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

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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 them were retrospective and cross-sectional studies with small sample size on a mixture of SSRIs with small sample sizes and included data on a mixture of SSRIs. As different SSRIs have different pharmacological profiles, the specific effects of a single of individual SSRIs on RSWA should be studied. In an 8-week, open-label trial of sertraline in depressed patients (n=31), depressed patients were administered 50 mg sertraline at 8 am on the 1st day; this dose was subsequently titrated up to a maximum of 200 mg/day. All patients had undergone repeated video-polysonmography (vPSG) (baseline, 1st day, 14th day, 28th day, and 56th day). Both tonic (submental) and phasic (submental and anterior tibialis) RSWA were visually counted. Tonic RSWA increased from 3.2±1.8% at baseline to 5.1±2.3% on the 1st day on sertraline and 10.4±2.7% on the 14th day; from then on, with stable measures 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. No RBD was observed. The increase in tonic muscle tone during REM
sleep over time correlated with reduced REM sleep latency $\text{latency}$ ($r=0.56$, $p=0.004$), PLMI $r=0.39$, $p=0.047$), and improvement-improved in depression (HRSD score, $r=-0.43$, $p=0.03$). The increase-in phasic submental RSWA ($r=-0.51$, $p=0.02$) and anterior tibialis ($r=0.41$, $p=0.04$) RSWA were were correlated with decreased REM sleep latency, and were was not correlated with patient's demographics and or clinical characteristics. Sertraline could-induced or exacerbated RSWA— but did not induce RBD. Compared with idiopathic RBD, the sertraline-related RSWA had some specific characteristics of being correlated with REM latency and no predominance of male sex and elder-age, suggesting that RSWA might have-involve different mechanisms with-than idiopathic RBD.

**Keywords:** 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 polysomnogram of depressive-depressed patients with insomnia,— 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 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 (Schenck and Mahowald, 2002, AASM, 2005). Idiopathic RBD is a male-predominant disorder that usually emerges after 50 years of age (Schenck and Mahowald, 2002, AASM, 2005), and it is frequently described before the onset and during the course of synucleinopathies including Parkinson’s disorder (PD), multiple system atrophy, and dementia with Lewy bodies (Iranzo et al., 2009). RBD is strongly associated with an abnormal increase of phasic and tonic muscle tone during REM sleep, a condition named REM sleep without atonia (RSWA). Whether RSWA is a sufficient and necessary condition for the emergence of RBD remains unknown; however, although some cases of RSWA have been documented, it is not known whether RSWA will later become...
full-blown RBD (Gagnon et al., 2006, Arnulf, 2012, AASM, 2005). According to the international classification of sleep disorders (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. Alternatively, the criteria for subclinical RBD only include the REM sleep PSG abnormalities but without a clinical history of RBD (AASM, 2005). The 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.

When using the American Academy of Sleep Medicine 2007 version (AASM-2007) criteria for measuring tonic and phasic muscle activity (Iber C, 2007), 18% of REM sleep time with any 3-second-lasting 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 with RBD associated with Parkinson’s disease and 30 matched controls (Frauscher et al., 2012). Gagnon argued that a similar cutoff (greater than 20%–25%) of the tonic submental muscle activity during REM sleep was a reasonable threshold for defining muscle activity as excessive or potentially pathological (Gagnon et al., 2006). In another study, 80 patients with idiopathic RBD, tonic submental muscle activity greater than 30% of the total REM sleep time and phasic submental muscle activity greater than 15%
were considered optimal cut-offs for the diagnosis of idiopathic RBD from normal controls (Montplaisir et al., 2010).

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 (Guilleminault et al., 1976, Bentel et al., 1979, Schenck et al., 1992, Onofrj et al., 2003, Winkelman and James, 2004, Zhang et al., 2010, Hoque and Chesson, 2010). A recent clinical epidemiological study on parasomnia in psychiatric out-patients revealed that the lifetime and 1-year prevalences of RBD and/or subclinical RBD among psychiatric out-patients are 5.8% and 3.8% respectively, respectively. These prevalences are ten times more common than the prevalence of RBD in the general population. Further, compared with RBD patients in the general population, these patients were younger in age, were predominantly female, being associated with more likely to be using antidepressants, usage, and had less concurrent neurodegenerative diseases compared to the RBD patients in the general population (Lam et al., 2008). In recent decades, the selective serotonin (5-HT) reuptake inhibitors (SSRIs) have become the first-line antidepressants; in recent decades, and their potential effects on RSWA can be suspected based on basic knowledge on muscle atonia during REM sleep. The normal loss of muscle tone during REM sleep results from two mechanisms, one passive and one active.

Serotonergic neurons descending to the nuclei of the cranial nerves and to the lower motor neurons reduce their firing, leading to the disfacilitation of the neurons...
during non-REM sleep, and the cease of firing during REM sleep (Siegel, 2006). 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, an active paralysis of postural muscle tone (termed atonia) occurs specifically during REM sleep and uses the cholinergic-glutaminergic-glycinergic pathway to eventually block the postsynaptic lower motor neurons. 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 because of the prevention of the normal sleep-related hypotonia (serotonergic drugs) or the normal REM sleep-related atonia (anticholinergics) (Arnulf, 2012). Previous studies suggested that compared with controls, SSRIs could intensify dreaming (Pace-Schott et al., 2001) and produce more RSWA than did controls, and might possibly increase the risk of developing RBD (Schenck et al., 1992, Winkelman and James, 2004, Gagnon et al., 2006, Zhang et al., 2010, Hoque and Chesson, 2010). However, most of these studies are retrospective and cross-sectional studies with small sample size on a mixture of SSRIs with small sample sizes that received a mixture of SSRIs. It is well known that not all SSRIs do not have the same pharmacological profiles; thus, different SSRIs might have different tendencies to induce RSWA. The specific effects of a single 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 protocol of this study was approved by the Independent Ethics Committee (IEC) of Guangdong Provincial Mental Health Centre. Written informed consents were 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 patient’s diagnosis of the patient would be ascertained by one of the authors (BZ) using the second version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-2) (First MB, 1996). None of the patients included in the study fulfilled any other current or lifetime diagnostic criteria of DSM-IV Axis I disorders. Patients were male and female, aged 18 to 65 years, with a Hamilton Rating Scale for Depression (HRSD) score ≥ 18 and a sleep disturbance factor score ≥ 3 in the HRSD (Hamilton, 1960), 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 analysis).
and urinary urine analysis analyses). Patients were excluded if they had experienced serious adverse events while taking sertraline, if they currently had significant suicidal or homicidal tendencies (either from their medical histories or HSRD 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], and so on), or if they had a serious medical condition in the previous 3 months.

After a 7-day washout phase for patients who had received medicine in the previous 3 months and a subsequent 2-night baseline vPSG assessment, patients received sertraline for 8 weeks. At baseline and during the 4 visits (1st day, 14th day, 28th day, and 56th day), the patients were assessed by the HRSD (clinical improvement), Treatment Emergent Symptom Scale (TESS-Severity [TESS-S] and TESS-Treatment [TESS-T]; side effects) (Guy, 1976), Epworth Sleepiness Scale (ESS: sleepiness) (Johns, 1992), and Pittsburgh Sleep Quality Index (PSQI: sleep quality) (Buysse et al., 1989). On the 1st day, 50 mg of sertraline was administered at 8 am on the 1st day. It was then, the dose was titrated according to the clinical efficacy and side effects, with a maximum dosage of 200 mg/day. Similar to the 1st day, sertraline was usually administered at 8 am during this throughout the clinical trial, except for cases of significant sedation and/or dosages of 200 mg/day. Sertraline would be administered at 8 pm for patients with experiencing significant sedation.
and sertraline would be administered twice daily (8 am and 4 pm) for patients receiving the dosage of 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 (Agnew et al., 1966). The vPSG variables on the second night and the MSLT on the third daytime were defined as baseline data. Because of daytime 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 fourth night, and 50 mg of sertraline was administered at 8 am on the fourth day. The acute effects of Sertraline on RSWA and sleep architecture were evaluated in the 1st day vPSG assessment, which was not conducted in most of previous research studies. Further, these patients were assessed by vPSG in three following subsequent visits (14th day, 28th day, and 56th day). On each of the subsequent 3 visits during the 8-week trial, patients were assessed by with one night of PSG followed by the MSLT.

According to the The nocturnal vPSG included the following basic recordings included a standard EEG (F4-A1, C4-A1, O2-A1, C3-A2), an electrooculography (EOG: LE-A2, RE-A1), a submental
electromyograph (EMG), a bilateral leg's EMG (anterior tibialis muscles), an ECG, nasal air flow pressure, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, breathing sound, and body position. All of the sleep variables were derived from the 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 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 stage REM divided by the TST) (Iber C, 2007). The 5-nap MSLT was performed according to the standard recommendation to determine the mean SL (Carskadon et al., 1986). All computerized sleep data were further edited by an experienced PSG technologist, and this technologist was who was blinded to the research study. Sleep stages, respiratory events, and periodic limb movements were scored according to the AASM-2007 criteria at 30-second intervals (Iber C, 2007), but the REM sleep was scored according to a modified method (Lapierre and Montplaisir, 1992). In this method, the first epoch with the occurrence of rapid eye movement and low-amplitude, mixed-frequency EEG was used to determine the onset of a REM sleep period. The termination of a 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 during for 180 seconds (Lapierre and Montplaisir, 1992). At the first night of baseline vPSG assessment, subjects with significant PLMS (PLM index [PLMI] ≥ 15), or significant OSA (apnea-hypopnea index [AHI] ≥ 15) on the first night of the baseline vPSG assessment would be excluded from the study. The video recordings were also examined by the sleep technician for any abnormal movement, behavior and 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 within which at least 50% of the duration of the epoch having had a submental EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep. 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 bursts were 0.1-5.0 seconds in duration and at least 4 times as higher in amplitude as than the background EMG activity. Tonic muscle activity was only scored in the submental EMG, while phasic muscle activity was scored in both submental and anterior tibialis EMGs (Iber C, 2007). To exclude the disruption of REM sleep by physiologic events for REM sleep, REM epochs in which an EEG arousal, a snore artifact in the submental EMG, PLMS, or hypopnea
was present were eliminated from further analyses (Winkelman and James, 2004). Finally, the numbers of 30-second epochs without atonia, 30-second epochs with phasic submental muscle activity, and 30-second epochs with phasic anterior tibialis muscle activity were computed separately for each REM period. The number of their epochs was then divided separately by the total number of epochs of REM sleep to obtain the exact percentages of phasic and tonic RSWA. Both of the abnormal tonic and abnormal phasic RSWA were defined as more greater than 18% in this study (Frauscher et al., 2012).

2.4. Data analysis

The data were 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). A one-way analysis of variance (ANOVA) and Kruskal Wallis Test tests were performed for comparing parametric and non-parametric data (≥ 3 groups). Significant effects in 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 the differences in categorical variables. The Correlations between the score rates of the clinical and polysomnographic measures and the
score rates of tonic and phasic EMG activities during REM sleep were performed using the Pearson test. A two-sided 5% level of significance was considered statistically significant. All statistical procedures were performed using 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 DSM-IV comorbid Axis I disorders, and 6 patients did not have moderate or severe insomnia (HRSD-sleep disturbance score < 3). Among these remaining patients, 11 patients without who were not taking any medication directly entered 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 of to participate in further sleep tests). One patient discontinued during the 14th and 28th day due to a revised diagnosis of bipolar disorder.
Three patients discontinued during between the 28th and 56th day (1 due to a revised diagnosis of OCD and 2 due to refusal of to participate in further sleep tests). Finally, 22 patients completed this trial. This recruitment process was shown in Figure 1.

3.2. Demographic and clinical characteristics

The thirty-one patients were predominantly young (32.7±9.2 years old) and female (female: 61.3%) subjects. Their demographic and clinical characteristics are presented in 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.
day. Only a few patients took 200 mg/day of sertraline (2 patients on the 28th day and 1 patient in the 56th day); so sertraline was administered twice daily for these patients (100 mg at 8 am and 100 mg at 4 pm). Further, no patient was administered sertraline at night for significant sedation. In addition, there were only limited side effects (TESS) observed during the 8-week trial. The HRSD scores started to improve starting from the 14th day of treatment. The HRSD-sleep disturbance scores became significantly lowered after the 28th day. The scores of PSQI and ESS scores decreased gradually during this trial: and both questionnaires on the 14th, 28th, and 56th days, the scores of both questionnaires were significantly lower than those at baseline. No patient reported any violent dreams or dreams enacted at home during the study, which could indicate clinical RBD.

3.4. Polysomnographic Assessment

There were no significant differences in the TRT2 during the trial. From the 14th day onward, the TST2 and SE2 became longer and higher than those at the baseline or the 1st day, respectively, respectively. 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 measure reached the highest level on the 1st day and showed a decrease at the subsequent visits. There were no statistical differences between baseline and the last 3 visits. The percentage of stage 1 sleep decreased during the trial; and 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 during throughout the trial. The percentage of stage 3 sleep increased gradually and was greater and was more than 10% at during the last 3-4 latter visits compared with baseline and the 1st day. Compared with baseline, the REM latency latencies were significantly prolonged significantly on the 1st day and decreased gradually during the treatment. However, the REM latency latencies were longer at during each of the visits than at baseline. No statistical difference was shown in the percentages of REM sleep during throughout the trial. Compared with baseline, PLMI scores increased as soon as the immediately after sertraline administration on the 1st day. From the 14th day onward, PLMI scores continued to increase and it became significantly higher in all three latter the last 3 visits than at baseline and the 1st day. The AHI kept scores remained stable during throughout the this clinical trial. During the daytime assessment (MSLT), the mean SL remained stable during the trial (Table 2).

3.5. Tonic and Phasic RSWA during REM Sleep

Tonic and phasic RSWA increased mildly and non-significantly from the baseline to the first night after sertraline intake treatment. Then, from the 14th day
onward, all of both tonic (submental) and phasic (submental and anterior tibialis) RSWA increased and became significantly higher in all three latter visits than compared with baseline and the 1st day. There were no further differences between the last three measures, taken on the 14th, 28th and 56th day. 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 cutoffs of abnormal tonic and phasic RSWA, the proportion of patients with abnormal phasic anterior tibialis RSWA became significantly higher in all three latter visits than at baseline and the 1st day, while the proportions of patients with abnormal tonic and phasic submental RSWA kept remained stable during the current trial throughout the trial (Table 3 & Figure 2 a-c). Notably, no abnormal movement, behavior and vocalization were observed during REM sleep on the video recordings in REM sleep.

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Insert Table 3

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Insert Figure 2 a-c

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

We calculated the reducing reductions in scores rates of the clinical and polysomnographic measures and tonic and phasic RSWA from endpoint to baseline ([the value at the endpoint - the value at baseline] / the value at baseline × 100%). The reducing-reduction in score rate of tonic RSWA scores (216.4% ± 53.9%) was positively correlated positively with the reducing-reduction score rates of REM Latency 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 negatively with the reducing-reduction in score rates of HRSD scores (-68.6% ± -21.3%) (r = -0.43, p = 0.03). The reducing score rates of reductions 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 correlated positively correlated with the reducing-reduction in score rates of REM latency scores. The amount of RSWA did not correlate with the dosage of sertraline.
On the other hand, no significant correlations were shown between the reducing score rates of reduction in RSWA scores and continuous demographic and clinical characteristics (such as age at the baseline) and the reducing score rates of RSWA scores were not significantly different among categorical demographic and clinical characteristics (such as gender) at the baseline.

4. DISCUSSION

In the current study, Sertraline exacerbated RSWA during the current study, but did not induce RBD. From the 14th day onward, the tonic and phasic RSWA and the proportion of patients with abnormal phasic anterior tibialis RSWA (> 18%) became significantly higher than that of baseline and the 1st day, and then remained stable. The results of To some extent, the phasic RSWA results were not consistent with those in Winkelman’s study. In Winkelman’s study, compared with normal control, only tonic RSWA was significantly increased in subjects taking serotonergic antidepressants compared with normal controls; only had significantly tonic RSWA; and the both submental and anterior tibialis phasic RSWA in levels both submental and anterior tibialis did not reach the change significantly level (Winkelman and James, 2004). This difference might be due to the small sample size (n=15) and a mixture of antidepressants used in Winkelman’s study. Two subjects were even taking bupropion (200 mg/day), which might have diminished RSWA (Winkelman and James, 2004). Further, using if the a cutoff of abnormal tonic RSWA greater than 20% was used (Gagnon et al.,
2006), the proportions of patients with abnormal tonic RSWA in the current study were similar among the current study and to that of two previous studies (the current study: 4.5% [1/21], Winkelman: 13.3% [2/15], Zhang: 14.3% [3/21]; χ²=1.44, p=0.09) (Winkelman and James, 2004, Zhang et al., 2010). In summary, these results support the notion that SSRIs could can induce or exacerbate RSWA, especially for phasic anterior tibialis RSWA. It was reported that most abnormal sleep behaviors seen observed in RBD have been reported to correspond to movements of the limbs (Schenck, 2005). However, no patients reported some abnormal behaviors being related with to RBD in the current study. This might be due to these the following reasons. Firstly, some subtle behaviors might have been ignored by patients and their bed-partners, and even could may not be have been detected by the concomitant videos. Second, the clinical meaning of RSWA was is elusive, and RSWA which might only be be identifiable from PSG findings and could not develop into overt clinical RBD. Third, RSWA could can develop into RBD, but, by chance, it this did did not happen occur in the current study with due to the small sample size. Further, RSWA could might also be a necessary (permissive) but not a sufficient (active) condition to promote RBD. One might also imagine that higher amounts levels of RSWA are necessary for the RBD-associated dreaming behavior to be enact occurred. In this direction, Moreover, a mean of 39% the amount of tonic RSWA was observed in patients with idiopathic and PD-associated RBD (Iranzo et al., 2005) is a mean 39%, which is large greater than the 12% found in our study (Iranzo et al., 2005). Additionally, RSWA amounts
are were higher in multiple systemic atrophy than those in PD or idiopathic RBD, but the severity of the corresponding behaviors is was milder (Iranzo et al., 2005). This suggests that both conditions, RBD and RSWA, are strongly, but not linearly, linked.

The REM sleep suppression (e.g., increased REM latency, decreased REM sleep duration, and so on) is characteristic of antidepressants, and is strongly linked to increased serotonergic tone (Rush et al., 1989, McNamara et al., 2010). In this study, the reducing reduction in score rate of REM latency scores positively correlated with the reducing reduction in score rates of all of both tonic and phasic RSWA. This result was consistent with Winkelman’s suggestion study, in which the extent of prolonging prolonged REM latency was suggested as a marker of the degree of RSWA (Winkelman and James, 2004). Since Because the correlation between REM latency and RSWA was has never been reported in previous studies for patients with idiopathic RBD or neurodegenerative disease-related RBD in previous studies, so the mechanisms of producing underlying RSWA should be are likely different between idiopathic RBD and antidepressant-related RBD. This notion might be supported by some certain risk factors (male sex and older age) for idiopathic RBD not that were being not shown found in this study and or some previous studies (Nash et al., 2003, Hoque and Chesson, 2010, Zhang et al., 2010, Winkelman and James, 2004, Gagnon et al., 2006). Unlike the effects observed with to most antidepressants, the percentage of REM sleep kept was stable during throughout the this trial. This phenomenon was also reported by another research study about testing the effects of sertraline on sleep architecture (Jindal et al., 2003), so it might
suggest that sertraline had 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 at baseline.

However, although all of them did not reach the same statistical difference, it might possibly be due to the small sample size in this research study to some extent. In some previous case reports, the antidepressant-related RBD could disappear as soon as the immediately following the discontinuation of antidepressant use discontinuation (Onofrj et al., 2003). In this study, the reducing-reduction in score rates of tonic RSWA scores was also significantly correlated with PLMI and HRSD scores. As some previous researches suggested, the extent of increased PLMI increment scores might reflect the pharmacological effect of sertraline on depression-related 5-HT and/or dopaminergic (DA) neurotransmission (Mendelson, 1996, Kugaya et al., 2003). Thus, RSWA, PLMS, REM latency, and HRSD scores might be involved in the mechanism of about 5% of 5-HT and/or DA neurotransmission to some extent; this likely explains why all of these scores were so it was understandable that all of them correlated with each other.

For clinicians, the central question is whether the sertraline-induced RSWA being induced by sertraline can be associated with clinical repercussions. According to subjective sleep and mood aspects and the objective sleep quality and continuity in PSG, sertraline-induced RSWA being induced by sertraline did not
have cause significant clinical disturbance in the current clinical trial. Or in other words, the potential adverse effects sertraline-induced of induction of RSWA by sertraline might be outweighed by the significant improvements of in mood and sleep parameters caused by sertraline. It was noted that depression Notably, depression is a common mental disorder with the a prevalence of 10-20% (Murray, 1996), and most of depressive patients were are currently treated by with antidepressants, especially SSRIs in the current time SSRIs. Thus, SSRIs-related RSWA should be considered a serious public problem in depressed patients, since because it might be represent a potential risk factor for RBD. However, the SSRIs-related RBD is usually ignored by most physicians. For If patients with the usage of use antidepressants, and if they reported abnormal movements, behaviors and vocalizations during sleep, vPSG should be a routinely be used to assess more accurately estimating their RSWA.

Some caution should be exercised in interpreting the effects results reported here. First, no a placebo-control group was not involved used in this research study. Second, the sample size in this study was small.

5. CONCLUSIONS

In the current study, Sertraline-sertraline exacerbated RSWA during the current study, but did not induced RBD. Unlike idiopathic RBD, the sertraline-related RSWA had was correlated with REM latency and no was not predominance predominantly associated with the of male sex and older age, suggesting the involvement of different mechanisms. Further, although the sertraline-induced RSWA seems did not
cause not to have significant clinical disturbance and no overt RBD was not found in current study—regarding these observations, RBD being the greater prevalence of RBD in patients with the usage of antidepressants than than that in the general population—indicates that the antidepressant-related RSWA should is be a potential public health problem issue for the depressed patients.

Acknowledgments

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

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Mean ± standard derivation (range) or Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>32.7±9.2 (18-57)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/19</td>
</tr>
</tbody>
</table>
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
Resident (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 illness episodes 2.7±1.9 (1-7)
Length of current illness (in weeks) 6.6±5.0 (2-12)

BMI: body mass index

Table 2. Clinical and polysomnographic measures across the sertraline treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=31)</th>
<th>1st day (n=31)</th>
<th>28th day (n=26)</th>
<th>56th day (n=25)</th>
<th>56th day (n=22)</th>
<th>Statistics</th>
</tr>
</thead>
</table>
| in-of depressed patients
|                        |                |                |                 |                 |                 |            |

32
Dosage (mg/day) & 50.0\textsuperscript{a} & 126.9±25.4\textsuperscript{b} & 144.0±30.0\textsuperscript{b} & 134.1±28.4\textsuperscript{b} & F=103.90, P<0.001  
HRSD & 22.4±5.3\textsuperscript{a} & 23.1±5.3\textsuperscript{a} & 14.5±4.1\textsuperscript{b} & 9.7±2.6\textsuperscript{c} & 6.9±1.9\textsuperscript{c} & F=13.02, P<0.001  
HRSD-sleep disturbance factor & 4.1±3.3\textsuperscript{a} & 4.0±3.6\textsuperscript{a} & 3.5±3.1\textsuperscript{a,b} & 2.7±1.4\textsuperscript{b} & 2.5±1.5\textsuperscript{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\textsuperscript{a} & 7.9±4.7\textsuperscript{a} & 6.3±3.4\textsuperscript{b} & 6.0±3.5\textsuperscript{b} & F=13.02, P<0.001  
ESS & 7.2±4.5\textsuperscript{a} & 5.3±3.9\textsuperscript{b} & 3.8±4.1\textsuperscript{b} & 4.0±3.5\textsuperscript{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 & F=0.79, P=0.87  
TST (min) & 364.9±103.5 & 347.5±114.3 & 423.2±98.6 & 440.1±103.7 & F=11.14, P<0.001  
SE (%) & 72.2±22.8 & 70.6±29.1 & 83.4±27.5 & 86.1±31.3 & F=15.57, P=0.003  
SL (min) & 51.9±29.5 & 46.6±23.5 & 25.3±14.1 & 21.7±11.8 & F=13.25, P<0.001  
REM Latency (min) & 77.3±38.1 & 134.3±82.9 & 121.3±67.0 & 109.4±73.1 & F=27.05, P<0.001  
PSQI (min) & 87.9±31.9 & 98.1±35.6 & 89.1±19.8 & 93.2±21.3 & F=35.93, P<0.001  
AI & 8.9±6.6 & 13.8±7.2 & 7.3±6.8 & 6.4±4.8 & F=6.66, P=0.04  
% Stage 1 & 12.8±5.9 & 15.2±6.6 & 9.6±4.4 & 7.9±1.7 & F=5.03, P=0.03  
% Stage 2 & 59.2±21.3 & 57.4±18.7 & 57.9±20.5 & 56.8±19.3 & F=1.73, P=0.34  
% Stage 3 & 3.2±1.5 & 2.8±2.2 & 12.9±5.8 & 14.1±8.4 & F=12.06, P=0.001  
% REM sleep & 24.8±7.1 & 24.6±6.9 & 20.2±8.5 & 22.1±10.4 & F=0.86, P=0.72  
PLMI & 3.6±1.5 & 5.1±3.9 & 8.7±3.1 & 8.3±3.7 & F=9.81, P=0.003  
AH1 & 6.2±1.7 & 6.3±1.7 & 5.9±2.0 & 6.0±1.9 & F=0.54, P=0.27  
Mean SL of MSLT (min) & 16.4±11.3 & 14.7±8.9 & 15.2±9.5 & 17.1±10.4 & F=0.30, P=0.34


\textsuperscript{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 across the sertraline treatment in-of depressed patients**
RSWA: REM sleep with atonia

% **tonic**RNSA 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, $\chi^2$: Chi-square test.

### Table 4. Percentages of epochs with tonic and phasic RSWA between single.

<table>
<thead>
<tr>
<th>30-second Epoch</th>
<th>Baseline (n=31)</th>
<th>1st day (n=31)</th>
<th>14th day (n=26)</th>
<th>28th day (n=25)</th>
<th>56th day (n=22)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Tonic RSWA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal tonic RSWA (&gt; 18%), n (%)</td>
<td>3.2 ± 1.8 a</td>
<td>5.1±2.3 a</td>
<td>10.4±2.7 b</td>
<td>10.2±2.5 b</td>
<td>12.0±4.3 b</td>
<td>$F=52.62$, $P&lt;0.001$</td>
</tr>
<tr>
<td><strong>% Phasic submental RSWA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal phasic submental RSWA (&gt; 18%), n (%)</td>
<td>3.4 ± 1.9 a</td>
<td>4.8±2.2 a</td>
<td>9.4±3.8 b</td>
<td>10.3±3.9 b</td>
<td>11.4±4.2 b</td>
<td>$F=32.38$, $P&lt;0.001$</td>
</tr>
<tr>
<td><strong>% Phasic anterior tibialis RSWA</strong></td>
<td>6.2± 2.1 a</td>
<td>8.2±2.8 a</td>
<td>14.6±6.8 b</td>
<td>15.5±6.6 b</td>
<td>15.1±6.6 b</td>
<td>$F=20.73$, $P&lt;0.001$</td>
</tr>
<tr>
<td>Patients with abnormal phasic anterior tibialis RSWA (&gt; 18%), n (%)</td>
<td>0 a</td>
<td>0 a</td>
<td>0</td>
<td>1 (4.0%)</td>
<td>0</td>
<td>$\chi^2=33.44$, $P&lt;0.001$</td>
</tr>
</tbody>
</table>

---

Table 4. Percentages of epochs with tonic and phasic RSWA between single.
**Single-type and recurrent-recurrent-type depression** across the sertraline treatment in of depressed patients

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

**RSWA**: REM sleep with atonia

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

T: independent *t*-test, MWU: Mann-Whitney U test.
**Legend of the figures**

**Figure 1.** Flow diagram documenting the recruitment and treatment of depressed patients with insomnia. PSG: Polysomnogram; 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.

- **Clinical interview:**
  55 depressive patients with insomnia

  Excluded patients:
  1. 11 patients: other DSM-IV Axis I disorders
  2. 6 patients: HRSD-sleep disturbance score < 3

- **PSG assessment:**
  38 depressive patients with insomnia

  Excluded patients:
  1. 3 patients: OSA
  2. 4 patients: PLMS

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