REM Sleep Latency in Major Depressed Patients Predicts Mood Improvement After Transdermal Nicotine Administration

Rafael J. Salín-Pascual, M.D., Ph.D.
and Lourdes Galicia-Polo, Ph.D.

Both acute and chronic transdermal nicotine patches administration produced rapid eye movement (REM) sleep increased in non-smoking major depressed patients as well as clinical improvement in mood. Antidepressant effect was also observed after four continuous days of nicotine administration in depressed patients. The main goal of the present study was to observe the relationship between sleep variables and mood changes after the administration of nicotine patches to non-smoking major depressed patients. Fifteen major depressed patients (DSM-IV) were studied under the following sleep laboratory conditions: habituation, two all-night polysomnography recordings, the first one was baseline and the second one was the nicotine patch night. Patients were scored with a HAMD-21 items, and should had 18 point or more for to be admitted into the study. At baseline and post nicotine mornings, a HAMD-10 items were applied, also a side effect scale were used after the nicotine night. A significant increase in REM sleep time and reduction in sleep stage II was observed with nicotine patches. Ten patients improved (reduction of 30 % in the HAMD-10), after nicotine administration. All the patients with mood improvement had an enhancement of REM sleep above baseline. Eight out of ten improved patients, had short REM sleep latency below 60 minutes at baseline. The hypersensitivity of the cholinergic system may explain the sleep changes in the depressed patients after the nicotine administration. (Sleep and Hypnosis 1999;1:32-34)

Key words: major depression, nicotine, antidepressants, sleep
was reported that nicotine increased REM sleep time in both groups. HAMD scores showed an average reduction of 43.9 % in the depressed patients (10). Taken together, these data suggest a relationship between nicotine, major depression, and sleep. Most of nicotine receptors at the central nervous system (CNS), are heteroreceptors, but autoreceptors also has also been reported (11). Nicotine administration tends to produce changes in different neurotransmitter systems. Dopamine, serotonin, acetylcholine and norepinephrine releases were reported as increased at the CNS, after systemic nicotine administration.

These four neurotransmitters have been related to some biochemical hypothesis in major depression (12), but also all of them have been related to some aspects of sleep mechanisms. In brief, the major components of the wake-sleep cycle involves wake active cells (i.e., cholinergic, histaminergic, noradrenergic, and serotonergic cells), also slow-wave sleep active cells (i.e., GABA) and REM-on cells (i.e., cholinergic) (13,14).

The main goal of the present study was to observe the relationship between both mood and sleep variables before and after the challenge with nicotine patches in non-smoking major depressed patients.

METHODS

Fifteen major depressed outpatients were studied; they were diagnosed as depressed patients after medical, psychiatric history and Structured Clinical Interview for DSM-IV were applied (15). After the procedure had been fully explained, patients signed the informed consent. Laboratory test and clinical EEG were also obtained. Non-smoking status was defined as no more than 3 cigarettes/day for no more than a month and no exposure to tobacco in the year before enter to the study. Patients should not have other medical conditions that may put them at health risk with nicotine administration. All the subjects were scored with HAMD-21 items, and as inclusion criteria was to have a HAMD rate equal or above 18 points. Ten patients (66.5%) had a mood improvement after the transdermal nicotine administration significant level. Ten patients (66.5%) had a mood improvement after the transdermal nicotine administration (HAMD-10 in those 10 patients: baseline 24.5±1.6 vs. postnicotine = 14.2±2.4; Students "t" test p<0.01), all of them showed REM sleep enhancement above their baseline values. From the 10 patients with mood improvement 8 had REM sleep latencies of less than 60 minutes at baseline, while all the five depressed patients without mood changes after nicotine challenge, had REM sleep latencies above 60 minutes.

Patients were studied with all night poly-somnographic recordings. Subjects underwent the following sleep laboratory procedure: one acclimatization night, one baseline night and one nicotine night. Polysomnographic studies started at 22.00 hours and ended eight hours later. Nicotine patches (Nicotinel, Ciba-Geigy 17.5 mg) were applied two hours before lights-out (20:00 h) on the upper right arm, and they were removed the morning after at 07:00 h. Clinical improvement was defined as a reduction in baseline HAMD-10 of 30 % or more. Cutaneous electrodes were applied according to the international 10-20 system; the polysomnographic recordings included electroencephalographic (EEG) channels in C4-A1 and C3-A1. Two channels recorded eye movements and one channel chin muscle. All recordings were scored by a technician, without knowledge of night order. Scoring was performed according to standard criteria (16).

Sleep onset was defined as the first epoch of eight continuous minutes of sleep after the lights had been turned off. Awake time was defined as the minutes awake after sleep onset. REM sleep latency was defined as the time from sleep onset to the completion of the two epochs of REM sleep (1 minute).

Statistical analysis was performed with Student's t test for repeated measures with correction to maintain the level at p<0.05 (Bonferroni’s correction) and Fisher exact test when indicated.

RESULTS

Thirteen females and two males were studied (average age ±SD=36.6±9.7 years). Polysomnographic variables at baseline and with nicotine are shown in Table 1. A significant increase in REM sleep time and reduction in sleep stage II were observed when patients received transdermal nicotine. REM sleep latency has a reduction, but not at significant level. Ten patients (66.5%) had a mood improvement after the transdermal nicotine administration (HAMD-10 in those 10 patients: baseline 24.5±1.6 vs. postnicotine = 14.2±2.4; Students "t" test p<0.01), all of them showed REM sleep enhancement above their baseline values. From the 10 patients with mood improvement 8 had REM sleep latencies of less than 60 minutes at baseline, while all the five depressed patients without mood changes after nicotine challenge, had REM sleep latencies above 60 minutes.

### Table 1. Sleep Variables in Depressed Patients with Transdermal Nicotine Patches.

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>Baseline</th>
<th>With Nicotine</th>
<th>Significance *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake time</td>
<td>77.06 ± 20.3</td>
<td>80.9 ± 3.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage I</td>
<td>32.06 ± 20.3</td>
<td>27.2 ± 12.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage II</td>
<td>20.30 ± 37.6</td>
<td>156.2 ± 65.0</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Stage III</td>
<td>32.1 ± 29.7</td>
<td>21.4 ± 13.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>52.8 ± 26.1</td>
<td>71.9 ± 35.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>REM sleep</td>
<td>82.5 ± 21.7</td>
<td>122.9 ± 32.3</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>REM latency</td>
<td>79.3 ± 23.7</td>
<td>68.3 ± 21.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>REM average</td>
<td>17.4 ± 3.5</td>
<td>22.8 ± 2.0</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>REM frequency</td>
<td>4.7 ± 1.1</td>
<td>4.6 ± 1.1</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Student’s t test for repeated measures. All values were in minutes except for REM sleep frequency (times of REM sleep along the night)
minutes (Fisher's exact probability test: p<0.007). No REM sleep latency changes were observed when patients were on nicotine patches.

Two out of the fifteen patients increased REM sleep time without changes in mood (i.e., in HAMD-10 scale), and only three out of fifteen showed a decrease in REM sleep time and no changes in mood. Fisher's exact probability test for the ten patients with increase in REM sleep time and mood improvement when they were on nicotine was significant (p<0.02). Sleep stages other than REM sleep and sleep stage II were unmodified. Side effects reported more often were nausea, and increase in saliva production, all of them were on the mild range (between 2 and 3).

**DISCUSSION**

REM sleep enhancement and mood improvement was observed in ten patients, eight of them had REM sleep latency below 60 minutes at baseline. These results are in accordance with previous reports, in which changes in mood were observed in major depressed patients when they were on nicotine patches (8,9). The increase in REM sleep with nicotine, may be related to the hypersensitivity of the cholinergic system, that has been proposed with some depressed patients (2). Cholinomimetic agonists, such as pilocarpine or arecoline also, increase REM sleep but not clinical changes have not been reported with those studies (3). On the other hand, physostigmine, an indirect cholinomimetic drug, has been reported with both, increase in REM sleep time and development of depression-like symptoms in normal volunteers, and first degree relatives of major depressed patients (1). In the present study it was found that 53% of the patients with mood improvement has also REM sleep latency below 60 minutes. REM sleep latency is related to the level of cholinergic functioning at mesopontine areas, short REM sleep latency has been related to hypersensitivity of the cholinergic system (3). The fact that the patients in the present study, with short REM sleep latency were the responders to nicotine challenge, support the idea of the relationship between hyperactivity of the cholinergic system and the mood improvement observed after nicotine administration. Nicotine, as has been mentioned before, produced release of acetylcholine (17), among other neurotransmitters, so this effect could explain the changes in REM sleep variables in some depressed patients in which cholinergic hypersensitivity may occur. Transdermal nicotine challenge could be useful for to explore the cholinergic status, in some depressed patients and first degree relatives, and in this way to get some more knowledge about the role of the cholinergic system in depression and may be in other neuropsychiatric disorders.

**REFERENCES**


