

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC
SWITCH

NEUROLOGIC IMPACT REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA
Consultative Review

NDA:	21-070
Sponsor:	Merck & Co.
Drug:	Flexeril® OTC (cyclobenzaprine)
Indication:	Treatment for back and neck muscle spasm
Dates of Submission:	December 18, 1998
Materials Reviewed:	Paul J. Andreason, M.D.
Consult requested by:	OTC Drug Division, Sharon Schmidt

The purpose of this consult was to review the sponsor's (Merck & Co.) safety claim that Flexeril® used in the treatment of back and neck muscle spasm, though sedating, did not effect motor skills. The sponsor presented six studies (protocols 001, 002, 003, 012, 014, and 015). Table A in the appendix lists these studies with the age groups studied, the dose and duration of treatment, and design. The following review describes each study individually then summarizes the findings and conclusions of the studies collectively.

Study 001- A double-blind study to compare the sedative and cognitive effects of cyclobenzaprine with diphenhydramine in volunteers

Investigators and Sites

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Objectives

The objective of the study was to compare the sedative and cognitive effects of the proposed OTC doses of FLEXERIL® (2.5 and 5-mg P.O.) with those of BENADRYL® (50-mg P.O.).

Study Population

Subjects in this study were healthy adult volunteers aged 18-50 years. Women were using medically acceptable contraceptives and not lactating. The planned sample size was 24.

Design

This was a single center, single dose, double blind, placebo-controlled, randomly ordered, four-period, crossover study. Subjects underwent a prestudy evaluation within 2 months prior to the first treatment. All females had a pregnancy test within 1 week prior to the first treatment. There was a one-week washout period between treatments.

Assessments

The sponsor's primary measure of sedation and cognition was the Visual Analogue Scale (VAS) at two and three hours post dosing.

At both 2 and 3 hours postdose (Hour 2 and Hour 3), the subjects evaluated how they felt by marking a line on 16 different VAS scales. These scales represented a range of subjective feelings. The subject responses were measured from the left except for scales 4,6,8,9,10,12,14, and 16 that were measured from the right. Each of the VAS scales was 100-mm in length. Thus, the possible scores ranged from 0 to 100. The 16 VAS scores (see table 001.1 in the appendix) were combined to form three variables or "factors" following a method derived from Bond and Lader¹. The equations are given below, where X_i is the natural log of the measurement of the i th scale. If X_i was measured as "0", it was changed to "1" in order to use the natural log transformation. The three factors are generated as follows:

$$\text{Factor 1 (Alertness)} = 0.827X_1 + 0.792X_{11} + 0.776X_6 + 0.755X_4 + 0.642X_5 + 0.635X_9 + 0.618X_3 + 0.614X_{15} + 0.593X_{12}$$

$$\text{Factor 2 (Contentedness)} = 0.823X_{13} + 0.738X_{14} + 0.697X_8 + 0.677X_7 + 0.594X_{16}$$

$$\text{Factor 3 (Calmness)} = 0.845X_2 + 0.677X_{10}$$

The following nine psychomotor tests were also administered at two hours post dosing:

Auditory Sustained Attention	Continuous Performance	Delayed Recall and Recognition
Visual Sustained Attention	Finger Tapping	Digit Span
Choice Reaction Time	Verbal Free Recall	Critical Flicker Fusion Threshold

Safety assessment included physical exam, hematology, blood chemistry, urinalysis, vital signs, and adverse event monitoring.

Analysis Plan

Based upon data from a previously conducted sedation trial, where a difference in mean VAS Factor 1 scores of approximately 4 points was observed between the lorazepam 2 mg P.O. and placebo treatments, with a within-subject standard deviation of 2.62, the sponsor decided that it was possible to detect a true difference in response of 2 points

¹ Bond A and Lader M, The use of analogue scales in rating subjective feelings. Br. J. Med. Psychol. (1974) 47:211-218.

between any two of the four treatment groups with greater than 80% power and 24 evaluable subjects. These estimates were based upon a one-tail test conducted at the 5% level of significance.

All parameters (except Delayed Recognition) were analyzed using Analysis of Variance (ANOVA). Multiple pairwise comparisons were made with and without correction for multiple comparisons. Statistical significance was set at $p < 0.05$.

Patient Disposition/ Baseline Demographics

Sixteen subjects (66.7%) were male and the mean age of all subjects was 22. All subjects were white. The treatment sequences were balanced with respect to other baseline demographics (age, sex). Though the protocol called for patients from 18-50, the range of participating patients was 18-29 years. There were no dropouts.

Results

Tabular summaries of means and statistical comparisons of VAS scales may be found in table 001.2 and 3 respectively in the appendix. Statistical comparisons of the three active treatments to placebo with regard to psychometric testing may be found in table 001.4 in the appendix. Though the sponsor chose a threshold p-value of 0.05 to define significance, we customarily use a threshold p-value of 0.10 when statistically exploring safety concerns. Flexeril exhibited significant drowsiness at the 3-hour mark as measured by the Raw Alert/Drowsy Score and for "Factor 1-Alertness" for the Flexeril 2.5-mg dose. Cognitive impairment was present when measured at the 2-hour mark for both the 2.5 and 5-mg Flexeril doses as measured by the mean decision time, total reaction time, and digit span backwards. Additionally, the 2.5-mg Flexeril dose lead to significant cognitive impairment as measured by critical flicker fusion.

Conclusions

This study is poorly designed to answer the questions that the sponsor puts forth. This is a very small study and the parameters are measured at the time when diphenhydramine shows peak drowsiness. Flexeril leads to peak drowsiness at 4-6 hours after dosing. Even with $N=24$ and measuring at times that are not at peak impairment, Flexeril exhibited significant drowsiness and cognitive impairment. Reaction time and total decision time are cognitive factors that are critically connected to safe driving.

The argument that there is no cognitive impairment with Flexeril at these doses while measuring the event at off peak times, with a small number of subjects, and using a p-value threshold of 0.05 is not compelling. Studies with small numbers of subjects are statistically under powered to show negative results. They are significant when there is a large effect that may be demonstrated, and they are not particularly informative if one wishes to study the absence of an event. Nonetheless, there was both significant drowsiness and cognitive/psychomotor impairment with both the 2.5 and 5-mg doses of Flexeril in comparison with placebo.

Study 002 A double-blind study to investigate the sedative and cognitive effects of multiple doses of cyclobenzaprine in volunteers.

Investigators and Sites

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Objectives

The objective of the study was to investigate the sedative and cognitive properties of Flexeril® when it is given according to the proposed maximum OTC regimen (5 mg t.i.d.; 10 doses).

Study Population

Subjects in this study were healthy adult volunteers aged 18-50 years. Women were using medically acceptable contraceptives and not lactating. The planned sample size was 18.

Design

This was a single center, (4-day) 10-dose repeated dose, double blind, placebo-controlled, randomly ordered, two-period, crossover study. Subjects received either placebo or Flexeril® 5-mg P.O., t.i.d. for 10 days. Subjects underwent a prestudy evaluation within 2 months prior to the first treatment. All females had a pregnancy test within 1 week prior to the first treatment. There was a one-week washout period between treatments.

Assessments

The assessments in study 002 were the same VAS scales and psychomotor testing employed in study 001 (see above).

Each VAS parameter was measured at six time points throughout the 4-day study period. Four of the VAS measurements were done prior to the afternoon dose. On Day 1 this was a baseline measurement since drug initiation began in the afternoon. The other two VAS measurements were taken on Days 2 and 4, 2 hours after Dose 4 and 10, respectively. These two time points were considered primary.

The nine computerized cognitive tests were administered to the subjects on Day 2 (beginning 2 hours after Dose 4) and on Day 4 (beginning 2 hours after Dose 10). Both time points are considered primary. Each cognitive testing period lasted approximately 1 hour.

Analysis Plan

All parameters (except Auditory Sustained Attention and Delayed Recognition) were analyzed using Analysis of Variance (ANOVA). A linear model for a two-period crossover design was utilized. Treatment sequence, subject (sequence), period, and

treatment were included in the model. The denominator mean square for subject (sequence) was used as the error term for testing sequence effect. All other effects were tested using the mean square error for the denominator. A significance level of 0.100 was used to test for sequence effect, and a significance level of 0.050 was used to test for treatment and period differences. The cognitive tests, Auditory Sustained Attention and Delayed Recognition, were analyzed using McNemar's test. These data were concentrated in two categories, "0 errors made" and ">1 error made" for Auditory Sustained Attention and "20 words recognized" and "<19 words recognized" for Delayed Recognition. This test was done separately for each time point. McNemar's test was also used to analyze the incidence of adverse experiences. A significance level of 0.050 was used to make treatment comparisons.

Patient Disposition/ Baseline Demographics

Eighteen healthy subjects entered this study, were randomly assigned to one of the two possible treatment sequences, and all 18 subjects completed the study. All 18 subjects were white; 11 were male and 7 were female. There were no significant differences in age or sex between the groups. Subjects' ages ranged from 21-43 years with 14 of 18 subjects being 21-29 years old.

Results

Results of the VAS factors 1-3 and Raw Alert/ Drowsiness scales may be found in tables 002.1 and 2 in the appendix. At a significance level of $p < 0.10$, there is a significant difference between placebo and Flexeril® on day 2 (at both doses 3 and 4) with regard to alertness (the VAS correlate to sedation).

Summary pairwise comparisons of cognitive test parameters may be found in table 002.3 in the appendix. These parameters were only measured on day 2 after dose 4 and day 4 after dose 10. Critical flicker fusion was significantly impaired at both time points. Digit span backwards was worse relative to placebo at day 4 (dose 10) and finger tapping was worse compared to placebo at day 2.

Conclusions

This study is also poorly designed to test the sponsor's hypothesis that there is no sedation or cognitive impairment with Flexeril® given 5-mg PO t.i.d. for 10 doses. The number of subjects is very small to demonstrate "no effect", the threshold p-value is only 0.05, and the time points measured are off peak for measuring the potential sedative and cognitive effects of Flexeril®. When one sets the threshold p-value at 0.10 (which is still quite liberal for a study of only 18 subjects) there are several measures of cognition that show impairment as well as a lower alertness factor score on the VAS. The data suggest that in young healthy individuals who take Flexeril® 5-mg P.O t.i.d. there is detectable sedation and cognitive impairment on the second day and continuing, but perhaps less impairment on the fourth day. Quantitative predictions of either the degree of sedation or cognitive impairment appear to be difficult, if not impossible to predict on an individual basis from this data.

Study 003 A double-blind study to investigate the sedative and cognitive effects of multiple doses of cyclobenzaprine, diphenhydramine, and placebo in elderly volunteers

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Objectives

The objective of study 003 was to investigate and compare the sedative and cognitive properties of BENADRYL®, FLEXERIL®, and placebo when given according to the proposed maximum OTC regimen for FLEXERIL® (5 mg t.i.d.; 10 doses) to elderly volunteers.

Study Population

Subjects in study 003 consisted of 20 men and women, aged 60 to 85 years, of good physical and mental health. Screening criteria included Mini-Mental State Examination score >27 and no other evidence of cognition deterioration.

Design

This was a double blind, placebo-controlled, three-period, crossover study. The planned sample size was 18. The duration of each arm of the study was 4 days. Patients randomly received either Flexeril® 5-mg P.O. t.i.d., Benadryl® 50-mg P.O. t.i.d., or placebo. Subjects underwent a prestudy evaluation within 1 month prior to the first treatment. Subjects also underwent a practice session within 2 weeks of the first treatment day to familiarize them with the cognitive test procedures. The 10 doses of drug or placebo were given according to one of two schedules (8 a.m., 2 p.m., 9 p.m.; 9 a.m., 3 p.m., 10 p.m.). Each subject was to adhere to the same schedule for all treatments. Subjects remained under observation for 24 hours following the last treatment dose.

Assessments

Assessments consisted of the VAS and cognitive battery of tests given in protocol 001 and 002 to measure sedation and cognitive impairment with two exceptions. Critical Flicker Fusion and Finger Tapping were not performed in this protocol. Cognitive testing was performed over a period of two hours, 2 hours after the first dose on day one and the second daily dose on day four. The VAS administration time relative to dosing varied throughout the study. VAS scales were elicited six times during the 4-day study. The times were baseline (pre-drug), two hours after dosing on days 2 and 3, three hours after dosing on days 1 and 4, and at the time of the second daily dose on day 2.

Safety assessments included physical exam, vitals signs (blood pressure, pulse), ECG, and clinical labs (clinical chemistry, hematology, urinalysis). All but the vital signs were performed at baseline and post-study only.

Analysis Plan

VAS factors were calculated as described above in the review of protocol 001. All parameters were analyzed using analysis of variance (ANOVA). A linear model appropriate for a 3 period crossover design was utilized. Treatment sequence, subject (sequence), period, carryover, and treatment were included in the model. If carryover effect was not significant ($p > 0.100$), it was removed from the model and treatment effect was estimated based on a model with the remaining terms. The denominator mean square for subject (sequence) was used as the error term for testing sequence effect. All other effects were tested using the mean square error for the denominator. A significance level of 0.100 was used to test for carryover effects, and a significance level of 0.050 was used to test for treatment, sequence, and period differences.

Baseline Demographics

There were 20 subjects who enrolled and 17 who completed the study. One patient dropped out of the study in each of the active treatment groups due to an adverse event. One other subject dropped out for reasons classified as "other". All subjects were white. There were 12 men and 8 women enrolled. Ages ranged from 62-80 years old.

Results

This small study of subjects aged 62-80 years demonstrated sedation and elements of cognitive impairment that could effect the ability to operate dangerous equipment safely. Tables 003.1 and 003.2 in the appendix list the pairwise comparisons for Flexeril and Benadryl with respect to VAS scores and visual sustained attention. The remaining 6 cognitive scale scores did not show a difference between placebo and Flexeril at a threshold p-value of 0.10. One must remember that as in protocols 001 and 002 these assessments were performed at off peak times for sedation for Flexeril and peak sedation times for Benadryl.

Conclusion

This is a small study that provides further evidence of sedation and mild yet potentially important cognitive impairment with Flexeril 5-mg P.O. t.i.d. for 4 days duration. The study is too small to provide confidence that there is "no difference from placebo" when significance is not reached on other parameters, or, when a difference is evident, to provide a quantitative idea of what that difference might be on either a group or individual basis.

Study 012 A double blind, multiple-dose, crossover, placebo-controlled study to investigate the sedative effects of cyclobenzaprine, clemastine, and diphenhydramine in healthy volunteers

Investigators and Sites

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Objectives

The objective of this placebo-controlled, exploratory study was to investigate the effects of single and multiple doses of cyclobenzaprine 5-mg t.i.d., clemastine 1-mg b.i.d., and diphenhydramine 50-mg t.i.d. on sedation in healthy, normal volunteers.

Study Population

Twenty-eight healthy male and nonpregnant female volunteers aged 18 to 50 years. Subjects had to be nonusers of tobacco products, and could not be sleep deprived at start of study.

Design

This was a double blind, multiple-dose, randomized, 4-treatment, 4-period crossover study. The planned sample size was 28.

Subjects were required to report to the study site on the morning of the first day of each treatment period and to remain in the unit 2 days (through the last sedation evaluation time on Day 2). Women of childbearing potential had to have a negative urine pregnancy test prior to dosing on the first day of each treatment period. All subjects received 4 treatments (cyclobenzaprine 5 mg t.i.d./4 doses, clemastine 1 mg b.i.d./4 doses, diphenhydramine 50 mg t.i.d./4 doses, and placebo/t.i.d. 4 doses) on separate occasions, according to a random allocation schedule which assigned patients to 1 of 4 treatment sequences. Since the clemastine treatment was the only b.i.d. regimen, in order to maintain the study blind an identical 4-dose schedule was used, but dose 2 was placebo.

CNS active drugs including antihistamines were prohibited for 7 days prior to study start and throughout the duration of the study. All prescribed or OTC medications, with the exception of oral contraceptives, were prohibited for 48 hours prior to each treatment period and throughout the treatment dosing period. Subjects followed a normal diet for the duration of the study. Subjects were not to consume alcohol from 48 hours prior to and through the end of each treatment regimen. Subjects were not to consume more than 3 cups per day of coffee or caffeine containing beverages for 10 days prior to the start of the study, and during the washout intervals between treatment periods. No caffeine containing beverages were permitted on study-drug dosing days.

Assessments

VAS scores were elicited as in protocols 001, 002, and 003.

Multiple sleep latency testing was performed. Subjects were asked to relax in a bed in a darkened bedroom and allow themselves to fall asleep. Polysomnographic recording techniques were used to measure the time needed to achieve sleep. When electrophysiologic criteria for sleep were achieved, the subjects were immediately awakened, and the elapsed time was recorded. The criterion for sleep in this study was three consecutive 30-second epochs of stage 1 sleep. If sleep was not achieved in 20

minutes, the test session was terminated, and the results recorded. Sleep diaries were also kept.

Psychomotor testing was also performed. This testing consisted of the Digit Symbol Substitution (DSS), and the Choice Reaction Time tests.

This version of the DSS consisted of four printed rows of 125 blank squares, each headed with a digit from 1 to 9 in random sequence. An association key at the top of the page displayed 9 consecutively numbered squares with a different letter-like symbol below each digit. Following a practice trial at the start of each session, 90 seconds were allowed for rapidly writing the appropriate symbol under each numbered square as displayed in the association key. The number of squares correctly completed was recorded as the score. Five alternate forms were used in a random fashion, one form per evaluation time. The forms were standardized and validated to provide the same degree of difficulty.

The CRT employed by the sponsor was described as follows. Subjects began the CRT with their index finger of the dominant hand on the central button of a panel of buttons. As soon as the lamp under one of the six peripheral buttons lit, the corresponding button was to be touched as quickly as possible. Subjects then returned their index finger to the central start button and waited for the next stimulus. The recognition movement time (time taken for the finger to move off the central start button) was displayed, as was the reaction time (time elapsed between when the stimulus light appeared and the appropriate button was pressed). The mean reaction time and the mean recognition time (in seconds) from 50 trials were calculated and recorded as the subject's scores for that evaluation time.

Safety screening assessments consisted of physical exams, ECG, vital signs, and clinical laboratories.

Analysis Plan

Analyses were then performed using the log-transformed values. A linear model with terms for subject (within sequence), period, treatment, sequence and carryover was fit to the data. Sponsor presented p-values of 0.05 or less in their discussion of the results in this study.

Baseline Demographics

Twenty-three (82%) of the subjects were female. The mean age was 31 years, with a range of 18 to 50 years. Twenty-seven of the 28 subjects were white. There were no dropouts for any reason.

Results

Data tables did not provide p-values that were greater than 0.05. Therefore, this reviewer's usual practice of using a threshold p-value of 0.10 for exploring safety issues could not be employed. Nonetheless, there was significant sedation and psychomotor impairment with cyclobenzaprine versus placebo.

Peak sedation (measured via MSLT) was noted for cyclobenzaprine 6 hours post dose on day 1 and 4 hours post dose on day 2 of this study. Cyclobenzaprine was significantly more sedating than placebo (by MSLT) at all time points on both study days. Diphenhydramine exhibited peak sedation at the second hour after dose and was not significantly sedating (by the sponsor's criterion p-value) after the 4th hour post dose on the first study day. By MSLT cyclobenzaprine was significantly more sedating than diphenhydramine after the 4th hour post dose on the 1st day of the study through the end of the study (see tables 012.1 and 012.2 in the appendix).

Cyclobenzaprine had greater ($p < 0.05$) psychomotor impairment than placebo at 5 hours after the first dose, as measured by mean recognition time ($p=0.03$) and mean reaction time ($p=0.04$) but not by digit symbol substitution. Diphenhydramine had greater psychomotor impairment than placebo at 3 hours after the first dose as measured by mean recognition time and mean reaction time. Clemastine had greater psychomotor impairment than placebo at 5 hours after the first dose as measured by mean recognition time and at 7 hours after the last dose as measured by digit symbol substitution.

Conclusions

Study 012 is quite small ($N=28$) yet the sedating and psychomotor effects of the drugs studied were great enough and occurred consistently enough to be detected. Study 012 provides further evidenced that cyclobenzaprine is not only sedating but has measurable effects on psychomotor functioning that is easily translatable to potentially impaired driving ability. Mean recognition time and reaction time were longer 5 hours post dose with cyclobenzaprine. Cyclobenzaprine was more sedating than diphenhydramine after the 4th hour post dose and continued to be more sedating than diphenhydramine with repeated dosing during the two day study period. Cyclobenzaprine was significantly more sedating than placebo at all time points during the study.

Study 014 A double-blind, multiple-dose, crossover, placebo-controlled study to investigate the effects of cyclobenzaprine HCl, diphenhydramine HCl, and amitriptyline on driving-related psychomotor skills in elderly volunteers

Investigators and Sites

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Objectives

The objective of this placebo-controlled study was to compare the performance impairment on cognitive skills associated with driving caused by the sedative effects of multiple doses of cyclobenzaprine 5 mg, relative to a single dose of diphenhydramine 50 mg, and to a single dose of amitriptyline 50 mg, each at its time of peak psychomotor impairment.

Study Population

Subjects were 32 healthy men and women volunteers aged 65-82.

Design

This was a double blind, two-day, 4-dose, randomized, 4-treatment period crossover study. The study was conducted at one site. Thirty-two healthy elderly volunteers were to be enrolled and were to complete all treatment periods.

Subjects were trained in two separate training sessions, during the week prior to the first treatment period. Training sessions were separated by at least 1 day. Successfully trained subjects were allocated to receive each of the 4 treatment regimens (cyclobenzaprine, diphenhydramine, amitriptyline, or placebo) in a randomized order. The same procedures were followed in each treatment period, with at least a 7-day (maximum 21-day) washout period between each. Dosing schedules follow in table 014.1.

	Treatment Period I	Treatment Period II	Treatment Period III	Treatment Period IV
	Regimen C	Regimen A	Regimen D	Regimen B
Day 1:	Each dose consisted of	Each dose consisted of	Each dose consisted of	Each dose consisted of
Dose 1 (at 8 to 9 AM) Dose 2 (at 2 to 3 PM) Dose 3 (at 8 to 9 PM)	1 tab Cyclo and 1 tab APbo and 1 cap DPbo	1 tab CPbo and 1 tab APbo and 1 cap DPbo	1 tab CPbo and 1 tab APbo and 1 cap DPbo	1 tab CPbo and 1 tab APbo and 1 cap DPbo
Day 2:	Hr 0 dose consisted of	Hr 0 dose consisted of	Hr 0 dose consisted of	Hr 0 dose consisted of
Dose 4				
Hr 0 - (at 8 to 9 AM)	1 tab Cyclo and 1 tab APbo	1 tab CPbo and 1 tab Amit	1 tab CPbo and 1 tab APbo	1 tab CPbo and 1 tab APbo
Hr 3 - (at 11 AM to 12 noon)	Hr 3 dose consisted of	Hr 3 dose consisted of	Hr 3 dose consisted of	Hr 3 dose consisted of
	1 cap DPbo	1 cap DPbo	1 cap Diphen	1 cap DPbo
Cyclo = Cyclobenzaprine HCl 5 mg; CPbo = Placebo to match cyclobenzaprine. Amit = Amitriptyline 50 mg; APbo = Placebo of similar size and shape to amitriptyline. Diphen = Diphenhydramine HCl 50 mg; DPbo = Placebo of similar size and shape to diphenhydramine. Day 1 drug doses were self-administered from bottles 1, 2, and 3 at home. Day 2 drug doses (Hrs 0 and 3) were staff-administered from bottles 4, 5, and 6 to subjects at the clinic. * This schedule is an example of sequence CADB. For all subjects, the sequence of treatment regimens was randomized across Periods I to IV according to the allocation schedule.				

Psychomotor testing and VAS sampling took place at hour #4 on day #2.

Assessments

Assessments consisted of the VAS described above, the Divided Attention Task (DAT), the Critical Tracking Task (CTT), and the Vigilance Task (VIG). Each are briefly described as follows:

Divided Attention Task (DAT)

This is a high-demand test that is sensitive to the effects of alcohol and drugs. Subjects divided their attention between multiple computer screens and performed visual searching and tracking tasks. The overall performance score, which is the average of the standardized scores for DAT tracking error and response time, is the first of the three primary parameters.

Critical Tracking Task (CTT)

A test that required subjects to control the movement of a vertical arrow on a computer screen by rotary control. As control of the arrow's movement becomes more unstable and difficult, a measure (i.e., the lambda score) of the subjects' highest difficulty level achieved just prior to loss of control was calculated. The lambda score is the second of three primary parameters.

Vigilance Task (VIG)

A low-demand, 40-minute test that requires subjects to follow the movement of a large square as it "jumps" from one position to the next in a clockwise direction around a circle of smaller squares. When the large square "skips" over a smaller square position, subjects were to signal. Skips were randomly placed and timed. Response time for VIG is the third of the three primary parameters. All tests were given at approximately the same time of day across all treatment periods. Subjects completed the VAS first and then the psychomotor tests. DAT was performed first, CTT was performed second, and VIG was last.

Analysis Plan

The sponsor's primary safety analysis was to compare cyclobenzaprine 5-mg T.I.D. and diphenhydramine 50-mg with regard to motor performance and somnolence. In this comparison the drugs were compared at peak effect times as determined from protocol 012 (cyclobenzaprine at 4-5 hours post-dosing and diphenhydramine at 1-2 hours post dosing).

Baseline Demographics

Thirty-two healthy elderly men and women entered and completed the study. There were 4 dose order groups with 8 subjects per group. 30 subjects were white, one subject was African-American, and one subject was Asian. 62% of subjects were 65-69 years old. 1 subject was over 80. 46% of the subjects were men. The group numbers were so small that statistical differences in demographic makeup were absent.

Results

There were no deaths, dropouts, or serious adverse events associated with this study. Geometric means and lambda scores of variables may be found in table 014.2 and 014.3 in the appendix. Cyclobenzaprine was associated with more impairment than diphenhydramine with respect to the number of errors for the Divided Attention Task. The analysis of the Alert/Drowsy score indicated that the subject's subjective assessment

of sedation was greater with cyclobenzaprine 4 hours postdose than with diphenhydramine 1-hour postdose.

Conclusion

This study provides further evidence that cyclobenzaprine is sedating and negatively affects psychomotor function. These studies are small yet the effects are powerful enough to be detected. Mean values of impairment are useful to detect the presence of this effect but offer no assurance that a significant minority will suffer greater impairment than the mean (just as a significant minority will suffer no impairment or somnolence at all). This is further evidence that the claim that there is no psychomotor impairment even in the presence of drowsiness is not supported. The psychomotor impairment and somnolence is in some ways worse than diphenhydramine at peak levels.

Study 015 A double blind, multiple-dose, crossover, placebo-controlled study to investigate the effects of cyclobenzaprine HCl, diphenhydramine HCl, and amitriptyline on driving-related psychomotor skills in young volunteers

Investigators and Sites

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Objectives

The objective of this placebo-controlled study was to compare the performance impairment on cognitive skills associated with driving caused by the sedative effects of multiple doses of cyclobenzaprine 5 mg, relative to a single dose of diphenhydramine 50 mg, and to a single dose of amitriptyline 50 mg, each at its time of peak psychomotor impairment.

Study Population

Thirty-three healthy male and nonpregnant female subjects, 21 to 40 years of age, of any race. Females must have been practicing a reliable method of birth control throughout the study period.

Design

This was a double blind, multiple-dose, randomized, 4-treatment period crossover study. The study was conducted at 1 site. Thirty-two healthy, young volunteers were to be enrolled and were to complete all treatment periods. Subjects received 4 doses of cyclobenzaprine 5 mg and single doses of amitriptyline 50 mg and diphenhydramine 50 mg. The dosing and randomization schedules were the same as in protocol 014 (see table 014.1 above). This protocol differs from protocol 014 only in the age range of the subjects studied.

Assessments and Analysis Plan

These were identical with protocol 014 described above.

Baseline Demographics

Thirty-three subjects were randomized to one of four treatment sequences. Although only 32 subjects were planned, 1 subject (AN 0227) withdrew from the study and was replaced by AN 0327. Eighteen (54.5%) of the subjects were male. The mean age was 27.9 years and the range was 21 to 39 years. Twenty-two subjects (66.7%) were white and 4 (12.1%) were African-American.

Results

There were no deaths, dropouts, or serious adverse events associated with this study. Geometric means and lambda scores of variables may be found in table 015.1 in the appendix. Both cyclobenzaprine and amitriptyline were associated with greater drowsiness than placebo; however, diphenhydramine was not associated with greater drowsiness than placebo in this study. Amitriptyline treated subjects were significantly more impaired than on all measures of psychomotor performance than placebo or cyclobenzaprine patients. The only psychomotor performance measure that was significantly worse in the cyclobenzaprine group than placebo was the mean absolute tracking error.

Conclusion

This study demonstrates that cyclobenzaprine is significantly more sedating than placebo. It also demonstrates measurable impairment on selected measures of psychomotor performance. This study and protocol 014 examine performance after the 4th dose of drug as opposed to the first dose. Patients become habituated to the sedating properties of all of the drugs in this study over time. Sedation is usually the most noticeable with the first or first few doses of all of these drugs. It would have been interesting to compare patients' sedation and psychomotor scores after a single dose of cyclobenzaprine as well as after the 4th dose to explore this effect.

Summary Conclusions and on studies of Psychomotor Performance

The sponsor presents six studies to support labeling that suggests that though Flexeril is sedating that there is not significant psychomotor impairment. All of the studies are small. Nonetheless, significant psychomotor impairment was detected in all of the studies. In studies 001, 002, and 003 the sponsor concluded that there was not significant psychomotor impairment based on the lack of statistical difference in treatment groups at a probability (p-value) of 0.05. It is our custom to view safety findings as statistically significant if they reach a p-value threshold of 0.10. This being the case, studies 001, 002, and 003 all detect psychomotor impairment.

Studies 001, 002 and 003 also sample the subjects' performance on psychomotor tests at peak sedation times for the active comparator and not for cyclobenzaprine. This is a bias as it measures the active comparator at a time where a difference from placebo is most detectable.

Peak sedating effects of cyclobenzaprine at 4 hours post dose was established in protocol 012.

Studies 014 and 015 measure impairment at peak sedation times for cyclobenzaprine yet after the 4th dose instead of the first dose. The sponsor makes the claim that sedation wanes with continued use. If this were the case, then this would bias the result against the active comparator as subjects had three previous doses of Flexeril® with which to habituate. Nonetheless, at least one measure of psychomotor impairment was detectable and sedation was present.

The sponsor presents these six studies to support the notion that these tests are related to cognitive functions involved with driving, yet the sponsor did not perform driving simulator testing. The sponsor states that they elected not to perform driver simulation tests with cyclobenzaprine because "standardized methods for assessing drug effects in simulators have not been validated or published" (Volume 1.1; Section 3.8.1, Page D-115). This is not so. It is common for sponsors to perform driving simulator testing when developing drugs that are sedating. Driving simulators are also used to test a drug's relative psychomotor effects with those of ethanol or placebo. A sample of references is provided in the appendix.

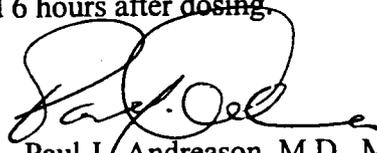
The Gengo (1989)² driving simulator study from the above list is cogent to the sponsor's argument that sedative and psychomotor effects are not connected. This study links sedative and psychomotor effects. The article states "The time course of diphenhydramine concentrations and effects on both mental performance and subjective feelings of drowsiness were assessed in 15 healthy men. Subjects received single oral doses of diphenhydramine, 50 mg, and placebo in this double-blind crossover study. Diphenhydramine plasma concentrations and central nervous system actions were assessed for 24 hours after each treatment. Cognitive impairment was assessed with an automobile driving simulator and digit symbol substitution scores, whereas drowsiness was self-assessed on a visual analog scale. Diphenhydramine produced significant feelings of drowsiness for up to 6 hours after the dose, whereas significant mental impairment was apparent for only 2 hours. **Despite the difference in duration of these effects, drowsiness and mental impairment have parallel slopes when effects are related to diphenhydramine concentrations. These data suggest that although the apparent diphenhydramine concentration thresholds to produce drowsiness are lower (30.4 to 41.5 ng/ml) than those needed to produce mental impairment (58.2 to 74.4 ng/ml), these effects have profiles consistent with their being manifestations of the same pharmacologic effect.**"

Recommendations

The sedative and psychomotor effects, by themselves, are not so great as to prevent the approval of Flexeril® 5-mg T.I.D. as an OTC drug; however, the sedative and psychomotor effects of Flexeril® 5-mg P.O. T.I.D. are significant and should be mentioned in product labeling as a potential safety concern. There is no support for the sponsor's claim that there are no significant psychomotor effects with the recommended

² Gengo, F., C. Gabos, et al. (1989). "The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance." Clin-Pharmacol-Ther 45(1): 15-21 issn: 0009-9236

dose of Flexeril®. The peak sedative and thus psychomotor impairment for Flexeril® occurs 4-6 hours after dosing. Patients therefore need to beware that sedation and psychomotor impairment may increase for up to 6 hours after dosing and be present for times that extend far beyond 6 hours after dosing.

 5/21/99

Paul J. Andreason, M.D., M.S.
Medical Reviewer, CDER, DNDP, HFD-120

cc: P Andreason
R Katz
T Laughren

5-24-99

Despite design flaws in several of these trials, they reveal a potential for both sedation & psychomotor impairment with cyclobenzaprine at usual therapeutic doses.

→ shows P. Laughren, MD
TL, PDP

Table A- Studies testing psychomotor performance with Flexeril®

Protocol Number	Design	N	Age Range	Tests Performed	Treatments	CYC Dosing
001	Double- blind, single- dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in young subjects	24	18 to 29	VAS	CYC 5 CYC 2.5 DPH 50 Placebo	One dose
002	Double- blind, multiple- dose, crossover psychomotor study of cyclobenzaprine in young subjects	18	21 to 43	VAS	CYC 5 Placebo	t. i. d. for 10 doses
003	Double- blind, multiple- dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in elderly subjects	17	62 to 80	VAS	CYC 5 DPH 50 Placebo	t. i. d. for 10 doses
012	Double- blind, multiple- dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, clemastine, and placebo in young subjects	28	18 to 50	VAS MSLT	CYC 5 DPH 50 CLM 1 Placebo	t. i. d. for 4 doses
014	Double- blind, multiple- dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in elderly subjects	32	65 to 82	VAS	CYC 5 DPH 50 AMI 50 Placebo	t. i. d. for 4 doses
015	Double- blind, multiple- dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in young subjects	32	21 to 39	VAS	CYC 5 DPH 50 AMI 50 Placebo	t. i. d. for 4 doses

CYC = Cyclobenzaprine. DPH = Diphenhydramine. AMI = Amitriptyline. CLM = Clemastine.
 VAS = Visual Analog Scales. MSLT = Multiple Sleep Latency Test.

Table 001.1 VAS scale employed in study 001

Scale No.	Factor No.	Dimension Ranges	
1	1	ALERT	DROWSY
2	3	CALM	EXCITED
3	1	STRONG	FEEBLE
4	1	MUZZY	CLEAR- HEADED
5	1	WELL- COORDINATED	CLUMSY
6	1	LETHARGIC	ENERGETIC
7	2	CONTENTED	DISCONTENTED
8	2	TROUBLED	TRANQUIL
9	1	MENTALLY SLOW	QUICK- WITTED
10	3	TENSE	RELAXED
11	1	ATTENTIVE	DREAMY
12	1	INCOMPETENT	PROFICIENT
13	2	HAPPY	SAD
14	2	ANTAGONISTIC	AMICABLE
15	1	INTERESTED	BORED
16	2	WITHDRAWN	GREGARIOUS

Factor 1 = Alertness; Factor 2 = Contentedness; Factor 3 = Calmness

Table 001.2- Adjusted Treatment Means - VAS Parameters study 001								
	Factor 1 (Alertness)		Raw Alert/ Drowsy Score		Factor 2 (Contentedness)		Factor 3 (Calmness)	
(Possible Range)	(0 to 28.8)		(0 to 100)		(0 to 16.3)		(0 to 7.0)	
	Mean ± S. E.		Mean ± S. E.		Mean ± S. E.		Mean ± S. E.	
Treatment	Hour 2	Hour 3	Hour 2	Hour 3	Hour 2	Hour 3	Hour 2	Hour 3
BEN 50 mg	24.7 ± 0.5	25.1 ± 0.6	65.5 ± 4.5	63.5 ± 4.1	10.9 ± 0.2	11.3 ± 0.2	4.2 ± 0.1	4.7 ± 0.1
FLEX 5 mg	22.6 ± 0.5	23.0 ± 0.6	48.0 ± 4.5	51.9 ± 4.1	11.0 ± 0.2	11.2 ± 0.2	4.9 ± 0.1	5.1 ± 0.1
FLEX 2.5 mg	22.8 ± 0.5	23.4 ± 0.6	46.9 ± 4.5	45.6 ± 4.1	11.0 ± 0.2	11.0 ± 0.2	4.8 ± 0.1	5.4 ± 0.1
Placebo	22.6 ± 0.5	21.7 ± 0.6	46.0 ± 4.5	35.8 ± 4.1	10.9 ± 0.2	10.6 ± 0.2	4.6 ± 0.1	5.2 ± 0.1

Table 001.3 Summary of Pairwise Treatment Comparisons - VAS Parameters study 001								
	Factor 1 (Alertness)		Raw Alert/ Drowsy Score		Factor 2 (Contentedness)		Factor 3 (Calmness)	
(Possible Range)	(0 to 28.8)		(0 to 100)		(0 to 16.3)		(0 to 7.0)	
Treatment Comparison	Hour 2	Hour 3	Hour 2	Hour 3	Hour 2	Hour 3	Hour 2	Hour 3
Overall Treatment p- value	0.017*	0.001*	0.008*	<0.001*	0.963	0.097*	0.001*	0.011*
BEN 50 mg vs. Placebo	0.007*	<0.001*	0.003*	<0.001*	0.860	0.020*	0.019*	0.016*
FLEX 5 mg vs. Placebo	0.997	0.101	0.754	0.007*	0.606	0.050*	0.125	0.425
FLEX 2.5 mg vs. Placebo	0.815	0.041*	0.886	0.095*	0.764	0.206	0.449	0.388

*denotes p<0.10

Treatment Comparison	Auditory Sustained Attention	Continuous Performance	Critical Flicker Fusion	Delayed Recall	Digit Span Backwards	Digit Span Forwards	Finger Tapping
Overall Treatment p- value	0.035*	<0.001*	0.001*	0.042*	0.090*	0.538	0.017*
BEN 50 mg vs. Placebo	0.013*	<0.001*	<0.001*	0.044*	0.024*	0.742	0.007*
FLEX 5 mg vs. Placebo	0.786	0.368	0.181	0.813	0.100*	0.325	0.254
FLEX 2.5 mg vs. Placebo	1.000	0.734	0.023*	0.530	0.033*	0.511	0.884

Treatment Comparison	Mean Decision Time	Mean Time	Total Reaction Time	Verbal Free Recall	Visual Sustained Attention	
					(False Alarms)	(Hits)
Overall Treatment p- value	0.014*	0.003*	0.001*	0.017*	0.807	<0.001*
BEN 50 mg vs. Placebo	0.001*	<0.001*	<0.001*	0.009*	0.959	<0.001*
FLEX 5 mg vs. Placebo	0.060*	0.304	0.051*	0.429	0.606	0.169
FLEX 2.5 mg vs. Placebo	0.078*	0.440	0.081*	0.756	0.642	0.902

* denotes $p \leq 0.10$

Table 002.1 Summary of Adjusted Treatment Means - VAS Parameters Study 002								
	Factor 1 (Alertness)		Raw Alert/ Drowsy Score		Factor 2 (Contentedness)		Factor 3 (Calmness)	
(Possible Range)	(0 - 28.8)		(0 - 100)		(0 - 16.3)		(0 - 7.0)	
	Mean ± S. E.		Mean ± S. E.		Mean ± S. E.		Mean ± S. E.	
Time Point	FLEX 5 mg	Placebo	FLEX 5 mg	Placebo	FLEX 5 mg	Placebo	FLEX 5 mg	Placebo
Day 1 (Baseline)	18.9 ± 0.8	18.1 ± 0.8	28.4 ± 3.0	24.4 ± 3.0	10.2 ± 0.5	9.7 ± 0.5	5.0 ± 0.2	5.1 ± 0.2
Day 2 (Dose 3)	21.9 ± 1.1	18.8 ± 1.1	38.5 ± 4.5	28.9 ± 4.5	11.6 ± 0.7	10.6 ± 0.7	5.1 ± 0.3	5.1 ± 0.3
Day 2 (Dose 4)	23.3 ± 0.8	21.2 ± 0.8	46.5 ± 5.0	43.2 ± 5.0	11.4 ± 0.6	9.9 ± 0.6	5.0 ± 0.2	4.9 ± 0.2
Day 3 (Dose 6)	20.7 ± 0.9	19.1 ± 0.9	30.6 ± 2.3	27.9 ± 2.3	11.5 ± 0.5	10.6 ± 0.5	5.4 ± 0.2	5.0 ± 0.2
Day 4 (Dose 9)	20.7 ± 0.8	20.2 ± 0.8	32.4 ± 3.4	34.4 ± 3.4	11.1 ± 0.5	10.8 ± 0.5	5.3 ± 0.2	4.8 ± 0.2
Day 4 (Dose 10)	21.7 ± 1.1	20.0 ± 1.1	37.9 ± 4.3	35.8 ± 4.3	10.9 ± 0.6	10.2 ± 0.6	5.3 ± 0.1	5.3 ± 0.1

Table 002.2 Summary of Pairwise Treatment Comparisons Between Flexeril® 5-mg and Placebo - VAS Parameters Study 002				
Time Point	Factor 1 (Alertness)	Raw Alert/ Drowsy Score	Factor 2 (Contentedness)	Factor 3 (Calmness)
(Possible Range)	(0 - 28.8)	(0 - 100)	(0 - 16.3)	(0 - 7.0)
Day 1 (Baseline)	0.447	0.363	0.492	0.987
Day 2 (Dose 3)	0.073*	0.153	0.324	0.904
Day 2 (Dose 4)	0.079*	0.642	0.122	0.489
Day 3 (Dose 6)	0.221	0.415	0.272	0.187
Day 3 (Dose 9)	0.621	0.681	0.689	0.062*
Day 4 (Dose 10)	0.297	0.727	0.483	0.856

* denotes a p-value ≤ 0.10

Time Point	Continuous Performance	Critical Flicker Fusion	Delayed Recall	Digit Span Backwards	Digit Span Forwards	Finger Tapping
Day 2 (Dose 4)	0.533	0.006*	0.807	0.837	0.383	0.036*
Day 4 (Dose 10)	0.625	0.093*	0.169	0.082*	0.390	0.160

Time Point	Mean Decision Time	Mean Motor Time	Total Reaction Time	Verbal Free Recall	Visual Sustained Attention (False Alarms)	Visual Sustained Attention (Hits)
Day 2 (Dose 4)	0.477	0.722	0.421	0.752	0.265	0.252
Day 4 (Dose 10)	0.427	0.820	0.559	0.556	0.938	0.484

Table 003.1 Summary of Pairwise Treatment Comparisons VAS Parameters Study 003

Time Point (Range)	Factor 1 (Alertness) (0- 28.8)		Raw Alert/ Drowsy Score (0- 100)		Factor 2 (Contentedness) (0- 16.3)		Factor 3 (Calmness) (0- 7.0)	
	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO
Day 1 (Baseline)	0.621	0.572	0.869	0.777	0.907	0.521	0.538	0.598
Day 1 (Dose 1)	0.486	0.009#	0.740	0.088#	0.087*	0.023*	0.338	0.376
Day 2 (Dose 3)	0.942	0.877	0.876	0.367	0.909	0.122	0.691	0.130
Day 2 (Dose 4)	0.780	0.502	0.764	0.152	0.625	0.426	0.633	0.494
Day 3 (Dose 7)	0.077*	0.160	0.005*	0.042*	0.761	0.833	0.732	0.085*
Day 4 (Dose 10)	0.920	0.744	0.915	0.902	0.873	0.544	0.954	0.071*

- *denotes p-value ≤ 0.10 (higher score than placebo)
- # denotes p-value ≤ 0.10 (lower score than placebo)

Table 003.2 Summary Adjusted Means Cognitive Test Parameters Study 003

Time Point	Visual Sustained Attention (False Alarms)		Visual Sustained Attention (Hits)	
	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO	BEN 50 mg vs. PBO	FLEX 5 mg vs. PBO
Day 1 (Dose 1)	0.033*	0.036*	0.121	0.431
Day 4 (Dose 10)	0.370	0.823	0.170	0.080*

*denotes p-value ≤ 0.10 (more impairment than placebo)

Table 012.1 Multiple Sleep Latency Test: Summary of Values (Minutes) by Time Point Study 012

Time Point Postdose	Cyclobenzaprine		Diphenhydramine		Clemastine		Placebo	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
1 (2)	6.3	(4.0)	6.2	(3.9)	8.8	(5.5)	9.2	(7.4)
(4)	4.6	(2.9)	4.7	(2.5)	5.7	(4.2)	8.7	(6.3)
(6)	4.2	(2.6)	6.3	(4.1)	5.6	(4.2)	8.1	(6.2)
2 (2)	5.0	(2.4)	8.3	(5.5)	6.7	(5.1)	8.0	(5.6)
(4)	3.1	(1.7)	6.6	(4.8)	4.5	(3.1)	6.3	(4.1)
(6)	4.4	(2.4)	7.7	(5.1)	5.6	(3.7)	7.2	(4.8)

Note: A lower score indicates greater sedation.

Table 012.2 Multiple Sleep Latency Test: Analysis of values by time point Study 012					
Time point		Comparison			
Day	Postdose (hrs)	Pbo vs. Cyc	Pbo vs. Dph	Pbo vs. Clm	Dph vs. Cyc
1	2	0.006 (Cyc)	0.005 (Dph)	ns	ns
	4	<0.001 (Cyc)	<0.001 (Dph)	0.002 (Clm)	ns
	6	<0.001 (Cyc)	ns	0.012 (Clm)	0.031 (Cyc)
2	2	0.009 (Cyc)	ns	ns	0.005 (Cyc)
	4	<0.001 (Cyc)	ns	0.038 (Clm)	<0.001 (Cyc)
	6	0.002 (Cyc)	ns	ns	<0.001 (Cyc)

Note: ns = not significant, p-value was greater than 0.050. The letter in parentheses indicates the treatment in the comparison that was more sedating. Results are from fitting a linear model with factors for sequence, subject, period and treatment to the untransformed data. Dph = Diphenhydramine, Cyc = Cyclobenzaprine, Clm = Clemastine, Pbo = Placebo.

Table 014.3 Comparison of Active Treatments to Placebo (N=32) Study 014						
Parameter	Cyclobenzaprine vs. Placebo		Amitriptyline vs. Placebo		Diphenhydramine vs. Placebo	
	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value
Critical Tracking Task						
Lambda score	1.08 (1.03, 1.12)	0.005*	1.26 (1.21, 1.31)	<0.001*	1.05 (1.00, 1.09)	0.080
Vigilance Task						
Response time (secs)	1.12 (0.99, 1.27)	0.132	1.81 (1.59, 2.05)	<0.001*	1.43 (1.26, 1.62)	<0.001*
Number of errors	1.39 (1.07, 1.81)	0.039*	3.03 (2.33, 3.93)	<0.001*	1.98 (1.52, 2.57)	<0.001*
Divided Attention Task						
Overall performance score	1.00 (0.98, 1.03)	0.801	1.11 (1.08, 1.14)	<0.001*	0.99 (0.97, 1.02)	0.697
Response time (secs)	1.00 (0.95, 1.04)	0.873	1.10 (1.06, 1.15)	<0.001*	0.97 (0.93, 1.02)	0.290
Mean absolute tracking error	1.00 (0.96, 1.03)	0.869	1.10 (1.07, 1.14)	<0.001*	1.01 (0.97, 1.05)	0.664
Number of errors	0.94 (0.76, 1.17)	0.643	1.28 (1.03, 1.58)	0.062	0.78 (0.63, 0.97)	0.062
Visual Analog Scale						
Alert/ drowsy score	1.09 (0.80, 1.50)	0.643	2.29 (1.67, 3.15)	<0.001*	0.86 (0.62, 1.18)	0.430

Table 014.2 Geometric Means and 95% Confidence Intervals (N=32)

Parameter	Cyclobenzaprine		Amitriptyline		Diphenhydramine		Placebo	
	Geometric Mean (95% CI)		Geometric Mean (95% CI)		Geometric Mean (95% CI)		Geometric Mean (95% CI)	
Critical Tracking Task								
Lambda score	2.97 (2.87, 3.08)		2.54 (2.45, 2.63)		3.06 (2.95, 3.17)		3.20 (3.09, 3.31)	
Vigilance Task								
Response time (secs)	1.85 (1.67, 2.06)		2.98 (2.68, 3.31)		2.35 (2.12, 2.61)		1.65 (1.49, 1.83)	
Number of errors	11.62 (9.33, 14.46)		25.23 (20.27, 31.40)		16.49 (13.25, 20.53)		8.34 (6.70, 10.38)	
Divided Attention Task								
Overall performance score	48.4 (47.3, 49.5)		53.5 (52.3, 54.7)		47.9 (46.8, 49.0)		48.2 (47.1, 49.3)	
Response time (secs)	4.46 (4.30, 4.62)		4.93 (4.76, 5.11)		4.35 (4.20, 4.51)		4.48 (4.32, 4.64)	
Mean absolute tracking error	4.44 (4.31, 4.57)		4.91 (4.77, 5.06)		4.49 (4.36, 4.63)		4.45 (4.32, 4.59)	
Number of errors	4.15 (3.47, 4.96)		5.62 (4.70, 6.72)		3.45 (2.88, 4.12)		4.40 (3.68, 5.27)	
Visual Analog Scale								
Alert/ drowsy score	25.7 (19.7, 33.6)		53.9 (41.3, 70.4)		20.2 (15.5, 26.4)		23.5 (18.0, 30.7)	

Table 014.3 Comparison of Active Treatments to Placebo (N=32) Study 014

Parameter	Cyclobenzaprine vs. Placebo		Amitriptyline vs. Placebo		Diphenhydramine vs. Placebo	
	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value
Critical Tracking Task						
Lambda score	1.08 (1.03, 1.12)	0.005*	1.26 (1.21, 1.31)	<0.001*	1.05 (1.00, 1.09)	0.080
Vigilance Task						
Response time (secs)	1.12 (0.99, 1.27)	0.132	1.81 (1.59, 2.05)	<0.001*	1.43 (1.26, 1.62)	<0.001*
Number of errors	1.39 (1.07, 1.81)	0.039*	3.03 (2.33, 3.93)	<0.001*	1.98 (1.52, 2.57)	<0.001*
Divided Attention Task						
Overall performance score	1.00 (0.98, 1.03)	0.801	1.11 (1.08, 1.14)	<0.001*	0.99 (0.97, 1.02)	0.697
Response time (secs)	1.00 (0.95, 1.04)	0.873	1.10 (1.06, 1.15)	<0.001*	0.97 (0.93, 1.02)	0.290
Mean absolute tracking error	1.00 (0.96, 1.03)	0.869	1.10 (1.07, 1.14)	<0.001*	1.01 (0.97, 1.05)	0.664
Number of errors	0.94 (0.76, 1.17)	0.643	1.28 (1.03, 1.58)	0.062	0.78 (0.63, 0.97)	0.062
Visual Analog Scale						
Alert/ drowsy score	1.09 (0.80, 1.50)	0.643	2.29 (1.67, 3.15)	<0.001*	0.86 (0.62, 1.18)	0.430

Table 015.1 Comparison of Active Treatments to Placebo (N=32) in Protocol 015

Parameter	Cyclobenzaprine vs. Placebo		Amitriptyline vs. Placebo		Diphenhydramine vs. Placebo	
	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value	Geometric Mean Ratio (90% CI)	p- Value
Lambda score	1.02 (0.96, 1.08)	0.585	1.31 (1.23, 1.39)	<0.001*	1.12 (1.06, 1.19)	0.002*
Response time (secs)	1.06 (0.94, 1.19)	0.450	1.84 (1.63, 2.08)	<0.001*	1.39 (1.23, 1.56)	<0.001*
Number of errors	1.22 (0.97, 1.55)	0.159	2.94 (2.32, 3.72)	<0.001*	1.85 (1.46, 2.34)	<0.001*
Overall performance score	1.02 (0.99, 1.04)	0.219	1.15 (1.13, 1.18)	<0.001*	1.02 (1.00, 1.05)	0.095
Response time (secs)	1.00 (0.96, 1.05)	0.877	1.17 (1.11, 1.23)	<0.001*	0.97 (0.93, 1.02)	0.324
Mean absolute tracking error	1.06 (1.02, 1.10)	0.020*	1.30 (1.25, 1.35)	<0.001*	1.08 (1.04, 1.12)	0.001*
Number of errors	0.91 (0.75, 1.12)	0.462	1.52 (1.24, 1.86)	0.001*	0.98 (0.80, 1.20)	0.887
Alert/ drowsy score	1.86 (1.36, 2.53)	0.001*	3.13 (2.30, 4.26)	<0.001*	1.11 (0.82, 1.51)	0.572

Critical Tracking Task

Vigilance Task

Divided Attention Task

Visual Analog Scale

Driving Simulator Testing of Drug Effects

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