Effect of treatment with bupropion on EEG sleep: relationship to antidepressant response

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Abstract

The objective of this study was to assess whether treatment with sustained-release bupropion (Wellbutrin-SR\textsuperscript{\textregistered}) produces alterations in electroencephalographic (EEG) sleep that are associated with clinical response to the drug. EEG sleep was measured in 20 patients with unipolar major depressive disorder before and after treatment with sustained-release bupropion. Each EEG sleep session consisted of two consecutive nights. Treatment with bupropion lasted for 8 wk. Compared to EEG sleep measures at baseline, treatment with bupropion significantly lengthened REM latency, increased REM activity and density during the first REM period, and increased total REM density. Differential response to treatment was associated with changes in REM activity and density, but not with REM latency. However, in contrast to many other antidepressants, REM sleep was not suppressed.

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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. There is a significant overlap in neurotransmitter systems and, possibly, the circuits that control sleep and mood regulation (McCarley et al., 1995; Nozinger et al., 1999; Wu et al., 2001). Sleep complaints are commonly associated with depression and form an essential criterion of the diagnosis (APA, 1994). Persistent sleep disturbances increase vulnerability to depression (Breslau et al., 1996; Ford and Kamerow, 1989). Accordingly, electroencephalographic (EEG) sleep changes associated with major depressive disorder are among the best-replicated findings in biological psychiatry (Benca et al., 1992; Kupfer, 1995).

Many antidepressant drugs have been shown to affect sleep, some affect REM sleep and others can change slow-wave sleep (Nozinger et al., 1995; Reynolds, 1998; Rush et al., 1998; Sharpley and Cowen, 1995; Sharpley et al., 1996; Staedt et al., 1998; Staner et al., 1995; Thase, 1998; van Bemmel et al., 1993; Vogel et al., 1990; Ware et al., 1994; Winokur et al., 2001). Certain EEG sleep measures, including reduced REM latency and reduced slow-wave sleep, have been shown to predict early recurrence after successful treatment of depressive episodes (Giles et al., 1987; Grunhaus et al., 1994; Kupfer et al., 1990; Reynolds et al., 1989). Moreover, reduced REM latency has been detected in some individuals prior to the onset of depressive illness (Giles and Kupfer, 1994; Rao et al., 1996). These features strongly support REM latency and related sleep characteristics as promising markers for studying the pathophysiology and treatment of depression.

The relationship between EEG sleep changes associated with antidepressant administration and clinical response has been studied. The results from initial reports suggested that REM sleep suppression might be associated with better antidepressant response (Dunleavy and Oswald, 1973; Hochli et al., 1986; Kupfer et al., 1976, 1981; Reynolds et al., 1991; Vogel et al., 1990; Wyatt et al., 1969). However, other studies did not replicate this finding (Gillin et al., 1978; Landolt et al., 2001; Mendlewicz et al., 1991; Staedt et al., 1998; Staner et al., 1995; van Bemmel et al., 1992, 1993; Wilson et al., 2000).
One possibility for the inconsistent findings in the association between EEG sleep and antidepressant response might be related to the antidepressant dosage regimen utilized (Berger and Riemann, 1993). Differences in response can be attributed to the type of antidepressant and the dosage (differences in sensitivity that might have been related to treatment response possibly were lost due to a ceiling effect, particularly at higher doses, as well as the duration of treatment). For example, Kuper et al. (1981) demonstrated that EEG sleep changes measured after acute antidepressant administration (specifically a tricyclic agent) predicted clinical response. However, the effect of EEG sleep measures on antidepressant response was no longer significant when the sleep studies were performed after longer treatment duration.

In contrast to the typical antidepressants, the effects of ‘atypical’ antidepressants, which appear to have different effects on REM sleep than typical agents (Nozinger et al., 1995; Rush et al., 1998; Schittecatte et al., 2002; Sharpley et al., 1992; Ware et al., 1994), on treatment response have not been well studied. With these agents, it might be possible to discern more subtle effects on sleep architecture that are more closely linked to their antidepressant activity. Bupropion is an atypical antidepressant agent (Preskorn and Othmer, 1984) with an unclear mechanism of action. It is purported to have some effects on dopamine and norepinephrine uptake, but shows little direct activity on serotonergic (5-HT) systems (Cooper et al., 1980, 1994; Ferris et al., 1981; Little et al., 1999). In this report, we assessed the EEG sleep changes associated with short-term bupropion treatment and their relationship to clinical response.

Materials and methods

Clinical assessments

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 (SCID; First et al., 1994) for the identification of major depressive disorder and comorbid conditions. Severity of depressive symptoms was determined by the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960). Diagnosis of major depressive disorder and a minimum score of 15 on the first 17 items of HAMD were required for acceptance into the study. Patients should have been free from antidepressant drugs and other psychotropic agents for at least 4 wk (8 wk for fluoxetine) for eligibility to participate in the study. All subjects were medically healthy, as determined by physical examination, full chemistry panel, thyroid function tests and electrocardiogram. Urine drug screens were negative for all subjects.

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 a 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.

Pre-treatment EEG sleep

Each participant was studied twice for two consecutive nights. The first night for each 2-night session was an adaptation night. In addition, in order to rule out the presence of major sleep disorders, a full sleep polysonmography was performed on the first night, including respiratory, oximetry and leg movement measurements. On the morning after the adaptation night, subjects were given placebo at 07:00 hours as part of a study to compare the acute effects of placebo with a single dose of bupropion SR (sustained release) on sleep (see Ott et al., 2002). The second night was a standard EEG recording (described below). Night-2 EEG sleep measures following placebo administration are considered as baseline values. These values are compared to the sleep EEG measures obtained following treatment with bupropion for 8 wk (see below).

As described previously (Poland et al., 1989, 1997), electrodes were attached by 21:00 hours and sleep recordings were obtained from 23:00 hours (lights out) to 07:00 hours. The International 10–20 System was used for EEG electrode placement, electromyogram (EMG), electro-oculogram (EOG) and electrocardiogram as described previously.

Treatment of depression with bupropion

After the second EEG sleep session, subjects began standard clinical treatment with bupropion SR under the care of a psychiatrist for approximately 8 wk [mean (± s.d.) = 55.1 ± 9.4 d], with weekly monitoring of symptoms and side-effects. The dosing schedule was twice daily; morning and afternoon. The protocol required 8 wk 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 wk. Dose adjustments were made based on reports of depressive symptoms and side-effects. By the end of treatment, the mean (± S.D.) daily dose was 290 ± 48.2 mg (range 150–400 mg/d).

Subjects who showed ≥50% reductions in HAMD scores in response to bupropion treatment were classified as responders. In order to determine change in HAMD score in response to treatment, the final HAMD score was subtracted from the baseline (pretreatment) value. For post-hoc analyses, remission from depression (a final HAMD of ≤7) was used as a secondary outcome measure.

Post-treatment EEG sleep
At the end of treatment, the sleep EEG was obtained for two consecutive nights. Night-2 data were compared with its counterpart pre-treatment baseline night.

Scoring of sleep records
Sleep records were coded and scored according to standard criteria (Rechtschaffen and Kales, 1968). All records were scored by a single person, who was trained to reliability, but blind to treatment response. Criteria for REM measures have been described previously (Kupfer, 1976; Ott et al., 2002; Poland et al., 1989, 1997).

Statistical analysis
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 the sleep latency, number of awakenings, REM latency and REM activity data prior to analyses. Repeated-measure ANOVAs were carried out for all major EEG sleep variables on baseline (pre-treatment placebo) and post-treatment nights. When the ANOVA was significant, paired and unpaired t tests were used to locate significant differences within and across groups respectively. Correlation procedures were used for assessing relationships between variables. Age and gender were used as covariates when appropriate. A p ≤ 0.05 (two-tailed) was considered statistically significant.

Results
Demographic and clinical parameters
Twenty subjects (10 men, 10 women) were recruited, and all 20 subjects completed the study. 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 HAMD score, duration of index depressive episode, recurrent vs. non-recurrent depression, number of treatment days, body mass index (BMI), or final dose of bupropion. However, as expected, the final HAMD score in the responders was significantly lower compared to the corresponding score in non-responders (t₁₈ = 3.22, p ≤ 0.005), even after controlling for the initial HAMD score (F₂,₁₈ = 14.92, adjusted R² = 0.59, p ≤ 0.0001).

Age did not correlate significantly with baseline HAMD score, final HAMD score, or change in HAMD score.
Duration of treatment did not correlate significantly either with the final HAMD score or with change in HAMD score. Finally, bupropion dose did not correlate significantly with change in HAMD score, or with the BMI. Men and women did not differ significantly with respect to age, BMI, treatment duration, or any of the HAMD scores. Men were taking a higher dose (mean ± S.D.) of bupropion than women (315.0 ± 33.8 vs. 265.0 ± 62.6 mg, \( t_{18} = 2.22, p \leq 0.05 \)). Nevertheless, the response rate was not significantly different between the two groups (60% in males, 50% in females).

**Effect of treatment with bupropion on EEG sleep**

Mean (± S.D.) sleep architecture and continuity values at baseline and following 8 wk treatment with bupropion are shown in Table 2. For details on the results of EEG sleep effects of single-dose bupropion administration, see Ott et al. (2002). Except for the number of awakenings, treatment with bupropion produced no significant effect on sleep continuity or non-REM sleep measures. However, there was a significant drug effect on REM latency (shown in Table 2). Treatment with bupropion lengthened REM latency. Bupropion also increased REM activity and REM density during the first REM episode, as well as total REM density (see Table 2).

### Table 2. EEG sleep measures (mean ± S.D.) before and after treatment with bupropion: responders vs. non-responders

<table>
<thead>
<tr>
<th></th>
<th>Responders to treatment</th>
<th>Non-responders to treatment</th>
<th>Two-way repeated measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td><strong>Sleep continuity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>29.3 ± 28.6</td>
<td>33.4 ± 36.3</td>
<td>36.5 ± 46.4</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>409.2 ± 46.4</td>
<td>394.1 ± 42.6</td>
<td>392.4 ± 47.2</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>87.2 ± 8.8</td>
<td>86.1 ± 8.7</td>
<td>85.1 ± 10.3</td>
</tr>
<tr>
<td>Awake time (min)</td>
<td>44.4 ± 43.1</td>
<td>43.6 ± 36.2</td>
<td>49.8 ± 38.3</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>19.0 ± 9.3</td>
<td>20.9 ± 12.1</td>
<td>15.1 ± 6.1</td>
</tr>
<tr>
<td>Number of arousals</td>
<td>45.3 ± 20.8</td>
<td>51.4 ± 19.2</td>
<td>39.3 ± 13.7</td>
</tr>
<tr>
<td><strong>Sleep architecture</strong></td>
<td></td>
<td></td>
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<tr>
<td>Stage 1 sleep (%)</td>
<td>7.1 ± 5.0</td>
<td>8.3 ± 4.8</td>
<td>5.9 ± 3.8</td>
</tr>
<tr>
<td>Stage 2 sleep (%)</td>
<td>56.2 ± 7.8</td>
<td>58.3 ± 8.3</td>
<td>55.0 ± 6.5</td>
</tr>
<tr>
<td>Stage 3 sleep (%)</td>
<td>8.3 ± 3.5</td>
<td>7.7 ± 4.8</td>
<td>8.0 ± 5.8</td>
</tr>
<tr>
<td>Stage 4 sleep (%)</td>
<td>4.2 ± 5.0</td>
<td>4.1 ± 5.2</td>
<td>3.9 ± 4.7</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>24.2 ± 3.0</td>
<td>21.6 ± 5.5</td>
<td>27.2 ± 4.2</td>
</tr>
<tr>
<td><strong>First REM episode</strong></td>
<td></td>
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<tr>
<td>REM latency (min)</td>
<td>52.5 ± 23.1</td>
<td>75.8 ± 38.1</td>
<td>51.5 ± 10.3</td>
</tr>
<tr>
<td>REM activity (units)</td>
<td>34.5 ± 19.5</td>
<td>61.3 ± 37.9</td>
<td>75.4 ± 66.9</td>
</tr>
<tr>
<td>REM density (units/min)</td>
<td>2.0 ± 1.2</td>
<td>2.7 ± 1.4</td>
<td>2.6 ± 1.4</td>
</tr>
<tr>
<td>REM duration (min)</td>
<td>19.0 ± 11.0</td>
<td>21.5 ± 10.6</td>
<td>26.5 ± 15.8</td>
</tr>
<tr>
<td><strong>All REM episodes</strong></td>
<td></td>
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</tr>
<tr>
<td>REM activity (units)</td>
<td>265.1 ± 73.8</td>
<td>243.3 ± 77.9</td>
<td>261.1 ± 91.8</td>
</tr>
<tr>
<td>REM density (units/min)</td>
<td>2.7 ± 0.7</td>
<td>2.9 ± 0.7</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>REM duration (min)</td>
<td>99.0 ± 17.1</td>
<td>86.5 ± 28.2</td>
<td>107.0 ± 23.0</td>
</tr>
<tr>
<td>Number of REM episodes</td>
<td>4.4 ± 1.1</td>
<td>3.8 ± 0.9</td>
<td>4.1 ± 0.9</td>
</tr>
</tbody>
</table>

* \( p \leq 0.05 \).

**Relationship between the effect of bupropion on EEG sleep and clinical response**

Although bupropion treatment significantly increased REM latency, the increase was not different in
responders and non-responders. For treatment responders, REM activity during the first REM period was significantly increased in the responders only ($p \leq 0.05$). There also was a trend for REM density during the first REM period to be increased in the responders ($p \leq 0.1$). In contrast, treatment-induced changes in total REM density were found for non-responders only ($p \leq 0.005$).

Discussion

Treatment with bupropion SR significantly increased REM latency by approx. 40% (22 min). These findings are consistent with results obtained with most other antidepressant drugs (Sharpley and Cowen, 1995; Thase, 1998). However, this finding is in contrast to a report by Nofzinger et al. (2001) in which no change in REM latency was observed following 12 wk of treatment with bupropion SR. In a previous study, utilizing the immediate-release form of the drug, a shortening of REM latency and increased REM sleep were observed (Nofzinger et al., 1995). Another case report showed that bupropion treatment suppressed REM sleep by lengthening REM latency and reducing the number of sleep onset REM periods (SORMPS) during the Multiple Sleep Latency Test (MSLT). Upon treatment discontinuation, REM latency was shortened and more SORMPS were seen during the MSLT (Rye et al., 1998). Reasons for the divergent results are not clear. However, variations in demographic and clinical characteristics of the samples, form of the drug, dosage and duration of treatment, either singly or in combination, could account for the differences in findings.

In a previous report, responders to bupropion treatment showed an increase in pre-treatment REM latency after single-dose administration of the drug, whereas non-responders showed a decrease (Ott et al., 2002). However, as reported herein, after chronic treatment with bupropion, the increase in REM latency occurred in all but three patients. Bupropion not only increased REM latency, but also increased total REM density, as well as REM activity and density during the first REM period. These effects might be due to the delay in the appearance of REM sleep, which in turn increased REM pressure, and resulted in increased phasic activity. However, REM duration was not similarly affected. Comparable results for REM density were obtained with both imipramine (Kupfer et al., 1979) and nortriptyline (Kupfer et al., 1982; Reynolds et al., 1991).

No significant differences in EEG sleep measures were found between responders and non-responders, except for REM activity and density. Responders to treatment showed an increase in REM activity during the first REM period, whereas non-responders showed a significant increase in total REM density. It is not clear as to the reasons for this differential response. However, it should be noted that the REM activity response to a single-dose of bupropion correlated with clinical response (Ott et al., 2002). These data also suggest that different neuroregulatory systems are involved in the regulation of tonic and phasic REM sleep measures (Cabeza et al., 1994; Siegel, 1994), and possibly in the early vs. late phasic REM sleep measures as well. Taken together, the data suggest that the REM latency response to acute bupropion administration might be more helpful in predicting treatment response, whereas phasic REM sleep measures might be more closely associated with adaptive responses to treatment, such as efficacy.

Consistent with our observations, Reynolds et al. (1991) reported that nortriptyline treatment produced a differential effect on REM density in treatment responders and non-responders. Similarly, depressed patients who responded to cognitive behaviour therapy showed a decrease in REM density (Thase et al., 1998). However, these findings are not consistent with other studies in which EEG sleep measures following short-term antidepressant administration did not distinguish response to treatment with paroxetine (Staner et al., 1995), amitriptyline (Gillin et al., 1978; Staner et al., 1995), doxepine (Staedt et al., 1998), maprotiline (Staedt et al., 1998), or citalopram (van Bemmel et al., 1993). Reasons for this inconsistency might include patient demographics, length of treatment, and the antidepressant used for treatment. In addition, because these drugs have such marked effects on REM sleep measures, any relationship between REM activity and clinical response might have been masked due to the robust effects of many antidepressants on REM sleep. Also, the results from this study as well as data with other antidepressant drugs suggest that the immediate reactivity observed during acute antidepressant administration might offer the greatest precision for the prediction of treatment response, a finding that potentially could be of clinical utility (Kupfer et al., 1981; Ott et al., 2002).

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Statement of Interest

None.

References


ECT is associated with rapid recurrence of depressive symptomatology. Biological Psychiatry 36, 214–222.


