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Original Article

Sertraline and periodic limb movements during sleep: an 8-week open-label study in depressed patients with insomnia

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ABSTRACT

Background: Previous studies have reported that selective serotonin reuptake inhibitors (SSRIs) might induce or exacerbate periodic limb movements during sleep (PLMS). However, most of these studies were retrospective and cross-sectional studies with small sample sizes on a selective SSRI, fluoxetine. Because different SSRIs have different pharmacologic profiles, it was not certain if other SSRIs also might lead to PLMS.

Methods: Data were taken from an open-label 8-week trial of sertraline in depressive patients with insomnia ($n = 31$). Depressed patients were administered sertraline 50 mg at 8:00 am on the first day, and the dosage was subsequently titrated up to a maximum of 200 mg daily during the 8-week trial. All participants were tested by repeated polysomnography (PSG) (baseline, first day, 14th day, 28th day, and 56th day). Periodic leg movements (PLM) were visually counted and the PLM index (PLMI) was calculated. PLMS was defined as PLMI $\geqslant 5$, and significant PLMS was defined as PLMI $\geqslant 15$.

Results: Compared with baseline (PLMI, 3.6 ± 1.5), all PLMI indices increased on the immediate administration of sertraline on the first day (PLMI, 5.1 ± 3.9). From the 14th day onward, PLMI became stable and significantly higher than baseline and the first day (8.7 ± 3.1 on the 14th day, 8.3 ± 3.7 on the 28th day, and 8.5 ± 3.6 on the 56th day; $F[11.81]$; $P = .003$). The clinical responses and PSG characteristics continuously improved during the 8-week trial. The PLMS group (PLMI $\geqslant 5$) had a higher arousal index (AI) than the non-PLMS group on the 14th day (9.4 ± 5.5 vs 5.2 ± 3.7; t test, 4.22; $P = .03$) and the 56th day (8.1 ± 5.5 vs 4.3 ± 3.7; z score, 3.11; $P = .04$); albeit, there was no significant clinical disturbances in the PLMS group.

Conclusions: PLMS were increased during sertraline treatment, but only a few of the PLMS reached the significant level. This effect of sertraline on PLMS might be dosage dependent. Although the sertraline-induced PLMS did not seem to cause significant clinical disturbance, the PLMS group (PLMI $\geqslant 5$) had a higher AI than the non-PLMS group. Thus clinicians should pay more attention to PLMS during SSRI antidepressant treatment.

1. Introduction

Sleep disturbance is tightly linked to depression. A large European retrospective study ($n = 14{,}915$) reported that insomnia symptoms emerged before major depressive disorder (MDD) in 41% of patients, at the same time as MDD in 29% of patients, and after the depressive episode in 29% of patients [1]. Further, another national survey among US adults ($n = 9714$; aged $\geqslant 18$ years) reported that sleep apnea, a common sleep disturbance, was associated with probable major depression (odds ratio [OR], 2.4 [95% confidence interval {CI}, 1.5–3.6]) [2]. Sleep disturbance not only incurs risks for the onset of depression, but it also is associated with poor response to treatment. Even after successful treatment, the presence of residual sleep disturbance increases the risk for depression recurrence [3] and suicide [4]. Thus some recent researchers have proposed to treat sleep disturbance comorbid with depression. However, because some of the sleep disturbances may be mediated or induced by antidepressant agents (e.g., sleep-walking, periodic limb movement during sleep [PLMS], restless legs syndrome [RLS], obstructive sleep apnea [OSA]) [5,6], further

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study is needed to clarify the role of antidepressant agents related to sleep disturbances in depression.

PLMS are characterized by brief 0.5- to 10.0-s lower extremity movements during sleep, which typically occur at 20- to 40-s intervals. Most PLMS can result in electroencephalography (EEG) arousals or awakenings, which can contribute to insomnia, sleepiness, and fatigue [7]. It has been reported that antidepressant agents with a serotonergic mechanism might increase the risk for PLMS [8–14], though antidepressant agents with a dopaminergic mechanism (e.g., bupropion) might benefit PLMS [8,15]. In recent decades, the selective serotonin reuptake inhibitors (SSRIs) have been the first-line antidepressant treatment, but previous research has suggested that SSRIs might induce or exacerbate PLMS [8–12]. There are some limitations noted in these studies, including their retrospective and cross-sectional designs and small sample sizes. In addition, not all SSRIs have same pharmacologic profiles, so different SSRIs might have a differential tendency to induce PLMS [16]. It is crucial to clarify their specific effects on PLMS, as it can assist in the selection of an antidepressant agent, especially for depressed patients with insomnia. To date, most previous research on SSRIs is focused on the effects of fluoxetine on PLMS [9–11], and little knowledge is gathered about other SSRIs. For example, the relative selectivity of sertraline for inhibiting 5-hydroxytryptamine reuptake relative to dopaminergic reuptake is somewhat less than other SSRIs [17], so sertraline might have less theoretic risk for PLMS. Only one retrospective study reported that sertraline shared a similar periodic limb movement (PLM) index (PLMI) with other SSRIs, though the PLMI between sertraline and healthy control participants did not reach statistical difference [8]. Our retrospective study consisted of heterogeneous participants (more than 80% participants with depressive syndrome) with a wide dosage range of sertraline (25–300 mg) [8]. The main purpose of our study was to characterize the effect of sertraline on PLMS in depressed patients with insomnia in an 8-week clinical trial with repeated polysomnography (PSG) assessment.

2. Methods

2.1. Participants and study design

The protocol of our study was approved by the Independent Ethics Committee (IEC) of Guangdong Provincial Mental Health Center. Written informed consents were signed prior to participation.

All participants were enrolled from the inpatient population of Guangdong Provincial Mental Health Center. If a participant was diagnosed with a single or recurrent type of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), on admission, the participant's diagnosis would be ascertained by one of the authors (BZ, psychiatrist) using the second version of the Structured Clinical Interview for DSM-IV Axis I disorders [18]. None of participants included in our study fulfilled any other current or lifetime diagnostic criteria of DSM-IV Axis I disorders. Participants were men and women aged 18–65 years, with a Hamilton Rating Scale for Depression (HRSD) score of $\geqslant$18 and a sleep disturbance factor score in HRSD of $\geqslant$3 [19], 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, including EEG, electrocardiography, computed tomography scan, blood analysis, and urinary analysis. Participants were excluded if they had experienced serious adverse events while taking sertraline; if they currently had significant suicidal or homicidal tendencies (medical history or item 3 [suicide] in HRSD score of $\geqslant$4); if they currently were pregnant or breastfeeding; if they currently were shift workers; if they currently had significant sleep disorder (e.g., OSA, RLS, PLMS); or if they had a serious medical condition in the previous 3 months.

After a 7-day screen or washout phase and the baseline PSG assessment, participants received sertraline for 8 weeks. At baseline and during the four visits (first day, 14th day, 28th day, and 56th day), the participants were assessed by the HRSD (clinical improvement), the Treatment Emergent Symptom Scale (TESS-Severity [TESS-S] and TESS-Treatment [TESS-T] [side effects]) [20], the Epworth Sleepiness Scale (ESS) (sleepiness) [21], and the Pittsburgh Sleep Quality Index (PSQI) (sleep quality) [22]. All of these scales have validated Chinese versions [23]. Because RLS is associated with PLMS, we intentionally collected the RLS-related symptoms in the item 5j (other reasons for sleep disturbance) in PSQI. A remitted participant was defined as having in HRSD score of $\leqslant$7 at the end of treatment period, and suicidal ideation was defined as item 3 (suicide) in HRSD score of $\geqslant$2. Because PLMS might lead to hypertension [24,25], systolic and diastolic BP (mmHg) were recorded at 8:00 am on every visit. Sertraline 50 mg was administered at 8:00 am on the first day. It was then titrated according to clinical efficacy and side effects, with a maximum dosage of 200 mg daily. Concomitant use of central nervous system medications during the trial, especially benzodiazepines and sedatives, was prohibited.

2.2. PSG and leg movement detection

At baseline, the sleep laboratory test consisted of two consecutive nocturnal PSG assessments followed by a daytime multiple sleep latency test (MSLT). Because of first-night effect, the first night was regarded as an adaptation night [26]. The PSG variables on the second night and the MSLT on the third day were defined as baseline data. Because of daytime MSLT, the third night was not suitable for PSG assessment. Thus the PSG assessment for the first day of drug treatment was initiated on the fourth night, and 50 mg of sertraline was administered at 8:00 am on the fourth day. On each of the subsequent four visits during an 8-week trial, participants were assessed by one night of PSG followed by MSLT.

According to the nocturnal PSG, the basic recordings included a standard EEG (F4–A1, C4–A1, O2–A1, C3–A2), an electrooculography (LE–A2, RE–A1), a chin electromyography (EMG), a bilateral legs EMG (anterior tibialis muscles), an electrocardiography, 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 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), rapid eye movement (REM) SL (sleep onset to the first epoch in REM stage in minutes), wake after sleep onset (WASO) (stage W during TRT minus SL in minutes), and arousal index (AI) (the number of arousals divided by TST). The sleep architecture indices included the percentages of in each stage (the time in stage 1, stage 2, stage 3, and stage REM sleep divided by the TST) [27]. The 5-nap MSLT was performed according to the standard recommendation to determine the SL [28]. All computerized sleep data were further edited by an experienced PSG technologist, and this technologist was blind to the research. Sleep stages, respiratory events, and PLMs were scored according to American Academy of Sleep Medicine criteria at 30-s intervals [27].

PLMS was defined as limb movements in sleep with EMG bursts of 0.5–10 s in duration and $\geqslant$4 such events appearing at 5- to 90-s intervals. The timing of the onset of a limb movement (LM) event