Case series	70% Male Mean age 34±14 y.o.	Full or substantial control of injurious nocturnal behaviors
61	Schenck (1993)	ICSD-II	Not stated	50% of cohort had RBD that was causally associated with CNS disorders	67 (includes 2 from Schenck 1986)	61	High	Unclear	Strongly beneficial	Case series	87.5% Male for whole cohort Mean age at onset = 52.4 (SD 16.9) (range 9 to 81) y.o.	53 had complete treatment 8 had partial treatment 6 had suboptimal benefit and/or significant side effects
62	Schenck (1991)	ICSD-II	0.75 mg mean dose (range: 0.25 mg to 2.0 mg)	Patients with RBD in the ICU	11 patients with RBD were treated	9	High in approx. 71% of patients	Unclear	Strongly beneficial	Case series	Not stated	Clonazepam fully controlled problematic sleep behaviors and disturbing dreams in 7 patients and 2 partial with RBD for which there are data. 2 were refractory.

RBD Evidence Table—Clonazepam *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated in Study	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
63	Sforza (1997)	ICSD-II	Initial dose 0.5 mg, 2 hrs before bedtime	25% idiopathic and 75% secondary	52	47	High	Unclear	Strongly beneficial	Case series	Idiopathic, mean age: 66.2±2.1; Secondary, mean age: 59.9±1.2; Gender not stated	Clonazepam was effective in 90% of the cases within the first week.
64	Wing (2008)	ICSD-II ICSD-I	Ave. dose 1.4 mg	About one-third (33%, 27/82) of the series had a lifetime history of psychiatric disorders with a predominant diagnosis of depression 22%, 18/82). Sixteen patients (19.5%) had comorbid neurodegenerative disorders at first consultation, including Parkinson disease and dementia. After 4 years of follow-up, six (9. 0%) additional patients developed neurodegenerative disorders.	71/82	62	High	Low (5 reported intolerable daytime somnolence, and 1 had transient and reversible increase in liver enzyme)	Strongly beneficial	Case series	Only known for cohort (82% Male) Mean age at onset = 62.1 (SD 12.9) (range 7 to 80) y.o.	"Most patients responded well" Completely or partially successful in 87% (62/71) Significant fall in SRI after treatment with clonazepam (80.8% pre-treatment fell to 5.6% post-treatment) (p<0.05)
65	Bokey (1993)	PSG-confirmed RBD	2 mg	Problems began after return from Vietnam	1	1	High	None	Strongly beneficial	Case report	Male, 49 y.o.	Treatment with clonazepam has abolished the nocturnal behavioral disturbance
66	Kimura (2000)	ICSD-I	0.25 mg	Patient with a lesion in the pontine reticular formation	1	1	High	Unclear	Strongly beneficial	Case report	1 Female (75 y.o.)	Her behaviors came under control, though she still had infrequent vivid dreams
67	Kumru (2004)	Schenck and Mahowald criteria	0.5 mg	Patients with Park2	1/5	1	High	Unclear	Strongly beneficial	Case report	1 Male (61 y.o.)	Significant improvement in symptoms
68	Morfis (1997)	ICSD-II	1 mg	Idiopathic RBD	1	1	High	Low	Strongly beneficial	Case series	1 Female (77 y.o.)	Complete resolution of abnormal motor activity
69	Provini (2004)	ICSD-II	2 mg at night and viloxazine 200 mg at morning	Status dissociatus after surgery for a tegmental ponto-mesencephalic cavernoma	1	1	High	Unclear	Strongly beneficial	Case report	1 Male (36 y.o.)	Both the patient and his wife reported a striking reduction of the nocturnal episodes of motor agitation and disappearance of daytime hypersomnia, and he had resumed working as a manager in the family business.
70	Thomas (2004)	ICSD-I	0.5 mg	Idiopathic RBD	1	1	High	Unclear	Strongly beneficial	Case report	1 Female (74 y.o.)	Total resolution of symptoms

RBD Evidence Table—Clonazepam continued on following page

RBD Evidence Table—All other medications

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
all: **Melatonin**
78	Anderson (2009)	ICSD-II	10 mg	One patient had failed with clonazepam treatment, and the other used melatonin as a first-line treatment due to coexistent cognitive impairment and mild OSA. 9/36 patients had neurodegenerative conditions (PD or AD).	2/36	2	High	Unclear	Strongly beneficial	Retrospective case review	38/39 Male in cohort Mean age = 66 y.o. (Range 34-86)	Effective
81	Kunz (1997)	ICSD-II	3 mg	Idiopathic RBD patient	1	1	High	Unclear	Strongly beneficial	Case report	64-year-old Male	Significant reduction of motor activity during sleep and a full clinical recovery over a 5-month treatment period.
82	Kunz (1999)	ICSD-II	3mg, 30 min prebedtime	Four patients had symptoms of concomitant diseases such as hypertension (two patients), Parkinson's disease (one patient), and sympathetic dysautonomia (one patient). Except for these disorders and three patients having shortterm memory impairment and concentration difficulties in recent months, neurologic and psychiatric examinations did not show any other neurologic and/or psychiatric disease.	6	5	Moderate to high	Low or unclear	Weakly beneficial	Case series	3 Males and 3 Females Average 54 y.o., range 26–71 yrs	Dramatic clinical improvement in five of the six patients within a week, which extended beyond the end of treatment for weeks or months. PSG showed an increase in REM atonia (statistically significant) and a decrease in both stage shifts within REM and movement time in REM (both statistically significant) but phasic EMG levels in REM did not change nor did REM density.
83	Takeuchi (2001)	ICSD-I	3-9 mg/day	Idiopathic RBD	15	13	Moderate	Unclear	Weakly beneficial	Case series	93.3% Male Mean 63.5 y.o.	13 patients and their partners noticed a suppressing effect on problem sleep behaviors: one mild, nine moderate, and three remarkable.
84	Boeve (2003)	ICSD-R	Melatonin +/- Clonazepam; 3 mg, 6 mg, 9 mg and 12 mg—the mode was 6 mg/night; clonazepam 0.5 mg to 1 mg per night were also administered in 7 (50%) Melatonin was OTC	Patients with concomitant neurologic disease and RBD that was refractory to clonazepam or for whom there was a contraindication to its use. In the discussion, the authors note that NONE of the 14 subjects had a significant change in severity or frequency of RBD symptoms with donepezil.	14	10	Moderate to high	Low to moderate	Weakly to Strongly beneficial: 71% had either complete response or marked improvement	Case series	93% Male; median RBD onset age 56 years, range 20–77 years	Melatonin may be a viable option as either add-on Rx to clonazepam or as primary Rx for RBD in pts with a contraindication or side effect from clonazepam

RBD Evidence Table—All other medications continued on following page

RBD Evidence Table—All other medications *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
						Pramipexole						
86	Fantini (2003)	PSG-confirmed RBD	Mean final dosage was 0.78 ± 0.25 mg/d (range, 0.50 to 1 mg/d).	Idiopathic RBD patients	8	5	High	Unclear	Strongly beneficial	Case series	5 Males, 3 Females Mean 66 ± 6.8 y.o.	Seven patients experienced a reduction in the frequency (n = 7), the intensity (n = 6), or both (n = 6) of RBD clinical manifestations. In 5 patients, the effect was still present at 6 months, whereas for 2 patients it was transient, lasting 2 weeks.
87	Schmidt (2006)	PSG-confirmed RBD	Average evening dose = 0.89±0.31 mg; a divided dose regimen was used in 56% of patients	Two patients with RBD and RLS; four with mild RLS or PLMS, four with mild to moderate OSA	10	8	Moderate	Low - mild nausea and one had hallucinations	Weakly beneficial	Case series	90% Male Mean 72.9 y.o.	89% of pateints reported either a moderate reduction or complete resolution in the frequency of RBD symptoms; 67% reported at least a moderate reduction in symptom intensity.
88	Kumru (2008)	ICSD-II	0.7 mg tid	Patients with PD	11	0	None	No major side effects	Neutral	Case series	8 Males and 3 Females Mean age of 62.1 ± 8.0 years	Lack of efficacy in PD population is in contrast to iRBD population. Pt report: either no change or increased severity (in 3) VPSG measures of RBD showed no change ; PLMS index fell from ave. of 13.2 +/- 27.1 to 0/hr but NOT statistically significant
						Paroxetine						
34	Parish (2007)	Not specified	30 mg paroxetine with clonazepam 1 mg per day, sulfasalazine 1 gm once a day, and folic acid 1 mg per day.	A man with a history of depression treated with paroxetine with disrupted sleep.	1	Not applicable	Low	High	Do not recommend	Case report	1 Male, 50 y.o.	Case report of paroxetine-induced RBD—resolved with discontinuation of paroxetine.
49	Takahashi (2008)	ICSD-II	Fluvoxamine 50 mg / paroxetine 10 mg / tandospirone—not stated	Idiopathic RBD	1	1	High	Moderate	Weakly beneficial	Case series	1 Female, 72 y.o.	Fluvoxamine prescribed for depressive symptoms, and RBD noted to dramatically improve; however, unacceptable side effects. Therefore, paroxetine prescribed, after which RBD again dramatically improved. Again, unacceptable side effects such as thirst. Tandospirone was prescribed and made the RBD worse.

RBD Evidence Table—All other medications continued on following page

RBD Evidence Table—All other medications *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
50	Yamamoto (2006)	ICSD-I	Ave=22.1 mg qhs, range 10mg to 40 mg qhs	Idiopathic RBD	19	16	Low	Moderate	Weakly beneficial	Case series	79% male Mean age 64.7 +/- 7.8 y.o.	At baseline, all were severe; After: Mild—11; Moderate—5; Severe—3 Diarrhea, dizziness, nausea; 1 pt with each complaint; dizziness and diarrhea resulted in discontinuation of medication
				Levodopa								
89	Tan (1996)	Lacks PSG — diagnosed on clinical history of acting out dreams	Not stated	Started for PD symptoms and not RBD but, coincidentally, RBD-symptoms resolved/ improved	3	3	High	Unclear	Strongly beneficial	Case series	3 Males, 67, 67, and 69 y.o.	In 2 subjects, complete resolution of movements; in one subject, decrease by 80%
90	Garcia-Borreguero (2002)	ICSD-I	Lowest dose that provided adequate control of sx's for 3-9 months Mean 393 +/- 159 mg/day	Cohort is PD pts—intially none had RBD. Two comparison groups: the same cohort before, during, and after treatment with L-DOPA (off LD for 2-5 days) and a symptom-free gender-matched control group (slightly younger than PD group)	15	Not applicable	None	Unclear	Weakly harmful	Case series	67% Males Mean age 73.8 +/- 4.9 y.o.	Main outcome of this study was that levodopa is weakly harmful. 5/15 L-DOPA naïve patients developed RBD in under 1 year.
				Acetylcholiesterase Inhibitors: Donepezil								
59	Massironi (2003)	ICSD-I	10 mg	Case series of 3 patients with DLB and RBD.	3	1	Unclear	Unclear	Mixed	Case series	1 Male, 75 y.o. and 2 Females, 68 and 81 y.o.	All 3 subjects were tried on both clonazepam and donepezil. Two failed donepezil and responded to clonazepam and one failed clonazepam and did well on donepezil.
93	Ringman (2000)	ICSD-I	10 mg in two patients 15 mg in 1 patient	Case 1: previous (18 years) supracellular craniopharyngioma resection with possible AD; Cases 2 and 3 appear to be idiopathic	3	3	Moderate to high	Unclear	Weakly to Strongly beneficial	Case Series	3 Males, 29, 56 and 72 y.o.	Nocturnal symptoms markedly improved.
				Acetylcholiesterase Inhibitors: Rivastigmine								
94	Grace (2000)	ESS, PSQI, NPI (Suspected RBD)	Not stated	Patients with DLB and sleep disturbances	6	6	High	Unclear	Strongly beneficial	Case series	In cohort of 17, 13 Males Mean age 74.9 (range 62-90) y.o.	Reduction in both ESS and PSQI scores and reduced incidence of individual troublesome night-time behaviors, such as bad dreams, periodic limb movements and confusion on waking.
95	Maclean (2001)	ICSD-I—vague history only	4.5 mg bid to 6 mg bid—started with 1.5 bid and slowly titrated upward to max dose	Patients with DLB	4	4	High	Low	Strongly beneficial	Case series	All Males, mean age 74.8 y.o.	Four of the 8 subjects with DLB had possible RBD and treated with rivastigmine; all 4 showed improvement.

RBD Evidence Table—All other medications *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
					Zopiclone							
29	Bonakis (2008)	ICSD-II	7.5 mg	Patients with narcolepsy and RBD	1/2	1	Medium	Unclear	Strongly beneficial	Case series	1 Male, 33 y.o.	Patient initially treated with clonazepam 0.5 mg but had nausea and irritability although it was efficacious; "considerable improvement" in nocturnal behavior with zopiclone 7.5 mg (dexamphetamine 25 mg/day for narcolepsy)
78	Anderson (2009)	ICSD-II	3.75 to 7.5 mg per night	9/36 patients had neurodegenerative conditions (PD or AD).	11/36	8	High	Low: rash or nausea	Strongly beneficial	Retrospective case review	38/39 Males in cohort Mean age = 66 (range 34-86) y.o.	Nine patients used it alone and 2 in combination with another drug. Eight of 11 found it effective and well-tolerated. Three patients stopped usage: one was ineffective, one developed a rash, and one found if effective but felt nauseated.
				Benzodiazepines other than Clonazepam (Temazepam, Triazolam, Alprazolam)								
78	Anderson (2009)	ICSD-II	Temazepam plus zopiclone	9/36 patients had neurodegenerative conditions (PD or AD).	1/36	1	High	Unclear	Strongly beneficial	Retrospective case review	Not stated	The combination therapy of temazepam/zopiclone was used in 1 patient when a single medication failed to control symptoms.
29	Bonakis (2008)	ICSD-II	10 mg temazepam	Patients with narcolepsy and RBD	1/2	1	Moderate	Unclear	Strongly beneficial	Case series	1 Female, 26 y.o.	Patient was initially treated with clonazepam up to 2.0 mg without sufficient efficacy and with daytime drowsiness; "considerable improvement" in RBD symptoms with temazepam 10 mg (on modafinil 400 mg for narcolepsy)
7	Olson (2000)	Mahowald and Schenck criteria 1994	Triazolam, dose not stated	Patients with RBD seen at Mayo Sleep Disorders Center	2/93	1	Mixed	Unclear	Mixed	Retrospective case review	Not stated	Triazolam was used by 2 patients, with complete succes in one and uncertain results in the other.
60	Schenck (1997)	PSG-confirmed RBD	Alprazolam (1-3 mg) and/or carbamazepine (0.5-1.5 gm)	Patients with parasomnia overlap disorder	4/33	4	High	Unclear	Strongly beneficial	Case series	Not stated	Full or substantial control of injurious nocturnal behaviors
1	Schenck (1986)	PSG-confirmed RBD	Case 1: Alprazolam, 0.5 mg h.s.; Case 5: Dose not stated	Case 1: Idiopathic RBD; Case 5: A previous (6 years) spontaneous subarachnoid hemorrhage triggering RBD	2/5	0	Low	Unclear	Neutral	Case report	2 Males, 67 and 70 y.o.	Case 1: Gradually reduced vigorous sleep behaviors, but only lasted 8 months, despite increasing doses; Case 5: Alprazolam prescribed for Adjustment Disorder with mixed emotional features, but had no impact on RBD
76	Schenck (1996)	Not specified	1-3 mg alprazolam, personal communication	Patients with RBD	2	2	High	Unclear	Strongly beneficial	Retrospective case review	Not stated	The data indicate sustained efficacy for benzodiazepines with low risk of adverse effects, dosage escalation or abuse.

RBD Evidence Table—All other medications continued on following page

RBD Evidence Table—All other medications *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
				Yi-Gan San								
96	Shinno (2008)	ICSD-II	Before meals—in two pateints, dose was 7.5 g/day in three divided doses; One patient with DM and decreased renal function was given only 2.5 g once a day in the evening; One patient was treated with clonazepam 0.25 mg in addition to YGS but clonazepam at 0.5 mg, which was effective but caused sleepiness	Two were treated with clonazepam. Clonazepam caused unacceptable sleepiness in both and YGS was started and was solo treatment in one and used in conjunction with a low dose of clonazepam (0.25 mg/d) in the other. The third patient had poor renal function so an alternative was sought and treated low-dose YGS with full efficacy.	3	3	High	No side effects	Strongly beneficial	Case series	3 Females; 60, 74, and 87 y.o.	Elimination of events—full suppression in all 3 cases
				Desipramine								
1	Schenck (1986)	PSG-confirmed RBD	50 mg h.s.	Case 4: Generalized brain dysfunction; Atypical dementing process; Case 5: A previous (6 years) spontaneous subarachnoid hemorrhage triggering RBD	3/5	1	High but not lasting	Unclear	Weakly beneficial	Case series	3 Males, 67, 70, and 70 y.o	Case 1, desipramine was not well tolerated; Case 4, desiprimanine immediately suppressed vigorous sleep behaviors and restored diurnal alertness; however, after 12 months, he still frequently vocalized and had minor limb twitching during sleep; Case 5, desipramine suppressed sleep behaviors and hyperactive dreaming for only 3 weeks, even upon increasing dose to 250 mg, so it was discontinued. Clonazepam was effective.
				Clozapine								
7	Olson (2000)	PSG-confirmed RBD	Dose not stated	Patients with RBD seen at Mayo Sleep Disorders Center	2/93	2	Mixed	Unclear	Mixed	Retrospective case review	Not stated	Clozapine was used by two patients with dementia in whom clonazepam had failed; RBD resolved completely in one patient and partially in the other
11	Boeve (1998)	31/37 PSG-confirmed	Not stated	Patients with degenerative dementia and RBD symptoms	1/37	1	Moderate	Unclear	Moderately beneficial	Case report	Not stated	Clozapine reduced RBD in the only patient in whom it was used.

RBD Evidence Table—All other medications continued on following page

RBD Evidence Table—All other medications *(continued)*

Ref #	Author (yr)	Diagnostic Criteria	Dosage	Patient Population	N Treated	N Responding	Magnitude of Benefit	Side Effects	Net Benefit	Study Type	Age and Gender	Trial Results
					Carbamazepine							
60	Schenck (1997)	PSG-confirmed RBD	0.5-1.5 g	Patients with parasomnia overlap disorder	4/33	4	High	Unclear	Strongly beneficial	Case series	Not stated	Full or substantial control of injurious nocturnal behaviors
97	Bamford (1993)	ICSD-II	100 mg tid	Idiopathic RBD	1	1	High	Unclear	Strongly beneficial	Case series	1 Male, 68 y.o.	After 14 months, patient still responding to treatment; No longer had "crazy" dreams and wife not hit since CBZ started; wife did not that there was still some jerking movements in sleep but decreased by 75%
					Sodium Oxybate							
528	Anderson (2009)	ICSD-II	Not stated	This patient had failed treatment with clonazepam, temazepam, zopiclone, gabapentin, and melatonin. 9/36 patients had neurodegenerative conditions (PD or AD).	1/36	1	High	Unclear	Strongly beneficial	Retrospective case review	Not stated	Symptoms successfully controlled