Bupropion SR Reduces Periodic Limb Movements Associated With Arousals From Sleep in Depressed Patients With Periodic Limb Movement Disorder

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Background: Antidepressant-induced periodic limb movement disorder (PLMD) may limit the tolerability of some antidepressant medications and interfere with treatment response. Given the role of dopamine in PLMD and the effects of bupropion sustained-release (SR) on central dopaminergic function, we hypothesized that bupropion SR would not be associated with antidepressant-induced PLMD.

Method: In an expanded case-series design, we compared the effects of bupropion SR, after about 10 weeks of treatment, on measures of PLMD, depression, and sleep in 5 depressed (Research Diagnostic Criteria) patients who also met criteria for having pretreatment PLMD. Depression was measured using the Beck Depression Inventory and the Hamilton Rating Scale for Depression. Patients were considered to have PLMD if polysomnographic recordings showed > 5 periodic limb movements/hour of sleep that were associated with arousals from sleep.

Results: Bupropion SR treatment was associated with a reduction in measures of PLMD and an improvement in depression.

Conclusion: These results show that bupropion SR is not associated with antidepressant-induced PLMD. Rather, bupropion SR treatment reduces objective measures of PLMD in depressed patients with the disorder.

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In the selection of an antidepressant, patient tolerability is an important factor to consider. Several reports have demonstrated that antidepressant medications can be associated with a disruption in sleep that is related to an increase in periodic limb movements during sleep.[1–3] These movements may not be noticeable to the individual or easily detected in a clinical interview, since the arousals associated with these movements may not result in full awakenings from sleep. In periodic limb movement disorder (PLMD), frequent arousals from sleep can lead to a subjective sense of nonrestorative sleep and daytime fatigue. It can be difficult, therefore, to determine if a depressed patient's sleep complaints are simply a feature of depression that will resolve once the depression is treated, or if they may be a side effect of the antidepressant therapy. Also, periodic limb movements are often alerting; therefore, treatment-related exacerbation of this condition may very well undermine antidepressant efficacy and contribute to a worsened clinical course. While the incidence of PLMD in depressed patients is unknown, this disorder has been estimated to exist in 1% to 15% of patients with insomnia complaints and in up to 34% of patients over the age of 60.[4] Consequently, it is important to consider antidepressant-induced PLMD in the differential diagnosis of insomnia complaints in patients who are taking antidepressant medications as well as in the differential diagnosis of treatment nonresponse.

Although the pathophysiology of PLMD is not entirely known, it is considered to involve the dopaminergic system. Staedt et al.,[5] for example, demonstrated a decrease of central D_2 receptor occupancy in patients with PLMD. First-line treatments of PLMD include the use of dopaminergically active agents, such as bromocriptine, selegiline, and L-dopa combined with carbidopa. Bupropion sustained-release (SR) is reported to have effects on the dopaminergic system in addition to its effects on noradrenergic systems.[6] Given this dopaminergic activity, we hypothesized that treatment of depression with bupropion SR would not be associated with the induction of PLMD and may be associated with improvements in PLMD in

depressed patients who demonstrated this syndrome prior to therapy. We are aware of 1 clinical case report that supports this hypothesis.[7] To more formally test the hypothesis that bupropion SR may have beneficial effects on PLMD in depressed patients, we analyzed pretreatment versus posttreatment polysomnographically verified periodic limb movements of depressed patients who met criteria for having PLMD and who were treated with bupropion SR.

METHOD

Study Design

The study design was a retrospective case series. Five depressed subjects (3 men and 2 women, mean ± SD age = 42.1 ± 13.3 years) met the following inclusion criteria and were included in subsequent analyses: (1) Research Diagnostic Criteria (RDC)[8] for major depression on the basis of an interview with the Structured Clinical Interview for DSM-III-R,[9] (2) a minimum score of 15 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D),[10] (3) treatment with bupropion SR, (4) polysomnographic documentation of PLMD defined as > 5 periodic limb movements/hour of sleep that are associated with arousals from sleep, and (5) posttreatment polysomnographic monitoring for periodic limb movements.

Additionally, all subjects were required to be free of medications that could affect mood or sleep for at least a 2-week period of time (8 weeks for fluoxetine) prior to electroencephalographic (EEG) sleep studies. Subjects who could not remain drug- or alcohol-free during the study, verified by nightly drug screens, were excluded. Subjects were also excluded if they met RDC for schizophrenia, lifetime history of substance abuse or alcoholism, borderline or antisocial personality disorder, organic affective disorder, schizoaffective disorder, psychotic subtype of major depression, or bipolar depression. A medical history, physical examination, and laboratory tests were conducted on all subjects at entry into the study, and medical exclusion criteria were met as previously described.[11] Subjective sleep was assessed before and after treatment using the global scale of the Pittsburgh Sleep Quality Index (PSQI).[12] Subjective depression severity was assessed using the Beck Depression Inventory (BDI).[13]

EEG Sleep Methods

EEG sleep studies were performed and scored over 2 nights at the General Clinical Research Center, University of Pittsburgh Medical Center according to previously established methods. Assessment of periodic limb movements occurred on the patients' first night of sleep studies. Assessment of objective sleep measures to determine sleep quality was performed on nights 1 and 2. *Bedtime* was defined by the mean bed time over the 7 days preceding sleep studies as determined by review of a 7-day sleep log. The EEG sleep montage used on the first night of studies consisted of a C4/A1-A2 EEG channel, 2 electrooculographic (EOG) channels (right and left eyes) referenced to linked mastoids, a submental electromyographic (EMG) channel, and an anterior tibialis EMG channel for the monitoring of periodic limb movements. The EEG sleep montage used on the second night of studies consisted of a C4/A1-A2 EEG channel, 2 EOG channels (right and left eyes) referenced to linked mastoids, and a submental EMG channel. All electrode impedances were determined to be < 10,000 ohms. The EEG signal was collected using Grass 7P511 amplifiers (Grass-Telefactor, Inc., West Warwick, R.I.). Filter settings for the EEG were 0.3 to 100 Hz. The EMG was bipolar, with a filter setting of 10 to 90 Hz. Sleep was recorded and analyzed digitally according to previously published methods.[14] EEG sleep was scored visually by raters blind to clinical information, according to the Rechtschaffen and Kales criteria.[15]

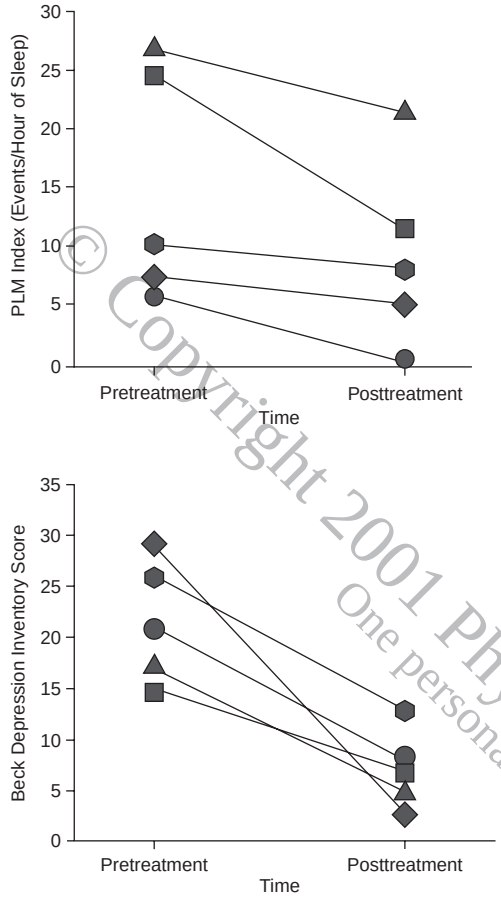
Periodic Limb Movement Scoring

Periodic limb movements (PLMs) were scored according to the rules provided by the American Sleep Disorders Association Atlas Task Force.[16] Four summary measures were calculated: (1) *PLM total* defined as the total number of periodic limb movements detected during sleep, (2) *PLMs associated with arousals* defined as the number of periodic limb movement associated with either arousals or awakenings, (3) *PLMs not associated with arousals* defined as "PLM total" minus "PLMs associated with arousals," and (4) *PLM index* defined as the "PLMs associated with arousals" divided by the number of hours spent asleep (minutes asleep/60 minutes/hour).

Statistical Analyses

Given the small sample size and the non-normality of the periodic limb movement data, we used the nonparametric Wilcoxon signed rank test to test paired pretreatment versus posttreatment differences in periodic limb movement and clinical and general sleep quality measures. Given our a priori hypothesis that bupropion SR would reduce periodic limb movements and improve depression, we used 1-tailed tests for the PLM and depression analyses. To report the pretreatment and posttreatment EEG sleep profiles for this group, we first compared the differences in EEG sleep between the first and second nights of recording at both pretreatment and posttreatment. In the absence of differences between the 2 nights, we subsequently averaged the data from the 2 nights. This provides for both the inclusion of sleep data from the same night of recording as the PLM data and the inclusion of sleep data from a second night of recording that would be more comparable with literature reports of EEG sleep in depression.

Figure 1. Effects of Bupropion Sustained-Release on Periodic Limb Movement (PLM) Index and Depression[a]



[a]The symbols for individual subjects are consistent across measures.

RESULTS

Clinical Measures

Prior to treatment, the depressed subjects (N = 5) had a mean ± SD pretreatment depression score on the 17-item HAM-D of 17.17 ± 4.07 and a mean pretreatment depression score on the BDI of 21.0 ± 5.5. At pretreatment, subjects (N = 4) complained of mild-to-moderate subjective sleep disturbances as evidenced by a mean ± SD PSQI global score of 7.8 ± 4.6. They met inclusion/exclusion criteria as noted above. Subjects were treated with bupropion SR for a mean ± SD duration of 10.5 ± 1.5 weeks. All subjects were taking a 400-mg total daily dose at the time of posttreatment sleep studies. As a group, the depressed patients had significant reductions in depression as measured by the BDI (Figure 1; median pretreatment to posttreatment change = –13, signed-rank statistic [S] = –7.5, 1-tailed p = .03) and a trend toward improvement on the HAM-D (median pretreatment to posttreatment change = –6, S = –6.5, 1-tailed p = .06). Two of 5 patients had achieved a 50% reduction of HAM-D scores at posttreatment. One additional subject had achieved a partial remission from depression at posttreatment defined as a HAM-D < 15 but > 7.

Table 1: Pre– and Post–Bupropion SR Treatment Electroencephalographic Sleep Measures[a]

	Pretreatment		Posttreatment	
Sleep Measures[b]	Mean	SD	Mean	SD
Sleep latency (min)	22.6	14.11	37.4	23.21
Time spent asleep (min)	387.9	36.98	386.7	37.20
Recording period (min)	446.3	36.67	467.9	52.41
Stage 1 %	6.94	2.65	10.90	3.89
Stage 2 %	56.09	10.27	58.28	9.62
Stage 3 %	4.72	4.91	3.79	4.57
Stage 4 %	4.09	7.34	1.87	4.16
REM time (min)	109.0	18.76	97.9	22.68
REM latency (min)	53.3	37.79	54.9	12.49

[a]Abbreviations: REM = rapid eye movement, SR = sustained-release.
[b]Mean of nights 1 and 2 of the series.

Periodic Limb Movement Measures

Treatment with bupropion SR was associated with reductions in the mean ± SD total number of PLMs (178 ± 116 pretreatment to 86 ± 57 posttreatment; S = –7.5, 1-tailed p = .03), the number of PLMs associated with arousal from sleep (88 ± 55 pretreatment to 53 ± 44 posttreatment; S = –7.5, 1-tailed p = .03), and the PLM index (see Figure 1; 14.9 ± 9.9 pretreatment to 9.1 ± 7.9 posttreatment; S = –7.5, 1-tailed p = .03). A nonsignificant trend was also noted for a reduction in the number of PLMs that were not associated with arousals (90 ± 83 pretreatment to 33 ± 21 posttreatment; S = –6.0, 1-tailed p = .09).

General Sleep Quality Measures

Table 1 shows the EEG sleep measures at both pretreatment and posttreatment for these subjects. In 4 subjects, the objectively recorded total sleep time increased from pre– to post–bupropion SR treatment. The other subject had excessively long sleep at pretreatment (466 min) that declined to the study group's median level (389 min) following treatment. Overall, sleep efficiency did not change from pretreatment to posttreatment (S = –3.5, 2-tailed p = .44). Therefore, the increase in total sleep time for these 4 subjects was related to a longer sleep period after bupropion SR treatment. For 3 of the 4 subjects for whom there were subjective sleep quality data, their overall subjective sleep quality (PSQI global score) improved. The subject with the most disturbed subjective sleep at pretreatment (PSQI global score = 14) also had the largest PLM index measure at pretreatment (27 PLMs/hour of sleep that were associated with arousals). This same subject had the most pronounced improvement in subjective sleep from pretreatment to posttreatment (a decrease in 9 points on the PSQI global score) as well as the most pronounced improvement on the 17-item HAM-D (22 to 4).

DISCUSSION

This report documents the beneficial effects of bupropion SR on PLMs in depressed patients with PLMD. As hypothesized, bupropion SR did not worsen PLMs in these patients as has been noted with other antidepressants.

The immediate clinical implication of this finding is that bupropion SR can be used without adversely impacting patient tolerability owing to antidepressant-induced PLMD in depressed patients who have already been diagnosed with PLMD. Future studies are required to more fully appreciate the potential broader clinical implications of these findings. For example, these findings raise the question of whether patients who are unable to tolerate other antidepressant trials because of antidepressant-induced PLMD[1,2] may subsequently find bupropion SR more tolerable. Dorsey et al.,[3] for example, found that 44% of fluoxetine-treated depressed patients and none of the nontreated depressed patients in their sample demonstrated polysomnographic evidence for PLMD. They concluded that a higher incidence of PLMD and frequent transient arousals associated with eye movements may be responsible in part for the complaint of insomnia made by patients treated with fluoxetine. Trivedi et al.[17] also reported a significant increase in awake and movement time in depressed patients associated with acute fluoxetine treatment and a reduction in awake and movement time after at least 7 weeks of fluoxetine discontinuation. Several additional reports exist demonstrating fluoxetine-induced oculomotor abnormalities, a potentially similar sleep-related movement disorder.[18–21] Most patients who experience antidepressant-induced insomnia have no formal sleep studies performed to rule out the possibility that the insomnia may be related to antidepressant-induced PLMD. The true extent, therefore, of this syndrome in general clinical practice, and its potential reversal by switching to an antidepressant that does not cause this problem, is unclear.

There may be broader clinical implications of antidepressant-induced PLMD. For example, Fawcett et al.[22] reported that global insomnia was one of the risk factors associated with suicide within 1 year of follow-up in a large scale study of patients with major affective disorders. Difficulty sleeping has also been found to increase risk for mortality of all causes in male and female adults according to a large scale 9-year community study.[23] Also, abnormal sleep profiles and higher pretreatment depression severity were independently associated with poorer outcomes in a longitudinal psychotherapy treatment study of depressed patients.[24] During follow-up, sleep abnormality was predictive of a lower recovery rate and a higher risk of recurrence. Given these risks of increased sleep disruptions, it is conceivable that further disturbances in sleep secondary to antidepressant-induced PLMD may be a significant factor in treatment nonresponse and poor outcome for depressed patients.

Limitations of This Study

Some limitations of this case-report design prevent more definitive interpretations of the findings. First, this study is not a placebo-controlled or nonpharmacologic treatment–controlled study. As such, we cannot definitively state that the reduction in the PLM index in the bupropion SR–treated patients is unrelated to either a nonspecific time effect or a nonspecific effect of improvement in depression. It is clear, however, that unlike other antidepressant medications, bupropion SR does not worsen PLMs in depressed patients. Second, parallel trials are needed in which bupropion SR is compared with other antidepressants prior to stating that there is a significant treatment by time interaction that would favor the clinical use of bupropion SR to either prevent the occurrence of an antidepressant-induced PLMD or not worsen a preexisting PLMD. Third, not all individuals who demonstrate PLMs on sleep recordings report clinically significant disruptions in sleep. Larger scale studies are needed, therefore, to clarify the true clinical significance of antidepressant-induced PLMD and its potential reversal by bupropion SR. The results from the current study suggest that this is a promising future area of investigation to explore in order to identify factors that influence tolerance and effectiveness of different antidepressant medications.

Drug names: bromocriptine (Parlodel and others), bupropion (Wellbutrin), carbidopa-levodopa (Sinemet), fluoxetine (Prozac), selegiline (Eldepryl).

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