Evaluating Drugged Driving:
Effects of Pain and Anxiety Medications

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Abstract

To extend the National Advanced Driving Simulator's research program into distracted driving and drug-influenced driving, our group studied the effects of a frequently prescribed combination of sedating drugs: hydrocodone/acetaminophen (an opioid pain-relieving medication) and alprazolam (a benzodiazepine useful for muscle relaxation and sedation).

We administered the drugs in a 'within-subjects design' utilizing a double-blind, double-dummy, placebo-controlled cross-over protocol. The four arms of the study included: placebo, alprazolam alone, hydrocodone/acetaminophen alone, and a combination of alprazolam and hydrocodone/acetaminophen. The eight subjects then completed a well-standardized NADS driving protocol on the MiniSim. Experimental parameters included measures of lateral and longitudinal control. The data were reduced and then statistically analyzed using SAS statistical software.

The statistical analysis revealed that alprazolam significantly affected measures of both longitudinal and lateral driving control – such as the standard deviation of lane position (SDLP). Detrimental effects appeared more in rural scenarios and at higher speeds.

Hydrocodone/acetaminophen results showed only minor nonsignificant deviations from the placebo condition. An analysis of the combination of alprazolam and hydrocodone/acetaminophen showed almost no interaction effects. Subjects also rated alprazolam as significantly more sedating than placebo or hydrocodone/acetaminophen.

Our findings show that alprazolam much more impressively affected measures of importance in driving control. Although both drugs produce psychoactive effects at the doses studied and in the driving conditions studied, the alprazolam showed more severe deviations from placebo; furthermore, in combination, alprazolam and hydrocodone/acetaminophen did not affect driving more than alprazolam alone. These

results may have significant implications for driving safety and accident morbidity and mortality.

1 Introduction

Prescription, over-the-counter and illicit drugs have a myriad of effects on driver performance. Psychoactive drugs have the greatest risk of adverse effects on drivers. Other factors such as age, fatigue, medical conditions, and psychological functioning may have adverse effects, and when combined with drugs or multiple drugs, driver performance may be impaired to such an extent that the driver is no longer capable of safe operation of a motor vehicle. Although the other areas of driver impairment have been described and studied, drug impairment is an area of inquiry still in its early development. Some drugs with central nervous system (CNS) activity have been studied. This includes prescription medications with pharmacological actions on brain function along with an illicit drug with multiple effects throughout the body [1-4]. The effects of alcohol on drivers have been extensively studied [5-8].

The use and abuse of prescription drugs in the United States continues to be an important issue for the public and policy-makers [9]. According to the National Center for Health Statistics [10], over 48% of Americans had used at least one prescription drug in the past 30 days, while over 21% had used two and over 10% had used five. Additionally, more than 10% had used illicit drugs, and 2.5 % had used medications for nonmedical use during the preceding month. There are about 210 million American drivers on the road [11]. To put this information in perspective, that means that in any given month, there would be more than 100 million drivers taking a prescription medication, and more than 5 million of those would be using them for nonmedical purposes. Driving simulators provide a safe environment in which to assess the effects of drugs on driver performance by minimizing the risk to participants, passengers, pedestrians, and property.

Opioids and benzodiazepines are the most frequently abused psychoactive substances [12]. Because of their powerful effects on humans and their abuse potential, both of these drugs are subject to regulation as a controlled substance by the federal Drug Enforcement Agency (DEA). Opioids relieve pain and benzodiazepines reduce anxiety, with the primary effects of these drugs in the CNS [13, 14]. They are commonly prescribed together to reduce the suffering associated with acute and chronic pain. Because of the nature of their pharmacologic effects, side effects include sedation, memory loss, muscle incoordination, and an inability to concentrate [15, 16]. Typically, patients are counselled to avoid driving, operating machinery, and/or doing any activities that require mental acuity. Clinicians advise patients in the most cautious manner at the risk of limiting normal functionality.

The purpose of this study is to examine the effects of the benzodiazepine alprazolam and the opioid hydrocodone individually and in combination on driver performance parameters in the safety of a driving simulator.

2 Methods

Data for this study were collected from a double-dummy double-blind, placebo-controlled crossover study evaluating the effects of a benzodiazepine (alprazolam) and an opioid (hydrocodone/acetaminophen) on performance. The study included dosing, collection of blood samples, pharmacokinetic evaluation of blood concentrations, subjective assessments of drowsiness, collection of EEG data, and assessment of driving performance. The analysis of the drug concentrations and EEG data are planned as part of future efforts in this research program.

2.1 Participants

Eight adult participants enrolled and completed all study procedures. Each possessed a valid driver's license and drove at least 5000 miles per year. Inclusion criteria included being 18 to 40 years old and having possessed a valid driver's license for at least the last two years. All participants passed a general physical and psychological examination with no evidence of chronic disease that may affect driving. Participants were screened for use of common drugs that may affect driving performance and for excessive use of tobacco, caffeine or alcohol. The mean age was approximately 30 years of age. The maximum age was 40, and the minimum age was 21. There were 4 males and 4 females. The mean age at which participants first started driving was 14 years of age. One participant started driving at the age of 12, while another did not start until the age of 17. The mean miles driven per year was approximately fourteen thousand. The maximum miles driven per year was 25,000, while the minimum miles driven per year was 5,000.

2.2 Procedures

Subjects were recruited for this study using the NADS subject registry and through emails to the University of Iowa community. Individuals who expressed interest were screened over the phone. Screening calls were used to provide a description of the

study and to collect driving and medical histories and times available for a screening visit. If subjects passed the phone screening, they were scheduled for a screening visit.

2.2.1 Screening Visit

The first step in the screening visit was to obtain informed consent from each participant. Once consented, they were asked to provide a urine sample, and a urine drug screen test was performed. Female subjects' urine specimens were additionally tested and screened to determine if they were pregnant. Results from the drug screen and pregnancy test remained confidential, and eligibility status was documented as either a yes or no. Subject participation ended if the drug screen test was positive or if the pregnancy test was positive. If the participant was still eligible, height and weight information were collected. Next, a brief physical exam and psychiatric evaluation was performed by a physician. A questionnaire (Driving Survey) that asked questions about demographic information, their driving record, driving behavior, and driving history was completed. At this point, subjects who failed to meet study criteria were paid for their time and effort. Subjects who met study criteria watched an overview presentation about the simulator cab and were trained on in-vehicle tasks. Subjects then drove the simulator for about 5-8 minutes. This drive allowed the subjects a chance to become comfortable with driving the simulator. After the practice drive, subjects filled out a questionnaire about how they felt. If the survey indicated a high propensity for simulator sickness, subjects were excluded from continuing in the study and paid for their time and effort. Subjects who continued in the study then completed a 45-minute Alertness Memory Profiler (AMP) Assessment. Finally, staff confirmed dates for the four study visits and asked subjects to arrange for third-party transportation to and from NADS on all study visit days. In the event that the subject could not arrange for third-party transportation, taxi transportation or transportation by NADS staff was arranged by study staff at no cost to the participant.

2.2.2 Study Visits

When participants arrived, staff first collected urine samples to screen for illicit drug use and pregnancy. Subjects then completed a sleep and food intake questionnaire, and they were required to show that they had gotten 7-9 hours of sleep the night before the study visit. They also filled out a questionnaire, the Stanford Sleepiness Scale (SSS), which asked about their current sleepiness level. A baseline 4 ml blood sample was drawn from the arm via a single needle stick done by a medical professional. Subjects who met study criteria were fitted with the B-ALERT® EEG wireless sensor headset. They were then escorted to the prep room, administered two capsules of study medication (based upon randomization), and asked to rest for approximately 120 minutes.

After 120 minutes, participants completed a 45-minute AMP assessment. A second 4 ml blood sample was then drawn. Subjects were escorted to the simulator, where any questions were answered. Subjects were then asked to complete the SSS again before completing a 35-minute simulator drive. After the drive, subjects completed a questionnaire about how they felt and a questionnaire about the simulator A third and final blood sample of 4 ml was obtained. If it was the fifth and final visit, payment was finalized.

2.3 Drugs

Two drugs were used as part of this research: hydrocodone/acetaminophen (Norco) 10 mg/325 mg, and alprazolam (Xanax) 1 mg. Placebo capsules filled with inactive lactose were used that matched the active drug. The typical dosage of Norco is 10 mg/325 mg for an “adult every four to six hours needed for pain (Norco dosage).” Norco has common side effects such as drowsiness, feeling relaxed and calm, sleepiness, dizziness, and lightheadedness. The typical dose for Xanax is .5 to 1 mg (Alprazolam dosage).

2.4 Simulator Drives

The study drive was a standardized driving environment used for testing impaired driving across roadway environments [17]. Originally developed for evaluating alcohol-impaired driving [18], it has been augmented to include drowsiness [19-21], distraction [22, 23], cannabis [1, 24, 25], and other drugs[2, 3, 26]. The drive involved an urban environment followed by an interstate and then a rural roadway. The rural portion of the drive included a 10-minute section of straight monotonous driving on a two-lane rural road at the end. The total drive duration was approximately 35 minutes. Three equivalent versions of this scenario were used so that each driver experienced each drive once followed by one repeat scenario on the final visit. The maps for the three scenarios are provided in Figure 1 - Figure 3.

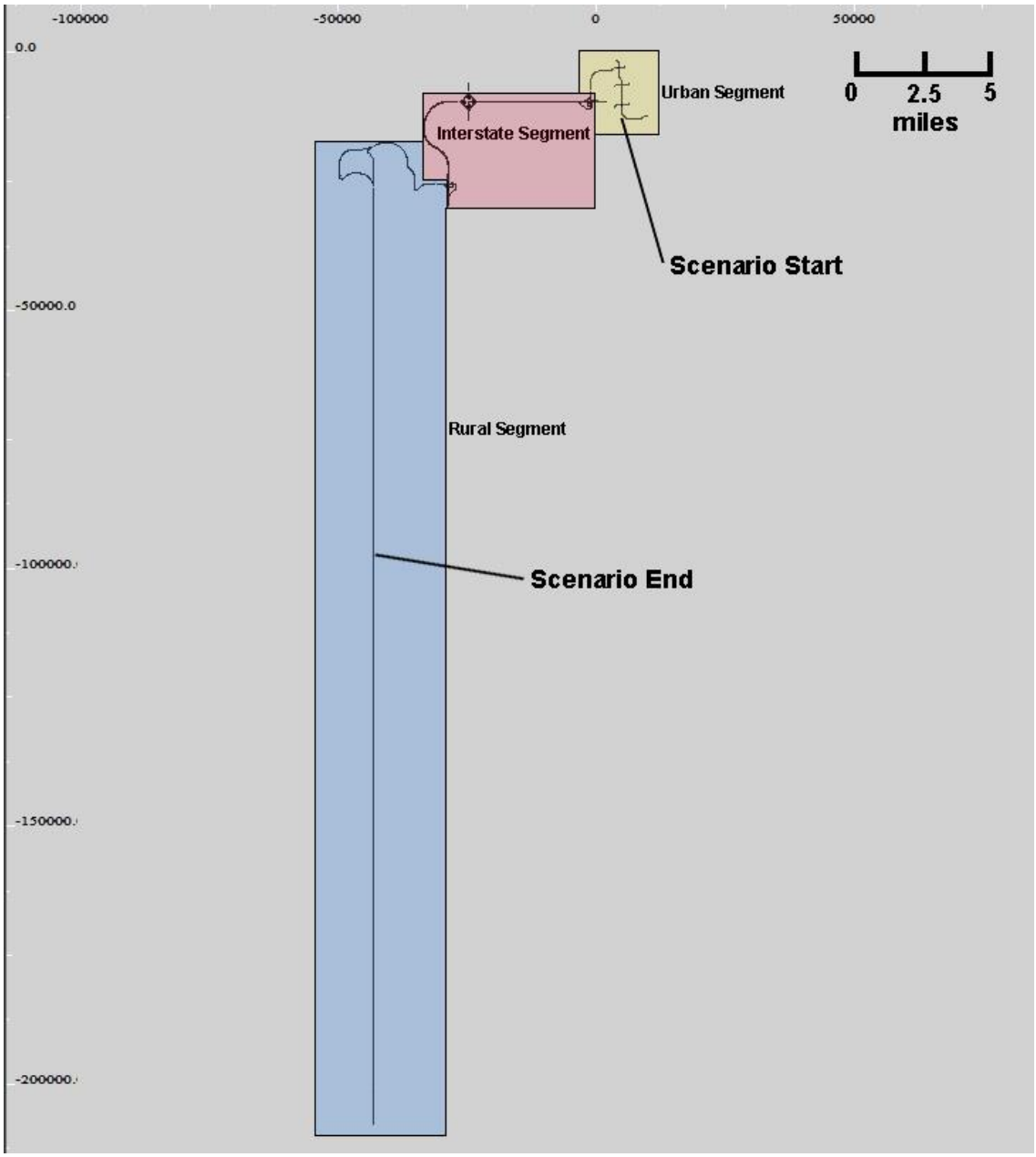

Figure 1. Scenario 1 road network

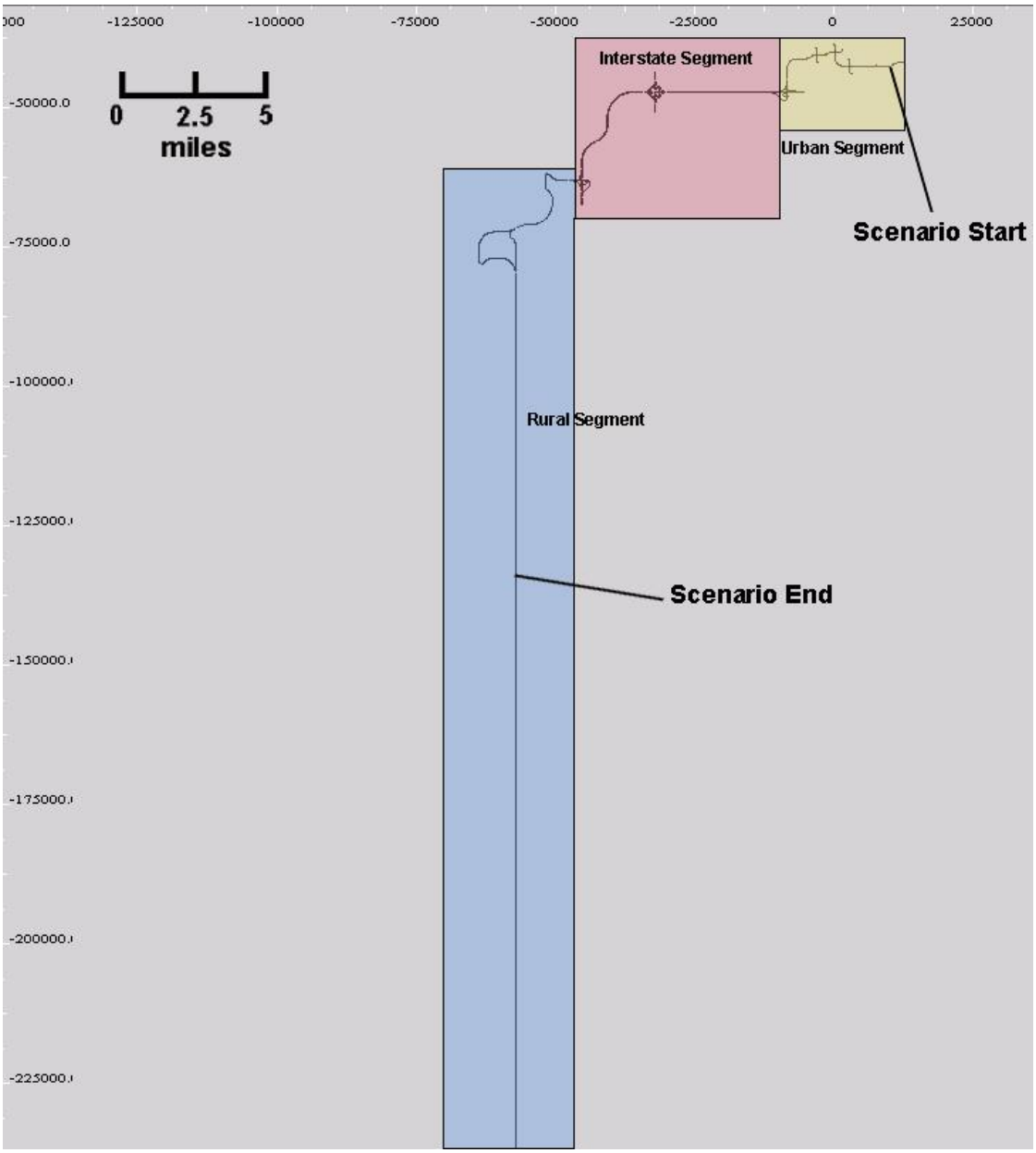

Figure 2. Scenario 2 road network

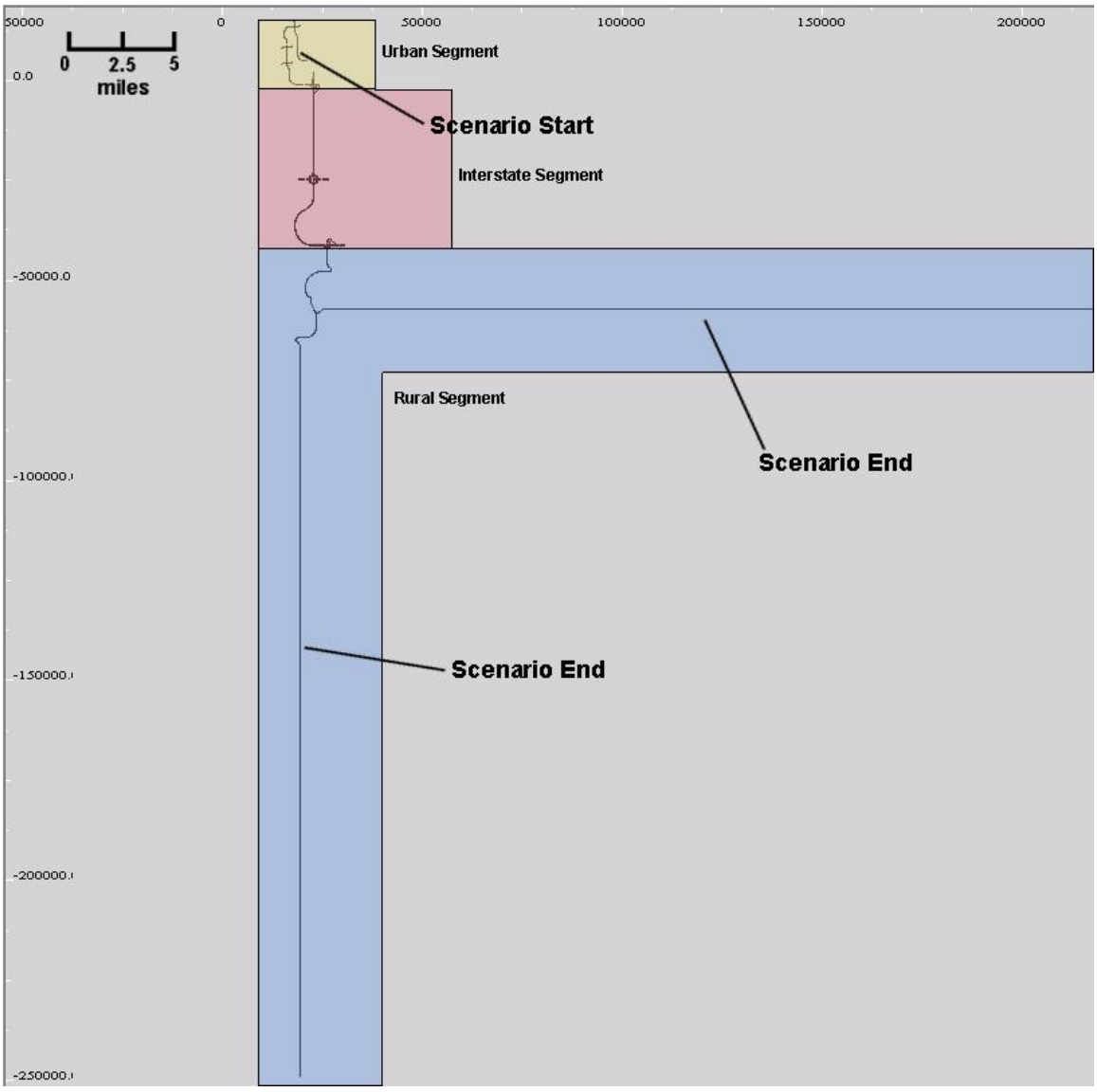

Figure 3. Scenario 3 road network

2.5 Apparatus

2.5.1 Driving Simulator

Driving simulation was carried out at the University of Iowa's National Advanced Driving Simulator using the miniSim™ research driving simulator, a PC-based and validated research driving simulator [27]. The simulator included a quarter cab with three 42" 720 p plasma LCD displays that provide a forward field of view of 130° horizontal x

24° vertical at a 48” viewing distance (see Figure 4). The simulator is comprised of functioning controls from a real vehicle, including a seat, steering wheel, column gear selector, and throttle and brake pedals. Steering feedback was provided with an active steering loader with DC motor/microprocessor control. The sound system includes a 2.1-channel sound system with a vibration transducer under the seat and an audio amplifier with external controls. Experimental controls were provided with a GUI interface to start/stop the simulation and choose scenarios on a 22” LCD display. Data were sampled at a rate of 60Hz. This configuration was chosen for compatibility with prior research [1-3] and to allow future work to be conducted at multiple sites using the same simulator and scenarios.

Figure 4. Quarter-cab minSim with daytime urban scene

2.5.2 EEG System

The B-ALERT® EEG wireless sensor headset (see Figure 5) developed by Advanced Brain Monitoring, Inc. (ABM), combines battery-powered hardware with a sensor-placement system to provide a lightweight, easy-to-apply method for acquiring and analyzing 9 channels of high-quality EEG, plus 1 additional channel for an optional signal (typically ECG, but can include GSR, respiration, or integrated eye tracking). The typical ECG leads are attached to the upper right clavicle and lower left rib, and plug directly into the wireless amplifier enclosure. Sensor site locations on the current B-ALERT® EEG wireless sensor headset system include the following options: Fz, F3, F4, Cz, C3, C4, P3, P4, and POz. Amplification and digitization of the EEG close to the sensor sites, in conjunction with secure wireless transmission of the data, facilitates the

acquisition of high-quality signals, even in environments with high electromagnetic interference.

Figure 5. B-Alert X10 headset

The AMP tasks were selected based on a review of the neuropsychological tests used to evaluate attention, learning, and memory [16-20] in combination with methods used by neurophysiologists to assess EEG indices of alertness and memory. ABM is building a database of AMP sessions to support comparisons across experimental conditions and populations; data is currently available from over 1000 participants. There are multiple components to the AMP, as described below.

2.5.3 3-Choice Vigilance Task (3CVT)

The 3CVT incorporates the most common measures of sustained attention: the Continuous Performance Test, Wilkinson Reaction Time, and the PVT-192 [17, 21]. The 3CVT requires discrimination between a primary (70%) and two secondary (30%) geometric shapes presented for 200 ms over a 20-minute period. Training provided prior to the start minimizes practice effects. Concurrent validity was established in sleep deprivation studies by correlation with behavioral evidence as measured by cessation of finger tapping, visually scored facial signs of drowsiness (e.g., eye closures, head nods), self-reported subjective sleepiness, visually scored EEG, modified MWT, handheld PVT-192 test, and driving simulator performance [22-23].

2.5.4 Eyes Open (EO) and Eyes Closed (EC) with paced button press

In EO, a 10 cm circular image presented every 2 s for 200 ms prompts the subjects to press the space bar. For EC, an auditory tone every 2 s prompts the subjects to press the space bar, and each task is administered over a 5-minute period.

2.5.5 Standard Image Recognition (SIR)

The SIR tests evaluate attention, encoding, and image-recognition memory. For the Standard IR, during the training session, 20 images are presented twice each. The testing session presents the 20 training images randomly interspersed with 80 additional images. Subjects indicate whether or not the image was in the training set. Five equivalent image categories are available: animals, food, household goods, sports, and travel.

2.6 Data

Dependent measures in this study were organized into those associated with lateral and longitudinal control. Measures of lateral control analyzed for this project were average lane position relative to the center of the lane, standard deviation of lane position (SDLP), and number of lane departures per minute. Measures of longitudinal control measures analyzed for this project were speed relative to the speed limit, standard deviation of speed, percent of time driver drove more than 10% above the speed limit (Percent Speed High), percent of time driver drove more than 10% below the speed limit (Percent Speed Low), and accelerator pedal holds. Percent measures were first transformed using a Logit transformation before analysis. Six pre-specified sub-segments of the drive were analyzed: urban, urban curves, interstate, interstate curves, dark rural with curves, and straight rural. These sections excluded periods where drivers

were turning or stopped at signals, in order to focus on lateral and longitudinal control during normal conditions.

Data from the EEG and blood samples will be analyzed for future use.

2.7 Objectives

The aim of this research was to assess the effect of benzodiazepines and opioids alone and in combination on driving performance. Additionally, data will be collected for future use in exploring the utility of the B-ALERT® EEG wireless sensor headset in conjunction with the AMP for detecting drug effects on driving and for pharmacodynamic modeling.

3 Results

The results will be presented in three sections:

- Lateral control: the ability to maintain vehicle lane position
- Longitudinal control: The ability to maintain speed and other driving parameters
- Subjective drowsiness.

In brief, the statistical analysis revealed that alprazolam differed significantly from placebo in sex variable dealing with all three areas of analysis: longitudinal control, lateral control, and sleepiness. There was almost no difference between hydrocodone/acetaminophen and the control placebo. No interactions were seen between alprazolam and hydrocodone/acetaminophen. Lastly, alprazolam produced a significant soporific effective as subjectively reported. (Note: significant results in the driving variables are marked by black borders in the figures.)

3.1 Lateral Control

The statistical analysis found a marked difference in driving performance when it came to lateral control. Administration of alprazolam resulted in marked degradation of

steering control in several driving scenarios (see Figure 6): urban curves ($F=12.00$; $p < 0.01$); interstate curves ($F= 21.66$; $P < 0.05$); and dark straight segments ($F = 21.59$; $P < 0.003$).

It was also shown that alprazolam significantly increased variability in lane keeping (see Figure 7). Significant differences in SDLP appeared in the interstate ($F= 5.79$; $p=0.<05$) and rural ($F= 6.60$, $p< 0.05$)) segments of the protocol drive. As speed increased, lane deviations also increased in magnitude. We found robust differences in straight dark driving conditions ($F= 14.24$; $p=0.010$), as well as interstate curves ($F=27.8$; $p=0.01$). Figure 8 graphically shows the impact of maintaining position under the influence of alprazolam. Analysis showed that alprazolam robustly increased lane departures; increases were significant in higher-speed segments: interstate ($F= 8.86$; $p<0.05$), interstate curves ($F= 21.44$ $p=0.005$); dark rural segments ($F= 24.25$; $p=0.005$); and dark straight segments ($F= 31.1$; $p<0.001$). We also found significant differences within subjects while negotiating urban curves ($F= 7.69$, $p=0.01$).

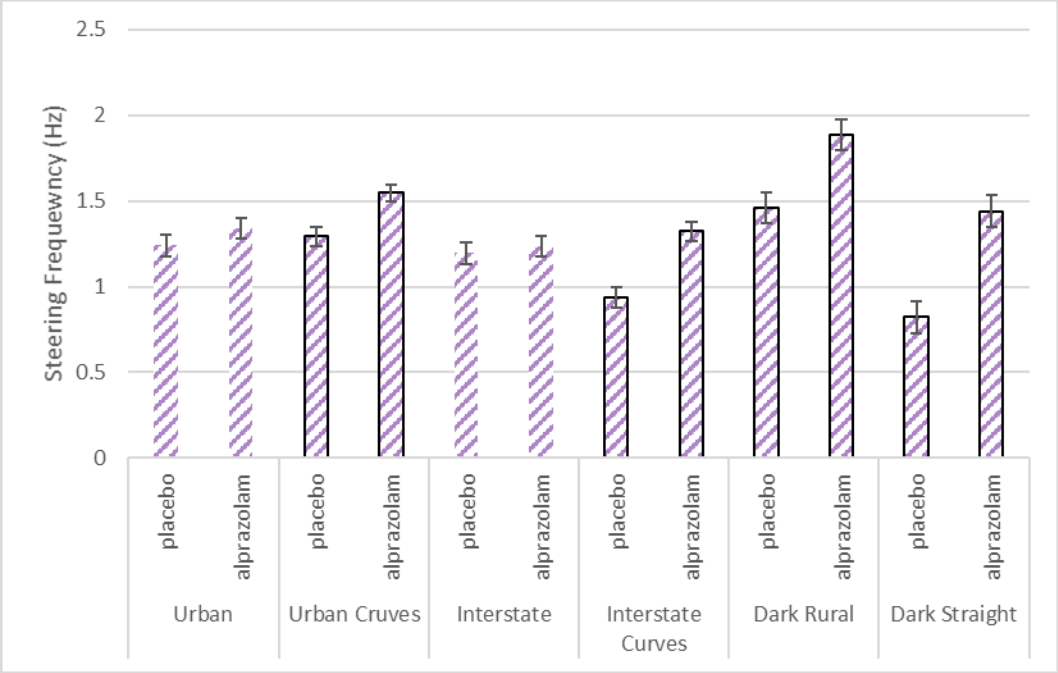

Figure 6. Alprazolam and steering input

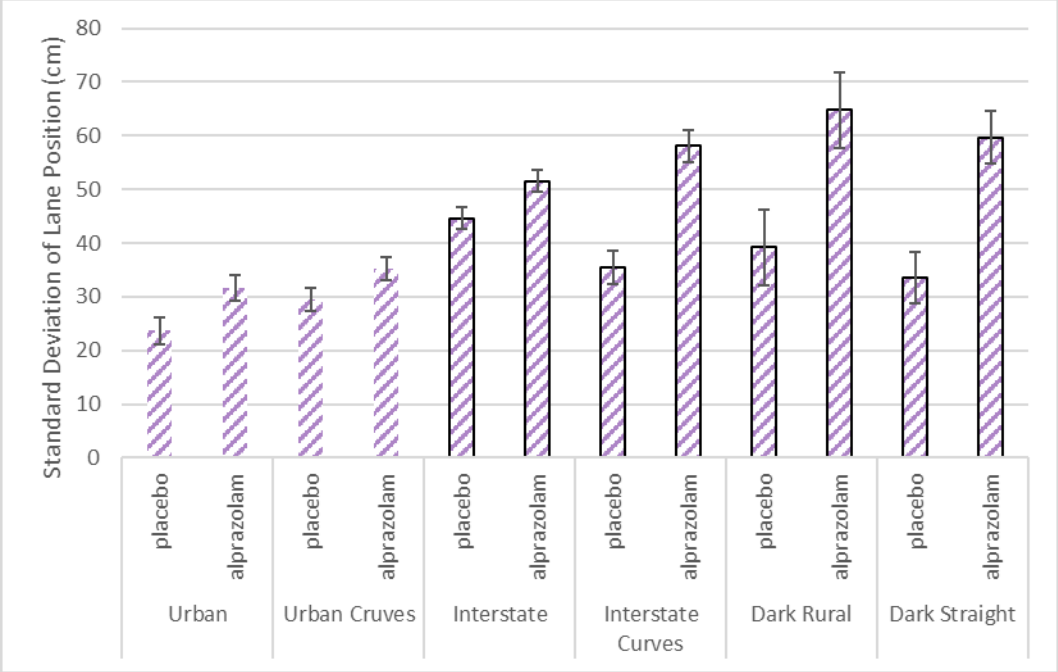

Figure 7. Alprazolam and lane keeping

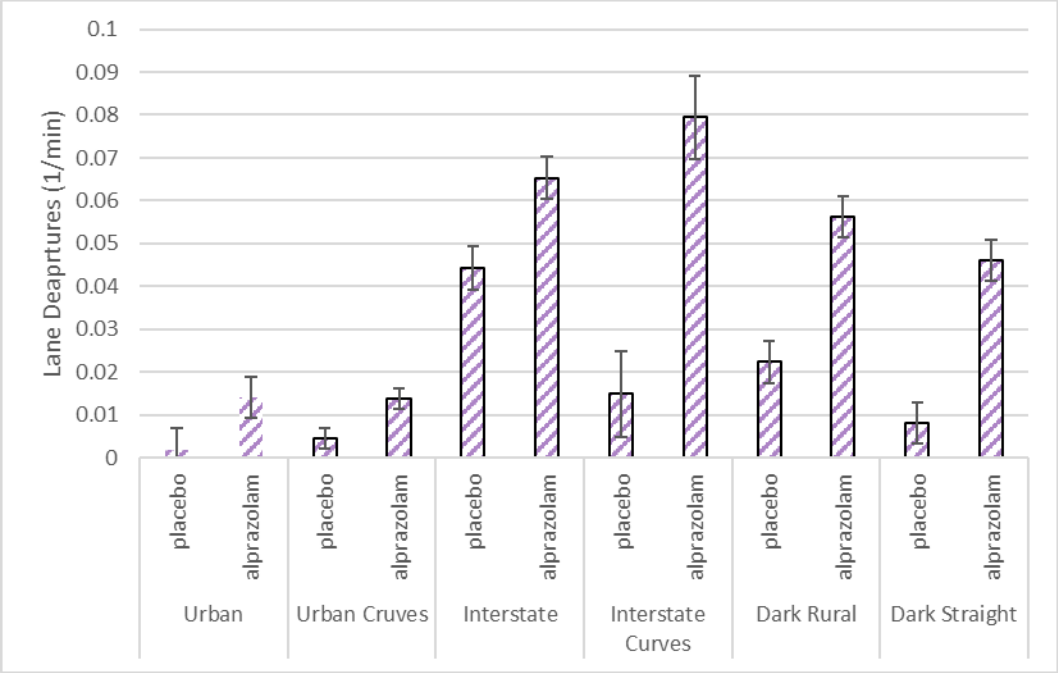

Figure 8. Alprazolam and departing the lane

3.2 Longitudinal Control

Alprazolam administration also significantly influenced the measure of speed control. A measure of discrete inputs to adjust the speed of the vehicle can be found in accelerator pedal holds. The results demonstrated that pedal holds were significantly fewer in the alprazolam condition during the urban ($F=6.93$; $p<0.05$) and dark straight ($F= 12.7$; $p=0.01$) segments of the drive (see Figure 9). For the standard deviation of speed under the influence of alprazolam, there was significantly greater variability (1.51 vs 0.93 m/s) in urban driving ($F= 5.97$; $p< 0.05$). Lastly, we noted a significant deviation on the percent speed high for the dark straight segment of the drive ($F=6.02$; $p<0.05$). During this segment of the drive, alprazolam deviated from placebo with a significantly greater proportion of time spent driving 5% above the speed limit compared to placebo (74.2% vs 0.5%). We found no significant differences in variables for average speed or percent speed low.

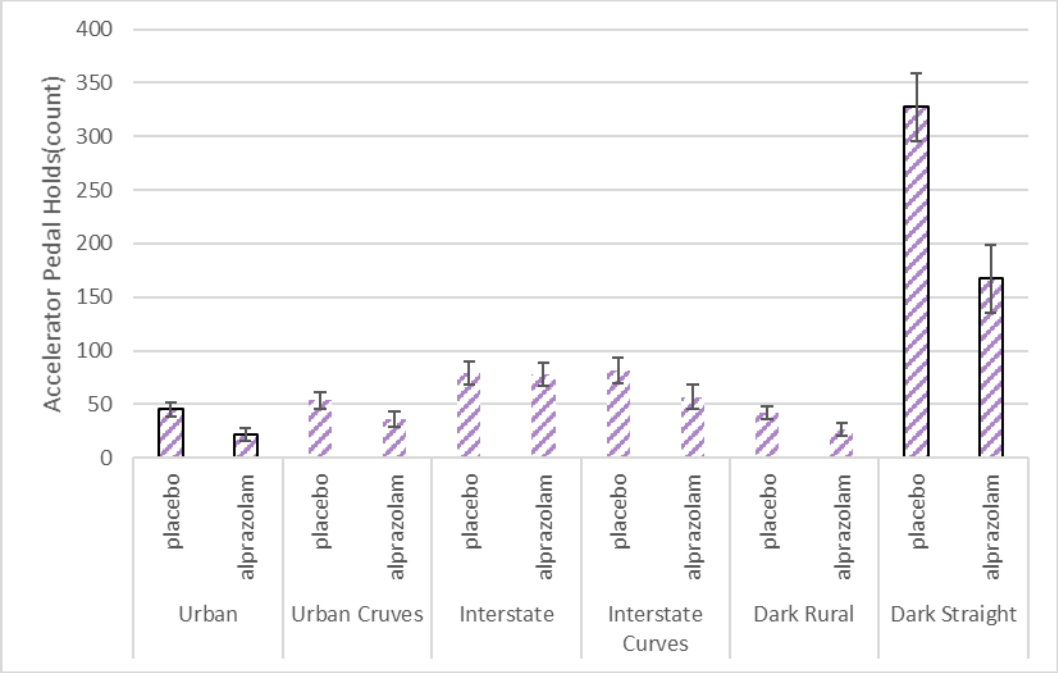

Figure 9. Alprazolam and throttle holds

3.3 Subjective Effects

We noted that in the self-rating of drowsiness, subjects experienced a significant increase in sedation during alprazolam administration during the drive ($F=8.85$, $p<0.02$). On the seven-point SSS, drivers had increases of 1.5 scale untits of drowsiness when under the influence of alprazolam but only 0.25 while taking the placebo. Subjects noted no increase in sedation for hydrocodone/acetaminophen ($F=0.29$, $p>0.05$). Additionally, there were no observed confounding differences in pre-drive SSS scores ($F<0.62$, $p>0.45$).

4 Discussion

Distracted and drugged driving continues to be a significant public safety issue, responsible for morbidity and mortality during driving. Continuing the NADS commitment to studying distracted driving, we offer the first study to examine the effects of a benzodiazepine and an opioid as well as the interaction between the two drugs on driving parameters. Although the subject size was small, the protocol was solid and well

documented. The results presented here should be a basis for more detailed and larger studies on the influence of both benzodiazepines and opiods and their co-use on driving.

Our data and statistical analysis indicate that alprazolam markedly degrades parameters of longitudinal and lateral control driving control. We noted only a very slight effect of hydrocodone/acetaminophen. Furthermore, there were no significant interaction effects of the two drugs in the study protocol. These results were gathered in the context of subject-noted sedation while under the influence of alprazolam. Therefore, at these clinically used doses, there was a robust negative influence on driving from alprazolam that was not exacerbated by the addition of hydrocodone/acetaminophen.

We confirmed earlier studies that showed that, in drivers under the influence of alprazolam, lateral vehicle control is impaired, and significantly so, as indicated by lane departures and SDLP. Further, these impairments increased with a reduction in ambient lighting and increased speed. Notably, interstate curve negotiation was robustly deteriorated. Considering the subjective sedation results, these results suggest that decreased alertness with impaired motor control lead to important degradation of vehicle lateral control, which can cause a loss of total vehicle control and an accident. There may be important cognitive impairments that contribute to these results; however, our protocol was not designed to detect detailed cognitive impairment.

We also discovered that the measure of longitudinal control—accelerator pedal holds at the beginning and the end of the drives—decreased under alprazolam influence. This indicated fewer discrete inputs to control speed under that condition. On the other hand, during the urban drive, there was a compelling increase in variability of speed. There was a fascinating violation of the speed limit during alprazolam administration showing that 75% of the last 10 minutes of the drive were above speed limit. This suggests that a driver using the benzodiazepine struggles with lateral control as well as speed control

during very trying conditions in the driving scenario. Again, these results reiterate the significant impairments of motor vehicle operation under alprazolam influence.

Our results using a moderate dose of hydrocodone/acetaminophen show little effects on measures in this Mini-sim driving protocol. This is in keeping with past studies. We extend those results to indicate that when both drugs are administered in tandem, the deleterious effects of driving are predominately due to the alprazolam. Thus, both in isolation and in combination, the degrading results of the benzodiazepine outweigh the effects of the opioid in these doses and in this sample.

There are many considerations when evaluating this study. First, subtle effects of the drugs may not be detectable in a small sample size. We also note that the subjects in the study represent a generally young and healthy group of drivers; thus, the results may not be totally applicable to younger or older drivers, or drivers taking these agents for particular medical conditions such as chronic pain. This study group may not be representative of the typical general population taking these drugs in combination.

We also note that this study used single administrations to measure the acute effects of drugged driving. In real-life medical clinics, such drugs are often used in combination for treating chronic medical conditions. Likewise, drivers may be taking other psychoactive drugs, which could also affect drug response or drug blood level.

It is interesting to consider how benzodiazepines and opioids affect the physiological and neurological processes involved with motor vehicle operation. Hypothesized mechanisms of driving ability include:

- sedation/wakefulness/alertness;
- sensory perception and processing speed of environmental stimuli;
- reaction time;
- executive functioning/cognitive processing of sensory stimuli and integration of related memory;

- motor control

Benzodiazepines and opioids could affect any or all of the proposed mechanisms of driving, and these effects may depend on dose, experience, age, and gender, as well as driving variables such as lighting, speed, urban v. rural, and other parameters. This pilot study was not designed to delineate the effects of the opioid or the benzodiazepine on each level of motor and congestive control; however, it does suggest several areas of study for the future. Future studies could tease out the effects of sedation, cognitive impairment, memory deterioration, motor impairment, reactions, sensory-perceptual impairments, and cognitive integration/executive function on overall driving measures such a longitudinal control and lateral control. A significant understanding of the pharmacological effects on normal driving could be attained using driving simulation, cognitive and psychological tests, psychological measures such as F-MRI and EEG, and other experimental manipulations; this would significantly contribute to knowledge about impaired and drugged driving and the risks of single and combination use of psychoactive drugs.

Many of the medication management issues are beyond the scope of this manuscript; however, considering the literature and looking at our pilot results, one caveat is clear: alprazolam, and benzodiazepines in general, potentially impair safe driving. Although there are many potential variables and complications in assessing risk, a combination of benzodiazepine and opioid introduces risk, which has the potential to result in serious and fatal outcomes.

5 Conclusion

In conclusion, our group studied the combination of alprazolam and hydrocodone/acetaminophen in a double-blind, placebo-controlled, crossover design to determine if any detrimental effects, singly or in combination, could be ascertained via

driving simulation. We found that the benzodiazepine alprazolam 1 mg produced robust negative effects on longitudinal control and lateral control measures during a period when subjects noted sedation. Hydrocodone/acetaminophen at 10/325 mg did not induce nearly the amount of adverse driving as alprazolam did, nor was it perceived as sedating. The combination of alprazolam and hydrocodone/acetaminophen showed no interaction effects. We conclude that the frequently prescribed drug alprazolam appears to adversely affect driving measures of motor vehicle control, especially in high-speed and low-ambient-light conditions, effects not seen as prominently with the opioid. Professionals prescribing or dispensing this short-acting, powerful benzodiazepine must be aware of potential potent adverse effects on driving that may result in significant driving impairment. Physiological mechanisms of such impairments remain speculative.

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