REM sleep and cortisol responses to scopolamine during depression and remission in women

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Abstract

Baseline electroencephalographic (EEG) sleep and the EEG sleep response to scopolamine were studied in 10 adult female patients with unipolar major depressive disorder. Subjects were studied twice for two consecutive nights while depressed and, again, during remission. On the second night of each two-night session, normal saline or scopolamine (1.5 µg/kg, i.m.) was administered in a randomized, double-blind, cross-over fashion. Nocturnal urinary free cortisol (NUFC) measures also were collected. Compared to the depressed state, NUFC was significantly lower during remission. In contrast, baseline EEG sleep measures did not differ from episode to remission. Scopolamine suppressed rapid eye movement (REM) sleep to a comparable extent during the depressive episode and in remission. Scopolamine also reduced NUFC secretion during both clinical states, but to a lesser extent than REM sleep suppression. The findings suggest that the dysregulation in cholinergic systems associated with depressive illness may be persistent during remission, at least for some cholinergic systems. The results also suggest that the central cholinergic system(s) that regulate(s) REM sleep may be more sensitive to dysregulation than the cholinergic system(s) that control(s) nocturnal cortisol secretion.

Introduction

Although REM sleep changes have been observed consistently in association with adult major depressive illness (Benca et al., 1992), the pathophysiological mechanism(s) underlying this phenomenon remain(s) to be clarified. Basic and clinical studies have demonstrated the involvement of muscarinic cholinergic systems in the regulation of REM sleep (George et al., 1974; Jones, 1993; McCarley et al., 1995; Sitaram et al., 1978), and it has been suggested that dysregulation of cholinergic systems may be responsible, at least in part, for the REM sleep 'abnormalities' and other symptoms of depression (Dilsaver, 1986; Janowsky and Overstreet, 1995; Shiromani and Gillin, 1987; Sitaram et al., 1982). For example, the direct muscarinic cholinergic agonist, arecoline, has been reported to induce depressive-like symptoms in some normal volunteers (Risch et al., 1983b). Many of the EEG sleep changes observed in depressed patients can be reproduced in normal volunteers by repeated administration of scopolamine, a non-specific muscarinic cholinergic antagonist, which functionally 'up-regulates' muscarinic cholinergic systems (Gillin et al., 1979). In addition, depressed patients show shortening of REM latency to a greater extent in response to administration of cholinergic agonists when compared with normal controls (Berger et al., 1989; Dahl et al., 1994; Gillin et al., 1991b; Riemann et al., 1994; Sitaram and Gillin, 1980; Sitaram et al., 1987).

Other lines of evidence suggest that neuropeptides, including corticotropin-releasing hormone, modulate the regulation of sleep and other behaviours (Steiger and Holsboer, 1997). Numerous investigations also have shown that REM sleep changes are frequently accompanied by nocturnal hypersecretion of cortisol

Key words: Cholinergic, cortisol, depression, EEG sleep, remission, scopolamine.
in patients with depression (Asnis et al., 1983; Ehlers and Kupfer, 1987; Kupfer et al., 1984; Poland et al., 1992; Rao et al., 1996; Steiger et al., 1989, 1991). Previous studies showed that corticotropin-releasing factor/hormone, adrenocorticotropic and cortisol/corticosterone secretion can be induced by cholinergic agonists (Assenmacher et al., 1987; Bugajski et al., 1995; Janowsky et al., 1983, 1986; Ohmori et al., 1995; Owens et al., 1991; Risch et al., 1986), with the effect antagonized by scopolamine (Calogero et al., 1988; Krieger et al., 1968; Poland et al., 1989). In addition to nocturnal hypersecretion of cortisol at baseline in depressed patients, the hypothalamic–pituitary–adrenal (HPA) response to cholinergic agonists also is augmented (Janowsky and Overstreet, 1995; Janowsky et al., 1972; Risch et al., 1983a).

In most studies, baseline REM latency and other REM sleep manifestations associated with depression remain 'abnormal' during remission (Buyssse et al., 1992; Giles et al., 1993; Hauri et al., 1974; Jindal et al., 2002; Kupfer et al., 1993; Lee et al., 1993; Rao et al., 1997; Rush et al., 1986; Steiger et al., 1989, 1991; Thase et al., 1994), with some (Gillen et al., 1982; Sitaram et al., 1982, 1987), but not all (Riemann and Berger, 1989), investigations reporting that the greater shortening of REM latency to cholinergic agonists also remains enhanced. In contrast to the state-independent baseline EEG sleep profile observed in depression, elevated HPA activity appears to be state-dependent, with reduction in HPA function occurring during remission (Carroll et al., 1976; Gerken et al., 1985; Greden et al., 1983; Holsboer et al., 1982; Rao et al., 1997; Steiger et al., 1989, 1991).

In a previous study, we found that remitted patients showed greater sensitivity to the REM-suppressing effects of scopolamine than currently depressed patients, suggesting that cholinergic tone had diminished, or aminergic tone had increased, during recovery (Poland et al., 1997). However, this was a cross-sectional study comparing depressed patients during an index episode to a separate group of remitted patients. In order to investigate further the relationships among baseline EEG sleep measures, cholinergic status and affective state, the EEG sleep response to scopolamine, a non-selective muscarinic antagonist, was studied in a group of female subjects while depressed and then again during remission.

In addition to EEG sleep, baseline HPA activity and the HPA response to scopolamine were also evaluated during both depressive and remitted states. In order not to cause potential disruption in sleep due to catheter insertion and blood drawing, as a reflection of the HPA activity, nocturnal urinary-free cortisol (NUFC) measures were collected. In addition to comparing the sensitivity of cholinergic systems to scopolamine during the depressive episode and in remission, we wanted to assess whether scopolamine differentially affects EEG sleep and HPA activity because prior data suggest that the observed EEG sleep changes persist during remission but HPA activity is state-dependent.

Methods

Clinical assessments

Subjects were recruited from the outpatient clinic at Harbor-UCLA Medical Center. The study was approved by the Institutional Review Board (IRB) and all research subjects signed the IRB-approved informed consent form prior to the evaluations being performed. 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 (DSM-IV code 296.2x/296.3x, ICD-10 code F32.x/F33.x; APA, 1994) and a minimum score of 15 on the first 17 items of HAMD were required for acceptance into the study. All subjects were medication-free for at least 3 months, and none of the subjects had received fluoxetine or a monoamine oxidase inhibitor. At the time of remission, the participants had to have a HAMD score of <6 for a minimum period of 3 months prior to and following the study.

All subjects were medically healthy, as determined by medical history, physical examination, full biochemistry panel, thyroid function tests, electrocardiogram and urine drug screens. Patients were excluded from the study if they had current or past (within the previous 5 years) history of alcohol or other substance use disorder(s), lifetime history of mania or hypomania, primary anxiety disorder, or schizoaffective disorder.

EEG sleep protocol and NUFC sampling

In order to rule out known sleep disorders, the Pittsburgh Sleep Quality Index (Buyssse et al., 1989) was completed prior to the laboratory sleep protocol. Subjects with a personal history of a major sleep disorder, or a family history of narcolepsy, were excluded from the study. Participants also were screened for the presence of sleep disorder(s) on the first night of the laboratory sleep protocol. Subjects were requested to
go to bed between 22:30 and 23:30 hours and to awaken between 06:30 and 07:30 hours for at least 1 wk prior to, and during, the sleep studies. A sleep log was maintained for determining the sleep/awake schedule.

Subjects were studied in the sleep laboratory twice for two consecutive nights approx. 1 wk apart (for a total of four nights). This protocol was performed while subjects were depressed and again during remission. All studies were performed during the follicular phase of the menstrual cycle. The first night was an adaptation night, and 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. On night 2, at 23:00 hours immediately prior to lights out, the subjects received normal saline or scopolamine (1.5 μg/kg, i.m.) in a randomized, double-blind, cross-over fashion.

The International 10–20 System was used for EEG electrode placement, electromyogram (EMG), electrooculogram (EOG) and electrocardiogram. 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). Bilateral EOG recordings were obtained referenced A1 + A2 along with a submental EMG recording. On all nights, conventional EEG electrodes were attached by 21:00 hours and sleep recordings were made from 23:00 hours (lights out) to 07:00 hours.

Subjects were asked to void urine at 23:00 hours prior to switching off the lights. All urine voided between 23:00 and 07:00 hours was collected. Subjects also were asked to void urine immediately upon awakening, and this sample too was added to the night sample of urine.

**Scoring of EEG sleep records and NUFC assay**

Sleep records were coded and scored ‘blindly’ according to standard criteria (Rechtschaffen and Kales, 1968). REM latency was calculated using both lenient and strict definitions. For the lenient criterion, REM latency was defined as the time between sleep onset (the first minute of any stage of sleep) and the first 30 s of REM sleep. The strict criterion was defined as the time between sleep onset (first minute of stage 2 or deeper sleep, followed by at least 9 min of stage 2 or deeper sleep, interrupted by no more than 1 min of waking or stage 1) and the first REM period ≥ 3 min in length. Although both REM latency values were used in the analyses, only the strict definition of REM latency is reported here, with and without intervening awake time subtracted. Other REM sleep measures, including REM activity and REM density, and additional sleep variables were scored according to the criteria of Kupfer (1976), as was done previously (Poland et al., 1989, 1997). REM activity was scored on a scale ranging from 0–8 units. Arousals were defined as increased fast frequencies (alpha, beta) lasting for a duration of 5–15 s between a sleep stage. If the fast frequency episode lasted longer than 15 s on a 30-s epoch, it was scored as an awake stage.

NUFC was assayed using the radioimmunoassay method, as described previously (McCready and Poland, 1989; Poland and Rubin, 1982; Rao et al., 1997). Both NUFC concentration and total NUFC were determined. The intra- and inter-assay coefficients of variation for the assays were less than 10%. Samples from the same subject were analysed in the same assay.

Changes in EEG sleep and NUFC values in response to scopolamine administration (magnitude of change) were expressed as per cent change from baseline:

\[(\text{scopolamine night – saline night})\times100/\text{saline night}\].

**Statistical analysis**

For all summary variables, data were examined for normality using the Shapiro-Wilk W statistic (Shapiro and Wilk, 1965). In cases of significantly non-normal distributions, logarithm transformations were performed to normalize the data prior to the application of statistical tests for significance. Repeated-measures analysis of variance (ANOVA) was employed for evaluating scopolamine’s effect on EEG sleep and NUFC measures during the two clinical states. If the ANOVA was significant, further analyses were performed using paired $t$ tests to locate significant differences. Alpha was set at 0.05. Non-parametric tests were used to compare the magnitude of change in response to scopolamine between different dependent variables and between the two clinical states. Correlation procedures were utilized for examining relationships between measures. Only EEG sleep and NUFC data from the second night of each two-night session were used in the statistical analyses, the first night being considered as an adaptation night.

**Results**

**Demographic and clinical characteristics**

In total, 10 women were studied in both depressed and remitted states. Table 1 shows demographic and clinical information on the subjects. None had significant
anxiety symptoms that met criteria for a disorder. Scopolamine administration did not produce any significant side-effects in the subjects. None of the subjects were treated with an antidepressant drug (or other psychotropic agents) for the index depressive episode. However, five patients received individual psychotherapy.

**Effect of scopolamine on EEG sleep during the depressive episode and during remission**

EEG sleep variables for all 10 subjects following placebo and scopolamine administration, while depressed and during remission, are outlined in Table 2. Age, weight, height, number of depressive episodes and treatment did not significantly influence any of the EEG sleep measures. With the following exception, there were no significant changes in EEG sleep variables from depressive episode to remission. Compared to the depressed state, there was higher REM density during the first REM episode during remission.

Scopolamine significantly increased arousals and stage 1 sleep both during the depressed state and during remission. Scopolamine also significantly delayed the onset of REM sleep during the depressive episode, as well as in remission. In addition, scopolamine suppressed tonic and phasic REM sleep measures during both clinical states. None of the other EEG sleep variables were significantly affected by scopolamine. Statistically, there was no differential effect of scopolamine between the two clinical states for any of the EEG sleep variables. However, scopolamine tended to delay the onset of REM sleep to a greater extent during remission than during the depressive episode.

**Effect of scopolamine on NUFC during the depressive episode and during remission**

Total NUFC excretion and concentration, while depressed and during remission, are shown in Table 3. Age and clinical parameters did not significantly influence the cortisol measures. Compared to the depressed state, there was a significant reduction in NUFC during remission. Scopolamine reduced cortisol excretion to a comparable extent in both clinical states.

**Magnitude of change in REM sleep and NUFC measures in response to scopolamine**

Although scopolamine suppressed both REM sleep and nocturnal cortisol secretion, the magnitude of REM sleep suppression was significantly greater than the reduction in NUFC. For instance, during the depressive episode, REM latency increased by $83.1 \pm 22.8\%$ in response to scopolamine administration, whereas NUFC was reduced only by $21.8 \pm 9.6\%$ ($Z = 2.70, p < 0.01$). Similarly, during remission, magnitude of changes in REM latency and NUFC were $201.2 \pm 83.2\%$ and $16.4 \pm 13.7\%$ respectively ($Z = 2.80, p < 0.005$). Similar results were obtained when magnitude of changes in NUFC concentration were examined ($5.1 \pm 2.4\%$ and $7.5 \pm 2.5\%$ during depressive episode and during remission respectively). The differential effects of scopolamine on REM latency and NUFC during the depressive episode, and in remission, are depicted in Figure 1 and Figure 2 respectively.

**Relationship between REM sleep and NUFC during depression and during remission**

Baseline REM latency and NUFC were significantly correlated during the depressive episode (Spearman $r = -0.80, p \leq 0.01$). The two measures were also correlated on the scopolamine night, but less robustly (Spearman $r = -0.46$, ns). The two variables showed a much weaker correlation during the remitted state (Spearman $r = -0.33$ and $-0.16$ respectively, ns). The pattern was similar when the association between REM latency and NUFC concentration was evaluated.

**Discussion**

The results of the present study provide further evidence for the relative stability of baseline EEG sleep measures in adult depressed patients during...
remission (Buysse et al., 1992; Giles et al., 1993; Hauri et al., 1974; Jindal et al., 2002; Kupfer et al., 1993; Lee et al., 1993; Rush et al., 1986; Steiger et al., 1989, 1991; Thase et al., 1994). In the present study, there was a tendency for baseline REM density to be even higher during remission, similar to what we observed previously in a cross-sectional study (Poland et al., 1997). This might reflect a scar marker of the illness,

Table 2. EEG sleep variables (mean ± s.d.) following normal saline and scopolamine (1.5 μg/kg, i.m.) administration during the depressive episode and in remission

<table>
<thead>
<tr>
<th>Sleep continuity</th>
<th>Depressive episode</th>
<th>Remitted state</th>
<th>Repeated-measures ANOVA (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal saline</td>
<td>Scopolamine</td>
<td>State Drug State × drug</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.4 ± 20.9</td>
<td>18.3 ± 14.8</td>
<td>23.5 ± 22.7 13.9 ± 8.1</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>4145.7 ± 21.5</td>
<td>410.5 ± 23.6</td>
<td>412.6 ± 43.6 414.7 ± 52.5</td>
</tr>
<tr>
<td>Total study time (min)</td>
<td>461.9 ± 15.7</td>
<td>462.4 ± 19.5</td>
<td>465.1 ± 21.8 452.5 ± 31.4</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>89.6 ± 1.7</td>
<td>88.3 ± 4.8</td>
<td>88.2 ± 6.2 88.5 ± 9.5</td>
</tr>
<tr>
<td>Number of arousals*</td>
<td>16.5 ± 5.3</td>
<td>30.9 ± 15.5</td>
<td>23.9 ± 9.4 39.2 ± 27.1</td>
</tr>
<tr>
<td>Awake time (min)</td>
<td>46.2 ± 22.7</td>
<td>51.9 ± 23.4</td>
<td>35.8 ± 26.6 42.9 ± 41.2</td>
</tr>
</tbody>
</table>

Sleep architecture

|                                       |                    |                |                            |
|                                       | Stage 1 sleep (%)  | 4.2 ± 2.2      | 4.8 ± 1.3 6.7 ± 3.5       | 0.13 9.75* 0.16               |
|                                       | Stage 2 sleep (%)  | 50.8 ± 8.9     | 52.5 ± 8.8 56.9 ± 8.2     | 1.76 2.44 0.64               |
|                                       | Stage 3 sleep (%)  | 7.9 ± 2.6      | 6.5 ± 2.7 6.1 ± 2.2       | 2.73 1.25 0.34               |
|                                       | Stage 4 sleep (%)  | 13.3 ± 7.4     | 13.1 ± 8.7 13.9 ± 9.2     | 0.06 3.78 1.24               |
| REM sleep (%)                         | 23.6 ± 5.2         | 17.2 ± 3.7     | 23.1 ± 8.0 16.3 ± 6.4     | 0.32 34.15**** 0.01          |

First REM episode

|                                       | REM latency (min)  | 66.2 ± 16.6    | 72.7 ± 27.3 174.0 ± 92.4 | 2.78 23.00**** 1.30          |
|                                       | REM latency – W (min) | 66.0 ± 16.5 | 71.4 ± 26.2 155.9 ± 66.9 | 2.09 23.75**** 1.05          |
|                                       | REM activity (units) | 29.3 ± 17.6 | 41.2 ± 22.7 23.6 ± 25.7 | 2.65 11.12* 0.24             |
|                                       | REM duration (min)  | 1.5 ± 0.7      | 2.1 ± 0.7 1.3 ± 0.8       | 5.60* 13.22*** 0.93          |
|                                       | REM activity (units) | 19.3 ± 9.9 | 19.2 ± 7.3 14.9 ± 7.0     | 0.49 5.18* 0.10              |
| All REM episodes                      | REM activity (units) | 201.5 ± 92.9 | 213.4 ± 76.1 147.0 ± 83.7 | 0.12 11.05** 0.46             |
|                                       | REM density (units/min) | 2.0 ± 0.7 | 2.3 ± 0.8 2.0 ± 1.0       | 4.17 2.14 0.09               |
|                                       | REM duration (min)  | 101.5 ± 23.9   | 98.0 ± 39.1 61.1 ± 32.3   | 1.57 21.29**** 0.38          |
|                                       | Number of episodes  | 4.2 ± 0.6      | 4.0 ± 0.7 3.5 ± 1.2       | 1.80 4.89 0.04               |

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Table 3. NUFC variables (mean ± s.d.) following normal saline and scopolamine (1.5 μg/kg, i.m.) administration during the depressive episode and in remission

<table>
<thead>
<tr>
<th>NUFC variables</th>
<th>Depressive episode</th>
<th>Remitted state</th>
<th>Repeated-measures ANOVA (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal saline</td>
<td>Scopolamine</td>
<td>State Drug State × drug</td>
</tr>
<tr>
<td>Total NUFC* (μg)</td>
<td>8.3 ± 6.1</td>
<td>6.8 ± 7.5</td>
<td>4.8 ± 4.4 3.9 ± 4.8</td>
</tr>
<tr>
<td>UFC concentration (ng/ml)</td>
<td>21.5 ± 12.1</td>
<td>20.2 ± 11.0</td>
<td>11.0 ± 5.6 10.0 ± 4.9</td>
</tr>
</tbody>
</table>

NUFC, nocturnal urinary free cortisol.

* Analyses were performed with log-transformed variables.

*p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.005; **** p ≤ 0.001; ***** p ≤ 0.0001.

remission (Buysse et al., 1992; Giles et al., 1993; Hauri et al., 1974; Jindal et al., 2002; Kupfer et al., 1993; Lee et al., 1993; Rush et al., 1986; Steiger et al., 1989, 1991; Thase et al., 1994). In the present study, there was a tendency for baseline REM density to be even higher during remission, similar to what we observed previously in a cross-sectional study (Poland et al., 1997). This might reflect a scar marker of the illness,
suggesting that recurrent episodes might lead to greater disturbances in sleep, or possibly due to differential inputs from the neuroregulatory circuits controlling REM sleep (Jindal et al., 2002; Rush et al., 1986; Steiger et al., 1989, 1991; Thase et al., 1995). Changes in cholinergic regulation of different components of REM sleep could be due to alterations in cholinergic tone, or possibly mediated by changes in serotonergic or noradrenergic input.

A number of studies have shown that muscarinic cholinergic systems are involved in the regulation of both the tonic and phasic measures of REM sleep (George et al., 1974; Jones, 1993; McCrley et al., 1995; Shiromani and Gillin, 1987; Sitaram et al., 1978). Increased cholinergic activity shortens REM latency, and increases REM activity and REM density (Berger et al., 1989; Berkowitz et al., 1990; Gillin et al., 1982, 1991b; Riemann and Berger, 1989; Sitaram et al., 1982, 1987), whereas reduced cholinergic tone produces the opposite effects (Gillin et al., 1991a; McCracken et al., 1997; Poland et al., 1989, 1997; Rao et al., 1999).

The observation that the magnitude of REM sleep suppression by scopolamine is comparable during the depressive episode and the remitted state is in contrast to the observations from a previous investigation in our laboratory. With a higher dose of scopolamine (4.5 μg/kg) in a previous study, we found more augmented REM sleep response to scopolamine in recovered subjects compared to currently depressed patients (Poland et al., 1997). One possible explanation for the differing results between the two studies is that, in the previous investigation (Poland et al., 1997),

![Figure 1. REM latency values following normal saline (Sal) and scopolamine (Scop) administration during the major depressive episode (MDE) and in remission.](image1)

Figure 1. REM latency values following normal saline (Sal) and scopolamine (Scop) administration during the major depressive episode (MDE) and in remission.

![Figure 2. Nocturnal urinary free cortisol (NUFC) values following normal saline (Sal) and scopolamine (Scop) administration during the major depressive episode (MDE) and in remission.](image2)

Figure 2. Nocturnal urinary free cortisol (NUFC) values following normal saline (Sal) and scopolamine (Scop) administration during the major depressive episode (MDE) and in remission.

the depressed and remitted subjects were two separate groups of patients. As there appears to be wide cross-individual variability in REM sleep response to scopolamine administration (see Figure 1), the group differences in our previous study might have been a reflection of individual variations in the two groups of patients rather than due to an actual difference in the clinical state. Also, it is not clear whether the less robust difference in REM sleep suppression between the two clinical states in the present study is a result of inadequate power due to modest sample size or due to the dose of scopolamine. Previously, we demonstrated that REM sleep response to scopolamine is dose-related (Poland et al., 1989). In the previous study, scopolamine had a less robust effect in some subjects who had longer REM latency or lower REM density values at baseline (Poland et al., 1997). In order to avoid a ceiling effect, we used a lower dose in the present study. Prospective studies, using both low and high doses of scopolamine in a larger group of patients, might be able to clarify this issue.

Baseline HPA activity, as reflected by NUFC, was higher during the depressive episode than during remission. In contrast to the state-independent EEG sleep profile observed in depression, increased HPA activity appears to be more state-dependent (Carroll et al., 1976; Gerken et al., 1985; Greden et al., 1983; Holsoer et al., 1982; Steiger et al., 1989, 1991; Rao et al., 1997). Increased HPA activity occurs in approx. 40% of depressed patients, with normalization occurring during remission. Non-normalization of HPA
activity has been associated with early relapse (Targum, 1983). Congruent with these reports, all of the subjects in the current study continued to remain in remission for at least 3 months following participation in the EEG sleep and neuroendocrine protocol in the remitted state.

In addition to increased baseline HPA activity in depressed patients, the HPA response to cholinergic agonists also is augmented (Janowsky and Overstreet, 1995; Risch et al., 1983a). Previous studies have shown that adrenocorticotropic and cortisol/corticosterone secretion can be induced by cholinergic agonists (Janowsky et al., 1983, 1986; Risch et al., 1986), with the effect antagonized by scopolamine (Krieger et al., 1968; Poland et al., 1989), but not by meth-scopolamine (Risch et al., 1986). Consistent with these observations, scopolamine suppressed NUFC both during depression and in remission. However, the effect of scopolamine on NUFC was less robust compared to its effect on REM sleep. This is congruent with our previous study of normal volunteers in which REM latency showed greater sensitivity to the effect of scopolamine than nocturnal plasma cortisol secretion (Poland et al., 1989). Thus, depressed patients might possess an up-regulated HPA axis, possibly mediated by dysregulated cholinergic systems, which tends to normalize during remission. However, even during remission, the HPA axis remains abnormal at least in a subgroup of patients (Kathol and Gehrts, 1986). Consistent with this observation, altered HPA activity has been reported in healthy subjects at high familial risk for depressive illness (Holsboer et al., 1995; Rao and Poland, 2003).

Baseline REM latency and NUFC values were correlated during the depressive episode. The changes in these measures in response to scopolamine also were correlated, albeit to a lesser degree, confirming their differential sensitivity to scopolamine. The close association between reduced REM latency and elevated cortisol secretion in major depressive disorder was reported by some other studies, suggesting that dysregulation of mood, sleep and HPA axis might be linked, at least in part, by common neuronal systems (Annseau et al., 1984; Asnis et al., 1983; Feinberg and Carroll, 1984; Giles et al., 1987; Kerkhofs et al., 1986; Mendlewicz et al., 1984; Poland et al., 1992; Rao et al., 1996; Rush et al., 1982; Shipley et al., 1989). However, the strength of this association diminished during remission. It is possible that pharmacological or psychosocial interventions might target the regulatory mechanisms of these three variables to different degrees, thus weakening their link at least temporarily. Longitudinal assessment of these measures at baseline and during the course of treatment would be helpful in determining the progression, or lack, of changes in response to treatment.

In summary, we found that low-dose scopolamine delayed the onset of REM sleep and also suppressed REM sleep during the depressive episode and during remission. Scopolamine also reduced nocturnal cortisol secretion during both clinical states, but to a lesser degree compared to its effect on REM sleep. Because the sample size was modest and only female patients were included, these results should be considered preliminary. Also, only a single dose of scopolamine was used and there was no normal control group for comparison purposes. Although a normal control group was not included in the study, based on prior investigations with normal controls in our laboratory, the depressed subjects in this study manifested reduced REM latency and related EEG sleep characteristics associated with depression, as well as higher NUFC level, compared to the values observed in normal volunteers. It is important to note that we, and other investigators, have shown that scopolaminesuppresses REM sleep in both adolescent and adult depressed patients and in normal volunteers. We also did not observe gender differences in EEG sleep response to scopolamine. Nevertheless, future investigations, using larger sample sizes and different doses of scopolamine in addition to studying more specific probes that target different cholinergic systems, would be beneficial to better discern the effects of cholinergic agents on EEG sleep and HPA measures in depressed and remitted states. A better understanding of the effects of cholinergic agents on these measures potentially might be helpful in not only identifying the pathophysiological mechanisms underlying depressive disorders, but also in developing and testing more specific interventions.

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Statement of Interest
None.

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