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Original Article

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 and 25 (56%) received antidepressants. Twenty-five patients received melatonin, 18 received clonazepam, and two 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 ($p_m = 0.0001$, $p_c = 0.0005$). Melatonin-treated patients reported significantly reduced injuries ($p_m = 0.001$, $p_c = 0.06$) and fewer adverse effects ($p = 0.07$). Mean durations of treatment were no different between groups (for clonazepam 53.9 ± 29.5 months, and for melatonin 27.4 ± 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.

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

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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 the 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

2.1. 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 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 two 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 and the initially assigned treatment combined. These six were combined with the two 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.

2.2. Survey instrument

We designed a three part questionnaire (Appendix A) that was completed by the 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 analog scale (VAS). Questions concerning medication use included treatment sequence, dosage, the duration of treatment, potential side effects, and concurrent antidepressant history.

2.3. 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 co-variate 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].

2.4. 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 Section 3 where applied). Significance level was set at an alpha of $p < 0.05$.

3. Results

3.1. Demographics and clinical data

Of the 45 patients surveyed, 35 (77.8%) were men and the 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 six (25%), MSA in five (21%), and DLB in three (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 five 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 three