# Sleep Microarchitecture in Depression: Association with Response to Bupropion Treatment

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TThe study examined the effect of sustained-release bupropion on sleep microarchitecture in unipolar depression, and evaluated the relationship between the observed sleep changes in response to a single-dose bupropion administration and clinical response to the drug during short-term treatment. Twenty adult patients with major depressive disorder were studied in the sleep laboratory twice for two consecutive nights. On the morning of second night during each session, either placebo or sustained-release bupropion (Wellbutrin SR7; 150 mg, PO) was administered. The participants then received open-label treatment with Wellbutrin-SR for eight weeks. Bupropion produced several effects on sleep microarchitecture. Overall, the frequency distribution of EEG was shifted towards faster frequencies, suggesting greater desynchronization. Bupropion also increased mean wave amplitude during REM sleep and exacerbated inter-hemispheric differences in the number of wave peaks. Neither sleep microarchitecture measures at baseline, nor those following bupropion administration, were related to treatment response. The lack of a predictive microarchitecture measure for response to bupropion treatment may be due to the modest sample size or due to its pharmacological profile of having minimal serotonergic activity. A simultaneous study of bupropion and serotonergic agents would be helpful in clarifying this issue. **(Sleep and Hypnosis 2002;4(2):77-84)**

***Key words:*** *depression, sleep, microarchitecture, antidepressant, bupropion, treatment*

## INTRODUCTION

There are a number of reasons to consider the regulation of sleep as an essential component for understanding the pathophysiology and treatment of depression (1). For instance, sleep complaints are commonly associated with depression and form an essential criterion of the diagnosis (2). Persistent sleep disturbances increase the vulnerability to depression (3,4). EEG sleep changes associated with major depressive disorder are the best replicated findings in biological psychiatry (5,6). Many antidepressant agents affect sleep, some on REM sleep and others on slow-wave sleep (SWS) (1,7-9). Also, antidepressant efficacy, for at least some drugs, can be predicted from baseline sleep polysomnographic measures (10), as well as from EEG sleep changes in

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response to acute antidepressant administration (9,11-14). Certain sleep variables, including reduced REM latency and diminished SWS, have been shown to predict early recurrence after successful treatment of depressive episodes (15-18). Moreover, reduced REM latency and related EEG sleep measures have been detected prior to the onset of depression in some individuals, suggesting that they are vulnerability markers for the illness (19,20).

Traditional visual scoring methods of polysomnographic data have provided valuable descriptions of sleep macroarchitecture changes associated with depression. Stage-scoring algorithms, however, describe only the global organization of sleep and they do not provide information about EEG frequency characteristics or rhythmicity that underlie sleep disturbances. Digital analysis of EEG frequencies provides a more comprehensive picture of brain electrical activity during sleep (21). Spectral analysis and digital period analysis (DPA) are the two most common methods employed for deriving sleep microarchitecture variables (21).

Compared with normal volunteers, depressed patients have been found to display decreased delta activity (17,22) and power (23), increased theta power (22,23), and increased beta power (23). However, no differences between depressed patients and normal controls in absolute delta power (24), delta activity (25), or total power of all frequencies combined (24) have been reported. The reduced delta activity and power, in conjunction with the increased theta activity and power, are consistent with the macroarchitecture findings of reduced SWS and increased REM sleep in depression.

In addition to baseline measures, the acute effects of antidepressant drugs on sleep microarchitecture have been studied. An increase in delta power after an acute dose of clomipramine was associated with more favorable response to treatment with the drug (26). Similarly, an increase in waking theta power after an acute dose of imipramine predicted better response to imipramine treatment, with the increase in theta persisting for two weeks into treatment (27). In contrast to these findings, the acute effects of citalopram administration on non-REM EEG power did not predict, or correlate with, response to treatment with the drug (28).

To the best of our knowledge, the effects of an Aatypical@ antidepressant drug on sleep microarchitecture in depressed patients have not been reported. Because these agents might have different and, possibly, more specific effects on sleep, it might be possible to discern more subtle effects on sleep that are related to antidepressant response. One of these newer atypical antidepressant compounds is bupropion (29). Bupropion differs pharmacologically from other antidepressant agents in that it has a major effect on the dopamine transporter. It also has some activity on norepinephrine uptake, but has little effect on serotonergic (5-HT) systems (29-31). The primary aim of this study was to determine the relationship between acute effects of bupropion on sleep microarchitecture and antidepressant response to short-term treatment with the drug.

## METHODS

### *Participants*

The study was approved by the Institutional Review Board, and all participants signed the written informed consent form prior to performing research procedures. Subjects were recruited from the outpatient clinic at Harbor-UCLA Medical Center and through advertisements in local newspapers. All potential participants were assessed using the Structured Clinical Interview for DSM-IV (32) for the identification of major depressive disorder and comorbid conditions. Severity of depressive symptoms was determined by the first 17 items of the Hamilton Depression Rating Scale (HAM-D) (33). Patients should have been free from antidepressant drugs and other psychotropic

agents for at least four weeks (8 weeks for fluoxetine) for eligibility to participate in the study. A minimum HAM-D score of 15 was required for acceptance into the study. All subjects were medically healthy, as determined by physical examination, full chemistry panel, thyroid function tests, electrocardiogram and urine drug screens.

Exclusion criteria included prior use of bupropion for the treatment of depression or for other conditions (e.g. smoking), history of seizure disorder or other neurological conditions, active suicidal ideation or recent suicide attempt, and current or previous diagnosis of anorexia/bulimia nervosa, primary anxiety disorder, bipolar disorder or psychotic disorder. Also, potential subjects with substance use disorder diagnosis in the previous 6 months, patients with a personal history of sleep disorder(s), and women with suspected pregnancy were excluded from the study.

### *Sleep Protocol and Scoring of Sleep Records*

Each participant was studied on two separate sessions for two consecutive nights during each session, approximately one week apart between sessions. Conventional EEG electrodes were attached by 9:00 p.m., and sleep recordings were made from 11:00 p.m. (lights out) to 7:00 a.m. On the morning of Night 2, subjects were given either placebo or sustained-release bupropion (Wellbutrin SR7; 150 mg, PO) in a randomized, double-blind, cross-over fashion. The first night of each sleep study was considered an adaptation night, and only data from the second night were utilized in statistical analyses. Sleep measures following placebo administration were considered as baseline values (unless stated otherwise, Wellbutrin SR7 will be referred to as bupropion).

The International 10-20 System was used for EEG electrode placement, electromyogram, electrooculogram and electrocardiogram. In order to rule out the presence of major sleep disorders, a full sleep polysomnography was performed on the first night, including respiratory, oximetry and leg movement measurements. Bilateral EEG recordings were obtained from left (C3) and right (C4) central leads referenced to the opposite mastoid, A2 and A1, as well as to a linked reference (A1+A2).

All polysomnographic records were sampled at 200 Hz directly to a hard disk using the SANDMAN computerized collection system, then copied to optical disk for later analysis. High and low frequency filters were set at 35 Hz and 0.1 Hz, respectively. A 60 Hz notch filter was also used. The following frequency distributions were defined: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (12-16 Hz), and beta (16-32 Hz). The records were coded and analyzed Ablind@ to the drug/placebo condition. Visual scoring was done according to standard criteria (34). For digital analysis, both DPA (full-wave zero-cross, half-wave zero-cross, and first-derivative) and power (FFT) analysis were performed for all 30-second epochs of stages 2, 3 and 4, as well as REM sleep (21). Tracing artifacts were removed by visual inspection.

### *Treatment Protocol*

After the second two-night sleep polysomnography session, patients began standard clinical treatment with bupropion under the care of a psychiatrist for approximately 8 weeks (mean=55.1 days; SEM=2.1 days), with weekly monitoring of symptoms and side effects. The protocol required eight weeks of treatment. However, due to scheduling difficulties for some subjects, the final assessment was not obtained exactly at week 8. Thus, treatment duration ranged from 7 to 9 weeks. Dose adjustments were made based on reports of depressive symptoms and side effects. The final dosage ranged from 150 to 400 mg/day.

Subjects who showed ∃50% reduction in HAM-D score in response to bupropion treatment were classified as responders. In order to determine change in HAM-D score in response

**Table 1. Demographic and clinical characteristics (mean+SEM) of the total sample, and in responders and nonresponders to bupropion treatment**

| | Total Sample (n = 20) | Responders (n = 11) | Non-responders (n = 9) |
|---|---|---|---|
| Age (years) | 46.2 + 2.8 | 44.7 + 4.2 | 47.9 + 2.0 |
| Gender (M/F) | 10/10 | 6/5 | 4/5 |
| Body mass index | 27.6 + 1.0 | 27.3 + 0.9 | 28.0 + 2.0 |
| Baseline HAM-D score | 20.3 + 0.8 | 21.1 + 0.9 | 19.3 + 1.4 |
| Final HAM-D score | 10.6 + 1.3 | 7.5 + 0.8 | 14.3 + 2.0* |
| Duration of index depressive episode (weeks) | 69.7 + 9.4 | 72.2 + 12.4 | 66.7 + 15.1 |
| recurrent depression (#/percent) | 13 (65.0) | 7 (63.6) | 6 (66.7) |
| Duration of treatment (days) | 55.1 + 2.1 | 55.3 + 2.7 | 54.8 + 3.5 |
| Final bupropion dose (mg/day) | 290.0 + 12.4 | 300.0 + 17.8 | 277.8 + 16.9 |

*p=.05

to treatment, the final HAM-D score was subtracted from the baseline (pre-treatment) value.

### *Statistical Methods*

Descriptive statistics were derived for all variables. Scrutiny of the W statistic revealed whether variables were suitable for parametric tests. Logarithmic transformations were performed for variables that did not meet normal distribution. Repeated measures ANOVA tests were carried out over the two nights on all major EEG sleep variables. Student=s t tests were utilized for group comparisons between responders and non-responders, and paired t tests were used for within- subject comparisons. Pearson-product moment correlations were used for assessing relationships between variables.

## RESULTS

### *Demographic and Clinical Characteristics*

Twenty subjects (10 men, 10 women) were studied. Of these, 11 were classified as treatment responders. Demographic and clinical characteristics of the entire group, and separately for responders and non-responders, are outlined in Table 1. There were no significant differences between responders and non-responders with respect to age, gender, baseline HAM-D score, number of treatment days, body mass index (BMI), or final dose of bupropion. However, as expected, the final HAM-D score in the responders was significantly less compared with the corresponding score in non-responders ($t_{18}$=3.3, p=.005).

Age did not correlate significantly with baseline HAM-D score, final HAM-D score, or change in HAM-D score in response to treatment. Duration of treatment did not correlate significantly either with the final HAM-D score or with change in HAM-D score. Finally, bupropion dose did not correlate significantly with change in HAM-D score, or with the BMI. Men and women did not differ significantly with respect to age, BMI, treatment duration, or any of the HAM-D scores. However, by the end of 6 weeks, men were taking a higher dose of bupropion than women (315.0 + 10.7 vs 265.0 + 19.8 mg, $t_{18}$=2.2, p=.05). Nevertheless, the response rate was not significantly different in two groups (the response rate=60% in males and 50% in females).

### *Effect of Bupropion on Sleep Microarchitecture*

Major sleep microarchitecture variables for all 20 patients following placebo and single-dose bupropion administration are shown in Table 2.

DPA: Full-Wave Zero-Cross Effects. Bupropion administration significantly reduced percent delta activity during REM sleep over the entire night ($F_{1,19}$=5.0, p=.05). This reduction

**Table 2. Significance levels for selected sleep microarchitecture variables following acute bupropion administration**

| | | ANOVA p-values | | | | |
|---|---|---|---|---|---|---|
| | | Delta | Theta | Alpha | Sigma | Beta |
| Full-wave | Total REM | 0.038 | - | 0.037 | 0.027 | - |
| | 1st REM | - | - | - | 0.006 | - |
| Half-wave | Total REM | 0.041 | - | 0.036 | 0.039 | - |
| | 1st REM | - | - | - | 0.014 | - |
| First-derivative | Total sleep | 0.000 | 0.003 | 0.008 | 0.006 | 0.005 |
| | Total non-REM | 0.001 | 0.003 | 0.018 | 0.015 | 0.007 |
| | Total REM | 0.000 | 0.007 | 0.018 | 0.003 | 0.007 |
| | 1st non-REM | 0.000 | 0.000 | 0.002 | 0.009 | 0.002 |
| | 1st REM | 0.003 | 0.006 | - | 0.005 | 0.003 |
| | 2nd non-REM | 0.044 | 0.032 | 0.025 | - | - |

Note: Underlined values indicate a decrease in activity for a given frequency range after drug administration

was accompanied by significant increases in alpha ($F_{1,19}$=5.0, p=.05) and sigma ($F_{1,19}$=5.7, p=.05) percentages during total REM sleep. Similar results were obtained for sigma activity during the first REM period ($F_{1,19}$=9.4, p=.01).

DPA: Half-Wave Zero-Cross Effects. Similar to the full-wave findings, bupropion administration significantly reduced delta percentage during total REM sleep ($F_{1,19}$=4.8, p=.05). This reduction was again accompanied by significant increases in alpha ($F_{1,19}$=5.1, p=.05) and sigma ($F_{1,19}$=4.9, p=.039) percentages. A significant increase was measured in the first REM period for sigma activity as well ($F_{1,19}$=7.2, p=.05).

DPA: First-Derivative Effects. Bupropion administration significantly decreased total night delta ($F_{1,19}$=19.8, p=.0001) and theta ($F_{1,19}$=11.4, p=.005) percentages, and increased alpha ($F_{1,19}$=8.7, p=.01), sigma ($F_{1,19}$=9.6, p=.01), and beta ($F_{1,19}$= 9.9, p=.005) percentages. This pattern was consistent for total non-REM sleep, total REM sleep, the first non-REM period, the first REM period (excluding alpha), and the second non-REM period (excluding sigma and beta).

Effects of Bupropion on Other Microarchitecture Variables. Bupropion administration significantly increased baseline crossings ($F_{1,19}$=4.4, p=.05) and wave mean amplitude ($F_{1,19}$=10.1, p=.005) during total REM sleep.

Inter-hemispheric Effects. A significant difference in the number of wave peaks was found between hemispheres during total sleep ($F_{1,19}$=7.2, p=.05), with the left hemisphere having greater number of peaks. Similar results were found for the number of peaks during total non-REM sleep ($F_{1,19}$=4.9, p=.05) and during REM sleep ($F_{1,19}$=14.4, p=.001), during the first REM period ($F_{1,19}$=12.3, p=.005), and during the second non-REM period ($F_{1,19}$=9.0, p=.01).

A significant drug x hemisphere interaction was found for the number of peaks during total sleep time ($F_{1,19}$=11.9, p=.005), with the number of peaks increased more in the left hemisphere after the bupropion administration. Similar results were obtained for peaks during non-REM sleep over the entire night ($F_{1,19}$=11.7, p=.005), total REM sleep ($F_{1,19}$=8.0, p=.05), the first non-REM period ($F_{1,19}$=12.3, p=.005), first REM period (F=16.1, p=.001), and second non-REM period ($F_{1,19}$=8.7, p=.01).

FFT: Power Effects. No significant effects of bupropion were found for any EEG power measures.

### *Association Between Sleep Microarchitecture and Clinical Response*

Neither baseline sleep microarchitecture measures, nor microarchitecture variables in

response to acute bupropion administration, predicted subsequent response to treatment with bupropion. Like wise, there were no significant correlations between any microarchitecture measures and response to treatment.

## DISCUSSION

We found that acute bupropion administration affected sleep microarchitecture variables. While several specific effects were found, bupropion altered the overall frequency distribution of EEG activity, shifting it towards faster frequency, most notably during REM sleep. Also, there were more baseline crossings during REM sleep. Together, these findings suggest that acute bupropion administration is associated with greater EEG desynchronization.

The effects of bupropion differed from those obtained with other antidepressant drugs. In a previous investigation, desipramine did not affect delta activity during the night (35). Although fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), also did not influence delta activity (35), acute treatment with a different SSRI, citalopram, was found to decrease power in the 8-9 Hz (low alpha) range during non-REM sleep (28). These findings, coupled with the bupropion-induced alterations reported herein, indicate that different antidepressant agents, even within the same class, produce different effects on sleep microarchitecture.

Somewhat surprisingly, acute bupropion administration increased mean wave amplitude during REM sleep, which would not be expected with the concurrent shift towards faster activity in EEG frequency distribution. This suggested that EEG waves were both >bigger= and >faster. It is possible that this combination of changes masked any effects of bupropion on power measurements. The increased amplitude (height) compensated for the reduced frequency (width) when areas under the waves were measured. Since the EEG reflects synchronicity in the firing of neurons, the increased frequency might indicate less synchronous firing (or fewer neurons firing together), while the increased wave amplitude suggests an increase in the voltage changes in individual neurons.

On the baseline night, significantly more peaks per epoch were found in the left hemisphere than in the right hemisphere, suggesting greater desynchronization and faster activity in the left hemisphere. This observation is only partially consistent with previous findings by Armitage and colleagues that depressed patients had more delta, theta and beta activity in the right hemisphere when compared with normal controls (36). More EEG peaks is consistent with faster frequency activity, so a greater number of peaks in the left hemisphere is consistent with less delta and theta activity in the that hemisphere. The patients in the current study had more peaks in the left hemisphere, which seemed somewhat inconsistent with depressed patients having less beta (fast frequency) activity in the left hemisphere. However, no other significant hemispheric differences were observed in our patients.

Although the frequency range definitions used in this investigation were comparable to those used by Armitage et al. (36), subjects in the latter study were younger, more severely depressed, and were predominately women. With respect to gender effects, Armitage and colleagues suggested that right-hemisphere abnormalities are more robust in depressed women than in depressed men (37). Therefore, the greater beta activity (as well as delta and theta activity) in the right hemisphere might have been due to higher proportion of female subjects in their study (36).

Bupropion administration also increased the number of peaks, more so in the left hemisphere than in the right hemisphere. Since both symptomatic and asymptomatic depressed patients have a higher prevalence of hemispheric EEG asymmetry than normal controls (36), by extension, the hemispheric differences noted herein on both baseline and drug nights also might be trait-related.

Although no baseline sleep microarchitecture measure was found that reliably predicted response to treatment, a previous study suggested that increased delta power, along with decreased theta, alpha, and beta power, predicted response to antidepressant treatment (38). The authors speculated that the microarchitecture differences between responders and non-responders might be due to 5-HT differences in the patients. If this were true, then the lack of a differential sleep microarchitecture effect of bupropion would be consistent with its pharmacological profile of having little 5-HT activity (29-31).

The lack of an acute predictive sleep microarchitecture measure was consistent with previous findings with citalopram (28), but not with imipramine (27) or clomipramine (26). Increased theta power after imipramine (27), and increased delta power after clomipramine (26), were associated with successful treatment response. Reasons for these inconsistent findings are unclear.

In summary, an acute dose of bupropion shifted the frequency distribution of EEG sleep towards faster frequencies, suggesting greater desynchronization. Bupropion also increased wave mean amplitude during REM sleep and exacerbated inter-hemispheric differences in the number of EEG wave peaks. However, no sleep microarchitecture variable was associated with response to treatment with bupropion.

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