Published in final edited form as:

Sleep Med. 2013 March ; 14(3): 237–242. doi:10.1016/j.sleep.2012.09.018.

Treatment Outcomes in REM Sleep Behavior Disorder

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Abstract

Objective—REM sleep behavior disorder (RBD) is usually characterized by potentially injurious dream enactment behaviors (DEB). RBD treatment aims to reduce DEBs and prevent injury, but outcomes require further elucidation. We surveyed RBD patients to describe longitudinal treatment outcomes with melatonin and clonazepam.

Methods—We surveyed and reviewed records of consecutive RBD patients seen at Mayo Clinic between 2008–2010 to describe RBD-related injury frequency/severity as well as RBD Visual Analog Scale (VAS) ratings, medication dosage, and side effects. Statistical analyses were performed with appropriate non-parametric matched pairs tests before and after treatment, and with comparative group analyses for continuous and categorical variables between treatment groups. The primary outcome variables were RBD VAS ratings and injury frequency.

Results—Forty-five (84.9%) of 53 respondent surveys were analyzed. Mean age was 65.8 years and 35 (77.8%) patients were men. Neurodegenerative disorders were seen in 24 (53%) patients,

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and 25 (56%) received antidepressants. Twenty-five patients received melatonin, 18 received clonazepam, and 2 received both as initial treatment. Before treatment, 27 patients (60%) reported an RBD associated injury. Median dosages were melatonin 6 mg and clonazepam 0.5 mg. RBD VAS ratings were significantly improved following both treatments ($p_m=.0001$, $p_c=.0005$). Melatonin-treated patients reported significantly reduced injuries ($p_m=.001$, $p_c=.06$) and fewer adverse effects ($p=0.07$). Mean durations of treatment were no different between groups (for clonazepam 53.9 $\pm$ 29.5 months, and for melatonin 27.4 $\pm$ 24 months, $p=0.13$) and there were no differences in treatment retention, with 28% of melatonin and 22% of clonazepam-treated patients discontinuing treatment ($p=0.43$).

Conclusions—Melatonin and clonazepam were each reported to reduce RBD behaviors and injuries and appeared comparably effective in our naturalistic practice experience. Melatonin-treated patients reported less frequent adverse effects than those treated with clonazepam. More effective treatments that would eliminate injury potential and evidence-based treatment outcomes from prospective clinical trials for RBD are needed.

Keywords

REM sleep behavior disorder; parasomnia; melatonin; clonazepam; treatment; side effects; tolerability; retention; injury; falls; synucleinopathy

1.Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia usually characterized by dream enactment behavior (DEB) and abnormal, excessive motor activity during REM sleep [1]. RBD is associated with REM sleep without atonia (RSWA), the loss of normal skeletal muscle atonia during REM sleep. RBD results in motor activity ranging from simple limb twitches to more complex, aggressive, and violent movements that may result in injury to the patient and/or sleeping partner [2–11]. Large population based studies have reported the prevalence of RBD to be 0.38–0.5% [9,12]. However, a recent study found probable RBD (i.e. typical history of RBD without video-polysomnography) in over 6% of community-dwelling 70–89 year old individuals, suggesting that the prevalence of RBD may be considerably higher than previously believed [10,11]. RBD, at least for older adults, is most common in men, but prior to age 50, women and men are equally likely to develop RBD [8,13–16]. RBD can be either idiopathic or symptomatic, especially as an early manifestation of the alpha-synucleinopathy neurodegenerative disorders including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2,4,5,8,17,18]. RBD treatment focuses on decreasing frequency of DEB and potential injuries, which may vary from bruises and limb fractures to subdural hematomas [2,5,19].

There have been no large controlled treatment trials for RBD. Reported treatment outcomes have instead largely come from clinical experience or case series [20–22]. Clonazepam has been the most commonly used first-line treatment since the original description of RBD in 1986, reportedly reducing injurious behaviors by as much as 87% in one study [3,5,21–23]. However, concerns with use of clonazepam in elderly patients include exacerbation of obstructive sleep apnea and cognitive impairment, so more tolerable therapies are needed [2,4,5,8,21,22, 24,25]. A single, small, randomized controlled cross-over study and several retrospective studies have shown that melatonin may be an effective alternative RBD treatment [23,24,26–30]. However, outcome data for clonazepam and melatonin remain limited, especially concerning comparative effectiveness for injury and DEB reduction, treatment retention rates, and tolerability. Our aim was to determine outcomes and side effects of RBD treatment in patients managed in our practice.

2.Methods

Subjects

A diagnosis and text based search identified 641 patients newly diagnosed with RBD at our institution between 1/1/2000 and 12/31/2009. Given the difficulty in designing suitable survey measures for children who may not have witnessed sleep to accurately report on DEBs, we excluded patients <18 years of age, resulting in 608 eligible subjects. All included patients met standard diagnostic criteria for RBD, including the presence of RSWA during polysomnography, a history of sleep-related injurious or potentially injurious disruptive behaviors, and/or abnormal REM sleep behaviors during polysomnography, absence of REM-related epileptiform activity, and absence of another sleep disorder that better explained their sleep disturbance [1]. Following approval from the Mayo Institutional Review Board, we sent a survey to 133 patients seen during 2008–2010, limiting the study sample to these years to reduce recall bias. Fifty-three surveys were completed and returned, 78 patients did not respond, and two patients died before the surveys were returned. Eight surveys were excluded due to incomplete responses, leaving 45 subjects (34%) for analysis. Treatment groups by initial therapy included 25 melatonin, 18 clonazepam and 2 patients who received polytherapy with clonazepam and melatonin. Six patients from the melatonin and clonazepam monotherapy treatment groups also eventually received adjunctive therapy with the alternative drug combined with initially assigned treatment. These 6 were combined with the 2 patients receiving both drugs initially in a secondary analysis comparing the outcomes of combined therapy to each monotherapy treatment group. Treatment assignments were non-randomized and allocated by the treating physician's preference.

Survey Instrument

We designed a three-part questionnaire (Appendix A) that was completed by patients together with a bed partner or family member who had observed their RBD during sleep that surveyed demographics; baseline and post-treatment RBD behavioral characteristics including frequency, severity, and type of behaviors; occurrence and frequency of falls, and patient or bed partner injury related to RBD; and a patient rating of RBD frequency and severity at baseline and following treatment by a visual analogue scale (VAS). Questions concerning medication use included treatment sequence, dosage, the duration of treatment, potential side effects, and concurrent antidepressant history.

Clinical data

We reviewed medical records to confirm RBD diagnosis, demographic information, treatment assignment, order of administration, and medication dosages, and to abstract clinically important covariate data concerning neurologic and psychiatric history, antidepressant administration, and polysomnography data. Patients with co-morbid neurological disorders met published criteria for clinically probable DLB [31], mild cognitive impairment (MCI) [32], Parkinson's Disease (PD), or MSA [33]. Diagnosis of obstructive sleep apnea (OSA) and restless leg syndrome (RLS) were in accordance to standard diagnostic criteria [1].

Data analysis

Study data were collected and managed using REDCap electronic data capture tools [34]. Statistical calculations were carried out using JMP statistical software (JMP, Version 9. SAS Institute Inc., Cary, NC). Qualitative and ordinal data were reported as absolute and relative frequencies, while quantitative data were reported as means, standard deviation, medians, and range. Wilcoxon signed rank tests were used to compare pre-treatment and post-treatment variables within each melatonin and clonazepam monotherapy treatment groups,

with outcomes in each patient determined prior to the institution of any later adjunctive polytherapy. Similarly, Wilcoxon rank-sum tests were used to compare continuous outcomes between groups, and categorical variables were compared with contingency tables and Chi Square Tests between the two initial monotherapy clonazepam and melatonin treatment groups, as well as between the combined therapy subgroup and each monotherapy treatment group (denoted by X^2 test statistics in Results section where applied). Significance level was set at an alpha of $p < 0.05$.

3. Results

Demographics and Clinical Data

Of the 45 patients surveyed, 35 (77.8%) were men and mean age was 65.8 years (range 29–86 years). Forty-three (96%) of patients reported that the bed partner verified any RBD symptoms. Average age of RBD symptom onset was 53.5 years (range 6–80 years) with mean duration prior to diagnosis of 14.6 years (range 1–55 years). Twenty-four (53.3%) had a co-morbid neurodegenerative disorder, including PD in 10 (42%), MCI in 6 (25%), MSA in 5 (21%), and DLB in 3 (12%). Thirteen patients had co-morbid depression. Twenty-five (56%) subjects received antidepressants, all receiving either selective serotonin or norepinephrine reuptake inhibitors. Nine patients used dopaminergic drugs with an average levodopa dose equivalent of 707.5 ± 455.3 mg, and 5 patients received anticholinesterase medications.

Thirty (67%) had OSA, 12 had RLS, 15 had periodic limb movement disorder, and 25 (57%) had hypersomnia symptoms with an average Epworth Sleepiness Score (ESS) of 13.3 (range 3–23). Median apnea-hypopnea index (AHI) for the entire cohort was 3 (range 1–68) with oxyhemoglobin saturation nadir of 86.8 ± 4.5 . Of those with OSA, (AHI ≥ 5) median AHI was 9 (range 5–68) with an oxyhemoglobin saturation nadir of 84.9 ± 4.3 . The median periodic limb movement index for the entire study group was 27.9 (range 0–188) and median movement arousal index was 2.6 (range 0–40.7).

Regardless of initial monotherapy treatment assignment, RBD severity was comparable by reported RBD VAS scale (melatonin vs. clonazepam groups, 6.56 vs. 6.52, $p = 0.95$), injuries (64% vs. 61%, $p = 0.85$), and falls from the bed (60% vs. 66%, $p = 0.66$). In addition, there were no significant differences in RBD severity by RBD VAS ratings between individuals with neurodegenerative disorders ($p = 0.95$), OSA ($p = 0.21$) or dopaminergic medication use ($p = 0.32$) and those who had no neurodegenerative disease, OSA or dopaminergic use. There were also no significant differences between frequency of co-morbid neurodegenerative disorders or antidepressant treatments between groups. However, concurrent antidepressant medication use was associated with more frequent behaviors ($p = 0.036$), but was not associated with injury.

Treatment

The majority of patients continued to have RBD behaviors following treatment, with only 3 patients in each treatment group reporting complete suppression of RBD features (melatonin vs. clonazepam treated patients, 12% vs. 16.6%, $p = 0.68$). Both treatments were reported to decrease RBD behaviors, although there were no differences in either the primary outcome measure of RBD VAS frequency-severity or in reported subjective improvement measures between melatonin and clonazepam. (Figures 1 and 2) There were no differences in treatment responses in patients with or without neurodegenerative disorders ($p = 0.85$), with both treatment groups showing improvement.

Patient RBD VAS frequency-severity ratings decreased significantly (pre- vs. post-treatment, 6.68 vs. 4.22, $p = 0.0001$) following melatonin treatment (Figure 1). In addition,

melatonin-treated patients reported substantial overall subjective improvement ratings (moderate or greater improvement was seen in 48%), (Figure 2), as well as reduced RBD frequency (pre- vs. post-treatment, $X^2 = 11.3$, $p = 0.01$), injuries (64% vs. 20%, $p = 0.001$), falls (60% vs. 20%, $p = 0.002$), and DEB (88% vs. 48%, $p = 0.004$) (Figure 3). Melatonin treatment was also associated with decreased reported severity of injuries (pre- vs. post-treatment, $X^2 = 14.6$, $p = 0.003$) (Figure 4). Melatonin-treated patients with neurodegenerative disorders ($n=11$) showed significant improvement in RBD VAS Ratings ($X^2 = 5.04$, $p = 0.025$).

Clonazepam-treated patients also reported significantly decreased RBD VAS frequency-severity ratings (pre- vs. post-treatment, 6.53 vs. 4.15, $p = 0.0005$) and DEB frequency ($X^2 = 14.8$, $p = 0.002$) (Figures 1 and 2). Clonazepam treatment was also associated with improved overall subjective improvement ratings (moderate or greater improvement seen in 78%, with a non-significant trend toward improvement seen in comparison to melatonin, $p = 0.06$). Clonazepam therapy resulted in reduced DEB (94% vs. 44%, $p = 0.004$), and non-significant trends were seen for clonazepam treatment towards reduced injuries (pre- vs. post-treatment, 61% vs. 33%, $p = 0.06$) and falls (67% vs. 33%, $p = .07$), but no change in injury severity ($p = 0.39$) (Figures 2,3, and 4). Clonazepam-treated patients with neurodegenerative disorders ($n=8$) showed non-significant improvement in RBD VAS Ratings ($X^2 = 2.20$, $p = 0.14$).

Duration of treatment was longer for clonazepam (53.9 ± 29.5 months, range 1–178 months) than for melatonin treatment (27.4 ± 24 months, range 2–121 months), but the difference was not statistically significant ($p = 0.13$). 36 (80%) subjects received median follow up of 29 months (range 1–178 months) by sleep specialists at our institution. Median reported effective doses were melatonin 6 mg and clonazepam 0.5mg. Reportedly effective doses for melatonin were 6 mg or less in 14 (52%) patients, 9 or 12 mg in 8 (32%) patients, and 15 or 25 mg in 4 (16%) of patients. Effective dosages reported for clonazepam were 0.5 mg or less in 10 (56%) patients, 1.0 mg in 2 (11%) patients, 2.0 mg in 4 (22%) patients, and 1 (6%) patient received 3.0 mg.

There were no significant differences in treatment retention between the melatonin and clonazepam treatment groups (respective discontinuation rates of 28% vs. 22%, $p = 0.71$). In the melatonin group, 7 patients discontinued treatment (5 due to ineffectiveness, 1 due to side effects, and 1 due to another physician's orders). In the clonazepam group, 4 patients stopped treatment (3 due to side effects and 1 due to ineffectiveness). There were no differences in discontinuation rates between symptomatic or idiopathic (21.7% vs. 27.3%, $p = 0.82$) RBD groups.

Of the 7 patients who discontinued melatonin, 5 began clonazepam and 2 received no second treatment. The 4 patients who discontinued clonazepam began taking melatonin. Overall, eight patients received combined therapy with clonazepam and melatonin, including 2 receiving initial combined therapy and 6 others who received second-line adjunctive combined therapy. Subjective improvement ratings and baseline/treatment VAS frequency-severity ratings with combined therapy were not statistically different from ratings of either individual therapy ($p = 0.60$ for both comparisons).

Patients treated with clonazepam reported more frequent side effects than those treated with melatonin, although the reported side effects were not significantly different between treatment groups for overall side effects (61% vs. 33%, $p = 0.07$), unsteadiness (39% vs. 8%, $p = 0.07$) or dizziness (22% vs. 4%, $p = 0.08$; Figures 5 and 6, online only).

4. Discussion

Treatment with melatonin and clonazepam both appeared to reduce patient VAS ratings of RBD frequency/severity, as well as reported injury frequency and falls, but neither treatment eliminated injury potential altogether. While no statistically significant differences were seen in tolerability, patients receiving melatonin reported a lower frequency of adverse effects, while those receiving clonazepam more frequently reported unsteadiness and dizziness. In our naturalistic practice based on experience, both clonazepam and melatonin appeared comparably effective and melatonin may be better tolerated.

This is one of the largest reported series of treatment outcomes in RBD with longitudinal follow up. Our older aged and predominantly male study population, with frequent co-morbid alpha-synucleinopathy diagnoses (53%) and frequent concurrent antidepressant use (56%) is consistent with previously published large RBD case series [2,5,35]. Our data also substantiates an association between antidepressant use and RBD frequency, which is of potential therapeutic importance since modulating antidepressant dose or changing antidepressant type could decrease RBD symptoms [37]. OSA was also present in 67% of our patients, with a median AHI of 9 (range 5–68) in those having OSA. While we did not recruit controls for comparison of apnea severity, our patients had an average severity of moderate co-morbid OSA, consonant with a recently published report showing that RSWA associated with RBD may be protective against greater OSA severity [38].

Melatonin and clonazepam both reduced patient VAS ratings of RBD frequency/severity, DEBs, and injury occurrence and severity. All reported treatment outcomes were significant for the melatonin treatment group, but not the clonazepam group, possibly due to the relatively small sample size. Clonazepam treated patients reported more frequent sleepiness, unsteadiness, and trouble thinking than those treated with melatonin. In the subgroup of symptomatic RBD patients with neurodegenerative disorders, both melatonin and clonazepam reduced VAS RBD frequency/severity ratings. Treatment retention was similar in each group, with 28% of melatonin patients and 22% of clonazepam patients discontinuing treatment. The main reasons for stopping treatment differed between the groups: in melatonin treated patients, it was lack of efficacy in treating symptoms, while in the clonazepam group, reported side effects were the primary reason for discontinuing treatment.

Randomized controlled trial level evidence is strongly preferred to guide treatment decisions, but currently no such evidence exists to inform best practices for RBD treatment. Until such trials are conducted, our data suggest that for current practice, melatonin may be considered as an appropriate first-line therapy for RBD due to favorable reported treatment outcomes for reduction of injury, potentially injurious falls from bed, and patient rated RBD frequency/severity. Melatonin also was reported to have favorable tolerability, with less frequent side effects compared to clonazepam. Further data from prospective randomized controlled trials is necessary to establish the efficacy and tolerability of these and other therapies for RBD.

While there were no statistically significant overall differences between clonazepam and melatonin for RBD treatment, there were some intriguing differences in subjective and objective treatment outcomes. Patients generally reported greater subjective outcome improvements following clonazepam treatment when compared to melatonin, yet only melatonin was associated with consistent statistically significant reductions in more clinically important treatment outcomes concerning occurrence and severity of injury and falls. While confounding biases may occur in a non-randomized study population such as ours, these differences in treatment outcomes could imply different mechanisms of action

between melatonin and clonazepam in modulating the pathophysiology of RBD. The mechanism by which melatonin decreases RBD symptoms remains unclear, but may be mediated in part by GABAergic inhibition [39]. Melatonin also increases sleep efficiency and shortens sleep latency with evening administration [40,41] and may stabilize circadian clock variability [42]. Internal circadian rhythm desynchronization may occur in RBD, misaligning circadian control over tonic and phasic REM atonia, and melatonin may act to re-entrain the suprachiasmatic nucleus, thereby restoring normal circadian REM sleep modulation [43]. In addition, melatonin influences tonic REM sleep and partially restores normal muscle atonia, potentially impacting RBD pathophysiology directly [26]. In contrast, clonazepam binds to benzodiazepine alpha-receptors, directly promoting GABAergic inhibition and reducing REM percentage, potentially decreasing obvious and frequent phasic motor twitches during REM sleep, but having little or no effect on REM muscle atonia that facilitates potentially injurious RBD dream enactment behavior occurrence [8,23,30,39].

A recent study demonstrated that transgenic mice with deficient glycinergic and GABAergic neurotransmission exhibited a similar motor and sleep phenotype to human RBD, indicating that GABAergic and glycinergic pathways may be of vital importance in RBD pathophysiology [39]. In this mouse model, clonazepam decreased both REM and NREM phasic motor bursts, but did not restore normal atonia. Melatonin also decreased motor behaviors during REM sleep and partially restored REM muscle atonia without impacting REM sleep time [39]. This research suggests that clonazepam and melatonin may have different and complementary mechanisms of action to control motor behaviors during REM sleep, although our small number of subjects receiving melatonin and clonazepam polytherapy did not suggest added benefit of polytherapy in humans with RBD. However, melatonin combined with a less potent benzodiazepine/non-benzodiazepine (ie. zopiclone) to minimize side effects may be a rational approach for future investigation. The transgenic mouse model provides a unique opportunity to develop more specific RBD treatments.

A strength of our study is a relatively large, longitudinal systematic survey of treatment outcomes in a representative, naturalistic clinical practice sample of RBD patients comparable to the clinical characteristics reported in most previously published large case series [5,6,9,22]. Our data support that the two most commonly used RBD treatments, melatonin and clonazepam, both have favorable impact on patient ratings of RBD frequency/severity, injury occurrence and severity, and potentially injurious falls over a relatively long duration of follow up. We also present specific RBD patient data on comparative tolerability and safety of these medications, showing that clonazepam-treated patients had more frequently reported adverse effects.

However, our study has several notable limitations. As a survey of subjective treatment outcomes with a relatively low return rate from a single tertiary care center of patients who were not randomized to treatment assignments, it is very likely that we may not have been able to identify and control for several potential confounding biases in selection, referral, sampling, response, and recall. Presumably our cases may be more likely to have more frequent and/or severe RBD than those evaluated in community-based sleep disorders centers, and thus our conclusions may not be generalizable to all RBD patients. Future prospective studies will be necessary to address these inherent methodological problems in survey-based research, and to determine the impact of treatments on patients' quality of life.

While both melatonin and clonazepam appear equally effective and tolerable, this study highlights the current limitations in available treatment options for RBD. Neither treatment, at the doses used, eliminated injury potential and both treatments had a comparable drop-out rate of near 25%. Several other potential treatments for RBD have been reported, including donepezil [28], pramipexole [29], levodopa [30], zopiclone [8,23], and sodium oxybate [2,8]

amongst others [2,4,5,8,20–24,26,44], and a single non-pharmacologic treatment, a bed alarm system, which decreased sleep-related injuries in 4 refractory RBD patients, may offer another treatment horizon [44]. However, considering the current relatively limited therapeutic armamentarium for RBD, development of novel, more effective and tolerable pharmacological and non-pharmacological treatments for RBD is an important public health initiative, especially in view of recent evidence suggesting that RBD prevalence in an older-aged general population may approach 6% [10]. However, until further notice and evidence-based treatments are established, our data suggest that clonazepam and melatonin appear comparably effective for RBD symptoms and injury prevention, and that melatonin may be more tolerable. Given these findings, melatonin may be considered as a reasonable treatment alternative to clonazepam, particularly for older or neurologically impaired RBD patients who may be more sensitive to adverse effects of treatments. More rigorous evidence from prospective, randomized, placebo controlled, clinical trials with rigorous exit criteria to prevent patients from harm are necessary to conclusively identify effective, safe, and tolerable treatment options for RBD.

Acknowledgments

The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number 1 UL1 RR024150-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. American Academy of Sleep Medicine. Diagnostic and coding manual. 2. American Academy of Sleep Medicine; 2005. International classification of sleep disorders.
2. Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. 2010; 1184:15–54.
3. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*. 1986; 9(2):293–308. [PubMed: 3505730]
4. Iranzo A, Santamaria J, Tolosa E. The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases. *Sleep Med Rev*. 2009; 13(6):385–40. [PubMed: 19362028]
5. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain: J Neurol*. 2000; 123(Pt 2):331–9.
6. Frauscher B, Gschliesser V, Brandauer E, et al. REM sleep behavior disorder in 703 sleep-disorder patients: the importance of eliciting a comprehensive sleep history. *Sleep Med*. 2010; 11 (2):167–71. [PubMed: 20022299]
7. Montplaisir J, Gagnon JF, Fantini ML, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. *Mov Disord: Off J Mov Disord Soc*. 2010; 25(13):2044–51.
8. McCarter SJ, St Louis EK, Boeve BF. REM Sleep Behavior Disorder and REM Sleep without Atonia as an Early Manifestation of Degenerative Neurological Disease. *Curr Neurol Neurosci Rep*. 2012; 12(2):182–92. [PubMed: 22328094]
9. Ohayon MM, Schenck CH. Violent behavior during sleep: prevalence, comorbidity and consequences. *Sleep Med*. 2010; 11(9):941–6. [PubMed: 20817553]
10. Boot B, Boeve B, Roberts R, et al. Probable REM sleep behavior disorder increases risk for mild cognitive impairment and Parkinson's disease: A population-based study. *Ann Neurol*. 2012; 71(1):49–56. [PubMed: 22275251]
11. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the mayo sleep questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep Med*. 2011; 12(5):445–53. [PubMed: 21349763]
12. Chiu HF, Wing YK, Lam LC, et al. Sleep-related injury in the elderly—an epidemiological study in Hong Kong. *Sleep*. 2000; 23 (4):513–7. [PubMed: 10875558]

13. Bodkin CL, Schenck CH. Rapid eye movement sleep behavior disorder in women: relevance to general and specialty medical practice. *J Women's Health*. 2009; 18(12):1955–63.
14. Ju YE, Larson-Prior L, Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. *Sleep Med*. 2011; 12(3):278–83. [PubMed: 21317035]
15. Bonakis A, Howard RS, Ebrahim IO, et al. REM sleep behaviour disorder (RBD) and its associations in young patients. *Sleep Med*. 2009; 10(6):641–5. [PubMed: 19109063]
16. Teman PT, Tippmann-Peikert M, Silber MH, et al. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. *Sleep Med*. 2009; 10(1):60–5. [PubMed: 18226952]
17. Iranzo A, Lomena F, Stockner H, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: A prospective study [corrected]. *Lancet Neurol*. 2010; 9:1070–1077. [PubMed: 20846908]
18. Iranzo A, Molinuevo JL, Santamaria J, et al. Rapid-eye movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*. 2006; 5:572–7. [PubMed: 16781987]
19. Schenck CH, Lee SA, Cramer Bornemann MA, et al. Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder (RBD): review of the literature and forensic implications. *J Forensic Sci*. 2009; 54:1475–84. [PubMed: 19788703]
20. Aurora RN, Zak RS, Maganti RK, et al. Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD). *J Clin Sleep Med*. 2010; 6(1):85–95. [PubMed: 20191945]
21. Gagnon JF, Postuma RB, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. *Neurology*. 2006; 67(5):742–7. [PubMed: 16966533]
22. Schenck CH, Mahowald MW. A polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89. 5% of 57 treated patients. *Clev Clin J Med*. 1990; 57(Suppl):S9–S23.
23. Anderson KN, Shneerson JM. Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. *J Clin Sleep Med*. 2009; 5(3):235–9. [PubMed: 19960644]
24. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med*. 2003; 4:281–284. [PubMed: 14592300]
25. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med*. 1996; 100(3):333–7. [PubMed: 8629680]
26. Takeuchi N, Uchimura N, Hashizume Y, et al. Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci*. 2001; 55:267–269. [PubMed: 11422870]
27. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res*. 2010; 19(4):591–6. [PubMed: 20561180]
28. Moraes WA, Poyares DR, Guilleminault C, et al. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: A double-blind placebo-controlled study. *Sleep*. 2006; 29:199–205. [PubMed: 16494088]
29. Fantini ML, Gagnon JF, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. *Neurology*. 2003; 61:1418–20. [PubMed: 14638967]
30. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of rem sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*. 2007; 130:2770–2788. [PubMed: 17412731]
31. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65(12):1863–72. [PubMed: 16237129]
32. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004; 256(3):183–94. [PubMed: 15324362]
33. Wenning G, Shlomo T, Magelhaes M, et al. Clinical features and natural history of multiple system atrophy: an analysis of 100 cases. *Brain*. 1994; 117:835–45. [PubMed: 7922469]

34. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42(2):377–81. [PubMed: 18929686]
35. Schenck C, Hurwitz T, Mahowald M. REM sleep behavior disorder: an update on a series of 96 patients and a review of the world literature. *J Sleep Res.* 1993; 2:224–231. [PubMed: 10607098]
36. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology.* 1996; 46(2):388–93. [PubMed: 8614500]
37. Ju YE, Larson-Prior L, Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. *Sleep Med.* 2011; 12(3):278–83. [PubMed: 21317035]
38. Huang J, Zhang J, Lam SP, et al. Amelioration of obstructive sleep apnea in REM sleep behavior disorder: implications for the neuromuscular control of OSA. *Sleep.* 2011; 34(7):909–15. [PubMed: 21731141]
39. Brooks PL, Peever JH. Impaired GABA and glycine transmission triggers cardinal features of rapid eye movement sleep behavior disorder in mice. *J Neurosci.* 2011; 31(19):7111–21. [PubMed: 21562273]
40. Attenburrow MEJ, Cowen PJ, Sharpley AJ. Low dose melatonin improves sleep in healthy middle-aged subjects. *Psychopharmacology.* 1996; 126:179–181. [PubMed: 8856838]
41. Zhdanov IV, Wurtman RJ, Morabito CJ, et al. Effects of low oral doses of melatonin, given 2–4 hours before habitual bedtime, on sleep in normal young humans. *Sleep.* 1996; 19(5):423–431. [PubMed: 8843534]
42. Kunz DR, Müller C, et al. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. *J Clin Endocrinol Metab.* 2004; 89(1):128–134. [PubMed: 14715839]
43. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: An open-labeled pilot study on the possible influence of melatonin on rem-sleep regulation. *Mov Disord.* 1999; 14(3):507–511. [PubMed: 10348479]
44. Howell MJ, Arneson PA, Schenck CH. A novel therapy for REM sleep behavior disorder (RBD). *J Clin Sleep Med.* 2011; 7(6):639–644A. [PubMed: 22171203]

FIGURE 1.

Patient ratings of dream enactment behavior frequency and severity (visual analog scale, VAS) for melatonin and clonazepam, showing that both treatments comparably reduced RBD behaviors. The difference between pre-treatment and post-treatment RBD VAS ratings was statistically significant for both treatments (melatonin treated patients pre-treatment vs. post-treatment VAS scores, 6.68 vs. 4.22, $p = 0.0001$; clonazepam treated patients pre-treatment vs. post-treatment VAS scores, 6.53 vs. 4.15, $p = 0.0005$).

FIGURE 2.

Percentage of RBD patients reporting comparatively worsened, neutral, or improved outcomes (mild, moderate, significant, or freedom from symptom) following treatment with melatonin or clonazepam. Both treatments showed overall subjective global improvements in RBD outcomes, with clonazepam trending toward a more significant proportion of patients achieving a moderate or greater level of improvement (clonazepam vs. melatonin, 78% vs. 48%, $p=0.06$). The frequency of reported complete suppression of RBD following treatment was similar (17% vs. 12%, $p=0.68$).

FIGURE 3.

Percentage of RBD patients reporting dream enactment behaviors, falls, and injury before and after treatment with melatonin or clonazepam. Statistically significant improvements were seen for melatonin in RBD DEB, falls, and injury. Trends toward similar improvements were seen with clonazepam treatment.

FIGURE 4.

Percentage of RBD patients reporting injuries (either no injury, or mild, moderate, or marked injury) before and after treatment with melatonin or clonazepam. Melatonin treatment was associated with statistically significant reported reductions in injury severity, while clonazepam treatment demonstrated similar but non-statistically significant trends for severity of injury reduction.

FIGURE 5.

Percentage of RBD patients reporting adverse effects (sleepiness, unsteadiness, trouble thinking, nausea, or sexual dysfunction) before and after treatment with melatonin or clonazepam. Adverse effects were more frequently reported following clonazepam than melatonin treatment, a group difference trending toward statistical significance ($p=0.06$).

FIGURE 6.

Percentage of RBD patients reporting adverse effects by category for sleepiness, unsteadiness, trouble thinking, and dizziness, with either no report, or mild, moderate, or severe level of the adverse effect, during treatment with melatonin or clonazepam. Sleepiness, unsteadiness, dizziness, and trouble thinking were more frequently reported with clonazepam than melatonin treatment, but these differences did not achieve statistical significance.