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 ~~and~~ was subsequently titrated up to a maximum of 200 mg/day. All patients ~~had~~ underwent repeated video-polysomnography (vPSG) (baseline, 1st day, 14th day, 28th day, and 56th day). Both tonic (submental) and phasic (submental and anterior tibialis) RSWA were visually counted. ~~The t~~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~~ were taken until the 56th day. A similar profile was observed for phasic RSWA, as well as ~~and~~ for the proportion of patients with abnormal phasic anterior tibialis. No RBD was observed. The increase ~~of~~ in tonic muscle tone during REM

sleep over time correlated with reduced REM sleep ~~Latency~~ 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~~s~~ ~~of~~ in phasic submental ~~RSWA~~ (r =-0.51, p=0.02) and anterior tibialis (r=0.41, p=0.04) RSWA ~~was~~ were correlated with decreased REM sleep ~~L~~latency~~,~~ and ~~it~~ were ~~was~~ not correlated with patient ~~s'~~ demographic~~s~~ ~~and~~ or clinical characteristics. Sertraline ~~could~~ induce~~d~~ or exacerbate~~d~~ 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~~ older age, ~~so~~ suggesting ~~they~~ that RSWA might ~~have~~ involve different mechanisms ~~with~~ than idiopathic RBD.

~~**Key words**~~**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 polysomnogram~~y~~ 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 t~~T~~omography; DA: dopaminergic; DSM-IV: diagnostic and statistical manual of

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mental disorders fourth edition; ECG: ~~Electrocardiograph~~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~~Parkinson's disorder; PLMI: periodic limb movement index; PLMS: periodic limb movement during sleep; PSG: ~~Polysomnogram~~polysomnogramy; 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~~ sleep ~~Efficiency~~efficiency; SL: ~~Sleep~~ sleep ~~Latency~~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-~~ploysomnography~~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 ~~the~~ of age ~~of 50 years~~ (Schenck and Mahowald, 2002, AASM, 2005)~~,~~ and ~~it~~ is frequently described before the onset and during the course of synucleinopathies, ~~that~~ include~~e~~ing 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~~ in phasic and tonic muscle tone during REM sleep, a condition named REM sleep without atonia (RSWA). ~~However, it is not known whether~~Whether RSWA is a sufficient and necessary condition for the emergence of RBD remains unknown~~,~~; however, ~~although~~ some cases of RSWA have been documented ~~with RSWA and~~to later become

full-blown RBD (Gagnon et al., 2006, Arnulf, 2012, AASM, 2005). According to the ~~international~~ International ~~classification~~ Classification of ~~sleep~~ Sleep ~~disorders~~ Disorders, S~~s~~econd ~~edition~~ Edition (ICSD-2), the criteria ~~of~~ 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~~ sleep-related injurious, potentially injurious, or abnormal REM sleep behaviors documented during polysomnographic (PSG) monitoring~~;~~. ~~while~~ Alternatively, the criteria ~~of~~ for subclinical RBD only include ~~the~~ REM sleep PSG abnormalities and ~~but without~~do not ~~a~~ include 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~~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~~ in which any ~~3 second lasting~~ tonic or phasic muscle activity lasted 3 seconds ~~on~~ in an epoch was ~~specific~~ characterized ~~of~~ as RBD in a series of 15 patients with idiopathic RBD, 15 with RBD associated with P~~p~~arkinson's disease and 30 matched controls (Frauscher et al., 2012). Gagnon argued that a similar cutoff (greater than 20~~%)~~%) 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 ~~being consisted of~~comprising 80 patients with idiopathic RBD, tonic submental muscle activity greater than 30% of the total REM sleep time~~,~~ and ~~a~~ phasic submental muscle activity greater than 15%

were considered optimal cut-offs ~~to~~ for the ~~diagnose~~ diagnosis of idiopathic RBD ~~from~~ in 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, Bental 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 ~~find out~~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. ~~It~~ These prevalences are ~~is~~ ten times ~~more common~~higher than ~~the prevalence~~the prevalence of RBD in the general population. Further, compared with RBD patients in the general population, these patients ~~are~~ were ~~of~~ younger~~–~~ in age, were predominantly female ~~predominance~~, ~~being~~ were ~~associated with~~more likely to be using ~~–~~antidepressants ~~usage~~, and ~~no~~ had less concurrent neurodegenerative diseases ~~compared to the RBD patients in the general population~~ (Lam et al., 2008). In recent decades, ~~The s~~selective serotonin (5-HT) reuptake inhibitors (SSRIs) ~~are~~ have become the first-line antidepressants~~; in recent decades, and~~ their potential effects on RSWA ~~can be~~are suspected ~~from~~ based on basic knowledge ~~on~~ of 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~~ing~~ ~~the~~ neurons

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during ~~non~~ non-REM sleep~~,~~ and the ~~cease~~ ceasing of firing during REM sleep (Siegel, 2006). As a consequence, muscle tone is reduced from light to deep non-REM sleep, as well as ~~and then~~ 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) ~~(named atonia)~~ occurs specifically during REM sleep~~,~~ and uses ~~a~~ the cholinergic-glutaminergic-glycinergic pathway to eventually block the ~~postsysnaptic~~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~~ due to their ~~they~~ prevention of ~~the~~ normal sleep-related hypotonia (serotoninergic 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~~ increase~~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 ~~researches~~ studies ~~are~~ were 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~~,~~; ~~so~~ thus, different SSRIs might have different ~~ial~~ tendenc~~y~~ies to induce RSWA. The specific effects of ~~a single~~individual SSRIs on RSWA should be studied. The main purpose of this study ~~is~~ was to characterize the effect of sertraline on RSWA

in depressed patients in an 8-week clinical trial ~~with~~ using repeated video-~~ploysomnography~~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 consent~~s~~ ~~were~~ was ~~signed~~ 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~~ was ~~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~~ for DSM-IV Axis I disorders. Patients were male and female, aged 18 to 65 years, ~~with~~ had ~~a~~ Hamilton Rating Scale for Depression (HRSD) score~~s~~ ≥ 18 and ~~a~~ sleep disturbance factor score~~s~~ ~~in HRSD~~ ≥ 3 in the HRSD (Hamilton, 1960), ~~reflecting~~ which reflected ~~a~~ moderate-to-high level~~s~~ 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,~~

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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 ~~history~~ histories or HSRD scores ≥ 4 on item 3, "suicide"), ~~in HSRD ≥ 4);~~ 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~~etc~~);~~.), or if they had a serious medical condition in the previous 3 months.

After a 7-day washout phase for patients ~~receiving~~ who had received ~~medicine treatment~~medication in the previous 3 months and a subsequent 2-night baseline vPSG assessment~~the following 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~~Then, the dose was titrated according to the clinical efficacy and side effects~~;~~ ~~with~~ the ~~a~~ maximum dosage ~~of~~ was 200 mg/day. Similar to the 1st day, sertraline ~~usually~~ 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~~was administered at 8 pm for patients ~~with~~ experiencing significant sedation~~,~~

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~~and sertraline would be administered~~and twice daily (8 am and 4 pm) for patients ~~with~~ 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~~ of the third day~~time~~ 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~~ 4th night, and 50 mg of sertraline was administered at 8 am on the ~~fourth~~ 4th day. The acute effects of ~~Sertraline~~ sertraline on RSWA and sleep architecture ~~was~~ were evaluated in the 1st day vPSG assessment, which was not conducted in most ~~of~~ previous ~~researches~~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 electrooculograph~~electrooculography (EOG: LE-A2, RE-A1), ~~a~~ submental

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~~electromyograph~~electromyography (EMG), ~~a~~ bilateral leg~~'s~~ EMG (anterior tibialis muscles), ~~an~~ ECG, nasal airflow 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 were~~ who was blinded to ~~this~~ 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, s~~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~~were 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 ~~with~~ in 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~~.~~: i~~I~~n 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 high~~higher in amplitude ~~as~~ than the background EMG activity. Tonic muscle activity was only scored in ~~the~~ submental EMGs, while phasic muscle activity was scored in both submental and anterior tibialis EMGs (Iber C, 2007). To exclude the ~~the~~ disruption of REM sleep ~~of~~ 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~~ respectivelyt~~, respectively (2 groups). ~~A one~~One-way analysis of variance (ANOVA) and Kruskal Wallis ~~Test~~ tests were performed ~~for~~ to ~~comparing~~ compare parametric and non-parametric data (≥ 3 groups). Significant effects ~~in~~ from ANOVAs were further examined with post-hoc tests using the least significant difference method with a ~~Boferroni~~Bonferroni correction for multiple comparisons. Mann–Whitney U tests with adjusted ~~p~~ 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 c~~Correlations between the ~~reducing~~ reduced score rates of the clinical and polysomnographic measures and the ~~reducing~~ reduced

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 ~~by~~ using ~~–~~Statistical Package for the Social Sciences 17.0 for Windows (SPSS, ~~Inc~~Inc., Chicago, IL).

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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~~ the 38 remaining patients, 11 patients ~~without~~ who were not taking any ~~medicine treatment~~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 ~~as~~ with significant OSA, and 4 patients were diagnosed ~~as~~ 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 ~~. Five~~ 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~~ between the 14th ~~–~~and 28th day due to a revised diagnosis of bipolar disorder~~.~~, and

~~Three~~ 3 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~~ is shown 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 (~~female:~~ 61.3%) ~~subjects~~. 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 ~~for sertraline~~ 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 took 2000mg/day of sertraline (2 patients in on the 28th day and 1 patient in the 56th day); so sertraline were was administratedadministered twice daily for to them these patients (1000mg at 8 am and 1000mg at 4 pm). Further, no patient was administered sertraline at night for significant sedation. In addition, there were only limited side effects (TESS) were observed during the 8-week trial. The HRSD scores started began to improve starting fromon 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 violentt dreams, or dreams enacted dreams at home during the study that, which could evoke indicate clinical RBD.

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3.4. Polysomnographic Assessment

There were no significant differences in the TRTs during the trial. From the 14th day onward, the TSTs and SEs became longer and higher than compared with those at the baseline or the 1st day respectivelyy, 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 awas decreased at the subsequent visits. There was were no statistical differencesignificant differences between baseline and the latter 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 ~~3 latter~~ visits compared with baseline and the 1st day. Compared with baseline, the ~~the~~ REM ~~latency~~ latencies ~~was~~ were significantly prolonged ~~significantly~~ on the 1st day and decreased gradually during the treatment. However, the REM ~~latency~~ latencies ~~was~~ were longer ~~at~~ during each of the visits than at baseline. No ~~statistical difference~~significant differences ~~was~~ were 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 ~~of sertraline~~ on the 1st day. From the 14th day onward, PLMI scores continued to increase~~,~~ and ~~it~~ were ~~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 (T~~t~~able 2).

Insert 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~~the last 3 ~~latter~~ visits ~~than~~ compared with baseline and the 1st day. There were no further differences between the last three ~~last~~ measures~~,~~ ~~–~~ taken on the ~~at~~ 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 ~~cutoffs~~ the cutoff of abnormal tonic and phasic RSWA of > 18%, the proportion of patients with abnormal phasic anterior tibialis RSWA ~~became~~ was significantly higher in ~~all three latter~~the last 3 visits than at baseline and the 1st day, while the proportion~~s~~ of patients with abnormal tonic and phasic submental RSWA ~~kept~~ remained stable ~~during the current trail~~throughout the trial (~~table~~ Table 3 & ~~figure~~ Figure 2 a-c). Notably, no abnormal movement, behavior ~~and~~ or vocalization ~~were~~ was observed during REM sleep on the video recordings ~~in REM sleep~~.

Insert Table 3

Insert Figure 2 a-c

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

Insert 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~~in 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 l~~L~~atency scores. The amount of RSWA did not correlate with the dosage of sertraline.

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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)~~ age at ~~the~~ baseline~~, , and~~ and the ~~reducing~~ reduction in ~~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~~ sertraline exacerbated RSWA ~~during the current study,~~ but did not induce~~d~~ 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~~ increased ~~than that of~~compared with baseline and the 1st day~~,~~ and then ~~then kept~~remained stable. ~~The results of~~To some extent, the phasic RSWA results were ~~not~~ inconsistent with those in Winkelman's study ~~to some extent~~. 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). ~~It~~ This different 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 (2000~~m~~ 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 proportion~~s~~ of patients with abnormal tonic RSWA in the current study ~~were~~ was 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]; χ^2=1.44, *p*=0.09) (Winkelman and James, 2004, Zhang et al., 2010). In summary, these results support the notion~~ed~~ that SSRIs ~~could~~ can induce or exacerbate RSWA, especially ~~for~~ phasic anterior tibialis RSWA. ~~It was reported that most~~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. ~~It~~ This might be due to ~~these~~ the following reasons~~. F~~: first~~ly~~, some subtle behaviors might ~~be~~ have been ignored by patients and their bed-partners~~,~~ and ~~even could~~may not ~~be~~ have been detected by the ~~concomitant~~ videos~~. ; Secondly~~second, the clinical meaning ~~for~~ of RSWA ~~was~~ is elusive, and RSWA ~~which~~ might only ~~be a~~be identifiable from PSG findings and ~~could~~ not develop into overt clinical RBD~~. ; Thirdly~~third, RSWA ~~could~~ can develop into RBD, but~~, by chances, it~~ this did ~~was~~ not ~~happened~~ 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 ~~may~~ might also imagine that higher ~~amounts~~ levels of RSWA are necessary for the RBD-associated dreaming behavior to ~~be enact~~occur~~ed~~. ~~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). Also,~~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 ~~for~~ of antidepressants~~,~~ and is strongly linked to increased serotoninergic 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. ~~It~~ 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. ~~It~~ This notion might be supported by ~~some~~ certain risk factors (male sex and ~~elder~~ 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~~suggesting that sertraline ~~had~~ has less of a suppressive effect~~on~~ on the duration of REM sleep ~~duration~~ 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~~none of these differences were ~~statistical difference~~significant ~~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~~ disappeared ~~as soon as the~~immediately following the discontinuation of antidepressant use~~s~~ ~~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 score~~s~~. As some previous ~~researches~~ studies suggested~~,~~ similarly~~similar~~ ~~with~~ to the antidepressant effectiveness ~~effectiveness~~ (HRSD) score~~s~~~~)~~, the ~~extent of~~extent of increased PLMI ~~increment~~ scores might reflect the pharmacological effect of sertraline on depression-related 5-HT and/or dopaminergic (DA) neurotransmission ~~being involved in depression~~ (Mendelson, 1996, Kugaya et al., 2003). Thus, RSWA, PLMS, REM latency, and HRSD score~~s~~ might be involved in the mechanism~~s~~ ~~about 5~~~~approximately~~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~~ remains whether ~~the~~ sertraline-induced RSWA ~~being induced by sertraline can be~~is 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 does~~did not

~~have~~ cause significant clinical disturbance in the current clinical trial. ~~Or in~~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, SSRI~~s~~-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~~ SSRI~~s~~-related RBD is ~~usually~~ ignored by most physicians. ~~For~~ If patients ~~with the usage of~~ use antidepressants~~,~~ and ~~if they~~ report~~ed~~ abnormal movements, behaviors and vocalizations ~~behaviours~~ during sleep, vPSG should ~~be a~~ routinely be used to assess ~~ment for a~~and~~n~~ accurately~~e~~ estimat~~e~~ing ~~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 induce~~d~~ 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 ~~elder~~ older age, suggesting the involvement of different mechanisms. Further, ~~although the~~ sertraline-induced RSWA ~~seems~~ did not

causenot to have significant clinical disturbance and no overt RBD was not found in current study,. regarding Despite these observations, RBD being the greater prevalence of RBD t in patients with the usageusing of antidepressants than than that in the general population,– indicates that the antidepressant-related RSWA should is be a potential public health problem issue forin the depressed patients.

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

	Mean ± standard derivation (range) or Number
Demographic characteristics	
Age (in years)	32.7±9.2 (18-57)
Gender (male/female)	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
Resident (city/town/country)	13/10/8
~~clinical~~Clinical **characteristics**	
Age at onset (in years)	23.9±8.0 (15-33)
BMI (kg/m^2)	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 ~~in~~ 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±28.4 [b]	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~~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~~ sleep ~~Efficiency~~efficiency, SL: ~~Sleep~~ sleep l~~L~~atency, 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 across the sertraline treatment ~~in~~ of depressed patients

30-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%)	χ^2=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	χ^2=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]	χ^2=33.44, P<0.001

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.

F: ANOVA, χ^2: Chi-square test.

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

	Single type	Recurrent type	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~~ 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 legends

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.

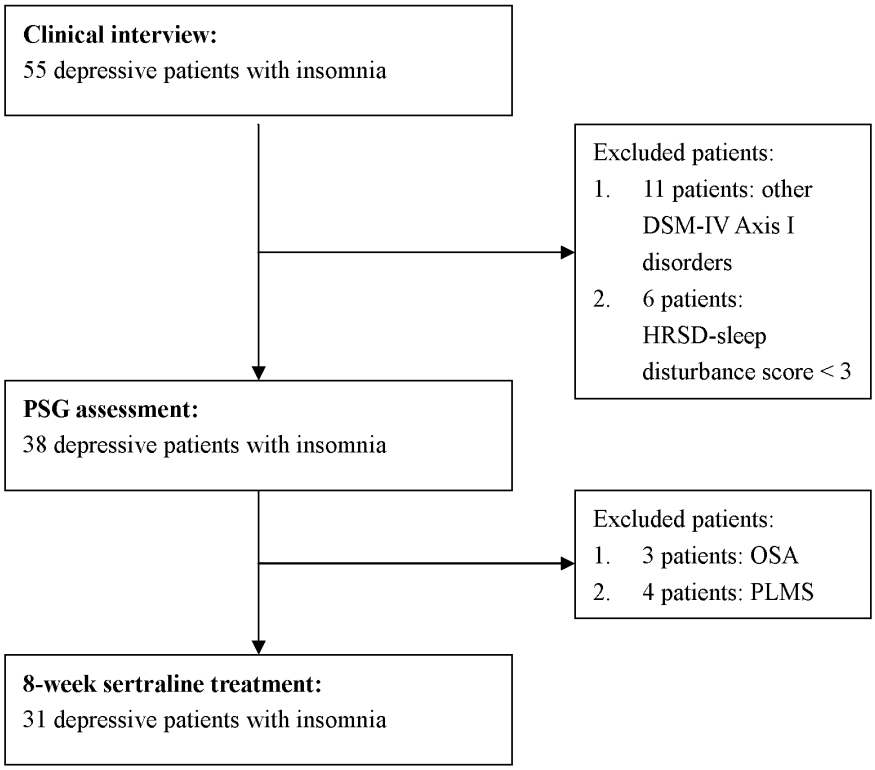

Figure 2 a-c. Tonic and phasic EMG activities in REM sleep across the sertraline treatment ~~in~~ of depressed patients. Figure 2 a. Tonic EMG activities in REM sleep (x axis~~,~~: baseline, the 1st day, the 14th day, the 28th day, and the 56th day; y axis~~,~~: % of 30-second epochs with tonic RSWA). 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.