Antidepressants Increase REM Sleep Muscle Tone in Patients with and without REM Sleep Behavior Disorder

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Study Objectives: REM sleep behavior disorder (RBD) is associated with antidepressant treatment, especially in younger patients; but quantitative REM sleep without atonia (RSWA) analyses of psychiatric RBD patients remain limited. We analyzed RSWA in adults receiving antidepressants, with and without RBD.

Design: We comparatively analyzed visual, manual, and automated RSWA between RBD and control groups. RSWA metrics were compared between groups, and regression was used to explore associations with clinical variables.

Setting: Tertiary-care sleep center.

Participants: Participants included traditional RBD without antidepressant treatment (n = 30, 15 Parkinson disease [PD-RBD] and 15 idiopathic); psychiatric RBD receiving antidepressants (n = 30); and adults without RBD, including antidepressant-treated psychiatric (n = 30), untreated psychiatric (n = 15), and OSA (n = 60) controls.

Interventions: N/A.

Measurements and Results: RSWA was highest in traditional and psychiatric RBD, intermediate in treated psychiatric controls, and lowest in untreated psychiatric and OSA controls ($P < 0.01$). RSWA distribution and type also differed between antidepressant-treated patients having higher values in anterior tibialis, and PD-RBD with higher submentalis and tonic RSWA. Psychiatric RBD had significantly younger age at onset than traditional RBD patients ($P < 0.01$).

Conclusions: Antidepressant treatment was associated with elevated REM sleep without atonia (RSWA) even without REM sleep behavior disorder (RBD), suggesting that antidepressants, not depression, promote RSWA. Differences in RSWA distribution and type were also seen, with higher anterior tibialis RSWA in antidepressant-treated patients and higher tonic RSWA in Parkinson disease-RBD patients, which could aid distinction between RBD subtypes. These findings suggest that antidepressants may mediate different RSWA mechanisms or, alternatively, that RSWA type and distribution evolve during progressive neurodegeneration. Further prospective RSWA analyses are necessary to clarify the relationships between antidepressant treatment, psychiatric disease, and RBD.

Keywords: REM sleep without atonia, REM sleep behavior disorder, parasomnia, synucleinopathy, depression, antidepressants, quantitative analysis, automated analysis, transient/phasic muscle activity, tonic muscle activity

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INTRODUCTION

REM sleep behavior disorder (RBD) is a complex and potentially injurious parasomnia that is strongly associated with neurodegenerative disorders, particularly the synucleinopathies.[1–5] Growing evidence suggests that psychiatric disorders, particularly depression and antidepressant use, are strongly associated with RBD.[4,6,7] While idiopathic RBD (iRBD) is considered to be an early manifestation of neurodegeneration and has a strong predominance in men with later-life onset, the natural history and disease course of RBD associated with psychiatric disorders is far less clear.[1–4,7–12] RBD before age 50 affects women equally to men, and frequently is associated with a history of a psychiatric disorder or concurrent narcolepsy.[2,8,11,13] Psychiatric diagnoses increase the odds of developing RBD tenfold, and antidepressant use increases the likelihood of RBD fivefold.[11] However, it is unclear whether or not psychiatric RBD associated with antidepressant treatment represents a distinct pathophysiologic process compared to neurodegeneration-associated RBD, or whether antidepressant use and psychiatric disease simply unmasks RBD symptoms, thereby allowing for an earlier appearance of dream enactment behaviors than may have otherwise occurred. Recent evidence supports the contention that antidepressants may unmask otherwise latent or subclinical RBD. RBD patients receiving antidepressants demonstrated similar autonomic dysfunction, color vision and olfactory impairments, and frequency of mild cognitive impairment (MCI) diagnosis compared with patients with iRBD who were not receiving antidepressants; although RBD patients receiving antidepressants had a decreased rate of conversion to symptomatic RBD, suggesting a potential inductive influence of antidepressants toward RBD development.[4] Furthermore, while anecdotal clinical experience has suggested that antidepressants, especially selective serotonergic reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), may increase REM sleep muscle tone in patients without RBD, previous quantitative analyses of REM muscle tone in patients receiving antidepressant treatment have been limited.[7,12,14,15] We aimed to determine whether quantitative measures of REM sleep without atonia (RSWA) differed between RBD patients with and without psychiatric

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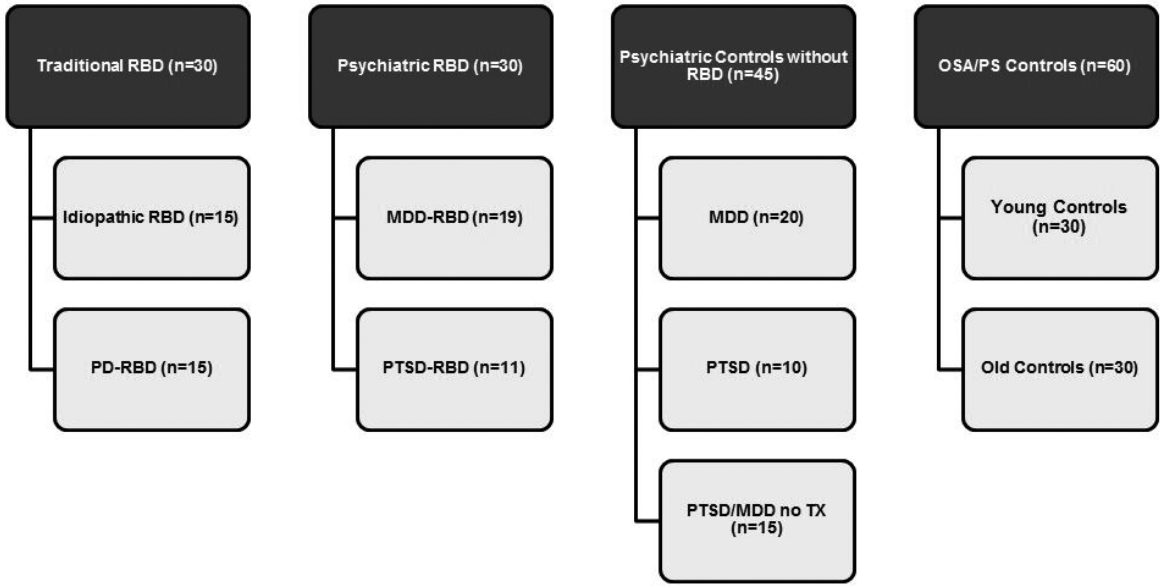

Figure 1—Patient subgroups. PD-RBD, Parkinson disease-RBD; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; Psych-T, psychiatric patients taking antidepressant medications at PSG; Psych-U, psychiatric patients not taking antidepressant medications at PSG; Young Controls, OSA/primary snorers age 28–60; Old Controls, OSA/primary snorers age 61–80.

disease and to systematically explore the impact of antidepressant therapy on RSWA.

METHODS

Patient Selection

One hundred sixty-five consecutive patients seen between 2008–2012 were identified for retrospective analysis of RSWA from the polysomnographic database at the Mayo Clinic Center for Sleep Medicine. Patient subgroups (see Figure 1) included traditional RBD (tRBD, n = 30) who were all antidepressant naïve, including iRBD (n = 15), and Parkinson disease (PD)-RBD (n = 15); psychiatric RBD (Psych-RBD, n = 30), which included RBD patients treated with antidepressants with underlying diagnoses of major depressive disorder (MDD, n = 19) and posttraumatic stress disorder (PTSD, n = 11); treated psychiatric controls receiving antidepressant therapy (Psych-T) with no history of RBD at polysomnography (PSG) including PTSD (n = 10) and MDD (n = 20); medically untreated psychiatric controls receiving no antidepressant therapy (Psych-U) at PSG with PTSD/MDD diagnoses (n = 15); and 60 patients with a diagnosis of OSA/primary snoring receiving no antidepressant therapy at PSG (28–60 years, n = 30; 61–80 years, n = 30). Chart review was performed for age, gender, and apnea hypopnea index (AHI) match of OSA controls in addition to other relevant clinical and demographic features. To assess severity of psychiatric disease, patient scores on the Patient Health Questionnaire (PHQ-9) closest to PSG were recorded and stratified as mild (< 10), moderate (10–19), or severe (> 20).[16] The most common reason for sleep referral for tRBD patients was parasomnia behavior (n = 14, 47%) followed by sleep disordered breathing (SDB) (n = 9, 30%) and excessive daytime sleepiness/fatigue (EDS) (n = 5, 17%). Psych-RBD patients were most often referred for parasomnia behavior (n = 15, 50%) followed by SDB (n = 10, 33%). Psych-T patients were most often referred for SDB (n = 19, 63%) and fatigue (n = 6, 20%) while Psych-U patients were referred for SDB (n = 9, 60%) and insomnia (n = 3, 20%). In both younger (≤ 60 years, n = 22, 73%) and older controls (> 60 years, n = 27, 90%), SDB was the most common reason for referral. For patients receiving antidepressants, daily dosages for each drug were recorded; daily dose equivalents were calculated similar to previously published methods.[17] All patients with a diagnosis of RBD met ICSD-2 standards.[18] Patients with PTSD and MDD met published criteria for each disorder,[19] and patients with Parkinson disease were diagnosed by board-certified neurologists at Mayo Clinic according to United Kingdom PD Society Brain Bank criteria.[20] The institutional review board approved this study.

Polysomnography

Video polysomnographic recordings were conducted on a 16-channel Nicolet Nicvue digital system with sensitivity at 5–7 μV/mm, bandpass filtered from 0.3–100 Hz; (Cardinal Health Corporation, Madison, Wisconsin) and digitized at a sampling rate of 500 Hz. Electroencephalogram recordings were performed according to the International 10–20 system electrode placements (Fp1, Fp2, Fpz, Fz, Cz, C3, C4, O1, O2, Oz) including electrooculography (left and right outer canthus, LOC and ROC placements), submental and tibial electromyography, and an electrocardiogram. Extensor digitorum communis (EDC) EMG leads were added for RBD patients only, but are not recorded routinely in patients who do not have a clinical suspicion for parasomnia in our center. Respirations were analyzed using an oronasal thermistor and nasal pressure sensor for airflow monitoring, with thoracoabdominal impedance plethysmography to monitor effort. Oxyhemoglobin saturation was evaluated by pulse oximetry. Muscle activity

was measured in the submentalis (SM) and linked anterior tibialis (AT) muscles. Standard 30-s epochs of PSG were used to score sleep in accordance with standard criteria.[21] The occurrence of the first REM in the electrooculographic channel was used to determine the onset of REM sleep periods. The end of REM sleep periods was determined when either no REMs were detected in 3 consecutive minutes or when an awakening, K complexes, or spindles were observed. Quantification of RSWA was performed by different investigators with a mean κ coefficient of 0.897, with interrater reliability as established by previously reported methods.[22–24] Patients with AHI > 25 and total REM time < 5 min were excluded from analysis.

Analysis of REM Sleep Muscle Activity

Quantitative analysis of electromyogram (EMG) activity was performed using HypnoLab sleep scoring software (ATES Medica Labs, Verona, Italy) according to previously published methods.[24] Combined overall tonic, phasic, and "any" (either tonic or phasic) muscle activity was manually scored and calculated for each patient. In addition, phasic and "any" muscle activity were calculated separately for SM and AT muscles. Background EMG was measured to serve as the reference standard prior to scoring REM muscle activity, and the lowest background was chosen as the standard, with an average of 0.5 μV.

Thirty-second epochs were used to score tonic muscle activity in both the SM and AT muscles. An epoch was considered tonic if > 50% of the epoch had any activity continuously greater than double the background EMG or ≥ 10 μV. Tonic muscle activity was calculated as the total number of positive 30-s epochs divided by the total number of analyzable 30-s REM sleep epochs.

Each 30-s epoch was broken down into 3-s mini-epochs for analysis of phasic and "any" activity in both the SM and AT muscles. A 3-s mini-epoch was considered positive for phasic activity with the presence of a phasic EMG burst and negative if there was no muscle activity. Phasic activity was defined as an EMG burst > 4 times the background amplitude, with a duration lasting from 0.1 to 14.9 seconds.[22,24,25] The return of muscle activity to baseline for ≥ 200 msec was considered to be the end of a phasic burst.

A 3-s mini-epoch was considered to be positive for "any" muscle activity if tonic or phasic muscle activity was present within that mini-epoch. In addition, bursts of phasic activity occurring simultaneously with tonic activity had amplitude twice the background tonic EMG activity within the same 3-s mini-epoch.[22] Any 3-s mini-epoch containing a breathing or spontaneous arousal-related event was scored as "artifact" and excluded from analysis. Overall phasic and "any" muscle activity was calculated as the total number of positive 3-s mini-epochs divided by the total number of analyzable 3-s mini-epochs. For the overall combined analysis, a 3-s mini-epoch was considered positive if there was phasic or "any" EMG activity in either the SM and AT muscles and negative if there was an absence of EMG activity in both muscles.

In addition, phasic muscle burst duration was calculated for both SM and AT muscles as published previously.[24] The automated REM atonia index (RAI) of the SM muscle was also calculated using HypnoLab sleep scoring software.[26,27]

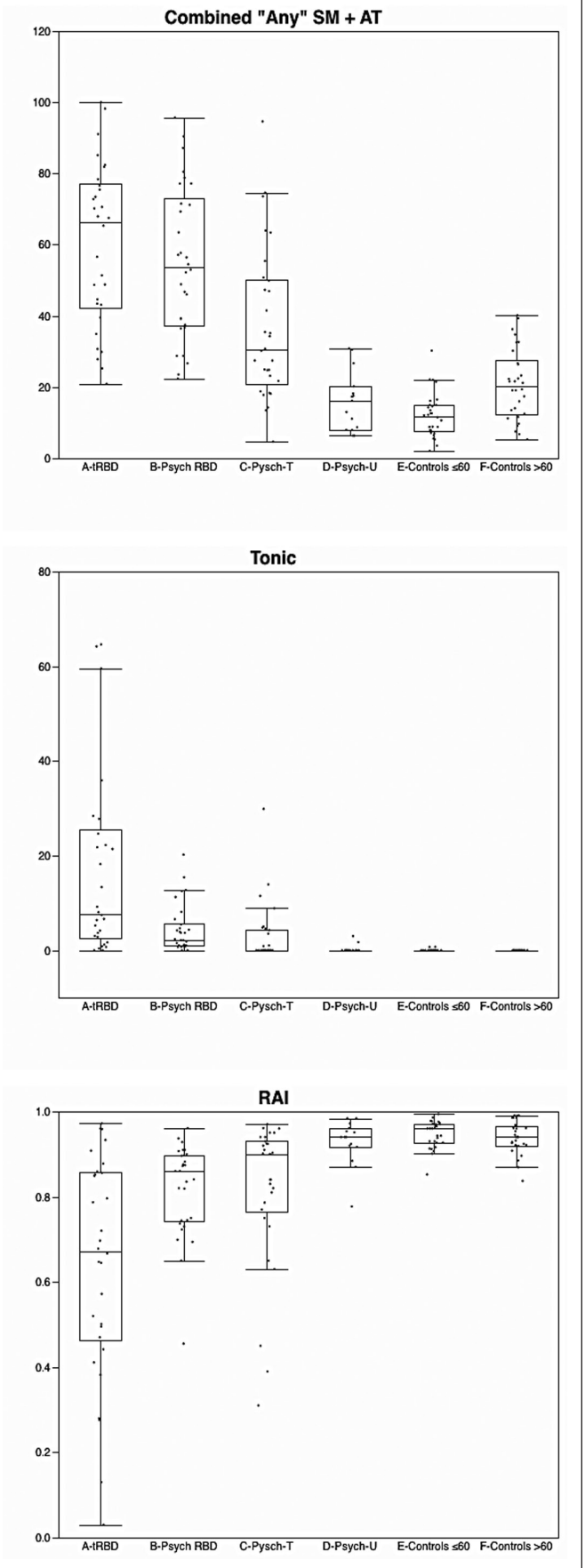

Figure 2—Comparison of combined "any" SM + AT, tonic percent muscle activity, and RAI between groups. AT, anterior tibialis; RAI, REM atonia index; SM, submentalis.

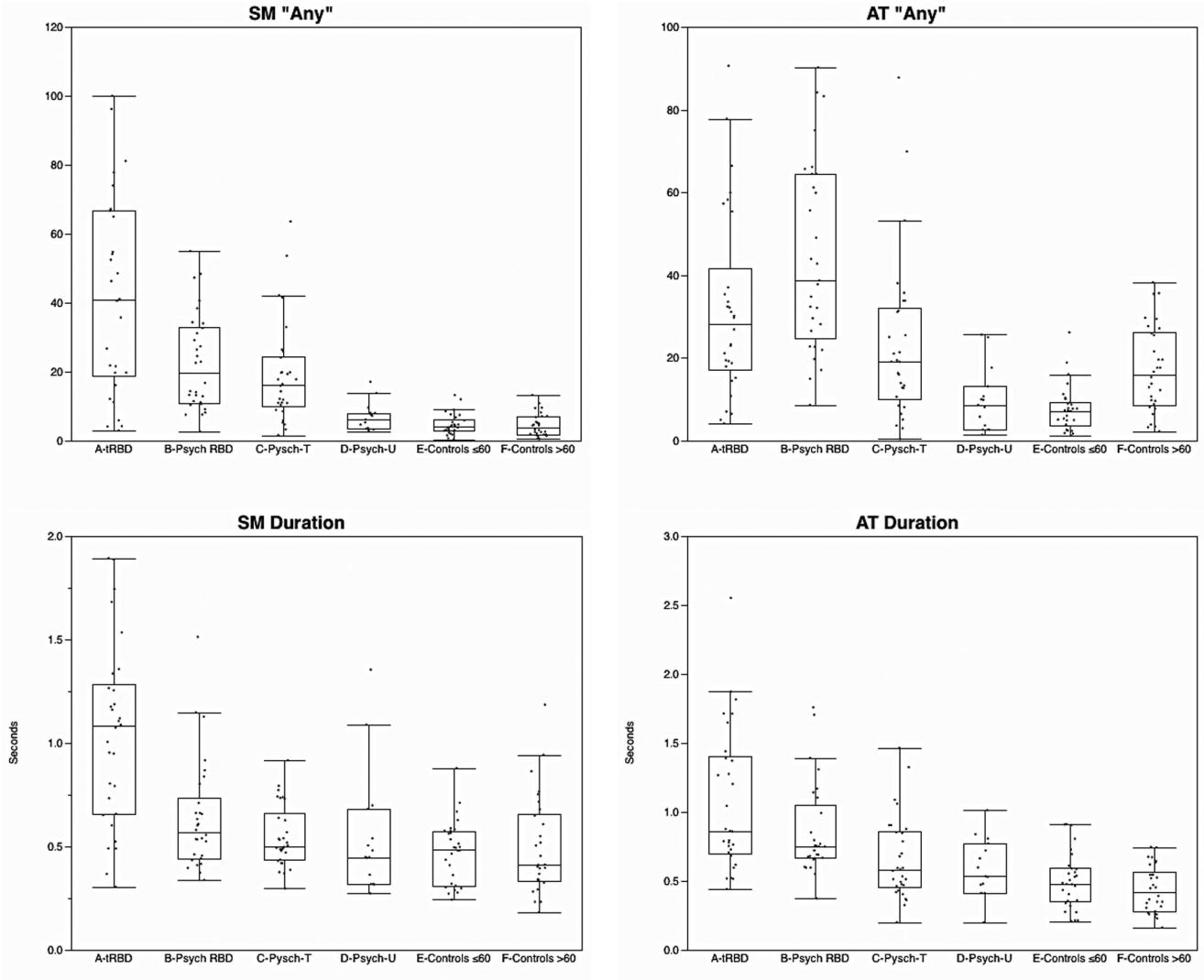

Figure 3—Comparison of "any" SM, "any" AT, SM duration, and AT duration between groups.

Statistical Analysis

Clinical, demographic, and PSG data are presented as means, standard deviations, and frequencies. The primary outcome was the group comparison of "any" muscle activity, while secondary outcomes were the group comparisons of other RSWA metrics and clinical variables. Quantitative variables were analyzed using nonparametric Kruskal-Wallis and Mann-Whitney tests, while χ^2 tests were used to analyze categorical variables using JMP statistical software (JMP, Version 9; SAS Institute Inc., Cary, NC). Relationships between clinical variables (RBD and age, psychiatric disease duration, antidepressant drug load, and antidepressant drug use duration) were regressed as independent variables against tonic, phasic, and "any" muscle activity indices utilizing multivariable linear or logistic regression analyses. An experiment-wise Bonferroni correction factor for multiple comparisons was applied, setting significance at α of $P < 0.01$. Exploratory receiver operating characteristic (ROC) curves were calculated for combined "any" muscle activity, phasic, and "any" muscle activity for SM and AT muscles, RAI, in addition to SM and AT durations. Cutoff diagnostic threshold values were chosen that yielded the highest combined sensitivity and specificity distinguishing Psych-RBD from Psych-T.

RESULTS

Overall RSWA Group Comparisons

Combined AT/SM "any" EMG muscle activity followed a descending gradient with tRBD significantly greater than all other groups as follows: tRBD (60.1 ± 22.7) > Psych-RBD (55.1 ± 21.1) > Psych-T (36.9 ± 21.3) > Psych-U (15.9 ± 8.4), with Psych-U similar to both young (12.0 ± 6.2) and old (20.8 ± 9.9) controls (Table 2). Combined phasic EMG muscle activity was similar between tRBD and Psych-RBD patients (50.7 ± 16.6 vs. 53.7 ± 20.9) but was higher in both the tRBD and Psych-RBD patients than in the other groups. Tonic muscle activity (18.3 ± 22.8) and "any" SM muscle activity (42.5 ± 28.3) were significantly higher and RAI (0.64 ± 0.26) significantly lower in tRBD patients compared to the other groups (Figures 2 and 3). Phasic SM muscle activity, "any" AT activity, and phasic AT activity comparisons can be found in Table 2. In addition, SM phasic muscle burst duration (1.04 ± 0.43 sec) was longer

in tRBD patients than all other groups, and AT phasic muscle burst duration (1.07 ± 0.51 sec) was significantly longer than all groups except for Psych-RBD (Table 2).

Psych-RBD patients had significantly greater combined SM/AT "any" (55.1 ± 21.1) and phasic (53.7 ± 20.9), tonic (4.5 ± 5.1), "any" SM (22.6 ± 14.0), "any" AT (44.6 ± 22.9), and phasic AT (44.0 ± 22.6) muscle activity compared to Psych-T, Psych-U, and controls (Table 2). There was no association between antidepressant dose or type of psychiatric disease and any measure of RSWA. Psych-T had greater combined "any" muscle activity (36.9 ± 21.3), combined phasic muscle activity (35.8 ± 20.0), SM "any" muscle activity (19.2 ± 14.7), and SM phasic muscle activity (18.3 ± 13.2) compared with Psych-U and controls. Tonic muscle activity (3.0 ± 6.3) was greater in Psych-T than controls but no different compared to Psych-U. RAI (0.82 ± 0.17) was significantly lower in Psych-T compared to Psych-U and controls (Table 2). Active psychiatric symptoms, antidepressant dose, and antidepressant therapy duration, periodic limb movement index (PLMI), age, and REM time were not associated with any measure of RSWA.

A SM + AT combined "any" cutoff value of 36.5 was 83% sensitive and 64% specific for a diagnosis of RBD when attempting to distinguish between Psych-RBD and Psych-T patients. In addition, an AT phasic burst duration of 0.60 s was 93% sensitive and 60% specific for diagnosis of RBD when differentiating between Psych-RBD and Psych-T. With reclassification of patients meeting the "any" muscle activity cutoff of 36.5 for RBD diagnosis, based on whether they also exceeded cutoff values for phasic muscle burst duration cutoff for RBD in the AT, sensitivity and specificity both improved to 100% and 77%, respectively.

RSWA Comparisons between PD-RBD, iRBD, and Psych-RBD Patients

Subgroup analysis of RBD patients revealed a significantly younger age of onset of RBD symptoms in Psych-RBD patients (41.5 ± 18.4 years) compared to both iRBD (57.7 ± 14.6 years) and PD-RBD patients (59.5 ± 11.1 years, both comparisons $P < 0.01$). PD-RBD patients had significantly higher tonic (28.2 ± 27.6 vs. 4.5 ± 5.1, $P < 0.01$) and SM "any" (54.0 ± 27.7 vs. 22.6 ± 14.0, $P < 0.01$) muscle activity, lower RAI (0.52 ± 0.26 vs. 0.82 ± 0.11, $P < 0.01$) (Figure 4), and longer SM duration (1.2 ± 0.45 vs. 0.64 ± 0.26, $P < 0.01$) than Psych-RBD patients (Table 3); iRBD patients were not significantly different on any measure of RSWA compared to either PD-RBD or Psych-RBD groups (Table 3). All associations between RSWA metrics and PD-RBD group remained after adjusting for age, gender, REM time, and REM AHI. Fifteen PD-RBD, 14 iRBD, and 11 Psych-RBD patients had available arm EMG recorded from the EDC. Any EDC % was significantly greater in the PD-RBD (29.8 ± 19.0) and iRBD (26.6 ± 16.9) groups than Psych-RBD (11.7 ± 10.9, $P < 0.01$). Phasic EDC % was also significantly greater in the PD-RBD (27.8 ± 15.0) and iRBD (23.9 ± 15.3) than Psych-RBD (11.2 ± 10.8, $P < 0.01$).

RSWA Comparisons between Psychiatric Patients taking SSRI and SNRI Medications

Seventeen (57%) Psych-T patients received SSRI medications and 8 (27%) took serotonin-norepinephrine reuptake

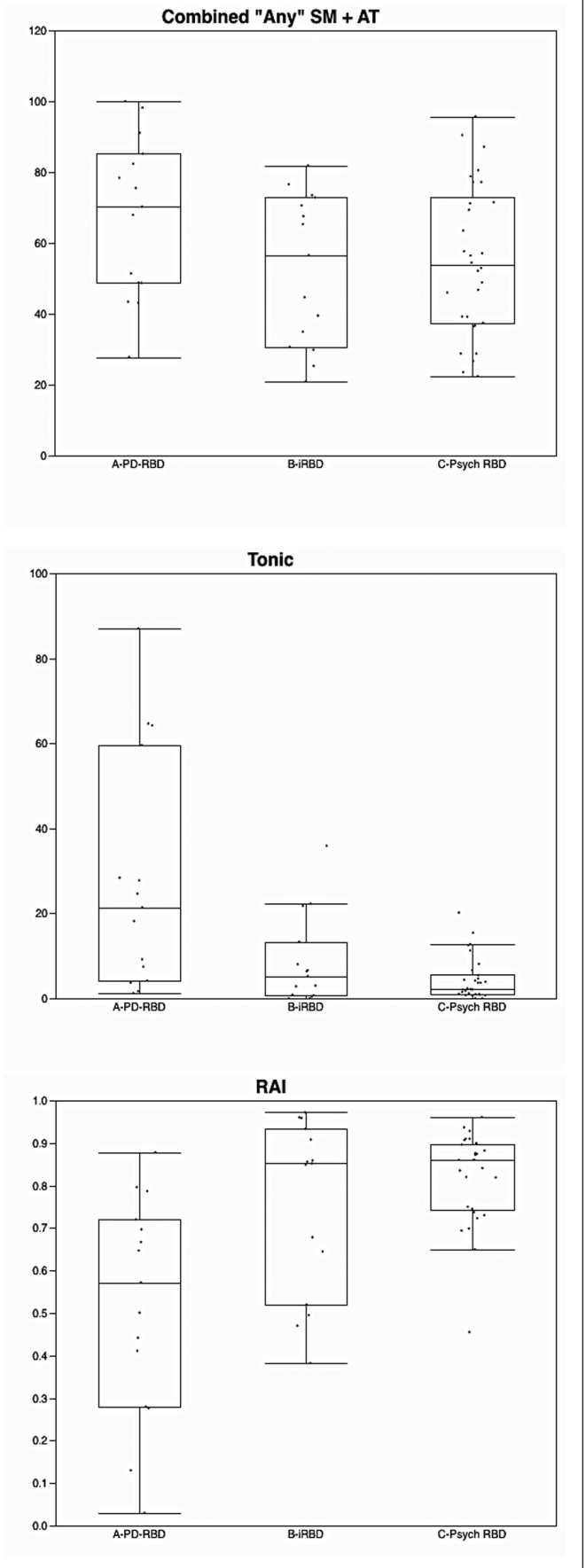

Figure 4—Combined "Any" SM + AT, Tonic Muscle activity, and RAI Comparisons between PD-RBD, iRBD and Psych-RBD Subgroups.

Table 1—Clinical and demographic variables of all groups.

	RBD[a]	Psych-RBD[b]	Psych-T[c]	Psych-U[d]	Controls ≤ 60[e]	Controls > 60[f]	P value < 0.01
Age	65.1 ± 11.1	51.8 ± 17.0	42.6 ± 11.3	47.8 ± 11.5	42.1 ± 9.6	71.3 ± 6.0	a > b,c,d,e b > c,d f > b,c,d,e
Gender M/F	27/3	24/6	20/10	5/10	18/12	25/5	a > c,d,e b > c,d f > c,d,e
BMI	29.9 ± 4.1	30.2 ± 7.3	33.8 ± 7.8	34.8 ± 11.6	32.0 ± 6.3	27.9 ± 3.8	b > f e > f
Epworth	11.2 ± 5.4	9.8 ± 4.9	9.9 ± 5.9	12.2 ± 4.8	11.2 ± 4.7	7.5 ± 5.1	d > f
Age RBD onset	58.6 ± 12.8	41.5 ± 18.3	N/A	N/A	N/A	N/A	a > b
RBD Duration	7.1 ± 5.7	9.5 ± 10.1	N/A	N/A	N/A	N/A	
Depression	0	24	26	7	0	0	
PTSD	0	11	11	10	0	0	
Anxiety	0	12	13	6	0	0	
DDE	N/A	1.96 ± 0.90	1.76 ± 1.1	N/A	N/A	N/A	
SSRI/SNRI/Bupropion/ Other	N/A	20/6/2/2	17/8/4/1	N/A	N/A	N/A	
Antidepressant Use Duration (years)	N/A	13.1 ± 8.0	11.6 ± 9.4	N/A	N/A	N/A	

RBD, REM sleep behavior disorder; Psych-RBD, psychiatric patients with RBD; Psych-T, psychiatric patients taking antidepressant medications at PSG; Psych-U, psychiatric patients not taking antidepressant medications at PSG; Controls ≤ 60, OSA/primary snorers age 28–60; Controls > 60, OSA/primary snorers age 61–80; BMI, body mass index; PTSD, posttraumatic stress disorder; DDE, daily dose equivalent of antidepressant medications; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin- norepinephrine reuptake inhibitors.

inhibitor (SNRI) medications at time of PSG. RSWA indices were no different between SSRI and SNRI treated-patient subgroups. Four (13%) Psych-T patients receiving bupropion had nonsignificantly lower amounts of RSWA than patients taking SNRIs and SSRIs. However, patients taking bupropion still had significantly higher RSWA than Psych-U and controls. Twenty (67%) Psych-RBD patients received SSRI medications at time of PSG compared with 6 (20%) patients taking SNRI medications. RSWA indices were no different between the subgroups of Psych-RBD receiving SSRIs or SNRIs, apart from a trend toward longer SM phasic muscle burst duration in SNRI-treated RBD patients ($P = 0.05$). When comparing all patients receiving SSRI or SNRI medications, no significant differences in RSWA were observed. In the overall group, SM phasic muscle burst durations were slightly longer in those receiving SNRIs, although this was not significant ($P = 0.08$).

Clinical, Demographic, and PSG Group Comparisons

tRBD patients were older than Psych-RBD patients at time of PSG (65.1 ± 11.1 vs. 51.8 ± 17.0 years, $P < 0.01$). RBD onset occurred earlier in Psych-RBD patients (41.5 ± 18.3 vs. 58.6 ± 12.8 years, $P < 0.01$), but RBD symptom duration was no different between groups, similar to previously published studies.[4,7] RBD onset occurred concurrently with or after antidepressant medication therapy initiation in 15 (50%) Psych-RBD patients, 5 (16.6%) patients reported dream enactment prior to antidepressant initiation, and timing between dream enactment and antidepressant therapy was unclear in 10 (33.3%) patients.

Psych-RBD patients (51.8 ± 17.0 years) were older than both Psych-T (42.6 ± 11.3 years) and Psych-U (47.8 ± 11.5 years) patients ($P < 0.01$). In addition, there were more men in the Psych-RBD than Psych-T and Psych-U groups ($P < 0.01$).

There were no differences in gender and other clinical or demographic variables between RBD groups (Table 1). There were no differences between groups in REM time, AHI, REM AHI, PLMI, or other PSG variables (Table 4). SSRIs, SNRIs, and bupropion were the most commonly used antidepressant medications in our cohort. Antidepressant daily dose equivalent and duration of use did not differ between Psych-RBD patients and Psych-T patients (Table 1). Further details concerning psychiatric history and medications are provided in the supplemental material.

DISCUSSION

This study highlights several important clinical and electrophysiologic relationships between antidepressant use, psychiatric disease, and RBD. Patients taking antidepressant medications had higher RSWA compared to subjects who were not taking antidepressant medications, but lower RSWA than those with clinical RBD, suggesting that antidepressants alter central nervous system REM atonia control mechanisms to enable dream enactment rather than simply altering dream mentation and provoking nightmares. RSWA abnormality profiles also differed between RBD groups and patients taking antidepressants. Patients with tRBD were distinguished from other groups by higher tonic muscle activity and longer phasic burst durations, while antidepressant-treated patients with or without RBD had higher phasic RSWA in AT than SM. Antidepressant therapy, but not depression, appears to have a mediating role in promoting RSWA, given that only patients taking antidepressants had significantly higher muscle activity

Table 2—RSWA muscle activity in all groups.

	tRBD[a]	Psych-RBD[b]	Psych-T[c]	Psych-U[d]	Controls ≤ 60[e]	Controls > 60[f]	P value < 0.01
Any EMG %	60.1 ± 22.7	55.1 ± 21.1	36.9 ± 21.3	15.9 ± 8.4	12.0 ± 6.2	20.8 ± 9.9	a > b,c,d,e,f b > c,d,e,f c > d,e,f f > e
Phasic EMG %	50.7 ± 16.6	53.7 ± 20.9	35.8 ± 20.0	15.6 ± 8.1	12.0 ± 6.2	20.8 ± 9.9	a > c,d,e,f b > c,d,e,f c > d,e,f f > e
Tonic EMG %	18.3 ± 22.8	4.5 ± 5.1	3.0 ± 6.3	0.31 ± 0.86	0.05 ± 0.18	0 ± 0	a > b,c,d,e,f b > c,d,e,f c > e,f
Any SM %	42.5 ± 28.3	22.6 ± 14.0	19.2 ± 14.7	6.9 ± 4.1	4.8 ± 3.0	4.5 ± 3.2	a > b,c,d,e,f b > c,d,e,f c > d,e,f
Phasic SM %	29.6 ± 17.2	21.5 ± 13.1	18.3 ± 13.2	6.8 ± 3.8	4.8 ± 3.0	4.5 ± 3.3	a > d,e,f b > d,e,f c > d,e,f
Any AT %	32.0 ± 22.1	44.6 ± 22.9	23.2 ± 19.5	9.8 ± 7.7	7.7 ± 5.5	17.2 ± 10.4	a > d,e,f b > c,d,e,f c > d,e f > e
Phasic AT %	30.8 ± 19.8	44.0 ± 22.6	22.4 ± 18.2	9.7 ± 7.8	7.7 ± 5.5	17.2 ± 10.4	a > d,e,f b > c,d,e,f c > d,e f > e
RAI	0.64 ± 0.26	0.82 ± 0.11	0.82 ± 0.17	0.93 ± 0.05	0.95 ± 0.3	0.94 ± 0.04	a > b,c,d,e,f b > d,e,f c > d,e,f
SM Duration (sec)	1.04 ± 0.43	0.64 ± 0.26	0.55 ± 0.15	0.55 ± 0.30	0.47 ± 0.15	0.50 ± 0.24	a > b,c,d,e,f b > e
AT Duration (sec)	1.07 ± 0.51	0.86 ± 0.33	0.66 ± 0.30	0.59 ± 0.21	0.50 ± 0.20	0.44 ± 0.17	a > c,d,e,f b > c,d,e,f c > f

SM, submentalis muscle; AT, anterior tibialis muscle; RAI, REM atonia index; Psych-T, psychiatric patients taking antidepressant medications at PSG; Psych-U, psychiatric patients not taking antidepressant medications at PSG; Young Controls, OSA/primary snorers age 28–60; Old Controls, OSA/primary snorers age 61–80.

and lower RAI than psychiatric patients not taking antidepressant medications. In addition, PHQ-9 scores were not associated with RSWA in any of the psychiatric patient groups. Psychiatric diagnosis alone or severity of symptoms without antidepressant treatment did not alter RSWA, as Psych-U and controls had similar RSWA metrics. Taken together, our findings suggest that either REM sleep atonia control mechanisms differ in antidepressant-associated and neurodegeneration-associated (which is usually synucleinopathy) RBD, or that these mechanisms evolve differently during progressive stages of neurodegeneration. Additional RSWA analyses in patients with and without RBD will be necessary to distinguish the respective influence of antidepressants, psychiatric disease, and synucleinopathy upon RSWA and RBD.

Similar to previously published studies, Psych-RBD patients were significantly younger and had an earlier onset of RBD symptoms than tRBD patients.[4,7,11] Further, 50% of Psych-RBD patients reported symptom onset after initiating antidepressant therapy, indicating a potential relationship between antidepressant therapy initiation and the development of clinical RBD symptoms. Subtle motor behaviors without frank dream enactment may also be readily missed, potentially leading to underreporting of the relationship between "subclinical" RBD onset and antidepressant medication initiation.[28,29] Previous studies have shown that iRBD is more frequent in patients with a psychiatric history or antidepressant use.[11] Somewhat contrarily, our results suggest that antidepressant use, but not psychiatric diagnosis or symptom severity, is most strongly associated with RSWA. These complex relationships require further research given the intimate links between RBD, PD, depression and mood disturbance, and antidepressant use.[30] There were several differences in RSWA characteristics between tRBD and Psych-RBD patients, with higher "any" combined SM/AT, tonic, and "any" SM muscle activity, RAI, and SM phasic burst duration in tRBD than Psych-RBD patients, which interestingly appeared to be driven primarily by PD-RBD patients. When comparing iRBD patients with Psych-RBD patients, there were no significant differences in any measure of RSWA, supporting growing evidence that Psych-RBD may not be a different or distinct pathophysiologic entity, but instead simply an earlier appearance of RBD symptoms associated with an otherwise covert neurodegenerative

disorder (usually a synucleinopathy) that is unmasked by antidepressant use.[1,3,4,7] A similar mechanism has been suggested for the increased frequency of Parkinson disease (some with pathologic confirmation of Lewy body disease) among those who develop drug-induced parkinsonism due to dopamine antagonists. Pathologic analyses in those who meet the criteria of Psych-RBD and Psych-T in this study will provide additional insights on this important issue.[31–34]

Previous literature has suggested that RSWA increases, especially tonic muscle activity, with progression of RBD to symptomatic PD, dementia with Lewy bodies, and multiple system atrophy.[35] Group differences between our RBD groups were driven primarily by increased tonic muscle activity in PD-RBD patients. Previous RSWA studies have found that the degree of tonic SM activity predicts future PD development.[36] This difference may suggest that our iRBD and Psych-RBD subgroups are both undergoing a neurodegenerative process, albeit with sampling at different time-points during progression from "unveiled" RBD associated with antidepressant use or iRBD stage to later evolution of symptomatic RBD as indicated by higher tonic RSWA muscle activity in PD-RBD patients. This contention is supported by a recent study that found similar autonomic dysfunction and other "soft signs" of neurodegeneration in Psych-RBD patients compared with iRBD patients, but a decreased rate of conversion to symptomatic neurodegenerative disease.[4] Interestingly, this study also performed RSWA analysis on the SM muscle, finding no difference in tonic muscle activity between RBD patients treated with antidepressants and those who were not, although RBD antidepressant users

Table 3—RSWA muscle activity in PD-RBD, iRBD, and Psych-RBD subgroups.

	PD-RBD[a]	iRBD[b]	Psych-RBD[c]	P < 0.01
Age (yrs)	68.0 ± 8.3	62.3 ± 8.3	51.8 ± 17.0	a > c
Age RBD Onset (y)	59.5 ± 11.1	57.7 ± 14.6	41.5 ± 18.4	a,b > c
RBD Duration (y)	8.1 ± 5.5	6.1 ± 5.8	9.5 ± 10.1	
Any SM + AT %	67.5 ± 22.4	52.7 ± 21.2	55.1 ± 21.1	
Phasic SM + AT %	52.3 ± 15.8	49.1 ± 17.9	53.7 ± 20.9	
Tonic %	28.2 ± 27.6	8.5 ± 10.5	4.5 ± 5.1	a > c
Any SM %	54.0 ± 27.7	31.1 ± 24.8	22.6 ± 14.0	a > c
Phasic SM %	31.9 ± 13.5	27.4 ± 20.9	21.5 ± 13.1	
Any AT %	32.3 ± 27.0	31.7 ± 16.9	44.6 ± 22.9	
Phasic AT %	30.1 ± 23.0	31.6 ± 16.8	44.0 ± 22.6	
Any EDC %	29.8 ± 19.0	26.6 ± 16.9	11.7 ± 10.9	a,b > c
Phasic EDC %	27.8 ± 15.0	23.9 ± 15.3	11.2 ± 10.8	a,b > c
RAI	0.52 ± 0.26	0.76 ± 0.20	0.82 ± 0.11	a > c
SM Duration (sec)	1.2 ± 0.45	0.91 ± 0.39	0.64 ± 0.26	a > c
AT duration (sec)	1.1 ± 0.61	1.0 ± 0.40	0.86 ± 0.33	

SM, submentalis muscle; AT, anterior tibials muscle; RAI, REM atonia index.

Table 4—PSG variables of all groups.

	RBD[a]	Psych-RBD[b]	Psych-T[c]	Psych-U[d]	Controls ≤ 60[e]	Controls > 60[f]	P < 0.01
AHI	5.2 ± 5.9	4.5 ± 3.7	5.1 ± 8.6	4.6 ± 5.9	4.1 ± 4.8	5.0 ± 5.2	
REM AHI	4.1 ± 5.8	2.9 ± 4.1	5.2 ± 6.5	4.4 ± 5.9	3.7 ± 4.3	3.8 ± 4.4	
Hypoxic Time (min)	1.5 ± 3.5	3.9 ± 10.4	5.8 ± 23.8	4.7 ± 12.6	0.48 ± 0.99	8.7 ± 25.2	
SE %	74.6 ± 16.2	82.0 ± 9.5	81.9 ± 11.8	77.2 ± 15.4	78.4 ± 12.4	80.6 ± 42.8	b > f c > f
TST (min)	268.0 ± 117.8	281.4 ± 119.9	249.7 ± 131.0	241.7 ± 104.3	289.2 ± 103.5	287.3 ± 100.0	
ISL (min)	14.1 ± 17.7	12.4 ± 10.9	16.9 ± 14.4	3.5 ± 29.6	23.9 ± 21.8	22.1 ± 37.6	
IRL (min)	89.8 ± 77.0	127.3 ± 93.2	113.4 ± 86.5	77.8 ± 33.5	89.6 ± 66.8	90.1 ± 81.1	
WASO (min)	74.5 ± 79.4	41.9 ± 27.4	28.8 ± 24.4	50.6 ± 45.9	48.3 ± 40.7	74.6 ± 44.6	a > c
REM Time (min)	69.8 ± 37.4	65.1 ± 30.2	54.9 ± 31.0	51.6 ± 29.4	65.4 ± 18.3	70.0 ± 23.8	f > c
REM %	23.7 ± 12.1	23.1 ± 13.6	19.9 ± 10.2	19.3 ± 7.8	21.7 ± 7.6	21.1 ± 6.4	
N1 %	14.7 ± 8.2	12.8 ± 6.1	11.3 ± 6.2	8.7 ± 5.4	8.0 ± 5.1	14.9 ± 10.3	a > e b > e f > e
N2 %	45.0 ± 13.2	48.0 ± 14.4	55.4 ± 12.5	54.6 ± 12.1	50.9 ± 13.2	48.6 ± 13.7	c > a
N3 %	16.6 ± 13.9	16.4 ± 14.5	13.4 ± 11.1	16.9 ± 9.3	19.4 ± 8.7	18.1 ± 19.1	
PLMI	49.7 ± 60.7	35.5 ± 34.3	12.1 ± 14.8	11.4 ± 30.8	9.0 ± 12.7	42.7 ± 34.1	a > c,d,e b > e f > c,d,e
PLMAI	7.9 ± 9.1	6.7 ± 8.6	3.8 ± 4.5	1.6 ± 4.5	3.1 ± 5.9	9.4 ± 9.5	a > d,e b > d f > c,d,e
RDI	5.3 ± 4.5	5.9 ± 5.5	6.1 ± 6.9	4.8 ± 7.1	3.3 ± 2.8	7.3 ± 8.6	

AHI, apnea hypopnea index; hypoxic time, minutes spent under 90% oxygen saturation; SE, sleep efficiency; TST, total sleep time; ISL, initial sleep latency; IRL, initial REM latency; WASO, wake after sleep onset; PLMI, periodic limb movement index; PLMAI, periodic limb movement arousal index; RDI, respiratory disturbance index; Psych-T, psychiatric patients taking antidepressant medications at PSG; Psych-U, psychiatric patients not taking antidepressant medications at PSG; Young Controls, OSA/primary snorers age 28–60; Old Controls, OSA/primary snorers age 61–80.

had higher phasic muscle activity.[4] Our findings were similar when comparing iRBD and Psych-RBD patients, in that we found no difference in tonic muscle activity between groups, but a slightly higher phasic muscle activity in the Psych-RBD group, especially in AT, which we feel more likely represented variability within our sample.[23]

We were also interested in comparing the effects of antidepressants on RSWA metrics in patients without RBD. Psych-T patients had significantly greater SM and AT phasic muscle activity and lower RAI than Psych-U patients and controls but lower muscle activity than those seen in tRBD and Psych-RBD patients. Tonic muscle activity was also increased in Psych-T compared to old and young controls. Similar findings have been reported in both prospective and retrospective studies of depressed patients without a history of dream enactment.[12,14] However, unlike previous studies, we found no association between RSWA and REM latency prolongation.[7,12,14] Previous studies have focused on patients receiving SSRI medications. We did not have sufficient numbers of patients receiving different antidepressant types to reliably determine whether RSWA indices vary between patients receiving different types of antidepressant medications. Due to its different pharmacologic profile, bupropion has been theorized to have a lower risk of RBD in observational studies[1]; however, we found that RSWA in patients treated with bupropion was still increased compared to controls and no different than patients receiving SSRIs and SNRIs. Unfortunately, too few Psych-RBD patients received bupropion to enable comparisons within that group, warranting further study. We found that Psych-T had higher RSWA indices than Psych-U, which has important public health implications given that antidepressants are among the most commonly prescribed medications in the world.[37,38] Physicians who are prescribing antidepressants must be aware of potential RSWA/RBD induction that could result in injurious dream enactment behavior.[39]

Six (40%) of the Psych-U patients had previously received antidepressant medications but were no longer receiving medication treatment at the time of PSG. However, there was no difference in RSWA between these patients and control patients, indicating a transient effect of antidepressant medications on RSWA. This is consistent with previous reports in the literature of more frequent and severe dream enactment in RBD patients receiving antidepressant treatment,[40] with frequency and severity decreasing after stopping or changing antidepressant medications.[10,41] However, there are also reports of dream enactment persisting despite discontinuance of antidepressant treatment.[10,41] Additional prospective studies of patients receiving antidepressants are necessary to determine the role of these drugs in inducing RSWA and RBD symptoms and the degree to which these alterations may be reversible once antidepressants are discontinued.

Taken together, our results support the hypothesis that antidepressants are strongly associated with RSWA, possibly unveiling clinical RBD earlier than it may occur otherwise, rather than primarily causing RBD symptoms. The mechanism by which antidepressants may cause RSWA, particularly SSRIs, is unclear. Normal REM sleep atonia is primarily dependent on GABAergic and glycinergic hyperpolarization of spinal motor neurons mediated by descending projections of the medullary gigantocellularis, with promotion by the excitatory glutamatergic dorsal pontine sublateral dorsal nucleus.[42,43] However, studies suggest that decreases in the excitatory neurotransmitters serotonin, norepinephrine, and histamine during REM sleep are also necessary for muscle tone suppression.[42,43] SSRIs may increase serotonin levels in ventral horn motor nuclei, thus counteracting hyperpolarization of motor neurons and inducing RSWA, particularly in patients who may be predisposed to RBD.[44] However, this theory does not explain why RBD symptoms persist in some patients even after cessation of antidepressant medications. Given a likely transient effect of antidepressant medications on RSWA, patients with dream enactment behaviors that are exacerbated by antidepressant use may benefit from stopping or changing medications.[40] Agomelatine is a novel antidepressant medication with a melatoninergic mechanism that has been shown to decrease both dream enactment behaviors and RSWA.[45] Given its comparable efficacy to other commonly prescribed antidepressant medications, agomelatine could be especially beneficial to consider for use in RBD patients with depression.[46]

This study has several limitations. As a retrospective study we were limited to chart review in order to determine medication type, compliance, and dose. In addition, degree of psychiatric symptom severity at time of PSG was difficult to ascertain. However, in those patients whose symptoms could be assessed, active psychiatric symptoms were not associated with any marker of RSWA. Recall bias may also have impacted the relationship between initiation of antidepressant medication and RBD symptom onset. Twelve control patients had periodic leg movements of unclear clinical significance. However, PLMI was not associated with any measure of RSWA in any patient subgroup. We did not analyze RSWA metrics of PD-RBD patients with psychiatric disease. However, a recent study has shown patients with comorbid RBD and depression are at significantly greater risk of developing PD than non-depressed RBD patients.[30] Future studies are planned to determine whether RSWA differs between PD-RBD patients with and without depression. Finally, in our analysis comparing RSWA patients receiving SSRI and SNRI medications, patient numbers were small and groups unbalanced in this retrospective study. The small group differences observed were likely driven by variability between RBD patients, and there were no significant differences in RSWA between patients taking different antidepressant medications without RBD. Future studies comparing RSWA metrics in a larger number of subjects with and without RBD (including subjects with and without Parkinson disease) receiving SSRIs, SNRIs, TCAs, bupropion, and agomelatine are planned to determine whether there could be any difference in RSWA between different antidepressant medication treatments.

CONCLUSIONS

Traditional and psychiatric RBD patients have largely similar RSWA abnormalities, although distinct RSWA abnormality profiles of higher tonic muscle activity in traditional RBD patients with Parkinson disease and higher RSWA in AT in psychiatric RBD patients may aid distinction between neurodegeneration (usually synucleinopathy) and antidepressant-associated RBD patient groups. Psychiatric and iRBD patients had similar electrophysiologic findings, suggesting a similar

pathophysiology, whereas PD-RBD patients had significantly higher tonic RSWA muscle activity and longer phasic burst durations in comparison to other groups. These findings suggest that those with underlying neurodegeneration (usually synucleinopathy) might be distinguished by more prominent abnormalities in REM sleep atonia control and implying that RSWA mechanisms may evolve or be distinct at different clinical stages in the progression of neurodegeneration. However, we also found that antidepressant medications are strongly associated with RSWA even in the absence of RBD symptoms; and future prospective studies analyzing RSWA in patients with and without RBD will be necessary to establish the influence of antidepressants and psychiatric disease on RSWA and RBD, to delineate whether antidepressant medications play a mediating role in unveiling RSWA and RBD earlier than it may otherwise present in predisposed patients, or if antidepressants instead cause a distinctive and potentially reversible pathophysiology. Our findings have important public health implications since antidepressants are among the most commonly prescribed medications, and physicians should counsel their patients to be aware of the potential for RSWA and potentially injurious dream-enactment behaviors associated with these medications.

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Clinical Psychiatric and Medication Group Details

Two (7%) tRBD patients reported some symptoms of anxiety but were not treated with antidepressant medications. Four Psych-RBD patients received clonazepam and two received lorazepam for anxiety at PSG. Four Psych-RBD patients were taking dopaminergic agonists for treatment of restless legs symptoms at PSG. No tRBD patients were taking medications known to alter REM sleep muscle tone at PSG. Thirteen tRBD patients were taking dopaminergic medications at PSG with an average levodopa dose equivalent of 590.86 ± 330.8.

MDD was the most common diagnosis in the Psych-RBD group, followed by generalized anxiety disorder (GAD) and PTSD. Twelve (40%) Psych-RBD patients had comorbid depression and anxiety disorder diagnoses. All Psych-RBD patients received antidepressant therapy and 29 (97%) reported active psychiatric symptoms at PSG. MDD was the most common diagnosis in the Psych-T group, followed by PTSD. Twenty-three (77%) Psych-T patients reported active symptoms of depression or anxiety at PSG. Four (13%) Psych-T patients also received lorazepam and two (7%) took clonazepam for anxiety. In the Psych-U group, PTSD and MDD were the most common underlying diagnoses with 9 (60%) patients having active psychiatric symptoms at time of PSG. Six (40%) Psych-U patients had previously received antidepressant medications, with discontinuance of medications by a mean of 18.1 months prior to PSG, and none were taking antidepressant medications at time of PSG. PHQ-9 scores within 6 months of PSG for each group were as follows: Psych-RBD (13.0 ± 8.3), Psych-T (11.9 ± 4.2), Psych-U (15.5 ± 5.2) and did not differ significantly apart from a trend between Psych-T and Psych-U patients (P = 0.08).

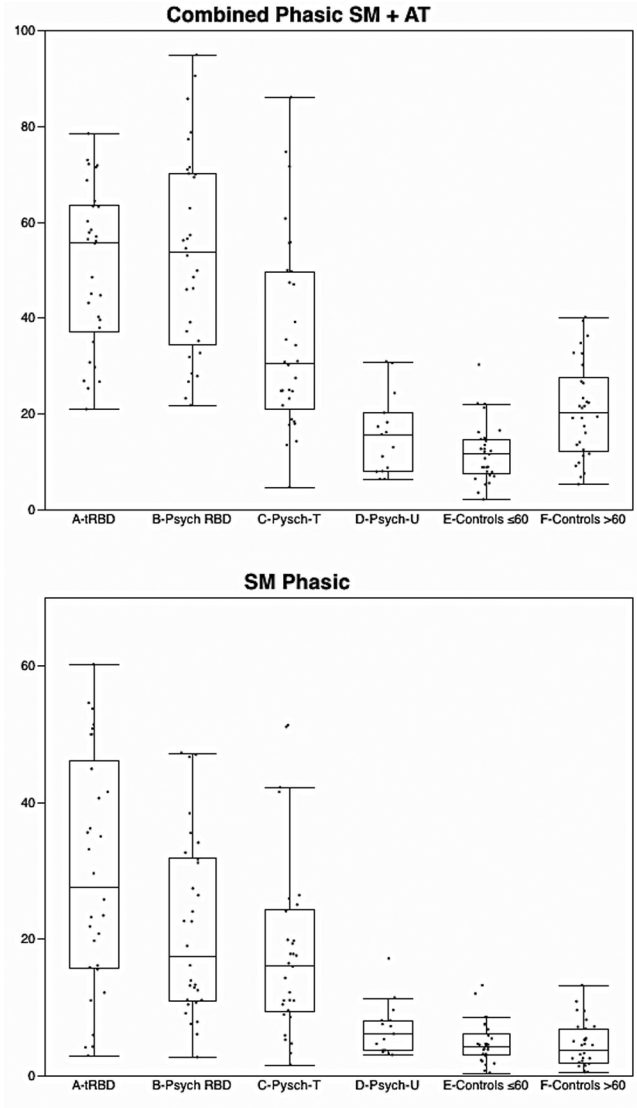

Figure S1—Comparison of combined phasic SM + AT and phasic SM between groups.

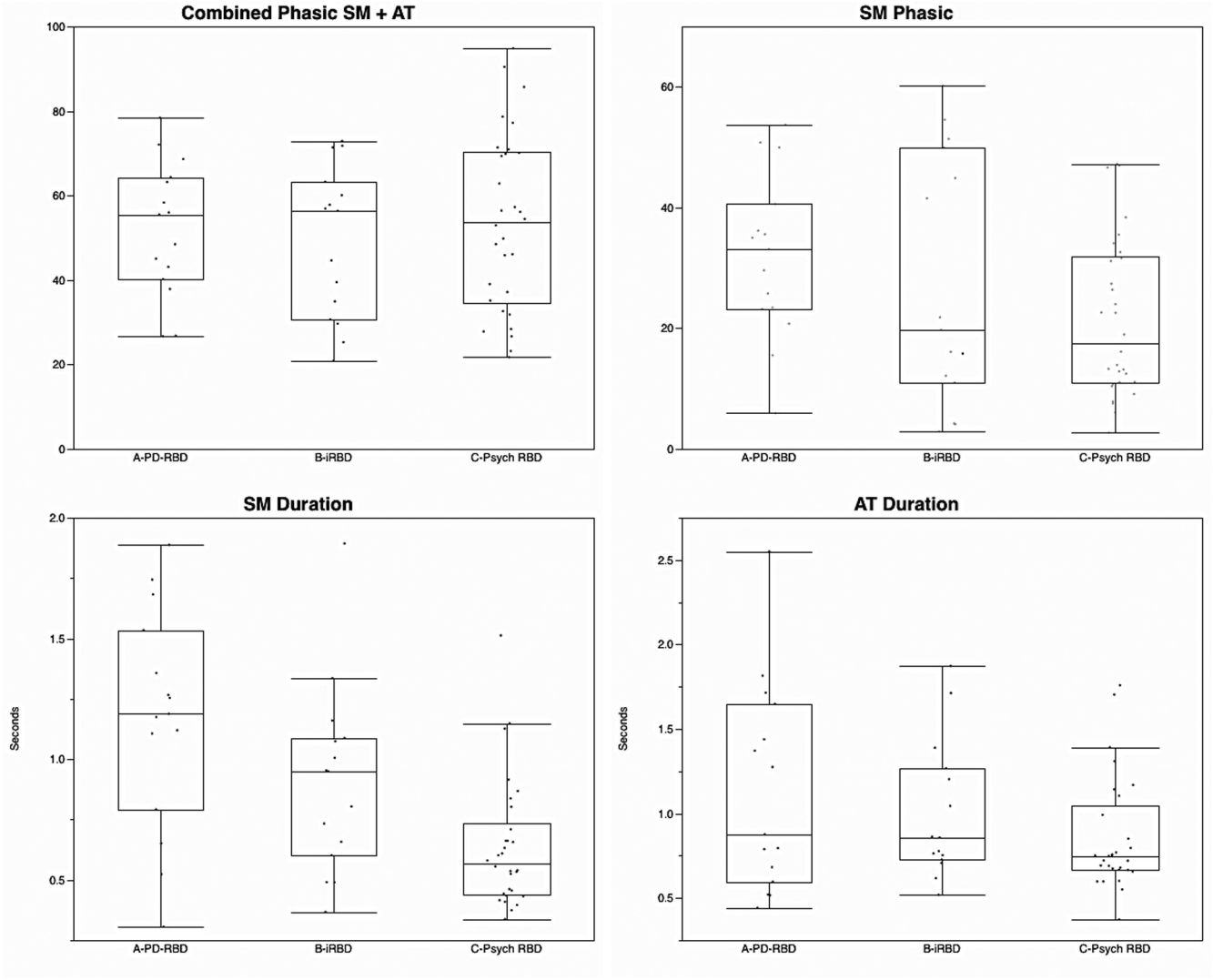

Figure S2—Combined phasic SM + AT, phasic SM muscle activity, and SM and AT duration comparison between RBD subgroups.

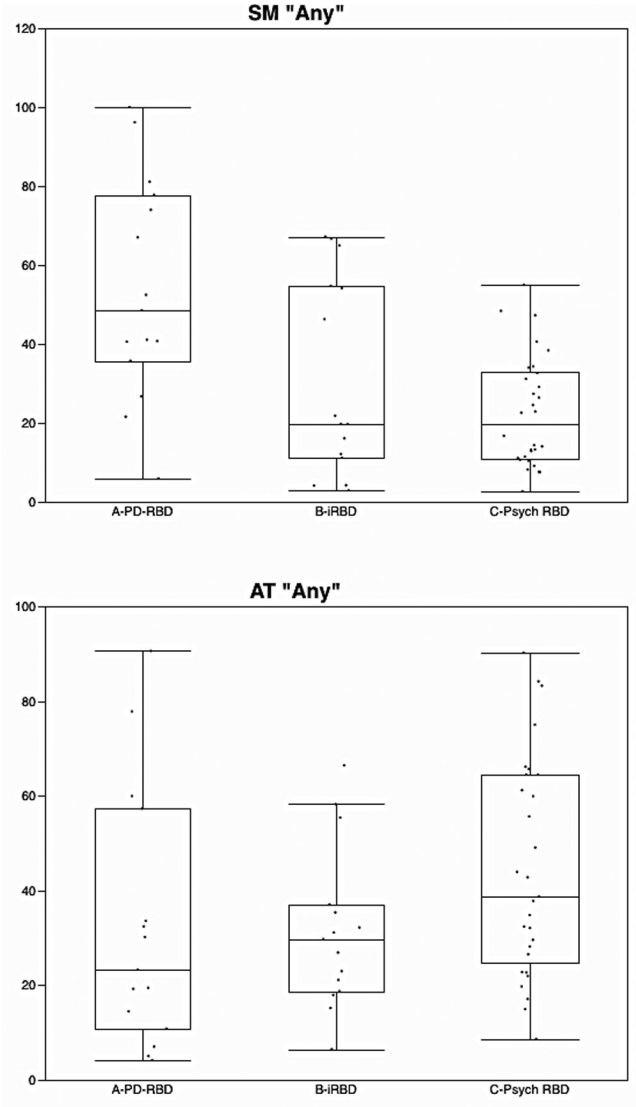

Figure S3—"Any" SM and "any" AT comparisons between RBD subgroups.