Effect of Gaboxadol on Sleep in Adult and Elderly Patients with Primary Insomnia: Results From Two Randomized, Placebo-Controlled, 30-Night Polysomnography Studies

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Study Objectives: To evaluate the efficacy and tolerability of gaboxadol in the treatment of adult and elderly patients with primary insomnia.

Design: Randomized, double-blind, placebo-controlled, multicenter, 30-night, polysomnography studies.

Setting: Sleep laboratory.

Patients: Primary insomnia, 18-64 y (adult study), or ≥65 y (elderly study).

Interventions: Adult study: gaboxadol 15 mg (GBX15; N = 148), 10 mg (GBX10; N = 154), or placebo (N = 156); elderly study: GBX10 (N = 157), gaboxadol 5 mg (GBX5; N = 153), or placebo (N=176).

Measurements and Results: Primary endpoints were wake after sleep onset (WASO) and latency to persistent sleep (LPS). Slow wave sleep (SWS) was a secondary endpoint. Analyses were based on the change from baseline for the average of nights 1/2, and nights 29/30, and compared gaboxadol versus placebo. Exploratory endpoints included patient's subjective assessment of total sleep time (sTST), WASO (sWASO), time to sleep onset (sTSO), and number of awakenings (sNAW); these analyses were based on weekly means. 1) Adult study. GBX15 significantly ($P \leq 0.05$) improved WASO through nights 29/30 but had no significant effects on LPS. No significant differences were seen for GBX10 versus placebo on WASO or LPS. GBX15 and GBX10 enhanced SWS. GBX15 significantly improved sTST, sWASO, sTSO, and sNAW at weeks 1 and 4. 2) Elderly study. GBX10 significantly improved WASO through nights 29/30; a significant improvement was also seen for GBX5 at nights 1/2 but this was not maintained through nights 29/30. GBX10 significantly improved LPS at nights 1/2 but the improvement was not maintained through nights 29/30; no significant differences were seen for GBX5 versus placebo on LPS. GBX10 and GBX5 enhanced SWS. GBX10 significantly improved sTST at week 1, and sTST, sWASO, and sNAW at week 4. Gaboxadol was generally well tolerated in both studies.

Conclusions: The maximum studied doses of gaboxadol (GBX15 in adult patients and GBX10 in elderly patients) were effective at enhancing objective polysomnography measures of sleep maintenance and SWS, and also some subjective sleep measures, over 30 nights but had little or no effects on sleep onset. The clinical relevance of the enhancement of SWS by gaboxadol is unclear.

Keywords: gaboxadol, primary insomnia, polysomnography, sleep, slow wave sleep, GABA, selective extrasynaptic $GABA_A$ agonist, SEGA

Citation: Lankford DA; Corser BC; Zheng YP; Li Z; Snavely DB; Lines CR; Deacon S. Effect of gaboxadol on sleep in adult and elderly patients with primary insomnia: results from two randomized, placebo-controlled, 30-night polysomnography studies. *SLEEP* 2008;31(10):1359-1370.

GABOXADOL IS A NOVEL HYPNOTIC WITH A DISTINCT MECHANISM OF ACTION COMPARED WITH CURRENT HYPNOTICS.[1,2] TRADITIONAL BENZODIAZEPINE (e.g., triazolam) and non-benzodiazepine (e.g., zolpidem) hypnotics, collectively referred to as benzodiazepine receptor agonists (BzRAs), share a similar mode of action as allosteric modulators of γ-aminobutyric acid type A (GABA-A) receptors. By contrast, gaboxadol is an agonist that acts directly on the GABA binding site of the GABA-A receptor and has no affinity for the benzodiazepine binding site. It has highest functional activity for δ-containing GABA-A receptors where it behaves as a super-agonist (i.e., more efficacious than GABA in a functional assay). δ-Containing GABA-A receptors are insensitive to BzRAs, probably exist mainly extrasynaptically, and are localized predominantly in the thalamus, dentate gyrus, cerebellum, and cortex. These characteristics have led to gaboxadol being classified as a selective extrasynaptic GABA-A agonist (SEGA).[3]

The functional consequences of these anatomical and pharmacological differences are yet to be understood. Both BzRAs and gaboxadol appear to have sleep maintenance properties and beneficial effects on sleep onset, although less consistently with regard to sleep onset for gaboxadol. Two previous exploratory PSG studies demonstrated that short term treatment with gaboxadol 10, 15, and 20 mg increased sleep continuity over an initial 2 nights of treatment in patients with primary insomnia.[4,5] Effects on measures of sleep onset were only observed in one study with gaboxadol 15 mg.[4] Effects on sleep onset, as well as maintenance, have also been observed for gaboxadol in larger studies using a model of transient insomnia.[6,7]

From a sleep architecture perspective, clear differences are observed between BzRAs and gaboxadol. Numerous studies have shown that classical benzodiazepines promote stage 2 NREM sleep and reduce both slow wave sleep (SWS) and REM sleep, while non-benzodiazepines may increase stage 2 sleep but have no effect on other visually scored sleep stages.[8-13] Gaboxadol has shown consistent increases in SWS with no significant effect on stage 2 or REM sleep in healthy adult/elderly subjects

Submitted for publication February, 2008
Accepted for publication February, 2008
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and early phase studies in patients with primary insomnia.[4-6,14-17] Clear differences in NREM EEG spectral profiles are also observed between zolpidem and gaboxadol, with the latter selectively enhancing lower frequency slow wave activity (SWA), underlining a neurochemical difference in the mechanism of action between zolpidem and gaboxadol.[6] Other putative sleep agents, including the 5-HT2A/2C receptor antagonists ritanserin and seganserin and the GABA reuptake inhibitor tiagabine, as well as α2δ calcium channel modulators, also increase SWS/SWA.[18-21]

In terms of the functional significance of sleep there has been much interest in SWS and the development of SWS-enhancing compounds for treating insomnia. There are marked age-related changes in sleep maintenance and continuity measures, but perhaps the most striking observation is that SWS is reduced with age.[22-24] SWS is a marker of homeostatic sleep drive, and it is an intriguing question whether increased sleep problems seen with age are in fact the result of changes in SWS, and whether enhancement of SWS might result in more restorative, less fragmented sleep in the elderly.

The objectives of the present studies were to confirm the efficacy and SWS-enhancing properties of gaboxadol in 2 large phase 3 PSG studies, one in adult and one in elderly adult patients with primary insomnia, and to determine whether the short term efficacy (1-3 nights) on objective measures of sleep seen to date could be maintained over 30 nights. Based on previous findings suggesting greater drug exposure in elderly patients (C_{max} and $AUC_{0\text{-inf}}$ of gaboxadol 20 mg increased by approximately 40%, $t_{½}$ increased from 1.5 to 2 h),[25] the maximum gaboxadol dose investigated was 10 mg in the elderly patients versus 15 mg in adult patients. To our knowledge, the elderly study constitutes the largest PSG dataset yet available in this population and is the first to evaluate the PSG effects of a SWS-enhancer in elderly patients over an extended period. Since SWS declines with age, there is interest in the potential differential effects of a SWS-enhancer in the elderly compared to adult insomniac patients. The adult study is therefore presented here in the same paper to allow an illustrative comparison of elderly and adult primary insomnia patients before and after treatment with gaboxadol in large 4-week treatment studies with identical designs and specifically identical PSG entry criteria.

METHODS

Design

Both studies were randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter, sleep laboratory PSG studies. The adult study (Merck protocol 004) was conducted at 50 sites in the United States from November 2004 to March 2006. The elderly study (Merck protocol 002) was conducted at 57 sites in the United States and Canada from November 2004 to March 2007.

Patients

In both studies, patients were enrolled based on the DSM-IV criteria for primary insomnia.[26] The adult study enrolled patients 18-64 y of age and the elderly study enrolled elderly patients ≥65 y of age. Patient's regular bedtime had to be between 20:00 and 01:00. Patients met the following PSG criteria on the first 2 nights of a 7-night single-blind placebo run-in period (these measures are defined further below): (1) mean wake after sleep onset (WASO) ≥45 min and >30 min on each individual night, (2) mean latency to persistent sleep (LPS) >20 min and >15 min on each individual night; (3) mean total sleep time (TST) ≤6.5 h and ≤7 h on each individual night.

Patients with a history of sleep disorders other than primary insomnia (e.g., narcolepsy, sleep apnea) or those with evidence of underlying sleep pathology identified at the screening PSG session were excluded, as were patients with a history of transmeridian travel (across time zones) or shift work in the 2 weeks prior to the screening visit. Patients who had an active Axis I or II disorder other than primary insomnia, those with a history of bipolar or psychotic disorder, or those with a history of alcohol or drug abuse as defined in DSM-IV (unless they fulfilled DSM-IV criteria for sustained remission) were also excluded. Inclusionary and exclusionary diagnoses were determined by a physician using the MINI International Neuropsychiatric Interview, a structured sleep diagnostic interview/sleep history, medical and psychiatric history, and physical and neurological examination. Patients were not eligible if they had been taking any of the following medications within 2 weeks prior to the screening visit: hypnotics, melatonin, stimulants, diet pills, sedating antihistamines, over-the-counter medications that could affect sleep (e.g., valerian), and any central nervous system depressants, anxiolytics, benzodiazepines, antipsychotics, or antidepressants. Patients were also not eligible if they had been taking fluoxetine or depot neuroleptics within 4 weeks prior to the screening visit, or any investigational compound within 12 weeks.

All patients gave written informed consent and the study was approved by the ethics committee responsible for each participating site. The studies were performed according to Good Clinical Practice guidelines and in accordance with the principles of the Declaration of Helsinki. Patients were paid for their participation in the trial, on a per-visit basis. The payments were approved by the ethics committees.

Procedure

Patients attended a medical screening visit during which their demographic data, medical, psychiatric and medication histories and symptoms of primary insomnia according to the DSM-IV criteria were recorded. Vital signs, electrocardiogram and blood biochemistry, hematology, and a urine analysis were carried out at screening visit. Medical reviews and physical, neurological, and psychiatric examinations were performed. A screening PSG lasting 8 h was conducted to ensure patients met minimum criteria for WASO (>25 min) and LPS (>15 min) and to exclude other sleep and neurological disorders (e.g., periodic limb movement disorder).

Patients who satisfied entry criteria then entered a 7-night single-blind (patients were blinded) placebo run-in period. PSGs were performed on the first 2 nights starting at the patient's habitual sleep time (median of the time previously recorded on a diary card over 7 days) and lasting for 8 h. Patients who met the PSG entry criteria outlined in the "Patients" section above then

entered a 30-night double blind treatment phase. In the adult study, adult patients were randomized to treatment with gaboxadol 10 mg, gaboxadol 15 mg, or placebo in a 1:1:1 ratio. In the elderly study, elderly patients were randomized to gaboxadol 5 mg, gaboxadol 10 mg, or placebo in a 1:1:1 ratio. Treatments were provided as capsules to be taken orally 30 min before the usual bedtime. PSGs were recorded on nights 1/2, nights 15/16, and nights 29/30. The present report focuses on the analysis findings for nights 1/2 and 29/30. Patients also completed morning questionnaires to assess aspects of their sleep during week 1 and week 4. The following measures were recorded: self-reported WASO (sWASO), self-reported time to sleep onset (sTSO), self-reported number of wakenings (sNAW), self-reported total sleep time (sTST), self-reported quality of sleep (sQUAL), and self-reported freshness on waking (sFRESH). The sQUAL and sFRESH measures were assessed using 0-100 visual analog scales (100 = best).

Following the double-blind treatment phase, patients entered a 7-night double-blind run-out phase to assess possible rebound insomnia or withdrawal effects, in which half the patients previously assigned to gaboxadol were switched to placebo and the remaining patients remained on gaboxadol; patients assigned to placebo remained on placebo. These data are not discussed in this report since gaboxadol is no longer in clinical development for insomnia and the results are not of clinical concern; generally, no rebound insomnia or withdrawal effects were observed.

Adverse events were recorded throughout the study and were rated by the investigator with regard to severity and likelihood of being drug-related. Vital signs, electrocardiogram, routine laboratory assessments, and physical examinations were performed at regular intervals.

Patients were asked to limit alcohol to 2 drinks a day and avoid alcohol at least 3 h before going to bed on non-PSG visit days during the study; patients were asked to avoid alcohol on PSG visit days. Patients were asked to limit caffeine consumption to 5 cups a day and to refrain from caffeine consumption after 16:00. Patients were also asked to refrain from napping >1 h per day.

The allocation schedule for treatment assignment was computer-generated using the clinical allocation schedule system at Merck Research Laboratories. Study supplies consisted of visually identical capsules provided in numbered bottles. Investigators used an interactive voice response system to determine which bottle number should be used for an individual patient. Study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the double-blind portions of the studies; unblinding took place after all patients had completed the study, medical/scientific review had been performed, protocol violators had been identified, and data had been declared final and complete.

PSG Scoring

Visual scoring of PSG data was performed by blinded personnel at CliniLabs (NY, USA) in 30-sec epochs according to the criteria described by Rechtschaffen and Kales.[27] Visually scored measures of hypnotic efficacy included: WASO, defined as the total amount of time spent awake from the start of 10 consecutive min of stage 1, 2, 3, 4 or REM sleep to lights on; LPS, defined as the time from lights out to the start of 10 consecutive min of stage 1-4 or REM sleep; TST, defined as the total time spent in stage 1-4 and REM sleep from lights out to lights on; number of awakenings (NAW) from onset of persistent sleep to lights on, with an awakening defined as a recording of at least two consecutive wake epochs bracketed by an epoch of stage 1-4 or REM sleep. Effects on sleep architecture were evaluated by measuring the duration of time (in min) spent in each sleep stage (stages 1-4 and REM). SWS was defined as the sum of stages 3 and 4.

Data Analysis

In the adult study, the primary efficacy hypotheses were that gaboxadol 15 mg would be superior to placebo as measured by the change from baseline in mean WASO or mean LPS during the first 2 treatment nights after randomization (nights 1/2). Secondary hypotheses were that gaboxadol 15 mg would be superior to placebo as measured by the change from baseline in mean WASO or mean LPS after 30 nights of treatment (PSG nights 29/30), or mean SWS duration after the first 2 nights of treatment (nights 1/2).

In the elderly study, the primary efficacy hypotheses were that gaboxadol 10 mg would be superior to placebo as measured by the change from baseline in mean WASO during the first 2 treatment nights after randomization (nights 1/2) and after 30 nights of treatment (nights 29/30) and that gaboxadol 10 mg would be superior to placebo as measured by change from baseline in mean LPS during the first 2 treatment nights after randomization (nights 1/2) and after 30 nights of treatment (nights 29/30). The secondary hypothesis was that gaboxadol 10 mg would be superior to placebo as measured by the change from baseline in mean SWS during the first 2 treatment nights after randomization (nights 1/2).

The primary efficacy analysis for both studies used log-transformed mean (i.e., transform of the arithmetic average of 2 nights on a log scale) data for WASO and LPS; hence treatment comparisons were based on geometric mean ratios. The log transformation for these measures was prespecified based on previous unpublished data which suggested that the distributions of the residual errors were skewed. For each treatment, the ratio of nights 1/2 to baseline or nights 29/30 to baseline were calculated, and then these values were used to calculate the gaboxadol-placebo treatment ratios; baseline was the arithmetic average of the first 2 nights of the 7-night single blind placebo run-in period. A longitudinal data analysis (LDA) model was used based on a full-analysis set population, which included all patients who took at least one dose of study medication and had at least one post-randomization assessment (and a baseline assessment for change from baseline analyses).[28,29] The LDA used a data-as-observed approach for handling missing data, which assumed that the missing data were missing at random. No explicit imputation was made for missing data. The LDA model in the adult study included factors for study center, time (as categorical variable), and time-by-treatment, time-by-center, and corresponding time-by-baseline interactions. In the elderly study, the time-by-baseline and time-by-center interactions were removed from this model since the variability of center

and baseline over time was ignorable; comparison of analyses for the primary endpoints (WASO and LPS) indicated that the 2 models provided consistent results. An unstructured covariance was used for the within-subject correlation in both studies.

The analytic methods for SWS, TST, and NAW were similar except that untransformed data were used (hence arithmetic means are used to display the results and the treatment comparisons were based on absolute differences). Similar methods were used to analyze the duration of time spent in each sleep stage separately (stages 1, 2, 3, 4, and REM); the percentage of the TST spent in each sleep stage was also calculated (the percentage of TST for each specific sleep stage was calculated for each patient individually, then averaged across all the patients in the same treatment group to obtain the mean) but not otherwise analyzed.

For the subjective assessments of sleep using morning diaries, the mean of assessments made during week 1 and week 4 (for each week, the average of measurements made over 3 to 5 days excluding days spent in the sleep laboratory) of the study were analyzed. The analytic methods were similar to those described above for the PSG endpoints. Nominal P-values were provided for exploratory subjective sleep measures.

Both studies had the same power calculation and sample size determination. A total of 465 patients (155 patients per treatment group) were planned to be enrolled in each study to yield a total of 459 (i.e., 153 patients per treatment group) with at least 1 night of PSG data after randomized dosing. Assuming an SD of 56 min for the change from baseline in PSG measured WASO at nights 29/30, 153 patients per group provided 80% power to declare a difference between the higher gaboxadol dose and placebo if the true underlying difference in the change from baseline in PSG-measured WASO was 18 min (5% level, 2-sided test). Assuming an SD of 39 min for the change from baseline in LPS at nights 29/30, 153 patients per group provided 83% power to declare a difference between the higher gaboxadol dose and placebo if the true underlying difference in the change from baseline in LPS was 13 min (5% level, 2-sided test).

For the adult study, there were 2 primary efficacy hypotheses and 3 secondary hypotheses; therefore, a 2-stage procedure was employed to control for multiplicity. If at least one of the 2 hypotheses was positive according to Hochberg's procedure at the 5% level, then the secondary hypotheses were evaluated using Hochberg's procedure at the 5% level. The lower gaboxadol dose (10 mg) was included primarily to help characterize the dose-response and safety of gaboxadol; therefore, only hypotheses that were positive for the higher dose (after multiplicity adjustment) were concluded on at the 5% level for the lower dose. Furthermore, the secondary hypotheses of the lower dose were not concluded on at the 5% level if none of the 2 primary hypotheses of the lower dose was positive.

To account for multiplicity related to the 4 primary hypotheses in the elderly study, a closed (ordered) testing procedure was used. After the first hypothesis was tested, each subsequent hypothesis was tested only if all previous tests were significant; the prespecified order was WASO at nights 1/2, WASO at nights 29/30, LPS at nights 1/2 and LPS at nights 29/30. Each test was performed at the 0.05 significance level (2-sided) conditional on positive results for prior hypotheses. The secondary hypothesis was tested following the same strategy (i.e., conditional on positive results for all primary hypotheses). The lower dose of gaboxadol (5 mg) was included primarily to help characterize the dose-response and safety of gaboxadol; therefore, only hypotheses that were positive for 10 mg (according to the multiplicity strategy) were concluded on at the 5% level for 5 mg.

All other endpoints were considered exploratory in nature and are presented to help characterize the full profile of gaboxadol on sleep fragmentation (PSG); patient perception of sleep and sleep architecture which are useful to consider when determining the clinical relevance of the primary and key secondary endpoints. Nominal P-values are provided for all statistical tests. The term "significant" in the remainder of the text refers to nominal significance at the 0.05 level; instances where a test was nominally significant but declared not significant according to the above testing strategies for the primary and/or secondary hypotheses are identified.

The primary analysis of safety data in both studies was based on adverse events occurring during the double-blind 30-night treatment period. The population for safety analyses was the all-patients-as-treated set, i.e., all patients who took ≥one dose of randomized study medication. Data for categories of adverse events (e.g., discontinuations due to adverse events) were analyzed using Fisher exact test.

RESULTS

Patient Accounting and Baseline Characteristics

Adult Study

A total of 2734 patients were screened; of these, 458 patients were randomized (placebo = 156, gaboxadol 10 mg = 154, gaboxadol 15 mg = 148) and 414 completed (placebo = 140, gaboxadol 10 mg = 144, gaboxadol 15 mg = 130) the 30-night double-blind treatment period. The main reasons for the screening failures were failure to meet the PSG screening or single-blind run-in entry criteria (N = 1058), screening PSG suggestive of a sleep disorder other than primary insomnia (N = 346), and clinically significant abnormality on screening physical examination, ECG, or laboratory test (N=145). The baseline demographic and sleep characteristics of patients were similar across treatment groups (Table 1). The mean age of patients was 44 years, and approximately 66% were females.

Elderly Study

A total of 1886 patients were screened; of these, 486 patients were randomized (placebo = 176, gaboxadol 5 mg = 153, gaboxadol 10 mg = 157) and 460 completed (placebo = 170, gaboxadol 5 mg = 145, gaboxadol 10 mg = 145) the 30-night double-blind treatment phase. The main reasons for screening failures were screening PSG suggestive of a sleep disorder other than primary insomnia (N = 490), failure to meet the PSG screening or single-blind run-in entry criteria (N = 475), and clinically significant abnormality on screening physical examination, ECG, or laboratory test (N = 184). The baseline demographic and sleep characteristics of patients were similar across

Table 1—Baseline Characteristics of Patients in the Adult Study

	Placebo (N = 156)	Gaboxadol 10 mg (N = 154)	Gaboxadol 15 mg (N = 148)
Demographics			
Mean (SD) age, y	43.5 (11.0)	45.3 (11.6)	42.8 (10.4)
Mean (SD) body mass index, kg/m^2	25.9 (4.0)	26.5 (3.7)	26.4 (3.9)
Female, %	66.7	64.9	66.9
White, %	62.8	57.1	56.8
PSG sleep measures, mean (SD)[1]			
WASO, min	102.4 (37.5)	102.2 (34.4)	101.0 (39.1)
LPS, min	69.4 (37.4)	64.6 (37.8)	66.5 (33.3)
TST, min	315.4 (52.8)	319.1 (45.0)	319.1 (49.3)
NAW, n	16.2 (6.7)	16.4 (5.8)	15.1 (5.7)
SWS, min	42.6 (27.3)	42.9 (28.7)	46.2 (29.9)
Sleep architecture, mean (SD) min in each stage[1]			
Stage 1	37.7 (18.1)	38.2 (18.2)	37.2 (17.5)
Stage 2	174.3 (41.5)	177.3 (39.7)	171.4 (40.9)
Stage 3	24.8 (14.4)	25.1 (15.7)	25.8 (15.9)
Stage 4	17.8 (21.8)	17.7 (23.1)	20.4 (23.0)
REM,	60.8 (21.9)	60.4 (20.0)	64.3 (22.2)
Subjective sleep measures, mean (SD)[11]			
sWASO, min	71.6 (53.7)	71.6 (43.3)	75.6 (54.6)
sTSO, min	77.8 (46.0)	67.2 (32.2)	69.5 (39.4)
sTST, min	322.4 (64.8)	338.3 (59.3)	333.1 (64.1)
sNAW, n	2.2 (1.3)	2.4 (1.4)	2.4 (1.6)
sQUAL, 0-100; 100 best	51.3 (16.3)	51.4 (14.9)	48.9 (15.1)
sFRESH, 0-100; 100 best	45.5 (17.1)	45.3 (15.9)	47.0 (15.3)

[1]Mean of the first 2 nights of the single-blind placebo run-in period.
[11]Mean of between 3 to 5 nights of the single-blind placebo run-in period. Sample sizes were slightly lower for these measures by approximately 10 patients per group, depending on the measure.

treatment groups (Table 2). The mean age of patients was 71 years, and approximately 61% were females.

Effects on PSG Measures

Adult Study

The effects of treatment on the primary endpoints, PSG measures of sleep maintenance (WASO) and onset (LPS), are shown in Table 3. Compared with placebo, gaboxadol 15 mg significantly improved WASO through nights 29/30 but had no significant effects on LPS. However, in a post hoc analysis, it was noted that baseline LPS became less severe over time (i.e., patients recruited towards the end of the study enrollment period had less severe baseline LPS scores than those recruited when the study first started) and that a shorter baseline LPS (<30 min) was associated with a reduced treatment effect (data not shown). No significant differences were seen for gaboxadol 10 mg versus placebo on WASO or LPS. Significant (at the 10% level) treatment-by-gender interactions were seen with regard to WASO for the gaboxadol 15 mg and gaboxadol 10 mg groups at nights 29/30 (P values = 0.051 and 0.093, respectively). These interactions were quantitative in nature (Gail and Simon P values > 0.200) and suggested that the effect of gaboxadol was larger in women than men.

Results for exploratory PSG measures of TST and NAW are shown in Table 3. Compared with placebo, gaboxadol 15 mg significantly increased TST at nights 1/2 while gaboxadol 10 mg had no significant effect. No significant differences versus placebo were seen at nights 29/30 for either gaboxadol dose. Gaboxadol 15 mg significantly reduced NAW at nights 1/2 and nights 29/30, and a significant reduction was also seen for gaboxadol 10 mg at nights 29/30.

Elderly Study

The effects of treatment on PSG measures of sleep maintenance (WASO) and onset (LPS) are shown in Table 4. Compared with placebo, gaboxadol 10 mg significantly improved WASO through nights 29/30; an improvement was also seen for gaboxadol 5 mg at nights 1/2 but this was not maintained through nights 29/30. Gaboxadol 10 mg significantly improved LPS at nights 1/2 but the improvement was not maintained through nights 29/30. No significant differences were seen for gaboxadol 5 mg versus placebo on LPS. Significant (at the 10% level) treatment-by-gender interactions were seen for WASO at nights 1/2 and 29/30. These interactions were quantitative in nature (all P values of Gail and Simon test for qualitative interaction > 0.200) and suggested that the efficacy of gaboxadol 10 mg was larger in women than in men.

Results for exploratory PSG measures of TST and NAW are shown in Table 4. Compared with placebo, gaboxadol 10 mg and 5 mg significantly increased TST at nights 1/2 and nights 29/30. No significant effects of gaboxadol on NAW were seen at nights 1/2 or nights 29/30.

Table 2—Baseline Characteristics of Patients in the Elderly Study

	Placebo (N = 175)	Gaboxadol 5 mg (N = 153)	Gaboxadol 10 mg (N = 157)
Demographics			
Mean (SD) age, y	71.4 (5.2)	70.6 (4.9)	71.0 (5.2)
Mean (SD) body mass index, kg/m^2	26.0 (3.6)	26.7 (3.4)	26.8 (3.6)
Female, %	64.6	60.8	58.0
White, %	86.9	82.4	83.4
PSG sleep measures, mean (SD)[1]			
WASO, min	123.2 (35.7)	118.7 (40.1)	124.6 (37.4)
LPS, min	52.4 (31.1)	61.8 (38.7)	56.4 (29.8)
TST, min	313.1 (43.0)	308.6 (51.4)	308.4 (44.9)
NAW, n	16.9 (6.3)	16.6 (6.2)	17.5 (7.4)
SWS, min	41.2 (29.1)	39.2 (29.9)	36.7 (28.0)
Sleep architecture, mean (SD) min in each stage[1]			
Stage 1	40.4 (21.7)	41.6 (21.6)	41.1 (20.7)
Stage 2	172.1 (38.6)	166.5 (39.0)	172.2 (40.7)
Stage 3	25.6 (18.1)	25.6 (18.8)	23.8 (18.2)
Stage 4	15.6 (21.9)	13.6 (21.0)	12.9 (20.5)
REM	59.4 (18.0)	61.4 (20.1)	58.3 (20.5)
Subjective sleep measures, mean (SD)[11]			
sWASO, min	90.3 (54.2)	88.4 (59.0)	91.1 (66.0)
sTSO, min	63.2 (54.2)	71.6 (55.2)	65.0 (62.9)
sTST, min	326.2 (61.7)	330.2 (64.3)	328.9 (66.7)
sNAW, n	2.4 (2.0)	2.3 (1.1)	2.4 (1.2)
sQUAL, 0-100; 100 best	51.4 (13.4)	52.0 (14.9)	53.0 (14.6)
sFRESH, 0-100; 100 best	49.7 (12.7)	49.9 (15.2)	50.0 (14.7)

[1] Mean of the first 2 nights of the single-blind placebo run-in period.
[11] Mean of between 3 to 5 nights of the single-blind placebo run-in period. Sample sizes were slightly lower for these measures by approximately 20 patients per group, depending on the measure.

Effects on Sleep Architecture

Adult Study

The effects of gaboxadol on SWS are summarized in Table 3. Both doses of gaboxadol showed an enhancement of SWS versus placebo throughout the study, with the effect being more marked for the higher dose. The difference between gaboxadol 10 mg and placebo on nights 1/2 was declared not significant according to the testing strategy to adjust for multiplicity.

Analysis of the complete sleep architecture profile by treatment group (Table 5) indicated that gaboxadol 15 mg significantly decreased the amount of time spent in stage 1 sleep compared with placebo, while significantly increasing the time spent in stage 3 and 4 sleep, and having no effects on stage 2 or REM sleep. Gaboxadol 10 mg significantly decreased stage 1 sleep compared to placebo (nights 1/2 only), while significantly increasing stage 4 sleep, and having no effects on stage 2, stage 3, or REM sleep.

Elderly Study

The effects of gaboxadol on SWS are summarized in Table 4. Both doses of gaboxadol showed an enhancement of SWS versus placebo throughout the study, with the effect being more marked for the higher dose. The differences between gaboxadol 10 mg and placebo and gaboxadol 5 mg and placebo on nights 1/2 were declared not significant according to the testing strategy to adjust for multiplicity.

Analysis of the complete sleep architecture profile by treatment group (Table 6) indicated that gaboxadol 10 mg significantly increased the amount of time spent in stage 2, stage 3, and stage 4 (nights 1/2 only) sleep compared to placebo, while having no effects on stage 1 or REM sleep. Gaboxadol 5 mg significantly increased the amount of time spent in stage 2 and stage 3 sleep compared with placebo, while having no effect on stage 1 or stage 4 sleep; an increase in the amount of time spent in REM sleep was seen for gaboxadol 5 mg on nights 1/2 but not on nights 29/30.

Effects on Subjective Sleep Measures

Adult Study

Results are shown in Table 3. Gaboxadol 15 mg significantly improved sWASO, sTSO, sTST, and sNAW compared to placebo at both week 1 and week 4 but had no significant effects on sQUAL or sFRESH. Gaboxadol 10 mg did not significantly improve any subjective measure at either time point.

Table 3—Estimated Effect of Gaboxadol on PSG and Subjective Sleep Measures in Adult Primary Insomnia Patients: Difference (95% CI) Between Gaboxadol and Placebo in Mean Change from Baseline Score

	Week 1[1]		Week 4[1]	
Measure	**Gaboxadol 10 mg**	**Gaboxadol 15 mg**	**Gaboxadol 10 mg**	**Gaboxadol 15 mg**
PSG measures, N	153	147	145	130
WASO, min[11]	–7.0 (–14.7, 0.7)	–14.2 (–21.9, –6.5)***	1.8 (–6.9, 10.4)	–9.8 (-18.7,-1.0)*
LPS, min[11]	–3.5 (–9.8, 2.9)	–7.5 (–13.8, –1.1) *	–3.2 (–9.4, 3.0)	–2.0 (–8.4, 4.3)
TST, min	9.4 (-0.7, 19.4)	20.6 (10.5, 30.7)***	0.5 (–10.5, 11.5)	10.8 (–0.5, 22.0)
NAW, n	-0.7 (-1.8, 0.4)	–1.7 (–2.9, –0.6)**	–1.3 (–2.5, –0.1)*	–1.5 (–2.7, –0.2)*
SWS, min	7.6 (2.8, 12.4)** [a]	15.1 (10.3, 19.9)***	6.8 (1.4, 12.3)*	12.7 (7.1, 18.3)***
Subjective measures, N	148	137	145	130
sWASO, min	0.3 (-8.0,8.6)	–10.7 (–19.1, –2.2)*	–4.9 (–12.8, 3.0)	–16.4, (–24.4, –8.3)***
sTSO, min	1.4 (-5.5,8.3)	–7.7 (–14.7, –0.7)*	–5.6 (–13.7, 2.4)	–15.5 (–23.6, –7.3)***
sTST, min	1.6 (-9.4, 12.6)	12.9 (1.8, 24.1)*	7.4 (–5.8, 20.5)	21.0 (7.7, 34.4)**
sNAW, n	-0.1 (-0.2, 0.1)	–0.3 (–0.5, –0.2)***	–0.0 (–0.2, 0.2)	–0.5 (-0.7, –0.2)***
sQUAL, 0-100 VAS	0.8 (-2.0,3.7)	1.4 (–1.5, 4.3)	1.1 (–2.4, 4.6)	1.9 (–1.6, 5.5)
sFRESH, 0-100 VAS	0.9 (-2.1,3.9)	1.4 (–1.7, 4.4)	0.2 (–3.3, 3.7)	1.5 (–2.1, 5.1)

Data shown are estimated treatment effects derived from the statistical model. The sample sizes indicate the number of patients with a measurement at the time point; all patients with any data were included in the statistical model used to provide estimated effects.

[1]For PSG measures, data are the average of measurements made over 2 nights (nights 1/2 for week 1, nights 29/30 for week 4). For subjective measures, data are the average of measurements made over 3 to 5 nights.

[11] The primary prespecified analysis used log transformed data and was based on the geometric mean ratio between gaboxadol to placebo. The untransformed means are shown here for illustrative purposes. Statistical significance shown is for the analysis of untransformed data; this gave identical results to the pre-specified primary analysis except in the case of gaboxadol 15 mg on LPS for nights 1/2, which was significant ($P \leq 0.05$) in the analysis of untransformed data but not significant in the pre-specified primary analysis. The results of the pre-specified primary analysis for geometric mean ratios were as follows: WASO on nights 1/2: gaboxadol 15 mg versus placebo = 0.79 (95% CI: 0.70, 0.89), $P < 0.001$; gaboxadol 10 mg versus placebo = 0.91 (95% CI: 0.81, 1.02), $P = 0.104$. WASO on nights 29/30: gaboxadol 15 mg versus placebo = 0.86 (95% CI: 0.75, 0.97), $P = 0.019$; gaboxadol 10 mg versus placebo = 1.02 (95% CI: 0.90, 1.16). $P = 0.763$. LPS on nights 1/2: gaboxadol 15 mg versus placebo = 0.89 (95% CI: 0.76, 1.03), $P = 0.121$; gaboxadol 10 mg versus placebo = 0.95 (95% CI: 0.82, 1.11), $P = 0.529$. LPS on nights 29/30: gaboxadol 15 mg versus placebo = 0.99 (95% CI: 0.83, 1.19), $P = 0.955$); gaboxadol 10 mg versus placebo = 0.99 (95% CI: 0.83, 1.18), $P = 0.904$.

*$P \leq 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo. Nominal P values are provided for all measures.

[a] Declared not significant according to the prespecified testing strategy to adjust for multiplicity.

Elderly Study

Results are shown in Table 4. Gaboxadol 10 mg significantly improved sWASO, sTST, and sNAW compared to placebo at week 4 (and week 1 for sTST and SQUAL) but had no significant effects on sTSO, sQUAL (week 4), or sFRESH. Gaboxadol 5 mg significantly improved sNAW at week 4 but had no significant effect on any other measure at either time point.

Safety

Adult Study

The numbers of patients evaluable for safety were 156 for placebo, 154 for gaboxadol 10 mg, and 148 for gaboxadol 15 mg. Gaboxadol 10 mg and 15 mg were generally well tolerated during the 30-night double-blind treatment period. There were no significant differences among treatment groups in the percentages of patients with adverse events (placebo, n = 54 [34.6%]; gaboxadol 10 mg n = 46 [29.9%]; gaboxadol 15 mg n = 59 [39.9%]) or serious adverse events (placebo n = 0; gaboxadol 10 mg n = 0; gaboxadol 15 mg n = 2 [1.4%]), and no patients died. The 2 serious adverse events in the gaboxadol 15 mg group were breast cancer and cerebrovascular accident and were not considered drug-related by the investigator. The percentages of patients who discontinued due to adverse events were: placebo n = 1 (0.6%), gaboxadol 10 mg, n = 4 (2.6%), gaboxadol 15 mg, n = 7 (4.7%); significantly more patients discontinued due to adverse events in the gaboxadol 15 mg group than the placebo group ($P \leq 0.05$). The only adverse event resulting in discontinuation that occurred in more than 1 patient was dizziness (n = 2). The most common adverse events were nausea (placebo, n = 2 [1.3%]; gaboxadol 10 mg, n = 4 [2.6%]; gaboxadol 15 mg, n = 13 [8.8%]), headache (placebo, n = 11 [7.1%]; gaboxadol 10 mg, n = 14 [9.1%]; gaboxadol 15 mg, n = 13 [8.8%]), and dizziness (placebo, n = 4 [2.6%]; gaboxadol 10 mg, n = 6 [3.9%]; gaboxadol 15 mg, n = 15 [10.1%]). These adverse events occurred somewhat more frequently in patients treated with gaboxadol 15 mg and in women, but the majority of events were of short duration and mild to moderate in severity. No clinically relevant treatment group differences were seen in vital signs, ECGs, routine laboratory assessments or physical examinations.

Elderly Study

The numbers of patients evaluable for safety were 175 for placebo, 153 for gaboxadol 5 mg, and 157 for gaboxadol 10 mg. Gaboxadol 5 mg and 10 mg were generally well tolerated.

Table 4—Estimated Effect of Gaboxadol on PSG and Subjective Sleep Measures in Elderly Primary Insomnia Patients: Difference (95% CI) Between Gaboxadol and Placebo in Mean Change from Baseline Score

	Week 1[1]		Week 4[1]	
Measure	**Gaboxadol 5 mg**	**Gaboxadol 10 mg**	**Gaboxadol 5 mg**	**Gaboxadol 10 mg**
PSG measures, N	152	155	146	145
WASO, min[11]	–10.5 (–18.0,–3.1)**	–19.6 (–27.0, –12.2)***	–3.4 (–11.1, 4.4)	–14.6 (–22.4,–6.8)***
LPS, min[11]	–4.4 (–9.7,0.9)	–6.6 (–11.9,–1.3)*	–3.6 (–9.7,2.6)	–0.4 (–6.5,5.8)
TST, min	16.2 (8.1, 24.3)***	26.5 (18.4, 34.6)***	11.1 (1.6, 20.7)*	17.0 (7.4, 26.5)***
NAW, n	–0.2 (–1.3, 0.9)	–0.4 (–1.5, 0.7)	0.4 (–0.7, 1.5)	–0.1 (–1.3, 1.0)
SWS, min	5.3 (0.5, 10.1)* [a]	10.1 (5.3, 14.8)*** [a]	5.2 (0.3, 10.1)*	11.1 (6.2, 16.1)***
Subjective measures, N	138	139	127	135
sWASO, min	–5.2 (–14.1, 3.6)	–8.6 (–17.5,0.2)	–5.4 (–14.9, 4.1)	–11.7 (–21.2, –2.3)*
sTSO, min	3.0 (–5.3, 11.3)	–0.1 (–8.4, 8.2)	–-1.1 (–10.7, 8.5)	3.8 (–5.8,13.3)
sTST, min	–3.6 (–12.1, 5.0)	10.1 (1.6, 18.6)*	5.7 (–5.5, 16.9)	15.5 (4.4, 26.6)**
sNAW, n	–0.2 (–0.4, 0.0)	–0.2 (–0.4, 0.0)	–0.2 (–0.5, –0.0)*	–0.2 (–0.5, –0.0)*
sQUAL, 0-100 VAS	2.1 (–0.4, 4.6)	2.8 (0.3, 5.3)*	1.3 (–1.8, 4.3)	2.1 (–1.0, 5.2)
sFRESH, 0-100 VAS	0.5 (–2.0, 3.0)	1.2 (–1.2, 3.7)	0.6 (–2.4, 3.7)	1.9 (–1.1, 5.0)

Data shown are estimated treatment effects derived from the statistical model. The sample sizes indicate the number of patients with a measurement at the time point; all patients with any data were included in the statistical model used to provide estimated effects.

[1]For PSG measures, data are the average of measures made over 2 nights (nights 1/2 for week 1, nights 29/30 for week 4). For subjective measures, data are the average of measurements made over 3 to 5 nights.

[11] The primary prespecified analysis used log transformed data and was based on the geometric mean ratio between gaboxadol and placebo. The untransformed means are shown here for illustrative purposes. Statistical significance shown is for the analysis of untransformed data; this yielded identical results to the pre-specified primary analysis. The results of the pre-specified primary analysis for geometric mean ratios were as follows: WASO on nights 1/2: gaboxadol 10 mg versus placebo = 0.82 (95% CI: 0.76, 0.88), P < 0.001; gaboxadol 5 mg versus placebo = 0.89 (95% CI: 0.82, 0.95), P = 0.002. WASO on nights 29/30: gaboxadol 10 mg versus placebo = 0.86 (95% CI: 0.79, 0.93), P < 0.001; gaboxadol 5 mg versus placebo = 0.97 (95% CI: 0.90, 1.05), P = 0.447. LPS on nights 1/2: gaboxadol 10 mg versus placebo = 0.87 (95% CI: 0.76, 0.98), P = 0.028; gaboxadol 5 mg versus placebo = 0.90 (95% CI: 0.79, 1.02), P = 0.101. LPS on nights 29/30: gaboxadol 10 mg versus placebo = 0.95 (95% CI: 0.81, 1.10), P = 0.464; gaboxadol 5 mg versus placebo = 0.93 (95% CI: 0.80, 1.08) P = 0.357.

*P ≤ 0.05, **P < 0.01, ***P < 0.001 versus placebo. Nominal P values are provided for all measures.

[a] Declared not significant according to the prespecified testing strategy to adjust for multiplicity.

There were no significant differences among treatment groups in the percentages of patients with adverse events (placebo, n = 63 [36.0%]; gaboxadol 5 mg, n = 47 [30.7%]; gaboxadol 10 mg, n = 58 [36.9%]), serious adverse events (placebo, n = 0; gaboxadol 5 mg, n = 1 [0.7%]; gaboxadol 10 mg, n = 0), or discontinuations due to adverse events (placebo, n = 5 [2.9%]; gaboxadol 5 mg, n = 3 [2.0%]; gaboxadol 10 mg, n = 4 [2.5%]). No patients died. The serious adverse event in the gaboxadol 5 mg group was a transient ischemic attack and was not considered drug-related by the investigator. The most common adverse events were dizziness (placebo, n = 4 [2.3%]; gaboxadol 5 mg, n = 2 [1.3%]; gaboxadol 10 mg, n = 9 [5.7%]) and nausea (placebo, n = 4 [2.3%]; gaboxadol 5 mg, n = 0; gaboxadol 10 mg, n = 7 [4.5%]). These adverse events occurred somewhat more frequently in patients treated with gaboxadol 10 mg and in women, but the majority were of short duration and mild to moderate in severity. One male patient who took 2 doses of gaboxadol 10 mg in a single night experienced nausea, hypertension, vomiting, anxiety, and diarrhea. No clinically relevant treatment group differences were seen in vital signs, ECGs, routine laboratory assessments, or physical examinations.

DISCUSSION

These phase 3 studies confirmed that short-term treatment over an initial 2 nights with gaboxadol 15 mg (adults) or 10 mg (elderly) improved sleep maintenance as assessed by an objective PSG measure, WASO, in patients with primary insomnia. These effects were still apparent after 30 nights of treatment. For the objective PSG measure of sleep onset, LPS, a significant improvement was seen only for gaboxadol 10 mg in the elderly patients at nights 1/2. The findings confirmed that the minimum effective dose of gaboxadol was lower in elderly patients (10 mg) than adult patients (15 mg). The studies also established a dose-response by demonstrating that the lowest gaboxadol doses in each study (10 mg in adults and 5 mg in the elderly) generally had no significant effects or reduced effects. There was a suggestion of a gender effect in both studies, with the effects of gaboxadol on WASO being more marked in women than men. Whether this reflects a genuine gender difference or is due to differences in body weight or body mass index is unclear, but gender differences have been reported in some other studies with gaboxadol (unpublished data on file). In addition to effects on WASO, the maximum doses of gaboxadol in each study consistently increased TST. A reduction in NAW was seen in the adult patients but not the elderly patients.

The observation that gaboxadol had an effect on sleep maintenance is notable, as it has a relatively short half-life of approximately 1.5 h. The mechanism for the effect of the drug on sleep maintenance is unclear but could potentially be related to the action of gaboxadol on extrasynaptic receptors, which is thought to result in a more prolonged tonic form of activation (resulting in

Table 5—Effect of Gaboxadol on PSG Sleep Architecture in Adult Primary Insomnia Patients: Mean (SD) Min Spent in Each Sleep Stage

Time	N	Stage 1	Stage 2	Stage 3	Stage 4	REM
Nights 1/2						
Placebo	156	38.0 (18.1)	202.5 (39.1)	28.6 (16.1)	20.1 (22.9)	74.9 (24.2)
Gaboxadol 10 mg	153	35.9 (19.1)	207.6 (37.7)	31.2 (18.1)	25.4 (28.2)**	75.0 (22.3)
Gaboxadol 15 mg	148	33.4 (15.4) **	207.6 (43.0)	35.7 (21.0)***	30.7 (29.3)***	79.4 (23.8)
Nights 29/30						
Placebo	144	37.1 (17.9)	212.8 (41.8)	29.6 (17.3)	21.3 (23.8)	78.7 (25.0)
Gaboxadol 10 mg	145	34.5 (18.0)*	211.9 (38.5)	32.8 (18.2)	25.6 (27.1)*	77.1 (21.5)
Gaboxadol 15 mg	131	33.1 (15.4)***	214.2 (41.6)	34.5 (18.3)**	29.9 (29.5)***	82.4 (22.3)

*P ≤ 0.05, **P < 0.01, ***P < 0.001 versus placebo (nominal P values); analysis based on differences between treatments in change from baseline duration in min.

inhibition, since GABA is an inhibitory transmitter) than that of synaptic receptors.[30,31] The reason why gaboxadol does not appear to have as consistent an effect on sleep onset is uncertain. An interesting observation in the adult study was that patients recruited later in the study had shorter (i.e., less impaired) baseline LPS than those recruited early in the study, and this correlated with a decline in treatment efficacy on this measure. This observation might suggest that a relatively high level of impairment on LPS at baseline is necessary in order to detect treatment benefits, although this hypothesis requires confirmation in prospective trials. It is possible that the metric of sleep onset used in the present studies may not be relevant for a drug which primarily affects SWS, since LPS measures time to onset of persistent sleep, which is typically stage 1 sleep. Variables such as latency to deeper sleep may be more valid endpoints for SWS-enhancing drugs, but it is not known whether measuring latency to different sleep stages would have any clinical relevance.

The elderly PSG study is the largest yet reported, and the first to examine a SWS-enhancer over 30 nights of treatment in a primary insomnia population. A previous study with tiagabine, a selective GABA reuptake inhibitor, found that it increased SWS but had no effects on WASO, LPS or TST in elderly primary insomnia patients over 2 nights of treatment.[32] The identical design of the present elderly and adult studies allows unique illustrative comparisons to be made between the 2 patient populations before and after treatment. In comparison to normal adult subjects, normal elderly subjects typically show less TST and more WASO.[24] This profile was generally confirmed when looking at the baseline characteristics of the patients in the present adult and elderly studies, even though both groups of patients had to meet the same minimum severity for the diagnosis of primary insomnia as defined by PSG entry criteria, which may have diluted the effect of age. Compared to adult patients, the elderly patients showed slightly less TST, more WASO, and slightly more NAW. The findings on the effects of age on sleep latency in normal subjects are less clear-cut but suggest that latency may either show no change or a small increase with increasing age.[24] In the present studies, the elderly patients had a shorter LPS at baseline than the adult patients. Despite these baseline differences, the minimum effective doses of gaboxadol in each study population appeared to work similarly (in terms of consistently improving WASO and TST). An exception was NAW, where the adult patients showed significant improvement with gaboxadol, but no significant differences were observed for the elderly.

The results from the present study confirmed findings in previous studies in healthy subjects and primary insomnia patients, indicating that gaboxadol has a distinct profile of effects on sleep architecture.[4-7,14-17] Previous studies have demonstrated that traditional benzodiazepine hypnotics prolong stage 2 sleep and reduce both SWS and REM sleep, whereas nonbenzodiazepine hypnotics may prolong stage 2 sleep.[10-13] In both of the present studies, visual inspection of the data and nominal P values suggested an initial dose-related enhancement of SWS that was maintained after 30 nights of treatment. It is not clear at present whether enhancing SWS translates into clinical benefits for treating insomnia. There is some evidence using gaboxadol in a model of sleep restriction which shows that gaboxadol may protect the body from the detrimental effects of sleep restriction on daytime sleep propensity and that the effect may be related to the change in SWS.[33] There are also some reports indicating that SWA may be involved in the consolidation of certain forms of memory. For example, Peigneux showed that overnight improvements in a motor memory task were significantly correlated to changes in SWA in the region of the brain implicated in the involvement of the task.[34]

A consistent finding in the literature on the effects of aging on sleep architecture in normal subjects has been that there is a reduction in SWS with increasing age.[22-24] Whether this is also the case in primary insomnia patients is less clear. At baseline in the present studies, the elderly patients appeared to spend a somewhat lower percentage of TST in SWS compared to the adult patients but the difference was not large. However, both the adult and elderly patients had to meet the same minimum severity for the diagnosis of primary insomnia as defined by PSG entry criteria and this may have diluted the effect of age on SWS compared to the disorder itself. While gaboxadol enhanced SWS in both the adult and elderly patients, a detailed look at the sleep architecture profiles suggested some differences in the effects of treatment. In adult patients, gaboxadol 15 mg significantly decreased the amount of time spent in stage 1 sleep, had no effect on stage 2 sleep, and increased the amount of time spent in stages 3 and 4 sleep. In elderly patients, gaboxadol 10 mg had no effect on stage 1 sleep and increased the amount of time spent in stage 2 and stage 3 sleep; effects on stage 4 sleep were also seen but tended to be less consistent than the stage 4 sleep enhancement observed in adult patients. Generally, these findings suggest that gaboxadol enhanced relatively lighter sleep stages (predominantly stages 2 and 3) in

Table 6—Effect of Gaboxadol on PSG Sleep Architecture in Elderly Primary Insomnia Patients: Mean (SD) Min, Spent in Each Sleep Stage

Time	N	Stage 1	Stage 2	Stage 3	Stage 4	REM
Nights 1/2						
Placebo	174	39.4 (20.3)	185.0 (39.2)	25.9 (17.4)	20.0 (27.8)	63.9 (17.8)
Gaboxadol 5 mg	152	40.3 (21.5)	190.1 (42.2)*	30.2 (21.0)**	19.0 (26.4)	67.6 (22.8)
Gaboxadol 10 mg	155	37.7 (18.2)	201.1 (41.4)***	32.1 (21.2)***	19.0 (25.8)	66.6 (20.5)*
Nights 29/30						
Placebo	169	38.5 (22.1)	190.8 (38.9)	26.3 (17.9)	18.6 (27.6)	67.5 (20.1)
Gaboxadol 5 mg	146	39.6 (19.6)	193.3 (40.9)	30.6 (20.1)*	18.1 (25.8)	68.8 (22.1)
Gaboxadol 10 mg	145	37.0 (17.3)	202.3 (45.8)*	31.1 (21.6)***	18.9 (28.4)*	66.0 (20.1)

*P ≤ 0.05, **P < 0.01, ***P < 0.001 versus placebo (nominal P values); analysis based on differences between treatments in change from baseline duration in min.

elderly patients compared with adult patients (stages 3 and 4). Whether this reflects a genuine age difference in the effects of gaboxadol, is due to the different doses studied in the 2 populations, or is an artifact is unknown.

The subjective correlates of the objective PSG endpoints also indicated that gaboxadol was effective on some measures. In the adult patients, significant differences from placebo were seen for gaboxadol 15 mg on sWASO, sTSO, sTST, and sNAW during both the first week and last week of the study. In the elderly patients, the subjective effects were less clear. By week 4, significant differences from placebo were seen for gaboxadol 10 mg on sWASO, sTST, and sNAW, but no significant effect on sTSO was seen at either week 1 or week 4. There was no consistent evidence in either study that gaboxadol improved patients' perceptions of the quality of their sleep, or how refreshed they felt on waking.

In terms of its safety profile, gaboxadol was generally well-tolerated over 30 nights of treatment. The most common adverse events in both studies were dizziness and nausea. There was a suggestion in both studies that adverse events occurred more frequently in women than in men, but most events were mild or moderate in severity and of short duration.

In conclusion, the present large phase 3 studies showed that an initial 2 nights of treatment with gaboxadol 15 mg (adults) and 10 mg (elderly) improved an objective PSG measure of sleep maintenance (WASO) in patients with primary insomnia, and this benefit was maintained over 30 nights of treatment. An improvement on an objective PSG measure of sleep onset (LPS) was seen only in the elderly patients on the first 2 nights of treatment with gaboxadol 10 mg. The previously reported enhancement of SWS by gaboxadol was observed in both the adult and elderly patients. Exploratory analyses suggested benefits of gaboxadol on some traditional subjective sleep efficacy measures in both studies. Gaboxadol is no longer in clinical development for the treatment of insomnia based on an assessment of its overall clinical profile in phase 3 trials, including limited or variable efficacy and the occurrence of psychiatric side effects at supratherapeutic doses in an abuse liability study involving drug abusers.[35]

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of William Ball and Jonas Lundahl in designing the studies, Carol Sable, Sylvia Wu, and Erin Paradis in performing the studies, and Jean Wang in analyzing the data.

Clinical Trial Registry Information: These trials are registered at the ClinicalTrials.gov website with the following identifiers: adult study = NCT00094627, elderly study = NCT00094666.

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DISCLOSURE STATEMENT

The studies reported in this paper were funded by Merck Research Laboratories as part of a collaboration with Lundbeck Ltd. to develop gaboxadol as a sleep medication. Use of gaboxadol for treatment of insomnia was investigational. Dr. Lankford has received research support from Actelion, Arena, Cephalon, Evotec, GlaxoSmithKline, Eli Lilly, Merck, Neurim, Neurocrine, Neurogen, Organon, Pfizer, Respironics, Sanofi-Aventis, Somaxon, Takeda, Transcept, Vanda, and Warner-Lambert and has consulted or been on the advisory board of Actelion, Cephalon, Concert, GlaxoSmithKline, Neurocrine, Neurogen, Ovation, Pfizer, Somaxon, and Transcept. Dr. Corser is the medical director of Community Research, an independent investigative site; has served as an investigator on numerous studies funded by industry; and has participated in speaking engagements for Takeda, Sanofi, Cephalon, and GlaxoSmithKline. Dr. Deacon was an employee of Lundbeck Ltd. at the time of this study. Drs. Zheng, Li, Lines, and Mr. Snavely are employees of Merck and own stock/stock options in the company.

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