

Next-day residual effects of gabapentin, diphenhydramine, and triazolam on simulated driving performance in healthy volunteers: a phase 3, randomized, double-blind, placebo-controlled, crossover trial

Gary G. Kay^{1*}, Howard I. Schwartz², Mark A. Wingertzahn³, Shyamalie Jayawardena³ and Russell P. Rosenberg⁴

¹Cognitive Research Corporation, St. Petersburg, Florida, USA

²Miami Research Associates, South Miami, Florida, USA

³Pfizer Consumer Healthcare, Madison, New Jersey, USA

⁴Neurotrials Research Inc., Atlanta, Georgia, USA

Objective Next-day residual effects of a nighttime dose of gabapentin 250 mg were evaluated on simulated driving performance in healthy participants in a randomized, placebo-controlled, double-blind, multicenter, four-period crossover study that included diphenhydramine citrate 76 mg and triazolam 0.5 mg.

Methods At treatment visits, participants ($n = 59$) were dosed at ~23:30, went to bed immediately, and awakened 6.5 h postdose for evaluation. The primary endpoint was the standard deviation of lateral position for the 100-km driving scenario. Additional measures of driving, sleepiness, and cognition were included.

Results Study sensitivity was established with triazolam, which demonstrated significant next-day impairment on all driving endpoints, relative to placebo ($p < 0.001$). Gabapentin demonstrated noninferiority to placebo on standard deviation of lateral position and speed deviation but not for lane excursions. Diphenhydramine citrate demonstrated significant impairment relative to gabapentin and placebo on speed deviation ($p < 0.05$). Other comparisons were either nonsignificant or statistically ineligible per planned, sequential comparisons. Secondary endpoints for sleepiness and cognitive performance were supportive of these conclusions.

Conclusions Together, these data suggest that low-dose gabapentin had no appreciable next-day effects on simulated driving performance or cognitive functioning. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—diphenhydramine; gabapentin; residual effects; simulated driving performance; sleep

INTRODUCTION

Occasional disturbed sleep (consisting of difficulties initiating or maintaining sleep, waking too early, not sleeping long enough, or experiencing nonrestorative sleep) is prevalent among adults in the USA (Ancoli-Israel and Roth, 1999; National Sleep Foundation, 2009; National Sleep Foundation, 2015) and is commonly treated with over-the-counter (OTC) and prescription sleep medications. Safety is a concern with both drug classes, and the US Food and Drug Administration has issued a safety communication regarding the risk of next-day impairment following use of medications to treat insomnia symptoms (US Food

and Drug Administration, 2013). Negative residual drug effects on driving are especially dangerous and have prompted regulatory guidance to study the effects of nighttime dosing on next-day driving performance. A number of variables (e.g., drug, dose, half-life, time of dosing, and participant characteristics) contribute to the likelihood and severity of residual effects, but in general, many sleep agents, including non-benzodiazepines, are associated with impaired next-day driving (Vermeeren, 2004; Mets *et al.*, 2011; Roth *et al.*, 2014).

Gabapentin (600–1800 mg) is approved for the treatment of certain types of neuropathic pain, restless legs syndrome, and seizure-related disorders (XenoPort Inc, 2013; Pfizer Inc, 2015), and over the course of development, relatively high doses have shown positive effects on sleep (e.g., reduction in pain-related sleep interference, increases in total sleep time, sleep efficiency, and/or slow-wave sleep in various patient populations) (Backonja *et al.*, 1998; Rowbotham *et al.*, 1998; Placidi *et al.*, 2000; Garcia-Borreguero *et al.*, 2002). Low-dose

*Correspondence to: G. G. Kay, PhD, Cognitive Research Corporation, 200 Central Avenue, Suite 1230, St. Petersburg, FL 33701 USA. Tel: (727) 897-9000; Fax: (727) 897-9009 E-mail: gkay@cogres.com

Names of institutions at which research was conducted: Miami Research Associates; Neurotrials Research Inc.

Study sponsor: This clinical study was sponsored by Pfizer Consumer Healthcare, Madison, NJ, USA.

gabapentin (250 mg) may serve as a potential treatment for occasional difficulties with sleep maintenance. Support comes from randomized controlled studies of healthy individuals self-reporting occasional disturbed sleep, wherein low-dose gabapentin (250 mg) was associated with significant improvements of sleep duration and quality (relative to placebo) in a model of transient insomnia and during home use (Furey *et al.*, 2014; Rosenberg *et al.*, 2014). In these same studies, gabapentin showed no significant next-day sleepiness or impairment of cognitive/psychomotor function (Furey *et al.*, 2014; Rosenberg *et al.*, 2014), suggesting a unique profile of sleep improvement without next-day impairment, although treatment differences in sleep time may have offset any potential differences in next-day residual effects.

The present study was undertaken to specifically characterize the effect of low-dose gabapentin (250 mg) on next-day simulated driving performance. Two medications were included as comparators: diphenhydramine (DPH) citrate, a widely used OTC sleep aid with no published data regarding effects on next-day driving performance, and triazolam, a prescribed benzodiazepine hypnotic used to treat severe insomnia and shown to impair next-day driving (Riedel *et al.*, 1988). The latter was included as an active comparator to confirm study sensitivity. The study's primary objective was to determine the next-day residual effects of nighttime administration of gabapentin at a dose of 250 mg, under evaluation as a potential treatment for occasional disturbed sleep, and DPH citrate 76 mg, the recommended dose of the citrate formulation in OTC sleep aids (which is the molar equivalent to DPH hydrochloride 50 mg), compared with placebo and each other on simulated driving performance in healthy participants as measured by the standard deviation of lateral position (SDLP; primary endpoint), a sensitive measure of a driver's ability to maintain consistent lane position. Secondary endpoints included other commonly used measures of simulated driving, specifically, speed deviation (a measure of speed variability) and lane excursions (a measure of the driver's ability to stay within their lane). Measures of next-day sleepiness and cognitive functioning were also included.

METHODS

Study design

The study (ClinicalTrials.gov number NCT01888497) was a randomized, single-dose, double-blind, multi-center (2 sites), four-period crossover study, approved by an institutional review board (Chesapeake Research

Review, LLC) and conducted in accordance with legal and regulatory requirements as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Declaration of Helsinki and its amendments, and in compliance with the International Conference on Harmonisation Guideline for Good Clinical Practice. All participants provided written informed consent prior to the initiation of study procedures.

Study population

Eligible participants were healthy men or women of non-child-bearing potential between 25 and 55 years of age (inclusive) with approximately half of the participants at each study center <40 years of age. All participants were required to have a body mass index of 17.5 to 30.0 kg/m² and a total body weight of >50 kg. Eligible participants needed to reliably perform study assessments (SDLP no higher than 1 standard deviation greater than the mean of healthy adults in similar studies on practice trials), have a valid driver's license, and to have driven a minimum of 10 000 mi/year for the previous 3 years. Additionally, participants were required to have a regular sleep pattern (usual bedtime between 21:00 and 24:00), a score <10 on the Epworth Sleepiness Scale, and Simulator Sickness Questionnaire scores that were not indicative of simulator sickness (both tests administered at the screening visit). Participants were compensated monetarily for their time. The compensation was reviewed and approved by the institutional review board and was not tied to performance in any way.

Major exclusion criteria included females who were pregnant, breastfeeding, or of child-bearing potential; a history of a clinically significant medical, neurologic, or psychiatric disorder (or laboratory abnormality); a recent history (within 2 years) of, or currently being treated for, a sleeping disorder (including excessive snoring, obstructive sleep apnea, or a chronic painful condition that interfered with the individual's sleep) or in the opinion of the investigator had difficulty either falling asleep or staying asleep in the previous 3 months; visual or auditory impairment; screening supine blood pressure of ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic); a positive response at screening to any question in the suicidal behavior section or questions 4 or 5 in the suicidal ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS); or a history of an allergic reaction or significant intolerability to gabapentin, DPH, or triazolam. Individuals currently taking or expected to take any of the following medications during the study were excluded: sedative hypnotic agents, melatonin, dehydroepiandrosterone, herbal sleep/relaxation

remedies, first-generation antihistamines, opiates or propoxyphene, monoamine oxidase inhibitors, ketconazole, itraconazole, nefazodone, gabapentin, DPH, or triazolam, within 28 days of randomization; amphetamines, cocaine, methadone, marijuana, or phencyclidine within 6 months prior to randomization; or selective serotonin reuptake inhibitors, within 10 years prior to randomization. Individuals were also ineligible if they had a history of substance abuse, consumed excessive amounts of alcohol daily or on a regular basis before bedtime, smoked cigarettes (other than social smoking) or used nicotine (or nicotine-containing products), consumed excessive amounts of caffeinated beverages per day, and/or traveled across ≥ 1 time zones in the 2 weeks prior to randomization or were expected to travel across time zones (≥ 1) during the study.

Procedures

At screening, a routine physical examination (including vital signs and clinical laboratory tests) and medical history were conducted. A urine specimen was obtained and processed for drug screening (iCup® Drug Screen, Alere Toxicology, Clearwater, FL, USA), and a breath alcohol measurement was collected. Drug testing included amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamine, methadone, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants, and marijuana. The Epworth Sleepiness Scale, C-SSRS, and Karolinska Sleep Diary were administered. Participants were screened for simulator sickness and received standardized training on the driving simulator and cognitive test battery. Training procedures were completed within 14 days prior to treatment period 1 (additional training sessions were scheduled if necessary).

Participants returned to the study site for treatment period 1 (within 21 days after screening) and arrived ~ 3.5 h prior to dosing. The following were obtained: a review of concomitant medications, an updated medical history, urine specimen, breath alcohol measurement, vital signs, C-SSRS assessment, and a predose blood sample (for pharmacokinetic assessment). Practice on driving simulator and cognitive test battery was conducted. Eligible participants were required to meet the following randomization criteria at the first and all subsequent treatment visits: no use of alcohol within 48 h of the visit and a negative result on a breath alcohol measurement at the time of the visit, no use of caffeine-containing products from bedtime on the night before inpatient sleep assessments, bedtime between the hours of 22:00 and 01:00 and 7 to 9 h in bed on the nights before visits, and no travel across time zones or work on a rotation shift since screening.

Individuals whose urine specimens returned positive for any prohibited drugs were discontinued from the study. Participants who did not meet the randomization/continuation criteria regarding alcohol and/or tobacco use or sleep routine prior to the first treatment visit were discharged but remained in the study as long as they could return to the site within 42 days of screening. Study treatment assignments across treatment periods were determined by a computer-generated randomization schedule. A meal was served ~ 2.5 h prior to dosing, participants were dosed with study product at $\sim 23:30$ (designated as time 0), went to bed immediately after dosing (lights out), and were awakened (lights on) 6.5 h after dosing. The duration of the sleep period was chosen based on evidence that a large percentage of American adults sleep no more than 6.5 h each night (National Sleep Foundation, 2008); data for typical sleep times were not collected for this population.

A blood sample was collected immediately upon awakening to assay plasma concentration of assigned study treatment (data not included). Participants were permitted up to 30 min after lights on for personal hygiene and a light breakfast (noncaffeinated beverages and breakfast foods). Blood pressure (supine), pulse rate, and respiratory rate were assessed. Approximately 7.25 h postdose, participants completed the Karolinska Sleepiness Scale and then performed the driving simulator task (Country Vigilance-Divided Attention [CVDA] driving scenario on the Cognitive Research Corporation Driving Simulator [CRCDS]-MiniSim). Following completion of the drive, the participant's motivation and a self-appraisal of their driving performance were obtained using a visual analog scale. Approximately 8.25 h postdose, participants completed the Karolinska Sleepiness Scale, CogScreen® Symbol Digit Coding test, and the Psychomotor Vigilance Test. During the period between the time of lights on and completion of all assessments, participants were instructed to stay out of bed. Participants were discharged after the postdose procedures were completed at each treatment period at the investigator's discretion but were not permitted to drive.

Participants returned for subsequent treatment visits at intervals of 7 to 14 days (minimum of 5 days to a maximum of 22 days) and received study treatment according to the randomization schedule. For treatment period 4, participants completed the C-SSRS after completion of all activities and prior to discharge (in addition to completing the C-SSRS prior to dosing).

All nonprohibited concomitant medications taken during the study were recorded with indication, daily dose, and start and stop dates of administration.

Drug administration

Doses were chosen based on previous experimental studies and/or recommended doses for promoting sleep. Gabapentin 250 mg was chosen because this is the specific dose under evaluation for the treatment of occasional disturbed sleep and has demonstrated efficacy. DPH citrate 76 mg (which is equivalent to DPH hydrochloride 50 mg) is the recommended dose of the citrate formulation as a nighttime sleep aid. Triazolam 0.5 mg, recommended for the short-term treatment of insomnia, was used as a positive control to confirm study sensitivity. DPH citrate 76-mg caplet was overencapsulated to match the gabapentin 250-mg and placebo capsules. Triazolam 0.5 mg was administered as a tablet. To maintain study blind, participants were blindfolded during dosing and a double-dummy blinding scheme was used. Participants were given one active or placebo capsule plus two active or placebo tablets at bedtime/lights out on the evening prior to testing in the research unit and were instructed to consume with ~240 mL of water without chewing or crushing the product.

Assessment of next-day effects

CVDA driving scenario on the CRCDS-MiniSim. The CVDA driving scenario is a 62.1 mi (100 km), monotonous, two-lane highway driving task that includes a secondary visual vigilance task (divided attention). The monotonous country vigilance scenario is sensitive to the effects of sleepiness and central nervous system depressants (e.g., alcohol) on driving performance (Kay *et al.*, 2013). The sensitivity of the scenario to residual effects of nighttime administration of a hypnotic was demonstrated in a study with zopiclone (Simen *et al.*, 2015). The scenario has proven useful in evaluating individuals with a variety of conditions, including obstructive sleep apnea with excessive daytime sleepiness (Kay and Feldman, 2013; Sun *et al.*, 2013). Results obtained with a full-motion driving simulator (i.e., the National Advanced Driving Simulator), which served as the basis for the CRCDS-MiniSim (Lee *et al.*, 2013), are generalizable to results obtained using on-the-road driving tests (Brown *et al.*, 2007; Senserrick *et al.*, 2007).

The prespecified primary endpoint of the study was the SDLP in the simulated driving task. Secondary endpoints were speed deviation and lane excursions. After completing the driving simulation, participants were asked to assess their own performance and level of motivation to perform at their best during the driving simulation using a 100-mm visual analog scale.

Cognitive and sleepiness endpoints

Cognitive testing included the CogScreen Symbol Digit Coding task and the Psychomotor Vigilance Test. Symbol Digit Coding, a computer analog of the conventional digit symbol substitution test, was used to measure attention, visual scanning, working memory, and speed of information processing. The Psychomotor Vigilance Test is a 10-min sustained attention test, in which the participant is asked to press a button as quickly as possible when a target is presented on the screen of the device. The test records the participant's reaction time to the target stimuli. The Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990) was used to assess subjective level of sleepiness. This is a self-report measure of situational sleepiness at a particular point in time; participants indicate their responses on a 9-point Likert scale from "extremely alert" to "extremely sleepy—fighting sleep." The Karolinska Sleepiness Scale has been found to correlate with electroencephalogram and behavioral variables (Kaida *et al.*, 2006).

Safety: vital signs, Columbia-Suicide Severity Rating Scale, and adverse events

At each treatment period, vital signs were collected predosing and postdosing (upon awakening). The C-SSRS was completed prior to dosing. All observed and participant-reported adverse events (AEs) (including serious AEs) regardless of suspected causal relationship to the investigational products were recorded throughout the study.

Sample size and statistical analysis

Sample size determination was based on a similarly designed, on-the-road driving study (ClinicalTrials.gov number NCT01106859). A sample size of 48 participants would provide 90% power to establish noninferiority between gabapentin and placebo on the primary endpoint, SDLP, assuming (i) within-subject standard deviation of the SDLP of 3.5 cm; (ii) the true difference between gabapentin and placebo is zero; and (iii) the noninferiority margin is 2.4 cm, which is considered equivalent to the effects of 0.05% blood alcohol concentration (based on an on-the-road driving test (Louwerens *et al.*, 1987)). To obtain a minimum of 48 participants completing all four treatment periods, ~52 participants were planned for enrollment.

SDLP, speed deviation, and lane excursions were analyzed using nonparametric methods using the intent-to-treat population because the usual parametric model assumptions were not satisfied (Tudor and Koch, 1994). Treatment sequences were pooled into two

groups, one estimating a specific pairwise treatment difference within a subject, and the other, the negative of the same treatment difference, such that the comparison of these two groups would cancel out the period effect and estimate twice the treatment difference. This variable was used to obtain the *p*-values and confidence intervals for treatment differences based on the Wilcoxon Rank Sum test as well as the estimated treatment differences based on the Hodges–Lehmann estimate. For the primary and secondary endpoints, four pairwise comparisons (alternative statistical hypotheses) were evaluated in the following order: (i) triazolam versus placebo (triazolam is worse than placebo); (ii) gabapentin versus placebo (gabapentin is no worse than placebo with prespecified noninferiority margins); (iii) DPH citrate versus gabapentin (DPH citrate is worse than gabapentin); and (iv) DPH citrate versus placebo (DPH citrate is worse than placebo). For comparisons (i), (iii), and (iv), the alternative hypothesis was considered established if the treatment effect comparing the first treatment to the second was positive, and the corresponding *p*-value was ≤ 0.05 . For comparison (ii), the alternative hypothesis was considered established if the upper 95% confidence limit for the gabapentin—placebo difference was less than the prespecified noninferiority margin. Based on historical data (from an on-the-road driving study (Louwerens *et al.*, 1987)), the protocol-specified noninferiority margin was 2.4 cm for SDLP. The noninferiority margins were 0.1 m/s and 8 for speed deviation and lane excursions, respectively. These values for speed deviation and lane excursions were based on the effect of alcohol at 0.05% blood alcohol concentration on the CVDA Driving Scenario using the CRCDS-MiniSim (CRC, data on file). If the alternative hypothesis was not accepted, the subsequent comparisons were not eligible to be declared as significant.

Endpoints related to sleepiness and the cognitive test battery were analyzed using a mixed model with site, period, and treatment as fixed effects and subject within site as a random effect.

RESULTS

Participant demographics/baseline characteristics

Fifty-nine participants were randomized to the study (safety population), and of these, 55 completed all four treatment periods. Four participants discontinued ($n = 1$, adverse event; $n = 3$, withdrew consent) after completing period 1 ($n = 2$) or period 2 ($n = 2$). Demographic and baseline characteristics are summarized in Table 1. Participants were mostly male (78.0%), white (45.8%), and had a mean age of 41.1 (SD = 9.0; range = 25–55) years.

Table 1. Demographic and baseline characteristics (safety population)

	Summary statistics $n = 59$
Age (year)	
Mean (SD)	41.1 (9.0)
Range	25–55
Sex, n (%)	
Male	46 (78.0)
Female	13 (22.0)
Race, n (%)	
White	27 (45.8)
Black	13 (22.0)
Hispanic	1 (1.7)
Asian or Pacific Islander	1 (1.7)
White/Hispanic	17 (28.8)
Weight (kg)	
Mean (SD)	79.9 (12.2)
Range	57–109
Body mass index (kg/m ²)	
Mean (SD)	26.0 (2.8)
Range	20–30
Karolinska Sleepiness Scale ^a	
Mean (SD)	2.6 (1.6)
Range	1–7

^aBased on rating scale from 1 (extremely alert) to 9 (extremely sleepy—fighting sleep) conducted at screening.

Next-day effects measures

Simulated driving performance. Next-day effects on simulated driving performance as measured by the SDLP are shown in Table 2. Participants treated with triazolam performed significantly worse than placebo ($p < 0.001$), thus establishing model sensitivity (Table 2, Figure 1). The upper 95% confidence limit for the gabapentin versus placebo treatment difference was less than the prespecified protocol value of 2.4 cm, thus establishing noninferiority of gabapentin compared with placebo (i.e., gabapentin was no worse than placebo) (Table 2, Figure 1). DPH citrate showed a numerically greater impairment versus gabapentin, but the difference was not statistically significant (Table 2). The final comparison between DPH citrate and placebo was significant but technically ineligible (given the sequential analysis procedure employed) (Table 2).

Among the two secondary endpoints, participants treated with triazolam showed a significant impairment compared with placebo on both speed deviation and lane excursions ($p < 0.001$; Table 2, Figure 2), again supporting study sensitivity. Gabapentin demonstrated noninferiority relative to placebo on speed deviation based on the prespecified margin (0.1 m/s), whereas DPH citrate showed a statistically significant impairment relative to gabapentin and placebo ($p < 0.05$) (Table 2, Figure 2). Noninferiority was not established for gabapentin relative to placebo on lane excursions (based on the prespecified noninferiority

Table 2. Next-day effects on simulated driving performance

Descriptive statistics	Placebo (<i>n</i> = 58)	Gabapentin 250 mg (<i>n</i> = 55)	DPH citrate 76 mg (<i>n</i> = 57)	Triazolam 0.5 mg (<i>n</i> = 56)
Standard deviation of lateral position (cm)				
Mean (SD)	33.2 (8.0)	34.2 (10.0)	35.4 (8.9)	47.4 (12.0)
Median	30.7	32.0	33.8	46.8
Speed deviation (m/s)				
Mean (SD)	0.9 (0.3)	0.9 (0.3)	1.0 (0.3)	1.3 (0.6)
Median	0.9	0.9	0.9	1.2
Lane excursions				
Mean (SD)	37.8 (45.9)	46.7 (58.5)	52.4 (62.0)	147.7 (113.6)
Median	17.5	22.0	24.0	133.5
Pairwise comparisons ^a				
Standard deviation of lateral position (cm)				
Treatment difference	Triazolam versus placebo	Gabapentin versus placebo	DPH citrate versus gabapentin	DPH citrate versus placebo
95% CI	13.82	0.55	1.02	2.37
<i>p</i> -value	10.85, 17.40	-0.66, 2.33	-0.39, 2.51	1.01, 3.98
	<0.001	0.372 ^b	0.134	<0.001 ^c
Speed deviation (m/s)				
Treatment difference	0.36	-0.01	0.07	0.06
95% CI	0.26, 0.47	-0.07, 0.05	0.02, 0.12	0.01, 0.12
<i>p</i> -value	<0.001	0.749 ^b	0.012	0.014
Lane excursions				
Treatment difference	103.25	5.00	3.00	11.00
95% CI	72.00, 130.50	-4.00, 16.50	-3.00, 9.00	4.00, 20.50
<i>p</i> -value	<0.001	0.281	0.213	0.003 ^c

CI, confidence interval; DPH, diphenhydramine; SD, standard deviation.

^aAnalyzed using nonparametric methods. Treatment difference (first treatment–second treatment) is the Hodges–Lehmann estimate. The *p*-values and the CIs are based on the Wilcoxon Rank Sum test.

^bFirst treatment (gabapentin) is no worse than the second treatment (placebo) (upper CI ≤ 2.4 cm for standard deviation of lateral position and ≤ 0.1 m/s for speed deviation).

^cSecond treatment (placebo) significantly better than the first (DPH citrate) but comparison is technically ineligible.

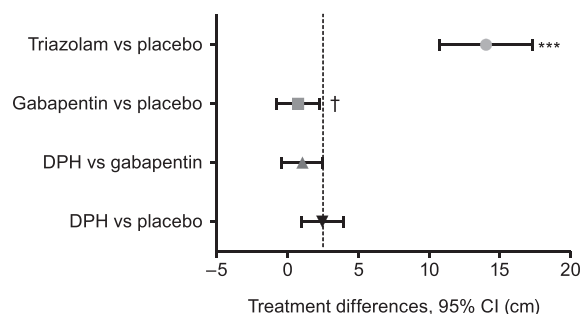


Figure 1. Sequential pairwise treatment comparisons (treatment difference and 95% CI) on simulated driving performance as measured by the standard deviation of lateral position (primary endpoint). CI, confidence interval; DPH, diphenhydramine citrate. ****p* < 0.001 for indicated comparison. †Noninferiority: gabapentin is no worse than placebo (upper CI is < 2.4 cm). Treatment difference (first treatment–second treatment) is the Hodges–Lehmann estimate; *p*-values and confidence intervals are based on the Wilcoxon Rank Sum test as detailed under the ‘Sample size and statistical analysis’ section. The prespecified upper limit for demonstrating noninferiority of gabapentin relative to placebo is 2.4 cm (dashed vertical line). Participants per treatment group: placebo (*n* = 58), gabapentin (*n* = 55), DPH (*n* = 57), and triazolam (*n* = 56)

margin, 8); subsequent pairwise comparisons of DPH citrate with gabapentin and placebo were technically ineligible (Table 2, Figure 2).

When participants were asked to rate their driving performance (“How well did you drive?”), triazolam resulted in a self-rating of significantly poorer driving performance versus placebo (*p* < 0.001). Likewise, when asked, “How motivated did you feel?” triazolam again resulted in ratings of lower motivation compared with placebo (*p* = 0.007). No other pairwise treatment comparisons were significant.

Sleepiness

On the Karolinska Sleepiness Scale, participants reported a significantly higher level of sleepiness with triazolam compared with placebo (*p* < 0.001) and a small but significantly higher level of sleepiness with both gabapentin and DPH citrate versus placebo (*p* < 0.05) prior to completing the morning drive (Table 3). At the postdriving assessment (8.25 h postdose), triazolam and DPH citrate, but not gabapentin, continued to show significantly decreased alertness compared with placebo (*p* < 0.05; Table 3).

Cognitive test battery

Performance was assessed approximately 8.25 h postdosing using sensitive measures of information processing speed (Symbol Digit Coding Test) and

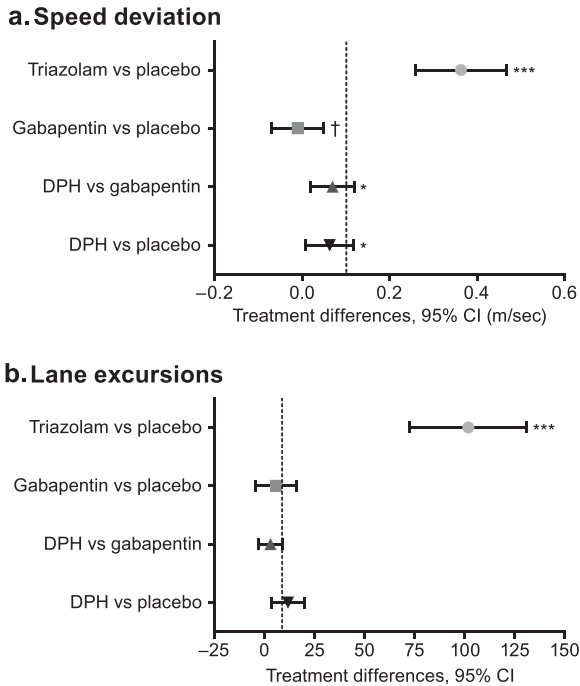


Figure 2. Sequential pairwise treatment comparisons (treatment difference and 95% CI) on next-day simulated driving performance as measured by speed deviation and number of lane excursions. CI, confidence interval; DPH, diphenhydramine citrate. * $p < 0.05$, *** $p < 0.001$ for indicated comparison. †Noninferiority: gabapentin is no worse than placebo (upper CI is < 2.4 cm). Treatment difference (first treatment–second treatment) is the Hodges–Lehmann estimate; p -values and confidence intervals are based on the Wilcoxon Rank Sum test as detailed under the ‘Sample size and statistical analysis’ section. The prespecified upper limit for demonstrating noninferiority of gabapentin relative to placebo is 2.4 cm (dashed vertical line). Participants per treatment group: placebo ($n = 58$), gabapentin ($n = 55$), DPH ($n = 57$), and triazolam ($n = 56$)

sustained attention (Psychomotor Vigilance Test). Overall, numeric differences observed among placebo, gabapentin, and DPH citrate were not statistically

significant, whereas performance following triazolam (vs. placebo) was significantly impaired ($p < 0.001$) (Table 3).

Safety

A total of 25 AEs (experienced by 18 participants) were reported across treatments, all mild to moderate in severity, with the greatest number associated with triazolam ($n = 14$). No serious AEs were reported, and only one participant discontinued because of a non-treatment-related AE after completing the DPH citrate treatment period (Table 4). The most frequent AEs (occurring in ≥ 2 participants) were somnolence, nausea, and lethargy occurring among gabapentin, DPH citrate, and triazolam treatments (Table 4), with all but one considered treatment-related. During the study, there were no self-reports of suicidal ideation or suicidal behavior as characterized by the C-SSRS. No clinically significant vital sign values or clinical laboratory values (the latter conducted at screening only) were reported.

DISCUSSION

This randomized controlled study used sensitive and objective measures of driving, alertness, and cognitive performance to evaluate potential next-day residual effects of gabapentin and DPH citrate. Study sensitivity was established with triazolam, which consistently demonstrated significant impairment of next-day performance relative to placebo. Safety profiles associated with gabapentin, DPH citrate, and triazolam were consistent with their known tolerability profiles (most frequent AEs consisted of somnolence, lethargy, and nausea). Treatment-related AEs were infrequent, occurring in only one individual each following gabapentin and DPH citrate.

Table 3. Next-day effects on measures of sleepiness, cognition, and psychomotor vigilance

Parameter	Placebo ($n = 58$)	Gabapentin 250 mg ($n = 55$)	DPH citrate 76 mg ($n = 57$) Mean (SD)	Triazolam 0.5 mg ($n = 56$)
Karolinska Sleepiness Scale				
Predrive (7.25 h postdose)	3.7 (1.9)	4.3 (2.0)*	4.3 (1.9)*	5.2 (2.0)***
Postdrive (8.25 h postdose)	5.2 (2.4)	5.6 (2.5)	5.9 (2.4)*	6.5 (2.4)***
CogScreen Symbol Digit Coding ^a				
No. of correct responses	64.9 (10.2)	64.9 (11.0)	63.9 (9.0)	58.1 (11.9)***
Psychomotor Vigilance Test ^b				
Median reaction time (ms)	258.9 (34.8)	261.3 (39.7)	266.6 (37.9)	285.3 (47.4)***

DPH, diphenhydramine; SD, standard deviation.

^aOther outcome measures (such as median response time for correct responses and SD of RT) showed a similar pattern of results (triazolam versus placebo, $p < 0.001$).

^bOther outcome measures (such as SD of RT, number of minor lapses [$RT \geq 500$ ms], and % of responses, where RT is $> 2 \times$ SD of RT) showed a similar pattern of results (triazolam versus placebo, $p < 0.001$).

* $p < 0.05$, *** $p < 0.001$ versus placebo (analysis of variance mixed model with site, period, and treatment as fixed effects and subject within site as a random effect).

Table 4. Summary of treatment-emergent adverse events

Parameter	Placebo (n = 58)	Gabapentin 250 mg (n = 55)	DPH citrate 76 mg (n = 57) No. (%)	Triazolam 0.5 mg (n = 56)
No. of treatment-emergent AEs	5	2	4	14
Participants with treatment-emergent AEs	3 (5.2)	2 (3.6)	3 (5.3)	10 (17.9)
Participants with serious AEs	0 (0)	0 (0)	0 (0)	0 (0)
Participants discontinued because of AE	0 (0)	0 (0)	1 (1.8)	0 (0)
Participants with treatment-related AEs	2 (3.4)	1 (1.8)	1 (1.8)	10 (17.9)
Most frequent AEs ^a (occurring in ≥2 participants)				
Somnolence	0 (0)	0 (0)	1 (1.8)	6 (10.7)
Nausea	0 (0)	2 (3.6)	1 (1.8)	2 (3.6)
Lethargy	0 (0)	0 (0)	0 (0)	3 (5.4)

AE, adverse event; DPH, diphenhydramine.

^aMedical Dictionary for Regulatory Activities (MedDRA) version 16.1 preferred term.

Overall, low-dose gabapentin had no appreciable effect on next-day performance. In the simulated driving task, gabapentin was no worse than placebo on SDLP and speed deviation, suggesting no impact on driving performance, although noninferiority was not established for lane excursions. Consistent with these findings were the absence of next-day residual effects on measures of sleepiness and cognitive performance (attention, working memory, and information processing speed), with one exception, an increase in self-reported sleepiness upon waking, an effect that dissipated by the second evaluation 1 h later. The lack of next-day effects on sleepiness (1 h after awakening) and cognitive performance are consistent with previous findings (Furey *et al.*, 2014; Rosenberg *et al.*, 2014). This study appears to be the first to examine next-day residual effects of low-dose gabapentin on driving performance. Data from driving simulation studies conducted following nighttime administration of the extended-release formulation, gabapentin enacarbil, were provided as part of a regulatory submission; results suggested next-day impairment following a relatively high dose (1200 mg) (US Food and Drug Administration, 2010).

In contrast to gabapentin, results with DPH citrate suggest residual next-day impairment. DPH citrate was associated with significantly worse performance relative to gabapentin and placebo on speed deviation. Although technically ineligible because of the prespecified order of pairwise comparisons, the 2.37 cm increase in SDLP for DPH citrate compared with placebo was also highly significant. This effect is comparable to that observed following nighttime dosing of the sedative hypnotic zopiclone 7.5 mg (Simen *et al.*, 2015). To our knowledge, this is the first demonstration of next-day driving impairment following a nighttime dose of DPH. No significant residual effects were observed with DPH citrate on measures of cognitive performance, but

significant effects were observed on next-day sleepiness upon awakening and 1 h later. This prolonged sedative effect appears to have contributed to driving impairment.

Although there appear to be no published studies examining next-day residual effects of DPH on driving (following nighttime dosing), there are reports of driving impairment when participants are tested up to 5 h following same-day administration (Ramaekers and O'Hanlon, 1994; Weiler *et al.*, 2000; Verster *et al.*, 2003). This is consistent with the well-known same-day sedative and psychomotor/cognitive-impairing effects of DPH (Kay *et al.*, 1997). Nighttime doses of DPH have been evaluated on next-day sleepiness and cognitive functioning, with some evidence suggesting an impact, but differences in study methodology and sample population may contribute to inconsistent results. For example, an overnight study conducted in healthy male participants demonstrated next-day impairment of DPH 50 mg (testing occurred ~9 to 11 h and 13 to 15 h after drug administration) on one cognitive task, % errors on the 1-back test, among a battery of tests (Katayose *et al.*, 2012). In contrast, no next-day effects (on digit symbol substitution task, manual tracking task, and memory assessment tasks) were observed in a sample of older individuals with insomnia who received nighttime DPH 50 mg (although the amount of time between dosing and testing with DPH was not provided) (Glass *et al.*, 2008).

Together, the driving results reported herein are potentially clinically significant, suggesting that nighttime administration of low-dose gabapentin, unlike DPH citrate and triazolam, is not likely associated with next-day impairment following 6.5 h of sleep. As the primary endpoint, SDLP has face validity as a measure of driving safety (i.e., ability to maintain lane position). Its predictive validity in terms of accident risk is not firmly established (Verster and Roth, 2011), but indirect support is demonstrated by the high

correlation between alcohol-induced changes in SDLP in a driving study and the real-world risk (based on epidemiologic studies) of having a traffic accident as a function of blood alcohol concentration (Owens and Ramaekers, 2009). Thus, a comparable level of increase in SDLP in a driving study is inferred as demonstrating the risk associated with a specified blood alcohol concentration. It should be noted, however, that there are differences in simulators and on-the-road driving tests (Daurat *et al.*, 2013; Helland *et al.*, 2013), and the validity of the present results has not been demonstrated in the latter.

Limitations

Study interpretation is limited by the evaluation of single doses in a fairly homogenous population of young healthy, predominantly male, individuals. Gender differences on next-day driving performance have been reported (Verster and Roth, 2012); however, the present study was not balanced (males vs. females) or powered to assess gender effects. In addition, participants were generally healthy with regular sleep patterns, and results may differ in individuals with insomnia or occasional disturbed sleep. From a methodological perspective, objective measures of sleep were not recorded, and thus potential differences in treatment-associated sleep time could have contributed to next-day residual effects (e.g., improved sleep in the gabapentin group may have masked next-day effects when compared with the placebo group which may have had additional impairment because of fatigue); however, the restriction to 6.5 h of sleep time and the late evening bed time would help to ameliorate this concern. Also, it should be emphasized that the protocol-specified noninferiority margin for the primary endpoint was based on historical data from an on-the-road driving study as opposed to the simulated driving task (CRCDS) used in the present study. Since then, data collected using the CRCDS simulated driving task determined that the noninferiority margin (based on the effects of 0.05% blood alcohol concentrations) was *less* conservative than the one derived from the historical on-the-road driving study. Although the empirically derived value would be more appropriate, its use in the present analysis would deviate from the *a priori* statistical analysis plan. Lastly, because the study was powered for the primary endpoint, the power to detect significant treatment differences on endpoints related to sleepiness and cognitive performance may not have been adequate, and therefore, results for these endpoints should be interpreted with caution.

CONCLUSIONS

Unlike triazolam and to some extent DPH citrate, low-dose gabapentin (250 mg) had no appreciable next-day effects on simulated driving performance or cognitive functioning.

CONFLICT OF INTEREST

Shyamalie Jayawardena is an employee of and holds stock and/or stock options in Pfizer Inc. Mark Wingertzahn was an employee of Pfizer Inc and held stock and/or options during study conduct and manuscript development. Russell Rosenberg and Howard Schwartz served as clinical investigators of the study. Russell Rosenberg has received research funding and acted as a consultant or member of an advisory board or speakers bureau for Aerial BioPharma, InSleep Technologies, Jazz Pharmaceuticals, Merck, Pfizer, Philips-Respironics, and Purdue. Gary Kay served as a consultant for the present study, and his institution, Cognitive Research Corporation, received payment from Pfizer for consultancy, travel support, equipment rental (driving simulators), development of a white paper, and other contract research organisation support services. Independent of the current study, Gary Kay has served as a consultant for Avanir, Dart, Pfizer, and Sprout; Cognitive Research Corporation has received grants and consultancy payments from Avanir, Dart, Pfizer, and Sprout. Gary Kay is the publisher of CogScreen[®] for which he receives licensing fees.

ACKNOWLEDGEMENTS

Medical writing support was provided by Diane Hoffman, PhD, of Engage Scientific Solutions and was funded by Pfizer. Thomas Hochadel, PharmD, of Cognitive Research Corporation, played a key role in study design, logistics, and conduct of the trial. David McLaughlin of Cognitive Research Corporation played a significant role in site setup, data quality monitoring, and editorial support.

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