The Effects of Mirtazapine on Sleep: A Placebo Controlled, Double-Blind Study in Young Healthy Volunteers

Selcuk Aslan, MD;1 Erdal Isik, MD;2 and Behcet Cosar, MD3

1Chief Resident of Psychiatry, Department of Psychiatry, Gazi University Faculty of Medicine, Ankara, Turkey; 2Professor of Psychiatry, Department of Psychiatry, Gazi University Faculty Of Medicine, Ankara, Turkey; 3Associate Professor of Psychiatry, Department of Psychiatry, Gazi University Faculty Of Medicine, Ankara, Turkey

INTRODUCTION

ANTIDEPRESSANT DRUGS OFTEN INDUCE CHANGES IN THE SLEEP POLYSOMNOGRAM. The duration of rapid eye movement (REM) sleep is reduced and its onset latency is prolonged.1 The existence of a correlation between the antidepressant and REM-suppressing effects of these drugs has already been suggested.2-4 However, drugs that display antidepressant effects without REM-sleep suppression are known to exist; nefazodone, trimipramine, trazodone, bupropion, moclobemide, and mirtazapine are some of the examples.5-7

Mirtazapine, being a noradrenergic, specific serotonergic drug, is classified as a tetracyclic antidepressant in the piperazine group. It specifically antagonizes central α2 adrenergic, as well as 5-HT2 and 5-HT3 serotonergic receptors, which results in the potentiation of central noradrenergic and serotonergic neurotransmission, producing a clinical antidepressant effect. When compared with selective serotonin reuptake inhibitors (SSRIs), it has fewer undesired effects such as insomnia, sexual dysfunction, and nausea, due to its selective blocking properties on postsynaptic neurons. Mirtazapine appears to be equivalent in efficacy to tricyclic antidepressants.8 One placebo-controlled study, investigating the immediate effects of a single dose of oral mirtazapine, demonstrated its lack of ability to significantly prolong REM latency and suppress REM sleep, despite observation of a trend toward an increase in REM latency.6 These results suggest that mirtazapine mediates its antidepressant activity through a mechanism other than REM suppression, while a literature search reveals no conclusive evidence on the issue. The aim of the present study was to objectively assess the effects of mirtazapine, a new antidepressant drug, on sleep patterns of young healthy adults.

METHODS

Subjects

After approval of the study protocol by the local ethics committee, a total of 20 young adult volunteers, with a mean age of 24 (range, 18-30 years) were recruited from a group who responded a newspaper ad. Subjects read and signed a consent form. They were in good physical health as determined by physical examination and clinical laboratory tests. On the basis of a clinical interview, Hamilton Depression9 and Hamilton Anxiety Scales,10 all subjects were found to be free of depression and anxiety. Exclusion criteria included chronic mental illness, treatment with psychoactive medication in the previous year, tobacco or substance addiction, and a history of extreme stress in the previous month. Sleep history and diary were also obtained. Abnormal sleep patterns, such as staying up and waking up late, reduced (<6 hours) or prolonged (>10 hours) sleep time, segmented sleep, sleep onset latency greater than 30 minutes, or an antecedent history of a sleep disorder (insomnia, hypersomnia, restless legs, nocturnal myoclonus, parasomnias, etc.) led to exclusion from the study.

Design

Subjects were randomly allocated to receive either mirtazapine (n=10) or placebo (n=10) in a double-blind manner. There were 7 male and 3 female subjects in the mirtazapine group, while the age-matched placebo group consisted of 5 male and 5 female volunteers. Identically appearing tablets of mirtazapine (30 mg) or placebo were given at 10.30...
7.1 µV/mm respectively. Polygraphic records were analysed and per second. Sensitivity on the EEG and EOG channels was 10 µV/mm and low-frequency filter settings were 30 and 0.1 Hz, respectively, for (EOG) and electromyographic (EMG) activity were also recorded. High-targets: C3-A2 or C4-A1 and O1-A2 or O2-A1. The electroculogram nel polysomnographic EEG monitoring was used in the following mon-
jects were allowed to sleep undisturbed throughout the night, and they EEG recordings started at 23.00 h and the lights were turned off. Sub-
Using alcohol for the duration of the study, a few cigarettes during day-
caffeine. In the morning, another questionnaire was completed concern-
Subjects completed a presleep questionnaire each night, asking their sleep evaluation, and c) investigation of either drug or placebo effects. The Effects of Mirtazapine on Sleep—Aslan et al

RESULTS

Sleep Continuity Measures

Although a significant prolongation of wake time after sleep onset in mirtazapine group (t=2.1, p=0.048) at baseline was noted, it was decreased by the administration of the drug, which also decreased the number of awakenings, while the sleep efficiency index was significantly increased (p<0.05). Statistical analysis showed no effects of mirtazapine on time spent in bed, sleep-period time, total sleep time, sleep-onset latency, and wake time after final awakenings (Table).

REM Sleep Measures

A significant baseline REM latency (REML) prolongation (t=2.1, p=0.046), as well as total REM sleep time (TREM) (t=2.4, p=0.027) and percentage (REM%) (t=2.6, p=0.016) reduction was observed in sub-
jects allocated to the mirtazapine group. The REM sleep time in the sec-
d half of night (REM2) was also shorter in this group (t=2.9, p=0.009). The TREM, REM%, REML, REM sleep time in the first half of night, and REM2 showed no significant suppression with mirtazap-
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Non-REM Sleep Measures

At baseline, stage 1 sleep time (t=2.3, p=0.023), slow wave sleep time in the second half of night (t=2.4, p=0.025) and non-REM sleep time in the second half of night (t=3.3, p=0.004) was significantly pro-
longed in the mirtazapine group. Although mirtazapine significantly increased the duration of stage 3 and slow wave sleep, as well as the percentage of slow wave sleep (p<0.05), when analysed separately the effect on the duration of slow wave sleep time in the first half of night and second half was not significant. Stage 1 sleep time was significantly reduced by mirtazapine administration (p<0.05) (Table). Stage 2 sleep time, non-REM sleep time in the first and in the second half of the night were not affected significantly by the drug (Table).

DISCUSSION

Mirtazapine increased the sleep efficiency and enhanced the sleep continuity, as previously reported by Ruitge et al on 6 volunteer sub-
jects.6 Our finding of a lack of REM-sleep suppression is supported by

Statistical Analysis

Sleep variables analysed by using one-sample Kolmogorov-Smirnov test revealed no skewed or otherwise nonnormal distributions. Inter-
group differences between baseline sleep variables and effects of place-
bo or drug administration on baseline values were calculated by means of a two-tailed Students t-test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Mirtazapine</th>
<th>DIFFERENCES FROM BASELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Placebo Mean±SD</td>
</tr>
<tr>
<td>Time Spent in Bed (min)</td>
<td>427.0 ± 34.5</td>
<td>445.0 ± 22.2</td>
<td>30.2 ± 32.8</td>
</tr>
<tr>
<td>Sleep Period Time (min)</td>
<td>410.9 ± 34.3</td>
<td>428.4 ± 21.1</td>
<td>26.9 ± 33.7</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>401.4 ± 30.4</td>
<td>415.3 ± 21.8</td>
<td>28.2 ± 30.5</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>12.1 ± 7.5</td>
<td>11.7 ± 7.2</td>
<td>2.4 ± 14.5</td>
</tr>
<tr>
<td>Sleep Efficiency Index</td>
<td>94±3.01</td>
<td>93 ± 3.3</td>
<td>1 ± 2.04</td>
</tr>
<tr>
<td>Number of Awakenings</td>
<td>2.0 ± 1.6</td>
<td>3.7 ± 2.8</td>
<td>0.1 ± 1.4</td>
</tr>
<tr>
<td>Wake Time After Sleep Onset (min)</td>
<td>5.4 ± 4.5</td>
<td>13.4 ± 11.0</td>
<td>2.7 ± 5.5</td>
</tr>
<tr>
<td>Wake Time After Final Awakenings (min)</td>
<td>7.8±10.7</td>
<td>4.4 ± 12.5</td>
<td>-2.7 ± 11.4</td>
</tr>
<tr>
<td>REM Latency (min)</td>
<td>106.5 ± 39.4</td>
<td>138.5 ± 26.1</td>
<td>7.4 ± 50.9</td>
</tr>
<tr>
<td>Total REM Sleep Time (min)</td>
<td>101.4 ± 18.9</td>
<td>79.4 ± 21.7</td>
<td>-9.8 ± 28.3</td>
</tr>
<tr>
<td>Percentage of REM Sleep</td>
<td>25 ± 6</td>
<td>19 ± 5</td>
<td>-6 ± 7</td>
</tr>
<tr>
<td>Stage 1 Sleep Time (min)</td>
<td>13.5 ± 9.1</td>
<td>29.4 ± 19.1</td>
<td>6.4 ± 18.0</td>
</tr>
<tr>
<td>Stage 2 Sleep Time (min)</td>
<td>218.3 ± 43.7</td>
<td>233.5 ± 30.6</td>
<td>31.7±39.0</td>
</tr>
<tr>
<td>Stage 3 Sleep Time (min)</td>
<td>33.5 ± 14.2</td>
<td>40.3 ± 18.7</td>
<td>-0.7 ± 19.4</td>
</tr>
<tr>
<td>Stage 4 Sleep Time (min)</td>
<td>37.1 ± 29.2</td>
<td>35.1 ± 24.3</td>
<td>4.2 ± 29.5</td>
</tr>
<tr>
<td>Total Slow Wave Sleep Time (min)</td>
<td>71.4 ± 28.6</td>
<td>75.9 ± 25.6</td>
<td>-4.0 ± 22.9</td>
</tr>
<tr>
<td>Percentage of Slow Wave Sleep</td>
<td>17.9 ± 6</td>
<td>18.3 ± 6.2</td>
<td>-2 ± 6</td>
</tr>
<tr>
<td>REM Sleep Time in the first ½ part of night (min)</td>
<td>22.4 ± 9.3</td>
<td>28.0 ± 22.1</td>
<td>4.1 ± 20.8</td>
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<tr>
<td>REM Sleep Time in the second ½ part of night (min)</td>
<td>79.0 ± 15.3</td>
<td>51.0 ± 25.7</td>
<td>-8.0 ± 20.7</td>
</tr>
<tr>
<td>Non-REM Sleep Time in the first ½ part of night (min)</td>
<td>176.2 ± 22.0</td>
<td>175.6 ± 29.8</td>
<td>0.6 ± 24.6</td>
</tr>
<tr>
<td>Non-REM Sleep Time in the second ½ part of night (min)</td>
<td>123.1 ± 25.7</td>
<td>161.7 ± 25.7</td>
<td>25.2±35.9</td>
</tr>
<tr>
<td>Slow Wave Sleep Time in first ½ part of night (min)</td>
<td>49.4 ± 24.6</td>
<td>50.3 ± 18.9</td>
<td>0.7±34.1</td>
</tr>
<tr>
<td>Slow Wave Sleep Time in second ½ part of night (min)</td>
<td>11.2 ± 12.6</td>
<td>25.3 ± 13.2</td>
<td>5.7±19.6</td>
</tr>
</tbody>
</table>

min, minutes; NS, not significant; SD, standard deviation; SIG, significance; REM, rapid eye movement; * p<0.05, significantly different from placebo, differences between baseline and treatment values were compared.
their results. They found a slight, but nonsignificant reduction in the duration of REM sleep and prolongation of REM-sleep latency. Mirtazapine did not decrease the percentage of REM sleep. Tricyclic antidepressants, SSRIs and monoamine oxidase inhibitors (MAOIs) strongly suppress REM-sleep latency. In our study, we could not demonstrate a significant REM-sleep-suppressing effect of mirtazapine. Due to its distinct effects on human sleep, this compound merits a separate classification.

The effects of mirtazapine were also notable for a significant increase in slow wave sleep. Although some antidepressants such as clomipramine, trazodone, and ritanserine (a specific antagonist of 5-HT2 receptors) have been reported to increase the slow wave sleep, SSRIs and MAOIs have very little or no effect on it. Mirtazapine may produce its effects by deepening the sleep in patients with depression. While some studies report an association of increased deep sleep with antidepressant effect, a clear knowledge on such a relation is lacking. Although the neurochemical basis for this effect of mirtazapine is unknown, it may be related to its 5-HT2-receptor antagonism. Other 5-HT2 blockers such as nefazodone also lack the sleep-disturbing effects of SSRIs. The deepening of sleep after 5-HT2 antagonism may be of particular help in depressed patients and should be studied further.

Our study has two important limitations. Primarily, the number of our subjects may have been insufficient to evaluate the effects of the drug on REM sleep. Our groups of 10 individuals each showed a power of 56% and 64% respectively, to detect a difference from baseline values in REM latency and total REM time. A power analysis regarding the number needed to have an 80% power to reveal REM-latency and REM-time differences from baseline showed that at least 17 and 14 subjects were required, respectively. However, recruitment of healthy subjects was difficult, and we had to carry out the study on a limited number of individuals. The second concern is the significantly suppressed baseline REM parameters in the mirtazapine group, which might have produced a bias against observing drug effects on REM sleep. Further studies are needed to reach conclusive decisions on REM-suppressing effects of this drug.

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REFERENCES