The effects of trazodone on sleep in patients treated with stimulant antidepressants

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Abstract

Background and purpose: To evaluate the effects of trazodone on subjective and objective measures of sleep in depressed insomnia patients treated with selective serotonin reuptake inhibitors (SSRIs). SSRIs can exacerbate or cause new insomnia while alleviating other symptoms of depression. Trazodone has been reported to be an effective hypnotic for patients with antidepressant-associated insomnia.

Patients and methods: Twelve female patients were given either 100 mg trazodone or placebo for 7 days in a double-blind crossover design with a 7-day washout period. Polysomnographic recordings were repeated on the 3rd, 9th and 17th, 23rd nights after treatment with trazodone or placebo. Sleep was assessed by Pittsburgh sleep quality index (PSQI) at the beginning and end of the study. Psychological evaluation was done by Hamilton depression rating scale (HDRS).

Results: Trazodone significantly increased total sleep time, percentage of stages 3 + 4, sleep efficiency index, sleep continuity index and decreased percentage of stage 1, number of awakenings, stage shifts compared to the baseline. This improvement was also obtained after 7 days of treatment. The PSQI score was reduced to 5 ± 1.6 at the end of the study. HDRS was reduced to 11.5 ± 4.5 with trazodone and to 12.2 ± 3 with placebo.

Conclusion: Trazodone is effective in the treatment of antidepressant-associated insomnia.

Keywords: Insomnia; Depression; Trazodone; Serotonin reuptake inhibitors; Polysomnography; Hypnotic

1. Introduction

Insomnia is a hallmark or core symptom in the majority of depressed patients. It has been estimated that more than 70% of depressed women and 80% of depressed men have difficulty falling and/or staying asleep or in early morning awakenings [1,2]. Insomnia may also occur as a side effect of antidepressant treatments such as selective serotonin reuptake inhibitors (SSRIs). Depressed individuals taking SSRIs often report persistent insomnia. These agents are stimulating antidepressants that can fail to treat preexisting insomnia, exacerbate preexisting insomnia or cause new insomnia while alleviating other symptoms of depression [3,4]. It was reported that a total of 35% of patients receiving SSRIs or clomipramine were also taking medications to treat anxiety and insomnia [5].

Trazodone, a sedating triazolopyridine antidepressant, is chemically and pharmacologically different from SSRIs. It possesses antidepressant and also some anxiolytic and hypnotic activities. The effects of trazodone on sleep have been evaluated in a variety of subjects, including patients with insomnia and depression and normal controls. It has been demonstrated to be effective in resolving depressive symptomatology [6] and improving sleep architecture [7,8]. Trazodone has also been reported to be an effective hypnotic for patients with antidepressant-associated insomnia. Jacobsen [9] gave trazodone, 25–150 mg at night, in an open design to 48 consecutive patients who had persistent or worsened insomnia while taking either monoamineoxidase inhibitors (MAOIs) or other antidepressants. He found that 65% had complete resolution of insomnia, 31% had partial response and 4% had no response. Metz and Shader [10] reported that 31% of patients who took trazodone at a dose of 25–75 mg nightly to treat fluoxetine-associated insomnia had to stop taking trazodone because of excessive daytime
sedation. Nierenberg et al. [11] reported that patients taking either fluoxetine or bupropion and having antidepressant-associated insomnia showed clinically significant improvement, according to the Pittsburgh index measure of sleep duration and the Yale-New Haven inventory measure of early morning awakenings, after taking trazodone. There was also a trend toward improvement in the Pittsburgh index subscales for sleep quality and sleep latency.

The above clinical reports are limited by the lack of polysomnographic recordings (PSG) and a placebo control. The aim of the present study is to evaluate the effects of trazodone on subjective and objective measures of sleep in depressed insomnia patients treated with different SSRIs. It is a double-blind placebo-controlled study to find out if trazodone would improve sleep in depressed patients whose depression has been treated with SSRIs but in whom insomnia was not resolved or insomnia was subsequently developed.

2. Materials and methods

2.1. Patient selection

Female subjects between the ages of 20 and 50 were recruited from Psychiatry outpatient clinic. All of them had been diagnosed with major depression according to the DSM 4 criteria. They had been treated with SSRIs for at least 3 weeks, were receiving antidepressants at the time of study, had complaints of new, exacerbated or untreated insomnia, and continued with their treatment during the study. An initial score of at least 18 on the Hamilton depression rating scale (HDRS) was required. The exclusion criteria were:

1. Suffering from concomitant mental illness other than major depression
2. Alcohol abuse and addiction to other drugs
3. Pregnancy or lactation
4. Suffering from any other causes of insomnia, such as periodic leg movement during sleep (PLMS), sleep related breathing disorders (SRBD), etc.
5. Having cardiac conduction delays or arrhythmia in the ECG
6. Having a history of intolerable adverse reaction to trazodone

A total of 12 female patients with a mean age of 42 ± 9 (range: 30–59, median: 43.5), responding to inclusion and exclusion criteria participated in the study and signed informed consents.

Eight patients complained of difficulties with falling asleep and maintaining sleep, and four described relatively isolated difficulty with falling asleep. Ten patients were suffering from untreated insomnia, while the remaining two developed insomnia during treatment with SSRIs. Different SSRIs were being used for the treatment of depression, with the dosages in the low normal range. Five patients were taking paroxetine (20 mg/day), three were taking sertraline (50 mg/day), two were taking fluoxetine (20 mg/day), and one was taking citalopram (20 mg/day). One patient was taking venlafaxine (37.5 mg/day), which is both serotonin and also norepinephrine reuptake inhibitor.

SSRI treatment duration had ranged from 4 weeks to 3 months at the beginning of the study. The mean duration of SSRI treatment was 9 ± 2.7 weeks (median: 9.5 weeks). It was 9 ± 2.6 (median: 9.5 weeks) in Group 1 and 9.1 ± 2.9 (median: 9.5 weeks) in Group 2. There was no statistical significance between groups 1 and 2 in terms of SSRI treatment (Mann–Whitney U test = NS).

Half of the randomly selected patients took placebo in the first treatment phase while the other half took trazodone, and vice versa in the second treatment phase.

2.2. Study design

During an adaptation night in the sleep laboratory, each patient’s sleep was evaluated and checked for other causes of insomnia, such as PLMS, SRBD, etc. Following the adaptation night, they underwent baseline PSG (N2). After baseline recordings, patients were randomly assigned to either 100 mg trazodone (Group 1) or matching placebo tablets (Group 2) in phase 1, and were administered the alternative in phase 2. Each phase lasted 7 days, with a washout period of 7 days between the two sets of procedures.

PSGs were repeated on 3rd (N3), 9th (N9), 17th (N17) and 23rd (N23) nights after the start of trazodone or placebo treatment. A 100 mg dose of trazodone was selected to investigate its hypnotic effect, which is substantially less than the 150–600 mg dose range recommended for an antidepressant effect [12]. Medications were given 1 h before bedtime.

2.3. Subjective data

HDRS [13] was used for the evaluation of depression. It was done before baseline night and repeated after N9 and N23. Sleep was assessed by subjective rating of Pittsburgh sleep quality index (PSQI) [14], as sleep quality represents a complex clinical construct that is difficult to define and measure objectively. The PSQI is a self-noted questionnaire that assesses sleep quality and sleep disturbance over a 1-month period, changed to the time frame used in this study to avoid misinterpretation of PSQI. Since the treatment phases were only 7 days, PSQI was measured at the baseline and end of the study. This design was implemented with the understanding that all subjects at entry would be free of hypnotics and that at the end of the study there would be a 50% chance for the subjects to be on placebo when PSQI was administered. Study design and clinical evaluation of patients is shown in Fig. 1.
2.4. Polysomnographic data

PSG recordings included two EEGs (C3-A2, C4-A1), two EOGs and one chin EMG. Respiration was recorded by standard measures of airflow (oro-nasal thermistors), effort (abdominal and thoracic strain gauges) and oxygen saturation (finger pulse oximetry). Leg movements were recorded by right and left tibialis EMGs during the adaptation night.

The time of retiring was the same as at home but time in bed was controlled at 8 h in all PSGs. The following PSG parameters were evaluated: total sleep time (TST), percentage of stages 1, 2, 3 + 4 and REM sleep, sleep latency, REM sleep latency, sleep efficiency index (SEI), sleep continuity index (SCI), number of awakenings (# awake; 15 s), number of stage shifts (# shifts) and mean duration of each sleep cycle (cycle). SEI is TST per time in bed (from lights out to lights on) and SCI is TST per total sleep period (from the first falling asleep to last awakening).

All PSG recordings were scored by blinded sleep specialists.

2.5. Statistics

The order of the treatments was assigned randomly. There was no significant difference between phases 1 and 2 subjects in the overall PSQI data and HDRS scores after placebo treatment (Mann–Whitney U test = NS). Therefore, PSG data and HDRS scores were grouped based on the treatment, regardless of the order. There was an equal number of subjects in each group as none of the subjects dropped out of the study.

The data were grouped as baseline, drug, and placebo conditions. The 14-day time difference between the two groups was not taken into consideration. The drug condition data consisted of data from the ‘first trazodone’ group (Group 1) on N3-N9 and ‘first placebo’ group (Group 2) on N17-N23. The placebo condition data consisted of data from the first trazodone group on N17-N23 (Group 1) and first placebo group on N3-N9 (Group 2).

The following comparisons were made using the Wilcoxon matched pair signed rank test. Mean percentage of reduction in HDRS as of the last treatment nights of placebo and trazodone were compared with the baseline condition. PSQI scores were tabulated at the beginning and end of the study and compared between groups 1 and 2. PSG sleep parameters of baseline night were compared with those of the first and last treatment nights of trazodone and placebo. Sleep parameters in the first treatment night (acute effect) were also compared with those in the last treatment night (short-term effect), after 7 days of treatment with trazodone and placebo.

3. Results

3.1. Subjective data

The initial HDRS score was 23.4 ± 3.7. It was reduced to 12.2 ± 3 (P < 0.005) with placebo and to 11.5 ± 4.5 (P < 0.005) with trazodone treatment. This represented a mean decrease of 46.3 and 49.2%, respectively. The effects of trazodone and placebo on mean HDRS scores did not differ significantly.

The mean global score of the PSQI was 15 ± 2.5 at the beginning of the study (range: 9–19). It was 14.6 ± 3.4 for Group 1 (n = 6) and 15.5 ± 1.5 for Group 2 (n = 6) at entry (Mann–Whitney U = NS). After 3 weeks of trazodone/placebo treatment with washout period, it was reduced to 5 ± 1.6 (range: 2–7) (P < 0.005). It was 4.83 ± 2.14 for Group 1 and 5.17 ± 1.17 for Group 2. There was no significant difference between the two groups at the end of the study. According to the last PSQI, there was a similar improvement in subjective sleep quality in both groups, despite the fact that 50% of the subjects had just received placebo for 15 days. Compared to baseline, the change in PSQI score was significant for both groups (Wilcoxon matched pair rank test = 0.027). The global PSQI score was 5 or less in half of the patients, 6 in four patients and 7 in only two patients. It was 4.8 ± 2.1 for Group 1 and 5.1 ± 1.1 for Group 2 (Fig. 2).

Side effects: Complaints were minimum. During the trazodone intake one subject reported mild and transient acid indigestion and two others had mild daytime sedation in the morning. Neither complaint was mentioned during the placebo phase.
3.2. Polysomnographic data

Baseline sleep parameters of our patients are shown in Table 1. Large numbers of awakenings (25.1 ± 11) and stage shifts (106.2 ± 37.6) led to low SEI (79.8 ± 12.4%) and low SCI (85 ± 9%). Mean sleep duration was 382.1 ± 57.9 min and mean sleep latency was 18.8 ± 28.7 min. Slow wave sleep (SWS) was well preserved (19.5 ± 8.9%), while REM sleep was reduced (13.2 ± 4.9%) and stage 2 was increased (60.7 ± 11.1%). Prolonged REM latency (222.9 ± 93.4 min) was observed on baseline night.

The administration of trazodone significantly increased TST (435 ± 34, *P < 0.01), percentage of stages 3 + 4 (28 ± 14, *P < 0.05), SEI (90 ± 7%, *P < 0.01) and SCI (94 ± 6%, *P < 0.01) and significantly decreased percentage of stage 1 (3 ± 1, *P < 0.001), number of awakenings (13 ± 6, *P < 0.01) and number of stage shifts (69 ± 21, *P < 0.05) on the first night, compared to the baseline night (acute effect).

At the end of trazodone treatment period (short term effect), TST (428 ± 39, *P < 0.05), SEI (89 ± 8%, *P < 0.01) and SCI (93 ± 7%, *P < 0.05) tended to decrease slightly compared to the first treatment night, although they were still significantly higher than the baseline condition. However, decreases in stage1 (3 ± 2%, *P < 0.001), number of awakenings (12 ± 13, *P < 0.05) and number of stage shifts (64 ± 46, *P < 0.01) and increases in percentage of stage 3 and 4 (31 ± 13%, *P < 0.01) were more significant in the last treatment night of trazodone. Sleep latency was reduced from 17 to 14 min. Percentage of REM sleep was slightly lower in the last night (16 ± 8%) than in the first (18 ± 9%), while its latency prolonged to 230 from 200 min.

In summary, the significant improvement in sleep parameters in the first night of trazodone administration was also observed after 7 days of treatment, compared to the baseline night. The improvement in sleep parameters was more marked in the last treatment night, but no significant difference was found between two treatment nights of trazodone.

Placebo treatment produced no significant alterations in sleep parameters, either in the first or last night compared to the baseline. Sleep latency was prolonged to a mean of 24 and 33 min in the first and last treatment nights, respectively. Though the number of stage shifts was reduced to 89 with acute administration, it reached 128 in the last treatment night, which was higher than the baseline night.

![Fig. 2. Global PSQI scores of patients at the beginning and at the end of the study.](image)

Table 1

<table>
<thead>
<tr>
<th>Sleep parameters</th>
<th>Baseline night</th>
<th>Trazodone (first night)</th>
<th>Trazodone (last night)</th>
<th>Placebo (first night)</th>
<th>Placebo (last night)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (min)</td>
<td>382.17 ± 58</td>
<td>435 ± 34^b</td>
<td>428 ± 39^a</td>
<td>386 ± 35</td>
<td>383 ± 66</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>6.42 ± 2</td>
<td>3 ± 1^a</td>
<td>3 ± 2^a</td>
<td>5 ± 2</td>
<td>7 ± 3</td>
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<tr>
<td>Stage 2 (%)</td>
<td>60.75 ± 11</td>
<td>51 ± 17</td>
<td>50 ± 16</td>
<td>62 ± 11</td>
<td>59 ± 9</td>
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<td>SWS (%)</td>
<td>19.58 ± 9</td>
<td>28 ± 14^a</td>
<td>31 ± 13^b</td>
<td>19 ± 8</td>
<td>19 ± 9</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>13.25 ± 5</td>
<td>18 ± 9</td>
<td>16 ± 8</td>
<td>19 ± 5</td>
<td>15 ± 6</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>18.83 ± 29</td>
<td>17 ± 23</td>
<td>14 ± 14</td>
<td>24 ± 26</td>
<td>33 ± 53</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>222.92 ± 3</td>
<td>200 ± 103</td>
<td>230 ± 91</td>
<td>231 ± 116</td>
<td>244 ± 122</td>
</tr>
<tr>
<td>SEI (%)</td>
<td>7.93 ± 12</td>
<td>90 ± 7^b</td>
<td>89 ± 8^a</td>
<td>80 ± 7</td>
<td>79 ± 14</td>
</tr>
<tr>
<td>SCI (%)</td>
<td>85.08 ± 9</td>
<td>94 ± 6^b</td>
<td>95 ± 7^a</td>
<td>85 ± 12</td>
<td>85 ± 9</td>
</tr>
<tr>
<td># Awake</td>
<td>25.17 ± 11</td>
<td>13 ± 6^b</td>
<td>12 ± 13^a</td>
<td>24 ± 11</td>
<td>30 ± 18</td>
</tr>
<tr>
<td># Shifts</td>
<td>106.25 ± 38</td>
<td>69 ± 21^a</td>
<td>64 ± 46^b</td>
<td>89 ± 36</td>
<td>128 ± 53^b</td>
</tr>
<tr>
<td>Duration of sleep cycle</td>
<td>210.5 ± 109</td>
<td>180 ± 92</td>
<td>203 ± 100</td>
<td>209 ± 117</td>
<td>220 ± 141</td>
</tr>
</tbody>
</table>

*P* values compared to baseline night. ^*P* < 0.05; ^a*P* < 0.01; ^b*P* < 0.005; ^c*P* < 0.001.
The only significant finding with placebo treatment was an increase in the number of stage shifts during the last night (128 ± 3, P < 0.01) compared to its acute administration (89 ± 36). Sleep parameters with trazodone and placebo treatment are shown in Table 1.

4. Discussion

Our study confirms the finding that the administration of a low dose of trazodone objectively improves sleep duration in patients who are being treated with antidepressants and have insomnia [11]. Insomnia may be a side effect of some antidepressants such as SSRIs, or may be related to depression. It has been reported that 6 days of fluoxetine treatment leads to significant decrease in REM sleep and increase in sleep latency and REM latency, without a significant increase in the number of awakenings during the night [15]. Hendricks et al. [16] reported that fluoxetine appeared to increase in stage 1, suppress REM sleep and increase REM latency. Another study done with fluoxetine supported these findings and also showed decrease in SWS [17], Paroxetine has been reported to reduce TST, REM sleep and SEI, and increase REM latency and number of awakenings, compared to placebo [18].

The sleep disturbances seen in depression are well described. They include increased nocturnal wake time, decreased SWS and shortened REM latency. The mean HDRS score was 23.4 ± 3.7 at the beginning of our study, reflecting moderate depression despite SSRI treatment for a mean of 9 weeks (minimum 4 weeks). The elevated HDRS scores in our patients suggest that depression may have been impacting sleep disturbance. Sleep onset complaints during SSRI treatment show that sleep problems are a side effect of these drugs. Although it is not possible to calculate a percentage of sleep problems arising from depression versus SSRIs, we know that both components affect sleep.

The baseline PSG data of our patients reflects the overall effects of SSRIs and depression on sleep parameters. A reduction of TST and SEI, increase in the number of awakenings, and preservation of SWS was found. REM duration was reduced (13.2 ± 4.9%) while REM latency was increased (222 ± 93.1 min).

Mouret et al. [8] studied the polysomnographic changes induced by trazodone (100–600 mg) in 10 depressed patients not taking other medications. On the night following the first dose of 100 mg trazodone, their patients had increased TST and stage 2 and decreased sleep latency and number of awakenings. When the dose was increased within 4 days to 400–600 mg nightly stage 4 and REM latency increased in addition to sustained improvement of sleep variables observed after 1 day of treatment. We found an insignificant decrease in stage 2 NREM sleep, but our findings were otherwise the same. After 1 week of trazodone 100 mg treatment all sleep parameter improvements were highly significant, with reduction in stage 1 sleep, number of awakenings and stage shifts, and augmentation of SWS. The findings in our patients were more marked than those reported by Mouret et al. after only one night of drug intake. Scharf and Sachais [19] reported on six depressed patients who took 150 mg doses of trazodone for 2 days, 200 mg for 2 days and 250 mg by the end of the first week. Their subjects had decreased sleep latency and increased TST, stage 4 NREM sleep and REM latency. The observed effects on REM sleep after the first day and after 1 week of treatment were different than those seen in our patients, who initially had an increase in percentage of REM sleep with a shortening of its latency. REM sleep latency was longer after 1 week of trazodone than at baseline.

A polygraphic study of the effects of trazodone on sleep parameters of depressed patients being treated with daily doses of SSRIs is lacking. In our study, trazodone, compared to placebo, produced significant improvement in sleep parameters with augmentation of TST, SWS, SEI and SCI and reduction in stage 1, number of awakenings and number of stage shifts after 1 week of treatment; there was no significant difference between the first and last night effects of trazodone on polysomnographic data. Although there was a notable reduction in HDRS, none of the sleep parameters significantly improved with placebo treatment. These findings indicate that trazodone ameliorated sleep disturbance in depressed patients, independent of changes in depression, and that it was effective after the first night.

The PSQI was administered at the beginning and end of our study. None of the subjects had been treated with trazodone at the outset, and subjective complaints were clear. At the end, 50% of the subjects had not received trazodone for at least 2 weeks (due to washout and placebo periods). Despite this situation, the mean PSQI score of our patients was significantly reduced from 15 to 5; it has been previously reported that global PSQI ≤ 5 correctly identified 89.6% of healthy, middle-aged control subjects [14]. There was no significant difference in PSQI scores between the two groups at the conclusion of the study, and the scores were significantly better than those obtained at baseline. The fact that PSQI scores in Group 2 were improved after 2 weeks without trazodone indicates the importance of close and repetitive subjective evaluations of sleep and the subjective effect of the attention given to the sleep problem by the research team. One may question, however, whether there is a spillover effect from the initial (first 7 days) use of trazodone. Despite the fact that such an effect has never been reported, similar results are often observed in crossover design protocols, even with controlled placebo, as in our case. However, the polysomnographic data clearly show the dissociation of subjective and objective results. When placebo intake was associated with improved subjective scores, polysomnographic data showed declines. Objective sleep improvement declined within a short period (maximum 15 days) in our population. These polygraphic
results support evidence of the beneficial effect of the trazodone administration in these depressed patients.

It has been mentioned that the persistence of insomnia may be responsible for recurrence of depressive symptoms, emphasizing the importance of treating poor sleep in these patients. The insomnia may be related to the symptoms themselves, and to side effects related to SSRIs. Our study indicates that subjective reports may not be a good indicator of the severity of sleep disruption and that polysomnography may be necessary.

It has been reported that trazodone causes less severe anticholinergic side effects than tricyclics. As a sedating antidepressant, it has a short half-life. It is effective in inducing and maintaining sleep throughout 5-week trials, but very little information is available about longer treatments [19].

In conclusion, trazodone 100 mg improved objective measurements of sleep in adult female patients with moderate depression receiving low/normal dosages of SSRIs, even from the first administration of treatment. A long-term study comparing the efficacy and adverse reaction profiles of trazodone and of conventional hypnotics for antidepressant-associated insomnia is warranted.

References