**Sertraline and rapid eye movement sleep without atonia: an 8-week, open-label study in depressed patients**

Bin Zhang 1 \*, MD, PhD; Yanli Hao 2 \*, MD, PhD; Fujun Jia 1, MD, PhD; Yi Tang 1, MD, PhD; Xueli Li 1, Mphil; Wuhan Liu 1, Mr; Isabelle Arnulf a \*, MD, PhD 3

\* These authors contributed equally to this work

1 Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangdong Mental Health Centre, Guangzhou 510120, China.

2 Department of Human Anatomy, Guang Zhou Medical University, Guangzhou 510182, China

3 Sleep Disorder Unit, Pitié-Salpêtrière Hospital, Centre de Recherche de l'Institut du Cerveau et de la Moëlle épinière - Pierre and Marie Curie University; Inserm UMR\_S 975; CNRS UMR 7225, Paris, France

**Word Count:** 4480 words (main body) with 2 figures and 4 tables

**Article submitted to**: Prog Neuropsychopharmacol Biol Psychiatry

**Version**: 1

**Corresponding author**: Bin Zhang, MD, PhD, Guang Dong General Hospital, Guang Dong Academy of Medical Science, Guang Dong Mental Health Center, No 123, Hui Fu Xi Road, 510120, Guang Zhou, China.

**Tel.**: +86-20-81888553, **Fax**: +86-20-81862664, **E-mail:** [zhang73bin@hotmail.com](mailto:zhang73bin@hotmail.com)

**Abstract**

Previous studies have reported that selective serotonin reuptake inhibitors (SSRIs) may induce or exacerbate rapid eye movement (REM) sleep without atonia (RSWA) and increase the risk of developing REM sleep behavior disorder (RBD). However, most of these studies were retrospective and cross-sectional in nature with small sample sizes, and they included data on a mixture of SSRIs. Because different SSRIs have different pharmacological profiles, the specific effects of individual SSRIs on RSWA should be studied. In an 8-week, open-label trial of sertraline in depressed patients (n=31), patients were administered 50 mg of sertraline at 8 am on the 1st day; this dose was subsequently titrated up to a maximum of 200 mg/day. All patients underwent repeated video-polysomnography (vPSG) (at baseline and on days 1, 14, 28, and 56). Both tonic (submental) and phasic (submental and anterior tibialis) RSWA were visually assessed. Tonic RSWA increased from 3.2±1.8% at baseline to 5.1±2.3% on the 1st day on sertraline and to 10.4±2.7% on the 14th day; this value then remained stable until the 56th day.A similar profile was observed for phasic RSWA as well as for the proportion of patients with abnormal phasic anterior tibialis RSWA. No RBD was observed. The increase in tonic muscle tone during REM sleep over time was correlated with reduced REM sleep latency (*r*=0.56, p=0.004), PLMI (*r* =0.39, p=0.047) and improvement in depression (HRSD score, *r* =-0.43, p=0.03). The increases in phasic submental (*r* =-0.51, p=0.02) and anterior tibialis (*r*=0.41, p=0.04) RSWA were correlated with decreased REM sleep latency and were not correlated with patient demographics or clinical characteristics. Sertraline induced or exacerbated RSWA but did not induce RBD. Compared with idiopathic RBD, sertraline-related RSWA had specific characteristics correlated with REM latency and no predominance of male gender or older age, suggesting that RSWA and idiopathic RBD might involve different mechanisms.

**Key words:** rapid eye movement (REM) sleep without atonia (RSWA); REM sleep behavior disorder (RBD); sertraline; depressed patient

**Clinical Trial Registry**: An 8-week, open-label study to evaluate the effect of sertraline on the polysomnographic results of depressive patients with insomnia ([http://clinicaltrials.gov/ct2/show/NCT01032434](http:/--clinicaltrials.gov-ct2-show-NCT01032434)). Registry identifier: NCT01032434.

**Abbreviations:** 5-HT: serotonin; AASM-2007: American Academy of Sleep Medicine 2007 version; AHI: apnea-hypopnea index; AI: arousal index; ANOVA: one-way analysis of variance; BMI: body mass index; CT: computed tomography; DA: dopaminergic; DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition; ECG: electrocardiograph; EMG: electromyogram; EOG: electrooculography; ESS: Epworth sleepiness scale; HRSD: Hamilton rating scale for depression; MSLT: multiple sleep latency test; OSA: obstructive sleep apnea; OCD: obsessive-compulsive disorder; PD: Parkinson’s disease; PLMI: peri­odic limb movement index; PLMS: periodic limb movement during sleep; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; REM: rapid eye movement; RSWA: REM sleep without atonia; RLS: restless legs syndrome; SCID-2: the second version of the Structured Clinical Interview for DSM-IV Axis I Disorders; SE: sleep efficiency; SL: sleep latency; SSRI: selective serotonin reuptake inhibitors; TESS-S: treatment emergent symptom scale-severity; TESS-T: treatment emergent symptom scale-treatment; TRT: total recording time; TST: total sleep time; vPSG: video-polysomnography; WASO: wake after sleep onset.

**1. INTRODUCTION**

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the loss of normal atonia during REM sleep and dream-enacting behavior [[1](#_ENREF_1), [2](#_ENREF_2)]. Idiopathic RBD is a male-predominant disorder that usually emerges after 50 years of age [[1](#_ENREF_1), [2](#_ENREF_2)] and is frequently described before the onset and during the course of synucleinopathies, including Parkinson’s disease (PD), multiple system atrophy, and dementia with Lewy bodies [[3](#_ENREF_3)]. RBD is strongly associated with an abnormal increase in phasic and tonic muscle tone during REM sleep, a condition termed REM sleep without atonia (RSWA). Whether RSWA is a sufficient and necessary condition for the emergence of RBD remains unknown; however, some cases of RSWA have been documented to later become full-blown RBD [[2](#_ENREF_2), [4](#_ENREF_4), [5](#_ENREF_5)]. According to the International Classification of Sleep Disorders, Second Edition (ICSD-2), the criteria for RBD include the appearance of elevated submental electromyogram (EMG) tone and/or excessive phasic submental or anterior tibialis EMG activity during REM, combined with sleep-related injurious, potentially injurious, or abnormal REM sleep behaviors documented during polysomnographic (PSG) monitoring. On the other hand, the criteria for subclinical RBD only include REM sleep PSG abnormalities and do not include a clinical history of RBD [[2](#_ENREF_2)]. An “abnormal amount” of RSWA (as a percentage of REM sleep) has been determined by different methods, based on measures in normal subjects and in patients with idiopathic RBD. Using the American Academy of Sleep Medicine 2007 version (AASM-2007) criteria for measuring tonic and phasic muscle activity [[6](#_ENREF_6)], 18% of REM sleep time in which any tonic or phasic muscle activity lasted 3 seconds in an epoch was characterized as RBD in a series of 15 patients with idiopathic RBD, 15 patients with RBD associated with Parkinson’s disease and 30 matched controls [[7](#_ENREF_7)]. Gagnon argued that a similar cutoff (greater than 20%) of tonic submental muscle activity during REM sleep was a reasonable threshold for defining muscle activity as excessive or potentially pathological [[4](#_ENREF_4)]. In another study that included 80 patients with idiopathic RBD, tonic submental muscle activity accounting for more than 30% of the total REM sleep time and phasic submental muscle activity accounting for more than 15% of the total REM sleep time were considered optimal cut-offs for the diagnosis of idiopathic RBD in normal controls [[8](#_ENREF_8)].

In view of the clinical lore and a small number of published studies, antidepressants may induce or exacerbate RSWA and increase the risk of developing RBD or subclinical RBD [[9-15](#_ENREF_9)]. A recent clinical epidemiological study on parasomnia in psychiatric outpatientsrevealed that the lifetime and 1-year prevalences of RBD and/or subclinical RBD among psychiatric outpatients were 5.8% and 3.8%, respectively. These prevalences are ten times higher than the prevalence of RBD in the general population. Further, compared with RBD patients in the general population, psychiatric outpatients with RBD were younger in age, were predominantly female, were more likely to be using antidepressants, and had fewer concurrent neurodegenerative diseases [[16](#_ENREF_16)]. In recent decades, selective serotonin (5-HT) reuptake inhibitors (SSRIs) have become first-line antidepressants, and they are suspected to exert effects on RSWA based on basic knowledge of muscle atonia during REM sleep. The normal loss of muscle tone during REM sleep occurs due to two mechanisms: one is passive, while the other is active. During non-REM sleep, the firing of serotonergic neurons descending to the nuclei of the cranial nerves and to the lower motor neurons is reduced, leading to disfacilitation; during REM sleep, the firing of serotonergic neurons ceases [[17](#_ENREF_17)]. As a consequence, muscle tone is reduced from light to deep non-REM sleep as well as during REM sleep, leading to hypotonia (postural muscle tone is reduced but still present). In addition to this passive mechanism, active paralysis of postural muscle tone (termed atonia) occurs specifically during REM sleep, and the postsynaptic lower motor neurons are eventually blocked via the cholinergic-glutaminergic-glycinergic pathway. In humans, drugs that stimulate the serotonin system (e.g., fluoxetine, paroxetine, and venlafaxine) and those that block acetylcholine transmission (tricyclics such as clomipramine) can induce RSWA and/or RBD, possibly due to their prevention of normal sleep-related hypotonia (serotoninergic drugs) or normal REM sleep-related atonia (anticholinergics) [[5](#_ENREF_5)]. Previous studies have suggested that compared with controls, SSRIs could intensify dreaming [[18](#_ENREF_18)], increase RSWA, and possibly increase the risk of developing RBD [[4](#_ENREF_4), [9](#_ENREF_9), [11](#_ENREF_11), [12](#_ENREF_12), [15](#_ENREF_15)]. However, most of these studies were retrospective, cross-sectional studies with small sample sizes, and the subjects received a mixture of SSRIs. It is well known that all SSRIs do not have the same pharmacological profiles; thus, different SSRIs might have different tendencies to induce RSWA. With this in mind, the specific effects of individual SSRIs on RSWA should be studied. The main purpose of this study was to characterize the effect of sertraline on RSWA in depressed patients in an 8-week clinical trial using repeated video-polysomnography (vPSG) assessment.

**2. METHODS**

**2.1. Patients and Study Design**

The study protocol was approved by the Independent Ethics Committee (IEC) of Guangdong Provincial Mental Health Center. Written informed consent was obtained from each patient prior to participation.

All patients were enrolled from the inpatient population of Guangdong Provincial Mental Health Center. If a patient was diagnosed with a single or recurrent type of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) upon admission, the specific diagnosis of the patient was determined by one of the authors (BZ) using the second version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-2) [[19](#_ENREF_19)]. None of the patients included in the study fulfilled any other current or lifetime diagnostic criteria for DSM-IV Axis I disorders. The patients were males and females aged 18 to 65 years with Hamilton Rating Scale for Depression (HRSD) scores ≥ 18 and HRSD-sleep disturbance factor scores ≥ 3 [[20](#_ENREF_20)], reflecting a moderate-to-high level of illness severity (depression and insomnia). Possible concurrent medical disorders were ruled out by a thorough medical examination and laboratory tests (electroencephalograph [EEG], electrocardiograph [ECG], computed tomography [CT], and blood and urine analyses). Patients were excluded if they experienced serious adverse events while taking sertraline, if they currently had significant suicidal or homicidal tendencies (either based on their medical histories or HRSD scores ≥ 4 on item 3, “suicide”), if they were currently pregnant or breastfeeding, if they were currently shift workers, if they currently had a significant sleep disorder (e.g., RBD, obstructive sleep apnea [OSA], periodic limb movement during sleep [PLMS], restless legs syndrome [RLS]), or if they had a serious medical condition in the previous 3 months.

After a 7-day washout phase for patients who had received medication in the previous 3 months and a subsequent 2-night baseline vPSG assessment, the patients received sertraline for 8 weeks. At baseline and during 4 visits (days 1, 14, 28, and 56), the patients were assessed by the HRSD (which measures clinical improvement), Treatment Emergent Symptom Scale (TESS-Severity [TESS-S] and TESS-Treatment [TESS-T], which measure side effects) [[21](#_ENREF_21)], Epworth Sleepiness Scale (ESS, which measures sleepiness) [[22](#_ENREF_22)], and Pittsburgh Sleep Quality Index (PSQI, which measures sleep quality) [[23](#_ENREF_23)]. On the 1st day, 50 mg of sertraline was administered at 8 am. Then, the dose was titrated according to the clinical efficacy and side effects; the maximum dosage was 200 mg/day. Similar to the 1st day, sertraline was usually administered at 8 am throughout the clinical trial, except for cases in which the patient was significantly sedated or was receiving a dosage of 200 mg/day. Sertraline was administered at 8 pm for patients who were significantly sedated and twice daily (8 am and 4 pm) for patients receiving 200 mg/day. Concomitant use of central nervous system medications during the trial, especially benzodiazepines and sedatives, was prohibited.

**2.2. Video-Polysomnographic Study**

At baseline, the sleep laboratory test consisted of two consecutive nocturnal vPSG assessments followed by a daytime Multiple Sleep Latency Test (MSLT). Because of the first night effect, the first night was regarded as an adaptation night [[24](#_ENREF_24)]. Measurements of the vPSG variables on the second night and the MSLT result obtained on the third day were defined as baseline data. Because the MSLT was conducted during the day, the third night was not suitable for vPSG assessment. Thus, the vPSG assessment for the 1st day of drug treatment was initiated on the 4th night, and 50 mg of sertraline was administered at 8 am on the 4th day. The acute effects of sertraline on RSWA and sleep architecture were evaluated during the 1st day vPSG assessment, which was not conducted in most previous studies. Further, these patients were assessed by vPSG in three subsequent visits (days 14, 28, and 56). On each of the subsequent 3 visits during the 8-week trial, the patients were assessed with one night of PSG followed by the MSLT.

The nocturnal vPSG included the following basic recordings: standard EEG (F4-A1, C4-A1, O2-A1, C3-A2), electrooculography (EOG: LE-A2, RE-A1), submental electromyography (EMG), bilateral leg EMG (anterior tibialis muscles), ECG, nasal airflow pressure, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, breathing sound, and body posi­tion. All the sleep variables were derived from visual scoring of the recordings using standard criteria and were divided into two groups: sleep continuity indices and sleep architecture indices. Sleep continuity indices included the total recording time (TRT, “lights out” to “lights on” in minutes), total sleep time (TST), sleep efficiency (SE, the TST divided by the TRT), sleep latency (SL, “lights out” to the first epoch of any sleep in minutes), REM latency (sleep onset to the first epoch in the REM stage in minutes), wake after sleep onset (WASO, stage W during the TRT, minus the SL, in minutes) and arousal index (AI: the number of arousals divided by the TST). The sleep architecture indices included the percentages of time spent in each stage (the time in stage 1, stage 2, stage 3, and the REM stage divided by the TST) [[6](#_ENREF_6)]. The 5-nap MSLT was performed according to the standard recommendations to determine the mean SL [[25](#_ENREF_25)]. All computerized sleep data were further edited by an experienced blinded PSG technologist. Sleep stages, respiratory events, and periodic limb movements were scored ac­cording to the AASM-2007 criteria at 30-second intervals [[6](#_ENREF_6)]; however, REM sleep was scored according to a modified method [[26](#_ENREF_26)]. In this method, the first epoch in which rapid eye movement and a low-amplitude, mixed-frequency EEG were observed was used to determine the onset of an REM sleep period. The termination of an REM sleep period was identified either by the occurrence of specific EEG features (K complexes, sleep spindles, or EEG signs of arousal) or by the absence of rapid eye movement and low-amplitude, mixed-frequency EEG for 180 seconds [[26](#_ENREF_26)]. Subjects with significant PLMS (PLM index [PLMI] ≥ 15) or OSA (apnea-hypopnea index [AHI] ≥ 15) on the first night of the baseline vPSG assessment were excluded from the study. The video recordings were also examined by the sleep technician to identify any abnormal movement, behavior and/or vocalization during REM sleep.

**2.3. Tonic and Phasic EMG Activities during REM Sleep**

According to the AASM-2007 criteria, tonic muscle activity during REM sleep was defined as an epoch of REM sleep in which the submental EMG amplitude was greater than the minimum amplitude demonstrated in NREM sleep for at least 50% of the duration of the epoch. Phasic muscle activity during REM sleep was defined by following criteria: in a 30-second epoch of REM sleep divided into 10 sequential, 3-second mini-epochs, at least 5 (50%) of the mini-epochs contained bursts of transient muscle activity. These excessive bursts of transient muscle activity were 0.1-5.0 seconds in duration, and their amplitudes were at least 4 times higher than that of the background EMG activity. Tonic muscle activity was only scored in submental EMGs, while phasic muscle activity was scored in both submental and anterior tibialis EMGs [[6](#_ENREF_6)]. To exclude the disruption of REM sleep by physiologic events, REM epochs in which EEG arousal, a snore artifact in the submental EMG, PLMS, or hypopnea was present were eliminated from further analyses [[11](#_ENREF_11)]. Finally, the numbers of 30-second epochs without atonia, with phasic submental muscle activity, and with phasic anterior tibialis muscle activity were computed separately for each REM period. The number of epochs was then divided separately by the total number of epochs of REM sleep to obtain the exact percentages of phasic and tonic RSWA. In this study, abnormal tonic and abnormal phasic RSWA were defined as being greater than 18% [[7](#_ENREF_7)].

**2.4. Data Analysis**

The data are presented as the mean ± standard deviation for continuous variables and as numbers or percentages for categorical variables. Parametric and non-parametric data were compared using the independent *t*-test and Mann-Whitney U test, respectively (2 groups). One-way analysis of variance (ANOVA) and Kruskal Wallis tests were performed to compare parametric and non-parametric data (≥ 3 groups). Significant effects from ANOVAs were further examined with post-hoc tests using the least significant difference method with a Bonferroni correction for multiple comparisons. Mann-Whitney U tests with adjusted P-values (significant at P=0.005) were used for multiple pairwise comparisons. The chi-square test was used to analyze differences in categorical variables. Correlations between changes in the clinical and polysomnographic measures and changes in tonic and phasic EMG activities during REM sleep were determined using the Pearson test. A two-sided 5% level of significance was applied. All statistical procedures were performed using the Statistical Package for the Social Sciences 17.0 for Windows (SPSS, Inc., Chicago, IL).

**3. RESULTS**

**3.1. Recruitment Process**

Fifty-five patients with major depressive disorder were initially enrolled in this study. Seventeen patients were excluded for the following reasons: 11 patients had other comorbid DSM-IV Axis I disorders, and 6 patients did not have moderate or severe insomnia (HRSD-sleep disturbance score <3). Among the 38 remaining patients, 11 patients who were not taking any medication directly underwent the baseline vPSG assessment. During the first night of baseline vPSG assessment, 7 patients were excluded for the following reasons: 3 patients were diagnosed with significant OSA, and 4 patients were diagnosed with significant PLMS. Therefore, a total of 31 depressed patients with insomnia were enrolled in this study. Nine patients discontinued treatment during the trial period. Of these 9, 5 patients discontinued treatment before the 14th day (2 due to worsening symptoms and combinations with other drugs, 1 due to a gastrointestinal side effect, 1 due to emerging psychotic symptoms requiring the addition of antipsychotic drugs, and 1 due to refusal to participate in further sleep tests). One patient discontinued between the 14th and 28th day due to a revised diagnosis of bipolar disorder, and 3 patients discontinued between the 28th and 56th day (1 due to a revised diagnosis of OCD and 2 due to refusal to participate in further sleep tests). Finally, 22 patients completed this trial. The recruitment process is illustrated in Figure 1.

-------------------------------------

Insert Figure 1

--------------------------------------

**3.2. Demographic and Clinical Characteristics**

The thirty-one patients were predominantly young (32.7±9.2 years old) and female (61.3%). Their demographic and clinical characteristics are presented in Table 1.

-------------------------------------

Insert Table 1

--------------------------------------

**3.3. Clinical Assessment**

Table 2 shows selected clinical and polysomnographic measures. The mean daily sertraline doses were 126.9±25.4 (100-150) mg on the 14th day, 144.0±30.0 (100-200) mg on the 28th day, and 134.1±28.4 (100-200) mg on the 56th day. Only a few patients received a sertraline dose of 200 mg/day (2 patients on the 28th day and 1 patient on the 56th day); sertraline was administered twice daily to these patients (100 mg at 8 am and 100 mg at 4 pm). Further, sertraline was not administered to any of the patients at night for sedation. Only limited side effects (TESS) were observed during the 8-week trial. The HRSD scores began to improve on the 14th day of treatment. The HRSD-sleep disturbance scores were significantly decreased after the 28th day. The PSQI and ESS scores decreased gradually during this trial; on the 14th, 28th, and 56th days, the scores of both questionnaires were significantly lower than those at baseline. No patient reported any violent, enacted dreams at home during the study that could indicate clinical RBD.

**3.4. Polysomnographic Assessment**

There were no significant differences in TRTs during the trial. From the 14th day onward, the TSTs and SEs became longer and higher, respectively, compared with those at baseline or on the 1st day. From the 14th day onward, the SL and WASO scores decreased significantly, and the SL scores reached a normal range (<30 minutes) after the 14th day. The AI reached the highest level on the 1st day and was decreased at subsequent visits. There were no significant differences between baseline and the last 3 visits. The percentage of stage 1 sleep decreased during the trial; it was significantly lower on the 28th and 56th days than on the 1st day and at baseline. The percentage of stage 2 sleep remained stable throughout the trial. The percentage of stage 3 sleep increased gradually and was greater than 10% during the last 3 visits compared with baseline and the 1st day. Compared with baseline, the REM latencies were significantly prolonged on the 1st day and decreased gradually during the treatment. However, the REM latencies were longer during each of the visits than at baseline. No significant differences were observed in the percentages of REM sleep throughout the trial. Compared with their levels at baseline, the PLMI scores increased immediately after sertraline administration on the 1st day. From the 14th day onward, the PLMI scores continued to increase and were significantly higher during the last 3 visits compared with baseline or the 1st day. The AHI scores remained stable throughout the trial. During the daytime assessment (MSLT), the mean SL remained stable during the trial (Table 2).

-------------------------------------

Insert Table 2

--------------------------------------

**3.5. Tonic and Phasic** **RSWA during REM Sleep**

Tonic and phasic RSWA increased non-significantly from baseline to the first night after sertraline treatment. Then, from the 14th day onward, both tonic (submental) and phasic (submental and anterior tibialis) RSWA increased and became significantly higher in the last 3 visits compared with baseline and the 1st day. There were no further differences between the last three measurements, which were taken on the 14th, 28th and 56th days. At the endpoint of this clinical trial (the 56th day), tonic RSWA reached 12.0%±4.3%, phasic submental RSWA reached 11.4%±4.2%, and phasic anterior tibialis RSWA reached 15.1%±6.6%. According to the cutoff for abnormal tonic and phasic RSWA of >18%, the proportion of patients with abnormal phasic anterior tibialis RSWA was significantly higher in the last 3 visits than at baseline and on the 1st day, while the proportion of patients with abnormal tonic and phasic submental RSWA remained stable throughout the trial (Table 3 & Figure 2 a-c). Notably, no abnormal movement, behavior or vocalization was observed during REM sleep on the video recordings.

-------------------------------------

Insert Table 3

--------------------------------------

-------------------------------------

Insert Figure 2 a-c

--------------------------------------

Because recurrent major depression (defined as up to 7 episodes in this study) should share some biological and clinical features with bipolar spectrum disorders, we compared tonic and phasic RSWA between single depression and recurrent depression. No significant difference was shown between the two groups during the trial (Table 4).

-------------------------------------

Insert Table 4

--------------------------------------

We calculated the changes in clinical and polysomnographic measures and tonic and phasic RSWA from endpoint to baseline ([value at the endpoint - value at baseline] / value at baseline × 100%). The change in tonic RSWA score (216.4%±53.9%) was positively correlated with the changes in REM latency (37.0%±22.7%) (*r*=0.56, p=0.004) and PLMI (129.4%±49.8%) (*r*=0.39, p=0.047) scores and was negatively correlated with the change in HRSD score (-68.6%±-21.3%) (*r* =-0.43, p=0.03). The changes in phasic submental (202.9%±87.1%) (*r* =-0.51, p=0.02) and anterior tibialis (151.3%±61.5%) (*r*=0.41, p=0.04) RSWA scores were positively correlated with the changes in the REM latency score. The amount of RSWA did not correlate with the dosage of sertraline. On the other hand, no significant correlations were observed between the changes in RSWA scores and continuous demographic and clinical characteristics,such as age at baseline, and the changes in RSWA scores were not significantly different among categorical demographic and clinical characteristics,such as gender, at baseline.

**4. DISCUSSION**

In the current study, sertraline exacerbated RSWA but did not induce RBD. From the 14th day onward, tonic and phasic RSWA and the proportion of patients with abnormal (>18%) phasic anterior tibialis RSWA were significantly increased compared with their levels at baseline and on the 1st day; subsequently, these levels remained stable. To some extent, the phasic RSWA results were inconsistent with those described by Winkelman and James. In that study, only tonic RSWA was significantly altered in subjects taking serotonergic antidepressants compared with normal controls; phasic (submental and anterior tibialis) RSWA levels did not change significantly [[11](#_ENREF_11)]. This difference might be due to the small sample size (n=15) and mixture of antidepressants used in the study performed by Winkelman and James. Indeed, two subjects were taking bupropion (200 mg/day), which might have diminished RSWA [[11](#_ENREF_11)]. Further, if a cutoff of abnormal tonic RSWA greater than 20% was used [[4](#_ENREF_4)], the proportion of patients with abnormal tonic RSWA in the current study was similar to that in two previous studies (current study: 4.5% [1/21], Winkelman and James: 13.3% [2/15], Zhang et al.: 14.3% [3/21]; χ2=1.44, *p*=0.09) [[11](#_ENREF_11), [12](#_ENREF_12)]. In summary, these results support the notion that SSRIs can induce or exacerbate RSWA, especially phasic anterior tibialis RSWA. Most abnormal sleep behaviors observed in RBD have been reported to correspond to movements of the limbs [[27](#_ENREF_27)]. However, no patients reported abnormal behaviors related to RBD in the current study. This result might have occurred due to the following reasons: first, some subtle behaviors might have been ignored by patients and their bed partners and may not have been detected in the videos; second, because the clinical significance of RSWA is still unclear, RSWA might simply be an unusual PSG finding and may not develop into overt clinical RBD; third, it is possible that RSWA can develop into RBD, but this did not occur in the current study due to the small sample size. Further, RSWA might be necessary (permissive) but not sufficient (active) to promote RBD. One might also imagine that higher levels of RSWA are necessary for RBD-associated dreaming behavior to occur. Moreover, an average of 39% of patients with idiopathic and PD-associated RBD experienced tonic RSWA in a previous study [[28](#_ENREF_28)], which is greater than the 12% found in our study. Additionally, RSWA was more common in patients with multiple systemic atrophy than in those with PD or idiopathic RBD; however, the severity of the corresponding behaviors was milder [[28](#_ENREF_28)]. This suggests that RBD and RSWA are strongly, but not linearly, linked.

REM sleep suppression (e.g., increased REM latency and decreased REM sleep duration) is characteristic of antidepressants and is strongly linked to increased serotoninergic tone [[29](#_ENREF_29), [30](#_ENREF_30)]. In this study, the reduction in REM latency scores was positively correlated with the reduction in both tonic and phasic RSWA. This result is consistent with the study of Winkelman and James, in which the extent of prolonged REM latency was suggested to serve as a marker of the degree of RSWA [[11](#_ENREF_11)]. Because the correlation between REM latency and RSWA has never been reported for patients with idiopathic RBD or neurodegenerative disease-related RBD in previous studies, the mechanisms underlying RSWA are likely different between idiopathic RBD and antidepressant-related RBD. This notion might be supported by certain risk factors (male gender and older age) for idiopathic RBD that were not found in this study or previous studies [[4](#_ENREF_4), [11](#_ENREF_11), [12](#_ENREF_12), [15](#_ENREF_15), [31](#_ENREF_31)]. Unlike the effects observed with most antidepressants, the percentage of REM sleep was stable throughout this trial. This phenomenon was also reported by another study that tested the effects of sertraline on sleep architecture [[32](#_ENREF_32)], suggesting that sertraline has less of a suppressive effect on the duration of REM sleep than most antidepressants. In addition, the percentages of REM sleep after sertraline administration were somewhat lower than those at baseline; however, none of these differences were significant, possibly due to the small sample size in this study. In some previous case reports, antidepressant-related RBD disappeared immediately following the discontinuation of antidepressant use [[10](#_ENREF_10)]. In this study, the reduction in tonic RSWA scores was also significantly correlated with PLMI and HRSD scores. As some previous studies suggested, similar to the antidepressant effectiveness (HRSD) scores, the extent to which the PLMI scores increased might reflect the pharmacological effect of sertraline on depression-related 5-HT and/or dopaminergic (DA) neurotransmission [[33](#_ENREF_33), [34](#_ENREF_34)]. Thus, RSWA, PLMS, REM latency, and HRSD scores might be involved in the mechanisms of 5-HT and/or DA neurotransmission to some extent; this likely explains why all of these scores were correlated.

For clinicians, the central question remains whether sertraline-induced RSWA is associated with clinical repercussions. According to subjective sleep and mood parameters and the objective sleep quality and continuity observed via PSG, sertraline-induced RSWA did not cause significant clinical disturbance in the current clinical trial. In other words, the potential adverse effects of sertraline-induced RSWA might be outweighed by the significant improvements in mood and sleep parameters caused by sertraline. Notably, depression is a common mental disorder with a prevalence of 10-20% [[35](#_ENREF_35)], and most depressive patients are currently treated with antidepressants, especially SSRIs. Thus, SSRI-related RSWA should be considered a serious public health problem in depressed patients because it might represent a potential risk factor for RBD. However, SSRI-related RBD is ignored by most physicians. If patients use antidepressants and report abnormal movements, behaviors and vocalizations during sleep, vPSG should routinely be used to assess and accurately estimate RSWA.

Some caution should be exercised in interpreting the results reported here. First, a placebo control group was not used in this study. Second, the sample size in this study was small.

**5. CONCLUSIONS**

In the current study, sertraline exacerbated RSWA but did not induce RBD. Unlike idiopathic RBD, sertraline-related RSWA was correlated with REM latency and was not predominantly associated with male gender or older age, suggesting that different mechanisms are involved in idiopathic RBD and sertraline-related RSWA. Further, sertraline-induced RSWA did not cause significant clinical disturbance, and overt RBD was not observed in the current study. Despite these findings, the increased prevalence of RBD in patients using antidepressants compared with than that in the general population indicates that antidepressant-related RSWA is a potential public health issue for depressed patients.

**Acknowledgments**

The work was supported by an Investigator-Initiated Research (IIR) Program grant from Pfizer Pharma (Study Code: WS458774) and a grant from the National Natural Science Foundation of China (Grant No: 30800303), both awarded to Dr. Bin Zhang.

**REFERENCES**

1. Schenck CH, Mahowald MW (2002) REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 25:120-138

2. AASM (2005) International classification of sleep disorders: Diagnostic and coding manual. 2nd edn. American Academy of Sleep Medicine, Westchester, Illinois

3. Iranzo A, Santamaria J, Tolosa E (2009) The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases. Sleep Med Rev 13:385-401. doi:10.1016/j.smrv.2008.11.003

4. Gagnon JF, Postuma RB, Montplaisir J (2006) Update on the pharmacology of REM sleep behavior disorder. Neurology 67:742-747. doi:10.1212/01.wnl.0000233926.47469.73

5. Arnulf I (2012) REM sleep behavior disorder: motor manifestations and pathophysiology. Mov Disord 27:677-689. doi:10.1002/mds.24957

6. Iber C A-IS, Cheeson A, and Quan SF for the academy of Sleep Medicine (2007) The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st edn. American Academy of Sleep Medicine, Westchester, Illinois

7. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, Ehrmann L, Sola N, Salamero M, Tolosa E, Poewe W, Santamaria J, Hogl B (2012) Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep 35:835-847. doi:10.5665/sleep.1886

8. Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, Rompre S, Paquet J (2010) Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 25:2044-2051. doi:10.1002/mds.23257

9. Schenck CH, Mahowald MW, Kim SW, O'Connor KA, Hurwitz TD (1992) Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep 15:226-235

10. Onofrj M, Luciano AL, Thomas A, Iacono D, D'Andreamatteo G (2003) Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology 60:113-115

11. Winkelman JW, James L (2004) Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 27:317-321

12. Zhang B, Li XL, Zhou P (2010) The effect of selective serotonin reuptake inhibitor on Electromyography of rapid eye movement sleep in depressive patient. Chin J Psychiatry 43:201-205

13. Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W (1976) Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. Acta Neurol Scand 54:71-87

14. Bental E, Lavie P, Sharf B (1979) Severe hypermotility during sleep in treatment of cataplexy with clomipramine. Isr J Med Sci 15:607-609

15. Hoque R, Chesson AL, Jr. (2010) Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 6:79-83

16. Lam SP, Fong SY, Ho CK, Yu MW, Wing YK (2008) Parasomnia among psychiatric outpatients: a clinical, epidemiologic, cross-sectional study. J Clin Psychiatry 69:1374-1382

17. Siegel JM (2006) The stuff dreams are made of: anatomical substrates of REM sleep. Nat Neurosci 9:721-722. doi:10.1038/nn0606-721

18. Pace-Schott EF, Gersh T, Silvestri R, Stickgold R, Salzman C, Hobson JA (2001) SSRI treatment suppresses dream recall frequency but increases subjective dream intensity in normal subjects. J Sleep Res 10:129-142

19. First MB SR, Williams JBW, Gibbon M, Williams JWB (1996) User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders: SCID-II Clinician Version. American Psychiatric Association,

20. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-62

21. Guy W (1976) ECDEU assessment manual for psychopharmacology, revised. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, Rockville, MD

22. Johns MW (1992) Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 15:376-381

23. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193-213

24. Agnew HW, Jr., Webb WB, Williams RL (1966) The first night effect: an EEG study of sleep. Psychophysiology 2:263-266

25. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S (1986) Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 9:519-524

26. Lapierre O, Montplaisir J (1992) Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 42:1371-1374

27. Schenck CH (2005) Clinical and research implications of a validated polysomnographic scoring method for REM sleep behavior disorder. Sleep 28:917-919

28. Iranzo A, Santamaria J, Rye DB, Valldeoriola F, Marti MJ, Munoz E, Vilaseca I, Tolosa E (2005) Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology 65:247-252. doi:10.1212/01.wnl.0000168864.97813.e0

29. Rush AJ, Giles DE, Jarrett RB, Feldman-Koffler F, Debus JR, Weissenburger J, Orsulak PJ, Roffwarg HP (1989) Reduced REM latency predicts response to tricyclic medication in depressed outpatients. Biol Psychiatry 26:61-72

30. McNamara P, Auerbach S, Johnson P, Harris E, Doros G (2010) Impact of REM sleep on distortions of self-concept, mood and memory in depressed/anxious participants. J Affect Disord 122:198-207. doi:10.1016/j.jad.2009.06.030

31. Nash JR, Wilson SJ, Potokar JP, Nutt DJ (2003) Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology 61:1161; author reply 1161

32. Jindal RD, Friedman ES, Berman SR, Fasiczka AL, Howland RH, Thase ME (2003) Effects of sertraline on sleep architecture in patients with depression. J Clin Psychopharmacol 23:540-548

33. Mendelson WB (1996) Are periodic leg movements associated with clinical sleep disturbance? Sleep 19:219-223

34. Kugaya A, Seneca NM, Snyder PJ, Williams SA, Malison RT, Baldwin RM, Seibyl JP, Innis RB (2003) Changes in human in vivo serotonin and dopamine transporter availabilities during chronic antidepressant administration. Neuropsychopharmacology 28:413-420. doi:10.1038/sj.npp.1300036

35. Murray DJ, Lopez AD (1996) The global burden of disease: a comprehensive assessment of morality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 Harvard School of Public Health, Cambridge, MA

**Table 1. Demographic and clinical characteristics of the depressed patients (n=31)**

|  |  |
| --- | --- |
|  | Mean ± standard deviation (range) or number |
| **Demographic characteristics** |  |
| Age (in years) | 32.7±9.2 (18-57) |
| Gender (males/females) | 12/19 |
| Marriage (married/single/divorced or widowed) | 17/9/5 |
| Occupation (full-time/part-time/no job or retired) | 16/7/8 |
| Education (university or above/middle school/primary school or below) | 11/16/4 |
| Residence (city/town/country) | 13/10/8 |
| **Clinical characteristics** |  |
| Age at onset (in years) | 23.9±8.0 (15-33) |
| BMI (kg/m2) | 23.2±6.2 (19.4-25.3) |
| Total duration of illness (years) | 9.7±10.4 (0-27) |
| Single type/recurrent type | 8/23 |
| Number of episodes of illness | 2.7±1.9 (1-7) |
| Length of the current illness (in weeks) | 6.6±5.0 (2-12) |

BMI: body mass index

**Table 2. Changes in clinical and polysomnographic measures during sertraline treatment of depressed patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Baseline  (n=31) | 1st day  (n=31) | 14th day  (n=26) | 28th day  (n=25) | 56th day  (n=22) | Statistics |
| Dosage (mg/day) |  | 50.0 a | 126.9±25.4 b | 144.0±30.0 b | 134.1±28.4b | F=103.90, P<0.001 |
| HRSD | 22.4±5.3 a | 23.1±5.3 a | 14.5±4.1 b | 9.7±2.6 b, c | 6.9±1.9 c | F=13.02, P<0.001 |
| HRSD-sleep disturbance factor | 4.1±3.3 a | 4.0±3.6 a | 3.5±3.1 a, b | 2.7±1.4 b | 2.5±1.5 b | KW=11.85, P=0.01 |
| TESS-S |  | 0.8±1.5 | 0.7±0.7 | 0.5±0.6 | 0.5±0.6 | KW =0.94, P=0.24 |
| TESS-T |  | 0.6±1.6 | 0.6±1.0 | 0.4±0.5 | 0.4±0.4 | KW =0.57, P=0.60 |
| PSQI | 13.5±6.2 a |  | 7.9±4.7 b | 6.3±3.4 b | 6.0±3.5 b | F=11.14, P<0.001 |
| ESS | 7.2±4.5 a |  | 5.3±3.9 b | 3.8±4.1 b | 4.0±3.5 b | KW=15.57, P=0.003 |
| TRT (min) | 504.7±71.9 | 492.2±86.0 | 507.4±77.2 | 511.1±59.4 | 499.5±63.4 | F=0.79, P=0.87 |
| TST (min) | 364.9±103.5 a | 347.5±114.3 a | 423.2±98.6 b | 440.1±103.7 b | 427.1±88.5 b | F=14.09, P=0.01 |
| SE (%) | 72.2±22.8 a | 70.6±29.1 a | 83.4±27.5 a, b | 86.1±31.3 b | 85.5±27.8 b | F=5.71, P=0.03 |
| SL (min) | 51.9±29.5 a | 46.6±23.5 a | 25.3±14.1 b | 21.7±11.8 b | 22.4±12.3 b | F=13.25, P<0.001 |
| REM latency (min) | 77.3±38.1 a | 134.3±82.9 b | 121.3±67.0 b | 109.4±73.1 b | 105.2±60.3 b | F=27.05, P<0.001 |
| WASO (min) | 87.9±31.9 a | 98.1±35.6 a | 58.9±19.8 b | 49.3±21.3 b | 50.0±17.7 b | F=35.93, P<0.001 |
| AI | 8.9±6.6 a | 13.8±7.2 b | 7.3±6.8 a | 6.4±4.8 a | 6.0±5.2 a | F =6.66, P=0.04 |
| % Stage 1 | 12.8±5.9 a | 15.2±6.6 a | 9.0±4.4 a, b | 7.0±1.7 b | 8.0±2.9 b | F=5.03, P=0.03 |
| % Stage 2 | 59.2±21.3 | 57.4±18.7 | 57.9±20.5 | 56.8±19.3 | 53.2±22.4 | F=1.73, P=0.34 |
| % Stage 3 | 3.2±1.5 a | 2.8±2.2 a | 12.9±5.8 b | 14.1±8.4 b | 16.0±7.9 b | F=12.06, P<0.001 |
| % REM sleep | 24.8±7.1 | 24.6±6.9 | 20.2±8.5 | 22.1±10.4 | 22.8±9.6 | F=0.86, P=0.72 |
| PLMI | 3.6±1.5 a | 5.1±3.9 b | 8.7±3.1 c | 8.3±3.7 c | 8.5±3.6 c | F=9.81, P=0.003 |
| AHI | 6.2±1.7 | 6.3±1.7 | 5.9±2.0 | 6.0±1.9 | 5.9±1.9 | F=0.24, P=0.27 |
| Mean SL of MSLT (min) | 16.4±11.3 | 14.7±8.9 | 15.2±9.5 | 17.1±10.4 | 14.6±9.0 | F=0.30, P=0.34 |

HRSD: Hamilton rating scale for depression, TESS-S: treatment emergent symptom scale-severity, TESS-T: treatment emergent symptom scale-treatment, PSQI: Pittsburgh sleep quality index, ESS: Epworth sleepiness scale, TRT: total recording time, TST: total sleep time, SE: sleep efficiency, SL: sleep latency, WASO: wake after sleep onset, AI: arousal index, REM: rapid eye movement, PLMI: peri­odic limb movement index, AHI: apnea-hypopnea index, MSLT: multiple sleep latency test.

a, b, c Groups with different superscript letters are significantly different.

F: ANOVA, KW: Kruskal-Wallis test.

**Table 3. Percentages of epochs with tonic and phasic RSWA during sertraline treatment of depressed patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Thirty-second Epoch | Baseline  (n=31) | 1st day  (n=31) | 14th day  (n=26) | 28th day  (n=25) | 56th day  (n=22) | Statistics |
| % Tonic RSWA | 3.2 ± 1.8 a | 5.1±2.3 a | 10.4±2.7 b | 10.2±2.5 b | 12.0±4.3 b | F=52.62, P<0.001 |
| *Patients with abnormal tonic RSWA (>18%), n (%)* | 0 | 0 | 0 | 0 | 2 (9.1%) | χ2=7.42, P=0.12 |
| % Phasic submental RSWA | 3.4 ± 1.9 a | 4.8±2.2 a | 9.4± 3.8 b | 10.3±3.9 b | 11.4±4.2 b | F=32.38, P<0.001 |
| *Patients with abnormal phasic submental RSWA (>18%), n (%)* | 0 | 0 | 0 | 1 (4.0%) | 0 | χ2=3.44, P=0.49 |
| % Phasic anterior tibialis RSWA | 6.2± 2.1 a | 8.2± 2.8 a | 14.6± 6.8 b | 15.5± 6.6 b | 15.1± 6.6 b | F=20.73, P<0.001 |
| *Patients with abnormal phasic anterior tibialis RSWA (>18%), n (%)* | 0 a | 0 a | 8 (30.8%) b | 9 (36%) b | 7 (31.8%) b | χ2=33.44, P<0.001 |

RSWA: REM sleep with atonia.

% Tonic and phasic RSWA: the numbers of 30-second epochs with tonic and phasic RSWA were divided separately by the total number of epochs of REM sleep.

F: ANOVA, χ2: chi-square test.

**Table 4. Percentages of epochs with tonic and phasic RSWA in patients with single and recurrent depression undergoing sertraline treatment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Single | Recurrent | Statistics |
| **Baseline** | n=8 | n=23 |  |
| % Tonic RSWA | 2.9 ± 1.9 | 3.3 ± 2.1 | MWU=1.82, P=0.39 |
| % Phasic submental RSWA | 3.6 ± 2.1 | 3.3 ± 1.9 | MWU=1.14, P=0.51 |
| % Phasic anterior tibialis RSWA | 6.0± 2.5 | 6.3±2.2 | T=1.37, P=0.47 |
| **1st day** | n=8 | n=23 |  |
| % Tonic RSWA | 5.2±2.6 | 5.1±2.4 | T=0.54, P=0.72 |
| % Phasic submental RSWA | 5.0±2.7 | 4.7±2.3 | T=0.77, P=0.63 |
| % Phasic anterior tibialis RSWA | 8.5± 3.3 | 8.0± 2.9 | T=1.32, P=0.46 |
| **14th day** | n=8 | n=18 |  |
| % Tonic RSWA | 9.8±3.2 | 10.7±3.0 | T=1.37, P=0.38 |
| % Phasic submental RSWA | 9.6± 4.0 | 9.3± 3.7 | T=0.90, P=0.53 |
| % Phasic anterior tibialis RSWA | 12.9± 5.7 | 14.8± 7.0 | T=1.76, P=0.27 |
| **28th day** | n=7 | n=18 |  |
| % Tonic RSWA | 12.1±3.9 | 10.0±2.7 | T=1.08, P=0.56 |
| % Phasic submental RSWA | 10.2±4.4 | 10.1±3.8 | T=0.27, P=0.68 |
| % Phasic anterior tibialis RSWA | 18.1± 8.2 | 15.1± 6.7 | F=1.50, P=0.47 |
| **56th day** | n=6 | n=16 |  |
| % Tonic RSWA | 13.9±5.7 | 11.6±4.7 | T=0.93, P=0.49 |
| % Phasic submental RSWA | 12.7±5.8 | 11.1±4.6 | T=0.46, P=0.67 |
| % Phasic anterior tibialis RSWA | 14.5± 7.8 | 15.3± 5.9 | T=0.62, P=0.55 |

RSWA: REM sleep with atonia.

% Tonic and phasic RSWA: the numbers of 30-second epochs with tonic and phasic RSWA were divided separately by the total number of epochs of REM sleep.

T: independent *t*-test, MWU: Mann-Whitney U test.

**Figure legends**

**Figure 1.** Flow diagram illustrating the recruitment and treatment of depressed patients with insomnia. PSG: Polysomnography; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HRSD: Hamilton Rating Scale for Depression; OSA: obstructive sleep apnea; PLMS: periodic limb movement during sleep; OCD: obsessive-compulsive disorder.

****

**Figure 2 a-c**. Tonic and phasic EMG activities in REM sleep during sertraline treatment of depressed patients. Figure 2 a. Tonic EMG activities in REM sleep (x axis: baseline and days 1, 14, 28, and 56; y axis: % of 30-second epochs with tonic RSWA). Figure 2 b. Phasic submental EMG activities in REM sleep (x axis: baseline and days 1, 14, 28, and 56; y axis: % of 30-second epochs with phasic submental RSWA). Figure 2 c. Phasic anterior tibialis EMG activities in REM sleep (x axis: baseline and days 1, 14, 28, and 56; y axis: % of 30-second epochs with phasic anterior tibialis RSWA). EMG: electromyogram; REM: rapid eye movement; RSWA: REM sleep without atonia.

