Effects of Fexofenadine, Diphenhydramine, and Alcohol on Driving Performance

A Randomized, Placebo-Controlled Trial in the Iowa Driving Simulator

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Background: Sedating antihistamines may impair driving performance as seriously as alcohol.

Objective: To compare the effects of fexofenadine, diphenhydramine, alcohol, and placebo on driving performance.

Design: Randomized, double-blind, double-dummy, four-treatment, four-period crossover trial.

Setting: The Iowa Driving Simulator.

Participants: 40 licensed drivers with seasonal allergic rhinitis who were 25 to 44 years of age.

Intervention: One dose of fexofenadine (60 mg), diphenhydramine (50 mg), alcohol (approximately 0.1% blood alcohol concentration), or placebo, given at weekly intervals before participants drove for 1 hour in the Iowa Driving Simulator.

Measurements: The primary end point was coherence, a continuous measure of participants’ ability to match the varying speed of a vehicle that they were following. Secondary end points were drowsiness and other driving measures, including lane keeping and response to a vehicle that unexpectedly blocked the lane ahead.

Results: Participants had significantly better coherence after taking alcohol or fexofenadine than after taking diphenhydramine. Lane keeping (steering instability and crossing the center line) was impaired after alcohol and diphenhydramine use compared with fexofenadine use. Mean response time to the blocking vehicle was slowest after alcohol use (2.21 seconds) compared with fexofenadine use (1.95 seconds). Self-reported drowsiness did not predict lack of coherence and was weakly associated with minimum following distance, steering instability, and left-lane excursion.

Conclusions: Participants had similar performance when treated with fexofenadine or placebo. After alcohol use, participants performed the primary task well but not the secondary tasks; as a result, overall driving performance was poorer. After participants took diphenhydramine, driving performance was poorest, indicating that diphenhydramine had a greater impact on driving than alcohol did. Drowsiness ratings were not a good predictor of impairment, suggesting that drivers cannot use drowsiness to indicate when they should not drive.


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See editorial comment on pp 405-407.
participants signed a consent form before participation in the study.

**Inclusion and Exclusion Criteria**

Key inclusion criteria were ability to remain for 5 hours after the drives, history of alcohol use and willingness to consume alcohol, age 25 to 45 years, seasonal allergic rhinitis caused by ragweed pollen, previous successful use of antihistamine to treat seasonal allergic rhinitis, status as a currently licensed experienced driver who drove an average of at least three times a week for at least 3 years, and 20/20 corrected vision. Key exclusion criteria were medical conditions that might interfere with ability to perform the study, pregnancy or lactation, unusual sleep patterns (including those of third-shift workers), excessive alcohol consumption, use of tobacco in the past year or excessive caffeine consumption, previous experience in the Iowa Driving Simulator, and a positive result on a drug screening test.

**Procedures**

At visit 1, participants were selected on the basis of inclusion and exclusion criteria. Qualified participants drove in the Iowa Driving Simulator for 8 minutes; those with a tendency to develop simulator sickness were excluded.

Visits 2, 3, 4, and 5 (treatment visits) occurred weekly on the same day at the same time. Participants avoided consuming food or beverages, except water, for 2 hours before these visits. Participants completed the baseline drowsiness visual analogue scale immediately before taking a capsule of fexofenadine, diphenhydramine, or placebo; the drive was scheduled to start 2.5 hours later to coincide with peak levels of antihistamine. Both researchers and participants were blinded to the treatment given. After treatment, participants were permitted to consume only fluids; caffeine, stimulants, and depressants were excluded. Vital signs were determined and participants completed the second drowsiness scale 1 hour after taking the capsule. The study beverage was dispensed 60 minutes before the scheduled drive and was consumed over 20 to 30 minutes with a light snack. The dose of alcohol (or placebo alcohol) was derived by using an algorithm that included the participant’s sex and weight to reach an estimated blood alcohol concentration of 0.1% (21.7 mmol/L) (10). Male participants received the equivalent of 800 mg of absolute alcohol per kg of body weight, and female participants received 640 mg/kg. Ninety-five percent alcohol (or placebo alcohol) was added to a glass, which was filled with the participant’s choice of noncaffeinated carbonated soda. Alcohol was swabbed on the rim of each glass to maintain blinding. Immediately before and after the drive, participants again completed drowsiness scales. After the drive, study staff determined vital signs. Participants were observed until they were sober. To maintain the double-blinding of the alcohol treatment, participants remained for 5 hours or until the blood alcohol level was less than 0.03% after alcohol and after one of the other treatments (selected randomly). An unblinded Clinical Research Center nurse with no other study role determined alcohol levels by using a breath analyzer (Alco-Sensor, Intoximeters, Inc., St. Louis, Missouri).

**Treatment Preparation and Randomization**

Capsules (fexofenadine, diphenhydramine, and placebo) were blinded and packaged by Hoechst Marion Roussel, Inc. (Kansas City, Missouri). The Division of Pharmaceutical Service, College of Pharmacy, University of Iowa, Iowa City, Iowa, prepared alcohol and placebo beverages.

**Driving Simulation**

The Iowa Driving Simulator allowed collection of data on driving performance measures in a manner not available with on-street driving (11, 12). Briefly, the simulator consists of a domed enclosure mounted on a hexapod motion platform. The inner walls of the dome act as a screen on which correlated images are projected.

The experimental drive was conducted in dry weather conditions, with good visibility, on a two-lane rural highway that was 72.4 km (45 miles) long. The lane widths were standard (3.66 m [12 ft]) and the road surface was standard blacktop. The posted speed limit was 88.6 km/h (55 miles/h) for most of the course. Vehicles in the oncoming lane simulated low-density traffic. Participants practiced driving in the simulator for 8 to 10 minutes before each experimental drive. The experimental drive consisted of two phases driven consecutively without interruption. In phase 1 (30% of the total driving distance), the driver followed a Volkswagen Golf. Phase 2 began when this lead vehicle turned off the main road and participants continued to drive “as you normally would” along the designated route. In the first three sessions, the experimental drive ended uneventfully. At the end of the fourth and final session, participants encountered a vehicle that unexpectedly pulled out from a driveway into the lane of the experimental vehicle. A truck with trailer simultaneously occupied the oncoming lane.

**Outcome Measures**

During the first phase, participants were instructed to maintain a constant distance behind a lead car, which had realistic random velocity fluctuations. The primary end point was coherence—the correlation between the velocity of the participant’s
vehicle and the velocity of the lead vehicle. Participants with high coherence were able to maintain a relatively uniform distance from the lead vehicle, whereas those with low coherence had more variability in distance between their cars and the lead vehicle.

In both phases of the drive, we evaluated steering instability, the root-mean-square deviation (in meters), of the participant’s car around the participant’s preferred position in the lane. Participants with high instability wandered left and right within (and sometimes out of) the lane. We measured deviations from the preferred position rather than the geometric center of the lane to avoid penalizing otherwise steady drivers who simply preferred to be closer to the center line or to the right shoulder line. We also evaluated left-lane excursions—the total number of times the participant partially or totally crossed the center line during the second phase of the driving session.

We measured participants’ responses to the blocking vehicle (the last event on the final drive). Videotapes and a computer-generated aerial view of the driving course and vehicles (generated by using Scenario Authoring Tool software [National Advanced Driving Simulator, Iowa City, Iowa]) were reviewed by three blinded investigators who evaluated two aspects of the participants’ responses to the blocking vehicle. Response time was the time from the moment the blocking vehicle began to move until the instant the participant started to respond. The blocking vehicle response category was based on whether the participant’s car came into contact with the incoming car or approaching truck (collision), stopped completely in the lane before passing the plane of the incoming car (clear avoidance), or either passed the plane of the incoming car or was more than a tire’s width out of lane before stopping (potentially unsafe avoidance). Finally, we evaluated drowsiness by using a visual analogue scale (3, 4, 13–15) that asked participants to rate drowsiness from “I feel wide awake” to “I feel extremely sleepy.”

Data Capture, Reduction, and Management

Simulator data were collected in real time at 30 Hz and were then reduced. During the data reduction stage, checks were performed to ensure that output was correct and meaningful. Data were visually inspected, sorted to identify extreme values, and plotted to ensure that all points were within naturally occurring boundaries. When extreme values were found, operator and experimenter source documents were consulted to determine an explanation. Videotape records were inspected to establish the origin of any anomalies in the data, and, if necessary, the raw data were fed into the Scenario Authoring Tool, which replayed the drive using animation.

Statistical Analysis

The experiment was run as a crossover design with four periods and four treatments so that each participant received all four treatments (alcohol, diphenhydramine, fexofenadine, and placebo) on four successive sessions in the driving simulator. With few exceptions, the sessions were 1 week apart at the same time of day. Treatments were presented in 24 different sequences (such as AFDP and FDAP).

To ensure that each treatment occurred equally often in each period, the sequences were arranged in six Latin squares (for example, ADFP/DFPA/FPDA/PDAF). Four of the squares were replicated twice, for a total of 40 participants. The design was balanced so that each treatment preceded and followed the others equally often. Each treatment effect was estimated with equal precision in a model with treatment, period, and first-order carryover effects.

In the design phase, we did an extensive Monte Carlo investigation of the robustness of this design to random loss of participants (rows of data) and found that the selected design (along with several similar designs) was robust, much more so than a design consisting of 10 replications of one Latin square.

Crossover designs have advantages and drawbacks. With four treatments, a crossover design requires one fourth the number of participants required by a completely randomized design in which each participant receives only one treatment. Furthermore, because each participant acts as his or her own control, it is, in theory, possible to compare treatments with much greater precision. One drawback of a crossover design is that early dropout of participants complicates the analysis and may have a comparatively greater impact on the precision of the results than the loss of a participant from a completely randomized trial. The most problematic aspect of crossover designs may be the effect of previous experiences on a participant’s reaction to the current treatment. Such effects can be broadly classified as period effects, such as learning or habituation, which are unrelated to previous treatments, and carryover effects, which are related to previous treatments. Although it is unlikely that any residual study drug remained after an interval of 1 week, drug effects can carry over in other ways. For example, if a drug promoted simulator motion sickness, the participant may have driven more cautiously the week after receiving that drug. Without statistical adjustment, this drug-induced caution is attributed to whichever drug was administered the week after that drug. Statistical adjustment to remove period and carryover effects from the treat-
ment means was accomplished by including variables for these effects in the analysis of variance model.

Another complication of crossover designs is the statistical relation among repeated measures in the same participant. Participants’ performance in the simulator is expected to be similar from week to week (that is, positively correlated), and variability may increase or decrease over time. Specifying the form of the “covariance structure” of the data deals with such issues (16). For simplicity, we chose the most general possible covariance structure.

Finally, the statistical method we used (the mixed general linear model) requires that the data be approximately normally distributed. Most of the outcomes we measured were significantly non-normally distributed, and it was necessary to re-express (transform) them to achieve normality. We used Box-Cox analysis (17) to select an appropriate power transformation of each variable. Specifically, left-lane excursion counts were re-expressed as log((count + 1)), coherence (c) was re-expressed as \((1 - \sqrt{1 - c^2})^{1/5}\), steering instability (s) was re-expressed as \(s^{-1}\), and minimum following distance (d) was re-expressed as \(d^{-1/4}\). Statistics for re-expressed data are difficult to interpret; what does it mean, for example, that “log crossing count plus one” is 2.1 points higher for 1 drug than for placebo? To make our statistics interpretable, we converted all statistical results—means, differences, and CIs—to the original, more interpretable measurement scales. Thus, crossing counts are reported as counts, steering instability and minimum following distance are expressed in meters, and coherence is expressed in its original form as the correlation between the velocity of the lead car and that of the participant’s car. We used a Markov chain Monte Carlo procedure (18, 19) to compute these statistics and CIs.

All data were analyzed by using SAS software, versions 6.12 and 7.0 for Windows (SAS Institute, Inc., Cary, North Carolina). The contrast tests were two-sided, and an \(\alpha\) level of 0.05 was required. Markov chain Monte Carlo computations were made by using WinBUGS, version 1.2 (19). For the primary and secondary outcome measures, we report treatment means and differences; CIs are given for differences between treatment means.

Response time to the blocking vehicle, which was measured in the fourth driving session only (so that only 25% of each treatment group was confronted with this situation), was analyzed by using a general linear model with treatments as the only effect. Response to the blocking vehicle (clear avoidance, potentially unsafe avoidance, or collision) was analyzed by using an exact permutation test (20).

Missing Data

One participant fell asleep after receiving alcohol and could not be roused for a driving session. Data for four other participants were missing for the second half of phase 2 in one session because these participants had simulator sickness. Mechanical problems resulted in the loss of phase 1 data for one participant in one session and data from the second half of phase 2 for another participant in one session. Thus, 2 of 160 sessions lacked phase 1 data and 6 of 160 sessions lacked data from the second half of phase 2.

The theory of missing data distinguishes between random and informative missing values (21). Randomly missing data are those that are missing for reasons unrelated to the participant’s response to the treatment; they are therefore distributed like the observed data and can be predicted from the observed values of this participant and other participants. Informative missing data are missing for reasons related to the participant or treatment and are likely to have been somewhat anomalous if observed. Consequently, the fact that these data are
missing gives some information about the unobserved value. For example, the participant who could not be woken up would probably have driven badly if she had been awakened, and the participants who developed simulator sickness would probably have driven badly if they had completed the session.

The statistical software that we used imputes randomly missing data with the predicted value but adjusts degrees of freedom and SEs to reflect the fact that these values are not real data. Regarding informative missing data, Chow and Liu (21) remark that “There is no satisfactory, well-developed methodology to account for missing values or intermittent missing values.” We believed that we should probe the sensitivity of the results to a range of plausible imputed values of the missing data. Therefore, we did analyses to assess whether the results were sensitive to possible values for the informative missing data. In one analysis, we treated them as missing at random; in another (the worst-case analysis), we imputed the nonrandomly missing values of impairment measures (high = bad) as the predicted value plus 2.5 SEs of the predicted value. We chose 2.5 SEs because it is pessimistic but does not distort the analysis by adding outliers. For performance measures (high = good), we subtracted 2.5 SEs from the predicted value. The results of the two analyses did not differ substantively. In this article, we report the results of the second analysis.

Role of the Study Sponsor

The industry sponsor had a consulting role in the design, conduct, and reporting of the study. Decisions in all aspects of the study, including the decision to publish the results, were made by the authors.

Results

Study Participants

Seventy-one participants were screened; 41 were randomly assigned and received double-blind treat-

Table 1. Primary End Point: Coherence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants, n</th>
<th>Mean Coherence Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>40</td>
<td>0.920 ± 0.014 (0.891 to 0.945)</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>40</td>
<td>0.877 ± 0.019 (0.837 to 0.911)</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>40</td>
<td>0.915 ± 0.014 (0.884 to 0.940)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40</td>
<td>0.906 ± 0.015 (0.875 to 0.933)</td>
</tr>
<tr>
<td>Alcohol vs. diphenhydramine</td>
<td>40</td>
<td>0.043 ± 0.012 (0.021 to 0.068)</td>
</tr>
<tr>
<td>Alcohol vs. fexofenadine</td>
<td>40</td>
<td>0.005 ± 0.009 (−0.012 to 0.024)</td>
</tr>
<tr>
<td>Alcohol vs. placebo</td>
<td>40</td>
<td>0.014 ± 0.009 (−0.004 to 0.033)</td>
</tr>
<tr>
<td>Diphenhydramine vs. fexofenadine</td>
<td>40</td>
<td>−0.038 ± 0.013 (−0.063 to −0.013)</td>
</tr>
<tr>
<td>Diphenhydramine vs. placebo</td>
<td>40</td>
<td>−0.029 ± 0.012 (−0.054 to −0.005)</td>
</tr>
<tr>
<td>Fexofenadine vs. placebo</td>
<td>40</td>
<td>0.009 ± 0.010 (−0.010 to 0.028)</td>
</tr>
</tbody>
</table>

* Data are expressed as the mean ± SD.

Phase 1

Coherence

As explained above, coherence was a participant’s ability to maintain a constant distance from a lead car that varied its speed randomly. Figure 1 provides a plot of distance fluctuations for three representative participants, one each with near-best, near-median, and near-worst coherence. Differences in coherence (Table 1) were observed among the four treatments. Pairwise comparisons revealed that after taking diphenhydramine, participants performed car-following with significantly less coherence than after taking alcohol, fexofenadine, or placebo (the CI excludes zero).

Minimum Following Distance

Significant differences in minimum following distance (Table 2) were observed among the four treatments. Pairwise comparisons indicated that when participants performed car-following after consuming alcohol, they had significantly smaller minimum following distances (15.1 m) than they did after taking fexofenadine (17.1 m) or placebo (17.4 m).

Steering Instability

Significant differences in steering instability (Table 2) were observed among the four treatments. Pairwise comparisons showed that after participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol (but not placebo). After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine.

Phase 2

After completing phase 1, participants drove the remaining 30 miles of the course “as you normally would drive.” Road signs and markings were the only guidance that they received in this phase.

Steering Instability

Significant differences in steering instability (Table 2) were again observed among the four treatments. Pairwise comparisons demonstrated that after participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol (but not placebo). After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine.
less steering instability than after consuming alcohol or diphenhydramine. After participants consumed alcohol, they had the same or less steering instability than after taking diphenhydramine.

### Lane Excursions

We determined the effect of treatment on the probability that the participant’s vehicle moved to the right and partially or totally crossed the right-edge lane marker or moved to the left and partially or totally crossed the center line (Table 2). No significant differences for lane excursions to the right were noted among the four treatments. For excursions to the left, however, significant differences were noted the four treatments. Pairwise comparisons demonstrated that after participants took diphenhydramine, they crossed the center line significantly more often than after taking fexofenadine or placebo. After participants took alcohol, they crossed the center line significantly more often than after taking fexofenadine and placebo. Fexofenadine and placebo did not differ significantly; the 95% CIs indicate that the difference is small (Table 2).

### Response to Blocking Vehicle

No significant main effect of treatment on the response time to the blocking vehicle was observed, although pairwise comparisons showed that after consuming alcohol, participants responded significantly more slowly (2.21 seconds) to the event than after they took fexofenadine (1.95 seconds) (difference, 0.26 seconds [CI, 0.02 to 0.66 seconds]).

Responses to the blocking vehicle were categorized as clear avoidance, potentially unsafe avoidance, or collision (Table 3). The overall differences were not significant (P > 0.2, Fisher exact test). Pairwise comparisons, expressed as odds ratios, were also insignificant. However, because this event occurred only during the fourth drive, there were only 9 to 11 participants in each group (rather than 40, as was the case for all of the other measures). As a result, this analysis had far less power than the analyses of the other secondary measures.

Crashes were evaluated for speed of the driver’s vehicle at the instant of the crash. For the 5 collisions, the speed at impact was 46 and 14 miles per hour after alcohol, 37 and 8 miles per hour after diphenhydramine, and 6 miles per hour after fexofenadine.

### Subjective Drowsiness Ratings

Drowsiness ratings were expressed as differences between the drowsiness scales completed after treatments and the baseline scale (Figure 2). Scores on the second visual analogue scale, given 1 hour after capsule administration, had small average differences from baseline (<10 points), and no significant
differences were seen among the treatment groups (the confidence limits for differences less than ±10 points). At the time of the third visual analogue scale, just before the drive, participants were most drowsy after taking diphenhydramine and least drowsy after taking fexofenadine or placebo. The differences between diphenhydramine and fexofenadine or placebo were significant (confidence limits ranged from 5 to 27 points on the 100-point visual analogue scale). The difference between fexofenadine and placebo was less than 1 point, with confidence limits of ±11 points. After the drive, participants were most drowsy with diphenhydramine and least drowsy with placebo. The difference between fexofenadine and placebo was insignificant (confidence limits were 2 to 7 points). We examined whether self-reported drowsiness immediately before driving predicted impaired driving performance. Drowsiness was expressed as the difference between the third and first self-ratings. The correlation between drowsiness and the primary end point, coherence, was not statistically significant (Table 4). Statistically significant but small correlations were found between subjective drowsiness and minimum following distance, steering instability, and left-lane excursions; no correlation was greater than 0.21.

Although a significant correlation indicates some relation between two variables, the size of the correlation coefficient is not a good indicator of the strength of that relation. To give an idea of the practical meaning of the correlations we observed, Table 4 shows mean driving performance values for participants who had increases in drowsiness scores in the upper quartile and lower three quartiles. Clearly, drowsiness was a weak predictor of poor driving. Indeed, only one of the five collisions occurred among the participants who were in the drowsiest quartile (as measured before or after the drive). Thus, “grounding” the drowsiest 25% of drivers would have prevented only 20% of the collisions. In contrast, three of five collisions occurred in participants who had the lowest quartile of following distances (following distance < 12.2 m), and four of five collisions occurred in participants who had the highest quartile of left-lane crossings (seven or more crossings).

### Adverse Events

No unusual or serious adverse events were observed in this study. Adverse events occurred with similar frequency after all four treatments, with no significant differences between any two treatments in any adverse event category.

### Discussion

First-generation antihistamines, such as diphenhydramine, cause sedation (2–6), which Gengo and

### Table 3. Clear Avoidance, Potentially Unsafe Avoidance, and Collision in the Final Driving Session

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clear Avoidance</th>
<th>Potentially Unsafe Avoidance</th>
<th>Collision</th>
<th>Odds Ratio for Collision vs. Clear Avoidance or Potentially Unsafe Avoidance (95% CI)</th>
<th>Odds Ratio for Potentially Unsafe Avoidance or Collision vs. Clear Avoidance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine (n = 11)</td>
<td>8 (72.7)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>0.88 (0.051–15.3)</td>
<td>2.00 (0.226–19.4)</td>
</tr>
<tr>
<td>Diphenhydramine (n = 10)</td>
<td>5 (50.0)</td>
<td>3 (30.0)</td>
<td>2 (20.0)</td>
<td>0.055–8.41</td>
<td>0.75 (0.073–7.87)</td>
</tr>
<tr>
<td>Alcohol (n = 9)</td>
<td>6 (66.7)</td>
<td>1 (11.1)</td>
<td>2 (22.2)</td>
<td>(2.14)*</td>
<td>4.00 (0.229–238.1)</td>
</tr>
<tr>
<td>Placebo (n = 9)</td>
<td>8 (88.9)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>(0.191)*</td>
<td>8.00 (0.558–416.7)</td>
</tr>
</tbody>
</table>

* The denominator of the odds ratio was zero. Only the lower limit of the CI is given; the upper limit was unbounded.

![Figure 2. Change from baseline in visual analogue drowsiness scores. Participants rated drowsiness on a scale from "wide awake" to "extremely drowsy," which corresponded to a score of 1 to 100 on a 159-mm scale.](image)
Gabos (22) have distinguished as impairment and drowsiness. Cognitive impairment refers to some interference with the patient’s ability to perform tasks and is measured by objective tests; drowsiness, which may or may not limit performance, is measured subjectively. The least desirable condition would be impairment without drowsiness because a patient might have no subjective clues suggesting impairment.

The second-generation antihistamines have difficulty crossing the blood–brain barrier and are believed to cause little or no central nervous system depression. In previous studies, fexofenadine and its parent compound, terfenadine, did not impair the performance of automobile drivers or airplane pilots (6, 23, 24).

In this study, participants in a driving simulator were first instructed to match the speed of the car they were following, then to drive “as you normally would.” Coherence was chosen as the primary end point because the added complexity of trying to match the variable speed of the lead car might lead to greater sensitivity if impairment did occur. Coherence was significantly better after participants took alcohol or fexofenadine than after they took diphenhydramine. The minimum following distance was slightly shorter than the recommended distance after all four treatments (15.1 m [49.4 ft] to 17.4 m [57.2 ft]). The mean minimum following distance was about one-half car length longer (and safer) after participants had taken fexofenadine or placebo than after they had consumed alcohol. The shorter following distance might also have contributed to increased coherence. However, during the car-following phase, steering instability scores were highest after diphenhydramine or alcohol use, indicating poorer steering control.

Thus, although participants under the influence of alcohol did surprisingly well at matching the velocity of the lead car, they did so at the expense of driving closer to that vehicle and having less control over steering. These findings agree with the results obtained in other studies in which alcohol was administered to participants who were engaged in complex tasks that required divided attention. Horne and Baumber (25) reported that drivers who had consumed alcohol were able to maintain lateral position in wind gusts but did not perform well at following another vehicle. Landauer and Howat (10) used a nondriving task involving reaction time and tracking accuracy and found that after participants consumed alcohol, reaction time improved slightly but the number of tracking errors increased. Moskowitz (26) and Kerr and Hindmarch (27) reviewed studies of alcohol and divided attention and suggested that if one part of a divided attention task is perceived to be primary and the other part secondary, only the secondary task becomes impaired.

When we examined how participants performed when driving “normally,” we found more steering instability after participants took diphenhydramine or alcohol than after they took fexofenadine or placebo. Participants with poorer steering were more likely to drive with part of the vehicle out of the lane. Lane excursions over the center line (causing potential exposure to oncoming traffic) may seriously affect safety. The numbers of lane excursions over the center line more than doubled after the participants had taken diphenhydramine compared with fexofenadine or placebo.

We also examined drowsiness and found that participants were significantly drowsier after taking diphenhydramine than after taking any of the other treatments. However, we found that subjective drowsiness either did not predict driving performance measures (coherence) or was a relatively weak predictor (for minimum following distance, steering instability, and left-lane excursion). This suggests that drivers who use alcohol or diphenhydramine are probably mistaken if they believe that lack of drowsiness means that they will be able to drive without impairment.

The potential crash scenario on the last drive provided some additional evidence of impairment. Participants had to react to a vehicle that unexpectedly pulled out of a driveway and blocked their lane.

### Table 4. Performance Measures according to Degree of Sleepiness before Drive 4

<table>
<thead>
<tr>
<th>Drowsiness Category*</th>
<th>Mean Coherence Value (95% CI)†</th>
<th>Mean Minimum Following Distance (95% CI)‡</th>
<th>Mean Steering Instability (95% CI)§</th>
<th>Left-Lane Excursions (95% CI)¶</th>
<th>Mean Collision Rate (95% CI)¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower three fourths</td>
<td>0.893 (0.869 to 0.923)</td>
<td>16.1 (13.8 to 18.7)</td>
<td>0.530 (0.503 to 0.557)</td>
<td>2.06 (1.00 to 3.53)</td>
<td>0.138 (0.012 to 0.263)</td>
</tr>
<tr>
<td>Upper one fourth</td>
<td>0.917 (0.864 to 0.919)</td>
<td>12.9 (10.0 to 16.6)</td>
<td>0.539 (0.538 to 0.591)</td>
<td>4.88 (1.69 to 10.41)</td>
<td>0.100 (0.000 to 0.263)</td>
</tr>
<tr>
<td>Difference</td>
<td>0.024 (–0.037 to 0.077)</td>
<td>3.2 (–1.7 to 7.1)</td>
<td>0.009 (–0.045 to 0.067)</td>
<td>2.62 [–0.72 to 8.60¶]</td>
<td>0.694 (0.013 to 8.44)</td>
</tr>
</tbody>
</table>

* Increase in drowsiness between baseline (first drowsiness evaluation) and the third evaluation (immediately before a drive).
† $r = 0.06; P > 0.2$.
‡ $r = 0.20; P = 0.01$.
§ $r = 0.20; P = 0.01$.
¶ $r = 0.21; P = 0.01$.
¶ Statistically significant ($P = 0.006$).

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Participants responded significantly more slowly to the event after consuming alcohol than after taking fexofenadine. At the posted speed, this slower reaction time resulted in a stopping distance that was approximately 8 m (26 ft) longer.

The observations reported here, combined with past reports, indicate that diphenhydramine clearly impairs driving performance, whereas the second-generation antihistamine fexofenadine was indistinguishable from placebo. Vermeeren and O’Hanlon (24) studied one driving variable, lateral position, and also reported that fexofenadine did not affect standard deviation of lateral position in an instrumented car used in an on-the-road study, nor did it affect various non-driving psychomotor tasks. In contrast, the first-generation antihistamine clemastine caused significant impairment.

In the United States, diphenhydramine is the top-selling over-the-counter medication sold for treatment of allergic rhinitis (28). It is estimated that 47% of persons with allergies treat themselves with over-the-counter products, most of which contain a sedating antihistamine (29). Consequently, millions of patients use first-generation antihistamines.

Several health programs have been developed that limit patient access to non-sedating antihistamines and emphasize the use of first-generation antihistamines (30, 31). The cost savings of these programs should be weighed against the potential increased risk to the driving public and against the laws of 27 states that prohibit driving under the influence of any drug or any substance (32, 33).

We conclude that participants performed similarly when treated with fexofenadine or placebo. Participants who consumed alcohol did well in performing the primary driving task but not the secondary tasks, resulting in poorer overall driving performance. This study demonstrates that the first-generation antihistamine diphenhydramine may have an even greater impact than does alcohol on the complex task of operating an automobile.

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