Effect of Tiagabine on Sleep in Elderly Subjects With Primary Insomnia: A Randomized, Double-Blind, Placebo-Controlled Study

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Subject Objective: This study further evaluated the effects of tiagabine on sleep in elderly subjects with primary insomnia.

Methods: Elderly subjects (aged 65-85 years) meeting DSM-IV-TR criteria for primary insomnia were randomly assigned to receive tiagabine 2, 4, 6, or 8 mg or placebo on 2 consecutive nights. Efficacy was assessed using standard polysomnography and a postsleep questionnaire. Additional assessments included the Assessment of Daily Functioning, Digit Symbol Substitution Test (for residual effects), and visual analog scale (for sleepiness/alertness).

Results: A total of 207 subjects were randomly assigned to study medication (tiagabine: 2 mg, n=43; 4 mg, n=38; 6 mg, n=45; 8 mg, n=43; placebo, n=38). Tiagabine did not significantly affect wake after sleep onset, latency to persistent sleep, or total sleep time compared with placebo (P>0.05). Significant increases in Stage 3+4 sleep (i.e., slow-wave sleep) were found for tiagabine 4, 6, and 8 mg versus placebo, with a corresponding significant decrease in Stage 1 sleep (P<0.05). At 6 and 8 mg, tiagabine also significantly reduced the number of awakenings and increased the ratio of Stage 3+4/(Stage 1 + wake after sleep onset). In general, there were no significant effects on subjects’ ratings of sleep or daily functioning with tiagabine 2, 4, and 6 mg versus placebo. These 3 doses had tolerability profiles comparable with that of placebo and were not associated with significant residual effects or reduced alertness. The 8-mg dose, however, significantly decreased subjective total sleep time and refreshing quality of sleep, as well as daily functioning. This dose was associated with troublesome adverse events, significant residual effects, and reduced alertness.

Conclusions: In elderly subjects with primary insomnia, tiagabine did not have a significant effect on wake after sleep onset, latency to persistent sleep, total sleep time, or the subjective rating of sleep. Tiagabine 4, 6, and 8 mg significantly increased slow-wave sleep, with a corresponding significant decrease in Stage 1 sleep. Tiagabine was generally well tolerated, with doses of less than 6 mg having tolerability profiles generally similar to that of placebo. The 8-mg dose, however, was associated with troublesome adverse events, residual effects, and reduced alertness.

Keywords: Primary insomnia, slow wave sleep, stage 1 sleep, elderly, tiagabine

Citation: Roth T; Wright KP; Walsh J. Effect of tiagabine on sleep in elderly subjects with primary insomnia: A randomized, double-blind, placebo-controlled study. SLEEP 2006;29(3):335-341.

INTRODUCTION

MANY STUDIES HAVE DEMONSTRATED THAT AGE REPRESENTS A SIGNIFICANT RISK FACTOR FOR INSOMNIA.1 FURTHERMORE, IT HAS BEEN SHOWN THAT THE elderly experience more time awake during the night than adults aged <65 years, and this contributes to daytime fatigue, unintended napping, and impaired daytime function.1

The benzodiazepines, which are gamma-aminobutyric acid type A (GABA) receptor agonists, are among the most widely prescribed classes of medication in elderly subjects.1 Although benzodiazepines have been reported to reduce time to sleep onset and increase sleep duration, they may also alter sleep architecture, reducing rapid eye movement (REM) sleep and slow-wave sleep (SWS).2 In addition, some benzodiazepines are associated with a number of adverse effects, including residual or next-day sedation and, in some populations, an increased risk of abuse. The short-acting, nonbenzodiazepine hypnotics, such as zolpidem and zaleplon, which act on a subset of the benzodiazepine receptors, are effective in reducing time to sleep onset and increasing total sleep time (TST), and are well tolerated in elderly subjects.1,3 However, they do not effect SWS nor sleep maintenance (i.e., number of awakenings and wake after sleep onset [WASO]).1,3

Tiagabine, a selective GABA reuptake inhibitor, increases synaptic GABA availability via selective inhibition of the GAT-1 GABA transporter.4-6 Tiagabine is rapidly absorbed, with a tmax of approximately 45 minutes in the fasting state, and has an elimination half-life of 7-9 hours; the rate, but not the extent of absorption, is reduced when ingested with food.7 In 2 preliminary studies, the effect of tiagabine on sleep parameters, at doses ranging from 2 mg to 8 mg, was evaluated in healthy elderly subjects.3,8 In these studies, tiagabine, at doses of 4 or 5 mg, was found to reduce intermittent wakefulness or WASO and increase SWS while being generally well tolerated. The current study evaluated the effects of tiagabine (2, 4, 6, and 8 mg) on sleep in elderly subjects...
with primary insomnia. The 2-mg dose of tiagabine was evaluated to confirm a minimally effective dose, while the 4-, 6-, and 8-mg doses provided dose-response information.

**METHODS**

**Study Design**

This double-blind, parallel-group, dose-response study was conducted in 30 sleep centers in the United States. Eligible elderly subjects diagnosed with primary insomnia were randomly assigned to receive study medication (tiagabine 2, 4, 6, or 8 mg or placebo) followed by polysomnographic assessment. The protocol was approved by an institutional review board at each center. All subjects provided written informed consent to participate in the study, which was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

**Subjects and Screening Procedures**

Men and women aged 65 to 85 years who were diagnosed with primary insomnia were eligible for inclusion in the study. Subject screening for general eligibility and specific sleep history was conducted during an initial clinic visit and involved a medical, sleep, and psychiatric history; physical examination; laboratory tests; and electrocardiogram. Subjects were required to meet the following inclusion criteria: (1) diagnosis of primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision) (DSM-IV-TR) criteria ²⁰; (2) self-reported sleep history as follows: latency to persistent sleep (LPS) of ≥ 15 minutes, WASO of ≥ 60 minutes, and TST of < 6 hours on ≥ 3 nights per week over the preceding month; and (3) habitually spending 6.5 to 9 hours in bed for ≥ 5 nights per week over the preceding month, with a habitual bedtime between 9:00 pm and midnight that cannot vary by more than an hour.

Subjects were excluded from the study for any of the following reasons: a diagnosis of any DSM-IV-TR axis-1 psychiatric disorder other than primary insomnia, symptoms or signs of any primary sleep disorder other than primary insomnia, a history of substance abuse, or a diagnosis of any disorder that may interfere with the pharmacokinetics of the study drug. Additional exclusion criteria included the following: performing shift work, traveling across ≥ 3 time zones in the past 2 weeks, taking any medication (including psychotropic medication) that may affect sleep-wake function, napping (≥ 30 minutes outside the usual sleep period) ≥ 5 times each week over the preceding month, daily consumption of ≥ 300 mg of xanthine-containing food or beverages over the preceding month, consuming ≥ 14 alcoholic units in any week (1 unit = 8 oz beer, 3 oz wine, or 1 oz hard liquor), or smoking ≥ 1 pack of cigarettes per day. Subjects with a body mass index of ≥ 34 or with a known sensitivity to sedative hypnotics, or those taking any cytochrome CYP3A4 hepatic enzyme-inducer/inhibitor within 2 weeks of screening were also excluded. Subjects were also ineligible for inclusion if they had previously received tiagabine or had received any investigational drug within 1 month before screening.

Individuals meeting all clinical entry criteria were scheduled for 2 consecutive nights of polysomnographic screening during which placebo was administered in a single-blind manner 30 minutes prior to lights out. The scheduled lights-out time for each subject was within 30 minutes of his or her usual bedtime and was fixed for the remainder of the study. Time in bed was 480 minutes after lights out. On the first screening night, subjects were evaluated for sleep apnea and periodic leg movements and were excluded if the apnea-hypopnea index was ≥ 15 or the periodic limb movement arousal index was ≥ 15 events per hour of sleep. Additional polysomnographic entry criteria were (1) LPS of ≥ 10 minutes for either screening night; (2) mean WASO of ≥ 45 minutes, with neither night < 30 minutes; and (3) TST of 240 to 390 minutes on each screening night.

**Procedures and Study Assessments**

Subjects meeting polysomnographic eligibility criteria were randomly assigned to treatment group and underwent 2 consecutive nights of polysomnography (PSG) (with study medication) within 5 to 12 days of the screening nights. Study drug was administered without food 30 minutes prior to lights out. Standard polysomnographic techniques, performed during the 8 hours of time in bed, were used in all study centers. ¹¹ Scoring of the polysomnographic recordings was performed at a centralized site according to standard criteria. ¹² Subjects’ reports of sleep were assessed using a post-sleep questionnaire, which was completed 15 to 25 minutes after lights-on on the morning following screening and treatment nights. Subjects’ ability to concentrate and think clearly, level of alertness, and sense of physical well-being (daily functioning) were assessed using the Assessment of Daily Functioning questionnaire, which was completed in the laboratory after the first screening and treatment nights and at home following the second screening and treatment nights.

Adverse events and vital signs were assessed throughout the study. Clinical laboratory tests, physical examination, and electrocardiograms were also performed at baseline and after completion of the study. Residual effects of the study drugs were evaluated using the Digit Symbol Substitution Test, and sleepiness/alertness by the visual analog scale (0 mm=very sleepy, 100 mm=very alert). Both assessments were administered following each PSG (approximately 1 hour after lights on).

**Statistical Analysis**

Subjects who were randomly assigned to and received at least 1 dose of study drug (tiagabine or placebo) and underwent subsequent PSG were included in the efficacy dataset. The primary efficacy variable was the change from baseline in WASO as measured by PSG. Other PSG parameters analyzed were TST, number of 30-second awakenings, LPS, time spent in Stage 1, 2, 3+4 (i.e., SWS), and REM sleep. Stage 3+4 sleep was also analyzed by hour of the night. Additional variables calculated were sleep efficiency during sleep period time (where sleep period time is the total time from persistent sleep onset to final awakening) and the ratio Stage 3+4/(Stage 1 + WASO). The latter ratio has previously been reported as a potential measure of sleep disruption, where increases in this ratio indicate less sleep disruption. ¹³ For PSG and all other assessments, the mean of 2 consecutive sleep-variable measurements for each subject was used and compared between study groups for change from baseline. The baseline value was the mean of the measurements from the first 2 screening nights for PSG variables. Paired comparisons were performed using an analysis of covariance model, with treatment and center as factors and baseline value as covariate. All tests were 2-tailed, with α set at .05. The differences in the mean scores from baseline were compared to 0 using a 2-tailed test.
are reported in text, and values for baseline and treatment nights are provided in tables.

The safety dataset included all subjects who received at least 1 dose of study medication. Adverse events were coded according to the MedDRA preferred terms.\textsuperscript{14}

**RESULTS**

**Subjects**

A total of 207 subjects were randomly assigned to study medication (tiagabine: 2 mg, n=43; 4 mg, n=38; 6 mg, n=45; 8 mg, n=43; placebo, n=38). The mean age was 71.3 years (range, 65-84 years); 62% were women and 76% were white. Mean body mass index was 26.4 kg/m\textsuperscript{2}. All subjects received at least 1 dose of study drug and were included in the safety analyses. Of the 207 subjects, all but 3 (n=1, 2 mg; n=2, 8 mg) had at least 1 postbaseline efficacy assessment and were included in the efficacy analyses; 6 patients (n=1, 6 mg; n=5, 8 mg) had only 1 postbaseline assessment. Subject disposition and reasons for discontinuation are shown in Figure 1. Subjects randomly assigned to tiagabine or placebo were generally well matched; there were no significant differences among groups in any demographic or sleep characteristics measured or assessed (Table 1 and 2).

**Polysomnographic Variables**

The effects of tiagabine on polysomnographic measures of sleep are shown in Table 2. Reductions in WASO were observed at all doses of tiagabine; the mean change from baseline were -10.7 ± 5.7 minutes (2 mg), -8.0 ± 6.2 minutes (4 mg), -18.3 ± 5.8 minutes (6 mg), and -9.9 ± 6.4 minutes (8 mg). These differences, however, did not reach statistical significance compared with placebo (−5.2 ± 5.2 minutes). There were also no significant differences between tiagabine and placebo on LPS or TST.

Significant, dose-dependent increases in Stage 3+4 sleep were found for tiagabine 4, 6, and 8 mg compared with placebo (all P<.05). The mean changes from baseline for tiagabine were 11.7 ± 2.2 minutes (2 mg), 19.9 ± 3.5 minutes (4 mg), 38.0 ± 5.2 minutes (6 mg), and 46.9 ± 6.4 minutes (8 mg), compared with 4.5 ± 2.5 minutes with placebo. When analyzed by hour of the night, tiagabine 6 mg and 8 mg were found to have similar effects on Stage 3+4 sleep (Figure 2). As a result of its effect on Stage 3+4 sleep, the ratio Stage 3+4/(Stage 1 + WASO) was significantly increased for tiagabine 6 mg and 8 mg compared with placebo (P<.001).

Stage 1 sleep was also significantly reduced with tiagabine 4, 6, and 8 mg compared with placebo (all P<.05). The mean changes from baseline for tiagabine were -6.6 ± 2.1 minutes (2 mg), -10.9 ± 2.2 minutes (4 mg), -10.6 ± 2.3 minutes (6 mg), and -17.5 ± 3.1 minutes (8 mg), compared with placebo (-2.1 ± 1.9 minutes).

The number of 30-second awakenings was significantly reduced with tiagabine 6 mg and 8 mg compared with placebo (P<.05). The mean changes from baseline with tiagabine were 1.2 ± 1.4 (2 mg), 1.5 ± 1.2 (4 mg), -2.0 ± 1.5 (6 mg), and -0.7 ± 1.8 (8 mg), compared with placebo (-0.7 ± 1.3 minutes). Tiagabine 6 mg and 8 mg significantly reduced REM sleep compared with placebo (P<.05). The mean changes from baseline with tiagabine were 4.3 ± 2.4 minutes (2 mg), 1.4 ± 2.6 minutes (4 mg), -6.1 ± 3.3 minutes (6 mg), and -13.9 ± 3.6 minutes (8 mg), compared with 2.6 ± 2.6 minutes with placebo.

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**Table 1—Demographic Characteristics of Randomized Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=38)</th>
<th>2 mg (n=43)</th>
<th>4 mg (n=38)</th>
<th>6 mg (n=45)</th>
<th>8 mg (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.3 (4.3)</td>
<td>71.3 (4.9)</td>
<td>71.3 (4.7)</td>
<td>71.3 (5.4)</td>
<td>71.2 (4.9)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (34)</td>
<td>25 (58)</td>
<td>21 (55)</td>
<td>22 (49)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>26.6 (3.7)</td>
<td>25.9 (4.2)</td>
<td>26.0 (3.6)</td>
<td>26.5 (3.5)</td>
<td>26.8 (3.9)</td>
</tr>
</tbody>
</table>

Data are mean (SD), unless indicated otherwise.

**Figure 1—Flow diagram of the patient disposition through the study**
Subjects’ Ratings of Sleep

There were no significant effects on subjects’ ratings of sleep with tiagabine 2, 4, and 6 mg compared with placebo (Table 3), nor were there any significant differences with these doses versus placebo in subjects’ ability to think clearly, level of alertness, and sense of physical well-being, as assessed by the Assessment of Daily Functioning questionnaire. Estimates of TST and refreshing quality of sleep were found to be significantly lower with tiagabine 8 mg compared with placebo. Similarly, significant mean changes from baseline were apparent with tiagabine 8 mg on the Assessment of Daily Functioning items: ability to think clearly (-6.3 ± 2.9; P<.01); level of alertness (-5.6 ± 2.6; P<.05); and sense of physical well-being (-6.1 ± 3.2; P<.05).

Tolerability

Tiagabine was generally well tolerated, with the majority (93%) of subjects reporting adverse events that were considered mild or moderate in nature. The tolerability profiles associated with tiagabine 2, 4, and 6 mg were generally similar to that of placebo (Table 4). Tiagabine 8 mg, however, was less well tolerated, as it was associated with a higher incidence of adverse events, and 1 of the 2 serious adverse events (confusional state, considered to be related to treatment). The other serious adverse event (deep vein thrombosis, 4 mg) was considered unrelated to treatment; both events resolved upon treatment discontinuation. Five of the 7 discontinuations due to adverse events were observed with the 8-mg dose. The most commonly reported adverse events in subjects receiving tiagabine 8 mg were dizziness (23% vs 3% with placebo) and nausea (16% vs 0%). Five subjects discontinued tiagabine 8 mg due to 1 or more of the following symptoms: nausea, dry mouth, oral hypoesthesia, chest discomfort, sluggishness, confusional state, panic attack, oropharyngeal swelling, and

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**Table 2—Effect of Tiagabine on Polysomnographic Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=38)</th>
<th>Tiagabine 2 mg (n=42)</th>
<th>Tiagabine 4 mg (n=38)</th>
<th>Tiagabine 6 mg (n=45)</th>
<th>Tiagabine 8 mg (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASO, min</td>
<td>Baseline 123.3 (5.9)</td>
<td>121.1 (4.7)</td>
<td>120.5 (5.5)</td>
<td>120.6 (4.9)</td>
<td>129.8 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 118.2 (6.6)</td>
<td>110.3 (6.5)</td>
<td>112.5 (6.6)</td>
<td>102.3 (6.5)</td>
<td>119.9 (7.6)</td>
</tr>
<tr>
<td>LPS, min</td>
<td>Baseline 47.6 (4.4)</td>
<td>39.9 (3.7)</td>
<td>52.0 (4.5)</td>
<td>48.6 (3.6)</td>
<td>44.5 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 30.9 (3.3)</td>
<td>27.8 (2.2)</td>
<td>40.2 (3.9)</td>
<td>38.8 (4.1)</td>
<td>28.8 (2.9)</td>
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<tr>
<td>TST, min</td>
<td>Baseline 318.1 (5.4)</td>
<td>326.7 (5.4)</td>
<td>317.3 (5.7)</td>
<td>319.8 (5.0)</td>
<td>314.0 (5.2)</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 338.7 (7.6)</td>
<td>347.9 (6.9)</td>
<td>336.1 (7.3)</td>
<td>347.4 (7.3)</td>
<td>337.1 (7.9)</td>
</tr>
<tr>
<td>30-s awakenings, no.</td>
<td>Baseline 31.5 (1.8)</td>
<td>30.9 (2.0)</td>
<td>31.9 (2.2)</td>
<td>32.6 (1.7)</td>
<td>33.0 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 35.4 (1.8)</td>
<td>32.1 (1.8)</td>
<td>33.4 (2.3)</td>
<td>30.6* (1.3)</td>
<td>32.2* (1.8)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>Baseline 66.3 (1.1)</td>
<td>68.1 (1.1)</td>
<td>66.1 (1.2)</td>
<td>66.6 (1.0)</td>
<td>65.4 (1.1)</td>
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<td></td>
<td>Posttreatment 70.6 (1.6)</td>
<td>72.5 (1.4)</td>
<td>70.0 (1.5)</td>
<td>72.4 (1.5)</td>
<td>70.2 (1.6)</td>
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Sleep stage, min

<table>
<thead>
<tr>
<th>Stage</th>
<th>Baseline</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41.2 (3.4)</td>
<td>44.4 (4.0)</td>
</tr>
<tr>
<td></td>
<td>39.1 (3.1)</td>
<td>37.8 (3.4)</td>
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<tr>
<td>2</td>
<td>185.1 (6.2)</td>
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<td>200.7 (8.0)</td>
<td>211.8 (5.3)</td>
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<td>3+4</td>
<td>30.7 (4.4)</td>
<td>26.8 (3.6)</td>
</tr>
<tr>
<td></td>
<td>35.2 (4.4)</td>
<td>38.5 (4.4)</td>
</tr>
<tr>
<td>REM</td>
<td>61.1 (2.4)</td>
<td>55.5 (3.2)</td>
</tr>
<tr>
<td></td>
<td>63.7 (2.9)</td>
<td>59.8 (3.2)</td>
</tr>
<tr>
<td></td>
<td>0.2 (0.04)</td>
<td>0.2 (0.03)</td>
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<td>0.3 (0.05)</td>
<td>0.3 (0.05)</td>
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<tr>
<td></td>
<td>0.3 (0.05)</td>
<td>0.3 (0.05)</td>
</tr>
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</table>

Data are mean (SEM) values.
LPS refers to latency to persistent sleep; REM, rapid-eye-movement; TST, total sleep time; WASO, wake after sleep onset—number of wake epochs from sleep onset to lights-on divided by 2; LPS, latency to persistent sleep, measured from lights-off to the first epoch of 20 consecutive nonwake epochs (sleep onset) divided by 2; TST, duration of rapid eye movement (REM) plus non-REM sleep epochs from lights-off to lights-on divided by 2; sleep efficiency, total time from persistent sleep onset to the end of the polysomnogram divided by time in bed multiplied by 100; Stage 1, total number of epochs of Stage 1 sleep during time in bed divided by 2; Stage 2, total number of epochs of Stage 2 sleep during time in bed divided by 2; Stage 3+4, total number of epochs of Stage 3+4 sleep during time in bed divided by 2; REM sleep, total number of epochs of REM sleep during time in bed divided by 2.

*P<.05 change from baseline vs placebo.
hypotension. One subject each discontinued tiagabine 6 mg and 2 mg due to anxiety and drug hypersensitivity, respectively. All of these adverse events resolved without residual effect. Tiagabine was not associated with any clinically meaningful changes in laboratory values and vital signs.

There were no significant differences in the mean number of correct responses on the Digit Symbol Substitution Test or mean visual analog scale values between the 2-, 4-, and 6-mg dose of tiagabine and placebo. There was a significant change from baseline on the Digit Symbol Substitution Test, with tiagabine 8 mg (mean change from baseline, -0.2 ± 4.06; P<0.05). The 8-mg dose was associated with lower mean visual analog scale scores, but the difference was not significant compared with placebo.

**DISCUSSION**

The results of this randomized, double-blind, placebo-controlled study show that tiagabine did not significantly affect WASO, LPS, or TST, the currently accepted measures of insomnia therapy. Tiagabine 4, 6, and 8 mg, however, did significantly increase SWS, with a corresponding significant decrease in Stage 1 sleep. Tiagabine 6 mg and 8 mg also significantly reduced the number of 30-second awakenings and duration of REM sleep and increased the ratio Stage 3+4/(Stage 1 + WASO) compared with placebo. In general, there were no significant differences in subjects’ ratings of sleep or daily functioning with tiagabine 2, 4, and 6 mg compared with placebo. These 3 doses of tiagabine also had tolerability profiles generally similar to that of placebo and were not associated with significant residual effects or reduced alertness. The 8-mg dose, however, significantly decreased subjective TST and refreshing quality of sleep, as well as daily functioning. This dose was associated with troublesome adverse events, significant residual effects, and reduced alertness.

These findings are generally consistent with those reported in studies of tiagabine in healthy elderly subjects and in adults with primary insomnia. That is, similar increases in SWS were observed in these previous studies, though they also found increases in TST and reductions in WASO. In healthy elderly subjects, tiagabine 5 mg significantly increased SWS while also increasing TST compared with placebo. In a larger cross-over study, tiagabine 8 mg doubled the time spent in SWS, but there were no significant changes in TST and WASO as compared with placebo. In adults with primary insomnia, tiagabine 12 mg and 16 mg significantly increased SWS (P<0.01 vs placebo), while numerical increases in SWS were observed with the 4-mg and 8-mg doses. In all 3 studies, tiagabine doses ≤ 8 mg had an adverse-event profile similar to that of placebo; however, higher doses were not well tolerated.

It has been reported that SWS contributes importantly to memory and cognitive function. Daytime cognitive performance (in adults aged 20-30 years and elderly aged > 60 years) has been reported to be adversely affected by a reduction in SWS. In fact, SWS has been proposed to be the most restorative stage of sleep and has been implicated in the homeostatic process necessary for restoring normal waking function. To give some perspective on the degree of improvement in SWS that was observed with tiagabine in the current study, the increases in SWS with

**Table 4—Most Commonly Reported Adverse Events (in ≥ 5% of Subjects) in Any Study Group**

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n=38)</th>
<th>2 mg (n=42)</th>
<th>4 mg (n=38)</th>
<th>6 mg (n=45)</th>
<th>8 mg (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>3 (7)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Adverse events coded according to the MedDRA preferred terms.
tiagabine 6 mg and 8 mg was nearly comparable to those reported in healthy older adults on the first recovery night following 36 to 38 hours of sleep deprivation.18,19 Interestingly, the large increases in SWS reported in this study did not result in a significant effect on the subjective rating of sleep or improved cognitive performance, and several studies have been unable to link SWS to a restorative role or improvement in cognitive performance.20,21

The current finding that tiagabine increased SWS and reduced Stage 1 sleep, but did not improve subjective sleep quality, suggests that objective improvement in sleep depth is not related to the perception of improved sleep. Although tiagabine also significantly reduced the number of awakenings, sleep continuity was still disturbed, as indicated by a high number of awakenings, more than 100 minutes of WASO, and sleep efficiencies < 75%. Based upon the latter findings and the findings reported in other studies,8,22,23 it is possible that sleep continuity may be more important than sleep depth with respect to subjective sleep quality in older patients with insomnia.

The search for insomnia therapies has primarily evolved around benzodiazepine receptor agonists. These compounds decrease time to sleep onset and wake time during sleep, but they may also alter sleep architecture, REM sleep, and SWS.2 Hypnotic drugs should generally be avoided in elderly patients due to their potential hazards, including accidents, and other adverse effects.24 In the elderly population, the new benzodiazepine receptor agonists, zolpidem, zaleplon, and eszopiclone, have a favorable risk-benefit profile compared with the classical benzodiazepines.25 These drugs reduce LPS and increase TST, but they do not affect SWS or sleep maintenance.26 Newer therapies, such as tiagabine, seem to exert their effect on sleep primarily by increasing SWS and decreasing stage 1 sleep. Future research is needed to determine the clinical benefits of these changes in sleep architecture.

In conclusion, the results of this study show that, in elderly subjects with primary insomnia, tiagabine did not have a significant effect on WASO, LPS, or TST. Tiagabine, at doses of 4, 6, and 8 mg, did significantly increase SWS, with a corresponding significant decrease in Stage 1 sleep. At the higher doses (6 mg and 8 mg), tiagabine also significantly reduced the number of awakenings and increased the ratio of Stage 3+4/(Stage 1 + WASO). Tiagabine doses of 6 mg or less did not affect subjects’ ratings of sleep. These doses were generally well tolerated and not associated with residual effects and reduced alertness. The 8-mg dose, however, did negatively impact subjective sleep and was associated with troublesome adverse events, residual effects, and reduced alertness.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the work of the following investigators and their staff: Daniel Aeschbach, PhD, Harvard Medical School, Boston, MA; Richard Bogan, MD, SleepMed of South Carolina, Columbia, SC; Gary Burns, MD, Neurotrials Research of New Orleans, LLC, Metairie, LA; Martin A. Cohn, MD, Sleep Disorders Center of Southwest Florida, Naples, FL; Bruce Corser, MD, Community Research, Cincinnati, OH; Karl Doghramji, MD, Center for Sleep Disorders, Inc., Pottstown, PA; Sean Drummond, PhD, San Diego VA Medical Center, San Diego, CA; Helene Emsellem, MD, Center for Sleep & Wake Disorders, Chevy Chase, MD; Neil T. Feldman, MD, Clinical Research Group, St. Petersburg, FL; James Ferguson, MD, Radiant Research, Salt Lake City, UT; Steven G. Hull, MD, Vince and Associates Clinical Research, Overland Park, KS; Andrew O. Jamieson, MD, Sleep Medicine Associates of Texas, P.A., Plano, TX; Andrew D. Krystal, MD, MS, Duke University Medical Center, Durham, NC; D. Alan Lankford, PhD, Sleep Disorders Center of Georgia, Atlanta, GA; David W. Mayleben, PhD, Community Research, Crestview Hills, KY; Dennis J. Munjack, MD, Southwestern Research, Inc., Beverly Hills, CA; Michael Perlis, PhD, University of Rochester, Rochester, NY; John F. Pinto, MD, Clinical Research Center of Nevada, Las Vegas, NV; Kathleen Rice, PhD, Clinilabs Inc., New York, NY; Russell Rosenberg, PhD, Neurotrials Research, Inc., Atlanta, GA; Murray Rosenthal, DO, BMR HealthQuest, Behavioral & Medical Research, San Diego, CA; R. Bart Sangal, MD, Clinical Neurophysiology Services, P.C., Troy, MI; Martin B. Scharf, PhD, Tri-State Sleep Disorders Center, Cincinnati, OH; Markus H. Schmidt, MD, PhD, Ohio Sleep Medicine and Neuroscience Institute, Inc., Dublin, OH; Paula Schweitzer, PhD, Sleep Medicine and Research Center, St Luke’s Hospital, Chesterfield, MO; David Seiden, MD, Broward Research Group, Pembroke Pines, FL; Eric Sheldon, MD, Miami Research Associates, Miami, FL; Edward Stepanski, PhD, Rush University Medical Center, Chicago, IL; Kenneth P. Wright Jr., PhD, University of Colorado, Boulder, CO.

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