PATH - POST-ACCIDENT TESTING HEURISTICS

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EXECUTIVE SUMMARY
PROJECT PATH: POST-ACCIDENT TESTING HEURISTICS

To begin, it is important to recognize that this was a "proof-of-concept" study. A key objective of this study was to develop and test procedures that can be used in a driving simulator and that could be used to evaluate the impact of several classes of prescription medications on the driving performance of commercial motor vehicle operators. The main point was to determine whether these procedures could be developed and whether they would demonstrate the issues that can arise under the influence of Triazolam and other prescription and over-the-counter medications.

Chapter One is a review of the drugs and driving literature and a discussion of how and why Triazolam was chooses as the study drug. The prescription drug chosen for this study is Triazolam, a typical short-acting benzodiazepine that is prescribed to assist persons who have insomnia to go to sleep and remain asleep. The doses used in this study are the recommended therapeutic doses of this benzodiazepine and have been, and continue to be, well studied.

Studies referenced in Chapter One of this paper have not always found statistically significant decrements from threapeutic dose levels. The findings of this study indicate that Triazolam at therapeutic dose levels causes reliable and statistically significant decrements in four measures of normal driving performance as well as decrements in standard psychomotor tests given in conjunction with each drive.

Chapter Two describes the experimental plan and its safeguards. The detailed experimental protocol received a full review by the University of Iowa Instructional Review Board (IRB) and was approved July 30, 2009. Participants were required to have a current Commercial Drivers' License and be currently employed as a bus driver. They were recruited by flyer, newspaper ads, and presentations to driver groups (with employer permission). A high-fidelity bus driving simulator, owned by the Paducah (Ky) Area Transit System, was leased for the two month-experimental period and parked in the parking lot of the National Advanced Driving Simulator (NADS) at the University of Iowa. A custom software package was coded by professionals at FAAC, Inc. in Ann Arbor, MI, the simulator manufacturer. The custom coding enhanced the data-capture capabilities of the simulator for research capability.

The PATH Project Director, Designer, Principal Analyst and Principal Investigator is John Morrison, Senior Partner with Cahill Swift, LLC. The PATH Co-Principal Investigators Dr. Daniel McGehee and Dr. Linda Boyd are, respectively, researchers at the University of Iowa and the University of Washington. Staff and professionals at NADS conducted the on-site portion of the project. In all, 71 bus drivers responded to the recruitment materials and 32 made it through screening and training. Of these 32, four failed to complete because of scheduling conflicts and four were released by the experimenters during the project. There were no adverse reactions that needed to be

reported to the IRB, but two of the participants were released because they had a measurable concentration of Triazolam in their saliva samples taken the next day 11 to 14 house post-dosing.

Chapter Three discusses the paper-and-pencil surveys completed by the participants at per-determined times in this project. The data gathered through this method provided insights into OTC and prescription medications currently being taken by participants that might have potentiated the Triazolam experimental doses. Other data helped the PATH experimenters to understand the perceptions of the participants to the experimental apparatus, and to the "realism" of driving a simulated bus in a driving simulator.

Chapter Three also presents the data from Immunalysis Laboratory, Inc. that performed an analysis of the concentration of Triazolam found in the saliva samples taken from the participants after each of the 15 experimental drives. It was considered impractical to require participants to allow blood to be drawn after each experimental drive. The saliva Triazolam levels were intended to serve as a surrogate for blood-drawn serum Triazolam levels. It was also desirable to have a method to compare serum and saliva Triazolam levels. Accordingly, participants were asked to voluntarily allow blood to be drawn after the last drive of each experimental session. Six participants volunteered to allow blood samples to be taken after each of the three experimental sessions. These provided a baseline of serum Triazolam concentration against which to match their saliva Triazolam levels from samples taken concurrently. There was a strong linear correlation between saliva and serum Triazolam (R^2=.97).

From this information, the PATH experimenters developed a set of variables that were thought likely to impact and modify the drug impact. These variables were included in linear regression studies in Chapter Four and Five and were found to have an impact on dose-related impairment.

Chapter Four presents the psychomotor tests and their methods. The psychomotor testing reliably show dose-related impairment on all measurements. Within the psychomotor battery, the scales to measure Mood (Happiness, Depression, Fatigue, etc) reliably showed dose-related increases in Fatigue, Sleepiness and Vigor measurements but no changes in the indexes of Happiness, Depression, Restlessness and Anxiety. It was observed that several participants had highly elevated concentrations of Triazolam in their saliva. The psychomotor test scores were calculated with the three participants with the highest concentrations of saliva in the data mix, and again after removing the scores of those participants. The ANOVA tests continued to show significant ($p<.01$) overall regression after the "outlier" data was removed. However, for several of the tests involving choices, the P-Value for Triazolam Concentration became less than significant. Pursuit Rotary Tracking and Simple Reaction Time, the simplest psychomotor tests, continued to show statistically significant impairment related to Triazolam concentration with the three "outliers "removed. The information supplied by the participants during the intake to this research were reviewed and possible explanations for the instances of highly elevated "outlier" Triazolam concentration were discussed.

Chapter Five of this report examines the impact of Triazolam on the driving performance of the participants in the bus driving simulator. The measurement Standard Deviation of Lateral Position (SDLP, also known as Standard Deviation of Lane Position) was the metric used to measure drug impact of the participant's ability to drive straight in their lane. Weaving in lane reliable increased with the 0.250 mg dose to Triazolam. That dose of Triazolam increased weaving in lane by .15 meters (6 inches) at low speeds. Due to the additive effect of speed, at higher speeds for uniquely susceptible drivers the 0.250 mg dose increased weaving in lane by 30 inches. Under those conditions the bus would exceed its lane and encroached into the adjacent lane by approximately 20 inches as it crossed back and forth across the lane markers.

SDLP was also used to measure the impact of Triazolam on curve following behavior. In this measure, there seemed to be less impairment than in straight driving. It appeared that participants may have adapted somewhat to the effects of Triazolam over the three experimental sessions and 15 experimental drives they performed in the simulator. Drivers who were randomized into the 0.250 mg dose on the first experimental drive showed increases in curve-following SDLP of approximately .2 meters (8 inches). A secondary measure of fine steering adjustments showed a significant reduction in fine steering control relative to the drivers randomized into the placebo or 0.125 mg dose. Drivers who were randomized into the 0.250 mg dose group on the third experimental session continued to exhibit SDLP of .2 meters, so there was no change in actual impairment. However there was a significant increase in their efforts at fine steering control. It appeared that they were equally impaired by the drug but were trying harder to control it.

The study also evaluated the performance of drivers approaching stop signs (or red lights) that could be seen from a distance. Drivers on the experimental sessions when had been randomized to the 0.250 mg dose took a longer time to transition from initial to full braking, by about 1.3 seconds, than drivers randomized to the placebo or 0.125 mg dose. Consequently, having achieved full braking, they had a shorter distance in which to stop the vehicle and maximum deceleration was significantly higher, at least for the drivers having received the 0.125 mg. The stopping profile of the drivers was further evaluated at the critical distance of 40 meters from the stop line. At that distance, there was a significant difference in the brake pressure applied by the drivers randomized to the 0.250 dose and the 0.125 mg dose compared with drivers who received the placebo dose. At 40 meters from the stop line, drivers on the experimental sessions on which they received the placebo dose had slowed their vehicles and were able to ease up on brake pressure. The same drivers, on sessions on which they received the 0.125 or the 0.250 mg dose, had not sufficiently slower their vehicles at the 40 meter distance and brake pressures were significantly elevated.

Finally, driver performance was evaluated while they drove around construction barrels with an arrow directing them to move into the adjacent lane. Drivers randomized to the 0.125 mg dose swung slightly wider than the placebo and the 0.250 mg dose drivers,

but the 0.250 mg dose drivers had more variability in the course they drove ($p<.05$) and made more steering corrections.
Chapter Six of this study reviewed the experimental data and was primarily concerned with the issue of individual differences. Chapter Six tried to determine whether it would be possible to develop a systematic model of performance under Triazolam that would encompass individual variances. Such a model seemed to have emerged from the psychomotor testing and the SDLP tests, but it was counterintuitive.

In the psychomotor tests, participants with higher Body Mass Index (BMI) scores regularly did more poorly on the tests per drug dose than participants with low Body Mass Index scores. This was counterintuitive because the higher BMI participants reliably had lower saliva Triazolam concentrations than moderate and low BMI participants. If impairment is dose-related, it was expected that high BMI participants would be less impaired because the drug would be diluted in a larger volume of bodily fluid.

Even more counterintuitive, the participants with higher Driver scores also were consistently slower on the psychomotor tests. The higher Driver score participants were rated higher on their appropriate responses to the driver challenges programmed into their first experimental drive, before any drug had been administered. Intuitively, it was assumed that the skew by Driver Score Index (DRI) would be in the other direction– that higher DRI drivers would have faster psychomotor response times and more accurate choice mechanisms than less trained and skilled peers.

Project PATH uses a cross-over design and all participants received all doses in a randomized order. For purposes of randomizing the dose-administration schedule, participants were assigned to “Drug Groups”. A post-facto review showed that the distribution of Driver Scores and Body Mass Index numbers were not equally distributed within Dose Groups. Group B had a preponderance of low-BMI participants with low Driver Scores (less skillful). Group D had a preponderance of high-BMI participants with high Driver Scores (more skillful). A hypothesis was put forward in Chapter Five that the order of impairment, from most to least impaired, would be relatively constant by Block Group and would be predicted by the average of BMI and DRI score, but in counterintuitive order. That is, Group B, with low-weight, low-skill drivers, would also be the group impaired the least on average by the drug. Participants in high-weight, high-skill drivers in Group D, in contrast, would generally be the most impaired.

This hypothesis seemed to hold together in the straight-driving tests using the group average SDLP scores as the index on impairment. However the expected ordering of impairment could not be confirmed in the data for the stopping profiles.

Additional Comments

The research reported in this study did not examine the responses of driver-participants under emergency conditions where rapid and accurate responses are needed. More research will be needed to identify specific scenarios where those drivers, under the

influence of Triazolam or other substances, could pose the greatest risk to themselves and their passengers.

The results need to be considered in light of the fact that there were several study limitations. The first limitation relates to the small sample size. This was due to subject dropout and some unforeseen technical difficulties within the simulator, which did not allow the for data collection for some participants. The next study limitation was the lack of consistency in the drive scenarios that were examined. For example, when selecting driving segments to measure the SDLP of the drivers, the researchers looked for straight stretches of roadway that had two lanes, no other traffic in the same lane as the participants, the same speed limit and of the same length. However, given the variability of the routes within the simulator, that criteria of same speed and length of the stretch of road was not always met. The analysts had find specific segments that met most of that criteria while trying controlling for the criteria that was not met via statistical procedures. These controls had introduced detrimental effects such as increased variability, numerical instability and reduced the statistical power of the models used in the analyses.

On balance, however, Project PATH was intended to be as much as possible a “natural” driving study. It was designed so that participants would encounter many of the driving challenges they face during normal operations but in a way that precluded their preparing in advance for the next challenge. As such, each of the 15 experimental drives were different, one from another. The driving scenarios were constructed in that manner so drivers could not “learn the route” and anticipate upcoming events.

It is encouraging that the magnitude findings of this study, especially the SDLP results, are in general agreement with the results of other studies. For instance, NHTSA (2006) in the Driver Workload Metrics Task 2 Final Report (see Table 3-40, page 3-61) reports that the SDLP of the drivers operating an instrumented vehicle on a test track varied between 0.4 and 0.8 inches depending on the type of distracting task being performed by the driver and length of the segment.

The parameter estimate from Project PATH from the current study is 0.69 feet SDLP at 35 MPH for the drivers receiving the placebo and 0.125 mg dose of Triazolam, and 0.990 feet for the drivers receiving the 0.250 mg dose of Triazolam. Although a conjecture, if there is a direct relationship among the comparative data, the implication is that the 0.250 mg dose indices a higher degree of lack of control than the most distracting task accomplished by the drivers in the NHTSA report.

The NHTSA study (Table 3-44 page 3-65) also reported that 10% of drivers performing the most distracting task exceeded the lane boundaries and encroached on the adjacent lane at least once in a segment of driving that required about 25 seconds to cross. Figure 5-21 in this section documents that approximately 15% of the participants (2 of 15 drivers with a quantifiable concentration of Triazolam in their saliva), exceeded their lane in a stretch of road that would have taken approximately 35 seconds to drive.

So again it may be surmised that the 0.250 dose of Triazolam is at least as impairing as the most complex distracting task used by NHTSA.

Conclusions

- It is possible to plan, develop and conduct a drugs and driver study in an academic setting which studies the impact of prescription medications on professional drivers, with full and careful review and approval by the Institutional Review Board. It is possible to recruit and screen participants and to conduct the experiment using modified commercial training equipment that can be purchased on the GSAdvantage website.

- A psychomotor test battery can be integrated into the study protocol and impairment on the psychomotor tests will be predictive of impairment on the driving tasks. Interestingly, the simplest psychomotor tasks appear to show drug impairment at lower concentrations of Triazolam than psychomotor tests that require choice behavior.

- The individual impact of drug on individuals is difficult to predict. Drug impact is modified in unexpected ways by the Body Mass of the driver and by the level of training and skill of the driver. The drug impact is also modified by concurrent medications being taken by the driver. That being said, there also appear to be idiosyncratic drug responses that are not explained by data gathered in this experiment.

- The measure Standard Deviation of Lateral Position (SDLP), a measure of weaving in lane while driving straight, is used to demonstrate diminishment of steering control. Group mean SDLP measurements are dose-dependent. The 0.250 mg Therapeutic dose of Triazolam increased lane deviation at all times by adding 6 to 10 inches of lane weaving. However, in impaired drivers, in addition to the additional 6-10 inches of weaving, the data indicated that there would be SDLP excursions of as much as 30 inches as frequently as 1 or 2 times an hour.

- At both dose levels studied, one impact of drug impairment is the loss of fine control of braking behavior. Drivers applied brake pressure more heavily and later in the stopping maneuver under both drug doses than after having received the placebo dose. Additionally, drivers exhibited a diminution of steering control while steering around construction barrels. The increase in SDLP, diminution of braking control and less exact steering control when avoidance maneuvers are required could contribute to an increased crash likelihood for drivers using Triazolam and driving.

- There appeared to be no carry-over effects of Triazolam on driving after a period of normal sleep. Drivers, returning for the next-day drive on the day after they had received the 0.250 mg dose, reported improved sleep the previous night relative to their normal sleep patterns. There were no reports of improved sleep on the next-day drives after having taken the 0.125 mg or placebo capsules.

1 SECTION ONE – BACKGROUND AND LITERATURE REVIEW

1.1 – Background

There has been a long history of debate concerning whether driving restrictions should be placed on commercial motor vehicle operators who are taking anxiolytic and sedative hypnotic drugs. Anxiolytic drugs are, typically, longer acting drugs prescribed to reduce anxiety, hyper-responsiveness and anger. Sedative hypnotic drugs are, typically, shorter acting drugs prescribed to promote relaxation and sleep. Many of these substances are members of the large benzodiazepine family.

In 1991, the Federal Highway Administration Conference on Psychiatric Disorders and Commercial Drivers[1] reported that "studies have demonstrated that benzodiazepines, the most commonly used anxiolytics and sedative hypnotics, in pharmacologically active dosages impair skills performance… Epidemiological studies indicate that the use of benzodiazepines and other sedative hypnotics is probably associated with an increased risk of automobile accidents." The task force recommended that:

1. Patients requiring anxiolytic medications should be precluded from commercial driving.
2. Individuals requiring hypnotics should use only drugs with half lives of less than 5 hours for less than 2 weeks under medical supervision and at only the lowest effective dose.
3. The urine drug screen performed as part of the biennial physical examination should include a screen for benzodiazepines and barbiturates.

No action has been taken on those recommendations. The medical examiner has the sole responsibility to decide whether a professional driver taking a prescription medication is medically qualified to drive. One Medical Review Officer recently wrote:

> There are few clear standards establishing which drugs are acceptable for particular jobs and which ones are not. Except for those few absolutely disqualifying drugs (insulin, methadone, seizure meds), the FMCSA rule tells medical examiners that impairing drugs are acceptable only if the patient can get the prescribing doctor (read "the patient's advocate") to write a note that it's ok for the patient to take the drugs and drive a truck. That approach is worse than no approach at all -- it comes close to obliging the medical examiner to accept whatever the prescribing physician says is ok! … It's understandable how doctors might favor allowing the patient/employee to work despite use of a potentially impairing drug. In the Part 40 (drug testing) rule, the standard of certainty that is required for MROs to notify employers of safety risks is a ***likely*** safety risk. Likely safety risks are few and far between; far more often, we're confronted with possible or theoretical safety risks.[2]

The findings of the Large Truck Crash Causation Study (LTCCS) have recently emphasized the importance of establishing a rational, scientifically based regulatory approach to the use of psychoactive prescription medication by commercial drivers. In the LTCCS, use of prescription medications was the most frequently identified contributing factor in collisions with other vehicles initiated by large trucks. Prescription drugs use by the CDL-holder was found in 28.7% of all such collisions. Prescription medications were identified as contributory factors in 33.9% of collisions with large trucks that were initiated by passenger vehicles. Over the counter medications were found to be contributory in 19.4% of collisions initiated by trucks and 10.3% of collisions with trucks initiated by passenger cars.[3] By way of comparison, Inadequate Surveillance (IS) was cited as a contributory factor in only 15.8% of truck-initiated crashes and 13.2% of passenger-vehicle initiated crashes. Table 1-1 is an excerpt from Table 10 in the LTCCS report.

Figure 1-1. Associated Factors identified in the LTCCS Report

Table 10 - Estimated Large Trucks and Passenger Vehicles in Two-Vehicle Crashes by Associated Factor

Reasons	Frequency		Percent	
	Large Truck*	Passenger Vehicle*	Large Truck**	Passenger Vehicle**
Drivers				
Prescription Drug Use	19,000	22,000	28.7%	33.9%
Over-the-Counter Drug Use	13,000	7,000	19.4%	10.3%
Unfamiliar with Roadway (Less Than 6 Times in 6 Months)	13,000	6,000	19.1%	9.7%
Inadequate Surveillance	10,000	9,000	15.8%	13.2%
Driving Too Fast for Conditions	10,000	7,000	15.2%	10.4%
Making Illegal Maneuver	8,000	9,000	11.5%	13.1%
Felt Under Work Pressure	6,000	2,000	9.9%	2.6%
Driver Inattentive to Driving	6,000	6,000	8.5%	9.2%
External Distraction	5,000	4,000	7.7%	5.6%
Driver Fatigue	5,000	10,000	7.5%	14.7%
Inadequate Evasion	4,000	5,000	6.5%	6.9%
False Assumption of Other Road User's Actions	4,000	2,000	5.9%	3.1%
Unfamiliar with Vehicle (Less Than 6 Times in 6 Months)	4,000	2,000	5.4%	2.4%
TOTAL DRIVER CONTRIBUTORY FACTORS	107,000	91,000	161.1%	135.1%

The National Transportation Safety Board (NTSB) is determined to gather more information on the prevalence of prescription and over-the-counter medications in serious commercial vehicle collisions. In three FTA accident investigations since 2000, the NTSB has made recommendations similar to the recommendation quoted below from a 2000 investigation:

> Establish, in coordination with the US Department of Transportation, the Federal Motor Carrier Administration, the Federal Railroad Administration, and the US Coast Guard, comprehensive toxicological testing requirements for an appropriate sample of fatal highway, railroad, transit, and marine accidents to ensure identification of the role played by common prescription and over-the-counter medications. Review and analyze the results of such testing at intervals not to exceed every 5 years.[4]

This FTA-funded research project, entitled Post-Accident Testing Heuristics (Project PATH), develops important information about the impacts of a short half-life sedative hypnotic benzodiazepine on the driving performance of public bus operators in a modern high-fidelity bus driving simulator. The data from Project PATH will be folded into other on-going FTA efforts to formulate a comprehensive strategy on the regulation of the use of prescription and over-the-counter medications by safety-sensitive transit personnel.

1.2 Methods for Studying the Driving Impact of Psychoactive Prescription Medications

This section discusses the three methods used to study driving performance and driving performance as impacted by the use of behaviorally active substances. These approaches are: Driving Simulators, Epidemiological Studies, and Actual Driving studies in an instrumented vehicle.

1.2.1 Driving Simulators as Models of Actual Driving Performance

In 2001, the use and prevalence of "Transit Bus Operator Driving Simulators" was reviewed in the Transit Cooperative Research Program (TCRP) Report 72[5]. According to the report's authors, a high-fidelity driving simulator will have "physical fidelity and psychological fidelity." For physical fidelity, the cab and forward, side and rear operator views must be a faithful three-dimensional representations of the driving environment and the simulated vehicle must perform like a real vehicle. For psychological fidelity, the training program must present realistic scenarios that facilitate and train proper driving techniques and that immediately translate into proper responses in the real world (Brook et. al., reference 5, page 9).

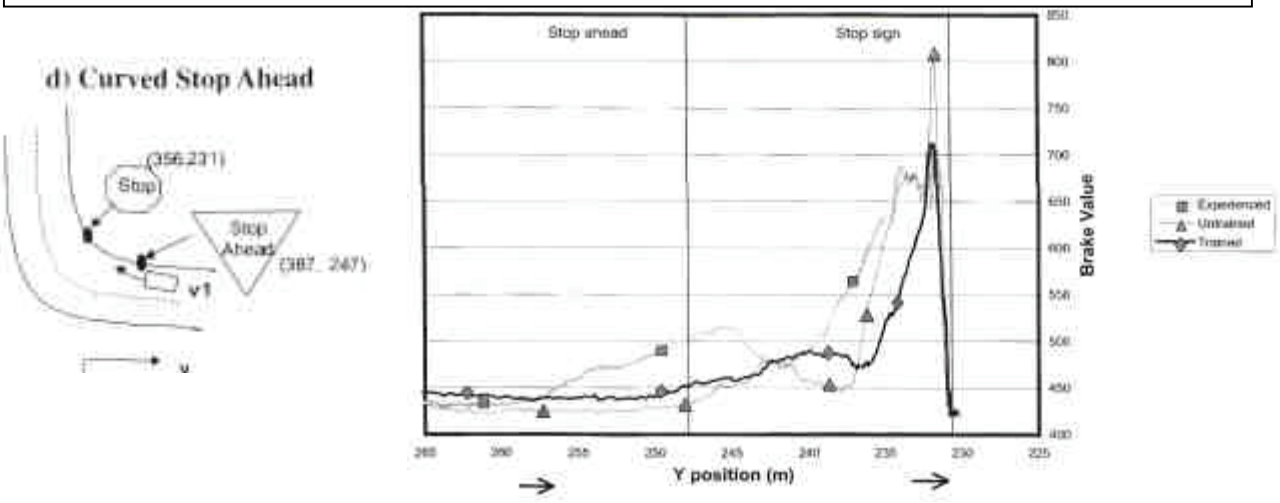
Fixed-base bus driving simulators, of the type purchased by many transit systems, confer both physical and psychological fidelity. They are becoming recognized as successful training and retraining devices. In a recent scientifically valid study comparing the effectiveness of training new bus operators in a simulator as against conventional on-the-street training, New York City Transit (NYCT) reported a 35% reduction in washout rates during the training period for new operators trained on the simulator compared to new operators trained conventionally. During the first 60 days of sensitive-safety duty, which is the period of the highest accident rates for operators, the simulator-trained operators had a 43% lower accident rate than the conventionally trained operators (31.9% accident rate for conventionally trained vs. 18.1% for simulator-trained). Moreover, none of the simulator-trained operators had a right-side accident, whereas 21% of the accidents of the conventionally-trained group were right-side accidents[6]. This study confirmed that there was immediate carry-over of simulator training into actual driving.

Fisher et al (2002) demonstrated that: 1) simulated driving can be used to distinguish between the performance of three driver groups: untrained young drivers, PC-trained young drivers; and experienced bus operators, and 2) that performance in a simulator

reflects the level of prior training and experience of the operator[7]. Fisher's study also demonstrates that PC-based low-fidelity driver training for 16-year old new drivers helps them better recognize and respond appropriately to the risk scenarios they encounter in a driving simulator. PC-trained new drivers anticipate and respond to risk situations in a simulator better than new drivers who have completed only conventional driver training. Ultimately, however, in simulator testing, Fisher's control group, Experienced student bus drivers at the University of Massachusetts, performed more appropriately to the risk scenarios than either the PC-trained or the conventionally-trained (i.e. untrained) group.

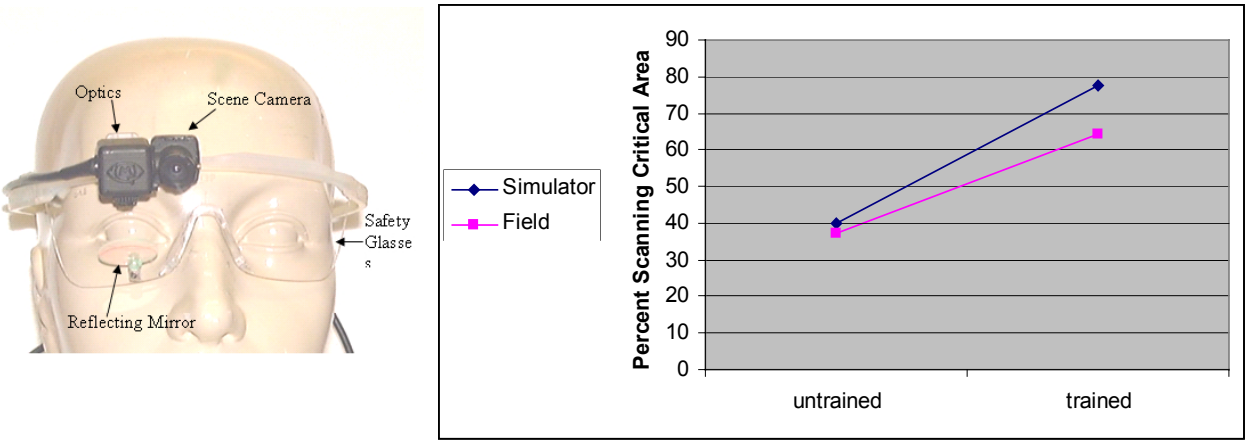
This study also demonstrates the utility of the data-collection and reporting capabilities of high-fidelity driving simulators. The left side of Figure 1-2, taken from Fisher's 2002 study, diagrams the simulator risk scenario: "Curved Stop Ahead". The diagram shows a scenario in which a simulated vehicle approaches a curve with a warning sign indicating the presence of a blind stop sign ahead and around the curve. The graph, on the right side of Figure 1-2, shows the braking pattern of untrained new drivers, trained new drivers and experienced bus operators as they approach the warning sign and stop sign in the simulator. The vertical lines in the plot mark the positions of the warning sign and the stop sign respectively. From the plot, it is obvious that the experienced bus operators react to the warning sign and apply their brakes earlier and more smoothly than either the trained or untrained operators. Thus, data collected in a driving simulator is capable of differentiating skillful and cautious driving from unskillful or reckless driving.

Figure 1-2: Driving simulator risk scenario and breaking patterns of untrained, trained and experienced drivers as they approach the risk point in a high-fidelity driving simulator. From Fisher (2002)



Fisher et al[8] (2007) have more recently extended these findings by mating eye tracking to virtual driving (Figure 1-3). These authors examined the visual search behavior of trained and untrained drivers operating an instrumented real vehicle in on-the-road driving wearing eye-tracking equipment. They compared this real-world visual search

Figure 1-3: From Fisher (2007) Percent of untrained and trained drivers wearing an eye tracker scanning critical areas to identify risks while driving in an instrumented real vehicle on the road and while operating a similar vehicle in a driving simulator.



behavior to visual search performance in a driving simulator. Trained and untrained drivers driving an instrumented vehicle gazed at, recognized, and responded to risk

scenarios to the same degree as matched control groups in a driving simulator wearing eye tracking equipment and exposed to similar risk scenarios. Untrained drivers fixated the critical regions of the risk scenarios 37.3% of the time driving the instrumented vehicle and 40.4% of the time in the simulator. The trained group fixated the critical regions of the risk scenarios 64.4% of the time in the instrumented vehicle and 79.7% of the time in the simulator. The authors concluded that data collected in a simulator accurately reflects and predicts actual driving behaviors for trained and untrained drivers.

Other researchers have employed high-fidelity driving simulators to study the impact of driver distraction on driving performance (Lee, Lee & Boyle, 2007)[9], the effectiveness of collision warning systems (Reinach & Everson 2005)[10], and the effects of drugs on driving behavior (Barkley et al, 2005)[11], Weiler et al (2000)[12]. These studies have validated the hypothesis that experiments conducted in high-fidelity driving simulators generate results that translate veridically to real-world driving situations.

1.2.2 Research on Drugs and Driving Behaviors – Epidemiological Studies

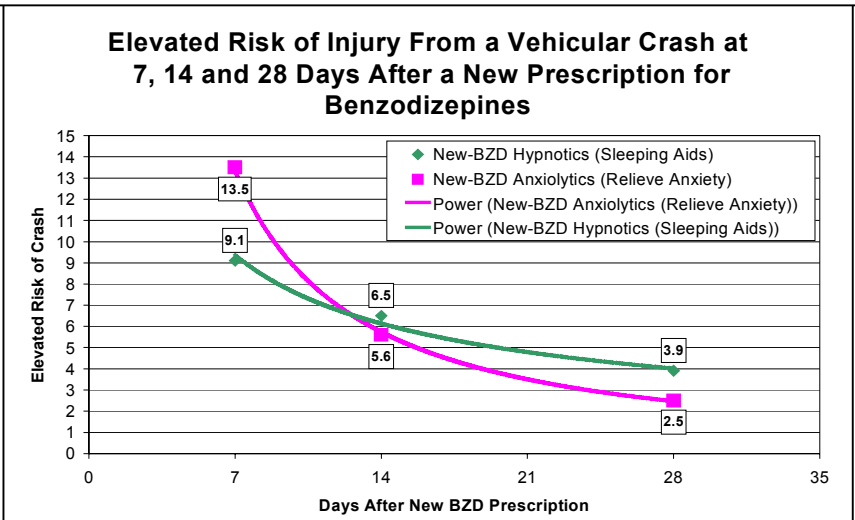
The preponderance of research on the impact of psychoactive drugs on driving behavior originates from two sources other than driving-simulator research: These are: 1) epidemiological studies and 2) real-driving studies conducted in instrumented vehicles.

Epidemiological studies correlate accident reportage with drug use to determine whether drivers who use drugs have a higher frequency of driving accidents than drivers who do not. Some studies also examine whether drivers who have used drugs are more frequently found to be culpable. There is an extensive body of this literature. Reports from Australia, Austria, the United States, England, Quebec, Norway, Canada,

the Netherlands, France, Luxembourg, Sweden and Switzerland concerning crash frequency and benzodiazepine use have reported common findings. A summary of these reports is included as Attachment 1. The reports find that drivers who have used benzodiazepines alone, or in combination with alcohol and/or other psychoactive drugs, have a higher likelihood of being in a vehicular accident and more frequently are found to be culpable, than non-drug involved drivers.

Researchers have also studied the relative impact of long half-life versus short half-life benzodiazepines on crash likelihood. There appears to be a reduction in crash likelihood for drivers using benzodiazepines for long periods of time. Neutel (1995)[13] calculated the Odds Ratio (OR) for an automobile crash in the first 7, the first 14, and the first 28 days after a person received a new prescription for a short half-life, or for a a long half-life, benzodiazepine. In a separate paper, Neutel (1998)[14] calculated the Odds Ratios of a crash for specific benzodiazepines for the first 28 days of a new prescription. In both Neutel studies, the ORs were reliably elevated for the first month of use, but declined towards an asymptote. Figure 1-4 presents Neutel's data from both studies♦.

Figure 1-4: Risk of a traffic accident for new users of prescription benzodiazepines.



Source: Neutel, C.I.. Risk of traffic accident injury after a prescription for a benzodiazepine. Ann. Epidemiol (1995) 5(3): 239-244

Risk of traffic accident injury in first 28 days of new benzodiazepine prescription, Odds Ratio (OR) +/- 95% Confidence Interval (CI)

	All Ages		Under 60 Years		60 Years or Older		Trade name	Half-Life
Benzodiazepine Prescription	OR	CI	OR	CI	OR	CI		(hours)
Triazolam (S-Hypnotic)	3.2*	1.4 - 7.3	3.5*	1.2 - 9.9	2.9	0.8 - 10.3	Halcion	2
Flurazepam (L-Anxiolytic)	5.1*	2.3 - 11.6	6.1*	2.2 - 17.1	3.4	0.9 - 13.9	Dalmane	40 - 250
Lorazepam (S-Anxiolytic)	2.4*	1.0 - 6.3	2.2	0.7 - 7.4	3.5	0.8 - 15.9	Ativan	10 - 20
Diazepam (L-Anxiolytic)	3.1*	1.4 - 6.5	3.0*	1.1 - 7.9	3.4*	1.0 - 11.4	Valium	36 - 200
Oxazepam (S-Anxiolytic)	1.0	0.3 - 3.7	1.3	0.3 - 5.6	---	---	Serax	4 - 15

S = Short acting BZD, half-line 24 hours or less. L=Long-acting BZD, half-life greater than 24 hours
***Statistically significant at p<0.05**

Source: Neutel, CI: Benzidiazepine-Related Traffic Accidents in Young and Elderly Drivers; *Hum. Psychopharmacol. Clin. Exp.*, 13, S115-S123 (1998)

♦ Note the data in the graph is plotted by this author from Neutel's published data. .

Neutel's1998 study also determined that older drivers have a reduced risk of a collision associated with a new benzodiazepine prescription relative to younger drivers. Hebert et al (2007)[15], extended this longitudinal data. These authors calculated the long-term elevation of the Odds Ratios for an accident, using two calculation methodologies, to be 1.45 and 1.53 respectively for senior drivers using benzodiazepines versus non-using seniors.

Törnros et al (2001)[16], also studying long-term users, tested long-term benzodiazepine users against a matched group in a simulated driving test and also evaluated driver performance with psychophysical[P] measurements. Both groups, users and non-users, were equivalent regarding brake reaction times and lateral position variation in the driving simulation test. However, there were significantly more intra-individual differences in speed variation among the benzodiazepine users than non-users. In the psychomotor testing, the long-term users as a group also had somewhat slower reaction times and performed worse on short-term memory tests.

Unpublished Odds Ratios calculated by J. Morrison from data available in the Fatality Analysis Reporting System (FARS) parallels the information of Neutel and Herbert. The FARS database contains information on the drugs detected in the post-mortem remains of injured drivers and also the number of prior accidents of those drivers. These data strings can be cross-tabulated to derive the Odds Ratio that drug-using drivers had a

Figure 1-5: Increased risk of multiple accidents by prescription drug users.

Prior Accident Risk Ratios for Benzodiazepines and Other Drugs

Drug 1 Found in Fatal Crash Driver	Number of Prior Accidents This Driver			Ratio of Accidents			Odds Ratio for Prior Accidents Against No Drug Found			Chi Sq Test of Significance (Pairs vs No Drug Found)
	None	One	Two or more	None	One	Two or More	One	Two or More	Sum	
No Drugs Reported	10025	1400	320	1	0.140	0.032	1.0	1.0	2.00	p = 1
OXYCODONE	23	11	4	1	0.478	0.174	3.4	5.4	8.87	p=.00004
METHADONE	61	12	8	1	0.197	0.131	1.4	4.1	5.52	p=.0003
OPIUM	34	10	3	1	0.294	0.088	2.1	2.8	4.87	p=.036
HYDROCODONE	98	22	8	1	0.224	0.082	1.6	2.6	4.16	p=.008
METHAMPHETAMINE	173	32	12	1	0.185	0.069	1.3	2.2	3.50	p=.016
BENZOYLECGONINE	200	45	12	1	0.225	0.060	1.6	1.9	3.49	p=.003
BENZODIAZEPINES	**111**	**27**	**6**	**1**	**0.243**	**0.054**	**1.7**	**1.7**	**3.44**	**p=.021**
DELTA 9	93	16	6	1	0.172	0.065	1.2	2.0	3.25	p=.199, ns
AMPHETAMINE	297	60	16	1	0.202	0.054	1.4	1.7	3.13	p=.007
DIAZEPAM	**80**	**13**	**5**	**1**	**0.163**	**0.063**	**1.2**	**2.0**	**3.12**	**p=.315, ns**
TETRAHYDROCANNABINOID	140	30	7	1	0.214	0.050	1.5	1.6	3.10	p=.065
CODEINE	40	3	3	1	0.075	0.075	0.5	2.3	2.89	p=.169, ns
THC	296	39	17	1	0.132	0.057	0.9	1.8	2.74	p=.057
BARBITURATES	15	1	1	1	0.067	0.067	0.5	2.1	2.57	p=.560, ns
"Cannabinoid, Type Unknown"	257	38	12	1	0.148	0.047	1.1	1.5	2.52	p=.434, ns
MARIJUANA/Marihuana	234	33	11	1	0.141	0.047	1.0	1.5	2.48	p=.462, ns
MORPHINE	69	13	2	1	0.188	0.029	1.3	0.9	2.26	p=.600, ns
"Other "	465	74	15	1	0.159	0.032	1.1	1.0	2.15	p=.595, ns
PROPOXYPHENE	21	6	0	1	0.286	0.000	2.0	0.0	2.05	p=.595, ns
COCAINE	364	53	11	1	0.146	0.030	1.0	0.9	1.99	p=.944, ns
ACETOMINOPHEN + CODEINE	51	9	1	1	0.176	0.020	1.3	0.6	1.88	p=.707, ns
ALPRAZOLAM	**52**	**6**	**1**	**1**	**0.115**	**0.019**	**0.8**	**0.6**	**1.43**	**p=.805, ns**
Midazolam	24	4	0	1	0.167	0.000	1.2	0.0	1.19	p=.636, ns

[P] Project PATH is, overall, an experiment in "psychophysics" because it is concerned with the relation between stimulus and response under pre-drug, drugged and post-drug conditions. The term "psychomotor" is used to describe some of the technologies used by others and the PATH experimenters to infer the relationship between stimulus and response in this experiment, or the results of those tests.

higher probability of having been involved in a previous crash than non-drug-involved drivers. The raw data, Odds Ratios (OR), and Chi Square tests of significance for drugs vs. no drugs are shown in Figure 1-5. Drivers using benzodiazepines had an OR of 1.7 for having had a previous accident versus drivers with no drugs found in their system, statistically significant at the 0.021 level. Inferentially, drivers using prescription benzodiazepines not only have a increased likelihood of having an accident, even when the drugs are being used long-term, but are also more likely to have had multiple accidents than their non-drug using counterparts.

In summary, a substantial body of data confirms that there is an elevation in crash likelihood among new users of both short and long half-life benzodiazepines. Although the Odds Ratios decline with extended prescription use, crash likelihood appears to asymptote at a sustained elevation of about 1.5 times the crash likelihood of the non-prescription peer group. Senior drivers may be less susceptible to the impairing effects of benzodiazepines than younger drivers.

1.2.1 Research on Drugs and Driving Behaviors – Instrumented Vehicles and Real Driving Studies

Most of what is directly known about the impact of prescription drugs on driver performance comes from studies of real driving in instrumented vehicles♦. These studies have developed prototypical measures of driving performance and have correlated those measures with psychomotor tests. Studies using these methodologies have provided data on the impacts of comparison drugs, the time course of drug effect, dose-response interactions, and performance decrements compared to standard concentrations of alcohol. Meta-analyses, the gathering of comparable data from multiple studies, has produced comprehensive, reliable and replicable summaries of drug impacts across a whole class of pharmacological substances.

Verster et al (2006)[17] conducted a meta-analysis of 10 randomized, placebo-controlled, double-blind trails of a variety of benzodiazepines and non-benzodiazepine hypnotics on real-driving behavior. The instrumented vehicle and the derivation of the primary common measurement, Standard Deviation of Lateral Position (SDLP), is shown in Figure 1-6. The graph in Figure 1-7, on the second following page, is taken from numerical data reported by Verster. All of the 10 studies in the meta-study graphed in Figure 1-7 measured changes in Standard Deviation of Lateral Position (SDLP), a measure of weaving in lane, and in Standard Deviation of Speed (SDS). Decrements in curve following and reaction time sometimes were gathered in the reviewed studies, and correlated with SDLP, but SDLP is the primary and reliable metric.

♦ However, this may be changing. As this report was being written, Verster's laboratory had a current recruitment notice on his website. His laboratory has purchased a driving simulator and is recruiting subjects to "calibrate" driver performance in the simulator after ingesting standard amounts of alcohol. Having established the performance decrements of three standard levels of alcohol, he will then conduct drug trials to determine impairments equivalent to these established BACs.

Figure 1-6: An instrumented vehicle and the measurement of Standard Deviation of Lateral Position (SDLP), a prototypical measure of weaving.

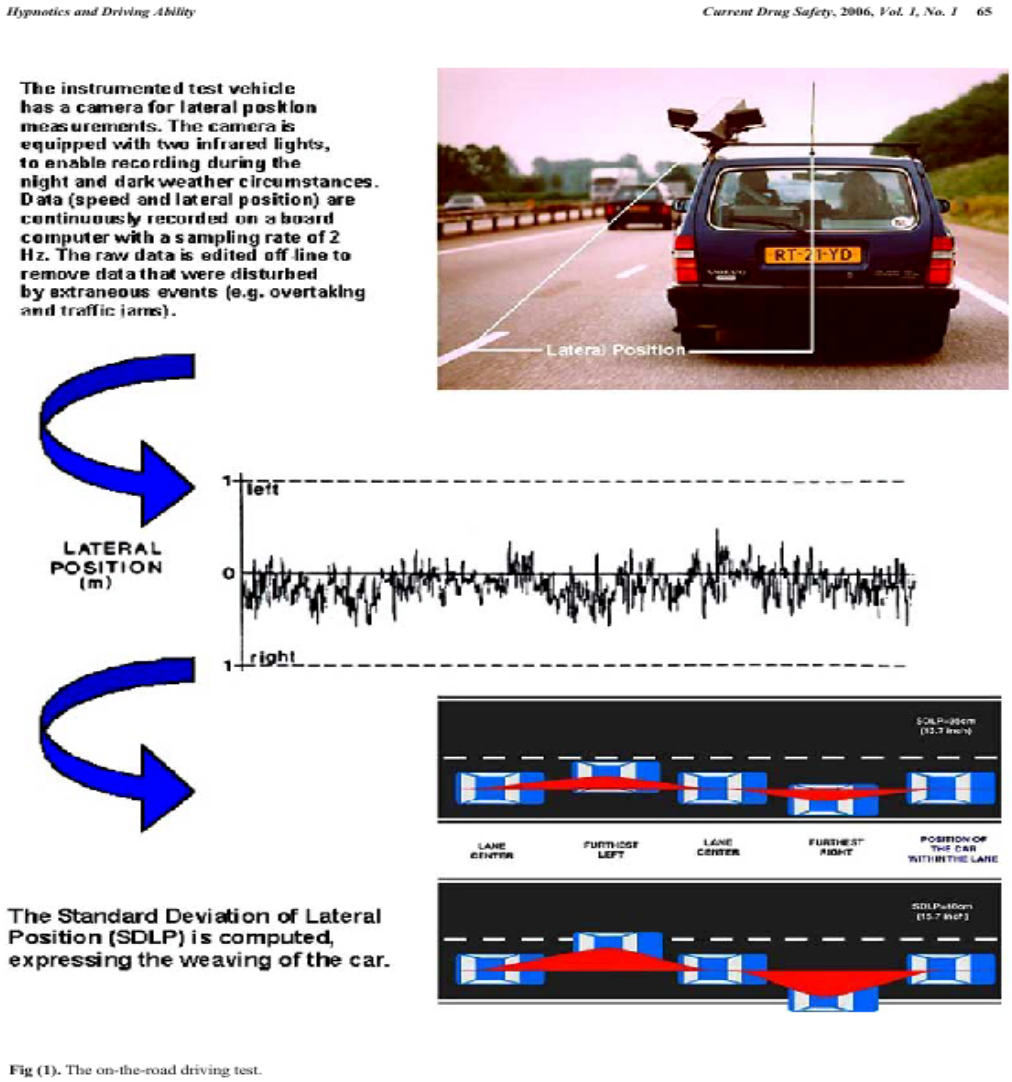


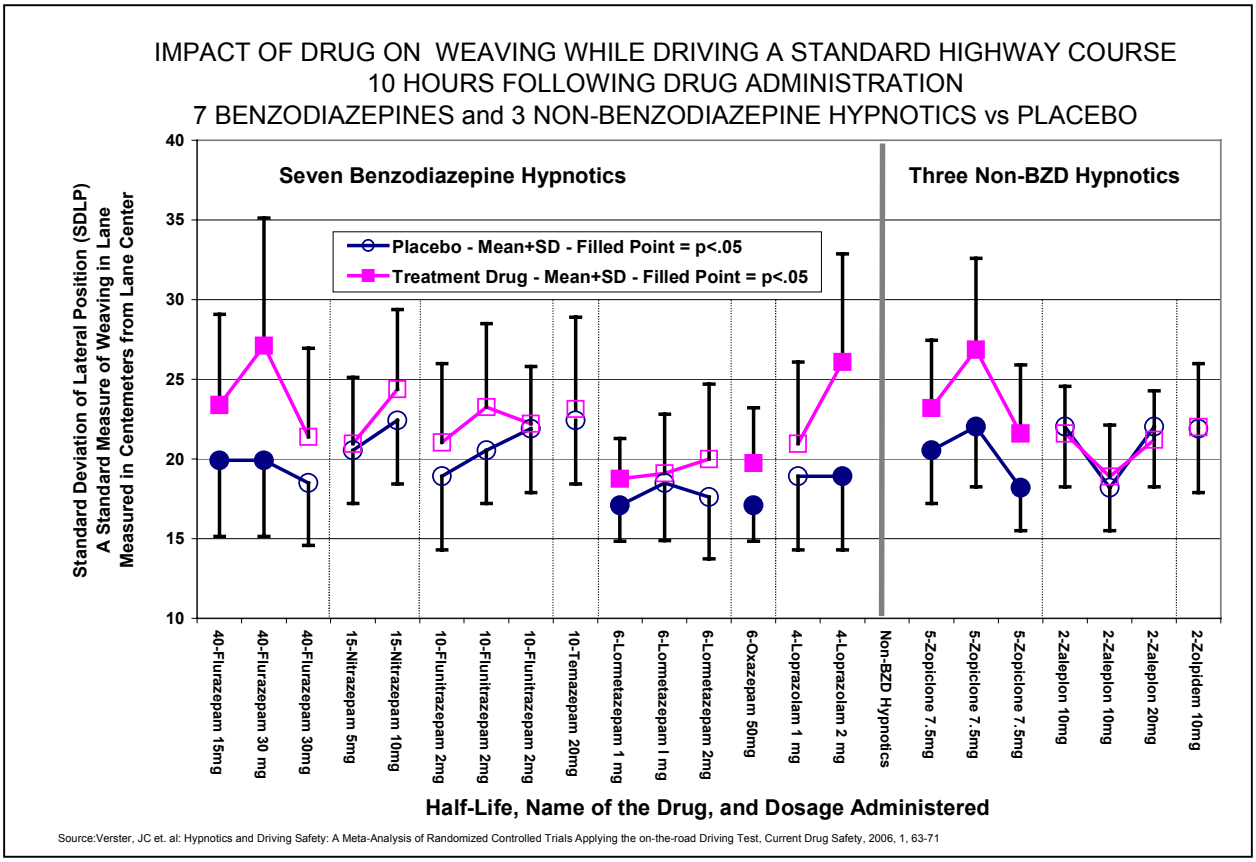
Fig (1). The on-the-road driving test.

"Hypnotic" benzodiazepines (i.e. short-acting, short half-life) are widely prescribed for relief of insomnia. Typically this class of medication is taken to hasten and prolong sleep. The assumption is that the user will be non-impacted by the next day. It is important, therefore, to determine the actual impact of these medicines on driving performance after a period of hours corresponding to a normal sleep cycle. The studies summarized by Verster determined drug impacts 10-11 hours after bedtime administration, 16-17 hours after bedtime administration, and 4- 6 hours after middle-of-the night administration.

Verster's data, reorganized and plotted by J. Morrison, is found in Figure 1-7. The data has been sorted to group the drug trials by half-life of the drug and by dose administered. The non-benzodiazepine hypnotics are separated from the

benzodiazepine treatment drugs. The vertical bars are the Standard Deviations (SD) of the SDLP values, providing a measure of the intra-subject variability in SDLP.

Figure 1-7: Impact of selected benzodiazepine and non-benzodiazepine hypnotics on driving performance in an on-the-road instrumented vehicle. (Verster (2006) Table 2)



Generally, all of the benzodiazepine hypnotics increased SDLP 10 hours following administration, as did one of the three non-benzodiazepine hypnotics. However, the increase in SDLP was not statistically significant for several of the substances tested. SDLP was significantly increased for two of the three trials of the longest half-life BZD (Flurazepam, trade name Dalmane, half-life 40 hours). SDLP was also elevated for several of the trials of the shortest half-life benzodiazepines tested (half-lives 4 to 6 hours). SDLPs were not elevated (elevated non-significantly) for the mid-range benzodiazepines (half-lives 10-15 hours). There was also no increase in SDLP for two of the three trails of non-benzodiazepine hypnotics (half-life 2 hours).

Verster's data is important for several reasons.

1. The data demonstrates that some hypnotic benzodiazepines may be safer than others for next-day driving after use as a sleep aid.

2. Some results are replicable but anomalous, such as the finding that mid-half-life BZDs do not appear to impair driving performance 10 hours after ingestion while long and short half-life BZDs may impair that performance.
3. The class of more recently developed non-benzodiazepine "Z drugs", particularly Zolpidem (Ambien) and Zaleplon (Sonata), may not impair driving performance 10 hours after administration.
4. Meta-analysis studies may not capture data on all drugs of interest. For instance, Verster's data does not include comparative data on Alprazolam (Xanax), currently the most widely prescribed benzodiazepine, or on Triazolam (Halcion), a short half-life benzodiazepine hypnotic that was, ten years ago, the most frequently prescribed sleep medication in the US.

1.3 Formulating the Experimental Question and Protocol

The question to be studied, then, is whether there are short-acting benzodiazepines or non-benzodiazepine hypnotic drugs (i.e sleep aids, sleeping pills) that do not result in decrements in driving behavior after a period equivalent to a normal sleep cycle even if the substance(s) do cause measurable decrements in driving performance shortly after administration. Such drugs might be considered safe for use by shift workers on an infrequent basis to aid in inducing sleep in the evening when pull-out times are in the early morning (e.g. 4 AM). If so, what are the therapeutic doses which assist in the induction of sleep but do not show driving impairments after a sleep cycle.

Accordingly, a set of standards was developed for Project PATH so that it would comply with the highest ethical standards and develop the most sophisticated and extensive data available to describe the driving performance of the operator. That is, the experiment was designed to be able to identify and quantify even subtle performance decrements that might increase the Odds Ratio of an accident, however slightly.

1.3.1 Performance Measures, Risk Mitigation and Project Design Considerations

Project PATH was designed and executed to meet the following exacting experimental design and research safety and ethical standards.

1.3.1.1 Performance Measurements Recorded

- The experiment was designed to capture several aspects of the physical performance of the operator in the cab (e.g. steering wheel excursions, brake pressure and speed of application).
- The experiment captured the gaze patterns and fixations of the operator during times of stressful driving and during times of normal driving.
- The experiment captured the prototypical measures for driving decrements commonly used in many studies in instrumented vehicles, e.g. SDLP, lane-following, curve-following, maintaining a constant distance from a lead car driving at variable speeds.
- The experiment captured the driving performance of the operator in a variety of urban, suburban and rural roadways.

- The experiment exposed the operator to a variety of risk and decision situations and capture the operator's reaction times and responses.

1.3.1.2 Time Course of Measurements

- The study was designed to gather individual baseline, drug-state and post-drug-state measurements. In each experimental session, the driving test was presented to gather operator performance data:
- Before the operator ingested any substances
- At three time periods after ingesting the test substance leading to, and bracketing, the expected peak effects
- And on the next day, after a normal sleep cycle, with no ingestion of a substance.

1.3.1.3 Substance Selection and Protocol

- The experimental substance was a well-researched short-acting benzodiazepine. A non-benzodiazepine hypnotic and a 3rd-generation barbiturate were considered but rejected.
- The half-life of the substance was short and the substance was metabolized with no confounding metabolic bi-products.
- The drug was detectable in small amounts through a non-intrusive, preferably quantitative, saliva drug test methodology. The non-intrusive methodology identify the presence of the substance and provided quantitative levels.
- A corollary procedure wasused to assure and affirm that the participants have not used other substances that would confound the results.
- The substance was tested at several sub-therapeutic and therapeutic levels.
- The experimental substance was administered in double-blind, randomized order, with placebo controls.
- The experimental protocol took into consideration known personal and medicinal contra-indications and carried that knowledge into the human subject protections protocol.

1.3.1.4 Considerations Regarding Protection of Human Participants

- The experiment provided full protection for human participants and was subject to and sanctioned by the Institutional Review Board (IRB) of the performing organization.
- Participating local agencies whose employees or volunteers could be participants were fully briefed on the project goals and human-subject protections.
- The recruitment of participants provided every prospective participant with complete anonymity and privacy during the application process and throughout and following the experiment.
- Each participant signed an Informed Consent Document initially and before each experimental trial. Participants had the right to back out before any trial. Any participant who backed out with sufficient cause (e.g. simulator sickness) during the project would receive the same compensation as participants who complete all trials (to eliminate expected loss of compensation as a reason for staying in against better judgement). Two participants who were eliminated by the research staff during the course of the project, through no fault of their own, received the same compensation

as they would have received if they had completed all experimental trials. Two other participants who were eliminated by the research staff for cause were compensated for all completed trials.

- Each applicant participant was pre-screened as defined in the IRB acceptance. Pre-screening included two short drives in the simulator to check for signs of "simulator sickness".
- Compensation was provided in a timely manner by direct deposit and each participant received a 1099-MISC at tax time.
- A physician knowledgeable in the experimental protocol was available on short notice if any of the participants experienced an objectionable side effect and/or required attention.
- All subjects were driven home under conditions arranged by the experimental team after each experimental session and returned to the experimental location in the same manner the next morning for a non-drug follow-up trial. That drive evaluated next-day performance against base-line performance. If the subject's performance had not returned to baseline, the subject would have been returneded home and returned to the experimental location the next day following for a second baseline trial.
- There was a briefing session for all participants following the completion of data collection. That briefing session reviewed the experiment and discussed observations about driving and the impact of this substance on operator performance.

1.3.2 US and EU Drugged Driving Research Guidelines

Project PATH was conducted in consort with recently published guidelines in the US and Europe for conducting drugs and driving research.

Walsh et al[18] recently conducted a Delphi research program among major research institutions and leaders to develop a set of guidelines to standardize and harmonize research efforts into the behavior, epidemiology and toxicology of drugged driving. Project PATH conducted its research, and developed data in a manner that conformed , with those guidelines.

More recently, in March 2011, the National Highway Traffic Safety Administration (NHTSA) published a set of guidelines for drugged driving research[19]. NHTSA recommends that drug driving research should integrate a Pharmacological-Toxicological Review, an Epidemiological Review, and set of Standardized Behavioral Assessment tools. The behavioral tools would include a psychomotor test battery and driving simulator testing, possibly with over-the-road testing. The design of Project PATH is in full conformance with the recommended protocol.

In Europe, Project DRUID (Driving Under the Influence of Drugs, Alcohol and Medicine) is the name of a major interdisciplinary study. Its object is to determine the effects of pharmacological agents on driving and to set standards for the safe (or excluded) use of

prescription and over-the-counter agents by drivers. As stated on its home page[20], "DRUID will bring together the most experienced organizations and researchers throughout Europe, involving more than 20 European countries. The aim is to gain new insights to the real degree of impairment caused by psychoactive drugs and their actual impact on road safety." Project DRUID has published several very useful documents that establish the common protocols for research sponsored by the governing committee. Among these, the "Theoretical Framework For Substance Effects on Safe Driving"[21] has been helpful to the planning of this research. Project PATH consulted DRUID documents as they become available and considered their applicability to this current project.

1.4 Selection of the Pharmacological Agent

Figure 1-8 is a list of the generic and trade names of common benzodiazepines. Figure 1-9 is a graph of the half-lives of 23 benzodiazepines and three non-benzodiazepines hypnotics commonly available in the U.S. The data for Figure 1-9 is from Table 1 of Ashton (2002)[22] plotted by Morrison and sorted by half-life. Half-life is the time required for the body to metabolize and excrete one-half of the current blood level of the substance and is a measure of speed of elimination. For a longer half-life benzodiazepine, repeated dosing will build up the blood level to a steady-state level. It may then take several days or weeks for blood levels to drop to zero after cessation. However, blood levels of short-half life drugs may reach sub-therapeutic or negligible levels after a few hours.

Therefore, for the treatment of anxiety, repeated dosing with long half-life drugs is used to build up to a steady blood level. Likewise, occasional or infrequent dosing with a short half-life BZD, or non-benzodiazepine hypnotic, is used to promote sleep.

Figure 1-8: Generic and Trade Names of Common Benzodiazepines Anxiolytics and Hypnotics, and Three Non-Benzodiazepine Hypnotics

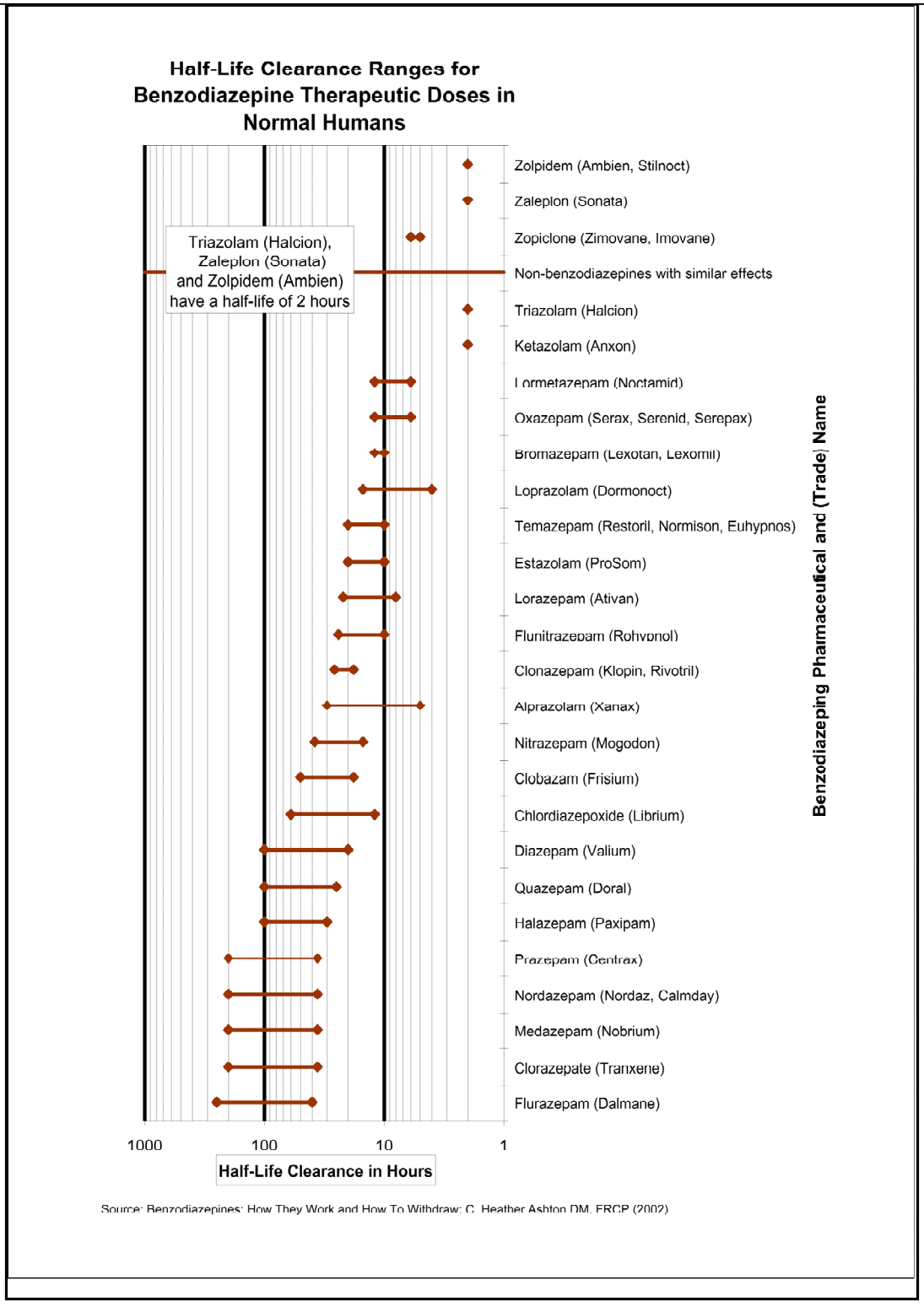
Benzodiazepine & non-BZD Hypnotics - Generic and (Trade) Names

Alprazolam (Xanax)
Bromazepam (Lexotan, Lexomil)
Chlordiazepoxide (Librium)
Clobazam (Frisium)
Clonazepam (Klopin, Rivotril)
Clorazepate (Tranxene)
Diazepam (Valium)
Estazolam (ProSom)
Flunitrazepam (Rohypnol)
Flurazepam (Dalmane)
Halazepam (Paxipam)
Ketazolam (Anxon)
Loprazolam (Dormonoct)
Lorazepam (Ativan)
Lormetazepam (Noctamid)
Medazepam (Nobrium)
Nitrazepam (Mogodon)
Nordazepam (Nordaz, Calmday)
Oxazepam (Serax, Serenid)
Prazepam (Centrax)
Quazepam (Doral)
Temazepam (Restoril, Normison)
Triazolam (Halcion)
Non-BZD Hypnotics
Zaleplon (Sonata)
Zolpidem (Ambien, Stilnoct)
Zopiclone (Zimovane, Imovane)

It is important to understand that all benzodiazepines, whether long or short half-life drugs, operate through approximately the same neurological mechanism and have approximately the same effect. Therefore, the impact of a short-acting BZD measured one-hour after dosage may be a fair model of the impact of a long-acting benzodiazepine 10 hours and more after dosage. However, since the longer half-life BZD may take longer to get into the blood stream, the slower drug may not cause performance decrements shortly after ingestion whereas the quick-acting drug certainly will.

There are two benzodiazepines listed in Figure 1-9 with half-lives of two hours – Triazolam (Halcion) and Ketazolam (Anxon). There are also two new non-benzodiazepine hypnotics with half-lives of two hours listed in Figure 1-9: Zaleplon (Sonata) and Zolpidem (Ambien). Anxon is an infrequently-prescribed drug and no drug profile is available on the National Institute of Health (NIH) website www.dailymed.nlm.nih.gov. (NLM is National Library of Medicine of the National Institute of Health). The remaining benzodiazepine, Triazolam (Halcion) and the two non-benzodiazepine hypnotics were considered as candidates for the challenge drug in this project. Zoleplon (Sonata) and Zolpidem (Ambien) are frequently prescribed sleeping aids and have largely supplanted Triazolam (Halcion) as a sleeping aid. However, during the 1980's, Halcion was the most frequently prescribed Benzodiazepine in the US, is still used and prescribed, and it has a long and continuing role as a research BZD.

Figure 1-9: Half-lives of 23 benzodiazepine anxiolytics and hypnotics, and 3 non-benzodiazepine hypnotics.



1.4.1 Benzodiazepine Impact on Driving Skills

A 1998 summary described the effects of benzodiazepines as follows[23]:

> All benzodiazepines have anxiolytic, sedative-hypnotics, muscle relaxant and anticonvulsant properties, and some possess antidepressant effects. … The general sedative effects of benzodiazepines are assumed to underlay their potential to impair driving skills, for example by decreasing alertness, slowing reaction times, reducing visual function and degrading motor skills and decision-making capacity.
>
> Benzodiazepines are also known to impair memory, both secondary to and independently of their sedative actions. However, in a recent survey, experts assigned relatively low weight to memory functions as being absolutely essential for driving, with the exception of spatial working memory.

The present study was designed to determine whether there are measurable impacts of standard therapeutic doses of Triazolam on driving skills and on the psychophysical functions identified in the above.

1.4.2 Psychomotor Impairment of Halcion and other Candidate Drugs

Studies with Triazolam (Halcion) demonstrate that Triazolam impairs psychomotor functioning in standard laboratory tests and driving performance in real driving experiments. At a typical clinical dosage (0.25 mg), the impairing effect of Triazolam on memory at peak levels is reported[24] to be approximately equal to the impairing effects of alcohol at a concentration in blood of 0.80 g/kg of body mass♦.

Regarding psychomotor tests of reaction time and cognition, Rush et al[25] compared the behavioral and abuse potential of Triazolam (Halcion) and Zaleplon (Sonata). In a separate publication, Rush et al[26] compared the behavioral and abuse potential of Triazolam and Zolpidem (Ambien). The Triazolam – Zaleplon comparison recorded the drug effects for 24 hours, and is somewhat more useful for purposes of this paper than the Triazolam – Zolpidem comparison, which followed the drug effects for five hours. Objective and subjective indicators of the peak effects of the Triazolam-Zolpidem comparisons are shown in Figure 1-10 and Figure 1-11 on the following pages.

The therapeutic doses of Triazolam were .25 mg, and the supra-therapeutic doses were .50 and .75 mg. Peak effects were observed for all three drugs in the 1-hour and 2-hour trials. Subjective ratings of drug effect for the lowest dose of each drug (the recommended therapeutic dose) returned to baseline by four hours, though the

♦ About 4 rapid drinks or a BAC of perhaps .09 if my calculations are correct - JBM.

subjective effects of super-therapeutic doses lasted longer. Similarly, the behavioral impairment measured in the psychomotor tests returned to baseline for the lowest dosage by four hours post administration, and by 12 hours post administration for all dosages. The behavioral impacts of Zaleplon, in the Zaleplon-Triazolam comparison, returned to baseline faster than the behavioral impacts of Triazolam, but otherwise were largely indistinguishable. The authors concluded that all three drugs produce comparable dose-related performance impairment.

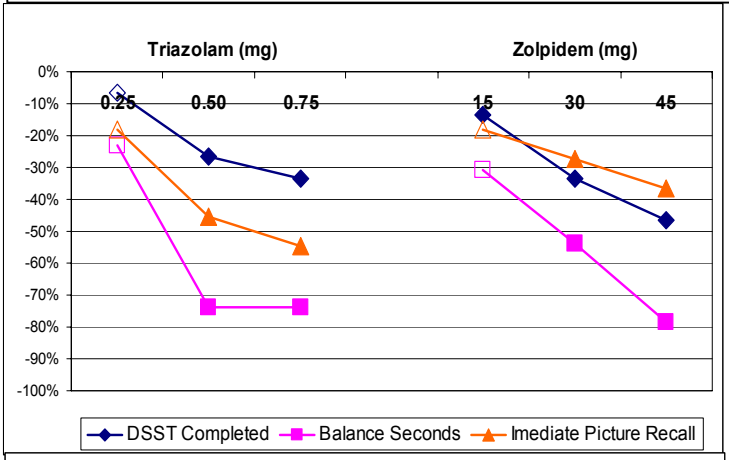
It is useful to note that, with the exception of the test "delayed picture recall" (a test of short term memory), the .25 mg dose of Triazolam did not cause impairment decrements in the psychomotor tests that were significantly different from placebo. That is, drug impacts on three of the four psychomotor tests reported in the two Rush et al articles were not significant for the 0.25 mg dose but were significant for the super-therapeutic doses.

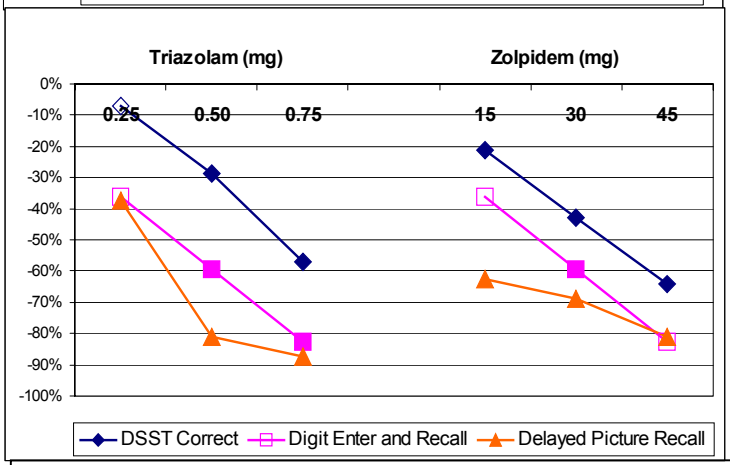
Human participants in both of these studies were volunteers with a history of drug abuse. As with the psychomotor findings, subjective rating scales intended to measure likelihood of drug abuse potential (scores for "Good Effects", "Like to Take Again", and "Willing to Pay on Street") were not significantly elevated above placebo for the lowest (therapeutic) dosage of Triazolam or Zolpidem, but were elevated for the therapeutic dosage of Zaleplon. Both supra-therapeutic doses of Zaleplon and Zolpidem also generated statistically elevated ratings associated with abuse potential, but only the highest dosage of Triazolam generated elevated subjective ratings indicative of abuse potential.

Carter, et al[27] compared the performance affects and abuse liability of Triazolam in comparison to an experimental drug, Indiplon, in human participants with a history of drug abuse. The findings were similar to the drug comparisons of Rush and his coworkers. Psychomotor and cognitive measures returned to baseline for the .25 mg (therapeutic) dose after 4 hours. Likewise, the subjective rating "Liking of Drug Effect" was significantly elevated for Triazolam relative to placebo for the two supra-therapeutic doses, .50 and .75 mg, but not for the .25 mg dose of Triazolam.

These studies indicate that the recommended 0.250 mg therapeutic dose of Triazolam has a behavioral effect between 1 and 2 hours after administration that is not greatly elevated above baseline, that behavioral effects measured by laboratory tests return to baseline after eight hours, and the drug at therapeutic doses has a low potential for abuse. Triazolam, Zolpidem and Zaleplon appear similar across these measures though Zaleplon may be somewhat shorter acting.

Figure 1-10 - Objective and Subjective Indicators of Degree of Impairment Comparing Three Dose Levels Of Triazolam (Halcion) And Zolpidem (Ambien).





	Triazolam			Zolpidem		
	0.25	0.50	0.75	15	30	45
Subject-rated drug-effect-questionnaire						
Bad mood	**0.10**	**0.40**	**0.90**	**0.10**	**0.50**	**0.30**
Willing to pay for	0.30	0.80	1.30	0.40	1.20	0.80
Concentration impaired	0.30	0.70	1.20	0.30	1.00	0.90
Like drug	0.20	0.90	1.10	0.40	1.30	1.20
Willing to take again	0.30	0.90	1.20	0.70	1.20	1.30
Happy	0.20	0.70	1.00	0.40	1.00	1.10
Mentally sharp	0.10	0.40	1.20	0.40	0.60	0.70
Strong	0.60	1.40	1.50	1.00	1.60	1.90
Performance impaired	0.30	0.60	1.20	0.30	1.00	1.20
Carefree	0.20	0.80	0.80	0.30	0.80	1.00
Bad effects	**0.10**	**0.20**	**0.30**	**0.10**	**0.60**	**0.80**
Elated	0.10	0.30	0.80	0.10	0.60	0.80
High	0.40	0.90	1.40	0.40	0.90	1.30
Friendly	0.50	1.00	0.90	0.30	0.80	1.20
Good effects	0.40	0.80	1.20	0.30	0.90	1.50
Talking about me	**0.00**	**0.40**	**0.50**	**0.10**	**0.60**	**1.10**
Mentally slow	0.20	0.80	0.90	0.20	0.40	1.10
Observer-rated drug-effects questionnaire						
Drunk	0.10	0.70	0.50	0.20	0.50	0.50
Tired	**0.90**	**1.50**	**2.20**	**0.60**	**1.30**	**1.30**
Carefree	2.20	2.60	2.50	0.20	2.30	2.40
Drowsy	0.90	2.10	2.90	0.80	1.90	2.00
Sleepy	**1.10**	**2.10**	**2.70**	**0.70**	**1.70**	**1.80**
Alert	1.90	2.00	1.80	0.10	1.80	2.00
Drug effect	1.00	2.20	2.90	1.00	2.00	2.30
Like drug	0.60	1.20	1.20	0.20	1.20	1.60
High	0.40	1.60	2.10	0.70	1.40	2.10
Speech slurred	0.10	0.30	0.60	0.10	0.20	0.80
Nervous	0.00	0.10	0.00	0.00	0.10	0.50
Bad mood	**0.00**	**0.20**	**0.00**	**0.30**	**0.10**	**0.90**
Talkative	**0.00**	**0.20**	**0.00**	**0.30**	**0.10**	**0.90**

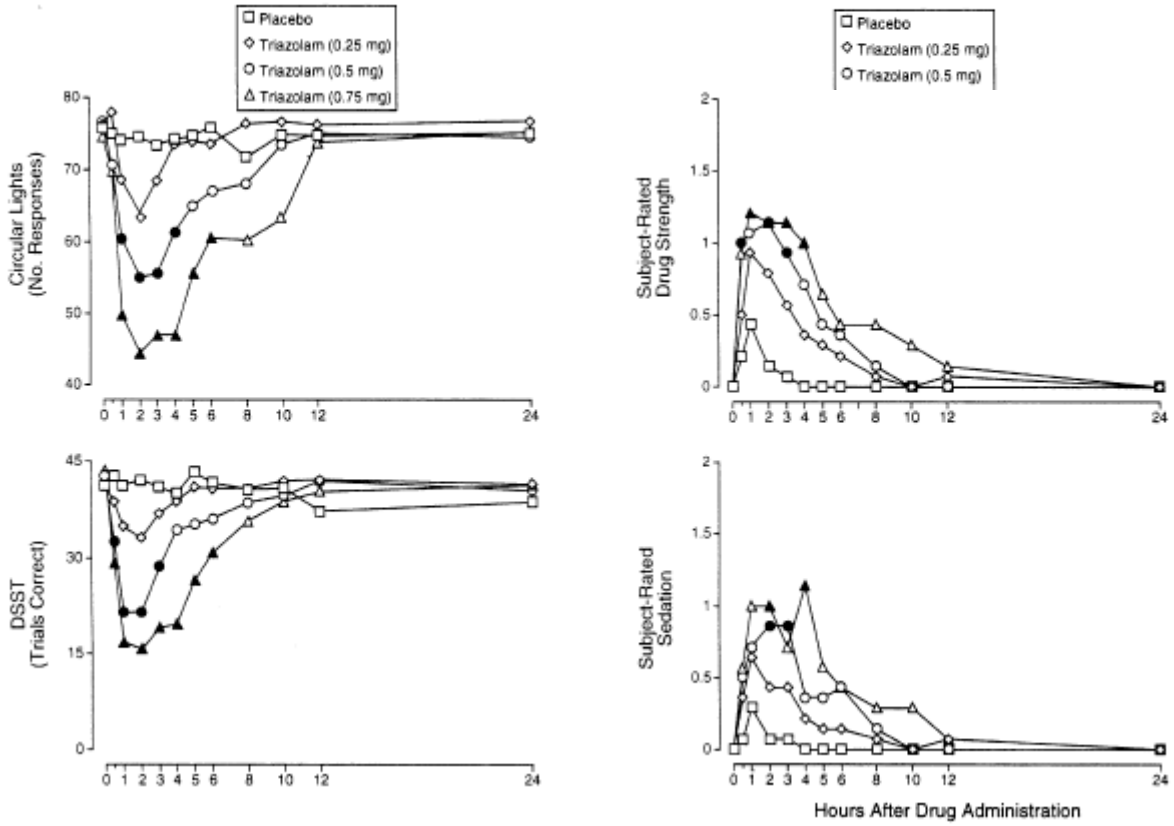
In Figure 8, the data has been regraphed to allow a comparison of Triazolam and zolpidem psychomotor impairment and to show the subjective ratings of participant and observers of the peak effects of the three doses. Data in the left-hand graph has been recalculated to show percent impairment relative to placebo scores, with placebo arbitrarily set to zero. Data on the right-hand table has been sorted from smallest percent change to largest percent change for zolpidem.

Note that, although impairments were observed at all dose levels, psychomotor performance was not statistically different that placebo scores for the lowest (therapeutic) doses of Triazolam for most of the objective measures.

Rush, CR, Baker, RW and Wright, K: Acute behavioral effects and abuse potential of trazadone, zolpidem and Triazolam in humans; Pyschopharmacology, 144:220-233 (1999)

Figure 1-11, on the following page, is a screen-grab of the 24-hour time course for the behavioral recovery of objective and subjective measures of impairment following three dose levels of Triazolam and Zaleplon from Rush et al[24].

Figure 1-11 – Objective and Subjective (Participant) Measures of Impairment for Three Dose Levels of Triazolam in Experienced-Drug-using Subjects



Rush, CR, Frey, JM, Griffiths, RR, Zaleplon and triazolam in humans: acute behavioral effects and abuse liability: Psychopharmacology, 145; 39-51 (1999)

In the graphs from the Rush et al studies, a filled symbol indicates a finding that is significantly different from placebo while an open symbol indicates data that is not significantly different from placebo. It is worth noting that, in the Rush et al studies, the psychomotor measurements for the Triazolam does of 0.25, while showing impairment, were not significantly different from placebo three of their four tests.

In Figure 1-11, for the 0.25 mg therapeutic dose, the psychomotor measures “Circular Lights” and “DSST” return to baseline after 4 hours, but at that time period, participants are still recording elevated measures for “Drug Strength” and “Sedation”. Those subjective measures return to baseline by 8 hours post administration.

In contrast, it can be seen that the two objective psychophysical measures of impairment are still elevated for Triazolam doses of 0.5 mg and Triazolam 0.75 mg at 8 hours, especially so for the tracking test “Circular Lights”. However, the subjective measures “Drug Strength” and “Sedation” have largely returned to baseline for the 0.5 mg Triazolam dose.

These studies may indicate that there may be a reversal of objective and subjective measures of impairment for supra-therapeutic doses of Triazolam. Persons taking a therapeutic dose may believe themselves to be more impaired than they actually are 8 hours following administration. Logically, those persons would attempt to compensate by more-careful maneuvering. Individuals taking a supra-therapeutic dose, on the other hand, may be more debilitated than they think they are 8 hours after administration and may fail to compensate for their impairment through more careful maneuvering.

1.5 Driving Studies Using Triazolam

Only two driving studies in which Triazolam was one of the test drugs were found in a comprehensive search of the literature .One is a real-driving study and one is an early driving simulator study. There also appears to be a third research paper, in German, which has not been obtained.

1.5.1 A Real Driving Experiment

In an exemplary 1988 real-driving driving study, Riedel et al[28] studied Midazolam, Triazolam and Temezepam taken by rotating shift workers to counteract insomnia when rotating from day-shift to night-shift. Their primary question was “If rotating shift workers suffering from insomnia after night shift are treated with hypnotics, what are the consequences in terms of sleep, residual performance effects and subjective feelings?” Their measures were onset and quality of sleep, subjective feelings on awakening and at 4, 8 and 12 hours post-awakening, and a comprehensive set of instrumented-vehicle real-driving city and country measures, including eye-tracking. Dose levels were Triazolam (Halcion) 0.5 mg (the then-excepted therapeutic dose), Midazolam (Versed), and Temezepam (Restoil). Midazolam is a very-short-life benzodiazepine not regularly prescribed but apparently used primarily in dentistry to calm very nervous patients – note that it is not mentioned in either Figure 1-8 or Figure 1-9 of this paper. Triazolam appears to have replaced Midazolam as the treatment of choice for this purpose in dentistry.

The authors, even in 1988, recognized that the 0.5 mg dose of Triazolam was, in their words, a “relatively high” dose and commented that a dose of 0.25 mg might have produced better driving and sleep performance.

Fourteen (14) rotating shift workers (12 men and 2 women) participated in and completed the study and were given 5-night regimens of each of the hypnotic drugs and placebo. It does not appear from the text that the order of drug administration was randomized, a possible weakness of an otherwise exemplary study. On the first and fifth night, the participants slept in the laboratory and, on awakening, drove a standard 9.3 km city driving course followed by a standard 10 km highway driving course.

To measure sleep latency and restlessness, the participants wore wristwatches that measured movement. Sleep induction was considered to have happened when the

watches recorded two consecutive 5-minute periods of no movement. Restlessness was calculated as the number of 5-minute periods with significant movement. Participants recorded periods of wakefulness, which was correlated to the data from the wristwatches when downloaded to the computers.

To measure driving impairment, the vehicle was instrumented to measure Standard Deviation of Lateral Position (SDLP), speed changes, brake pressure and similar metrics. In addition, participants wore eye-tracking equipment to record gaze direction, primarily at intersections.

On analysis, participants during the Triazolam 5-day trials were significantly impaired on next-day driving as compared to their placebo 5-day trials, and also in comparison to their 5-day Midazolam and Temezepam trials. During Triazolam-sessions, the eye-tracking equipment recorded that drivers made significantly more failures ($P<.01$) to scan side-streets for turning traffic than drivers during their Midazolam and Temezepam trials. Experts driving in the rear seat of the instrumented vehicles scored the Triazolam drivers with 15% more driving errors relative to placebo than the same drivers under Midazolam or Temezepam.

Drivers under Triazolam recorded a Standard Deviation of Lateral Position (SDLP) equivalent to drivers with a blood alcohol concentration of about 0.12 mg/ml driving the same route in a similarly instrumented vehicle. The same drivers under Midazolam produced a SDLP equivalent to drivers with a BAC of about 0.01 and when driving under Temezepam, produced a SDLP equivalent to drivers with a BAC of about 0.03.

Triazolam improved sleep relative to placebo only on the first day after rotating to the night shift, which was the first night of sleeping in the laboratory. It did not extend sleep on the 2nd, 3rd or 4th day-time sleeps (at home), or the 5th day-time sleep in the laboratory. Moreover, workers reported themselves to be groggy after Triazolam induced sleep (.50 mg), where as subjects during the Midazolam and Temezepam trials did not report grogginess on awakening. Midazolam improved sleep quality and duration overall.

The authors strongly recommended that Triazolam at .50 mg should not be prescribed as a sleep-aid for workers experiencing insomnia in attempting day-time sleep after rotating to a night shift, especially if driving will be required on awakening. Midazolam was recommended for that population and the authors were neutral on Temezepam.

The authors also reported two adverse reactions to Triazolam, each of which caused the participant to withdraw from the study before completion. Their data is not included in the data from the 14 participants who did complete the study. One 25 year old male participant became extremely somnolent and was hard to awaken. He could not keep his eyes open and the experimenter was not able to calibrate the eye-tracking device so the drive was aborted. The subject was driven home, slept and was able to work a regular shift that night. On further examination, the subject admitted “that his liver functions were not completely normal and that “they were being monitored by an

internal medicine specialist." One 23 year old female participant left the study complaining of severe headaches after her third day of Triazolam treatment. The headaches disappeared after stopping Triazolam. Additionally, five participants were so incapacitated that they failed to complete their city and/or highway test drives, either on day 1 or on day 5. Of the 11 incomplete drives, 7 were for drivers taking Triazolam, 1 driver taking Temezepam, 1 driver taking Midazolam, and 2 drivers taking the placebo.

1.5.2 A Simulated Driving Experiment

In a simulated driving study, Laurell and Tornros[29] tested drivers at 8 AM on the first and third night after taking either 0.25 mg Triazolam, 5 mg Nitrazepam or placebo at 11 PM the previous night.

Their test consisted of a monotonous 2.5 hour (sic) drive in an early medium-fidelity driving simulator followed by driving through an obstacle course of cones in a large parking lot. There was no significant impairment by either drug vs placebo on the driving course through cones on the day one and day three experimental trials. In the simulated driving test, there was a slight but significant decrement of reaction time in the participants taking Nitrazepam vs placebo on the day 1 trials but not in the participants taking Triazolam vs. placebo. There was no difference on the day three trials for either drug against placebo.

It is difficult to draw conclusions from these experiments because they are very different and because there is such a limited literature on Triazolam and driving. It may be that a dose of 0.50 mg dose of Triazolam causes significant driving impairment 8 to 12 hours after administration but that a .25 mg dose does not. Alternatively, it may be that Laurell and Tornros' measuring tools were not able to detect any actual driving decrements from the morning after the 0.25 mg dose. The current research will help to resolve that issue.

Finally, a 2004 literature review, "Residual Effects of Hypnotics: Epidemiology and Clinical Implications"[30], cited a meta-study (unfortunately in German and not available) that reported effects on driving performance of Triazolam at 0.25 mg and 0.5 g doses at 8 to12, 15 and 18 hours post-administration.

1.6 Triazolam (Halcion) Efficacy, Safety And Contra-Indications

As noted earlier, the intent of Project PATH is to examine the impact of Triazolam in doses of 0.000 mg (placebo), 0.125 and 0.250 mg on the performance of CDL-holding public bus operators driving in a high-fidelity bus simulator using a random, cross-over, double-blind protocol. Experimental trials were conducted just before administration of the substance, and at 40, 80 and 120 minutes post administration, with a repeat drive the next morning (12-14 hours post-administration) to determine if there are residual effects at these doses.

The participants in this study were currently-employed public transportation bus operators. As such, it was essential that the prescription medicine be safe in the doses

used and prescribed and effective in its intended use as a sleep aid. The intended benefit of the research was to develop a simulated driving model to test whether Triazolam, if taken as directed, would assist a driver on a swing-shift to rapidly fall asleep, have a restful sleep, and be ready to return to work 8-10 hours later.

1.6.1 The Institute of Medicine (IOM) Report

Most of the discussion to follow on safety and efficacy is from Halcion:An Independent Assessment of Safety and Efficacy Data[31], Division of Health Sciences, Institute of Medicine (IOM), The National Academies of Science (1997). For convenience, that report will be referred to as the IOM report. Particularly see pages 12 and 13 of the IOM report for more information on the history of safety and efficacy concerns regarding Triazolam.

In the late 1970s and early 1980s, Triazolam (Halcion) was the first of a new class of short-half-life benzodiazepines to be approved for general use. The IOM report states that it was first approved in 1977 in the Netherlands at a dose of 1.0 mg. In 1979, a Dutch psychiatrist published a report detailing Halcion adverse reactions, including depression, amnesia, hallucinations, and anxiety. The Netherlands regulatory body suspended Halcion from the market and sought to negotiate with Upjohn, the manufacturer, on labeling issues and dosages. Upjohn withdrew Halcion from the Dutch market in 1980. The Committee on Proprietary Medicinal Products of the European Union published two position papers in 1991 warning that Halcion should be used at a dosage of 0.25 mg (rather than the originally approved dosage of 1.0 mg) and only for short periods, not to exceed 10 days.

The United Kingdom revoked Upjohn's license in the UK in 1993. Following this revocation, there was a lively exchange of letters supporting and criticizing this decision in the British Medical Journal[32], and elsewhere[33]. The issue seemed to turn on the fact that most of the adverse reactions were associated with long-term use of the drug. Its labeling recommended its use only in acute situations but physicians were prescribing it for extended use.

Halcion was approved by the FDA in 1982 and it quickly became the most frequently prescribed drug in America. The FDA followed Halcion in post-marketing through the Spontaneous Reporting System (SRS), the system FDA uses to record and track adverse events reported by physicians and patients. The frequency of adverse reports in the SRS and a petition by Public Citizen, and consumer advocacy group, resulted a decision by the FDA to review the original studies reported by Upjohn in the New Drug Application (NDA), the SRS reports, and the literature published since Triazolam's approval in 1982.

In 1994, the FDA formed the IOM task force to investigate these scientific questions and regulatory concerns. The task force reported that Halcion was "safe when prescribed according to the current labeling" and "effective in the treatment of insomnia at doses

and durations currently recommended in the labeling" (IOM, p 14, quoting the 1996 FDA report). In addition, the FDA also recommended that "there should be a separate reassessment of the safety and efficacy of Halcion conducted by a panel of independent experts" (IOM, p 15).

The Institute of Medicine undertook an extensive review of the data from the Upjohn pre-clinical trials, and Upjohn sponsored two new, post-clinical trials to provide fresh data. IOM also reviewed the extensive Halcion literature and the SRS reports. Finally, IOM required Upjohn to provide the original raw data from its pre-clinical trials and IOM statisticians and clinicians conducted a new analysis of that subject matter.

1.6.2 IOM Determination of Halcion Safety

The main conclusion that emerged from the IOM review of the pre-clinical data was that reports of adverse reactions including anxiety, confusion, depression, psychosis, impaired concentration, insomnia, irritability, mood change, psychiatric miscellaneous, and unusual dreams, were primarily associated with the length of the study rather than the dose of Triazolam. In Figure 1-12, it can be seen that the risk ratio for adverse psychological reactions were not different for Triazolam in low and high doses compared to placebo for studies lasting one or two weeks regardless of dose given. Additionally, the risk ratios for low dose (0.25 mg) of Triazolam against placebo were equivalent for longer as well as for shorter studies.

Figure 1-12: Adverse Reactions and Subject Dropout Ratios from 25 Pre-Clinical Trials Comparing Triazolam to Placebo and to Flurazepam

Source:IOM Report Table 3-8 p 65:
FDA Analysis of Dropouts in the 25 Studies for the 1992 FDA Advisory Committee Meeting

	No. of Subjects with Adverse Event/Total of Subjects (%)			Risk Ratios for Dropouts	
Subject Group	Triazolam	Flurazepam	Placebo	Triazolam/ Placebo	Triazolam /Flurazepam
All Subjects	145/1,168	58/607	39/566	1.8	1.3
% Adverse Rx	12.40%	9.60%	6.90%	p<.05	p<.05
	Sorted by Duration of Study				
Short Term (1-2 weeks)	56/735	21/316	30/430	1.1	1.2
	7.60%	6.60%	7.00%	ns	ns
Long Term (3 to 6 weeks)	89/433	37/291	9/136	3.1	1.6
	20.60%	12.70%	6.60%	p<.05	p<.05
	Sorted by Dose				
Low Dose (<=.25 mg)	19/272	3/71	39/566	1	1.7
	7.00%	4.20%	6.90%	ns	ns
High Dose (>.25 mg)	126/896	55/536	39/566	2	1.4
	14.10%	10.30%	6.90%	p<.05	p<.05

Figure 1-13, presents the data from Table 3-10 of the IOM report. It can be seen that all of the studies of 1 or 2 weeks, regardless of dose, had adverse reaction reports of 8% or less, equivalent to the reports from placebo trials. All except one of the studies longer than 2 weeks had adverse reaction reports from more than 10% of participants, a rate statistically higher than placebo studies.

Figure 1-13: Adverse Event Reports Table and Graph Indicating that Length of Study Accounts for the Percentage of Adverse Reaction Reports, Rather Than Dose of Halcion

Table 3-10 Adverse Event Frequencies for Halcion-Treated Groups in 25 Parallel-Group Studies

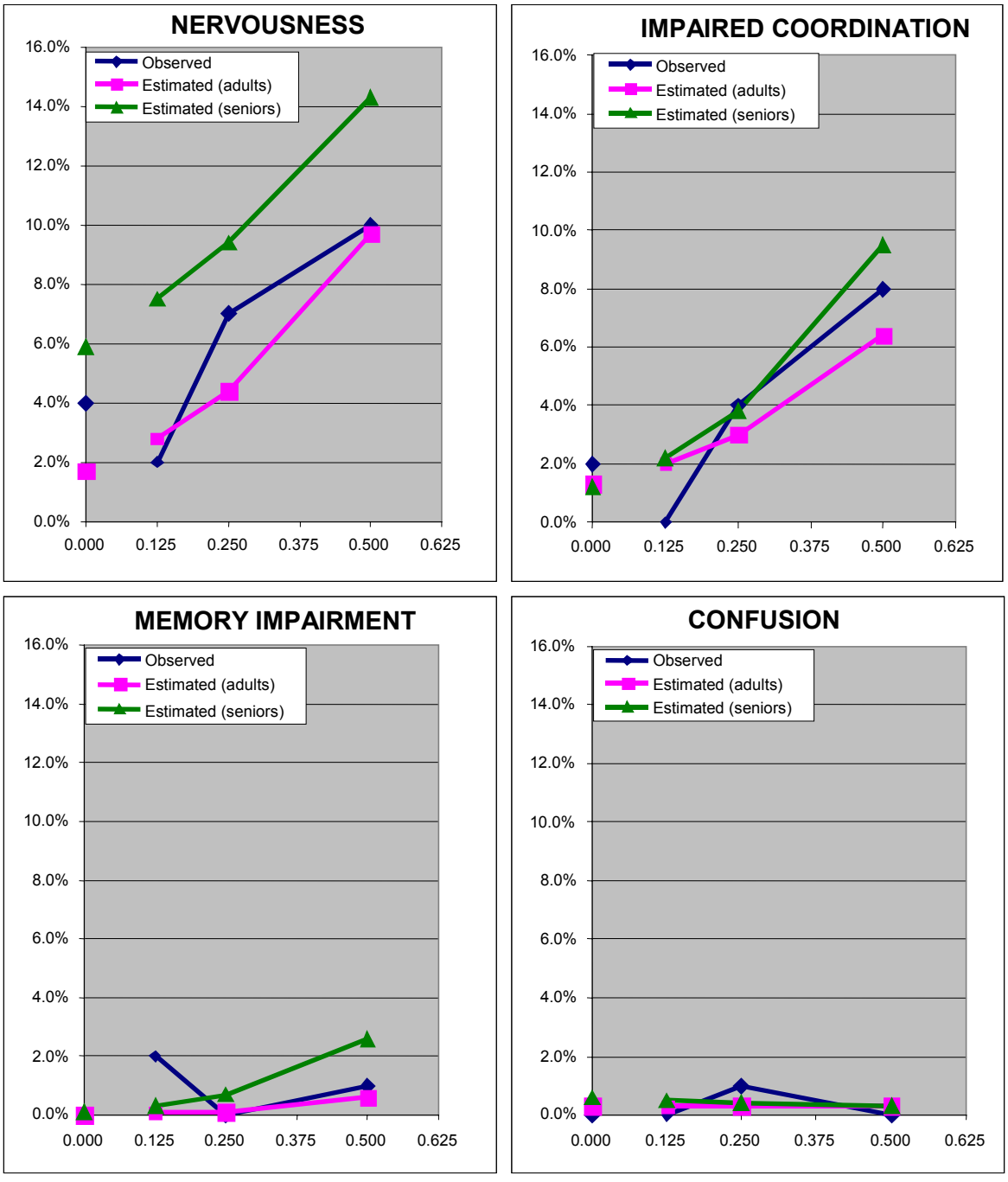
Protocol	Geriatric Subjects	Weeks	Dose(mg)	Sample Size	Anxiety	Pct Anxiety	Depression	Memory Impairment	All Psychiatric	Pct All Psychiatric
6401	No	1	0.25	35	1	2.9%	0	0	2	5.7%
2401	No	1	0.375	66	3	4.5%	0	0	4	6.1%
6400	No	1	0.375	53	4	7.5%	0	0	6	11.3%
6041	No	1	0.5	70	3	4.3%	1	0	4	5.7%
6042	No	1	0.6	62	3	4.8%	0	1	5	8.1%
6004	No	1	0.5	16	1	6.3%	0	1	4	25.0%
6043	No	2	0.5	138	11	8.0%	3	0	15	10.9%
6016	No	2	0.5	14	1	7.1%	0	0	1	7.1%
6044	No	2	0.5	112	8	7.1%	3	0	11	9.8%
6042	No	4	0.25	54	11	20.4%	2	0	14	25.9%
6045	No	4	0.5	31	5	16.1%	0	0	9	29.0%
6046	No	4	0.5	55	6	10.9%	1	0	7	12.7%
6047	No	6	0.5	59	9	15.3%	0	1	9	15.3%
6048	No	6	0.5	72	3	4.2%	3	1	7	9.7%
6023B	No	12	0.5	9	1	11.1%	0	1	1	11.1%
6023	No	12	0.6	33	3	9.1%	1	5	7	21.2%
6049	No	13	0.5	74	10	13.5%	5	5	17	23.0%
6417	Yes	1	0.125	46	1	2.2%	0	0	1	2.2%
6417A	Yes	1	0.175	18	0	0.0%	0	0	0	0.0%
6061	Yes	1	0.025	31	0	0.0%	0	0	0	0.0%
6062	Yes	1	0.25	36	0	0.0%	0	0	0	0.0%
6063	Yes	2	0.25	18	1	5.6%	1	0	2	11.1%
6064	Yes	2	0.25	20	2	10.0%	2	0	3	15.0%
6065	Yes	4	0.25	14	2	14.3%	0	0	2	14.3%
2601	Yes	4	0.375	32	10	31.3%	3	1	15	46.9%

Halcion: An Independent Assessment of Safety and Efficacy, Institute of Medicine, National Acadamy of Sciences (1997), p68

Project PATH is designed with requirement of a minimum of one week between Triazolam doses and no dose higher than 0.25 mg. The IOM data and conclusions indicate that the protocol is anticipated to be safe.

In a 1999 paper, Gibbons et al[34], the statistician on the IOM committee, discussed the original statistical procedures used by the committee to reanalyze the original pre-clinical data. The IOM committee developed a novel method for estimating the impact of Triazolam on non-geriatric and geriatric users on psychological and psychophysical performance. Gibbons concluded that the IOM data indicated that, for regimens of 2 weeks or less, reports of nervousness and impaired coordination were relatively common and dose-dependent, whereas reports of memory impairment and confusion were rare and not dose-dependent. Gibbon's data is graphed in Figure 1-14.

Figure 1-14: TRIAZOLAM:Observed and Estimated Percentage of Users Experiencing This Adverse Event in 2-Week Trials, Placebo Control Group Plotted at 0.0 Dose, Averages from 25 Clinical Trials

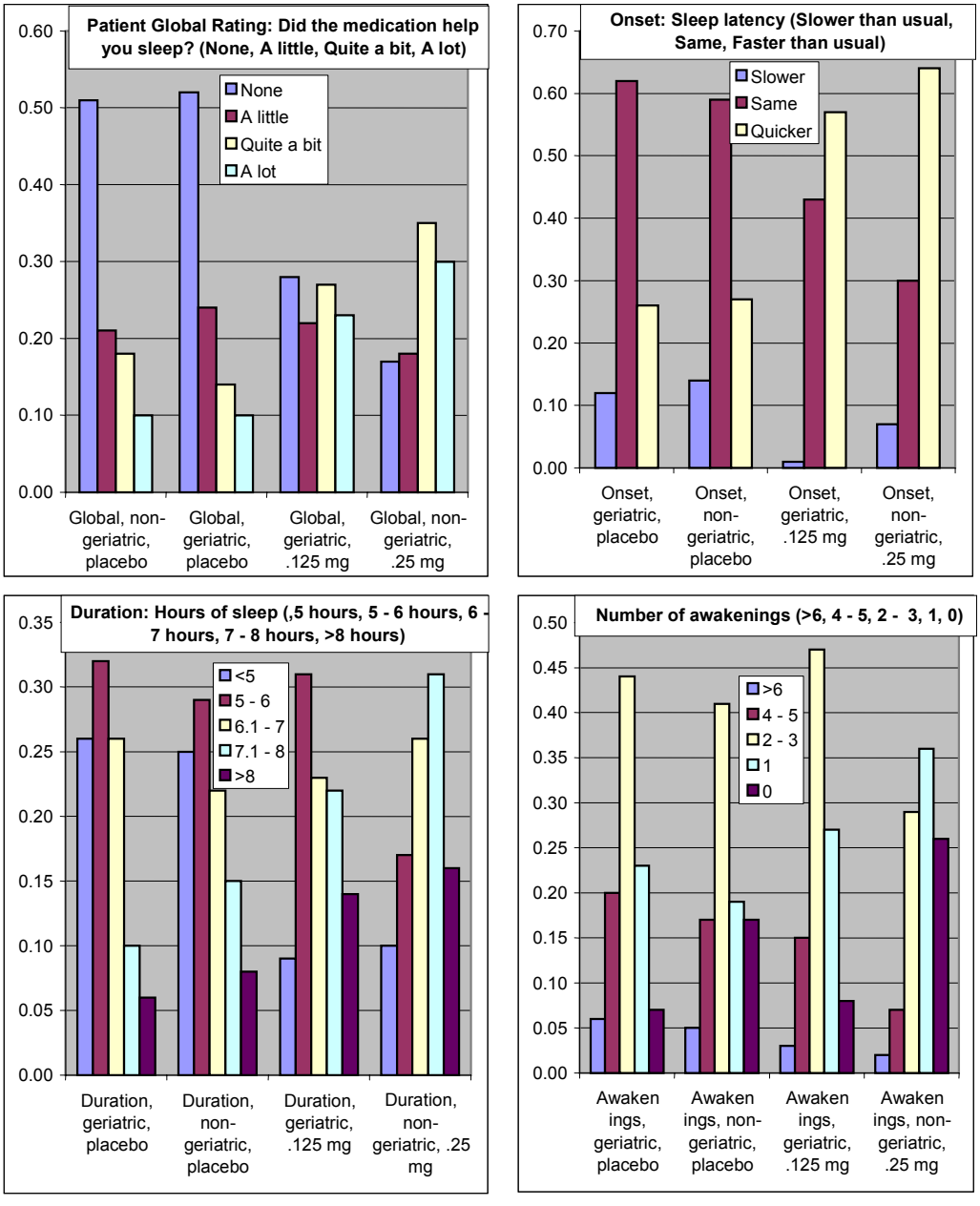


Gibbons et al: Assessing Drug Safety and Efficacy Data, Journal of the American Statistical Association, , Dec 1999 v94 i448 p9931999

1.6.3 IOM Conclusions on the Efficacy of Halcion as a Short-Acting Sleep Aid

The IOM committee also reviewed the efficacy of Triazolam as a sleep inducer and sleep maintainer. The committee concluded that, used as directed for periods of 2 weeks or less, Triazolam assisted subjects to go to sleep more rapidly, to reduce the number of nocturnal awakenings, and to increase the percentage of participants who slept 8 hours or longer. Figure 1-15 presents this data.

Figure 1-15: TRIAZOLAM: Efficacy for Inducing and Maintaining Sleep in Non-Geriatric and Geriatric Participants, Placebo and Therapeutic Dose, Averages from 25 Clinical Trials



Gibbons et al: Assessing Drug Safety and Efficacy Data, Journal of the American Statistical Association, 1999

1.6.4 Summary

Triazolam at the therapeutic dose levels of 0.125 and 0.50 mg was selected for the experimental drug in Project PATH because of its short half-life, its therapeutic use as short-term sleeping aid, and its low frequency of adverse reactions. Importantly, Traizolam has been the subject of a large number of psychometric studies to evaluate its impact on healthy subjects using psychomotor tests, and there is some literature on its impact on driver performance. The Project PATH research team recognized that most of the psychometric tests produced non-significant impairment at the recommended therapeutic doses of 0.125 and 0.250 mg, the dose levels chosen for the current study.

2 EXPERIMENTAL DESIGN

The following are the primary experimental questions for determination by Project PATH:

1. To determine whether Triazolam, a prototypical short-acting benzodiazepine, taken in therapeutic doses, impairs driving performance in a modern, high-fidelity bus driving simulator and in a battery of psychomotor tests taken in conjunction with the simulator drives.
2. To determine the types of impairments, time course and dose-dependency of such impairments, if found.
3. To determine whether impairments persist on next-day return-drives in the simulator and in the psychomotor test battery after a period of sleep.
4. The larger goal of Project PATH is to develop a protocol that can be standardized for the evaluation of the impact on same-day and next-day driving performance of therapeutic doses of prescription and over-the-counter medications. The protocol shall use commercial off-the-shelf technology (COTS technology) and integrate existent research with psychomotor and simulated driving challenges selected for their discriminatory power. The protocol shall give full consideration to the intervening variables that interact with drug effects and influence performance outcomes.

2.1 Experimental resources

2.1.1 Roles and Location of the Project and Project Team

The experimental team consists of professionals at three locations with differing responsibilities for the conduct of the experiment.

- The project was sponsored by the Federal Transit Administration (FTA) and project reports and the Final Reports were provided to the FTA as project documents.

- The team in Boston, at Cahill Swift, LLC was responsible for the development of the detailed experimental protocol, for programming the draft driving scenarios, for preparing the Institutional Research Board (IRB) submission, for overall program direction, and for the analysis of the psychomotor test battery results and for analysis and interpretation of the findings from the eye tracking software and hardware. The Boston team was also responsible for the interpretation of the project results and for subsequent use of those results for the preparation of training materials for transit personnel and for the preparation of policy and/or regulatory outcomes.

- The team at the University of Iowa received the Detailed Experimental Protocol, the Final Draft IRB submission (including the Informed Consent document), and final draft driving scenarios. The team at the University of Iowa was responsible for the

final preparation, submission and management of the IRB documents, for the final development of the 12 driving scenarios for the simulator, for participant recruitment, briefing, medical fitness determination and screening, for schedule management of the project and participants, and follow-up, for simulator and scenario operations and for data recording, data cleaning and organizing.

- The team at the University of Washington, working with the detailed driver performance files after they were cleaned and organized by the University of Iowa team, was responsible for the analysis of driver performance under drug and no-drug conditions and for interpretation of the results in light of the primary experimental questions.

2.1.2 Identity of The Experimental Team

Gerald Powers, Federal Transit Administration Drug and Alcohol Program Manager. Mr. Powers, as FTA Substance Abuse Management point person, maintained an active leadership interest and participation throughout the project. Mr. Powers was responsible for project finances, for liaison to other federal agencies with an interest in project outcomes, and for directing and evaluating regulatory and policy implications.

John B. Morrison, MS, Principal Investigator is the Senior Partner of Cahill Swift, LLC, a Boston-based consulting firm focusing on transportation safety & security auditing, research, and planning. As senior partner and senior auditor, Mr. Morrison has been involved with the FTA drug and alcohol audit program since its inception in 1997 and is a policy advisor to the USDOT. Mr. Morrison holds a Master's Degree with a concentration in Psychopharmacology from the University of Michigan and has an extensive background in transit operations and research. Mr. Morrison is a service-disabled veteran and Cahill Swift, LLC is a Service-Disabled Veteran-Owned Small Business Enterprise (SDVO SBE). Project PATH was conceived, researched and developed by Mr. Morrison. The experimental design was proposed to, and funded by, the Federal Transit Administration (FTA), Mr. Gerald Powers, FTA Drug and Alcohol Program Manager, as an Unsolicited Proposal. Mr. Morrison was the Project Manager and Principal Investigator for Cahill Swift, LLC.

Daniel V. McGehee, Ph. D, Principal Investigator, is the Principal Investigator responsible for PATH experimental operations at the University of Iowa. Dr. McGehee is the Director, Human Factors and Vehicle Safety Research Division, University of Iowa, Public Policy Center. Dr. McGehee managed and assisted with all dimensions of the project, especially organizational and methodological matters and the Human Subjects Protections and Informed Consent aspects. Mr. McGehee is the consortium manager of the Teen Driving Research program at the University of Iowa and has published in the area of crash avoidance warning research.

Linda Ng Boyle, Ph.D., Principal Investigator is a Principal Investigator responsible for PATH Data Analysis at the University of Washington. Dr. Boyle is an Associate Professor, Industrial and Systems Engineering, University of Washington. Prior to

joining the University of Washington, Dr. Boyle was the Director of the Human Factors and Statistical Modeling Laboratory at the University of Iowa. Prior to joining the University of Iowa in 2002, Dr. Boyle was the Senior Researcher, Office of Safety and Security, USDOT-Volpe Center, Cambridge Ma. Dr. Boyle conducts research to model driving behavior, quantify crash risks, examine user acceptance of new technologies and examine commercial vehicle operations and transportation safety.

Michele L. Reyas, M.S.E., was responsible for on-site project management and integration, for final protocol development and simulator programming, and for data reduction and cleaning.

Matthew Rizzo M.D., Researcher assisted with the vision and perception aspects of the experimental design, with development of driving simulator scenarios, and with the medical supervision of the human subjects. Dr. Rizzo is a Professor in the Department of Neurology in the University of Iowa Carver College of Medicine.

Gary Milavetz, D. Pharm., Researcher, was responsible for developing and examining the pharmokenetics of the project, for overseeing the preparation of blinded active and placebo drug doses, and for developing pharmacological monitoring procedures for human subjects involved in this project. Dr. Milavetz and his associate also develop a plasma assay for Triazolam. Gary Milavetz, Doctor of Pharmacy, is the Associate Professor of Pharmacy, College of Pharmacy, University of Iowa, Iowa City, Iowa.

Omar Ahmad, Senior Team Leader at the National Advanced Driving Simulator (NADS), Iowa City, IA. Mr. Ahmad was the coordinator of the extensive team of professionals at the NADS who are responsible for research operations.

David Ross, Simulator and Training Supervisor, Paducah Area Transit System, Paducah, KY. Mr. Ross participated as the simulator operator and lead simulator technician. Mr. Ross accompanied the simulator to Iowa City and participated as full-time on-site professional staff for the two-month duration of the project.

Mr. Christopher Diets, Graduate Student, Industrial and Systems Engineering, University of Washington. Under the direction of Dr. Linda Boyle, Mr. Diets was responsible for much of the data analysis.

2.1.3 The primary resources engaged in Project PATH are the following

1. A modern, high-fidelity bus driving simulator build by FAAC, Inc. of Ann Arbor Michigan, owned by the Paducah Area Transit System (PATS) and leased to Cahill Swift, LLC for Project PATH. The FAAC bus is built on a Gillig Bus front end and has a 360-degree display through seven video-channels (3 front video projectors, 2 side displays, 2 rear displays) and a complete set of bus controls. The simulator programming software enables the preparation of a variety of driving scenarios. FAAC professionals wrote custom software for Project PATH to capture driver

performance variables 30 times per second. The simulator is housed in a large climate-controlled truck trailer purpose-build for the simulator with 300 KV diesel electric generator for regulated electrical power for the simulator and computers. The simulator was driven from Paducah KY to Iowa City and parked in the parking lot of the National Advanced Driving Simulator (NADS) for the two-month duration of the experimental period.

2. Mobile Eye eye- tracking equipment built by Applied Science Laboratories, (ASL) of Bedford, MA. The Mobile Eye equipment recorded gaze location/pupil direction and pupil radius. Eye-racking data, captured at 30 frames per second, was integrated in real time into the custom driver performance software built by FAAC for this project.

3. A computerized battery of psychomotor tests, a subset of the ANAM4 (Automated Neuropsychological Assessment Metrics) performance assessment test battery available from the Center for the Study of Human Operator Performance in Norman OK. An abbreviated battery of six ANAM psychomotor tests was performed by each subject before each of the four drives on experimental sessions and immediately following the next-day baseline-recovery drive.

4. Quantisal saliva drug testing devices and saliva Triazolam drug testing analysis were provided by the Immunalysis Corporation of Pomona, CA. Saliva samples of 3 ml volume were collected from each participant immediately following each of the four drives on experimental days and immediately before the next-day baseline-recovery drive. These samples were analyzed by Immunalysis to determine the level of Triazolam in the participant's saliva. The Limit of Detection was 10 pg/ml and the Limit of Quantification was 50 pg/ml.

5. CupLap Rapid Urine Drug Test screening kits were provided by by Acro Biotech, LLC of Rancho Cucamonga, CA. A Rapid Urine Test and a Breath Alcohol Test were conducted on each participant before each experimental trial to assure that the experimental results would not be confounded by current drug or alcohol use.

6. The driver participants were asked if they were willing to volunteer (for no additional remuneration) to provide a blood specimen after the last drive of each experimental session. Only six participants volunteered. Samples from the volunteering drivers were analyzed by the pharmacology team at the University of Iowa to determine plasma Triazolam levels to provide a correspondence between blood plasma and saliva levels. The analyses produced a linear relationship between Saliva and Plasma levels, as seen at the end of this Section.

2.1.4 Participant Safeguards and Recruitment

The concepts embedded in the protection of human participants' doctrine, and the moral and legal obligations of researchers, have evolved steadily since World War II. The publication in 1979 of the "Ethical Principals and Guidelines for the Protection of Human Subjects in Research" by the National Commission for the Protection on Human

Subjects in Biomedical and Behavioral Research[35] established the standards around which subsequent legislation and regulations have been built.

This report, generally known as “The Belmont Report”, defines the basic ethical research principals of 1) Respect for Persons, 2) Beneficence, and 3) Justice in research involving human participants. These principals are expressed through research protocols, standards and controls that embody: 1) Informed Consent, 2) Assessment of Risks and Benefits, and 3) Appropriate selection of subjects. The application of these principals will be seen in the following pages.
DHEW published “Protection of Human Subjects”, regulations at 45 CFR Part 46, June 1991. These regulations codified ethical research principals and standards established by the “Belmont Report” into a set of regulations applicable to all research funded by the federal government. Institutional Research Boards (IRBs) in each federal department and at each university and research institution implement the principals and standards.

Project PATH, funded by the Federal Transit Administration and operated by and through the University of Iowa, was conducted after careful review, revision, and approval by the University of Iowa Institutional Research Board (Hawk IRB). Each person on the research team with access to data with individual identifying information was required to have taken and passed a certificate equivalent to the National Institutes of Health course “Protecting Human Research Participants” (July 2008)[36]. The University of Iowa “Guide for Human Subjects Research at the University of Iowa” regulated the conduct of its IRB and research conducted by the University[37]. The federal criteria for IRB approval are found at 45 CFR 46.111.

Figure 2-1. Federal Criteria for IRB Approval

Sec. 46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(3) Selection of subjects is equitable

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

2.1.5 The Institutional Research Board Submission and Approval

The Project PATH team in Boston prepared the Detailed Experimental Protocol and it was reviewed and edited by the University of Iowa and the University of Washington team members. Applicable parts of it were abstracted and entered in the University of Iowa form for electronic submission of the Institutional Research Board application. Additionally, draft versions of the proposed outreach and recruitment documents, the participant remuneration schedule, and the Informed Consent document were submitted to the IRB review committee. The IRB application was submitted in March 2009. The IRB committee requested minor revisions. The committee specifically requested the preparation of a table estimating the relative risks associated with adverse reactions to Triazolam as detailed in the experimental literature. That table was prepared and incorporated into the Informed Consent document. IRB approval was received at the end of July 30, 2009. A copy of the approval letter is attached at Appendix A, together with other documents approved as part of the IRB submission.

2.1.6 Project PATH Participants

Participants were CDL-holding bus drivers recruited from the several transit systems in the Iowa City area. Primary outreach was to the student-operated FTA-funded University of Iowa bus operation CamBus. Additional outreach was conducted to the

local public transit system in Iowa City, to the rural system in Johnson County, and to the neighboring transit systems in Coralville and Cedar Rapids, and to the school bus companies in the local area. Managers of each of the transit systems had been personally briefed by PATH staff on the research goals of the project, and its safeguards, before the initiation of the outreach effort.

The final version of the Informed Consent Document is found in Appendix A

The recruitment material instructed interested participants to telephone the PATH phone number for further information. PATH operators answered calls, read a prepared script and answered questions. If the potential participant was still interested, the PATH operator then explained the inclusion and the exclusion criteria and conducted the initial telephone screening.

The inclusion criteria were as follows:

- Between 18 – 65 years of age.
- Employed as a transit, school bus or charter bus driver with a commercial driver's license (CDL) with the passenger endorsement.
- Only restriction on the CDL driver's license was vision correction.
- Live within a 30 minute drive to the National Advanced Driving Simulator.
- Able to attend three simulator visits including a next day drive, with each visit 1-2 weeks apart.
- Must be willing to participate after their last shift of the week or with at least 2 days off before their next shift or professional driving job.

Exclusionary conditions centered around medications that were known to inhibit the metabolism of Triazolam. Persons who were taking anti-viral and some anti-bacterial and anti-fungal medications were excluded, as were females taking oral contraceptives. These classes of medications, by inhibiting the metabolism of the drug, prolong the duration of effect, increase the peak drug concentrations, and potentiate the behavioral impact.

Of the 71 potential participants who phoned the PATH number and were interested enough to provide intake information and pass the inclusion criteria, one (1) was screened out for a medical condition, seven (6) were screened out for excluded medications and eight (8) were screened out for oral contraceptives. Eleven (11) other otherwise-qualified participants showed lack of interest by failing to show up for the full screening visit or failing to return calls to set up a date for the full screening visit or for indicating, on second consideration, that there was a schedule conflict.

After potential participants signed the Informed Consent form, they underwent a medical examination and provided a blood sample for laboratory analysis. One (1) person was excluded based on the laboratory results. The remaining potential participants then were required to perform two training drives in the driving simulator. These training drives had the objectives of providing a measure of each participant's level of discomfort

driving in the simulator (Simulator Sickness) and their ability to follow the simulator's synthesized-voice driving directions. Seven (7) persons were excluded for Simulator Sickness.

Thirty-two participants were enrolled in the experiment. Of those, 24 completed all of the experimental drives. Of the eight (8) participants who were enrolled but failed to complete, one (1) person never actually started, four (4) were unable to comply with the schedule, one (1) person withdrew consent. Two (2) participants were eliminated because their next-day saliva samples indicated that they had measurable levels of Triazolam more than 12 hours following ingestion of the experimental capsule.

The distribution of the 71 potential participants by age, gender and outcome is seen in Figure 2-2. . There were 48 male persons recruited and 23 females. Thirty of the 48 males but only 2 of the 23 females made it through the screening process into enrollment.

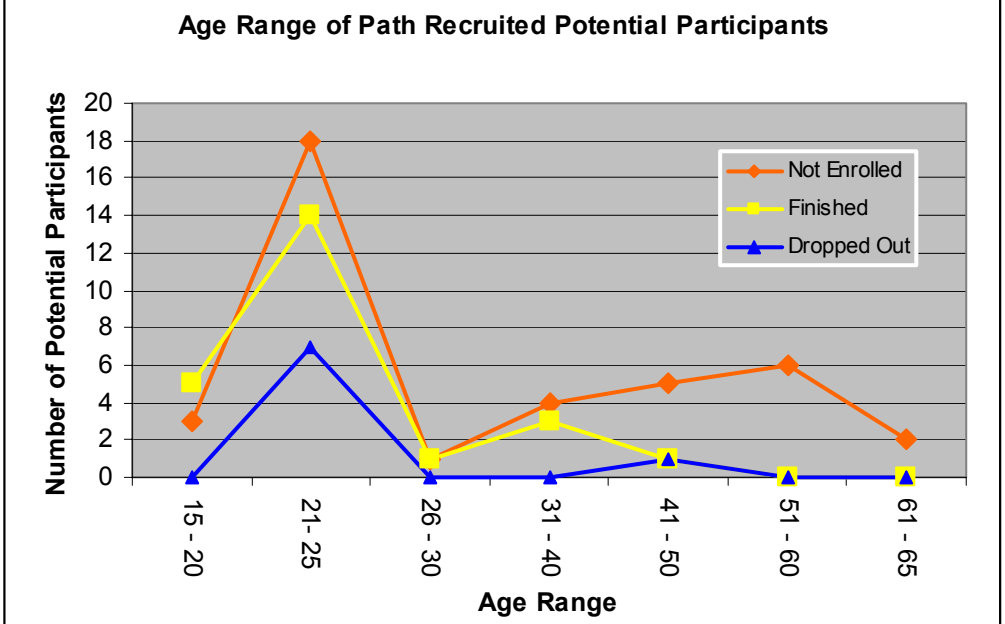
Figure 2-2: Path Participants Recruited by Age, Gender and Outcome

Participant Gender	Participant Outcome	Age Range of Participants							TOTALS
		15 - 20	21- 25	26 - 30	31 - 40	41 - 50	51 - 60	61 - 65	
Males	Completed	5	13	1	3	1	0	0	23
	Dropped	0	6	0	0	1	0	0	7
	Excluded	1	8	1	3	2	2	1	18
	Total	6	27	2	6	4	2	1	48
Females	Completed	0	1	0	0	0	0	0	1
	Dropped	0	1	0	0	0	0	0	1
	Excluded	2	10	0	1	3	5	0	21
	Total	2	12	0	1	3	5	0	23

Of the males who failed to pass screening, ten (10) were excluded for lack of interest, four (4) for excluded medications or medical conditions, three (3) for simulator sickness and one (1) for schedule conflicts. Of the females who failed to pass screening, five (5) were for lack of interest, twelve (12) for medications (mostly oral contraceptives), and four (4) were for simulator sickness.

As can be seen from Figure 2-2 and Figure 2-3, the ages of the cohort that completed the project were more representative of younger CDL bus drivers than of all CDL holders who had enquired about the project and passed the initial telephone screening. The literature review included in the Detailed Experimental Design for Project PATH referenced papers that indicated that older persons metabolized Triazolam more slowly than younger persons. Accordingly, the findings of this study may be more directly reflect the probably impact of benzodiazepines on younger commercial drivers.

Figure 2-3: Age Ranges of Project PATH Recruits by Outcome



2.1.7 Project PATH Experimental Terminology

The following are the definition of terms that will be used hereafter.

- An experimental drive was one of the five drives that constituted an experimental session.
- An experimental day was any of the six days on which a participant reported to the experiment.
- An experimental session consisted of the four drives on the first experimental day and the fifth, or next-day drive, conducted the next morning, after the participant had at least 8 hours of sleep.
- For each participant, the experiment course consisted of three experimental sessions or six experimental days. Each experimental session was conducted at least one week after the previous session.
- The dose regime required that, over the course of the three experimental sessions, each driver was given all three doses in a randomized, double blind, cross-over paradigm. That is, the "cross-over" design required that all drivers take all three doses -- the placebo capsule (also known as the .000 mg dose), the capsule containing the 0.125 mg dose and the capsule containing the 0.250 mg dose of Triazolam. A standard capsule was used, filled with sucrose, with either a Triazolam tablet or a sucrose tablet imbedded in the powder. The "randomized" design required that the capsules were given in a randomized order. The "double-blind" design required that the dose in each capsule could not be known to the to the

participant at any time, and not known to the experimenter until all experimental sessions had been completed and the capsule code was revealed.
- The training drives were the first two drives taken at least one day before the participant's first experimental session. These were screening drives, as explained below.
- A simulator run is one of the several experimental sessions in the daily schedule. The schedule allowed for as many as six experimental runs in a day, three in the morning and three in the afternoon.

2.2 Project PATH Experimental Design

In the project planning, the team had anticipated that as many as 50% of participants would make it through screening but drop out after enrollment. Accordingly, the design allowed for as many as 120 recruits to enter screening, with 60 participants to make it through screening and into the training drives. Of these, half or less were expected to finish the experimental course.

In order to accomplish this level of throughput, and utilize all of the integrated project resources, the project plan called for simulator experimental drives and sessions to be staggered and overlapping. A schedule of overlapping simulator runs was developed so that as many as three participants could be using the simulator concurrently in an overlapping manner. The project design is seen in Figure 2-4. Figure 2-4 is a truncated portion of the daily scheduling showing three runs, but only the first two drives of each of the runs. The full daily schedule graphic is too long to be printed on a page in portrait orientation. The schedule continues in a similar manner for the third and fourth drive of the day. This design made it theoretically possible to have six participants per day, three in the morning and three in the afternoon, or thirty per week, complete their experimental sessions in the FAAC simulator.

As was noted above, PATH actually recruited 71 potential participants, of which 32, or 45%, made it through screening and the training drives into the experimental portion. Of those, eight (8), or 33%, failed to complete all of the experimental drives. The goal for Project PATH was to have 28 participants complete all drives. The actual number of 24 participants completing simulator sessions was an adequate number to achieve statistically significant results at the level of impact expected from the literature review.

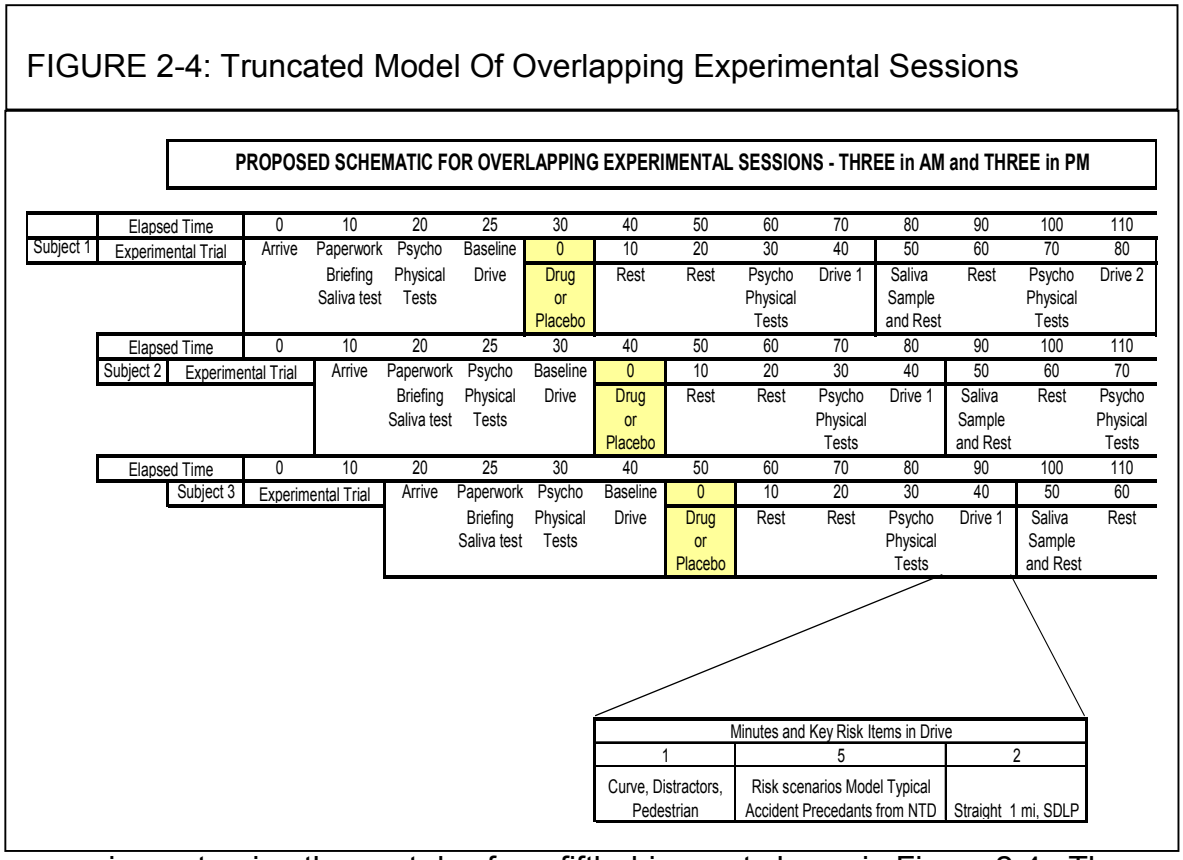
However, of those 24, six did not complete the last drive of the experiment course, the next-day drive of their third experimental session. The generator of the simulator developed an oil leak late in the experiment and it was deemed best not to conduct these last six next-day drives.

Thus, 18 participants completed all 15 experimental drives, and an additional six participants completed all but the last experimental (next-day) drive.

2.2.1 The Experimental Daily Schedule in Detail

The project plan required that each participant would complete four experimental drives

FIGURE 2-4: Truncated Model Of Overlapping Experimental Sessions



per session, returning the next day for a fifth drive, not shown in Figure 2-4. The next-day drive would be a repeat of the first drive of the previous day. The first drive of the day would be the baseline drive and the study medication would be administered immediately after the first drive of the day. The driver's performance data from the next-day drive would be compared to their performance on the first drive of the previous day to see if their next-day performance was equivalent to baseline.

Sessions would be scheduled at least one week apart and would start as soon as possible after the participant's last shift of the week. It was required that the participant would have at least two full days before their next professional drive. This would provide a wash-out period of at least two days as a provision against lingering after-effects of Triazolam. This provision seemed prudent, though the literature review did not find any reference to lingering after effects for Triazolam at 0.25 mg.

The literature indicated that the peak concentration and peak behavioral impact of therapeutic doses of Triazolam would occur between 90 and 120 minutes following administration[•]. The capsule containing the study medication or placebo would be taken immediately following the first drive of the day. The daily schedule was established so that the four daily experimental drives would be spaced 40 minutes apart. The second

[•] See Rush et all, citations 24 and 25.

experimental drive would be conducted 40 minutes following drug administration, the third at 80 minutes and the fourth at 120 minutes following ingestion. The experimental session would be followed by a normal sleep period and resume the next day at the time the participant would normally report to work.

Figure 2-5 depicts the actual experimental schedule for participant M2504. M2504 is primarily a week-end driver, so his work week concludes on Tuesdays. His experimental days were Tuesday October 20th, October 27th and November 3rd, with next-day drives on the 21st, 28th and 4th.

A part-time driver, M2504 has a morning shift and the report time to the PATH project was 14:20. On reporting, each participant provided a urine sample for a rapid drug-screen for a broad panel of substances including benzodiazepines. Each participant also provided a breath sample. If either test were positive on any of the experimental drives, the participant would be washed out of the project. M2504 had completed those tests by 14:21.

The participant then took a computerized battery of psychomotor tests. The PATH staff selected this sub-set of psychomotor tests from the full test battery available from ANAM4 (Automated Neuropsychological Assessment Metrics). The test battery is fully described in Section 4 of this report. On 10/20/2010, M2504's test battery lasted from 14:32 to 14:45.

The psychomotor test battery given before the first drive of the day, and before the next-day drive, contained the same test elements as the test battery given before the second, third and fourth drive of the day, but with more repetitions. The PATH psychomotor battery given before the first experimental drive of the session and before the next-day drive, generally required about 12 minutes to complete. The shorter version of the test battery, given before the second, third and fourth drives, required about six minutes to finish, as may be seen from Figure 2-5.

The project integrated data gathered from eye-tracking equipment worn by the participant (Mobile-Eye by ASL, Inc) with operator performance data gathered by the simulator. In the daily schedule above in Figure 2-5, note that the eye-tracking headgear is placed on the participant and calibrated immediately before each experimental drive.

The participant then completed the first experimental drive of the day. The participant was instructed to start the bus and put it in gear. The participant then followed the synthesized verbal instructions and drove the bus simulator through the scenario for the first drive of the day. That drive became the baseline drive against which the driver's performance on the remaining three experimental drives of that session, and the repeat drive on the next day, would be measured.

A saliva sample was then taken from each participant, after the baseline drive, and immediately after each subsequent experimental drive. The saliva specimens were collected with the Quantisal saliva collection device and analyzed by Immunalysis Laboratories. The saliva sample is a surrogate for the current level of Triazolam in the participant's blood. The saliva sample provided a current index of drug concentration associated with each experimental drive for each participant.

After completing the first drive of the day, the participant was given the capsule for the day. The capsule contained either the placebo dose, or the 0.125 mg or 0.250 mg dose. The dose order was randomized and unknown to the participant and experimental staff.

The participant was then walked back to the rest area and was allowed to rest, read, chew gum and drink water. Participants in the overlapping schedule were allowed to rest in separate rooms and were not in contact with each other during experimental sessions.

After a rest period of approximately 15 minutes, the participant continued the experimental cycle by performing the abbreviated computerized psychomotor battery. The abbreviated psychomotor battery, containing the same tests as the battery taken before the baseline drive but with fewer iterations of each test, usually required about six minutes to complete. The participant then walked with the PATH researcher to the simulator, put on the eye-tracking equipment completed the calibration. The participant then drove the bus through the next simulator scenario.

The PATH researcher observed the participant throughout each drive and completed a driver log sheet for each participant trip. The driver log is a description of each scenario

Figure 2-5: Example of the Three-Week Experimental Schedule

PARTICIPANT M2504	Experimental Day 1 and Next-Day Drive				Experimental Day 2 and Next-Day Drive				Experimental Day 3 and Next-Day Drive			
Complete last shift of the week	10/20/2009	12:38			10/27/2010	12:36			11/3/2010	12:36		
Report time	10/20/2009	14:20			10/25/2010	14:20			11/3/2010	14:19		
Urine drug screen (CupLab)		Neg				Neg				Neg		
Breath test (Breath Alcohol Conc)		0.000				0.000				0.000		
	Start	End	Duration	Minutes	Start	End	Duration	Minutes	Start	End	Duration	Minutes
Psychomotor battery (Pre-drive) 01	14:32	14:45	Minutes	Between	14:28	14:40	Minutes	Between	14:24	14:36	Minutes	Between
Equipment check and paperwork	Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant			
Drive 1 (pre-medication)	14:58	15:07	9.6		14:55	15:05	10.6		14:43	14:52	9.33	
Saliva sample	15:11				15:08				14:55			
Study medication	15:14			0		15:10		0		15:00		0
Rest												
Psychomotor battery 02	15:36	15:42			15:32	15:38			15:23	15:29		
Equipment check and paperwork	Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant			
Drive 2 (40 minutes)	15:53	16:09	16.46	0:39	16:00	16:12	12.6	0:50	15:40	15:48	8.84	0:40
Saliva sample	16:01				16:10		Note: late due to simulator issues		15:51			
Rest												
Psychomotor battery 03	16:18	16:24			16:16	16:22			16:07	16:13		
Equipment check and paperwork	Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant			
Drive 3 (80 minutes)	16:33	16:43	10.25	0:40	16:30	16:37	7.9	0:30	16:20	16:28	8.66	0:40
Saliva sample	16:44				16:40				16:32			
Rest							caught up to schedule					
Psychomotor battery 04	16:58	17:04			16:56	17:02			16:44	16:49		
Equipment check and paperwork	Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant			
Drive 4 (120 minutes)	17:13	17:22	9.18	0:40	17:10	17:22	12.07	0:40	17:00	17:09	9.96	0:40
Saliva sample	17:23				17:23				17:12			
Rest, then taxi home												
Next Day Drive	10/21/2010		Duration	Hours	10/28/2010		Duration	Hours	11/4/2010		Duration	Hours
Report time	8:46		Minutes	Between	8:52		Minutes	Between	8:48		Minutes	Between
Saliva sample	8:57	8:59			8:55				8:55			
Breath test	0.000				0.000				0.000			
Psychomotor battery (Pre-drive) 05	8:59	9:11			8:59	9:11			8:53	9:05		
Equipment check and paperwork	Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant				Calibrate eye-tracking equipment on participant			
Next-day drive	9:24	9:32	8.91	16:11	9:17	9:26	9.2	15:54	9:22	9:32	10.18	16:22

with check boxes to indicate whether or not the participant completed each task and a comment area for each phase of the drive. A typical driver log for M2504 is shown in Section 5 of this report. As can be seen in Figure 2-5, this cycle was repeated for the second, third and fourth experimental drive of the day.

As part of the research protocol, each respondent also completed a number of paper-and-pencil surveys. After completing each of the experimental drives, in the rest area each participant completed a short standardized written survey to assess any degree of discomfort due to simulator sickness. The simulator sickness results are reported in Section 3 of this paper. After the fourth (last) experimental drive of experimental days 1, 3 and 5, participants completed a written test to assess how "realistic" the simulator experience seemed that day. Each participant also completed a second survey asking whether they felt the experimental medication impacted their driving, and to what extent. Finally after completing each next-day drive, each participant completed a survey to assess the quality of their sleep the previous evening.

After the completion of all of the experimental trials for all of the participants, PATH researchers conducted a short telephone follow-up survey. The purpose of the survey was to gather general information about the research and to have each participant estimate which of the experimental sessions was the one on which they randomly received the high dose of Triazolam and whether and to what degree it impacted their driving ability. Finally, there were questions about what benefits they personally might have received from participating in this project, particularly with respect to driving after taking potent prescription medications.

Copies of these surveys are found in Appendix A.

2.2.2 Randomizing the Dosages of Triazolam

Triazolam was administered at three dose levels: 0.250 mg, 0.125 mg, and placebo (0.00 mg). The dose levels were randomized and administered in a double-blind format. That is, each participant received all three dose levels, but the order of administration was randomized. Each Triazolam tablet was placed in a gelatin capsule with a sufficient amount of filler to hide the taste and participants were instructed to swallow the capsule whole. These provisions were intended to prevent the participant from knowing whether they were ingesting a tablet or the placebo dose.

The tablets were administered in a double-blind protocol. That is, PATH Researcher, Gary Milavetz, D. Pharm, was responsible for overseeing the preparation of blinded active and placebo drug doses, and for developing pharmacological monitoring procedures for human subjects involved in this project. Dr. Milavetz prepared a series of three envelopes for each participant, one for each experimental session. Only Dr. Milavetz had the key to the randomized order of administration of the tablets in the envelopes and he was not involved in the administration of the experimental capsules. Thus, neither the participant nor the person administering the capsule knew the dose level administered to the participant on that experimental day. This precaution

eliminated the possibility that the researcher might inadvertently bias the results by providing subliminal cues to the participant about the dose level and the level of its potential impact.

There are six combinations of the order in which three things may be arranged. The randomized dose orders and associated participant IDs for the 24 participants that completed Project PATH are shown in Figure 2-6, as are the randomization schedule for the 8 participants that were enrolled but did not complete the study.

Figure 2-6 indicates that, although the doses were randomized, the final order in which they were administered to the 24 participants who completed the project appears skewed toward higher doses in earlier sessions. That is, 18 of the 24 participants received the high (0.25 mg) dose in their session 1 or session 2 and only six received the 0.25 mg dose in their session 3. The order of administration of the middle dose was balanced, but the order of administration of the placebo dose was skewed toward the last day of the three-day series.

This happened because more of the eight participants who failed to complete the study had been randomly assigned to Group C, the random group would have received the 0.250 mg dose on their third experimental session. Had these 8 not dropped out, the dose orders would have been correctly balanced. Because the PATH researchers were blind to the randomized dose order, there was no awareness of the apparently skewed order of administration before the randomization code was broken.

Post-facto tests for order effects are included in the statistical evaluation of the data.

Figure 2-6: PATH Randomization schedule

PARTICIPANTS WHO COMPLETED THE STUDY				
Subject number	Dose order	Session 1	Session 2	Session 3
M1902	A	0.25	0.125	0
M2212	A	0.25	0.125	0
M2322	A	0.25	0.125	0
M2428	A	0.25	0.125	0
M2618	A	0.25	0.125	0
M2007	B	0.125	0	0.25
M2031	B	0.125	0	0.25
M2314	B	0.125	0	0.25
M4005	B	0.125	0	0.25
M2301	C	0	0.125	0.25
M2524	C	0	0.125	0.25
M2029	D	0.25	0	0.125
M2225	D	0.25	0	0.125
M2504	D	0.25	0	0.125
M3417	D	0.25	0	0.125
M1909	E	0.125	0.25	0
M2130	E	0.125	0.25	0
M2315	E	0.125	0.25	0
M2426	E	0.125	0.25	0
F2320	F	0	0.25	0.125
M2023	F	0	0.25	0.125
M2110	F	0	0.25	0.125
M4003	F	0	0.25	0.125
M5011	F	0	0.25	0.125
Actual Dose	**Participants Completing Study**			
Order	Session 1	Session 2	Session 3	Total
0.000	7	8	9	24
0.125	8	7	9	24
0.250	9	9	6	24
Total	24	24	24	
PARTICIPANTS WHO DID NOT COMPLETE PATH				
M4619	A	0.25	0.125	0
M2221	B	0.125	0	0.25
F2116	C	0	0.125	0.25
F2213	C	0	0.125	0.25
M2132	C	0	0.125	0.25
M2208	D	0.25	0	0.125
M2106	E	0.125	0.25	0
M2227	F	0	0.25	0.125
Planned Dose	**Participants NOT Completing**			
Order	Session 1	Session 2	Session 3	Total
0.000	4	2	2	8
0.125	2	4	2	8
0.250	2	2	4	8
Total	8	8	8	
DOSE ORDER IF ALL HAD COMPLETED				
Planned Dose	**Dose Order If All Had Competed**			
Order	Session 1	Session 2	Session 3	Total
0.000	11	10	11	32
0.125	10	11	11	32
0.250	11	11	10	32
Total	32	32	32	

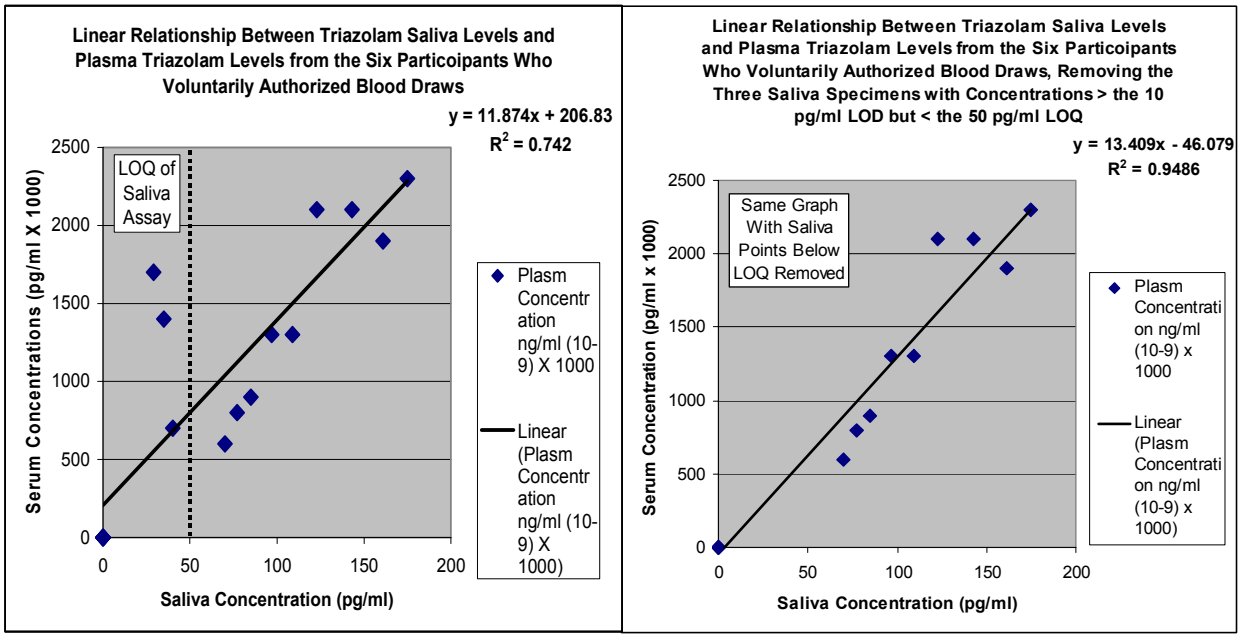
2.3 Plasma and Saliva Correspondence Triazolam Concentrations

The PATH team was fully aware that it would be very highly desirable, even essential, to have a method for correlating the saliva Triazolam concentrations that would come from the Immunalysis Laboratories analyses against analyses that established the serum drug concentration of Triazolam. However, the Team was very concerned that requiring participants to submit to blood draws as a condition of entrance into the project would highly limit and possible bias the available participant population. Moreover, the Team realized that it would not be feasible to plan to draw four blood specimens from each participant, one after each experimental drive, to provide a time-course of drug concentration. It was hoped that the saliva specimens would serve as a surrogate saliva to provide that important information.

Accordingly, the Team adopted a compromise. Blood specimens would be collected from volunteers after the 120 minute drives and correlated against the 120 minute saliva specimens to determine if the relationship was linear and quantitative.

During recruitment, all participants were asked if they would be willing to volunteer to have a blood sample taken after each of the 120 minute post-drug drives. It was make clear that decision would have no bearing on whether they would be accepted into the research project and they would receive no additional compensation. Six participants volunteered to authorize the blood samples to be drawn. The specimens were drawn by a registered phlebotomist and analyzed through an analytical quantitative procedure developed by the pharmacology members of the PATH Team at the University of Iowa. The correspondences are shown in Figures 2-7 A and B.

Figure 2-7 A and B: Linear correspondence between serum Triazolam concentration and saliva Triazolam concentration.



The Limit of Detection (LOD) of the saliva Triazolam analysis is 10 picograms/ml (10 x 10^{-12} g/ml, or 10 pg/ml) and the Level of Quantification (LOQ) is 50 pg/ml. The left-hand graph plots the correspondence between of the 120 minute saliva samples from the six volunteers and their corresponding serum Triazolam concentrations. There is a linear relationship with a regression value of R^2=.74. However, three of the saliva specimens have concentrations above the LOD but below the LOQ. Those three specimens are removed in the right-hand graph, yielding an improved linear relationship with a regression value of R^2=.948. It is reasonable to state that the saliva specimens are a veridical surrogate for serum levels, at least above the LOQ for the saliva assay.

The regression graph 2-7B indicates that the serum concentration is approximately 13 times the concentration of Triazolam in saliva. The data table is presented in Figure 2-8. Note that the serum concentrations are multiplied by 1000 for graphing so that the serum and saliva concentrations are expressed in the same units.

Figure 2-8: Data table for Serum-Saliva Correspondences

Random Assignment	Dose	Participant	Saliva Concentration Notes	Saliva Concentration pg/ml (10^{-12})	Plasm Concentration ng/ml (10^{-9}) X 1000	Plasma Concentration Results of Assay
B	0.125	M2007	Less than LOQ	35	1400	1.4
B	0	M2007		0	0	ND
B	0.25	M2007		123	2100	2.1
F	0	M2023		0	0	ND
F	0.25	M2023		77	800	0.8
F	0.125	M2023		70	600	0.6
E	0.125	M2106	Less than LOQ	40	700	0.7
E	0.25	M2106		161	1900	1.9
D	0.25	M2225		143	2100	2.1
D	0	M2225		0	0	ND
D	0.125	M2225		97	1300	1.3
A	0.25	M2322	Less than LOQ	29	1700	1.7
A	0.125	M2322		85	900	0.9
A	0	M2322		0	0	ND
C	0	M2524		0	0	ND
C	0.125	M2524		109	1300	1.3
C	0.25	M2524		175	2300	2.3

3 PAPER SURVEYS AND THE DETERMINATION OF INTERVENING VARIABLES

This section discusses the results of the paper and pencil surveys conducted at the end of every experimental run, on the morning of each next-day run, and in a follow-up telephone survey. These surveys tracked the perceptions of the participants concerning whether and to what extent Triazolam, the experimental drug, impacted their driving. Since neither the participants nor the experimenters knew what dose the participant had taken (placebo, 0.125 and 0.250), these surveys allowed the PATH team to compare the participants' unbiased responses for each of these doses.

This section also discusses the other indexes the PATH team developed to help it understand the impact of intervening variables of the behavioral effect of the drug and dose. The primary variable is, of course, drug dose. The intervening variables considered are: 1) Driver Score and Driver Score Index, 2) Body Mass and Body Mass Index, 3) Saliva Triazolam Level, 4) Session Order, and 5) Simulator Sickness. In addition, to determine whether there was a lingering or hang-over effect of the drug, a 6th variable, "Same Day-Next Day" was used to compare performance on the first day (pre-drug) drive against the next-day (8 hour post-drug) drive.

3.1 The Structure of the Surveys

There were five paper-and-pencil surveys conducted on a repetitive basis through the project. The survey title, objective, first question and scoring directions are shown below in Figure 3-1.

Figure 3-1: PATH paper and pencil surveys

AFTER EVERY DRIVE	AT THE END OF EACH SESSION	AT THE END OF EACH SESSION	BEFORE EACH NEXT-DAY DRIVE	AFTER ALL EXPERIMENTAL RUNS WERE COMPLETED
Wellness Survey	**Driving Realism Survey**	**The Post-Drive Drug Effect Survey**	**Sleep Quality Questionnaire**	**Follow-up Phone Survey**
A measure of Simulator Sickness and whether that perception is impacted by drug and dose.	A measure of the "Realism" of the Simulator and whether the operator's perception was impacted by drug and dose	A survey to determine driver self-perceptions of the impact of the drug and dose on the driving performance measures of interest in this experiment.	A survey to determine whether the drug and dose impacted the participant's sleep, and if so, in what direction and to what extent.	A survey after all experimental trials had been completed to gain overall participant reactions, to determine whether, retrospectively, the participants could identify the run on which they took the highest dose.
e.g. FIRST QUESTION IN THE SURVEY	e.g. FIRST QUESTION IN THE SURVEY	e.g. FIRST QUESTION IN THE SURVEY	e.g. FIRST QUESTION IN THE SURVEY	e.g. FIRST QUESTION IN THE SURVEY
Please rate your level of … (1) General Discomfort (0=None, 1= Slight, 2=Moderate, 3=Severe)	Please rate the "realism" of the simulator … (1) Response of Seat Adjustment Levers -- total 37 measures to -- (37) Overall appearance of driving scenes (0=Not realistic at all, 6=Completely Realistic, NA)	Did the ingested drug received today affect the way you drove in 2nd, 3rd and 4th drives? 1a) Driving at the posted speed limits (1=No Impact, 2=Mild Impact, 3= Moderate Impact, 4= Strong Impact, 5= No opinion)	1) Did the substance you took yesterday help you sleep? (0=Not at all, 1= A little, 2= Quite a bit, 3 = A lot)	1) Were the driving environments you experienced in the bus simulator representative of the driving environments you typically encounter while driving a bus 1 = not at all, 2 = a little, 3 = somewhat, or 4 = very representative of the driving environment)

Figure 3-1 presents the schedule, general structure and rationale for administering the survey and also presents the first question of the survey and the scoring instructions.

The “Wellness” survey, a measure of Simulator Sickness discomfort, was taken after each drive. During the two driver-training sessions before the experimental trials, the survey was used as a way to screen out persons very susceptible to simulator sickness. During the experimental drives, scores from this survey assured the researchers that no participant was experiencing an undue or unexpected amount of distress. Retrospectively, scores from this survey have helped to understand the impact of Triazolam on discomfort caused by driving in the simulator.

The “Realism” survey and the “Post-Drive Drug Effect” survey were completed by each participant after completing each experimental day and waiting for their ride home. The “realism” survey asked participants to quantify aspects of the simulator experience on a six-level continuum from “not realistic” to “completely realistic”. This scale objectified the discussion in Section 1.2.1., that a high-fidelity simulator is one with “physical fidelity and psychological fidelity”. This scale is also a possible gage of the degree to which lessons learned in Project PATH would be directly applicable to real bus driving. The “Post-Drive Drug Effect” survey at the end of each session was used as a gage of each persons’ perception of their own level of impairment, allowing a comparison against dose and saliva level.

The “Sleep Quality” questionnaire was administered when the participant returned for the “Next-Day” drives. It was used to gage of whether or not the drug had an impact of the ease of induction or quality of sleep, and also as a gage of how alert the participant felt the next day at the start of the “Next-Day” drive.

The “Follow-up Phone Survey” was only administered once to each participant. The follow-up survey was used to gage general impressions of the project and particularly to ask participants about lessons they might have taken away from their participation in Project PATH.

3.2 Development of Intervening Variables and Use of Multiple Linear Regression

For reasons that will be explained in the following sections, the PATH team recognized that there might be several variables, in addition to the dose level of Triazolam, which might modify Triazolam’s behavioral effect. These we refer to as “intervening variables” or “modifying variables”.

Body Mass Index (BMI) – This experiment used standard therapeutic doses of 0.125 mg and 0.250 mg doses. The doses were administered in standard capsules and the tablets were not crushed. Other researchers have used the weight of participants as a factor in administering the drug dose. In those cases, as with Rush et al (references 44 and 45), the tabled is crushed, the participant is weighed, and a calibrated equivalent dose, 0.25 mg/70 kg, was given to each participant. Accordingly, a 70 kg participant (177.8 lbs) would be given 0.25 mg of Triazolam but a participant weighing 240 lbs

would receive a dose of 0.337 mg (0.25 mg/70 kg), and a slender participant would be given a smaller dose.

Project PATH determined to use only standard therapeutic doses. However, to partially correct for differences in weight of the participants, and also to partially compensate for the body shapes of the participants, ranging from slender to obese, PATH used Body Mass Index (BMI) as an intervening variable.

BMI is useful because it combines weight and body shape into a single measure. If the drug were lipid-soluble, (as is marijuana), some percentage of a given dose would dissolve in body fat and, somewhat slowly, leach back out into the blood stream. If that were the case for Triazolam, participants with a higher proportion of body fat might have a blood level of Triazolam lower than participants with lower proportion of body fat. Including BMI as a variable in the tests of significance might help to explain individual variances in impact.

As a check, the team gathered height and weight from each participant. Participant BMI's were determined using the standard National Institute of Health (NIH) Body Mass Index table[38]. For ease of calculation, the participants were then assigned a "BMI Index" with values from 1 to 3, using the table break-points in the NIH Table.

Driver Score Index – It seemed possible that the individual driving style of the participant might be an intervening variable. That is, since Triazolam is member of the class of "tranquilizer" and "anti-anxiety" drugs, it might be differentially reactive when taken by "highly anxious" or "highly active" or "highly-responsive" drivers than when taken by "less-responsive" drivers. Obviously, these terms are undefined, and any impact might be slight, but needed to be controlled for in the assessment of drug impact.

A "Driver Score" for each participant was developed by scoring four elements of the driver's performance on the first drive of the first experimental session, before any drug had been administered. That score, ranging from four (4) (impulsive driving) to 10 (careful driving) was used as a potential "intervening variable" to determine whether drug effect correlated with this driving style metric. The continuous score was also broken into three categories (1,2, and 3) for computational simplicity.

Saliva Level – Each participant provided a saliva sample immediately following each drive (i.e. at 0, 40, 80 and 120 minutes) and again immediately before taking the next-day drive. The team felt the level of Triazolam in saliva might be a better predictor of drug impact than dose. That is, the saliva concentration might parallel the blood concentration and be a direct measure of the active principal of the substance.

Session Number – It seemed possible that participants might acclimate to the simulator or there might be some effect associated with whether this was the participant's first, second or third experimental session. Accordingly, the session number was included as a potentially intervening variable.

Dose Order – The "dose order" or "randomization group" into which the participant had been assigned was also included in the drug impact equations as a possible intervening variable.

Use of Multiple Linear Regression – In addition to the analysis of means and standard deviations using standard t and F tests, the analysis of drug effects in this study makes extensive use of the Multiple Linear Regression capabilities in Excel.

PATH assumed that the intervening variables might have independent effects on the behavioral impact of the drug. Some of those interactions might reinforce or potentiate the behavioral drug effect. Other combinations or other circumstances might act in opposite directions on the drug effect, weakening the behavioral impact.

The independent effects of these intervening variables can be estimated using multiple linear regression to analyze the impact of multiple columns of data simultaneously. The output will: 1) indicate whether there is a statistically significant overall direction for the data, 2) provide an estimate of the percent of variance in the data explained by the effect of the variables; and 3) indicate which of the variables are producing the impact.

As an example, Figure 3-2 illustrates the participant scores from the Drug Impact Survey conducted at the end of each experimental day. The intervening variables are arrayed on the left of the table and each question with the participant's response is on the right. With Multiple Linear Regression it is possible to determine, separately for each variable and as a group, whether there is an association between the driver's perception of the strength of the impact (if any) and the several variables of interest.

Figure 3-2: Data from the Drug Effect Survey Arrayed for Multiple-Regression

	Intervening Variables The "X" Values						Did the ingested drug received today affect the way you drove in the 2nd, 3rd and 4th drives? (1=No Impact, 2=Mild Impact, 3= Moderate Impact, 4= Strong Impact, 5= No opintion)						
Subject ID	Saliva Level	BMI	BMI Cat	Dose	Driver Index	Visit	1a) Driving at the posted speed limit	1b) Staying within my lane while driving straight?	1c) Following curves to the left or right	1d) Seeing people and things along the roadway	1e) Anticipating problems that may arise	1f) Following verbal directions	1g) Other (please describe)
F2320	0	20	1	3	3	1	2	1	1	1	1	3	.
F2320	144	20	1	1	3	2	2	3	2	1	1	2	.
F2320	79	20	1	2	3	3	1	1	1	1	1	1	1
M1902	127	23	1	1	1	1	2	2	2	1	1	1	.
M1902	49	23	1	2	1	2	2	1	1	1	1	1	.
M1902	0	23	1	3	1	3	1	2	2	1	1	2	.
M1909	34	39	3	1	1	1	1	1	1	1	1	1	1
M1909	95	39	3	2	1	2	2	3	2	1	1	1	.
M1909	0	39	3	3	1	3	2	2	2	1	1	1	.
M2007	35	20	1	2	2	1	3	2	2	1	1	1	.
M2007	0	20	1	1	2	2	1	1	1	1	1	1	1
M2007	123	20	1	3	2	3	1	3	3	2	1	1	1

Figure 3-3: Multiple Regression Results for "Staying in My Lane While Driving Straight" Regressed Against the Intervening Variables

Did the ingested drug received today affect the way you drove in 2nd, 3rd and 4th drives?
(1=No Impact, 2=Mild Impact, 3= Moderate Impact, 4= Strong Impact, 5= No opinion)

SUMMARY OUTPUT

1b) Staying in my lane while driving straight?

Regression Statistics	
Multiple R	0.4567
R Square	0.2086
Adjusted R Square	0.1238
Standard Error	0.7914
Observations	63.0000

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6.0000	9.2427	1.5405	2.4595	0.0351
Residual	56.0000	35.0747	0.6263		
Total	62.0000	44.3175			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.3220	0.8786	0.3664	0.7154	-1.4381	2.0821
BMI	0.0137	0.0375	0.3660	0.7157	-0.0614	0.0888
BMI Cat	-0.1249	0.2676	-0.4668	0.6425	-0.6609	0.4111
Saliva Level	0.0066	0.0021	3.0775	0.0032	0.0023	0.0108
Dose	0.1695	0.1705	0.9943	0.3243	-0.1720	0.5110
Driver Index	0.0680	0.1284	0.5299	0.5982	-0.1891	0.3252
Visit	0.0690	0.0634	1.0882	0.2812	-0.0580	0.1960

Figure 3-3 is the common format for the output of the Multiple Regression data function in Excel. The regression analysis indicates that the intervening variables taken together account for about 45% of the total variance in the participant responses to the question *"Did the ingested drug received today affect the way you drove in 2nd, 3rd and 4th drives?"* The data "Multiple R" is the calculation of the overall variance accounted for by the whole data set, in this case 45.6%. The data "Adjusted R Square", 12.4%, is a more conservative value for the percent of explained variance, taking into account the total number of variables in the analysis.

The data "Significance F" is the probability that these results could be produced by a chance arrangement of numbers. Note that all values of P calculated by Excel in the Regression function are for two-tailed probabilities. A value of 0.05 or less is considered a statistically significant estimate that the data could not have been produced by a random arrangement of the data. A value of P<=.05 rejects the "null hypothesis" that there is no impact. In this instance, the overall probability is P<=.0351 Clearly, the drivers' reported that they perceived an impact of the drug on their ability to drive in their lane while driving straight.

The lower box presents data to evaluate the impact of each of the variables considered in isolation. The column "P-value" is the key data associated with each variable in the

analysis. Values of P<= .05 indicate that that variable contributed a significant amount to the overall magnitude of the impact and its direction. In this data set, the variable "Saliva Level" is the only significant contributor to the impairment reported by the operators. Since the Coefficient for Saliva Level is positive, the direction is positive and drivers who have a higher saliva level of Triazolam report more impairment.

The regression set can also be used to estimate the magnitude of the statistically significant variables. The usual formula for the slope and intercept of a line is

$$Y = ax+b$$

In this case, each of the variables that have a probability value less than or equal to 0.05 can be included in the linear equation. For the multiple linear regression, the equation includes all of the significant variables. Thus, Y=ax+by+…+ z (etc) where z is the coefficient of the intercept at zero, the constants a, b, c etc are the coefficients of the statistically significant variables, and the variables x, y, etc are the quantities of the variables.

In Figure 3-3, saliva level is the only significant variable. Saliva concentrations of individual samples collected from the drivers range from 0 to 312 micrograms/ml of saliva (mc/ml). We can say that a 0 (zero) saliva concentration, the expected value of impairment for "Staying in my lane while driving straight" is 0.3220, the "z" value. The upper limit for the participant with the saliva Triazolam concentration of 312 is 0.3220 + (0.0066 * 324), or 2.38. On the adjective scale for this survey, 2 is Mild Impact and 3 is Moderate Impact.

Note that BMI, BMI Cat, Dose, Driver Index and Visit have non-significant probabilities and do not appear to contribute the impairment expressed by the participants.

The example in Figure 3-3 is not an ideal example of a multiple linear regression. That is because it contains "co-linear variables" in the analysis. These are variables that are not independent of each other. In the linear plots in Figure 3-4, Dose and Saliva Concentration are co-linear, as are BMI and BMI Cat (BMI score categorized into 1, 2 or 3). However, repeating the calculation and excluding the co-linear variables yields the same result. The Triazolam saliva concentration significantly correlates (P=0.001385) with the participants' perception of difficulty staying in their lane while driving straight. Dose is not significant (P=0.196216). Driver Score and BMI Score are not significant.

3.2.1 Multiple Linear Regression Graphs

The Excel Multiple Linear Regression function data analysis can also automatically produce graphs of data plots by variable. Excel can also estimate correlation that would be associated with the data points if there were no confounding interactions in the data. These plots are shown in Figure 3-4.

Figure 3-4: Linear plots of the analyzed variables showing the estimated data points (in pink) calculated by Excel as if there were no confounding interactions in the data.

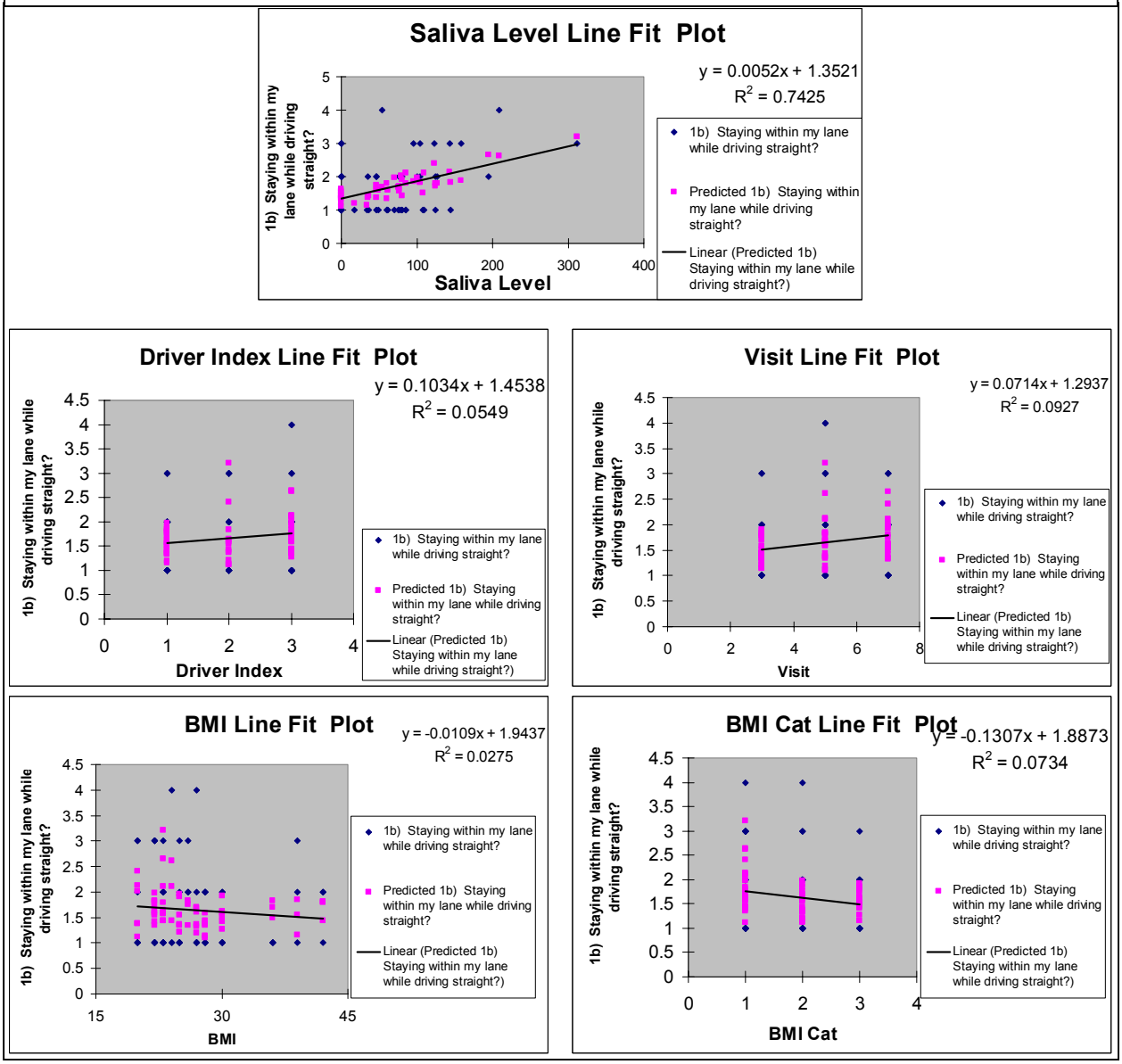


Figure 3-4 confirms that Saliva Level is the dominant variable in the participants' estimates of the level of drug-induced impairment, expressed as increasing inability to driving straight without weaving. An R^2 of .7425 indicates that Saliva Level accounts for approximately 75% of the variance in the sample. Driver Index accounts for only 5% of variance, 9% to Visit (i.e. the session number), and about 10% to a combination of BMI and BMI Index.

Note that, though non-significant, the trend for Driver Index and Visit in Figure 3-3 is positive. That is, the more cautious and skillful drivers (Driver Index 3) reported a higher degree of impairment than less cautious/skillful drivers (Driver Index 1). Additionally, drivers attending Session 3, their last drive in the experiment, tended to

report a higher level of drug-induced impairment than when they were novice drivers in Session 1 and 2. Also, note that drivers with a higher Body Mass Index tended to report less impairment than their cohorts with a lower BMI.

In summary, Excel's Multiple Regression function helps to tease out, isolate and explain seemingly contradictory elements in the PATH data sets.

3.3 Results of the Post-Drive Drug Effect Survey

From Figure 3-5, it can be seen that drivers in this study reliably (Significance F, P<.05 two-tailed) reported that they perceived themselves to be less able to drive in their lane at higher saliva levels of Triazolam. At a lower standard of significance (Significance F, p>.10 two-tailed), drivers also reported that they were impaired in their ability to accurately follow curves to the left and right. They reported no impairment in ability to Drive at the posted speed limit, See people and things along the roadway, Anticipate problems that may arise, and Follow verbal directions.

That is, the participants perceived themselves to be impaired in tasks that involved basic driving skills (driving straight without weaving, and to a less extent following curves), but not in driving skills that require attention, perception and problem solving skills. The perception of impairment was associated with the level of Triazolam in saliva collected from the participant at the conclusion of each drive. Impairment was not reliably associated with the dose of the drug ingested. There was no correlation with the self-perception of impairment with Body Mass Index or Driver Score or with Visit.

Figure 3-5: Multiple Regression table for the Self-Perception Post-Drive Drug Effect

Post-Drive Drug Effect Survey	*Regression Statistics*	Multiple R	*Significance F*		Intercept	BMI	BMI Cat	Saliva Level	Dose	Driver Index	Visit
Did the ingested drug received today affect the way you drove in 2nd, 3rd and 4th drives?				**(1=No Impact, 2=Mild Impact, 3= Moderate Impact, 4= Strong Impact, 5= No opinion)**							
1a) Driving at the posted speed limit		0.273	0.611	*P-value*	0.310	0.793	0.690	0.121	0.759	0.828	0.569
1b) Staying in my lane while driving straight?		0.457	0.035	*P-value*	0.715	0.716	0.642	0.003	0.324	0.598	0.281
1c) Following curves to the left or right		0.413	0.094	*P-value*	0.233	0.951	0.658	0.006	0.229	0.762	0.505
1d) Seeing people and things along the roadway		0.189	0.910	*P-value*	0.084	0.923	0.975	0.196	0.493	0.662	0.919
1e) Anticipating problems that may arise		0.172	0.942	*P-value*	0.009	0.439	0.806	0.705	0.799	0.865	0.811
1f) Following verbal directions		0.172	0.942	*P-value*	0.121	0.811	0.743	0.296	0.306	0.822	0.473
Did the drug made it easier or harder to drive safely during the 2nd, 3rd and 4th visit				**(1= somewhat easier, 2=No impact, 3= somewhat harder, 4 = much harder, 5= no opinion)**							
2a) driving at the posted speed limit		0.321	0.403	*P-value*	0.222	0.201	0.423	0.333	0.701	0.994	0.201
2b) Staying within my lane while driving straight		0.450	0.045	*P-value*	0.121	0.334	0.571	0.015	0.995	0.279	0.534
2c) Following curves to the left or right		0.248	0.720	*P-value*	0.085	0.197	0.221	0.728	0.567	0.585	0.441
2d) Seeing people and things along the roadway		0.316	0.434	*P-value*	0.041	0.198	0.521	0.643	0.363	0.167	0.364
2e) Anticipating problems that may arise		0.144	0.979	*P-value*	0.001	0.374	0.509	0.835	0.792	0.935	0.992
2f) Following verbal directions		0.364	0.242	*P-value*	0.029	0.222	0.953	0.770	0.980	0.064	0.706

Note that the six questions in this survey represent key areas of the potentially impairing effects of Triazolam (and all prescription medications). Questions 1a through 1f were chosen for the potential of comparing objective measures of impairment collected in the psychomotor tests and the driving simulator against self-perceptions.

In summary, from the Saliva Level plot in Figure 3-4, respondents estimated there was "No" Impact from a saliva level of 0 to approximately 100 ng/mL; "Mild" impact from 100 to 200 ng/mL, and "Moderate" impact above 200 ng/mL to 300 nl/mL.

3.4 Body Mass Indices and Saliva Concentrations

One of the reasons Triazolam was chosen as the study drug was that it has a simple metabolic path and there was no indication found during the literature review that the drug was lipid-soluble. However, as a post-facto precaution, height and weight data was requested from the respondents during the follow-up telephone interview. Height and weight data were converted to a Body Mass Index score using the standard National Institute of Health (NIH) tables referenced earlier. The BMI data was cross-tabulated against saliva Triazolam levels determined by Immunalysis Corporation, with the results shown in Figure 3-6.

Figure 3-6: Saliva Triazolam levels are higher for Participants with lower BMI.

Saliva Triazolam Concentrations as a Function of Body Mass Index (BMI), Dose and Time since Administration

Dose .125, Time 50 min, BMI <=25	Dose .125, Time 50 min, BMI >25	Dose .125, Time 90 min, BMI <=25	Dose .125, Time 90 min, BMI >25	Dose .125, Time 130 min, BMI <=25	Dose .125, Time 130 min, BMI >25	Dose .25, Time 50 min, BMI <=25	Dose .25, Time 50 min, BMI >25	Dose .25, Time 90 min, BMI <=25	Dose .25, Time 90 min, BMI >25	Dose .25, Time 130 min, BMI <=25	Dose .25, Time 130 min, BMI >25
0	46	77	43	35	0	63	0	100	100	144	105
0	0	28	0	79	0	28	124	64	95	104	62
88	31	88	34	44	54	0	0	49	24	77	46
69	0	62	0	70	0	0	0	46	43	29	81
57	0	0	0	85	0	0	0	61	0	312	0
0	81	100	53	37	31	181	0	195	75	175	77
0	0	49	59	109	77	165	54	127	108	103	83
0	0	0	13	49	51	81	74	289	90	186	120
65	0	57	22	86	76	147	145	142	0	122	0
23	34	56	59	42	16	116	0	209	95	143	81
87	0	101		97	14	0	38	12	48	46	125
0		0		17	60	52	0	158			
32.42	17.45	51.50	28.30	62.50	31.58	69.42	36.25	121.00	61.64	131.00	70.91
37.50	27.28	37.49	24.54	28.86	30.55	68.25	52.63	81.61	40.47	77.57	42.00

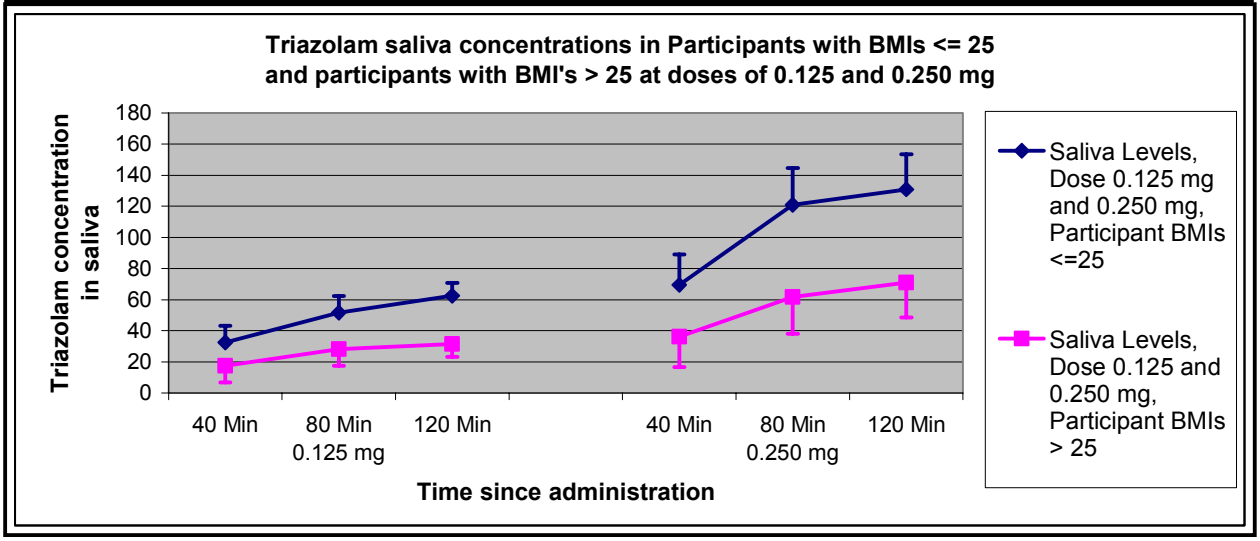
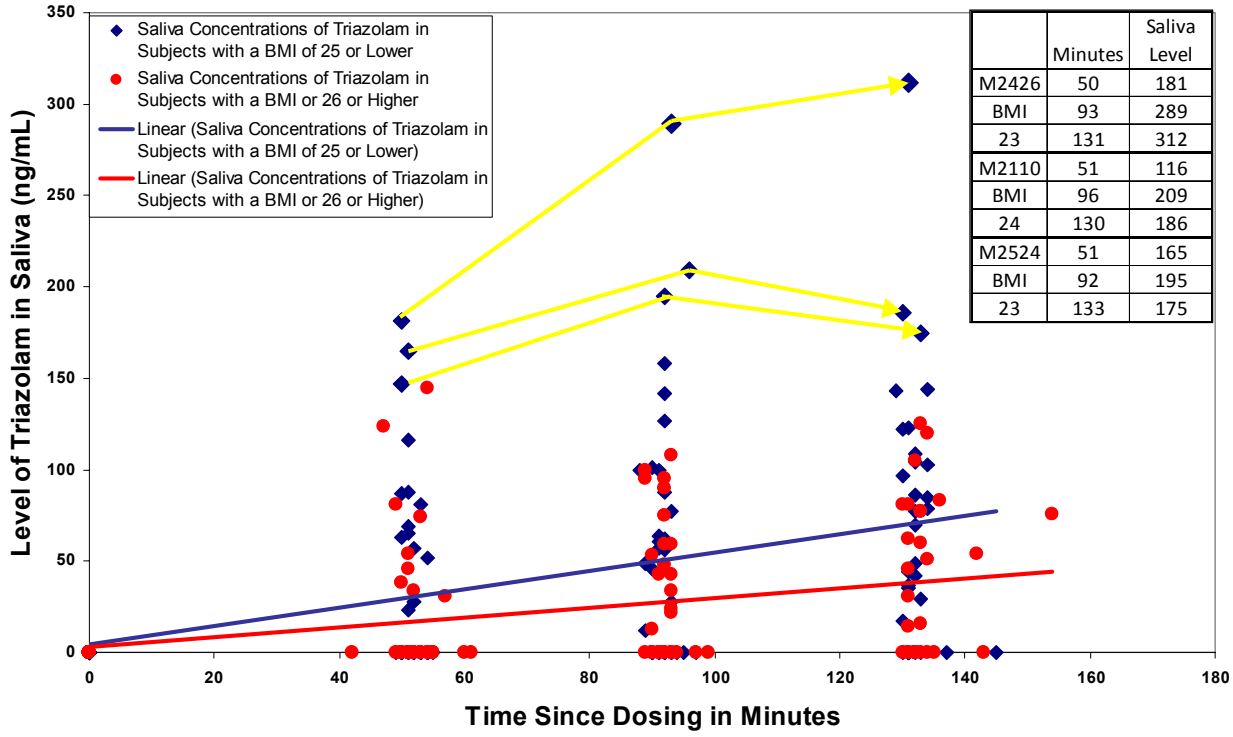


Figure 3-6 shows that saliva levels of Triazolam at a given dose and time are higher for persons with lean body mass (lower BMIs) and lower for persons with more fat body mass (higher BMIs). There are two possible explanations, and the true answer may be a combination. Heavier persons have a larger blood volume than lighter persons of the same height, and also have more body fat. The Triazolam dose may be dissolving in a larger reservoir of blood, and/or it may be partially soluble in body fat. If Triazolam is fat-soluble, it will reaching the blood stream more slowly and in lower concentrations for heavier persons than for lighter.

Figure 3-7 plots individual saliva concentrations at three time points for participants with BMI's of 25 or lower and for participants with BMIs of 26 or higher. The graph shows that participants with lower BMIs consistently have higher saliva concentrations. The graph also shows there were three participants who consistently had the highest saliva levels. The graph indicates that peak saliva levels were reached at 90 minutes and were declining in the 130-minute saliva samples. However, there is one participant, M2426, who has the highest levels of saliva Triazolam and those levels were still climbing in the 130-minute specimen. Two other participants, M2110 and M2524, had elevated saliva levels relative to the rest of the participants with BMIs less than 26, but their levels were dropping at 130 minutes.

Figure 3-7: Time course of saliva Triazolam concentrations for participants as a function of BMI



	Minutes	Saliva Level
M2426	50	181
BMI	93	289
23	131	312
M2110	51	116
BMI	96	209
24	130	186
M2524	51	165
BMI	92	195
23	133	175

This data validated the development of a BMI Index as an intervening variable in the analysis of Project PATH data.

3.5 Driver Score and Driver Score Index

The PATH team developed a method of analyzing and controlling for the influence of the skill level and driving style of the participants on the performance impact of the drug. The PATH team considered that, because the drug is a “tranquilizer”, there might a differential impact on drivers who drove impetuously from drivers who drove cautiously. Accordingly, the PATH team developed a rating system for driver style.

In preparation for the experiment, the PATH researchers created a “driver log” sheet for each of the 12 experimental drives. The driver log sheet listed the challenges and incidents that defined the segments of each drive (i.e. pedestrian in cross walk, truck makes a U-turn in front of bus, etc.). For each incident in the drive, the driver log sheet had a box to be checked if the driver negotiated the challenge correctly and a space for comments. The PATH researcher observed each participant making each drive and annotated the driver log.

Figure 3-8: Development of the Driver Score and Driver Index from the results of each driver’s base-line drive on day 1.

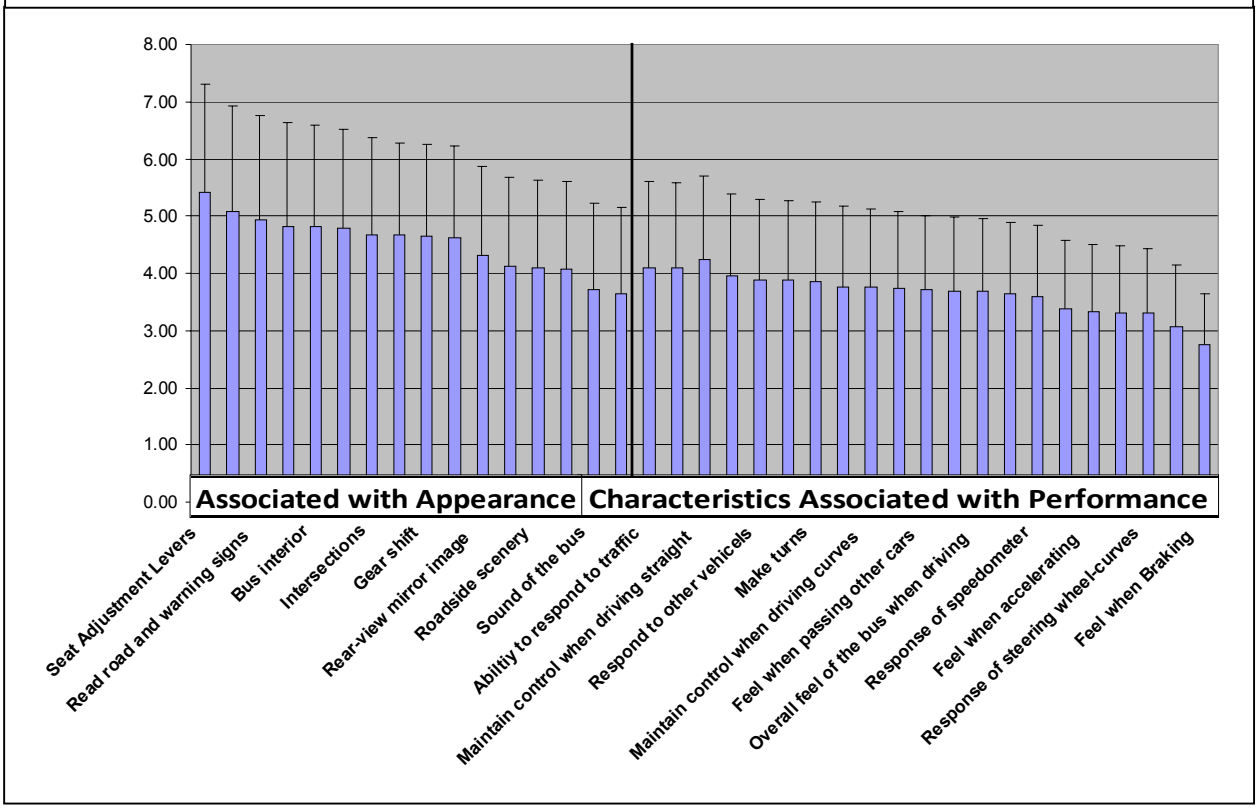
Subject Score V3D1	pedestrian swerve 1, ok 2	Ambulance, Collision 1, almost 2, stopped at yield 3	stop sign Collision 1, almost 2,no collision 3	Yield intersection, into other lane 1, ok 2	Total	Dose	Driver Score
M1902	1	1	1	1	4	0.125	1
M2314	1	1	2	1	5	0	1
M2618	1	1	3	1	6	0.125	1
M1909	2	1	1	2	6	0.25	1
M2031	1	1	3	2	7	0	1
M2310	2	1	3	1	7	0.125	1
M2225	2	1	3	2	8	0	1
M2130	2	1	3	2	8	0.25	1
M2106	2	2	2	2	8	0.25	2
M4005	1	3	3	1	8	0	2
M2212	1	3	2	2	8	0.125	2
M4003	1	3	3	1	8	0.25	2
M2007	1	3	3	2	9	0	2
M3417	1	3	3	2	9	0	2
M2322	2	3	3	1	9	0.125	2
M 5011	2	3	2	2	9	0.25	2
M2029	2	3	3	2	10	0	3
M2504	2	3	3	2	10	0	3
M2428	2	3	3	2	10	0.125	3
M2524	2	3	3	2	10	0.125	3
M4619	2	3	3	2	10	0.125	3
F2320	2	3	3	2	10	0.25	3
M2023	2	3	3	2	10	0.25	3
M2110	2	3	3	2	10	0.25	3
M2315	2	3	3	2	10	0.25	3
M2426	2	3	3	2	10	0.25	3

The PATH Team used the completed driver log sheets for the first (baseline) drive of the first experimental day, before the experimental capsule had been taken, to develop the index of driver style shown in Figure 3-8. Driver scores ranged from a low of 4 (a fast, impetuous driver) to 10, the slower, more cautious drivers. To simplify the analysis, the scores were then categorized into three groups as shown above. The Driver Score or Driver Score Index was included in the subsequent calculations of drug impact to identify and control for any differential impact associated with driver style.

3.6 Measures of Simulator Realism

After completing the experimental drives for the day, while waiting for their ride home, participants were asked to rate the "realism" of the simulator experience. Sixteen questions asked for ratings of qualities generally associated with the appearance of the bus and the scenery (e.g. Response of Seat Adjustment Levers, (0=Not realistic at all, 6=Completely Realistic, NA)). Twenty-one questions asked for ratings generally associated with the driving and handling performance of the simulated bus (e.g. Ability to keep straight in lane, (0=Not realistic at all, 6=Completely Realistic, NA)). The measures of simulator realism were collected to gain an understanding on how the participants rated the simulated driving experience as against real driving. This comparison might be useful in the discussion of the transferability of the experimental data to real driving.

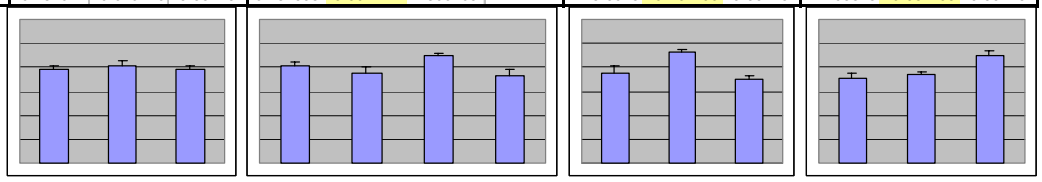
Figure 3-9: Overall ratings of simulator realism



As can be seen in Figure 3-9, drivers rated characteristics associated with the appearance the bus in the simulator generally higher (more realistic) than characteristics associated with the realism of the bus driving experience. Most of the ratings associated with the driving experience were above 3.0 on average, but "Feel when braking" generated an average score of 2.75. The scale used was an open rating scale (0=Not realistic at all, 6=Completely Realistic, NA). There were no adjectives associated with intermediate points in the open rating scale so it is not possible to associate an adjective level to a score.

Figure 3-10: ANOVA scores for Dose, Triazolam Index, Body Mass Index and Driver Score Index.

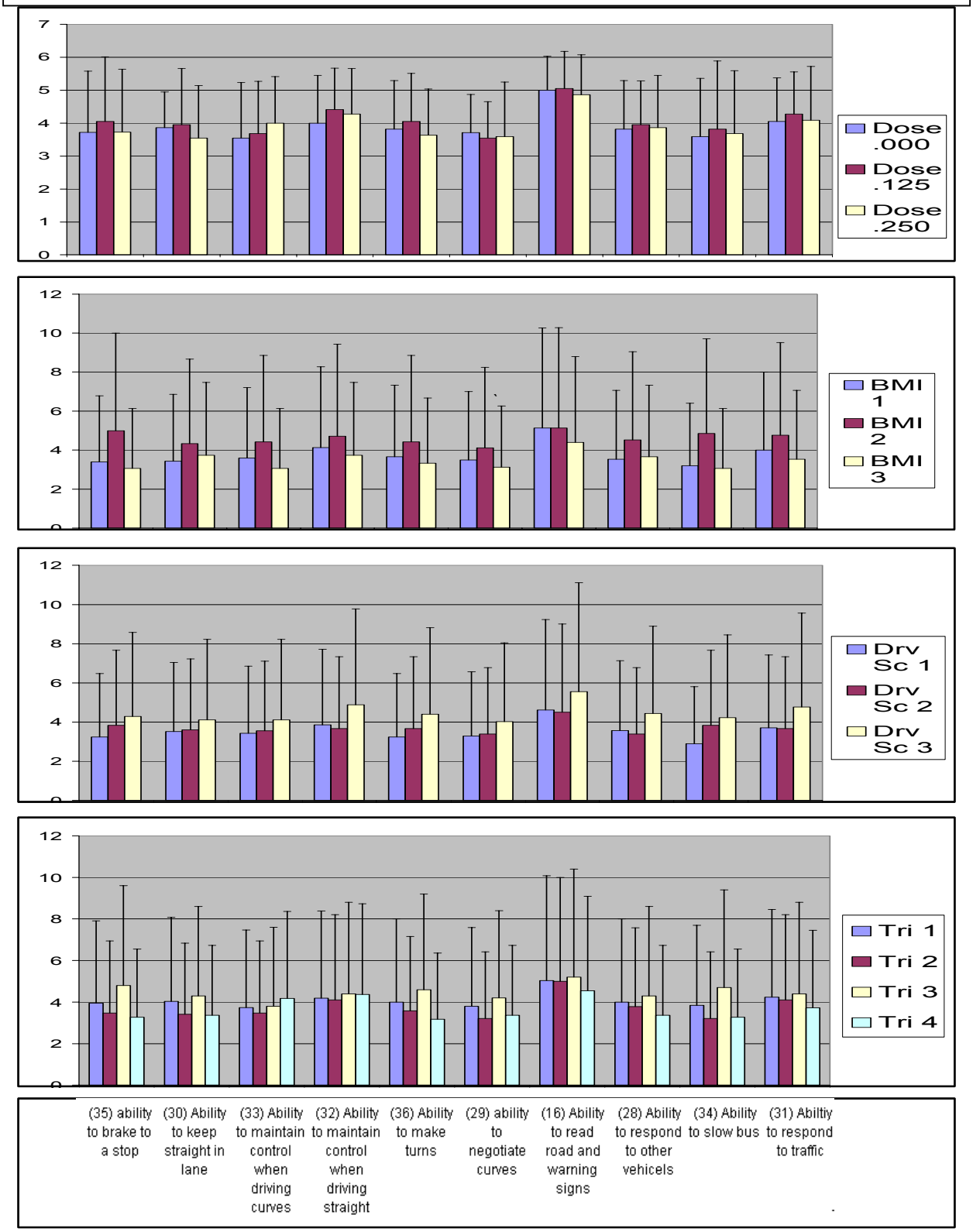
Similator Realism (0 - Not realistic to 6 Completely Realistic)	Dose of Triazolam			Triazolam concentration in saliva ng/mL				Body Mass Index			Driver Score Index		
	Dose .000	Dose .125	Dose .250	0 - 10	11 - 80	81 - 120	121 - 312	20 - 24	25 - 28	29 - 42	4 - 7	8 - 9	10
	Tri 1	Tri 2	Tri 3	Tri 4	BMI 1	BMI 2	BMI 3	Drv Sc 1	Drv Sc 2	Drv Sc 3			
(35) ability to brake to a stop	3.72	4.05	3.73	3.96	3.47	4.80	3.27	3.39	5.00	3.07	3.24	3.83	4.29
(30) Ability to keep straight in lane	3.86	3.95	3.55	4.04	3.42	4.30	3.36	3.43	4.33	3.73	3.52	3.61	4.11
(33) Ability to maintain control when driving curves	3.55	3.68	4.00	3.73	3.47	3.80	4.18	3.60	4.43	3.07	3.43	3.56	4.11
(32) Ability to maintain control when driving straight	4.00	4.41	4.27	4.19	4.11	4.40	4.36	4.13	4.71	3.73	3.86	3.67	4.89
(36) Ability to make turns	3.82	4.05	3.64	4.00	3.58	4.60	3.18	3.67	4.43	3.33	3.24	3.67	4.41
(29) ability to negotiate curves	3.71	3.55	3.59	3.79	3.21	4.20	3.36	3.50	4.12	3.13	3.29	3.39	4.02
(16) Ability to read road and warning signs	5.00	5.05	4.86	5.04	5.00	5.20	4.55	5.13	5.14	4.40	4.62	4.50	5.56
(28) Ability to respond to other vehicels	3.82	3.95	3.86	4.00	3.79	4.30	3.36	3.53	4.52	3.67	3.57	3.39	4.44
(34) Ability to slow bus	3.59	3.82	3.68	3.85	3.21	4.70	3.27	3.20	4.86	3.07	2.90	3.83	4.22
(31) Abiltiy to respond to traffic	4.05	4.27	4.09	4.23	4.11	4.40	3.73	4.00	4.76	3.53	3.71	3.67	4.78
Average	3.91	4.08	3.93	4.08	3.74	4.47	3.66	3.76	4.63	3.47	3.54	3.71	4.48
Variance	0.17	0.18	0.16	0.14	0.30	0.14	0.26	0.31	0.10	0.19	0.22	0.10	0.22
ANOVA	Anova: Single Factor			Anova: Single Factor				Anova: Single Factor			Anova: Single Factor		
Source of Variation	*F*	*P-value*	*F crit*	*F*	*P-value*	*F crit*		*F*	*P-value*	*F crit*	*F*	*P-value*	*F crit*
Between Groups	0.487977	0.619176	3.354131	6.484338	0.001271	2.866265		18.3045	9.46E-06	3.354131	14.05875	6.55E-05	3.354131



The realism scores were further examined to determine whether any of the intervening variables discussed earlier, Body Mass Index, Driver Score, Dose, or Saliva Level, would be reflected in the driver ratings for "Realism scores". Means and standard deviations were calculated for the realism scores sorted by Dose, Body Mass Index, Driver Score and Triazolam index. One-way Analysis of Variance (ANOVA) identified internal trends in the composite means of the realism data. The data table is in Figure 3-10 and the results are shown graphically in Figure 3-11.

The ANOVA for the means of the realism scores sorted by dose was not significant. However, there were significant ANOVA scores for realism means sorted by Driver Score, Body Mass Index and by Saliva Level. Participants with a Driver Score of 1 (the more impetuous drivers) gave the simulator experience lower realism scores than drivers with a Driver Score of 3, with participants with a Driver Score 2 falling in the middle ($p < .01$). This was the only linear relationship.

Figure 3-11: Means and standard deviations for the association of Dose, Body Mass Index, Driver Score and indexed value for Triazolam Level and participant scores for the simulator realism characteristics related to performance.



Bi-phasic relationships were found between the means of realism scores and Body Mass Index, and between realism scores and Saliva Triazolam levels.

As is seen in Figure 3-10, there is no correlation associated with Dose, at least as far as participant realism scores are distributed. However, there is a statistically significant pattern associated with the Triazolam saliva concentration, and it is not linear. Taking the scores for TRI 1 (no detected Triazolam in saliva) as a baseline; participants with low levels of Triazolam in saliva (Tri 2) give slightly lower realism scores. Participants with modest levels of saliva Triazolam (Tri 3) increase their scores for perceived realism on the driving experience, and participants experiencing higher levels of saliva Triazolam (Tri 4) again report a diminished perception of the realism of the experience.

This odd patterning of realism scores with Saliva Triazolam concentration is seen most clearly in the bottom graphs in Figure 3-11 in the responses to question 34 (Ability to slow the bus), 35 (Ability to brake to a stop), 36 (Ability to make turns), 28 (Ability to respond to other vehicles) and 31 (Ability to respond to traffic). Participants with Saliva Triazolam concentrations in the upper-middle range of 81-120 ng/mL (the third quartile) rated those elements of driving realism consistently higher than drivers with saliva Triazolam concentrations in the second or fourth quartiles of saliva concentrations.

This pattern factors into the next chapter's of the Project PATH analysis of the drug impact of the psychomotor tests. In that chapter we also have the conclusion that Triazolam may have a bi-phasic impact.

If Triazolam has a non-linear dose-related impact, that effect may be mitigated in complex ways by its interaction with the BMI of the participant and also his/her driving style. As can be seen in Figures 3-10 and 3-11, there is a strong "Inverted U" pattern associated with Body Mass Index. Participants with a middle range of Body Mass (BMI Index 2, BMI range 25 to 28) reliably provide scores indicating a higher level of perceived realism than participants with a low BMI index and also participants with a high BMI index.

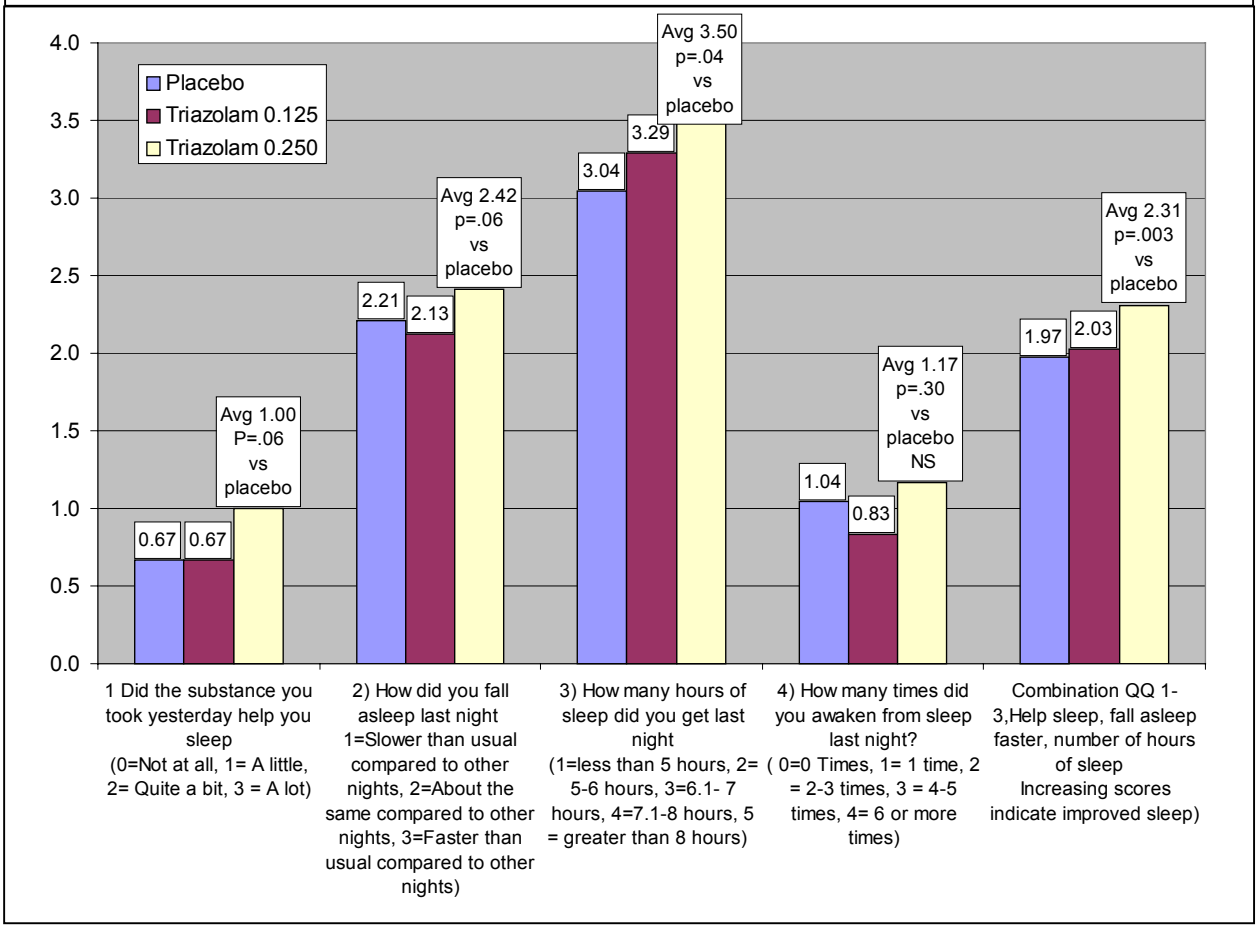
This complex relationship may be further mitigated by the driving style of the participant. As noted earlier, there is a linear and positive correlation between Driver Score (DRI SC in Figure 3-11) and realism scores. Drivers who are impetuous (at least as measured by the outcomes of their first experimental drive) report lower levels of perceived realism than the more cautious drivers with a Driver Score Index of 3 in the simulator.

3.7 Assistance with Sleep and Sleep Quality

When participants reported the next morning to take their next-day drive, they also filled out a questionnaire that asked whether the capsule they were given the previous day had any impact on their sleep pattern that night. The survey results are shown in Figure 3-12. Respondents reported that sleep patterns were slightly but statistically improved ($p<.003$ for the combined indices) on the night that the 0.25 mg dose had been received. There was no change in sleep quality on the night the 0.125 mg dose had

been received compared to sleep quality on the night that the placebo dose had been administered. This data replicates the findings of study to assess the safety and efficacy of Triazolam (Gibbons et al (1999))[33]. The higher (.25 mg) dose of Triazolam assisted the participants to fall asleep faster, sleep somewhat longer and have fewer nighttime wakenings.

Figure 3-12: Sleep Scores – Sleep Quality Improved by 0.250 mg Triazolam vs. Placebo, and No Change for the 0.125 mg Triazolam dose vs. placebo, and no Increase in Wakefulness Periods with Either Dose vs. Placebo



3.8 Simulator Sickness

Simulator sickness is a condition, somewhat similar to motion sickness, which many individuals experience in a simulator. The condition and intensity of simulator sickness has been examined for participants in flight simulators[39] and driving simulators[40]. There are two general theories of the cause of simulator sickness[41].

Figure 3-13: Simulator Sickness Cause Models

Cue Conflict Model

- Conflicting information about body orientation and motion received by the different senses
- Disparity between senses or within a sense
- The conflict thought to be at the root of simulator sickness is between the visual and vestibular senses.

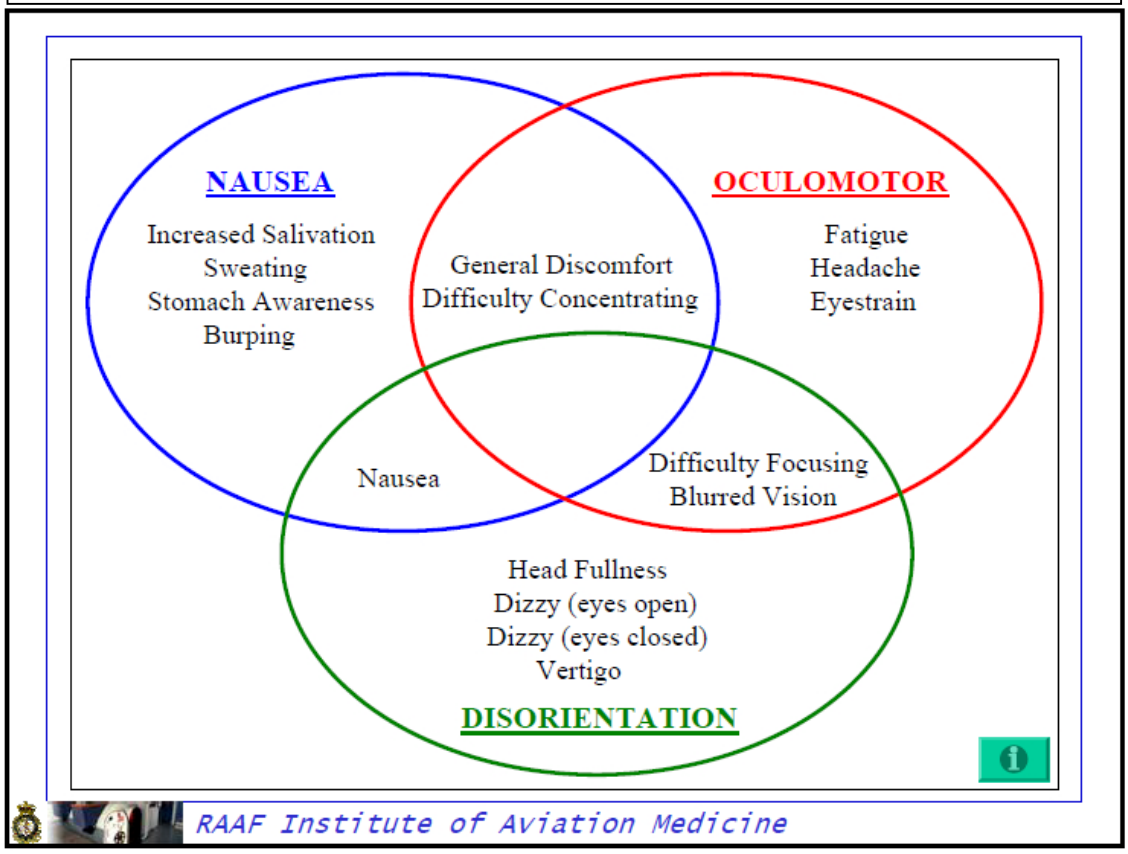
Expectancy Model

- A neural store of past experiences
- Compared to motion information received from senses
- A conflict between expected and experienced movement of sufficient magnitude can induce SIS, where an individual's ability to adapt is exceeded.

The conflict model states that the feelings of unwellness stem from the conflict between what your eyes experience and what your body fails to experience, i.e. feelings of acceleration, braking and turning. The expectancy model holds that simulator sickness arises because there is a conflict between remembered experiences of movement and the present virtual experience of motion without movement. That is, it is not the lack of movement per se, but the body's memory and preparation for movement where none follows. The theoretical explanations have not been resolved. However, the models shown in Figure 3-13 may imply a difference in the extrapolation of findings in a driving simulator to findings in real-driving situations, particularly for participants who experience noticeable levels of simulator sickness.

Simulator sickness is measured by a Simulator Sickness Questionnaire (SSQ) developed by Kennedy et al[42] in 1993. The questionnaire asks participants to rate, on a scale of None, Slight, Moderate, or Severe, their experience of 17 elements of unwellness. Those measures are then collected into three sub-scales: the N (Nausea) scale, the O (Occulomotor) scale, and D (Disorientation) scale. In addition, a total SSQ score is constructed by combining the subscores. A Venn diagram, from Corbett at al[40] showing the relationship of the rated items and the sub-scales is shown in Figure 3-14

Figure 3-14: Elements of the Simulator Sickness Sub-Scales from Corbett at al[40]



Before the start of the experimental runs, two simulator training drives were conducted by all potential participants, with the drives scheduled at least a day apart. PATH participants completed the Simulator Sickness Questionnaire (SSQ) after every drive, including the two training drives. The SSQ scores of participants on the training drives were used to screen out participants with a high susceptibility to simulator sickness. Simulator sickness is experienced more frequently by older participants [38,39,40], and experience in this experiment replicated those findings, as shown in Figure 3-15.

After completing two training drives, seven older PATH applicants were eliminated from the project due to high SSQ scores, as shown in Figure 3-15. Of the remaining 28 participants who were enrolled in the PATH project, (of whom four subsequently did not finish), 23, or 85%, reported a non-zero simulator sickness score on at least one session. The frequency of reports of simulator sickness are shown in Figure 3-16.

A cross correlation of the Simulator Sickness sub-scores with three variables, “Time since administration”, “Body Mass Index” and “Saliva concentration of Triazolam”, is shown in Figure 3-17. Figure 3-17 shows that O score and D score increase with increasing Triazolam concentrations, that Triazolam concentration is negatively correlated with BMI, and that persons with higher BMI scores record higher N (Nausea) scores - than persons with lower BMI scores.

Figure 3-15: Age of Participants Disqualified by Simulator Sickness from PATH Participation

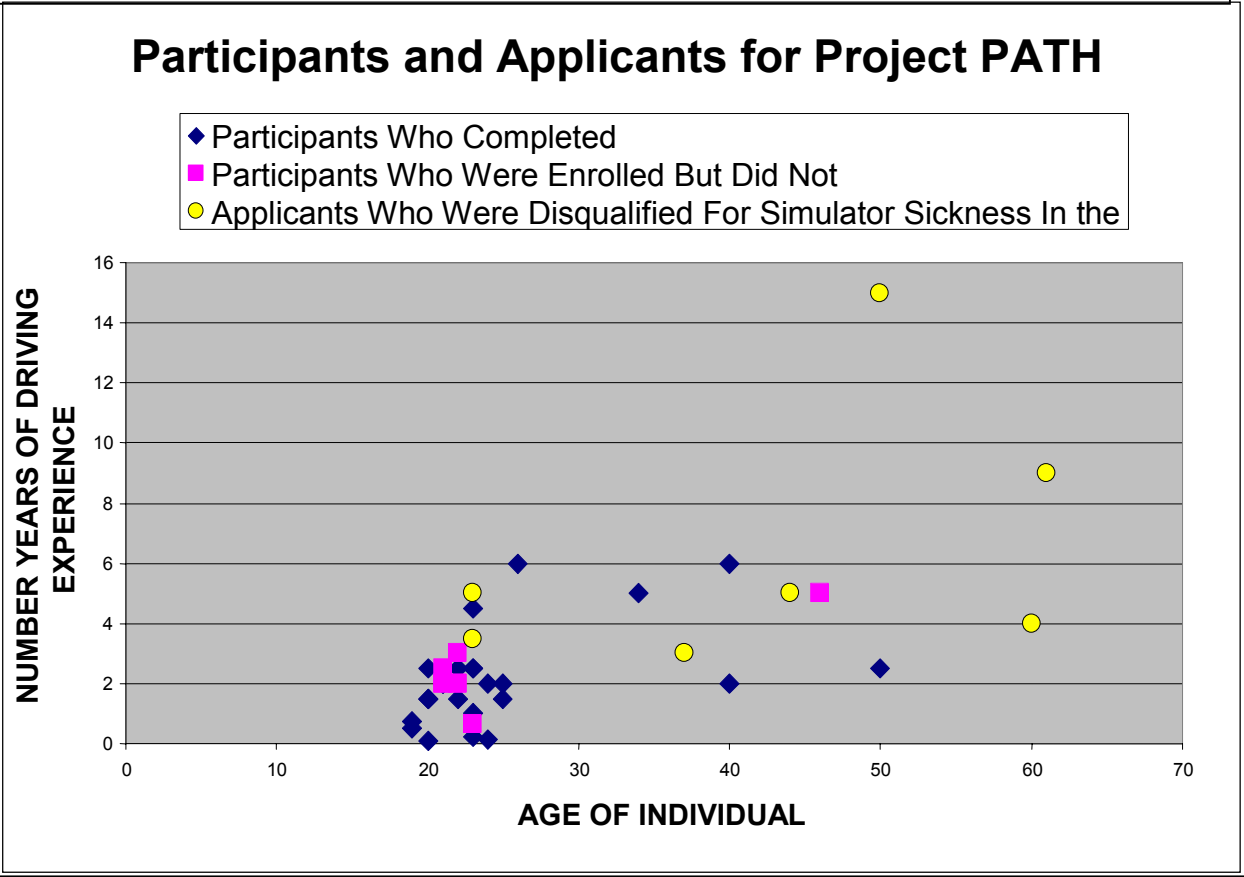


Figure 3-16: Frequency of drives and participants with simulator sickness

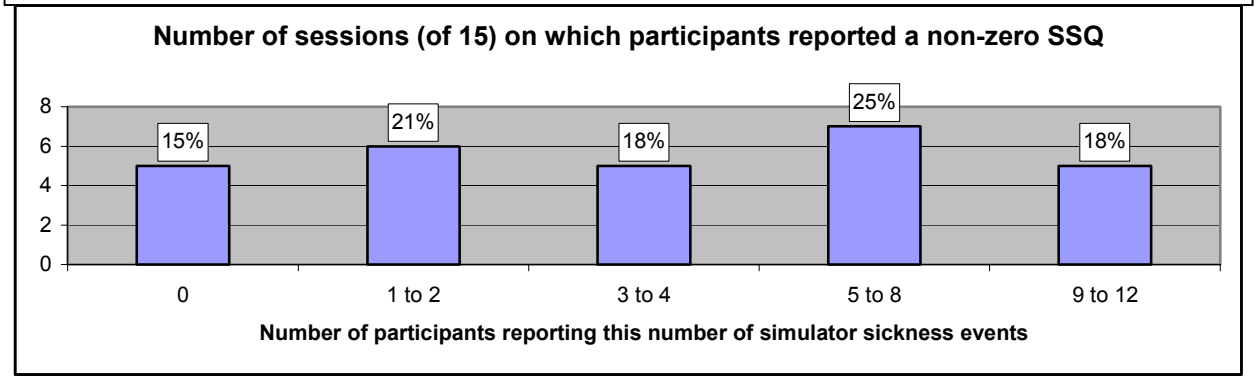


Figure 3-17: Correlation coefficients for PATH variables with SSQ

	BMI	*Time Since Dose Minutes*	*TRI Concentration pg/ml*	*N Score*	*O Score*	*D Score*
BMI	1					
Time Since Dose Minutes	0.009995513	1				
TRI Concentration pg/ml	-0.085765408	0.182070563	1			
N Score	0.10419997	0.030491594	0.068617599	1		
O Score	-0.067490872	0.113684192	0.200643398	0.711789363	1	
D Score	0.055465955	0.042180225	0.179804722	0.651128685	0.783665627	1

The average SSQ sub-scale scores by drive are in Figure 3-18 The Occulomotor scores are higher than either the Nausea or the Disorientation scores, with the general order of scores being O>D>N. This is the same order and magnitude of scores found by Mourant and Thattacherry (2000)[39]. Those authors reported that the ordering and magnitude of scores in their study was lower, and the ordering of scores was different, than reported in earlier studies. They speculated their lower SSQ scores and different ordering, with higher levels for Occolomotor than Nausea or Disorientation, may represent a higher level of realism associated with improved simulator technologies.

Figure 3-18: Average SSQ Scores by drive for all three experimental sessions

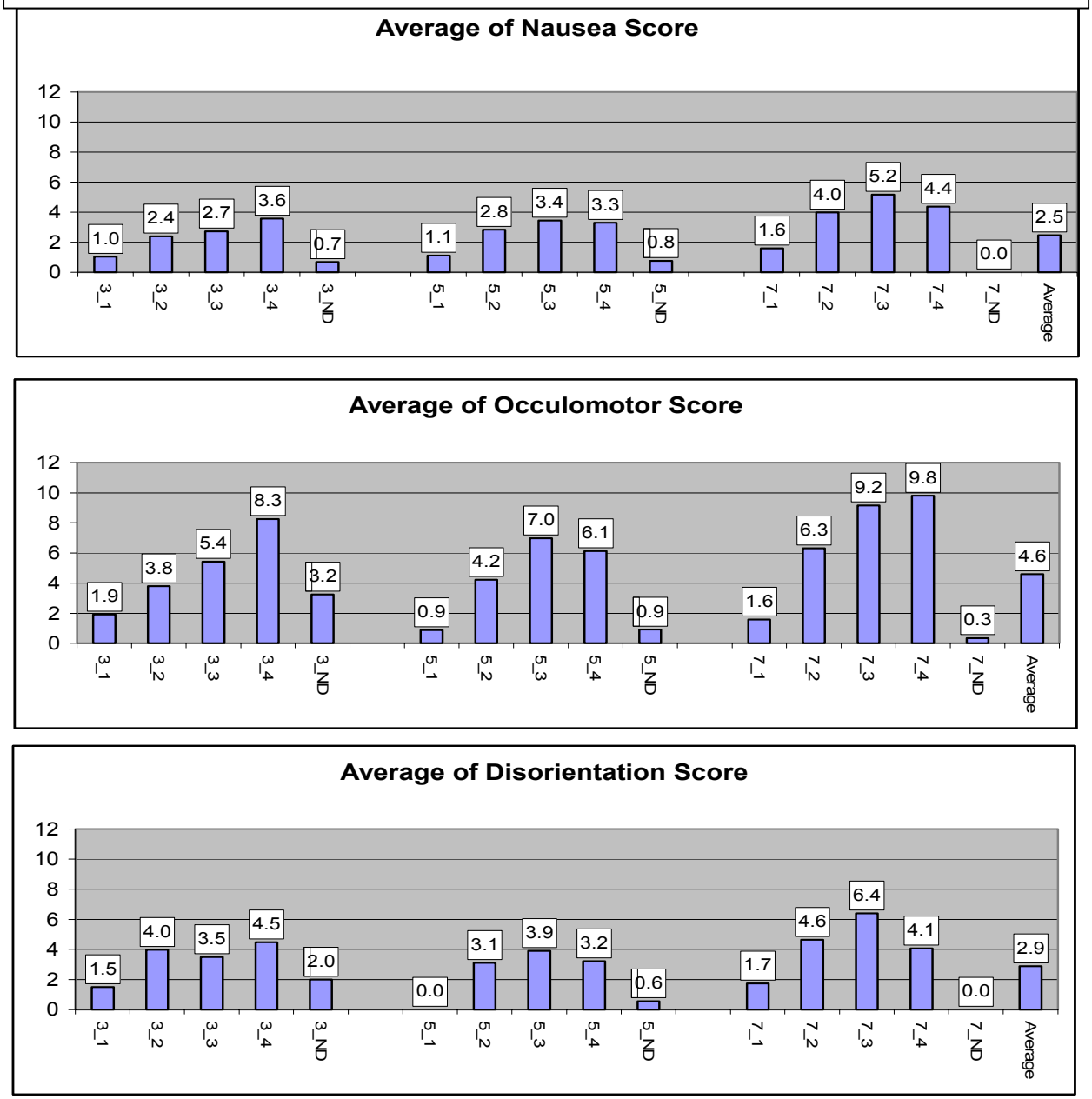


Figure 3-19 presents the results of the Multiple Liner Regression study of the SSQ score for the O (Occulomotor) component, the N (Nausea) component and the D (Disorientation) component regressed against Triazolam Concentration, BMI Score and Driver Score. The table presents the statistically significant intervening variables associated with elevated SSQ scores, together with the R^2 values, the probabilities and the coefficients. The column "Estimated SSQ Score" calculates the lowest and highest estimated value from the multiple regression linear estimate.

Triazolam concentration is the only significant contributor in the Occulomotor element of SSQ. The O score rises from a theoretical score of -0.53 at zero Triazolam to a theoretical score of 18.79 for the participant with the highest Triazolam concentration of 312 mg/ml. (The actual O score for this participant on this drive was 53.06, the highest recorded in this project.) BMI score and Triazolam concentration were significant contributors in the N (Nausea) score, and all three variables, BMI Score, Driver Score and Triazolam Concentration, significantly contributed to the final D (Disorientation) score.

Figure 3-19: SSQ Scores Regressed against Triazolam Concentration, BMI Score and Driver Score

Sig Variables	SSQ Factor	R^2 or P	Range of Variable		Estimated SSQ Score	
O Score			Min	Max	Min	Max
Multiple R		R^2 =0.278				
Regression	Coefficients	P=E-06				
Intercept	-0.53	0.90				
TRI Concentra	0.06	0.00	0	312	0.00	18.79
		Resulting Estimated Score			0.00	18.79
N Score						
Multiple R		R^2=0.183				
Regression	Coefficients	P=0.008	Min	Max	Min	Max
Intercept	-6.32	0.01			-6.32	-6.32
BMI Score	0.32	0.00	20	42	6.32	13.28
TRI Concentra	0.02	0.00	0	312	-6.32	6.78
		Resulting Estimated Score			-6.31	13.74
D Score						
Multiple R		R^2=0.218				
Regression	Coefficients	P=0.001	Min	Max	Min	Max
Intercept	-0.78	0.79			-0.78	-0.78
BMI Score	0.26	0.00	20	42	5.28	11.08
Driver Score	-0.49	0.03	4	10	-0.49	-1.48
TRI Concentra	0.04	0.00	0	312	-0.78	13.67
		Resulting Estimated Score			3.21	22.49

Calculated D Scores	Actual Combinations	BMI	Driver Score	Saliva Triazolam	Calculated D Score	Actual D Score
Participant with Highest BMI		42	9	125	12.91	14
Participant with Highest Triazolam		23	10	312	14.03	28

Figure 3-20 gives the final correlation coefficients for the intervening variables BMI Score, Driver Score and Triazolam concentration in relation to the categories in the Simulator Sickness Quotient. In the middle box, "Drives After Drug Taken", yields the following inference:

- Oculomotor Discomfort and Disorientation, but not Nausea, increased with increasing concentrations of Triazolam.
- Nausea scores, and to a lesser degree Disorientation scores, increased with increasing BMI scores.
- Driver scores and BMI scores are negatively correlated, as are Driver scores and Disorientation scores.
- The bottom box in Figure 3-20 yields the inference that, absent drug involvement, on the first drive of the day and the next day drive, N score, O score and D score was positively correlated with BMI score.
- The bottom box also yields the conclusion that the levels of Oculomotor discomfort and Disorientation were less on the Next-Day drive than on the Pre-Dose first drive of the day.

Figure 3-20: Final correlation matrix for PATH Intervening Variables

ALL 15 DRIVES

	Drivers Number 1-15	BMI Score	Driver Score	TRI Concentration (mc/ml)	N Score	O Score	D Score
Session Number	1						
BMI Score	-0.023888476	1					
Driver Score	0.005838229	-0.157321884	1				
TRI Concentration (mc/ml)	0.04465939	-0.04069014	0.020779165	1			
N Score	0.07160349	0.249920295	-0.034308352	0.147038802	1		
O Score	0.065156868	0.031104592	0.025478261	0.27612595	0.707349139	1	
D Score	0.026399681	0.190428213	-0.131668909	0.261127926	0.638376133	0.749650012	1

DRIVES AFTER DRUG TAKEN

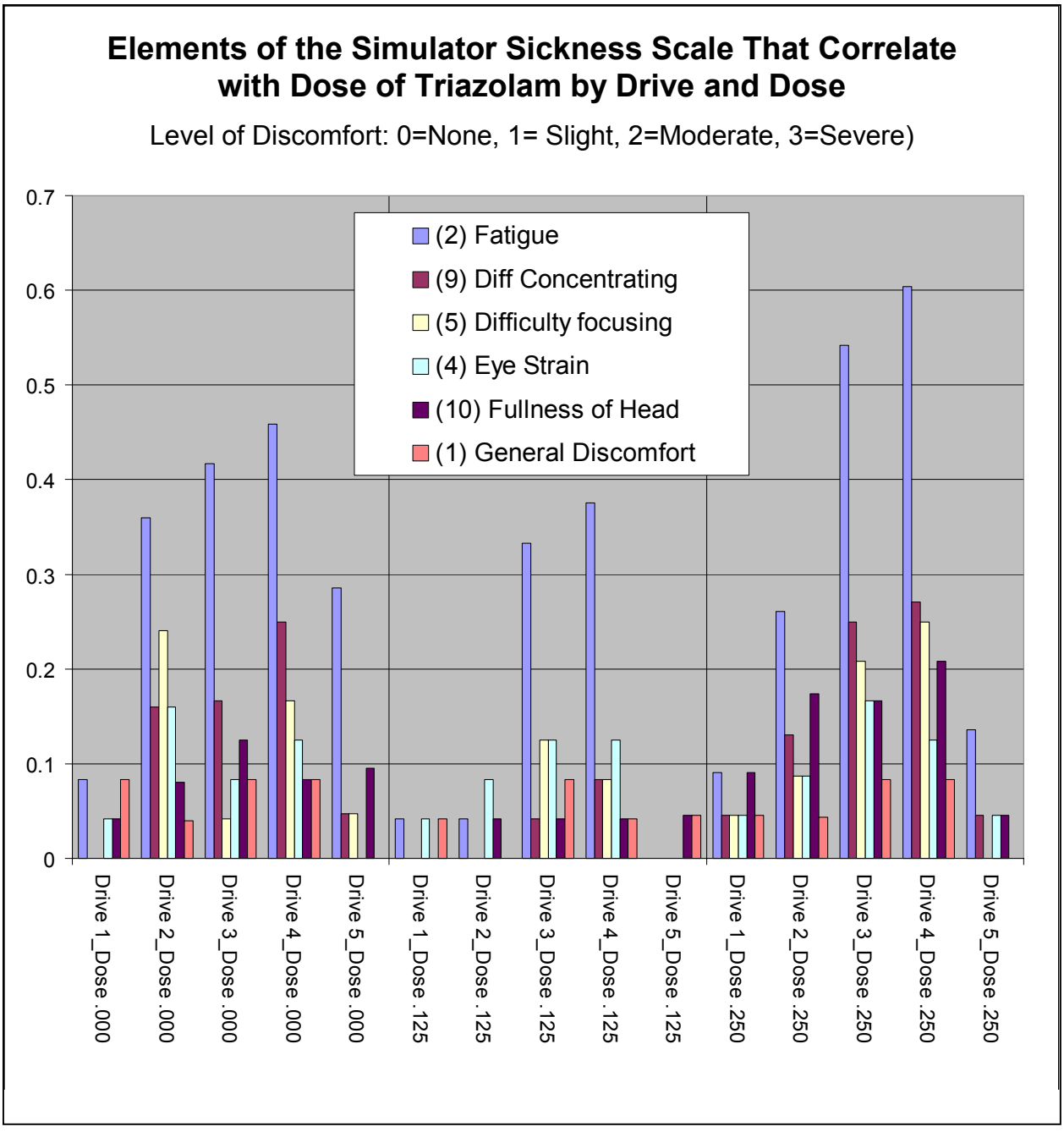
	Drives after drug administration	BMI Score	Driver Score	TRI Concentration (mc/ml)	N Score	O Score	D Score
Session Number	1						
BMI Score	-0.008556632	1					
Driver Score	0.007226529	-0.164264393	1				
TRI Concentration (mc/ml)	0.048478564	-0.061660194	0.025573581	1			
N Score	0.108975876	0.231888249	-0.024503385	0.07788177	1		
O Score	0.123824667	-0.007087095	0.032077543	0.210978312	0.722075223	1	
D Score	0.068835672	0.186939911	-0.136465578	0.219564703	0.636798414	0.742758588	1

DRIVES BEFORE DRUG AND NEXT DAY

	Drives before Drug vs Next day	BMI Score	Driver Score	TRI Concentration (mc/ml)	N Score	O Score	D Score
Day-Next Day	1						
BMI Score	-0.05946288	1					
Driver Score	0.014102048	-0.152803453	1				
TRI Concentration (mc/ml)	0.1358242	-0.029837392	0.021221051	1			
N Score	-0.035536107	0.371714211	-0.082311784	-0.02689046	1		
O Score	-0.130338189	0.180783279	0.00428718	-0.035236315	0.474911374	1	
D Score	-0.092263605	0.228443649	-0.150279545	-0.024943031	0.552394335	0.732623287	1

Figure 3-21 provides a further detailed look at the relationships between Triazolam (at the dose level) and the most significant elements of the Simulator Sickness Quotient. Fatigue is the largest contributor, and is an contributor to the Oculomotor subscale of SSQ. However, it can be seen that Fatigue scores were lower when the drivers received the 0.125 mg dose of Triazolam than when the drivers received the placebo or 0.250 mg dose. This is particularly so for the 2nd drive of the day (the 40 minute post-drug drive) and the next-day drive. The lower dose of Triazolam seems to energize,

Figure 3-21: Individual elements of the Simulator Sickness scale that are influenced Triazolam concentration.



rather than fatigue, the participants. There are also reductions in the average scores for "Difficulty Concentrating" and "Difficulty Focussing" for the 0.125 mg dose vs placebo and vs the 0.250 mg dose.

3.9 Summary of Section 3 – Intervening Variables

This chapter has examined the complex human factor interactions operating in this experiment which might impact the driving performance of each participant.

Some of these interactions can be predicted from Figures 3-20 and 3-21, the final table of correlation among the several variables under consideration. Some can only be known from their impact on experimental measures.

The summary table, Figure 3-22 indicates the following correlations:

Figure 3-22: Implications of correlations among PATH variables

Table to Reference	Correlation	Implication
ALL 15 DRIVES	Inverse relationship Driver Score and BMI Score	Heavier drivers tend to drive more impetuously
ALL 15 DRIVES	Positive relationship BMI Score and N and D Scales	Heavier drivers experience higher levels of sim sickness
ALL 15 DRIVES	Inverse relationship Driver Score and D Scale	Less impetuous drivers experience less sim sickness
ALL 15 DRIVES	Positive correlation TRI concentration and SSQ	Persons with higher levels of TRI have more sim sickness
DRIVES AFTER DRUG TAKEN	Increased N and O Scores by drive number	Simulator sickness increases within session
DRIVES AFTER DRUG TAKEN	Reduced Fatigue, Diff Concentrating and Diff Focussing scores for the 0.125 dose vs placebo and the 0.250 dose.	There appears to be a stimulatory effect, rather than a depressing effect, of the lower dose of Triazolam.
DRIVES BEFORE+NEXT DAY vs DRIVES AFTER DRUG	The Optomotor scale is much lower for high-BMI drivers after drug than before	Triazolam strongly reduces the level of Optomotor sim sickness for heavier drivers
DRIVES BEFORE+NEXT DAY vs DRIVES AFTER DRUG	The N and D scales are lower for high-BMI drivers after drug than before	Triazolam reduces the level of Nausea and Disorientation for high-BMI drivers

Other interactions discussed in this chapter yield the following inferences:

1. Participant drivers recognize and report the impairing effects of Triazolam on driving straight in lane, and to a less extent, on curve following. They do not report drug-induced impairment associated with seeing people and things along the way, anticipating problems that may arise or following verbal directions. The impairment correlates strongly with the concentration of Triazolam in their saliva at the time of the drive, but not with dose level.

2. There is a high level of individual variance in the concentration of Triazolam measured in the saliva samples. The inference is that there is a high level of individual variance in plasma Triazolam levels, presumably leading to individual variances in the level of drug impact.
3. The concentration of saliva in participant saliva is negatively correlated with the Body Mass Index of the participant. For the same dose, persons with a low BMI have almost twice the saliva concentration of Triazolam as compared participants with high BMIs. Inferentially, drivers with low BMIs are more impaired then drivers with high BMIs at the same dose.
4. Each participant's perception of the realism of driving the simulator is modulated in relation to the concentration of Triazolam in saliva, their BMI, and their style of driving.
   - Participants with high Driver Scores (conservative drivers) report a higher level of simulator realism than persons with low Driver Scores (aggressive drivers).
   - Participants with moderate BMIs report a higher level of simulator realism than persons with low or high BMIs.
   - Participants with a moderate concentration of Triazolam in their saliva report higher levels of simulator realism than persons with low or high Triazolam concentrations.
5. Virtually all (23 of 24) of the participants reported at least one instance of simulator sickness. Almost 50% of the participants reported feeling simulator sickness on five or more of their 15 drives.
   - The elements of SSQ included in the categories of Oculomotor Discomfort and Disorientation (Fatigue, Headache, Eyestrain, Difficulty Focussing, Blurred Vision, Head Fullness, Dizzy (eyes open), Dizzy (eyes closed) and Vertigo) correlate more highly with concentration of Saliva Triazolam that the elements in Nausea (Increased Salivation, Sweating, Stomach Awareness, Burping).
   - The Fatigue measurement is the primary component of the Oculomotor SSQ sub-scale. The relationship of dose of Triazolam to Fatigue, Difficulty Concentrating and Difficulty Focussing is not linear. Drivers report less discomfort associated with those elements after having taken the 0.125 mg dose than after having taken the placebo (0.000) and the 0.250 mg dose of Triazolam.

4 PSYCHOMOTOR TEST BATTERY

4.1 Research using psychomotor test batteries

As explained in Section 2, the PATH experimental design includes three separate methods for assessing operator performance. These are 1) the operator's performance in the driving simulator, 2) the operator's performance on a psychomotor test battery given immediately before each of the four experimental drives on the three experimental sessions and also immediately before performing the next-day drive, and 3) the use of eye-tracking technologies.

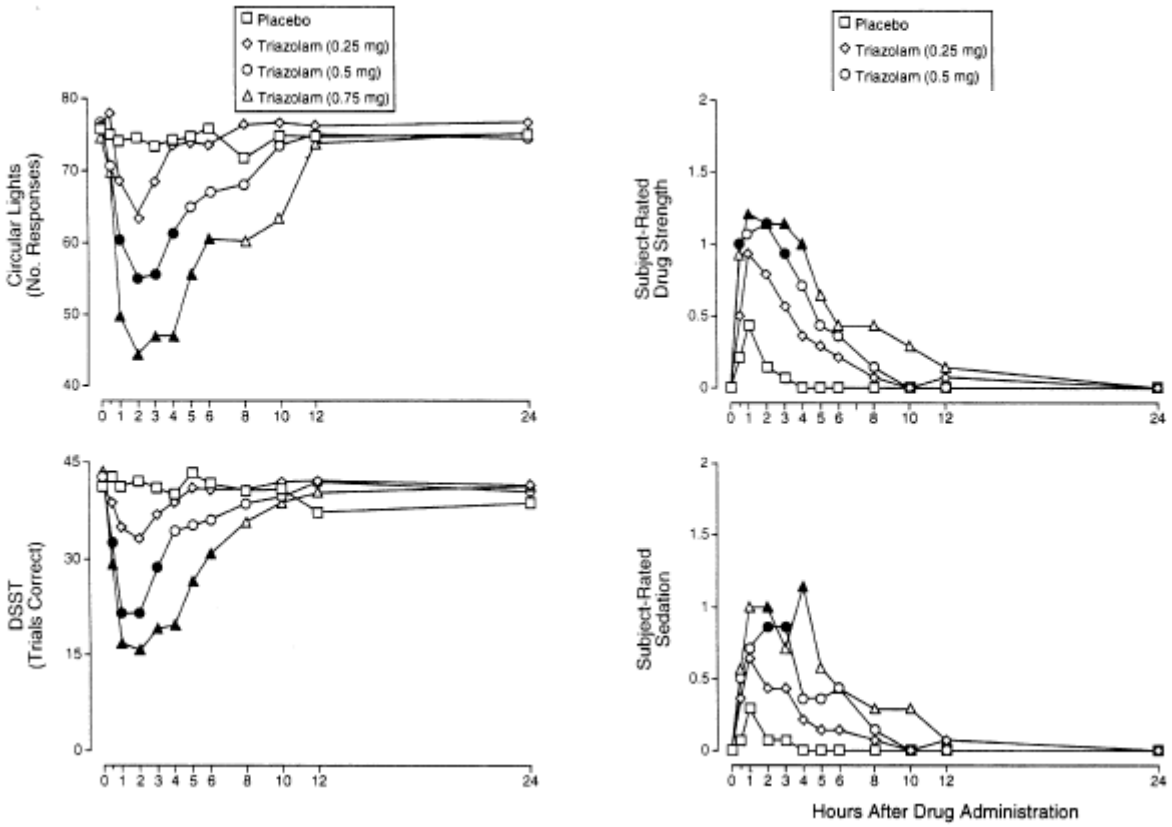
This section will discuss the design and results of the psychomotor test battery. The purpose of including a psychomotor test battery is to obtain objective measures of performance that might relate to several of the skills needed for safe driving. These include psychomotor tests include reaction time measures, indices of eye-hand coordination, measures of "stop or proceed" discrimination and reaction time, working memory indices, and shape visualization and retention tests.

Numerous researchers have included a psychomotor test battery in their research on the effects of Triazolam and other psychoactive drugs[43],[44]. Generally, the psychomotor test battery has included subjective-rating scores paired with a reaction-time test, a tracking test and a memory test. For instance, the experiment conducted by Rush et al (1999)[45] compared the behavioral impact and abuse potential of Triazolam (Halcion) and Zaleplon (Sonata). In a separate publication, Rush et al[46] compared the behavioral and abuse potential of Triazolam and Zolpidem (Ambien). The Triazolam – Zaleplon comparison recorded the drug effects for 24 hours, and is somewhat more useful for purposes of this paper than the Triazolam – Zolpidem comparison, which followed the drug effects for five hours. Objective and subjective indicators of the peak effects of the Triazolam-Zolpidem comparisons are shown in Figure 4-1 on the following page.

Peak effects were observed for all three drugs in the 1- and 2-hour trials. Subjective ratings of drug effect for the lowest dose of each drug (the recommended therapeutic dose) returned to baseline by four hours, though the subjective effects of super-therapeutic doses lasted longer. The therapeutic dose of Triazolam was 0.25 mg, and the supra-therapeutic doses were 0.50 and 0.75 mg. Similarly, the behavioral impairment measured in the psychomotor tests returned to baseline for the lowest dosage by four hours post administration, and by 12 hours post-administration for all dosages. Behavioral impacts of Zaleplon, in the Zaleplon-Triazolam comparison, returned to baseline faster than the behavioral impacts of Triazolam, but otherwise were largely indistinguishable. The authors concluded that all three drugs produce comparable dose-related performance impairment.

In Figure 4-1, for the 0.25 mg therapeutic dose, the psychomotor measures "Circular Lights" and "DSST", and the participant reports of "Drug Strength" and "Sedation" and never statistically different than the placebo measures (data markers are not filled), but the trends are obvious. The psychomotor test scores for the 0.250 mg dose return to

Figure 4-1: Objective and Subjective (Participant) Measures of Impairment for Three Dose Levels of Triazolam in Experienced Drug-Using Subjects



Rush, CR, Frey, JM, Griffiths, RR, Zaleplon and triazolam in humans: acute behavioral effects and abuse liability: Psychopharmacology, 145; 39-51 (1999)

baseline by four hours after administration and the subjective measures return to baseline by eight hours post-administration.

In contrast, it can be seen that the two objective psychomotor measures of impairment were still elevated for Triazolam doses of 0.5 mg and Triazolam 0.75 mg at eight hours, especially so for the tracking test “Circular Lights”. However, the subjective measures “Drug Strength” and “Sedation” have largely returned to baseline for the 0.5 mg Triazolam dose by eight hours.

These studies may imply that there may be a reversal of objective and subjective measures of impairment for supra-therapeutic doses of Triazolam. Persons taking a therapeutic dose may believe themselves to be more impaired that they actually are 8 hours following administration. Logically, those persons would attempt to compensate by more-careful maneuvering. Individuals taking a supra-therapeutic dose, on the other hand, may be more debilitated than they think they are 8 hours after administration and may fail to compensate for their impairment through more-careful maneuvering.

4.2 The PATH Psychomotor Battery

Walsh et al[47] , in "Guidelines for Research on Drugged Driving", in Recommendation B1, states "Researchers should use tests that have been validated to be sensitive to drug effects on driver performance, and to the extent possible, have demonstrated predictive validity of driving impairment." To this end, the PATH staff identified a computerized psychomotor research battery that seemed appropriate for this study. The test battery, originally developed for the US Army, has been generalized and "normed" with populations similar to the research subjects in this experiment.

After researching the available alternatives. The PATH team selected elements of the test battery available from the Center for the Study of Human Operator Performance (C-SHOP) at the University of Oklahoma. As described on the C-SHOP website[48],

ANAM® Battery and Test Descriptions

> The Automated Neuropsychological Assessment Metrics (ANAM®) test system consists of a library of tests designed for a broad spectrum of clinical and research applications. This library of computer-based tests was constructed to meet the need for precise measurement of cognitive processing efficiency in a variety of psychological assessment contexts that include neuropsychology, readiness to perform, neurotoxicology, pharmacology, and human factors research.
>
> The Automated Neuropsychological Assessment Metrics (ANAM®) was initially developed within the Department of Defense in the early 1990's. With ongoing DoD support, ANAM® has undergone several revisions and its use has spread from defense-related research to other academic research areas.
>
> An ANAM® battery is a collection of several tests that are selected by the test administrator to run in an overarching, sequential manner. The specific tests assess different basic functions (or domains) of cognition such as attention, reaction time, memory, and concentration. ANAM® can be self-administered by the user and takes approximately 30-90 minutes to complete depending on the battery selected. A standard PC is required for running ANAM®, as is a keyboard, standard monitor, and mouse.

As explained above, the ANAM battery in its default configuration would normally require 30-90 minutes to complete. That clearly would not meet the needs of the PATH experimental design. The PATH team worked with C-SHOP personnel to select a group of tests that would assess the desired psychometric dimensions and were tests that could not be "learned". That is, the tests selected do not have a confounding variable of improvement over repeated trials. Since each participant would perform the battery just before each experimental drive, each participant would complete fifteen (15)

iterations of each test bank. Also, the bank of tests selected would also need to be performable in a five-to eight-minute window to fit into the experimental schedule.

The elements of the ANAM full battery selected for PATH consist of the following tests performed in the following order.

Accordingly, the PATH Administrator worked with C-SHOP designers to select a representative sub-set of tests for this experiment. Having selected the prospective test battery, the PATH Administrator then prepared a version of that test battery with the default number of repetitions of each test (usually 20 presentations of the target stimulus) and also a shortened versions, with five repetitions of stimulus in each test.

For instance, in the Simple Reaction Time test, the participant clicks the mouse button as soon as the participant sees an asterisk (*) displayed on the screen. In the default arrangement, the asterisk is presented 20 times. The software calculates the means and standard deviations of the times between display and mouse click, as well as the number of anticipatory clicks (i.e. clicks concurrent with or less than 10 milliseconds after the display – too fast for human reaction). In the shortened version, the asterisk is presented 5 times rather than 20.

The PATH Administrator also recognized that there was more flexibility in time before the participant started the first drive of the day, and before the participant started the next-day drive, than there was flexibility in the schedule after the first drive. That meant that it would be possible to retain the default number of reiterations of each stimulus for the test battery given before the first drive of the day and before the next-day drive, while using the shorter battery for the between-drives tests.

In order to get a more accurate metric of any pre-drug vs. next day impact (if any), the Administrator determined to retain the default number of iterations of stimulus presentation in each task for the first drive of the day and the next-day drive. That longer battery of tests required about 12-15 minutes to complete. That was too long, however, for the period available between the daily runs. Accordingly, for the between-runs psychomotor battery, the Administrator determined to use the shortened version with 5 repetitions per test. That shorter test battery required about 7 minutes. It was feasible to administer the shorter battery just before the 40, 80 and 120 minute drives.

The elements of the PATH test battery used in this project are the following, in the order presented to the participants. The full name and three-letter test name are shown.

Test 1 - Modified Stanford Sleepiness Scale (i.e. “slp test”)

This test permits self-assessment of the user's sleep/fatigue state. The user is presented with seven different statements of alertness/sleepiness, ranging from “Feeling very alert, wide awake, and energetic” to “Very sleepy and cannot stay awake much longer.” The user is instructed to select the one statement that best matches their current state.

Test 2 - Mood Scale II – Revised (i.e. “moo test”)

As described in the ANAM website, “This test permits self-assessment of the user's mood state in seven categories: Vigor (high energy level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low energy level), Anxiety (anxiety level), and a new subcategory of Restlessness (motor agitation). The user is presented with a scale of numbered blocks ranging from 0 to 6, with "0" having the verbal anchor “Not at all,” the midpoint "3" labeled “Somewhat” and "6" labeled “Very much.” The user is presented a series of adjectives, each adjective contributing to one of the mood categories, and is instructed to select the box/number that best represents the current state with respect to the presented adjective.”

Test 3 - Simple Reaction Time (i.e. “srt test”)

This test measures simple reaction time by presenting the user with a series of "*" symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.

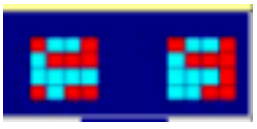
Test 4- Procedural Reaction Time (i.e “pro test”)

This test measures the reaction time and processing efficiency associated with following a simple set of mapping rules. In the Basic Block, the user is presented with a number constructed on the display using a large dot matrix (either a 2, 3, 4, or 5). The user is instructed to press the left mouse button for a “low” number (2 or 3) and the right mouse button for a “high” number (4 or 5).

Test 5 - Mathematical Processing (i.e. “mth test”)

This test assesses basic computational skills, concentration, and working memory. An arithmetic problem involving three single-digit numbers and two operators is displayed (e.g., "5 - 2 + 3 ="). The user presses the left mouse button to indicate whether the answer to the problem is less than five or and the right mouse button if the answer is greater than five.

Test 6 - Matching to Sample (i.e. “m2s test”)



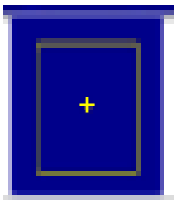
This test assesses spatial processing and visuo-spatial working memory. The user views a pattern produced by eight shaded cells in a 4x4 sample grid. The sample is then removed and two comparison patterns are displayed side by side. One grid is identical to the sample grid and the other grid differs by one shaded cell. The user is instructed to press the left or the right mouse button to select the grid that matches the sample.

Test 7 - Standard Continuous Performance Test (i.e. “scp test”)

This test assesses sustained attention, concentration, and working memory. A target character is displayed for memorization, in this case, a large letter “X”. As other individual characters are displayed in

sequence (e.g. a large letter “O”), the user presses a designated button only if the target letter is displayed and refrains from pressing if other than the target letter is displayed.

Test 8 - Pursuit Tracking (i.e. “pur test”)



This test assesses visuo-motor control. The user is instructed to move the mouse such that the mouse pointer tracks the little “+” in a moving box. The pointer should remain inside the box and be kept as close as possible to the "+". Options exist for the box to move horizontally, vertically, in a circle, along a square wave, or along a sine wave. For the PATH project, the box moved in a circular path.

The average time participants required to complete these tests, arranged by drive number, is shown in Figure 4-2. The pattern of test times is clear, with the longer versions of the battery, before the first drive of the day, and before the next-day drive.

The actual times were a little longer than in the table because the data is computed from the start time of each test, and there is no completion time for the test battery. Consequently, the time required for the final test in the battery, the pursuit test, is not included in the total time. That test probably added about another minute to the total.

Figure 4-2: Average times for completion of the PATH psychomotor test

AVERAGE TEST TIME	DRIVE 1	DRIVE 2	DRIVE 3	DRIVE 4	DRIVE 5
Start time of slp time	0:00:00	0:00:00	0:00:00	0:00:00	0:00:00
Start time of moo time	0:00:19	0:00:12	0:00:11	0:00:08	0:00:30
Start time of srt time	0:02:05	0:01:49	0:01:49	0:01:43	0:01:44
Start time of pro time	0:01:19	0:00:37	0:00:33	0:00:37	0:01:13
Start time of mth time	0:01:32	0:00:49	0:00:49	0:00:48	0:01:25
Start time of m2s time	0:01:52	0:00:58	0:00:58	0:01:04	0:01:51
Start time of scp time	0:04:06	0:01:24	0:01:24	0:01:30	0:04:02
Start time of pur time	0:01:41	0:01:39	0:01:38	0:01:38	0:01:37
Total Time	**0:12:54**	0:07:28	0:07:22	0:07:28	**0:12:23**
AVERAGE TEST TIME	DRIVE 6	DRIVE 7	DRIVE 8	DRIVE 9	DRIVE 10
Start time of slp time	0:00:00	0:00:00	0:00:00	0:00:00	0:00:00
Start time of moo time	0:00:20	0:00:08	0:00:08	0:00:14	0:00:08
Start time of srt time	0:01:47	0:01:36	0:01:44	0:01:42	0:01:44
Start time of pro time	0:01:13	0:00:34	0:00:39	0:00:34	0:01:14
Start time of mth time	0:01:25	0:00:46	0:00:49	0:00:51	0:01:23
Start time of m2s time	0:01:45	0:01:00	0:01:01	0:01:02	0:01:45
Start time of scp time	0:04:05	0:01:28	0:01:33	0:01:24	0:03:57
Start time of pur time	0:01:45	0:01:44	0:02:58	0:01:43	0:01:52
Total Time	**0:12:19**	0:07:16	0:08:51	0:07:29	**0:12:02**
AVERAGE TEST TIME	DRIVE 11	DRIVE 12	DRIVE 13	DRIVE 14	DRIVE 15
Start time of slp time	0:00:00	0:00:00	0:00:00	0:00:00	0:00:00
Start time of moo time	0:05:02	0:00:07	0:00:08	0:00:07	0:00:11
Start time of srt time	0:01:30	0:01:31	0:01:33	0:01:30	0:01:39
Start time of pro time	0:01:10	0:00:31	0:00:37	0:00:31	0:01:12
Start time of mth time	0:01:23	0:00:44	0:00:43	0:00:48	0:01:18
Start time of m2s time	0:01:37	0:00:55	0:00:57	0:00:54	0:01:55
Start time of scp time	0:03:52	0:01:22	0:01:21	0:01:23	0:03:44
Start time of pur time	0:02:00	0:02:02	0:02:02	0:02:03	0:01:51
Total time	**0:12:17**	0:07:12	0:07:21	0:07:17	**0:12:04**

4.3 First (Baseline) Drive vs Next Day Results

The primary purpose of comparing the psychomotor scores on the first drive of the day against the scores on the next-day drive, 12 to 18 hours later after a sleep cycle, was to begin to answer the question of whether Triazolam in the doses used in this project have a detectable hang-over effect. The hypothesis was that there would be no residual impact. If a residual impact was found, the object would become to determine whether it was a residual impact of the drug or the result of some other factor.

A secondary objective in comparing the baseline drive against the next-day drive was to identify any impact of the intervening variables identified in Section 3 on the psychomotor battery. Would any of these variables modify the results of tests taken before ingesting the 0.125 mg or 0.250 mg drug dose or placebo or after a normal sleep cycle.

4.3.1 Standard Continuous Performance Test (i.e. "scp test")

Figure 4-3 presents the results of the baseline drive-next-day drive results for the Standard Continuous Performance (SCP) test. The left column of the graphic shows the results of the T-test comparing the means of the reaction time for the SCP test on the baseline drive against the mean reaction time on the next-day drive. The mean reaction time of the baseline drives is 374 milliseconds and the mean reaction time of the next-day drives is 391 milliseconds. The differences are significantly different with a probability of P=.009.

There was a statistically significant elevation of response times on the scp test taken next-day relative to its baseline day. It is necessary to review the causes of that difference.

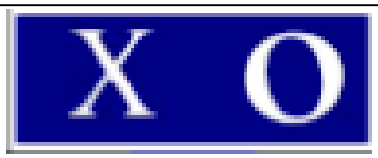
The Standard Continuous Performance (i.e. scp test) test is the only test in the battery that requires the participant to make a choice of whether or not he/she should click the mouse key in response to a stimulus. As such, it is the only "go/no-go" test.

A "target" stimulus presented briefly on the computer screen was a large "X". The screen then blanked out, after which a new stimulus was presented. If the stimulus is the pre-viewed target stimulus, the participant should click the key. If the stimulus is any other letter of the alphabet (e.g. a large "O"), the participant should not click the key. All of the other choice tests in the battery ask the participant to click either the left or the right key depending on the stimulus presented, but not to refrain from clicking.

As shown in Figure 4-3, there was a statistically significant difference between the pre-drive reaction time on this test and the next-day reaction times. The reaction times on the next-day test were slower than on the pre-drive tests ($p < .01$ two-tailed). This was the only test in the PATH battery for which a statistically significant difference was

determined for the pre-dose vs next-day test and for which no easy explanation could be found.

Figure 4-3: SCP Test -- t-Test for Means and Regression



Mean SCP Response Time Baseline and Next day
t-Test: Paired Two Sample for Means

	Baseline
Mean	374.90903
Variance	2409.9468
Observations	72
	Next Day
Mean	391.18236
Variance	3039.3677
Observations	72
Pearson Correlation	0.5075063
Hypothesized Mean Differen	0
df	71
t Stat	-2.656311
P(T<=t) one-tail	0.0048746
t Critical one-tail	1.666599
P(T<=t) two-tail	0.0097491
t Critical two-tail	1.9939444

SCP Mean Response Time
SUMMARY OUTPUT

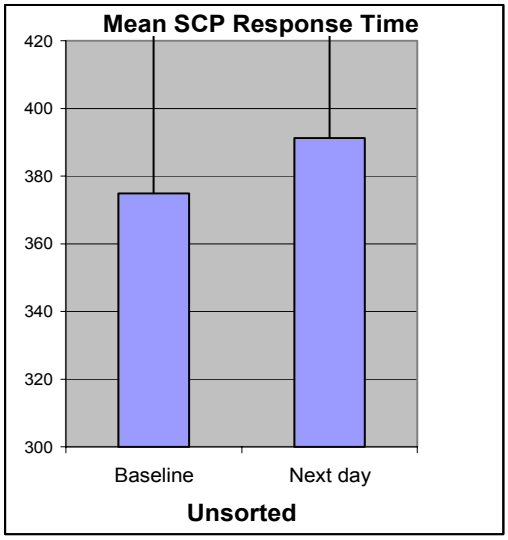
Regression Statistics	
Multiple R	0.472114293
R Square	0.222891906
Adjusted R Square	0.194735815
Standard Error	47.2484008
Observations	144
ANOVA	Regression
F	*Significance F*
7.916294585	1.3922E-06
	Coefficients
Intercept	316.1158293
Baseline (1) Next day (2	2.196266199
Session Number	3.519266784
Dose Level	-16.0255551
BMI Var	23.00830481
Drive Score	-0.89207904
	P-value
Intercept	2.07022E-34
Baseline (1) Next day (2	0.802809038
Session Number	0.000399566
Dose Level	0.680141612
BMI Var	1.00035E-05
Drive Score	0.850094876

Accordingly, the SCP Mean Response Time was examined with Excel's multiple regression function. The right side of Figure 4-3 presents the results of the multiple regression test. The F-test is significant for regression at p <.001. There is significant linear regression and the multiple R value of .472 indicates that as much as 47% of the variance can be explained by the variables.

The P values indicate that the variance in the data is explained by only two factors, the "Session Number" and the "BMI Variable". The variable "Baseline-Next-Day" is NOT a significant contributor, nor are "Dose Level" or "Driver Score".

From the coefficients table, it is clear that there is a positive regression with Session Number and also with BMI Variable. The data indicates that the average Standard Continuous Performance scores were greater the second and third times the participants took this test than on the first time. The data also indicates that participants with BMI indexed scores of BMI 2 and BMI 3 required increasingly longer to complete this test than participants with BMI index scores of BMI 1. Baseline-Next Day, Dose level and Driver Score do not participate statistically in explaining the variance in the data.

Figure 4-4: Interaction of the Intervening Variables with the SCP Baseline and Next Day Scores



Mean SCP Response Time Baseline and Next day
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Variance	3039.3677
Observations	72
Pearson Correlation	0.5075063
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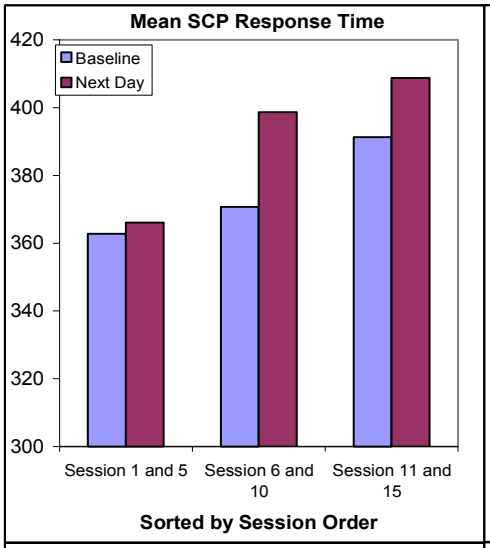
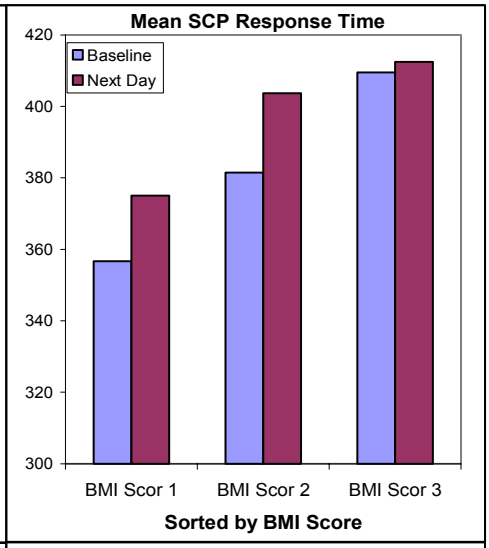
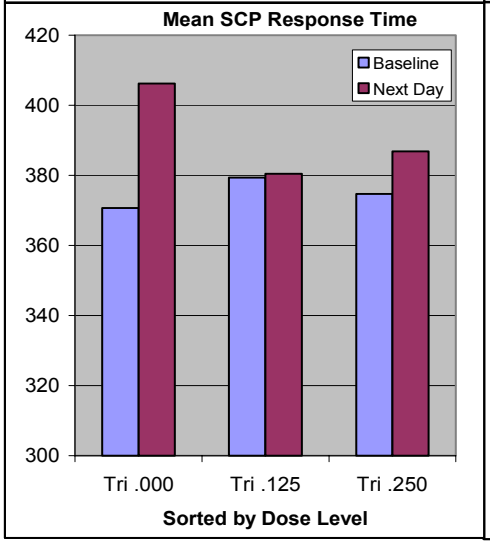
df	71
t Stat	-2.656311
P(T<=t) one-tail	0.0048746
t Critical one-tail	1.666599
P(T<=t) two-tail	0.0097491
t Critical two-tail	1.9939444







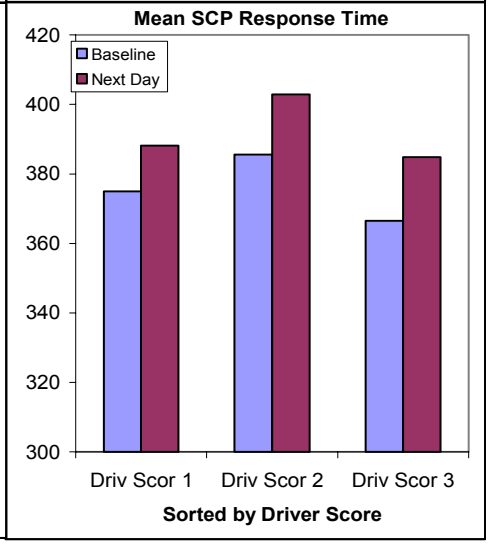


Figure 4-4 shows the interaction of the Session Number and BMI Score variable on the SCP - Standard Continuous Performance - test.

Sessions 1 and 5 were the baseline and next-day sessions for the first experimental day. Sessions 6 and 10 are the baseline and next day drives for the second experimental session, and 11 and 15 are the Baseline and Next-Day drives for the third session.

The SCP scores consistently elevate from session to session and the scores also are seen to be increased in participants that have Body Mass Index (BMI) scores of 2 and 3 relative to participants with BMI scores of 1. However, even taking into account the BMI scores chart, it is clear that the SCP scores are

increasing with time.

Using the same data file but sorting it differently, the rising pattern is not seen in the charts of SCP mean response scores sorted by Driver Score or by Dose. The key finding is that the Next-Day SCP scores do not correlate with the dose of Triazolam administered in that session. A subsidiary data run confirmed that there was no change in Baseline to Next-Day SCP scores that could be attributed to the individual level of saliva Triazolam detected in the participant.

The SCP test is unique among the tests in the PATH psychomotor battery. It is the only one of the eight tests in the PATH psychomotor battery that where there is a statistically significant difference between the baseline drives (drives 1, 6 and 11) and the next day drives (drives 5, 10 and 15) that is not easily explained.

The implications of this finding are that the participants required longer to make the "go/no-go" choice the more times they took the test. The differential between the baseline and next day tests per se was about 2 milliseconds (the baseline-next day coefficient in Figure 4-3) and was not significant. However, each time participants took this test, they added about 3.5 milliseconds to the time to reach the decision (the coefficient of session number). Moreover, participants with a higher BMI reliably required more time than participants with a low BMI to make the go/no-go decision (the BMI coefficient is 23 ms).

There are a few other PATH psychomotor tests in the battery for which there is a statistically significant difference between the baseline (pre-drug) scores and the next-day (post-drug) scores, but they operate a direction that is logical and desired. For instance, the psychomotor battery mood scores indicate lessened self-reports of Anxiety on the next-day versus the pre-drug drive (P.<01) and self-reports of reduced Restlessness (p. <.06) (both two-tailed) on the next-day drives relative to the base-line (pre-drug) drives. On the other hand, there is no significant difference on the scales for Sleepiness, Vigor, Depression, Anger, Fatigue and Happiness.

Also, on the Procedural Response Time ("PRO") test, there is no difference on the mean time for response. However, the standard deviation for Response Time, and the standard deviation for Response Time for Correct answers, increases from pre-drug to post-drug runs, which may indicate that there is a differential impact on a sub-set of respondents causing an increase in the variability of the data. This possibility was not researched further.

In summary, it appears that there is a unique impact of the design of this experiment on the operator's response to the Standard Continuous Performance (SCP) test. There was an increase in the SCP mean reaction time associated with pre-test, post-test scenarios. That increase in Next-Day reaction time, however, is not associated with the experimental dose of Triazolam or of the highest saliva concentration of Triazolam from the previous-day experimental drives. The increase in Next-Day reaction time is a function of the repeated-test design, with all participants apparently taking a little longer

to make the go/no-go decision each time they take the test. The Next-Day impact was also associated with higher BMI scores, but not with Driver Score or Drug level.

The SCP test is the only test in the battery that asks operator to refrain from responding in response to an incorrect (or unexpected) stimuli and it may be a test that distinguishes (as a matter of speculation) the impact of fatigue or impatience on a driver's performance.

4.3.2 Summary of the Baseline vs Next-Day Results

In summary, the Baseline-Next Day tests did not reveal any impacts that could be associated unambiguously with the impact of the drug taken subsequent to the Baseline Pre-Dose drive on the previous day. Differences in driver performance may be ascribed to serial effects of repeated drives and to exogenous effects such as BMI, but not directly to lingering drug effects.

4.4 Introduction to the Analysis of Drug Impact on Psychomotor Tests

The PATH psychomotor battery described earlier in Section 4.2 may generally be separated into two categories. Tests one and two, the Sanford Sleep Scale and Participant Mood Tests, assessed internal states such as level of sleepiness, arousal, depression and happiness. It is important to understand whether the prescription drug under review might directly impact such internal states, or whether the drug in combination with other intervening variables, specifically driver style (impulsive to cautious) might impact these internal states.

Tests three through eight (Simple Reaction Time, Procedural Reaction Time, Mathematical Processing, Matching to Sample, Standard Continuous Performance, and Pursuit Tracking) assess reaction time, response speed, driver choice capability, matching to sample and eye-hand coordination. These are skills essential for safe and efficient driving. It is necessary to determine whether the prescription drug under study, either by itself or in interaction with any of the intervening variables, would impair these essential driving skills, and to determine the resulting level of impairment.

As will be remembered, each participant drove four simulator scenario experimental drives on each experimental day, and returned the next morning to drive the "next day" route in the scenario. The "next-day" drive was a repeat of the pre-drug drive, to provide a direct comparison of driving performance after a period of sleep. Accordingly, each experimental session encompassed five experimental drives. The randomly assigned experimental capsule was taken immediately following the first drive of the day. The drives were spaced 40 minutes apart, at 0 minutes, and as close as possible to 40, 80 and 120 minutes following ingestion of the capsule.

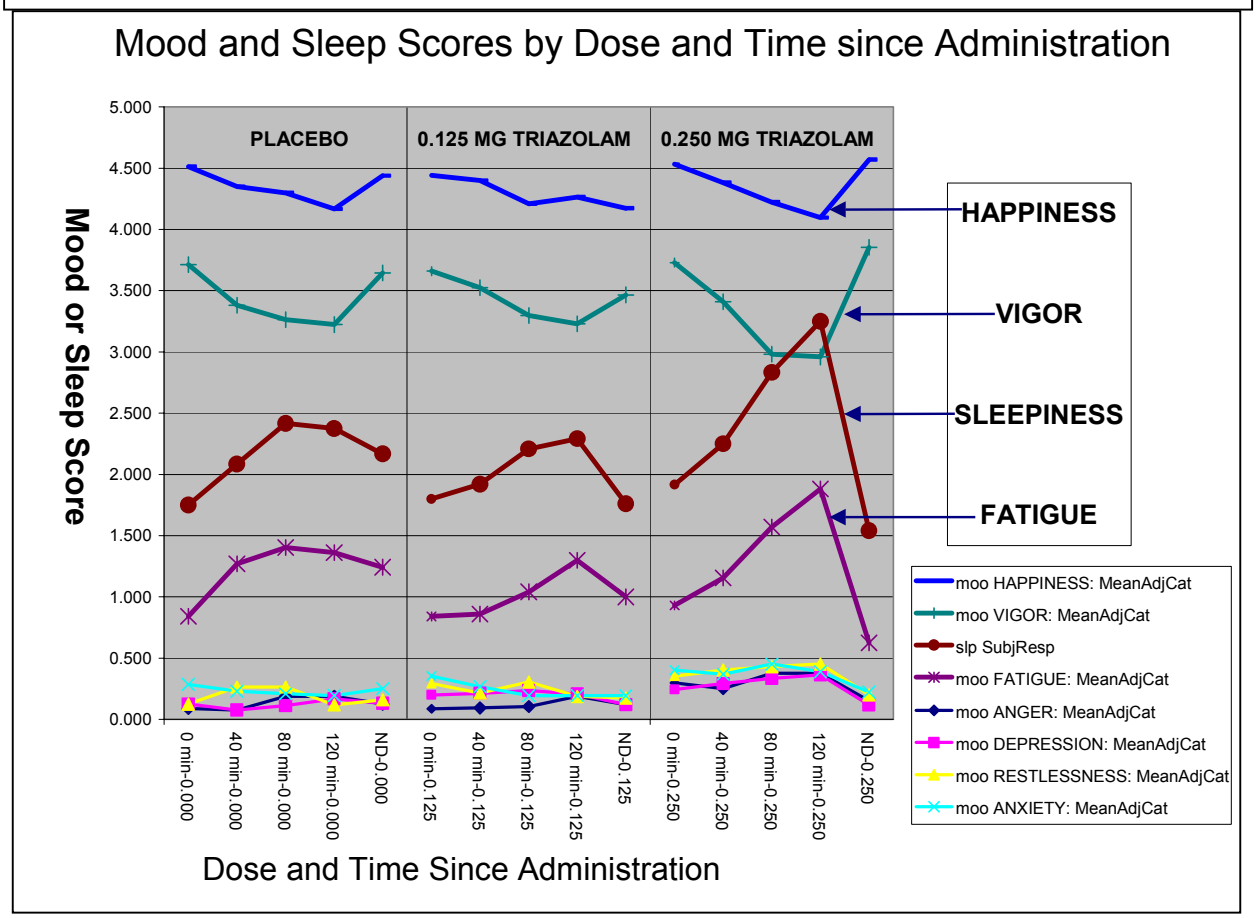
Over the course of the project, each driver drove three experimental sessions. This section of the PATH report will present the summary results of all 15 experimental drives. In this section, the data is sorted to compare the three pre-dose drives, the

three 40-minute drives, the three 80 minute drives, the three 120 minute drives, and the three next-day drives. That is, the drives are not presented in order, 1 through 15, but are sorted to directly compare the drug impact at equivalent times throughout the three experimental drives.

4.5 Results of the Sleep Scale and Mood Scores

Figure 4-5 presents the Mood and Sleep scores sorted to compare the psychomotor scores at equivalent times. It is clear that Fatigue and Sleepiness scores increased a the 0.250 mg dose relative to Placebo and the 0.125 mg dose. Vigor scores may decrease somewhat at the highest dose. There is no apparent impact on Happiness scores.

Figure 4-5: Mood and Sleep Scores at 0, 40, 80, 120 and next day (ND) sorted by drug dose



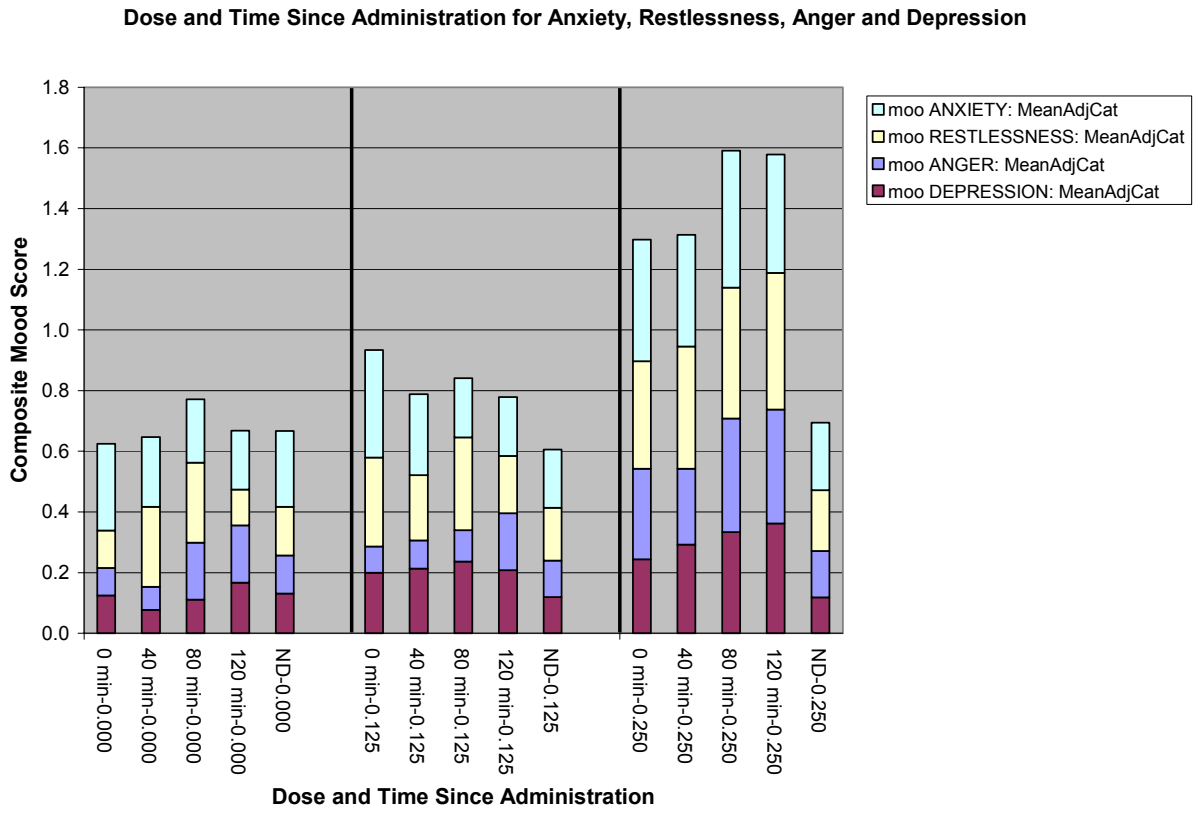
Note that the Next-Day (ND) scores for Sleepiness and Fatigue for the 0.250 dose are lower than their corresponding Baseline scores. This is in keeping with the earlier finding (Figure 3-12) that participants reported the quality of their sleep to be improved

on the night after the session on which they were administered the 0.250 mg dose of Triazolam.

4.4.1 Are there series effects in the psychomotor scores

However, the scores for Anger, Depression, Restlessness and Anxiety, shown in the stacked bar graph in Figure 4-6, appear to have a more complicated pattern than the scores for Fatigue, Sleep, Vigor, and Happiness. Observing the pre-dose composite scores for the placebo, 0.125 mg and 0.250 mg experimental days, note that the composite score (represented by the height of the bar graph) for these emotions appears to be higher for the participants about to receive the 0.125 dose than for the participants about to receive the placebo dose, and higher still for the participants about the receive the 0.250 dose.

Figure 4-6: The analysis of scores for Anger, Depression, Restless, and Anxiety is complicated by series effects. Note that the mood scores are increased for the Baseline drive on session participants received the 0.250 mg dose.

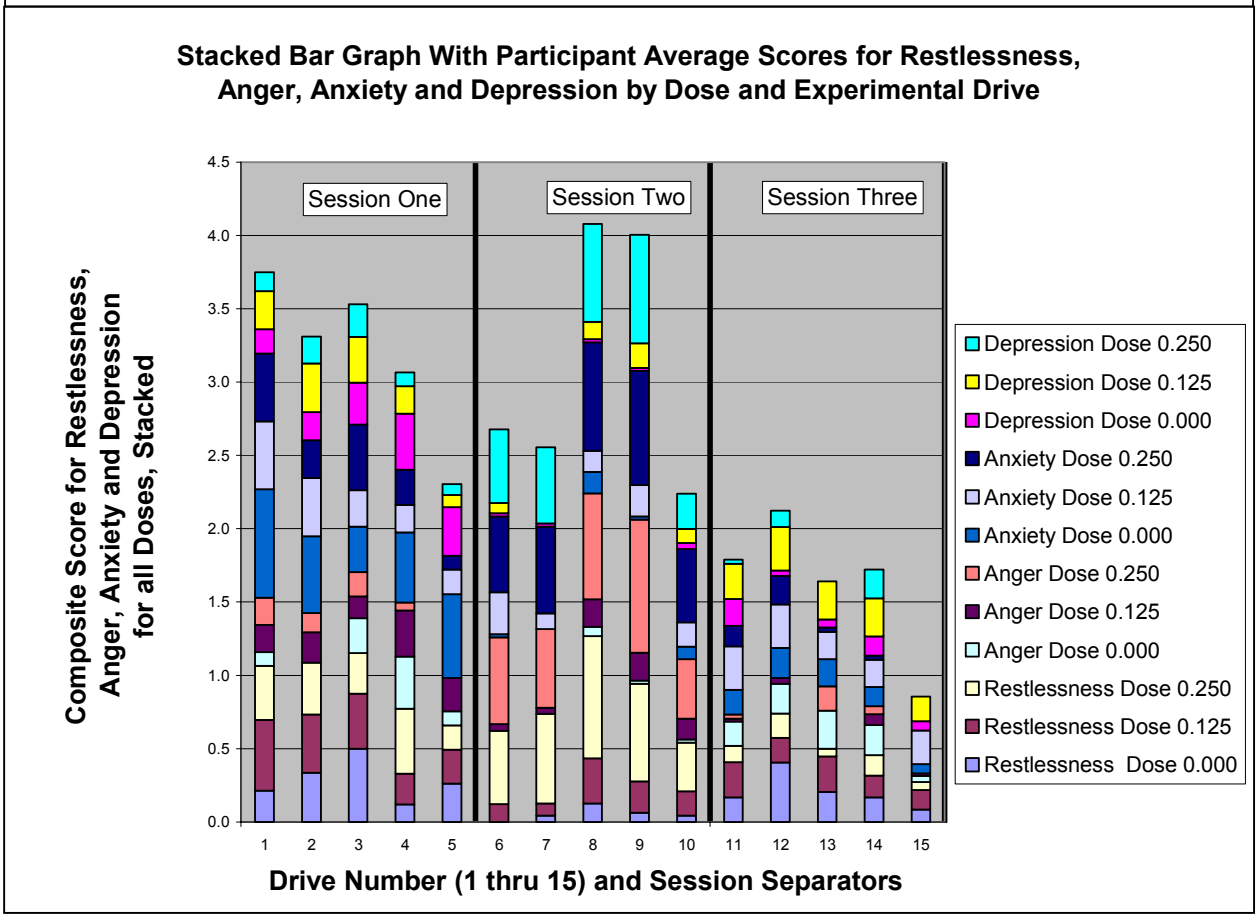


Since the scores for the zero-minute drives Figure 4-6 are scores recorded BEFORE these participants took the “randomized, double-blind” capsule for the day, it was necessary to further examine this pattern of scores. It is necessary to rule out the possibility that participants somehow had gleaned a hint of the dose they were about to take and felt a heightened level of anticipatory anxiety, etc. This possibility seemed

highly unlikely since the PATH researchers were unaware of the dose contained in the capsule they were about to administer and the capsules were unlabeled and indistinguishable one from another♦. That is, the doses were administered in a "randomized, double-blind" paradigm.

However, if the participants had been able to glean knowledge of the dose they were about to be administered, that knowledge might have biased their whole session and vitiated the results. It was therefore necessary to follow this question to its logical conclusion.

Figure 4-7: Composite Pattern for Restlessness, Anger, Anxiety and Depression for Experimental Drives 1 through 15, Sessions One through Three



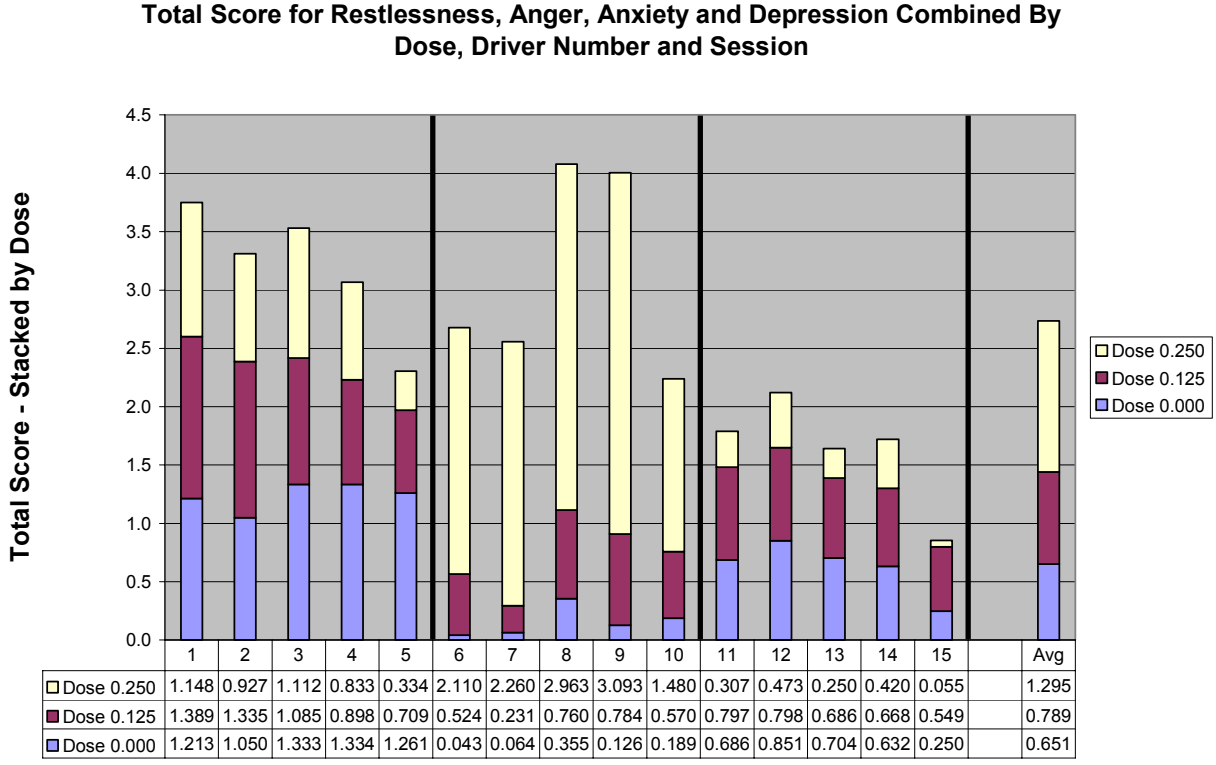
Accordingly, the Mood scores were sorted by drive number and replotted, with the results shown in Figure 4-7. In Figure 4-7, drives 1, 6 and 11 are the "0-minute" drives,

♦ In preparation for the experiment, this researcher and Dr. Milavetz, the project pharmacologist, compared a sample of available gel capsules against the Triazolam tablets that would be used. It was noted that the 0.125 mg tablet was manufactured to be wider and visually distinguishable from the 0.250 mg tablet. It was wide enough that it bulged out the sides of the capsule that best fitted the 0.250 mg tablet. Therefore, it was decided to use the next size up capsule so that the placebo dose, 0.125 and 0.250 doses were visually indistinguishable.

the drives BEFORE the participant was administered the capsule. Drives 5, 10 and 15 are the Next-Day drives. Plotted in this manner, Figure 4-7 shows that there was reduced level of agitation for the "0-minute" drives as the participants progressed through the experimental sessions.

Figure 4-7 shows that there was an elevated level of restlessness, anxiety, anger and depression (hereinafter "agitation" for simplicity) recorded in the psychomotor Mood scores for the first drive of the first session for each participant. These emotions subsided over the course of the session and were substantially lower than baseline on drive 5, the next-day drive of the first session. Session Two started with a reduced composite level of these agitated emotions, but there was a marked increase on drives 8 and 9, the 3rd and 4th drives of the second session. There was a much-reduced overall emotional level recorded on the Mood scales in Session Three.

Figure 4-8: Total Scores for Restlessness, Anger, Anxiety and Depression sorted by Dose and Drive Number



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		Avg
Dose 0.250	1.148	0.927	1.112	0.833	0.334	2.110	2.260	2.963	3.093	1.480	0.307	0.473	0.250	0.420	0.055		1.295
Dose 0.125	1.389	1.335	1.085	0.898	0.709	0.524	0.231	0.760	0.784	0.570	0.797	0.798	0.686	0.668	0.549		0.789
Dose 0.000	1.213	1.050	1.333	1.334	1.261	0.043	0.064	0.355	0.126	0.189	0.686	0.851	0.704	0.632	0.250		0.651

Figure 4-7 helps to explain the apparently elevated level of agitation for participants about to take the 0.250 dose shown in Figure 4-6. However, Figure 4-7 does not explain the elevation of these emotions in Session Two. Therefore the data was further simplified to show the total scores for Restlessness, Anger, Anxiety and Depression segmented by Dose and Drive Number. Also the PATH team reviewed the recorded

scores of individual participants. This was done to see if certain participants typically recorded higher than average "agitation" scores, and if the randomization schedules for those participants helped to explain the disparity of agitation scores in the three experimental sessions.

Figure 4-8 and its data table shows that the total "agitation" scores were roughly equally distributed by dose for all participants on Drive 1, the "0-minute" first drive of Session One. However, on Session Two, virtually all of the "agitation" scores were found in the group of participants randomized into the 0.250 dose group for Session Two. By comparison, in Session Three, the 0.250 dose group recorded by far the smallest total "agitation" score in the Mood test of the psychomotor battery.

A review of the individual scores of participants on Drive 1 explains this unexpected pattern of agitation scores. It appears that the elevation of agitation is accounted for by a single participant, M4003. On Drive One, his scores were representative of the group mean scores, and the scores were reasonably well distributed among all participants. The scores for participant M4003 where high but not among the highest. However, in Session Two and Three, the scores of Participant M4003 were the highest of all participants and his scores largely dominated the composite average of the group he had been randomized into.

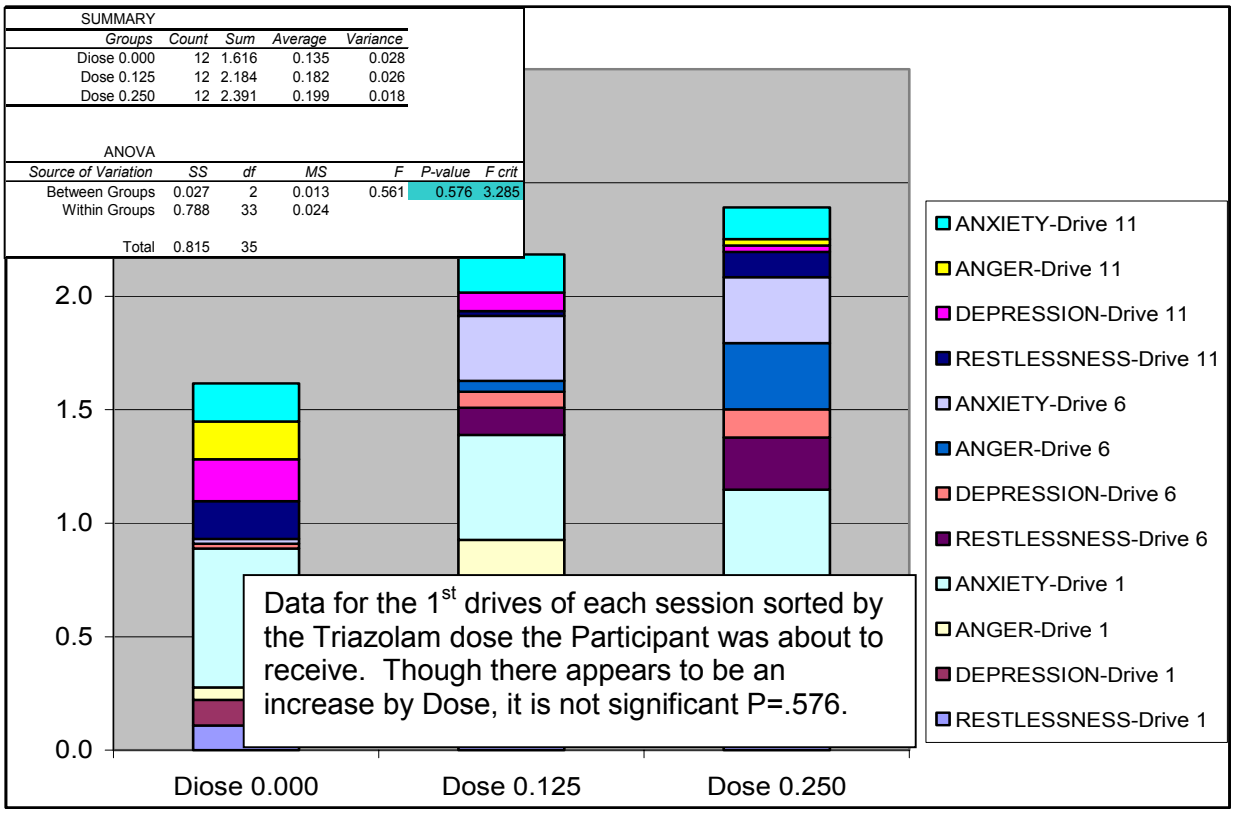
Figure 4-9 M4003 – Mood and Simulator Sickness Scores

M4003	Dose	Restlessness	Depression	Anger	Anxiety
Session 1 Drive 1	0.000	0.83	0.50	0.33	1.50
Session 2 Drive 6	0.250	2.67	3.50	3.00	2.33
Session 3 Drive 11	0.125	1.33	1.50	0.83	2.00
		Nausea	Optomotor	Disorientation	Overall
	SSQ Scores	38.16	53.06	41.74	44.08

The Simulator Sickness Scores (SSQ) for M4003 are also shown in Figure 4-9. Participant M4003 recorded the highest SSQ scores of any participant in the experiment. It seems likely that his Mood scores, and the increase in his scores from the first to the second session, reflect his Anxiety, Depression and Anger over his newly-discovered discomfort driving the simulator.

To close this investigation, the Mood scores of M4003 were deleted from the data set. The data for the first drive of each session was then reanalyzed. Figure 4-10 shows the results of that analysis.

Figure 4-10: Comparison of The Mood data for the "agitation" scores sorted by Dose (not significant) and by Session (highly significant).



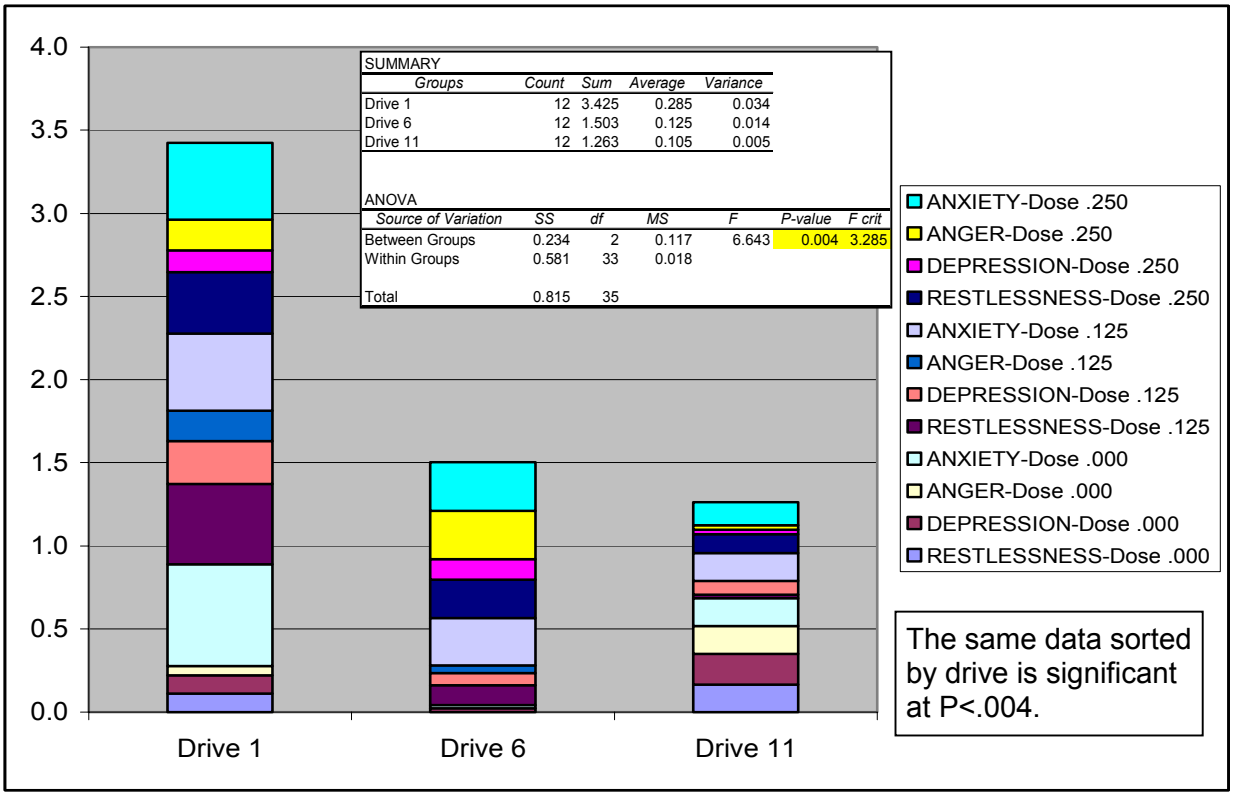


Figure 4-10 presents the data from the first drive of each of the three sessions. The data is sorted two ways. The data is sorted by the Dose that the participant was to receive after the 0-minute drive. If this sort produced a significant difference in agitation scores for the three pre-dose drives, that would imply that participants had some foreknowledge of the dose they were about to receive. That knowledge would vitiate the data. The data was also sorted by Session. If that sort were significant, it would indicate that the overall level of agitation (Restlessness, Anger, Anxiety and Depression) decreased over the three sessions. That result would be expected.

The top graph in Figure 4-10 indicates that, with the removal of the scores for M4003, the apparent increase in the total composite agitation score for dose 0.000 (placebo), and dose 0.125 and dose 0.250 is not significant. The data does not indicate that participants had foreknowledge of the dose they were about to ingest. The bottom graph in Figure 45 indicates that the overall level of Restlessness, Anger, Anxiety and Depression was significantly lower in Session Two and Three than in Session One, an expected finding. With the exception of participant M4003, participants became more comfortable with the experimental setting as they progressed from Session 1 to Session 2 to Session 3.

In summary, the data indicates that the overall level of “agitation” fell from Session One to Session Two to Session Three, which is an expected finding. However, there is no indication from the scores from the first drives of each of those Sessions that the participants had foreknowledge of the dose they were about to receive.

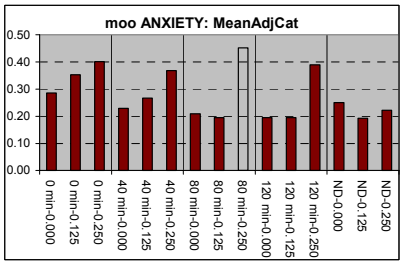
In summary, the data from the psychomotor tests is not contaminated by foreknowledge of the dose the participants were about to ingest.

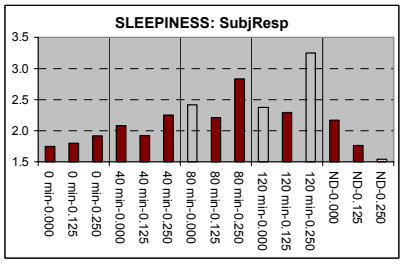
4.6 Comparison of psychomotor test scores

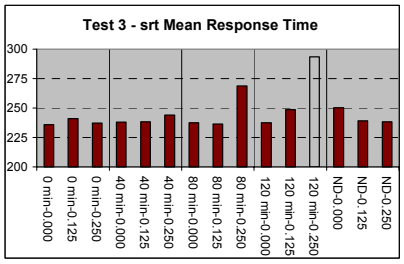
As will be remembered, tests 3 through 8 in the psychomotor battery were Simple Reaction Time, Procedural Reaction Time, Mathematical Processing, Matching to Sample, Standard Continuous Performance, and Pursuit Tracking. These tests assess reaction time, response speed, driver choice capability, matching to sample and eye-hand coordination. These are skills are presumed to be essential for safe and efficient driving. It is necessary to determine whether the prescription drug under study, either by itself or in interaction with any of the intervening variables, impaired these essential driving skills, and the level of impairment.

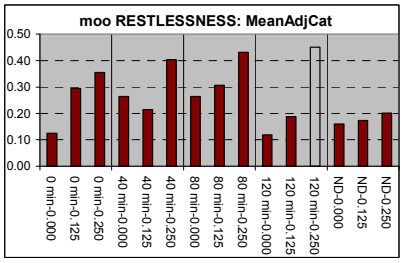
Figure 4-11 is a set of dose-response graphs for all of the PATH psychomotor tests, including the sleep and mood tests. Tests where the means of the participant scores are significantly different from placebo are indicated by a bar with a pattern. Filled bars are scores which are not different from the score of the placebo group at that time period.

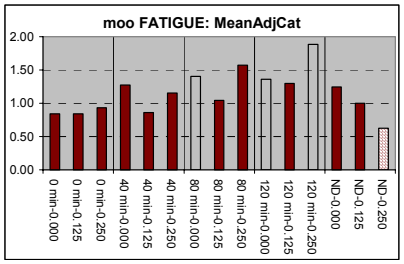
Figure 4-12: Dose response graphs for mood scores and reaction time scores for the PATH psychomotor test battery.

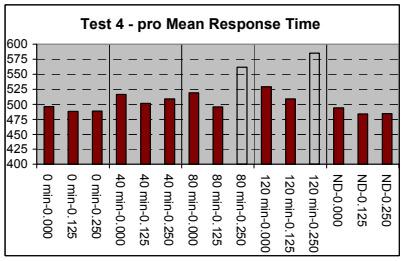


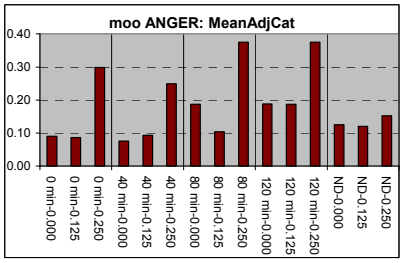


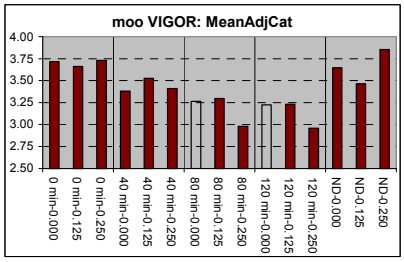


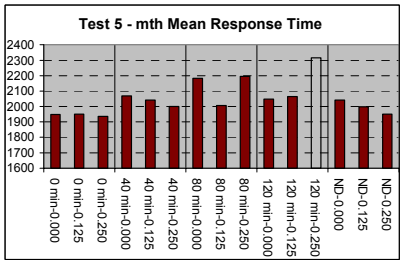


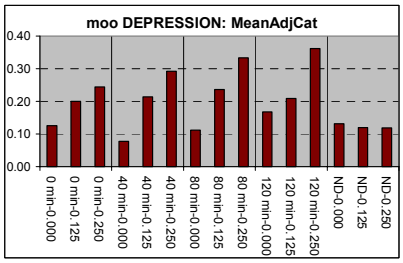


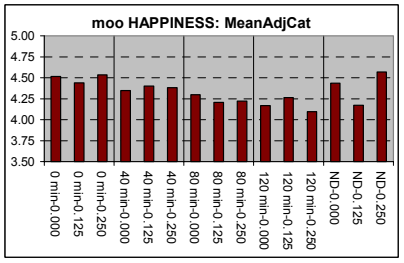


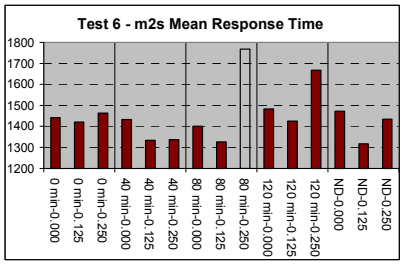


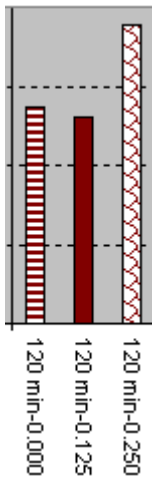






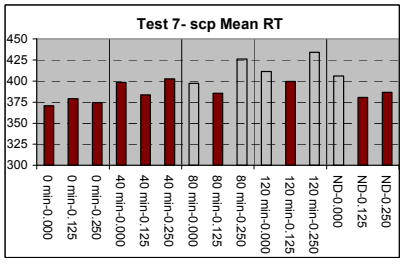


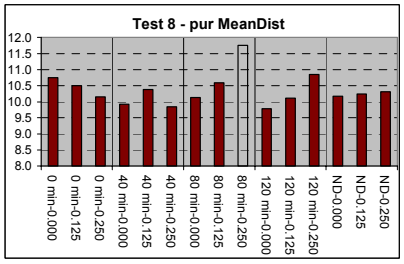




Legend: The 15 bars in each graph represent the average psychomotor test scores for tests taken immediately before the baseline, 40, 80, 120 minutes and Next Day drives on the placebo, 0.125 and 0.250 mg session.

Bars with horizontal lines are tests where the average placebo score is significantly different from the baseline (0 minute) placebo score. Bars with zigzag lines are tests where the average dosed score is significantly different from the placebo score at that time block.





Graphs in which the pattern of a bar is Horizontal Lines indicates that the value for the 0.000 dose graph at that time period is significantly different from the pre-doze (0 minute) value for that group. For instance, the 0.000 dose group (placebo) at 80 minutes recorded Sleepiness scores indicating they were significantly more sleepy than they were at pre-dose, 0 minutes. Likewise, the participants, having ingested the placebo capsule, reported less Vigor and more Fatigue at 80 minutes than at 0 minutes.

Graphs in which the bar pattern is zig-zag lines indicate that the dose group at that time recorded scores significantly different from the placebo group at that time. For instance, in Test 3, Simple Response Time, participants who had ingested the 0.250 mg capsule had significantly longer response times at 120 minutes than the participants who had ingested the placebo capsule at 120 minutes. The same is true for the participants taking Test 5, the Math test. For these two tests, the peak impairment effect was seen only at 120 minutes post dosing.

For two tests, Test 6 - Matching 2 Sample (m2s) and Test 8 – Pursuit Mean Distance, the peak effects were seen at 80 minutes rather than 120 minutes.

For the two remaining tests, Test 4 - Procedural Reaction Time (pro) and Test 7 – Standard Continuous Performance (scp), significant impairment is seen both at 80 and 120 minutes relative to the placebo group scores at those time points.

It is worth remembering that Project PATH utilized a cross-over design. Each participant received all doses in a randomized order. Thus, the participants in the “placebo” group are the same participants as in the “0.125 mg” and the “0.250 mg” group.

The implication that two of the tests (scp and pro) found impairment at 80 and at 120 minutes may be that the underlying skill set required for the performance of these tests is more susceptible to the impairing effects of Triazolam that the skill sets required for the rest of the test battery. An alternate explanation may be that these are tests that have a minimum level of individual variance in response time, and so are sensitive to smaller changes than tests that have a larger amount of individual variance. The explanation is supported by Figure 4-13, the compares the Intercept of the Multiple Regression values shown in Figure 4-14 to the Standard Errors shown in Figure 4-14.

The tests scp and pro have an Intercept to Standard Error (I/SE) ratios of 2.83 and 2.12 respectively, where as the tests srt, mth and m2s have I/SE ratios of 1.53, 1.15 and 0.71 respectively. Accordingly, it takes a much larger difference in the means of the drug to placebo ratios for those tests to create a statistically significant difference. The sensitive tests Standard Continuous Performance and Procedural Reaction Time find statistically significant mean differences when the drug to placebo differences are only 5 to 10% apart, where as the other tests are significant with 15% or more mean difference.

The Pursuit (pur) test is somewhat different in that it has the highest I/SE ratio, 5.29, but required a 15% level of impairment to achieve statistical significance. That is, the 11% difference between placebo and 0.250 drug score at 120 minutes was not significant. The answer may be found in the Multiple Regression Table in Figure 4-14.

Figure 4-13: Intercept to Standard Error Ratios for Statistically Significant Differences the Psychomotor Tests in Figure 4-12.

Intercept to Standard Error Ratios Partially Account for The Discriminatory Power of the Psychomotor Test						
	pur	scp	pro	srt	mth	m2s
Intercept	18.47	195.00	239.00	122.00	829.00	447.00
SE	3.49	69.00	113.00	80.00	722.00	632.00
Intercept/SE	5.29	2.83	2.12	1.53	1.15	0.71
Impairment at	80	80+120	80+120	120	120	80
Peak Value	11.70	435	585	290	2320	1775
Placebo	10.20	415	530	250	2050	1400
Pct Change	115%	105%	110%	116%	113%	127%
Peak 80 min		425	565			
Placebo 80 min		395	520			
Pct Change		108%	109%			

Figure 4-14 presents the Multiple Linear Regression values for key psychomotor test scores taking the intervening values developed in Section Three into account. It can be seen that the Pursuit test (pur) is the test most affected by Simulator Sickness variables. The participant BMI score is also a significant factor in the total level of impairment. For Pursuit Mean Distance, the Pursuit value charted in Figure 4-12, BMI score, Triazolam Saliva concentration, Oculomotor score and Disorientation score all factor into the final amount of impairment. Unexpectedly, the coefficient of the D score is negative, indicating the higher the D values the closer the participant is able to keep the cursor to the rotating “X” on the screen. The coefficients for BMI, TRI and O score are positive, indicating that each contributes to the participant’s difficulty pursuing the “X” with the computer cursor. Note that the Nausea SSQ score is not an impairing factor.

Pursuit is the only test requiring eye-hand coordination and the only psychomotor test in which the SSQ variables O and D, but not N, contribute to impairment. Thus, it would seem that there would be a direct impairment of Triazolam on activities requiring eye-hand coordination. Further, it would seem that these impairments would be most strong at about 90 minutes post-drug, and abating by 120 minutes. The coefficient of BMI is negative, implying that thinner participants are more strongly impacted, possibly a reflection of the fact that they have higher Triazolam concentrations.

Figure 4-14: Multiple regression table for key values of the psychomotor test battery used in Project PATH.

	scp Mean RT Corr	scp Mean RT	m2s Med RT	m2s Mean RT	pro Basic Block:1: Mean RT	pro Basic Block:1: Speed	pro Basic Block:1:Throughput	srt Mean RT Corr	srt Mean RT	srt StDev RT Corr
Regression Statistics										
Multiple R	0.472736	0.458057	0.440491	0.430846	0.434043	0.425476	0.40681	0.414853	0.414853	0.343552
R Square	0.22348	0.209816	0.194032	0.185629	0.188393	0.18103	0.165494	0.172103	0.172103	0.118028
Adjusted R Square	0.183512	0.169145	0.152548	0.143713	0.14662	0.138877	0.122542	0.129491	0.129491	0.072632
Standard Error	69.20357	69.92038	528.4042	623.2493	113.3909	17.77463	18.08319	79.94318	79.94318	169.0296
Observations	144	144	144	144	144	144	144	144	144	144
Regression										
Value F	5.591474	5.158834	4.677314	4.42857	4.509838	4.294602	3.852956	4.038806	4.038806	2.599989
Significance F	1.11E-05	3.14E-05	0.000101	0.000184	0.000151	0.000255	0.000744	0.000474	0.000474	0.015048
P-value	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*
Intercept	0.001279	0.001536	0.310698	0.403888	0.015195	3.14E-19	5.19E-18	0.077487	0.077487	0.541796
Session order	0.320125	0.394186	0.881355	0.951648	0.642515	0.657903	0.374529	0.552905	0.552905	0.57856
BMI Score (range 20-44)	0.014643	0.011095	0.043882	0.121058	0.003172	0.00452	0.008847	0.321036	0.321036	0.682202
Driver Score (range 4-10)	0.010922	0.008039	0.148128	0.119991	0.093749	0.140726	0.3358	0.191552	0.191552	0.382728
TRI Conc (range 0-312)	0.000202	0.000355	2.71E-05	8.85E-05	0.000247	0.00077	0.002058	7.09E-06	7.09E-06	0.000169
N Score	0.28303	0.521916	0.051309	0.027693	0.989992	0.817837	0.581648	0.39333	0.39333	0.496283
O Score	0.737386	0.673467	0.892432	0.882817	0.074479	0.032002	0.012844	0.503427	0.503427	0.84422
D Score	0.991201	0.929212	0.349323	0.365582	0.133228	0.136178	0.091605	0.06809	0.06809	0.106101
Coefficients	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*
Intercept	195.3727	194.0411	461.499	447.9151	239.3085	160.0446	155.3595	122.0636	122.0636	-88.73782
Session order	11.59594	10.03603	-13.26828	6.357995	8.858378	-1.324607	-2.705464	7.986047	7.986047	15.80508
BMI Score (range 20-44)	2.785216	2.930428	17.49471	15.82623	5.544267	-0.835357	-0.781808	1.295942	1.295942	1.12893
Driver Score (range 4-10)	8.909318	9.383269	38.33985	48.64795	9.547244	-1.313884	-0.871372	5.234549	5.234549	7.384385
TRI Conc (range 0-312)	0.398122	0.385821	3.457217	3.793287	0.643015	-0.092119	-0.085577	0.562492	0.562492	0.984991
N Score	1.170033	0.704222	16.29782	21.75824	-0.022352	0.064346	0.156669	1.073854	1.073854	1.808818
O Score	0.268328	0.340743	-0.826111	-1.062101	2.35199	-0.444413	-0.526144	0.61891	0.61891	0.384013
D Score	0.011871	0.096617	-7.704728	-8.784525	-2.659303	0.413692	0.477011	-2.282615	-2.282615	-4.269221

	pur StDev Dist	pur Mean Dist	pur Med Dist	mth Med RT	mth Mean RTCorr Less	mth Mean RT	mth Throughput	mth StDev RT
Regression Statistics								
Multiple R	0.429638	0.398821	0.393048	0.333182	0.319409	0.306064	0.257185	0.167004
R Square	0.184589	0.159058	0.154487	0.11101	0.102022	0.093675	0.066144	0.02789
Adjusted R Square	0.142619	0.115774	0.110968	0.065254	0.055802	0.047026	0.018078	-0.022145
Standard Error	1.428459	3.491598	3.551445	666.2406	783.0555	722.8815	10.10045	584.3518
Observations	144	144	144	144	144	144	144	144
Regression								
Value F	4.398137	3.674768	3.549861	2.426097	2.207338	2.008078	1.376111	0.557414
Significance F	0.000198	0.001147	0.001552	0.022572	0.037302	0.058385	0.220255	0.78927
P-value	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*	*P-value*
Intercept	2.27E-09	7.52E-09	1.83E-08	0.335861	0.346533	0.183341	1.29E-06	0.184878
Session order	0.386493	0.18305	0.198398	0.709966	0.611086	0.980243	0.922934	0.501497
BMI Score (range 20-44)	0.112396	0.006202	0.003311	0.020553	0.006804	0.019863	0.265119	0.383981
Driver Score (range 4-10)	0.049753	0.233315	0.248634	0.070643	0.041733	0.100922	0.079199	0.799488
TRI Conc (range 0-312)	0.000239	0.046146	0.09661	0.24953	0.651613	0.515092	0.089269	0.52487
N Score	0.424587	0.490145	0.394451	0.164212	0.589974	0.36986	0.458716	0.508402
O Score	0.011766	0.04159	0.062295	0.460247	0.82171	0.324488	0.725017	0.782681
D Score	0.009045	0.012459	0.02539	0.197848	0.859311	0.317068	0.573629	0.861117
Coefficients	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*	*Coefficients*
Intercept	7.852799	18.47545	18.24055	552.2864	634.8827	829.7758	43.93261	668.3996
Session order	-0.208399	-0.784643	-0.770774	41.6948	-67.02276	-3.01158	-0.164383	-66.131
BMI Score (range 20-44)	-0.037151	-0.158004	-0.172843	25.41296	35.028	27.72932	-0.183961	8.307141
Driver Score (range 4-10)	-0.141078	-0.208533	-0.205278	60.55937	80.30102	59.56098	-0.891177	7.419299
TRI Conc (range 0-312)	0.008118	0.010582	0.008949	1.160337	0.53366	0.710511	-0.026034	0.561032
N Score	-0.017946	0.037899	0.047592	14.61681	6.635007	10.20245	-0.117735	6.078137
O Score	0.042092	0.082883	0.077033	5.693444	2.040208	8.248882	-0.041085	1.86365
D Score	-0.058736	-0.137292	-0.124634	-13.38552	2.159065	-11.27054	0.088459	-1.590287

4.7 Individual differences among participants in the psychomotor scores

As was discussed in Section 3.4, there were substantial individual differences in the level of Triazolam found in the saliva samples among participants given the same dose. Participants with lower Body Mass Indices (BMIs) consistently ($p<.05$) had higher concentrations of Triazolam in their saliva samples than participants with higher BMIs. Additionally, there were three participants, M2110, M2524, and particularly M2426, who consistently had higher saliva Triazolam concentrations than their cohorts (see Figure 3-7).

It is important to understand if the dose-response curves shown in Figure 4-12 represent average levels of impairment that would be experienced by any person taking this drug at a 0.250 mg therapeutic doses. Alternatively, it might be that only a few people would be uniquely susceptible to drug effects at the 0.250 mg level, and most others would not be impaired at this dose level.

Accordingly, it was determined to test whether levels of impairment measured in the psychomotor tests would be reduced or disappear if the psychomotor test scores of these three individuals were removed from the data sample. Accordingly, dose-response graphs and tests of significance using the Excel linear regression capabilities were run against psychomotor scores at 80 and 120 minutes with these individuals in the data set and removed from the data set. That is, it was important to see whether significant levels of impairment would be found in the participants if the members most susceptible to the effects of Triazolam were not counted.

To do this, it was necessary first to see whether the psychomotor scores of participants correlated with their saliva levels. This would determine whether the saliva levels could be used as an increasing index of impairment. Then it was necessary to remove the three participants from the database and determine whether there was still a robust relationship between saliva level and impairment. This would indicate whether the excessive impairment of the top individuals was dragging the regression chart.

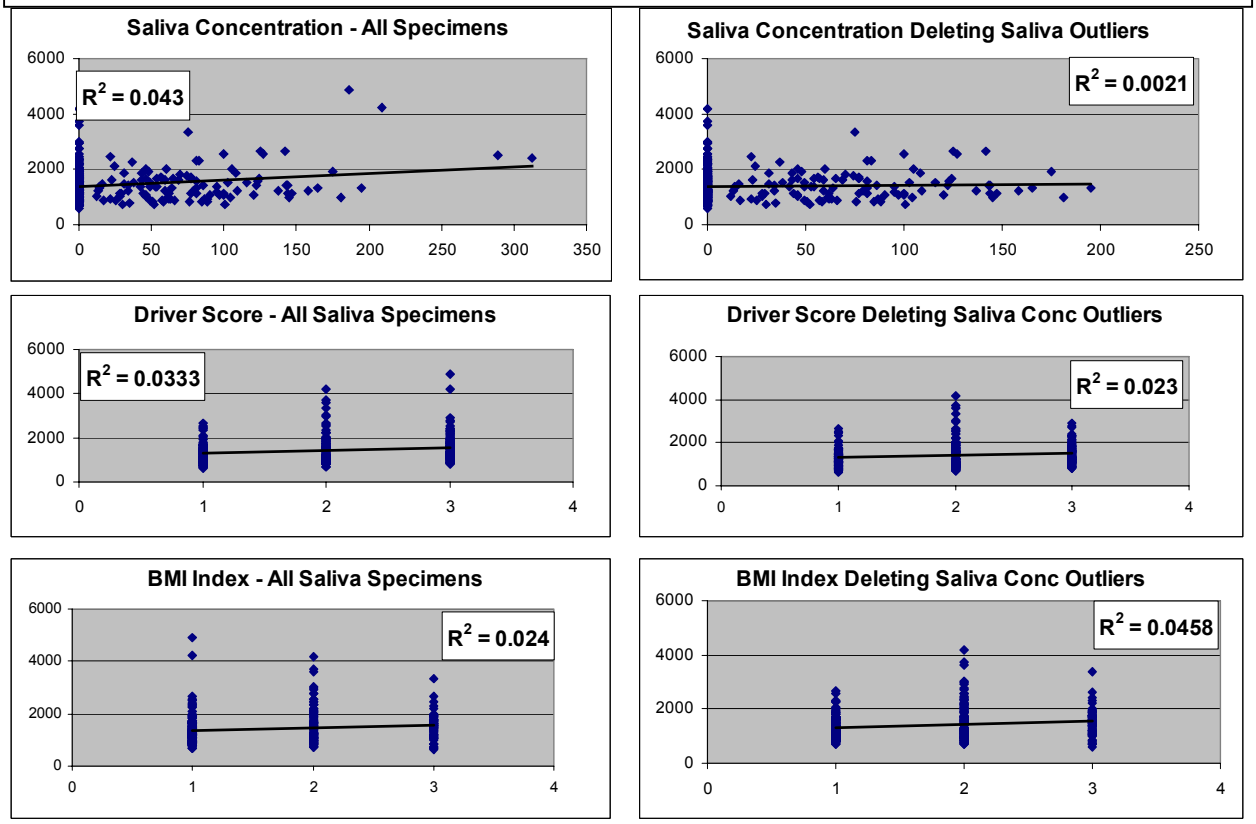
Figure 4-15 is a graph of the psychomotor task Matching to Sample (m2s) against saliva level, against Driver Score and against BMI Index. The left graphs present data from all participants, and in the right graph, the saliva outliers are removed. It is clear that the slope of the line depends largely on the inclusion of the outlier data, but there is a small amount of residual regression with them removed.

In Figure 4-15, the Y axis is in milliseconds and represents the time needed to make a choice on which of the two patterned squares matched the stimulus that had just been displayed. The least-squares line in the left-side grafts, with full saliva data, provides an estimate that drug-induced impairment added about one second (1000 ms) to the decision time at high saliva levels. That is, the average choice time increased from a little more than 1 second at low dose levels to a little more than 2 seconds at high dose

levels. However, with the outlier data removed, the regression almost disappears and the implication is that there is no impairment at any dose level.

This seemed to be an important finding which needed to be more fully explored.

Figure 4-15: Regression of m2s "Matching to Sample" with and without data from participants with the highest saliva triazolam concentrations.



4.7.1 Split-Sample Analysis of the Impact of Triazolam on SSQ Scores

The analysis used a "split-sample" approach to further identify the impact of the drug associated with the level of saliva in the participant sample for that drive as well as the dose of triazolam ingested.

Accordingly, a large table in Excel was constructed that has all of the data for experimental drives at 80 and 120 minutes post-drug. The data points for 80 and 120 minutes were combined to provide a larger sample size. The intervening variables discussed in the previous section were included in the analysis as well as the Simulator Sickness scores recorded by the participants following each drive. The table was sorted by dose, and within dose, was sorted by saliva level. Mean values for the intervening variables sorted by dose and "split-sample" are shown in Figure 4-16.

The data is sorted from lowest to highest using a continuous variable as the key, triazolam saliva concentration in this case. Then, within the table, data associated with the upper half of the range is compared to data associated with the lower half of the range. The saliva triazolam concentrations are found in the right column in Figure 4-15. The top three rows present the data set sorted only by dose (placebo, 0.125 mg and 0.250 mg). The bottom six rows present the split-table picture of the data. The first two rows show the scores associated with the placebo doses at 80 and 120 minutes. The second two rows show the data associated with the combined 80 and 120 minute 0.125 mg dose sorted by saliva concentration and split into a lower and upper range. The upper of the middle two rows has data associated with a dose of 0.125 mg and saliva levels ranging from 0 to 43 n/ml (the lowest to the middle of the range). The lower of middle the two rows has the data from 0.125 mg dose resulting in saliva levels from the middle to the highest end of the range, 44 to 109 ng/ml. Likewise, the bottom two rows split the 0.250 mg dose into two saliva ranges, 0 to 95 ng/ml and 96 to 312 ng/ml.

Figure 4-16: Intervening variables included in the "split-sample" analysis of Triazolam

Dose Plus Time Since Ingestion	BMI Index	Driver Index	Dose	N Score	O Score	D Score	Driver Score	BMI Score	TRI Concentration (mc/ml)
Dose Placebo, 80 + 120 Minutes	1.71	2.04	0.00	4.77	7.58	3.48	8.38	26.25	0.00
Dose 0.125 Mg, 80 + 120 minutes	1.71	2.04	0.13	2.19	6.32	3.19	8.38	26.25	42.71
Dose 0.250 mg, 80 + 120 minutes	1.71	2.04	0.25	4.87	10.34	6.96	8.38	26.25	100.79
Dose 0 80 Minutes	1.71	2.04	0.000	4.77	6.63	3.48	8.38	26.25	0.00
Dose 0 120 minutes	1.71	2.04	0.000	4.77	8.53	3.48	8.38	26.25	0.00
Dose .125, lower half, 0 to 43 ng	1.71	2.13	0.125	2.78	7.90	2.90	8.38	25.96	14.67
Dose .125 upper half, 44 to 109 ng	1.71	1.96	0.125	1.59	4.74	3.48	8.38	26.54	70.75
Dose .250 lower half, 0 to 95 ng	1.96	2.13	0.250	1.19	3.79	2.32	8.63	27.63	53.00
Dose .250, upper half, 95 to 312 ng	1.46	1.96	0.250	8.55	16.90	11.60	8.13	24.88	148.58

In Figure 4-16, it is clear that, within each dose level, there was an important difference in the magnitude of each of the intervening variables. For instance, look at the difference in the SSQ scores between the participants on the day they received the 0.250 mg Triazolam dose. Within that dose level, participants who were in the lower half of the saliva concentration spectrum had higher BMI Index scores and lower SSQ scores than participants in the upper half of the Triazolam saliva concentration spectrum. There is a disparity in the SSQ scores for the spectrum of saliva Triazolam concentrations for participants on the 0.125 dose day, but it is in the opposite direction from the 0.250 dose SSQ scores. As noted elsewhere in this report, the lower Triazolam dose appears to counteract simulator sickness, but the higher dose appears to potentiate the SSQ scores. Figure 4-16 suggests that participants with saliva Triazolam concentrations of 0 to about 50 micrograms/ml had no benefit from the Triazolam in reducing the sensations associated with simulator sickness. Participants with Triazolam saliva concentrations between 50 and 100 ng/ml received some relief

from the Triazolam. Above approximately 100 ng/ml, Triazolam apparently potentates the feelings of simulator sickness.

The simulator sickness scores shown in the middle SSQ columns of Figure 4-16 are particularly interesting and well illustrate the rationale for using split-sample saliva concentrations as well as dose level as a key variable. There is no indication in the top three rows of Figure 4-16 that the simulator sickness scores correlate in this extreme "U-Shape" pattern with saliva concentration. Especially for the "N" (Nausea) and the "O" "Oculomotor" indices, Triazolam in the middle ranges of saliva concentration, to at least a 100 mcg/ml concentration, substantially reduced the level of simulator discomfort experienced by participants. However, a suddenly and substantial increase in the level of simulator discomfort is associated with higher levels of saliva Triazolam.

4.7.2 Split-sample analysis of Triazolam impact on the PATH psychomotor tests

Having seen the difference in the SSQ scores associated with low and high saliva concentrations, it was determined to re-run several of the Multiple Linear Regression tests on the psychomotor data with the three outlier-participants removed from the data set. This analysis would help to determine whether all participants were equally impaired by the Triazolam, or only (or predominantly) the three with the highest Triazolam saliva concentrations.

To complete the understanding of the drug's impact on the performance tests in the PATH battery, it was necessary to examine the pattern of participant responses on tests in the PATH psychomotor battery that measure performance. It was then necessary to repeat that analysis with the outliers removed from the data. This would provide information about whether the doses of Triazolam used, 0.125 mg and 0.250 mg, were impairing for all users, or only for users who produced uniquely elevated saliva (and presumably serum) levels and so were uniquely exposed to elevated dose levels above the norm at that dose.

A subset of the Multiple Linear Regression test seen in Figure 4-14 was selected for reexamination against a second set of data from the same psychomotor tests prepared by removing all of the psychomotor scores of the three participants with the highest saliva levels at 120 minutes. The data set was prepared removing their scores at 80 and 120 minutes for their placebo, 0.125 and 0.250 dose days, or 18 data points in total.

The comparison data is presented in Figures 4-17 and 4-18. The circled data highlights the P-value for Triazolam concentration as a component of the overall probably of the explained variance. Comparing Figure 4-18 with 4-17, it can be seen that Triazolam concentration dropped out as a significant component in the regression equation for Procedural Reaction Time and Speed, for Standard Continuous Performance Mean RT, and for Matching 2 Sample Mean RT and Throughput, and almost dropped out for the Pursuit test. Triazolam concentration continued as a significant contributor only for Simple Response Time Mean RT, though at a highly reduced level of significance.

Figure 4-17: Linear regression tests for the Full data set yields highly significant regression attributable to the triazolam saliva concentration (p<.001 in most cases, p<.05 except for the math test, which was not significant).

Linear regression analysis of psychomotor performance variables in the PATH battery using the WHOLE data set, with outliers included

	mth MeanRT	mth Throughput	pro MeanRT	pro Speed	pur MeanDist	pur StDevDist	scp MeanRT	srt MeanRT	m2s Thruput	m2s MeanRT
Regression Statistics										
Multiple R	0.306064	0.257185	0.434043	0.425476	0.398821	0.429638	0.458057	0.414853	0.406681	0.440491
R Square	0.093675	0.066144	0.188393	0.18103	0.159058	0.184589	0.209816	0.172103	0.165389	0.194032
Adjusted R Square	0.047026	0.018078	0.14662	0.138877	0.115774	0.142619	0.169145	0.129491	0.122431	0.152548
Standard Error	722.8815	10.10045	113.3909	17.77463	3.491598	1.428459	69.92038	79.94318	15.14225	528.4042
Observations	144	144	144	144	144	144	144	144	144	144
ANOVA										
Regression F	2.008078	1.376111	4.509838	4.294602	3.674768	4.398137	5.158834	4.038806	3.850029	4.677314
Significance F	0.058385	0.220255	0.000151	0.000255	0.001147	0.000198	3.14E-05	0.000474	0.00075	0.000101
Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients
Intercept	829.7758	43.93261	239.3085	160.0446	18.47545	7.852799	194.0411	122.0636	77.17064	461.499
Session order	-3.01158	-0.164383	8.858378	-1.324607	-0.784643	-0.208399	10.03603	7.986047	-3.526423	-13.26828
BMI Score	27.72932	-0.183961	5.544267	-0.835357	-0.158004	-0.037151	2.930428	1.295942	-0.345751	17.49471
Driver Score	59.56098	-0.891177	9.547244	-1.313884	-0.208533	-0.141078	9.383269	5.234549	-0.974584	38.33985
TRI Concentration (mc/ml)	0.710511	-0.026034	0.643015	-0.092119	0.010582	0.008118	0.385821	0.562492	-0.070686	3.457217
N Score	10.20245	-0.117735	-0.022352	0.064346	0.037899	-0.017946	0.704222	1.073854	-0.587617	16.29782
O Score	8.248882	-0.041085	2.35199	-0.444413	0.082883	0.042092	0.340743	0.61891	0.111377	-0.826111
D Score	-11.27054	0.088459	-2.659303	0.413692	-0.137292	-0.058736	0.096617	-2.282615	0.066882	-7.704728
P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Intercept	0.183341	1.29E-06	0.015195	3.14E-19	7.52E-09	2.27E-09	0.001536	0.077487	2.29E-08	0.310698
Session order	0.980243	0.922934	0.642515	0.657903	0.18305	0.386493	0.394186	0.552905	0.167755	0.881355
BMI Score	0.019863	0.265119	0.003172	0.00452	0.006202	0.112396	0.011095	0.321036	0.162939	0.043882
Driver Score	0.100922	0.079199	0.093749	0.140726	0.233315	0.049753	0.006639	0.191552	0.199187	0.148128
TRI Concentration (mc/ml)	0.515092	0.089269	0.000247	0.00077	0.046146	0.000239	0.000355	7.09E-06	0.002355	2.71E-05
N Score	0.36986	0.458716	0.989992	0.817837	0.490145	0.424587	0.521916	0.39333	0.014598	0.051309
O Score	0.324488	0.725017	0.074479	0.032002	0.04159	0.011766	0.673467	0.503427	0.524937	0.892432
D Score	0.317068	0.573629	0.133228	0.136178	0.012459	0.009045	0.929212	0.06809	0.776472	0.349323

Figure 4-18: Linear regression tests on the TRUNCATED data set with scores for M2426, M2110 and M2524 removed.

Linear regression analysis of psychomotor performance variables in the PATH battery using the REDUCED data set, with outliers removed

	mth MeanRT	mth Throughput	pro MeanRT	pro Speed	pur MeanDist	pur StDevDist	scp MeanRT	srt MeanRT	m2s Thruput	m2s MeanRT
Regression Statistics										
Multiple R	0.3641	0.311226	0.40692	0.361482	0.427927	0.429353	0.467414	0.431615	0.360605	0.377505
R Square	0.132569	0.096861	0.165584	0.130669	0.183122	0.184344	0.218476	0.186292	0.130036	0.14251
Adjusted R Square	0.081111	0.043285	0.116084	0.079098	0.134663	0.135958	0.172114	0.138021	0.078428	0.091642
Standard Error	735.7892	10.17922	93.85184	17.24662	3.441202	1.415949	59.44939	40.27557	15.25976	539.9138
Observations	126	126	126	126	126	126	126	126	126	126
ANOVA										
Regression F	2.576263	1.807924	3.345171	2.533793	3.778911	3.809839	4.712432	3.859298	2.519683	2.80156
Significance F	0.016571	0.09194	0.002746	0.018271	0.000984	0.000915	0.000108	0.000813	0.018872	0.009835
Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients	Coefficients
Intercept	685.8178	47.4083	267.8938	159.3503	17.37811	7.337131	178.6413	149.2405	72.94886	770.9028
Session order	-22.0639	-0.538458	9.720135	-1.841851	-0.629771	-0.129631	19.23106	9.20367	-2.867118	-22.12191
BMI Score	25.27109	-0.142644	5.310725	-0.779313	-0.174482	-0.044258	2.848887	1.269707	-0.367544	17.00059
Driver Score	88.79451	-1.267582	7.917947	-1.390075	-0.075366	-0.085484	8.232239	2.122964	-0.670457	21.28552
TRI Concentration (mc/ml)	2.619343	-0.042186	0.211243	-0.053186	0.013019	0.009212	0.123318	0.192029	-0.052835	1.453563
N Score	11.08406	-0.130569	-0.325505	0.07505	0.031012	-0.020428	0.410643	0.828595	-0.56433	20.43537
O Score	10.67252	-0.07438	2.652847	-0.434588	0.091815	0.045825	0.716563	1.165779	0.104249	0.210957
D Score	-15.12589	0.125369	-2.007149	0.345117	-0.140282	-0.058387	0.630055	-1.755019	0.010022	-4.527783
P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Intercept	0.297258	7.39E-07	0.001731	2.53E-18	1.02E-07	5.15E-08	0.000999	6.02E-05	4.01E-07	0.111432
Session order	0.867837	0.769131	0.565717	0.553693	0.310858	0.611594	0.074567	0.206269	0.298194	0.820142
BMI Score	0.038442	0.394735	0.00078	0.006813	0.002492	0.059177	0.004181	0.057062	0.144721	0.057356
Driver Score	0.024497	0.020375	0.113862	0.130743	0.67999	0.256654	0.010102	0.321671	0.408475	0.458149
TRI Concentration (mc/ml)	0.088132	0.047595	0.27915	0.138993	0.070153	0.002118	0.318403	0.023027	0.097086	0.195983
N Score	0.348772	0.424735	0.828906	0.786293	0.574656	0.36946	0.667	0.201401	0.022661	0.019733
O Score	0.23251	0.54663	0.021035	0.039241	0.029213	0.008471	0.320682	0.018202	0.572993	0.974266
D Score	0.194819	0.436274	0.177549	0.206872	0.010938	0.010077	0.502774	0.006631	0.966844	0.5958

This analysis leads to the conclusion that the three participants with the highest saliva levels of Triazolam were responsible for the impaired response levels for most of the psychomotor tests. Only the Simple Response Time test continued to show significantly increased reaction times for all participants, and the Pursuit tests continued to show marginal levels of impairment for all participants. These are not the tests identified in Figure 4-14 as potentially the most sensitive to drug effect, but they seem to be the most robust in indicating a general level of impairment representative of the whole participant population.

4.8 The Outlier characteristics

It is necessary to review the psychomotor scores for the Outlier participants M2110, M2524 and M2426 to complete the analysis of the impact of Triazolam on the psychomotor tests. The averages of the intervening variables for these three participants (BMI Index/BMI score, Driver Index/Driver Score and Dose/TRI Concentration) are presented in Figure 4-18, together with their average simulator sickness scores. Figure 4-18 contains the averages for the intervening variables for these three participants sorted by dose compared with the corresponding dose-linked averages for all 24 participants, including the outlier participants.

Figure 4-18: Comparison of intervening variables for the outlier participants against the whole cohort of participants who completed all PATH drives.

	Intervening Variables for the Outlier Participants M2110, M2524 and M2426 compared to the full data set with them included								
	BMI Index	Driver Index	Dose	N Score	O Score	D Score	BMI Score	Driver Score	TRI Concentration (mc/ml)
Average 0 Dose, Outlier Data Set	1.00	3.00	0.00	1.59	6.32	2.32	23.33	10.00	0.00
Average .125 dose, Outlier Data Set	1.00	3.00	0.13	0.00	2.53	0.00	23.33	10.00	64.83
Average .250 dose, Outlier Data Set	1.00	3.00	0.25	6.36	17.69	9.28	23.33	10.00	227.67
Average 0 Dose,. Full Data Set	1.71	2.04	0.00	4.77	7.58	3.48	26.25	8.38	0.00
Average .125 dose, Fulll Data Set	1.71	2.04	0.13	2.19	6.32	3.19	26.25	8.38	42.71
Average .250 dose, Full Data Set	1.71	2.04	0.25	4.87	10.34	6.96	26.25	8.38	100.79

As a group, the outliers would be expected to be among the most proficient drivers in this study. That is true because all three had driver scores of 10, indicating accurate and conservative driving skills. Additionally, all three have Body Mass Scores indicative of normal height to weight ratios, whereas the cohort as a whole had higher BMIs. Yet, it can be seen from the TRI concentration column how much higher their saliva Triazolam concentrations were in comparison to saliva levels for all participants.

Figure 4-19 demonstrates that the three outlier participants expressed less Anger, Depression, Anxiety and Restlessness that the who group of participants, even at the highest dose levels, averaging saliva concentrations of over 200 mc/mL. At the highest dose levels, they reported themselves to be slightly more sleepy that the group as a whole, but at approximately the same levels of Happiness and Vigor. Thus, although their Triazolam saliva levels were the highest, they did not perceive themselves to be less vigorous or more fatigued that the overall group.

Figure 4-19: Mood scores for the Outlier participants against the whole cohort.

	Mood scores for the Outlier Participants M2110, M2524 and M2426 compared to the full data set with them included							
	moo DEPRESSION: Mean AdjCat	moo ANGER: Mean AdjCat	moo ANXIETY: Mean AdjCat	moo RESTLESSNESS: Mean AdjCat	moo FATIGUE: Mean AdjCat	slp: Subj Resp	moo VIGOR:Mean AdjCat	moo HAPPINESS: Mean AdjCat
Average 0 Dose, Outlier Data Set	0.00	0.00	0.03	0.00	1.22	2.33	3.11	4.64
Average .125 dose, Outlier Data Set	0.00	0.00	0.06	0.11	0.61	2.33	3.72	4.36
Average .250 dose, Outlier Data Set	0.03	0.17	0.17	0.39	1.81	4.00	2.83	4.17
Average 0 Dose,. Full Data Set	0.14	0.19	0.20	0.19	1.38	2.40	3.24	4.23
Average .125 dose, Fulll Data Set	0.22	0.15	0.19	0.25	1.17	2.25	3.26	4.24
Average .250 dose, Full Data Set	0.35	0.38	0.42	0.44	1.73	3.04	2.97	4.16

Finally, Figure 4-20 presents the psychomotor performance scores on key PATH tests for the outlier participants against the corresponding scores for all participants. There is no question that these participants are substantially more impaired in their performance on these tests than all participants as a whole. Moreover, there is a strong suggestion that they have better than average scores at the placebo and 0.125 mg dose.

Figure 4-20: Psychomotor performance scores for the outlier group compared to all participants.

	Psychomotor Performance Scores for the Outlier Participants M2110, M2524 and M2426 compared to the full data set with them included																	
	mth Mean RT	mth Throughput	pro Mean RT	pro Mean RT Corr	pro Speed	pro Throughput	pur Mean Dist	pur StDevDist	scp Mean RT	scp MeanRTCorr	scp NumCorr	slp RT	srt Mean RT	srt Mean RTCorr	srt Throughput	m2s Thru	m2s Mean RT	m2s Mean RT Corr	m2s Speed
Average 0 Dose, Outlier Data Set	1923.97	33.35	471.04	471.46	127.67	122.48	9.22	4.21	369.39	369.39	39.83	5454.50	235.48	235.48	258.32	46.83	1365.47	1261.20	47.91
Average .125 dose, Outlier Data Set	1612.43	36.22	476.63	477.30	126.33	123.72	7.08	4.28	397.79	397.79	40.00	4061.67	235.10	235.10	256.42	39.22	1657.20	1657.20	39.22
Average .250 dose, Outlier Data Set	2087.93	24.91	784.75	689.24	85.96	82.23	13.00	6.85	560.74	560.74	39.00	9385.00	472.01	472.01	174.22	23.22	2927.81	2887.48	24.85
Average 0 Dose,. Full Data Set	2115.16	29.62	524.40	526.87	118.65	114.37	9.96	4.86	404.30	402.77	39.92	3913.73	237.45	237.45	259.15	44.66	1441.96	1379.84	46.71
Average .125 dose, Fulll Data Set	2035.79	29.99	502.27	504.45	120.82	116.76	10.35	5.42	392.73	393.18	39.81	3537.98	242.48	242.48	253.24	45.37	1375.22	1359.18	48.29
Average .250 dose, Full Data Set	2255.86	28.66	573.53	563.49	110.37	106.41	11.30	5.80	430.27	432.74	39.73	5367.98	281.00	281.00	234.85	39.26	1718.08	1697.23	41.82

Thus, it is clear that the impairment is a direct effect of the drug and also that the impairment only is manifest at high individual drug concentrations in saliva, and by inference, high serum concentrations.

4.8.1 Review of Outlier Saliva Triazolam Concentration Characteristics

Two of the 28 participants who were accepted into Project PATH and completed at least the first of the three experimental sessions (five drives) were excluded from the project after their next-day saliva specimens showed detectable levels of saliva Triazolam. Since Triazolam has a reported half-life of two hours, it had been expected that all of the drug would have been eliminated after a period of eight or more hours since drive four of the previous day, equivalent to four half-lives. One of those two participants, M4619,

had a next-day saliva Triazolam level of 101 pg/ml. Three additional participants also had detectable levels of next-day saliva Triazolam, but their saliva assays were not available until after these participants had completed all of their experimental sessions and so they were not eliminated from the study in mid-stream.

Figure 4-21 shows the Triazolam levels of these participants on the session in which residual Triazolam levels were detected, as well as other participants with anomalous salive Triazolam concentrations. It can be seen that three of the five participants showed residual Triazolam after taking the 0.250 mg dose, but two had residual Triazolam after the 0.125 mg dose. The Project PATH intake records for these participants were compared to the intake records for all participants to see if a potential physiological basis for the delayed metabolism or excretion of the drug could be seen.

Figure 4-21: Participants with unusual Triazolam metabolism/excretion patterns

Session ID	Drive 1	Drive 2	Drive 3	Drive 4	Drive 5	Dose	Medications Taken	Start Date	Reason	Ongoing
Medications Competing for the Mechanisms that Metabolize and Excrete Triazolam										
	M4619_	M4619	M4619	M4619	M4619	**Dose**				
Driver, Session & Drive	S2_D1	S2_D2	S2_D3	S2_D4	S2_D5	**.125**	Avalide & Metoprolol	Jan-90	Blood pressure	Yes
Time Since Dose	0	0:56	1:35	2:18	11:44		Nexium, Lipitor, Synthroid	Jan-00	Weight control	Yes
Saliva Triazolam	0	0	13	16	**101**		Folic B, Flavonoid	Jan-90	Dietary supplement	Yes
	M2208	M2208	M2208	M220	M2208	**Dose**				
Driver, Session & Drive	S1_D1	S1_D2	S1_D3	S1_D4	S1_D5	**.250**	Allegra-D-BID	Apr-01	Environmental Allergies	Yes
Time Since Dose	0	1:06	1:42	2:20	12:29		Prilosec OTC-Daily	Sep-08	Heart Burn	
Saliva Triazolam pg/ml	0	0	0	73	**59**		Albuterol Inhaler	Oct-98	Asthma	
	M2106	M2106	M2106	M2106	M2106	**Dose**				
Driver, Session & Drive	S2_D1	S2_D2	S2_D3	S2_D4	S2_D5	**.250**	Zyrtec	Apr-99	Environmental & seasonal allergies	Yes
Time Since Dose	0	0:54	1:34	2:16	17:23					
Saliva Triazolam pg/ml	0	0	52	161	**30**					
	M2110	M2110	M2110	M2110	M2110	**Dose**				
Driver, Session & Drive	S2_D1	S2_D2	S2_D3	S2_D4	S2_D5	**.250**	Zyrtec-OTC	May-00		Yes
Time Since Dose	0	0:53	1:38	2:12	13:07		Cetaclor	Sep-09	Sinus Infection	
Saliva Triazolam pg/ml	0	116	**209**	186	**16**		Ibuprofin, Tylenol PRN	Sep-09	Headache, Sore Throat	
The "Outlier" Participants with the Highest Saliva Triazolam and the Highest Psychomotor Impairment Scores										
	M2524	M2524	M2524	M2524	M2524	**Dose**				
Driver, Session & Drive	S3_D1	S3_D2	S3_D3	S3D4	S3_D5	**.250**	No medications taken			
Time Since Dose	0:00	0:53	1:34	2:15	15:39					
Saliva Triazolam pg/ml	0	165	**195**	175	0					
	M2426	M2426	M2426	M2426	M2426	**Dose**				
Driver, Session & Drive	S2_D1	S2_D2	S2_D3	S2_D4	S2_D5	**.250**	Afrin Nasal Spray	Aug-09	Environmental allergies	Yes
Time Since Dose	0	0:52	1:35	2:13	21:28					
Saliva Triazolam pg/ml	0	181	**289**	**312**	0					
Delayed Excretion with No Obvious Explanation										
	M2225	M2225	M2225	M2225	M2225	**Dose**			**Dose .250**--Next-day drive -	
Driver, Session & Drive	S3_D1	S3_D2	S3_D3	S3_D4	S3_D5	**.125**	No medications taken	11/3/99	Driver reported-No memory	
Time Since Dose	0	0:55	1:35	2:15	11:57			Next-day	of 3rd or 4th drive of previous day	
Saliva Triazolam pg/ml	0	87	101	97	**30**					
Previous use of a Benzodiazepine for Sleeping										
	M4005	**M4005**	**M4005**	**M4005**	**M4005**					
Driver, Session & Drive	**D1**	**D2**	**D3**	**D4**	**D5**	**No Triazolam was found in any saliva sample**				
Saliva Triazolam pg/ml						**Dose**	Benzodiazepine,			Field
S1 - 5 Drives	0	0	0	0	0	**.125**	Unknown name	9/5/- 9/9/09	Difficulty sleeping	is blank
Saliva Triazolam pg/ml						**Dose**		11/5-		
S2 -5 Drives	0	0	0	0	0	**.000**	Ibuprofan, Tylenol	11/6/09	Headache, Fever	
Saliva Triazolam pg/ml						**Dose**				
S3 - 5 Drives	0	0	0	0	0	**.250**				

There appears to be a plausible explanation for the residual Triazolam found in four of the five participants. Participants M4619 and M2208, the participants excluded mid-project by the research team, and M2106 and M2110, are participants who have long-term on-going prescriptions or have been taking OTC medications for extended periods of time.

M4619 was taking combinations of medications to control blood pressure and control weight. He had the highest concentration of residual Triazolam, and that was following the 0.125 mg dose, taken on the second experimental session, rather than the 0.250 mg dose, which was taken on the first session. It may be that one or more of the medications prevented the absorption of Triazolam through the intestine. It is worthwhile to note that M4619 had taken the 0.250 mg capsule on the first session and no (0) Triazolam was detected on any of the five saliva specimens from that session. The absorption and excretion pattern for M4619 remains to be explained.

Three participants, M2110, M2208 and M2106, who had measurable levels of Triazolam in saliva next-day were taking anti-allergy medications. Anti-allergy medications are usually in the class of anti-histamine drugs. Allegra (Fexofenadine) and Zyrtec (Cetirizine) are both anti-histamines. Many individuals do not have a comprehension of the class of drugs they are using, only the trade name. On the enrollment form, each of these three participants stated that they were not taking anti-histamines, when in fact they had been taking them regularly for eight to ten years. Anti-histamines are known to slow the metabolism of Triazolam. Presumably that is the cause of the delayed metabolism and excretion. Note that M2110 is one of the participants identified as an "outlier" because of the manifest level of impairment on the psychomotor tests and very high saliva Triazolam concentration on Drive 3 of the session on which this participant had residual next-day Triazolam.

Figure 4-21 also presents data on four other participants with unusual patterns of saliva Triazolam levels – M2524, M2426, M2225 and M 4005.

M2524 and M2426 are the other two of the "outlyer" participants identified by high saliva Triazolam concentrations and manifest impairment on the psychomotor tests. M2524, a driver who is taking no medications, represents the top end of the spectrum of saliva concentrations for drivers not taking a medication that might slow metabolism and excretion.

The saliva Triazolam concentration pattern for M2426 would be explained by strong inhibition of metabolic degradation and excretion from a competing medication, Afrin nasal spray (Oxymetazolamine). However, Afrin is not an anti-histamine and there are no warnings in the literature that indicate drug interactions between benzodiazepines and Afrin. The coincidence between the use of Afrin and the otherwise inexplicably high saliva concentration is attractive and may be a previously not-known rare interaction.

M2225 is unusual because, returning for the next-day drive of the first session, this participant professed to have no memory of having completed Drive 3 or Drive 4 the previous day♦. This participant received the 0.250 mg dose on first session, and the 80 minute saliva Triazolam was 158 picograms per ml, high, but only the 10th highest saliva concentration detected in Project PATH. There was no residual Triazolam in saliva in the next-day sample from the first session. Also, this participant received the 0.125 mg capsule on the third session and had a next-day residual Triazolam concentration of 30 pg/ml. This participant also had the highest saliva Triazolam at 80 minutes of any of the driver on the day they received the 0.125 mg dose. M2225 stated that he was taking No Medications. M2225 is of normal weight with a BMI score of 25, so the body mass should not be a contributing factor. The absorption and excretion pattern for M2225 remains to be explained. M2225 may represent the upper limit of Triazolam absorption for persons with no other complicating factors such as prescription medications.

M4005 is the final participant with an anomalous saliva concentration of Triazolam. That driver never produced a saliva sample with that contained a detectable amount of Triazolam. M4005 is the only driver with zero saliva concentrations at the 0.250 mg dose, and only one of three drivers with all zeros for the 0.125 mg dose. M4005 reported, on his intake forms, that he had taken an unnamed benzodiazepine as a sleep aid for three days in September, a month before his experimental involvement. His rapid urine tests were negative for benzodiazepines within the level of detection of the test strips in the urine test. M4005 also was within the normal range on the psychomotor tests. (His scores on the 0.250 mg dose day were consistently better than the average of all other participants). Thus, there is no indication that he was debilitated by the Triazolam dose. The only reasonable explanation is that his previous experience with an unnamed benzodiazepine had significantly enhanced his ability to metabolize the drug to the extent that the saliva concentration never went above the 10 pg/ml level of detection. That explanation would make more sense if the participant had stated on intake that he had an on-going prescription for a benzodiazepine sleep aid, but that statement would have disqualified him for enrollment in the research program.

4.8.2 Summary

Drug combinations can interact to potentiate or reduce the efficacy of the desired or intended drug reaction. The interactive effects of drugs is a major problem in the effort to determine which drugs are “safe” to use when safety-critical thinking and responses are required. An outcome of Project PATH was the description of several possible or probably drug interactions that potentiated or may prolong the effect of Triazolam.

It is apparent that participants with an on-going reliance on anti-histamine based anti-inflammatory drugs for relief of allergies metabolized and excreted Triazolam slower than peers not reliant on anti-histamines. Interestingly, participants with that history reliably denied use of anti-histamines. It is probable that they did not know that the

♦ In accordance with the IRB protocol, a report of a “Moderate” intensity adverse event report was filed with Institutional Research Board, that he participant allowed to continue in the project.

OTCs they were taking were anti-histamine nasal decongestants. One of these participants, M 2110, spiked a Triazolam saliva concentration of 209 pg/ml and was one of the three manifestly impaired participants in the psychomotor testing.

However, the most impaired participant, M2426, was a participant with a new prescription for Afrin nasal decongestant spray. Afrin is a non-anti-histamine based compound. M2426 had the highest levels of saliva Triazolam as was the most impaired driver of the participants. There is no indication in the literature of a benzodiazepine contraindication for Afrin users. The Project PATH results would indicate that further research is needed to definitively state that there are no drug interactions that would warrant a safety warning. The fact that there may be a not-previously-defined drug interaction between benzodiazepines (if Triazolam is typical) and a popular non-anti-histamine based nasal decongestant points to the very difficult quandary of the medical examiner being asked “is it safe for me to take this prescription?”

4.9 Conclusion of Section 4 – PATH Psychomotor Tests

Section four yields the following information:

1. The Mood scores in the PATH battery are not directly dose-related or dose-dependent. While there are small mood score changes seen in the psychomotor battery seemingly associated with dose, they are in fact related to increased level of simulator discomfort, and their anticipation on the pre-dose drives, rather than to increased drug levels. Triazolam appears to mitigate simulator discomfort and low and moderate dose levels. However, above an internal concentration represented somewhere close to but above saliva Triazolam levels of 100 picograms/mL, the therapeutic effect breaks down and the higher Triazolam levels may in fact potentiate feelings of simulator discomfort.

2. There is rather little quantifiable impairment in the performance tests in the PATH battery that cannot be ascribed to the substantial impairment experienced at high dose levels by three of the 24 participants. The PATH test Simple Response Time (srt) appears to be the most robust test for capturing drug impairment independent of the intervening variables Body Mass Index, Driver Score and the impact of the Simulator Sickness variables. The Standard Continuous Performance (scp) test seems the most sensitive overall of the psychomotor tests, with significant impairment with only a 5% increase in Mean Response Time. However, scp is measuring response time with the combined impairment of drug effect and simulator sickness.

3. There are three participants among the 24 who showed much higher than normal saliva concentrations of Triazolam at both the 0.125 and the 0.250 dose. These participants were scored, on their first pre-drug drive, as cautious and proficient drivers (Driver Score 10), and they have Body Mass Indices in the low end of the range of this group. As seen in Section 3 of this report, participants with low BMI

had higher concentrations of Triazolam in their saliva than participants with higher BMIs. However, the differences between these individuals and their peers imply a level of difference that may have a physiological basis. Some of that physiological difference could be related to drug-drug interactions between Triazolam and their on-going use of anti-histamine medications, but not all.

4. These outlier participants showed higher levels of impairment on all psychomotor performance scales than their peers and are largely responsible for overall findings of impaired performance in the psychomotor tests at doses of 0.250 mg of Triazolam. Exempting these three participants, there were negligible impacts of the therapeutic doses of Triazolam.

5 DRIVER PERFORMANCE IN THE SIMULATOR

Many people suffer from some form of insomnia and as a result may take some type of sleep medication. There is some epidemiological evidence that residual effects of these medications may exist and that these effects can have a negative impact on cognitive and psychomotor functions[49] (Mintzer and Griffiths, 2002).

A major goal of this study is determine whether Triazolam taken in recommended therapeutic doses (0.125 mg and 0.250 mg) causes impairments in driving ability, to quantify those impairments in they exist, and to determine whether those impairments (if any) return to baseline after a night's sleep.

Standard Deviation of Lateral Position (SDLP), a measure of the amplitude of side-to-side weaving while driving on a straight stretch of road, is a widely-used measure of impairment (NHTSA, 2006). In the current experiment, the driving simulator continuously measures the distance between the center lane of the virtual line in which the bus is driving and the center of the bus at the front wheels. That data is created 30 frames per second. The standard deviation of those data points calculated over a straight stretch of road when there are no driver distractions or challenges, constitutes the SDLP value for that drive. Significantly greater dose-dependent variation would indicate that there is impairment due to the drug.

5.1 Residual Effects of Triazolam on SDLP on the Day after Being Taken

The first hypothesis to be tested is that is that a noticeable difference in lateral position exists for the day after the driver had taken the dose when compared to the SDLP for the day they had taken the drug. The null hypothesis is that no difference in SDLP would exist on a drive on the day after dose administration, following a normal period of sleep, as compared to the SDLP calculated for an equivalent drive taken before the dose of the experimental drive.

5.1.1 Driving Scenarios

Each of the driving sessions was composed of three experimental sessions and each session consisted of two days. Within a particular driving session, the first day consisted of four individual simulator drives and the second day consisted of a single day-after drive. On the first day of each experimental session, the participants were required to do one simulator baseline drive prior to administration of one of the three drug conditions. The drug doses, administered in a double-blind protocol, were a placebo, a 0.125mg dose of Triazolam, or a 0.250 mg dose of Triazolam. Over three experimental sessions, the participants received each of the three dosage types. The order of drug type were received in a randomized order and differed for each subject. The doses were provided to the participants immediately following the first drive.

This analysis centers on the first (baseline) drives of each individual session compared to the day-after drive. The baseline drives were performed and completed immediately prior to the participants taking the drug or the placebo. The day-after drives were a repeat of the base-line drives. The SDLP baseline and next-day measurements were made along the same section of road. The day-after drives were performed approximately 9 to 15 hours after the participants had taken their prescribed dose for that particular session and after they had been able to have a full night's sleep.

Due to design constraints, on different sessions the driving sections where the SDLP measures were collected did not have the same speed limits. Two sections had posted speed limits of 30 mph (in sessions 1 and 3) and one had a speed limit of 45 mph (in session 2). The 30 mph road in session 1 and in session 3 was 597 meters in length and the 45 mph road in session 2 was 497 meters in length.

After each of the experimental drives, the participants filled out a simulator sickness questionnaire modeled after Kennedy et.al (1993). This questionnaire allowed researchers to account for possible simulator sickness effects and their influence on the participants' SDLP. Additionally, after each experimental drive, the participant's mouth was swabbed for a saliva sample. This sample was analyzed for the concentration of Triazolam in the saliva, and intended as a surrogate for the current concentration of Triazolam in the participant's blood stream (serum).

5.1.2 Participants

Of the 24 participants who drove in all three sessions, there were only 17 drivers who completed the full study of all drive conditions on all three sessions, including the next-day drive. This was so because the diesel generator providing the regulated power supply for the simulator began to have mechanical problems in the final days of the experiment. Consequently, seven (7) participants were not able to perform their final (next-day) drive of session 3, though they did complete for four (4) same-day drives in session 3. Hence, this analysis includes only those 17 drivers.

These 17 participants had a mean age of 26.05 years (sd=8.43 years) and had a mean of 1.97 years of commercial driving experience (sd=1.45). There were 16 males and only one female. Due to this gender disparity, gender effects are not examined. The mean body mass index (BMI) of these study was 23.94 (sd=2.78) with a range of 20 (considered normal) to 30 (considered obese). Over the 3 experimental sessions of 2 drives per session and with 17 individual participants, there was a total of 102 individual drives examined in this analysis. Graphical depictions of the descriptive statistics are shown in figures 5-1 to 5-4.

Figure 5-1: .Distribution of BMI Scores

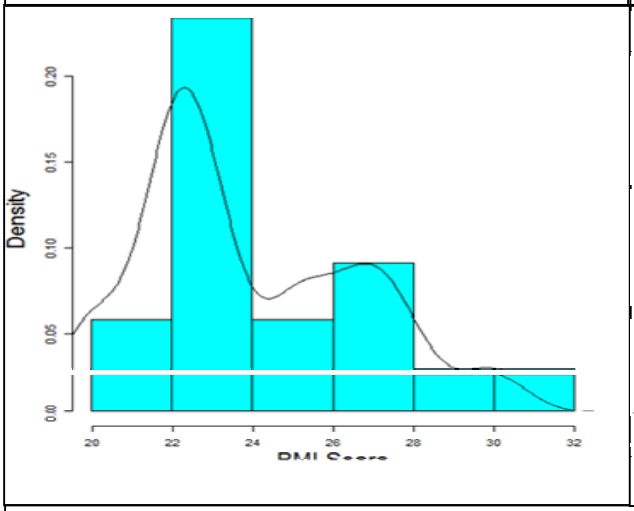


Figure 5-2: Driver Age and Experience

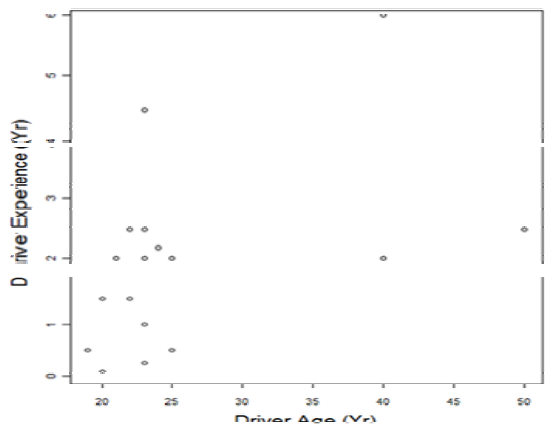


Figure 5-3: SDLP Mean (with standard error) by Dose Level

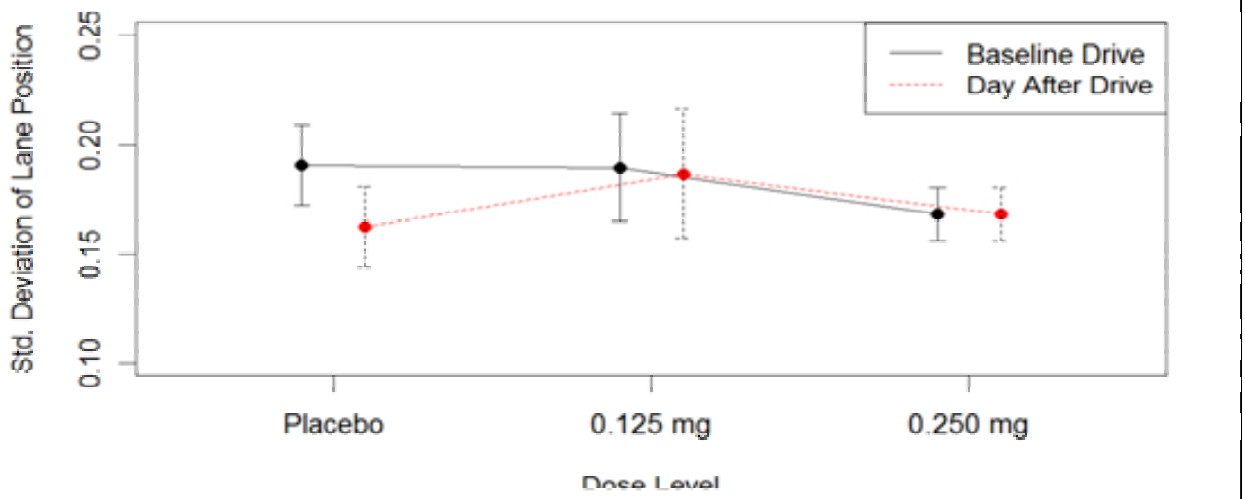
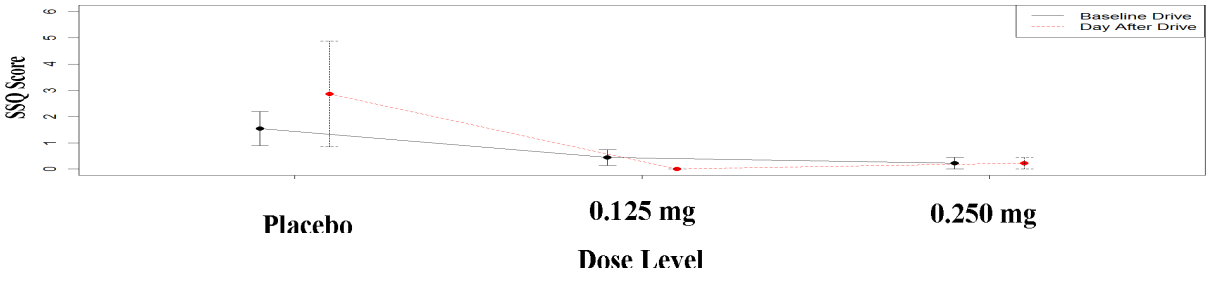


Figure 5-4: Simulator Sickness Score By Dose Level



5.1.3 Independent Variables for Next-Day Drive Analysis

The primary fixed effect of interest, the day-after effect of the drug, was examined across five levels: baseline vs. day-after effects, at placebo, 0.125 mg dose, and 0.250 dosage. The baseline level represented the SDLP of the participants before they took the drug or placebo. The remaining levels accounted for the day-after effects of the three drug levels on the driver's SDLP. There were six other covariates included in the linear mixed model, as follows:

- Differences in SDLP may also be due to different speed limits on the different driving segments. Hence, a continuous variable to account for the effect of driving speed was also added.
- A Driver Index score was also included as a factor. The driver index was a score that had been given to each driver and was based on how each individual driver performed in a variety of situations during familiarization drives in the driving simulator. This score had three levels, with 1 indicating the poorer performing drivers and 3 indicating the better performing drivers (Table 1).
- Body Mass Index was included by itself, but it also served as a representative of total years of commercial driving experience and age. The commercial driving experience of the participants and the driver's age were considered for use as an independent variable. However a strong correlation between these variables and BMI scores were detected (see Table 5-2). Hence, only one of the three variables Body Mass Index, years of driving experience or age could be included in the model to avoid issues of multicollinearity. Multicollinearity can cause a model to be unstable and occurs when two or more independent variables within a multivariate model are highly correlated. In the presence of multicollinearity, even minor changes in one of the independent variables can have significant effects on model estimates for all fixed effects. Body Mass Index was selected because results of the psychomotor tests in Section 4 indicated that it might be a significant variable.
- The interaction between time since dose and the participants' body mass index (BMI) was also included to account for the period of time within which the dose of drug had had to be absorbed into the participant's system. This variable included three levels (placebo, 0.125 mg and 0.250 mg) but was of a continuous nature (due to time effect).
- The total simulator sickness questionnaire (SSQ) score was included to account for any deleterious effects on the participant's SDLP due to the onset of simulator sickness. The computation is based on Kennedy et al. (1993) and consists of counts of the 16 symptoms of simulator sickness experienced by the participants. As shown in Figure 3-14, the counts are grouped into three different sickness type characterizations (i.e. nausea, oculomotor and disorientation). Some of the simulator sickness symptoms are classified based on two of the three sickness types. For example, "difficulty focusing" is classified as both the oculomotor and disorientation sickness type. Per the

Kennedy model, the counts for each of the three sickness types were summed and multiplied by 3.74 to give the category total SSQ used in the subsequent analyses. SSQ is modeled as a continuous variable because of the small sample size, the addition of several other parameter estimates, and the cross-classification of some of the symptoms.

- Since the model was fitted using a subset of the total study participants, the number of participants in each dose level was not balanced (see Tables 5-3 and 5-4). Due to the dose orders being unequal, a restriction on randomization was included that account for the six different orders.

Table 5-1: Participant Counts by Driver Index

	Driver Index		
	Level 1	Level 2	Level 3
Count	5	6	6

Table 5-2 – Correlation Between Driver's Age, Commercial Driving Experience and BMI Score for 17 Drivers in the Baseline Next-Day study

Correlation			
Variable	Age	Experience	BMI
Driver's Age	1	----	----
Commercial Driving Experience	0.45	1	----
BMI Score	0.75	0.32	1

Table 5-3 - Number of participants included in each Drug Administration Order

	Dose Order					
	A	B	C	D	E	F
Count	3	3	2	2	3	4

Table 5-4 – Driver Count by Dose and Drive Session

Dose	Count		
	Session 1	Session 2	Session 3
Placebo	6	5	6
0.125 mg Triazolam	6	5	6
0.250 mg Triazolam	5	7	5

The Triazolam Saliva concentration values of the participants were not included in this model since the baseline drive was performed before the participants had the Triazolam dose administered. Consequently, the participants would have no Triazolam in their saliva. Additionally, there was only two participants who had a non-zero concentration of Triazolam in their saliva on the day-after drive. Since there was only one person with a non-zero Triazolam saliva concentration, including the Triazolam saliva concentration in the model as an independent variable produced errors in the model due to the high influence that single observation had on the entire model estimation. For this study, the level of Triazolam in the saliva was measured in micrograms per milliliter (mcg/ml).

5.1.4 Linear Mixed Effects Model

A linear mixed effects model was used for this analysis. The linear mixed effects model accounts for the within-subject effects of each participant having multiple drives over multiple experimental sessions. The statistical software program that was used to fit the model was R (v. 2.10.1) using the "nlme" package. In order to model the random effects that were unique to the drivers, a random intercept was estimated for each of the drivers. The general form of the linear mixed model is:

$$\text{Log (SDLP)} = \beta x + Zu + \varepsilon \qquad \text{eq (1)}$$

Where β is the parameter estimate for each fixed effect factor x_i, Z is the random effects coefficient for each driver j and ε_{ij} is the random error term. After fitting the model and observing that there was a slight mean-variance relationship in the residuals, (when compared to the fitted values), SDLP was transformed to the natural log function.

5.1.5 Results of Next-Day Drive Analysis

The resulting model estimates (see Tables 5-5 and 5-6) showed that there was no significant effect on the driver's SDLP due to a residual narcotic effect from Triazolam, $F(3,81)=0.32$, $p > 0.05$, at any dose level when compared to the SDLP of the baseline drives. That is, there was no increase in weaving in lane on the day after having ingested the placebo, 0.125 mg or 0.250 mg dose as compared to their pre-dose driving performance.

The drivers' speed on each particular driving segment was found to be significantly different ($F(1,77)=46.57$, $p < 0.001$). This was expected since there were different posted speeds and this variable was used to account for those differences. The effects estimate of the driver's mean speed, $t(77)=6.82$, $p < 0.001$, was significant, and showed a positive relationship between mean speeds and SDLP. Higher speeds are associated with higher SDLPs. There were no significant differences for the other effects included in the model: the driver index, driver's BMI score, SSQ score, or the interaction between dose level and BMI score, and the dose order effect.

The "p-value" column in Table 5-5 presents the level of significance for each of the variables included in this portion of the study. The Parameter Estimate in Table 5-6 is the estimate of the magnitude of the effect.

Table 5-5– ANOVA Table for Residual Drug Effect Analysis

Fixed Effects	df	Den df	F-value	p-value*
(Intercept)	1	77	11.19	0.001
Avg. Speed	1	77	46.57	<0.001
Residual of Effect of Drug the Day After Driving Ability	3	77	0.32	NS
BMI Score	1	8	0.18	NS
SSQ	1	77	0.56	NS
Driver Index	2	8	1.60	NS
Dose Order	5	8	0.48	NS
Interaction BMI- Dose	3	77	0.34	NS

*Note: Not Significant(NS): p > 0.05

Table 5-6– Effect Estimates for Residual Drug Effect Analysis

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	77	-2.13	0.64	-3.35	0.001
Avg. Speed (meters/sec)	77	0.05	0.01	6.82	< 0.001
Residual Effect: Placebo	77	-0.18	0.73	-0.26	NS
Residual Effect: 0.125mg	77	0.59	0.70	0.84	NS
Residual Effect: 0.250mg	77	0.04	0.70	0.06	NS
BMI Score	8	-0.01	0.03	-0.42	NS
SSQ	77	-0.01	0.01	-0.75	NS
Driver Index: Level 2 of 3	8	0.04	0.18	0.21	NS
Driver Index: Level 3 of 3	8	-0.27	0.16	-1.66	NS
Dose Order B (compared to A)	8	-0.01	0.19	-0.49	NS
Dose Order C	8	0.11	0.27	0.39	NS
Dose Order D	8	0.01	0.24	0.04	NS
Dose Order E	8	-0.10	0.21	-0.42	NS
Dose Order F	8	-0.19	0.21	-0.88	NS
Interactions Residual Effect: Placebo – BMI	77	0.003	0.03	0.10	NS
Residual Effect: 0.125mg – BMI	77	-0.03	0.03	-0.94	NS
Residual Effect: 0.250mg – BMI	77	-0.01	0.03	-0.19	NS

*Note: Not Significant(NS): p > 0.05

5.2 Driver Performance 1:-- Standard Deviation of Lateral Position over Time

The next research issue addressed was the effect of Triazolam on driver performance over time and dose. Section 4 established that that there were no significant day-after effects on the psychomotor functions of the participants and the previous paragraphs in this section established that there was no lingering effect on next-day straight driving.

The experimenters next looked at how the participant's driving performance functions degraded over time after they had ingested Triazolam. The four driver performance measures that will be discussed are (1) Standard Deviation of Lateral Position on the four same-day drives under the three dose conditions; 2) Steering performance of drivers maneuvering around barrels in a road construction site, 3) Steering performance of drivers negotiating curves; and 4) Breaking performance of drivers approaching stop signs. Each of these measures examines the performance of drivers under normal driving conditions.

5.2.1 Scenarios Examined for Standard Deviation of Lateral Position Measurements

For this analysis, the scenarios examined were the 4 same-day driving scenarios across the 3 driving sessions. After having completed the first drive (pre-dose) drive, participants received the experimental capsule containing the placebo, 0.125 or 0.250 mg dose of Triazolam. They then completed three drives within the experimental session equally spaced at 40 minutes apart. That is, 40 minutes after taking the dose, participants completed a simulator drive of approximately 10 minutes, and another drive at 80 minutes and the last drive of the day at 120 minutes. Due to design constraints the driving segments that the standard deviation of lateral position was taken from had various lengths and speed limits but were chosen to be roughly 500 meters in length (see Table 5-7). The SDLP segments of several drives are seen in Figure 5-5.

Table 5-7– Length and Posted Speed Limit For Driving Scenarios Considered in the Model

Drive	Session 1		Session 2		Session 3	
	Length (m)	Speed (mph)	Length (m)	Speed (mph)	Length (m)	Speed (mph)
1	597	30	497	45	597	30
2	497	35	497	45	507	30
3	598	30	539	45	726	30
4	382	45	597	30	434	30

5.2.2 Participants

Of the 28 participants who entered the study there were only 24 drivers that had completed the four same-day drives of the three driving sessions (or the complete study). In order for the proper statistical models to be applied, only those 24 drivers, who had complete data, would be included with the model. Over the three experimental sessions, with 4 drives per experimental session and 24 participants, there

were a total of 288 individual drives examined in this analysis. The same individuals that had included in the residual drug effect analysis were the included in this analysis along with the 7 additional individuals who completed all 3 of the four same-day drives but missed the last next-day drives.

Figure 5-5. SDLP segments of typical simulator drives.

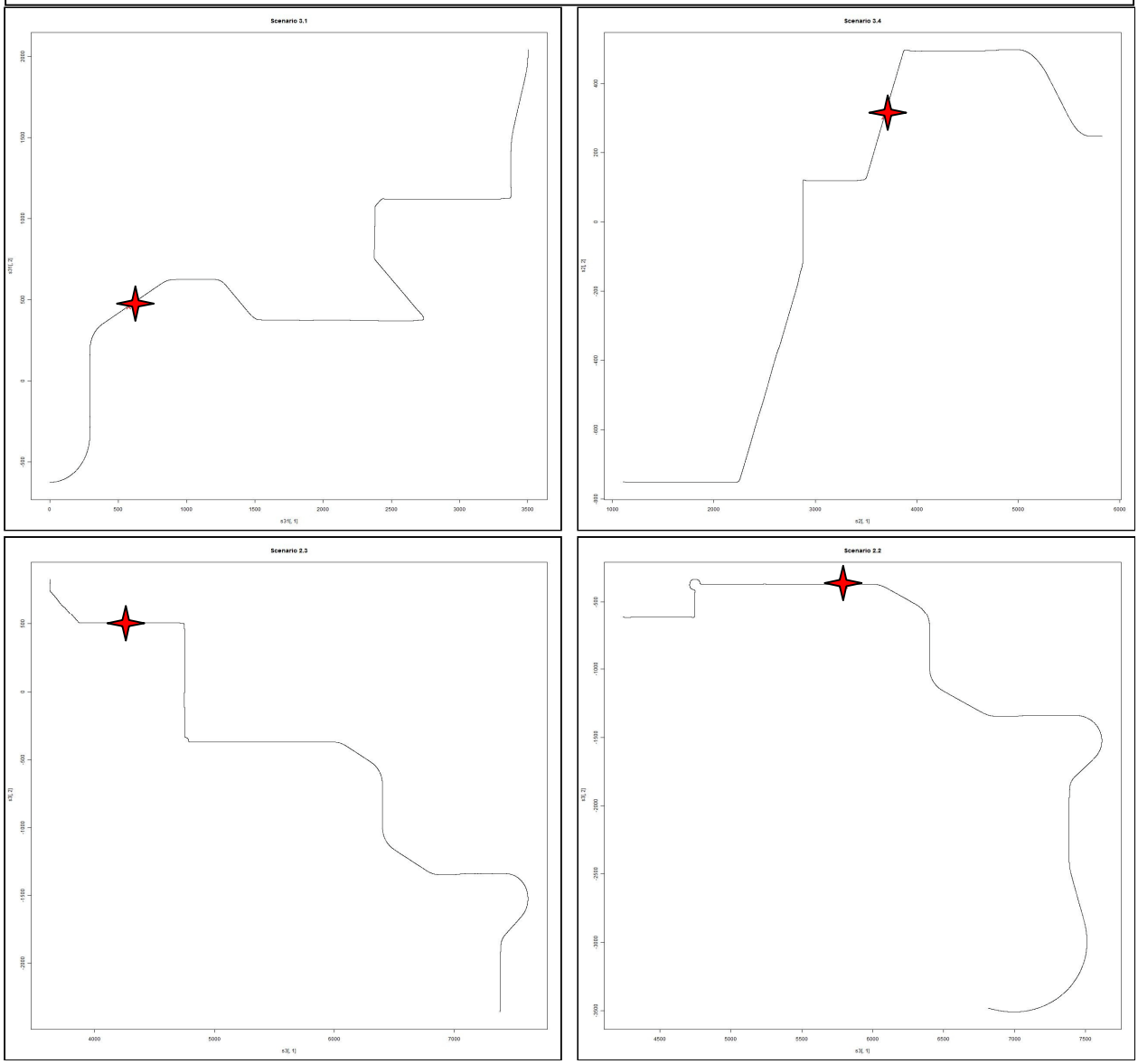


Table 5-8 - Number of participants included in each Drug Administration Order Dose Order

	A	B	C	D	E	F
Count	5	4	2	4	4	5

5.2.3 Independent Variables

There were a total of 13 fixed effects considered within this model. The primary fixed effect of interest was the interaction between dose level and time since the drug was administered. The drug impact on SDLP was estimated using the three level factor for dose (placebo, 0.125 mg dose and the 0.250 mg of Triazolam) over time. A total of 13 factors were included in the model to account for variables that might significantly impact the outcome. These included a variable (with 12 levels) account for differences in the lengths of the 12 experimental drives.

Table 5-9– Correlation Among Driver's Age, Commercial Driving Experience and BMI Score for the 24 Participants in the SDLP study

	Age	Experience	BMI
Driver's Age	1	----	----
CDL Experience	0.35	1	----
BMI Score	0.62	0.39	1

The Triazolam saliva concentration of the study participants was not included in the model since there was a high correlation between the time variable and the Triazolam Saliva concentration, approx. ρ=0.90, when taking the dose level into account. Thus, only the dose level times minutes since ingestion, or Triazolam saliva concentration variable, could be included into the model, but not both. After review of several models including one or the other of these variables, the Triazolam saliva concentration variable was removed as an independent variable. Dose effect over time was chosen as the primary independent variable.

The three-way interaction between the dose level, time and SSQ score was added to account for effects of simulator sickness on subjects that had been administered the Triazolam. The rationale would be that Triazolam over time might interact to heighten or diminish the feelings of simulator sickness relative to the placebo capsule. Additionally, the lower level interactions between SSQ score x time, Dose x SSQ score, along with a continuous SSQ score factor was included in the model since the higher order interaction of Dose Level x Time x SSQ was of interest.

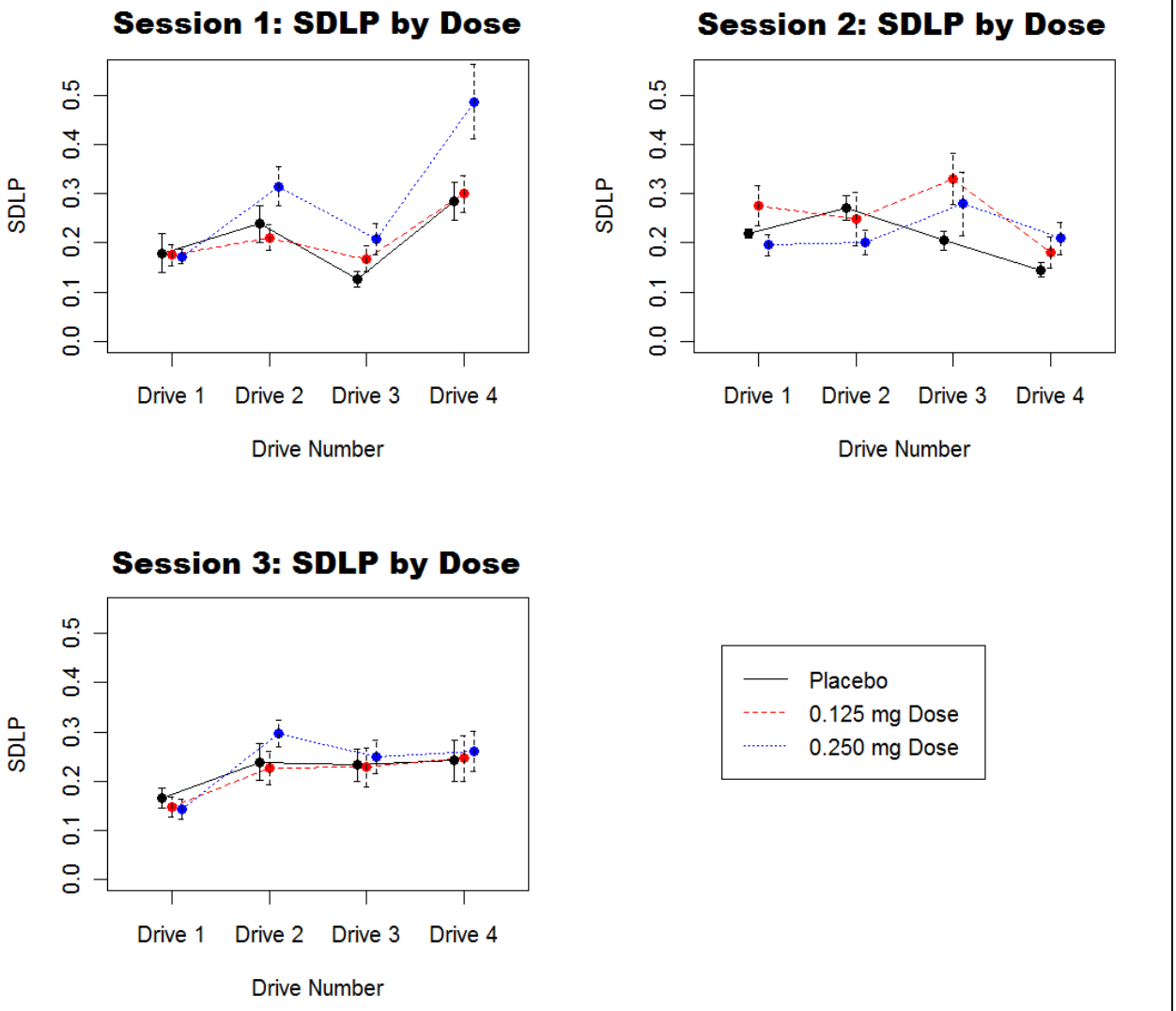
The other variables, average speed, BMI score, driver index, dose order, and BMI score – dose level interaction was also included for the same reasons as the previous analysis. Additionally, as before, the CDL experience for the participants and the driver's age was excluded in order to avoid multicollinearity in the model due the correlation between variables (shown in Table 5-9), with BMI serving as their surrogate.

5.2.4 Model Chosen for Standard Deviation of Lateral Position

The metric chosen to measure the possible decrements in driver simulator performance due to the effects of Triazolam was the standard deviation of lateral position (SDLP). Due to each participant having 12 drives over the 3 experimental sessions, the linear mixed effects model was chosen to allow within-subject effects to be accounted for.

The statistical software program that was used to fit the model was R (v. 2.10.1) using the "nlme" package.

Figure 5-7. SDLP Mean and Standard Error by Dose and Drive Session



Observations within driving scenarios and driving session were time-dependent and were therefore likely to be correlated. In order to account for this, an unstructured correlation structure was used with the model. A random intercept was also included to account for the random effects associated with each driver. After fitting the model and observing the residuals vs. fitted values, SDLP was transformed by the log function to remove a slight mean-variance relationship in the residuals.

Figure 5-8: Simulator Sickness Questionnaire (SSQ) Score by Drive

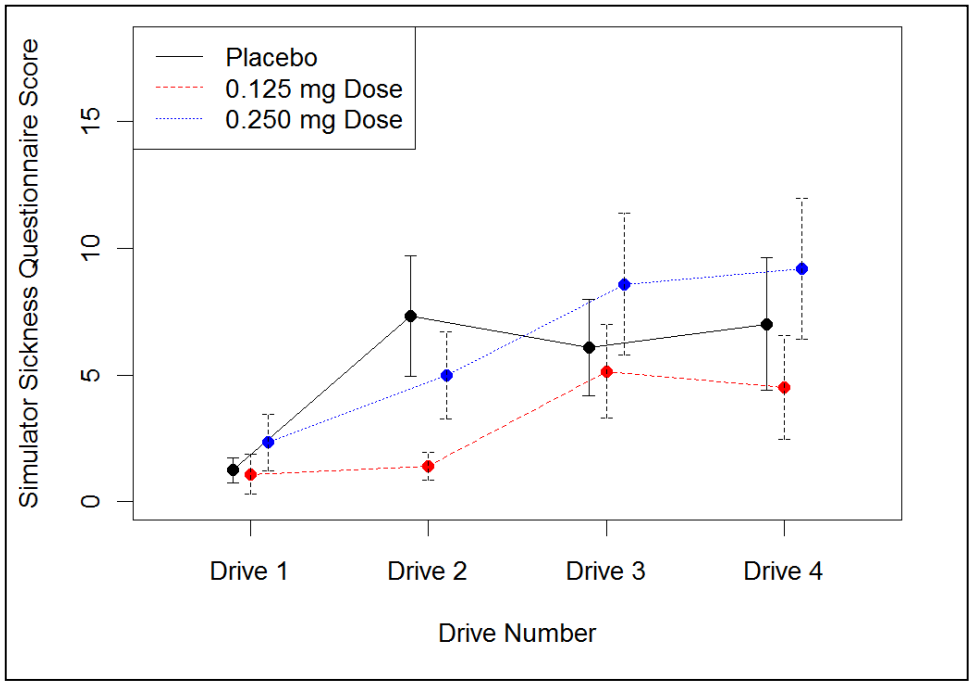
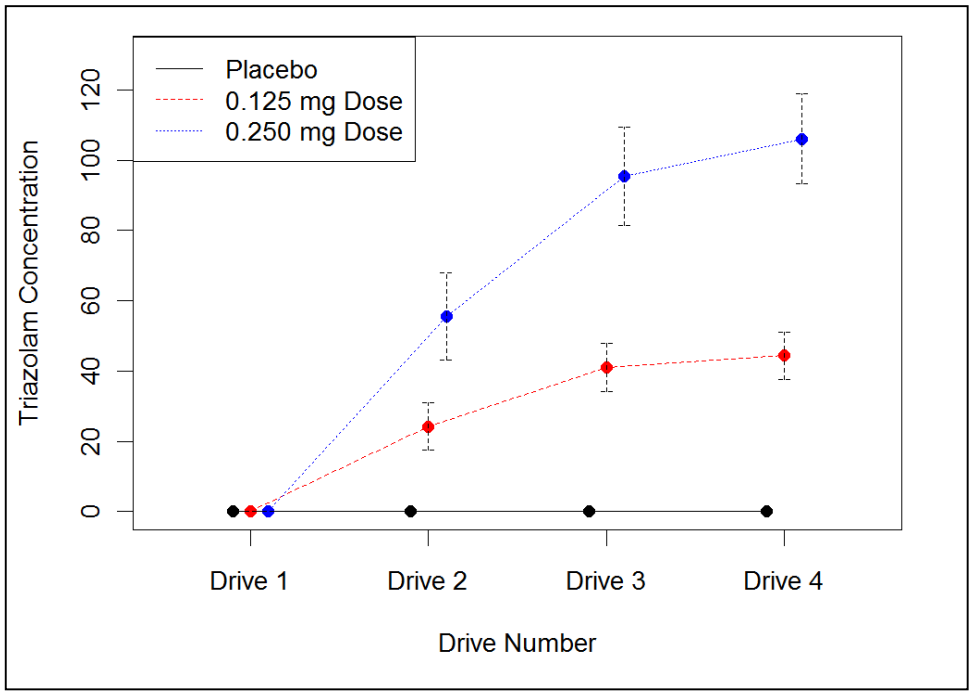


Figure 5-9. Triazolam Saliva Concentration (TSC) by Drive



5.2.5 Results of the SDLP Study

The resulting model for this analysis showed that four factors had a significant effect on SDLP (see Tables 5-10 and 5-11). The time-dosage interaction was found to be significant, $F(2,195)=0.84$, $p = 0.021$ but the only significant individual effect was from the 0.250 mg dose level when compared to the placebo, $t(132) =2.79$, $p =0.006$. This estimate indicated that over time, as the drug was being absorbed from the gut and entering the blood stream, it became more difficult for drivers to maintain lane position.

There was a significant effect due to the individual drive scenario, $F(11,132) = 6.18$, $p < 0.001$, but there was only one individual drive effect that was significantly different from the baseline drive, the first drive on the first driving session, at the α=0.05 level..

Dose Order was significant ($F(5,59)=2.37$, $p=0.05$) with two dose order groups, (Groups E and F) showing differences across SDLP when compared to the baseline group, group A. Drivers randomized into dose groups E and F drove with significantly less SDLP than drivers randomized into the other four dose groups.

As discussed earlier, mean speed of the drivers on each driving segment differed due to differences in posted speed and were accounted for in the model. Indeed, a significant difference was observed for the speed variable $F(1,195)=27.27$, $p < 0.001$. There was a significant different in driver's mean speed, with a positive relationship between higher average speeds and higher SDLP ($t(195)=5.222$, $p < 0.001$). Under both drug and non-drug conditions, driver weave more at higher speeds than at lower. But under drug conditions, their weaving increased at all speeds more than their weaving under non-drug conditions.

Table 5-10– ANOVA Table for the SDLP Drug Effect over Time Analysis

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	195	54.76	<0.001
Avg. Speed (m/s)	1	195	27.27	<0.001
Drive Scenario	11	195	5.61	< 0.001
BMI Score	1	59	0.001	NS
Dose Level	2	59	0.60	NS
Driver Index	2	59	1.37	NS
Time (min. since dose)	1	195	1.07	NS
Simulator Sickness Questionnaire Score	1	195	0.61	NS
Dose Order	5	59	2.37	0.050
Interactions				
BMI Score – Dose Level	2	59	0.92	NS
Time-Dose	2	195	3.93	0.020
Drive Time – SSQ Score	1	195	0.23	NS
Dose Level – SSQ	2	195	1.96	NS
Dose Level – Time – SSQ	2	195	1.70	NS

* Not Significant (NS): $p > 0.05$

Table 5-11– SDLP Drug Effects over Drive progression

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	195	-2.510	0.339	-7.400	<0.0001
Avg. Speed (m/s)	195	0.071	0.013	5.222	<0.0001
Session 1, Drive 2 (compared to S1, D1)	195	-0.324	0.300	-1.079	NS
Session 1, Drive 3	195	-0.722	0.495	-1.459	NS
Session 1, Drive 4	195	-0.875	0.710	-1.232	NS
Session 2, Drive 1	195	-0.236	0.147	-1.604	NS
Session 2, Drive 2	195	-0.622	0.313	-1.985	0.049
Session 2, Drive 3	195	-0.937	0.518	-1.808	NS
Session 2, Drive 4	195	-0.946	0.700	-1.351	NS
Session 3, Drive 1	195	-0.153	0.110	-1.402	NS
Session 3, Drive 2	195	0.074	0.287	0.258	NS
Session 3, Drive 3	195	-0.378	0.489	-0.767	NS
Session 3, Drive 4	195	-0.542	0.691	-0.784	NS
BMI Score	59	0.001	0.010	0.051	NS
Dose: 0.125mg	59	0.253	0.356	0.711	NS
Dose: 0.250mg	59	-0.133	0..357	-0.372	NS
Driver Index: 2 of 3	59	0.101	0.083	0.121	NS
Driver Index: 3 of 3	59	-0.118	0.081	-1.447	NS
Time (min. since dose)	195	0.005	0.005	1.032	NS
SSQ Score	195	-0.007	0.009	-0.783	NS
Dose Order: B	59	-0.109	0.101	-1.08	NS
Dose Order: C	59	-0.114	0.124	-0.917	NS
Dose Order: D	59	-0.039	0.105	-0.37	NS
Dose Order: E	59	-0.244	0.103	-2.360	0.022
Dose Order: F	59	-0.269	0.097	-2.785	0.001
Interactions BMI Score - Dose: 0.125	59	-0.015	0.013	-1.139	NS
BMI Score - Dose: 0.250	59	0.001	0.013	0.084	NS
Time (min. since dose) - Dose: 0.125	195	0.002	0.001	1.594	NS
Time (min. since dose) - Dose: 0.250	195	0.003	0.001	2.790	0.006
Time - SSQ Score	195	0.0001	0.0001	0.487	NS
SSQ Score – Dose: 0.125 mg	195	0.036	0.020	1.912	NS
SSQ Score – Dose: 0.250 mg	195	0.005	0.013	0.392	NS
Time-SSQ Score– Dose: 0.125 mg	195	-0.0002	0.0001	-1.745	NS
Time-SSQ Score –Dose: 0.250 mg	132	-0.0001	0.0010	-0.142	NS

Note* Not Significant (NS): $p > 0.05$

The other variables included in the model: the driver's BMI score, SSQ score, the dose level on a particular session, the driver index, the time of the drive, and the remaining interaction variables were not significant at $p<0.05$.

5.2.6 Magnitude Estimate

The magnitude of the dose-related increase in the Standard Deviation of Lateral Position may be calculated from the equation for the linear mixed-effects model.

Example Calculation for SDLP Model

For example, recall eq. (1)

$$\text{Log (SDLP)} = \beta x + Zu + \varepsilon$$

For SDLP the equation would be of the form:

Log(Distance) = Parameter Estimate for Intercept + Parameter Estimate for Speed + Parameter Estimate for Time Since Dose of 0.250 mg.

The two speeds for the SDLP road segments were 30 MPH and 45 MPH. Speed in the simulator is captured by the software in meters per second. Thirty (30) MPH is 13.4112 meters/second and 45 MPH is 20.168 meters/sec. SDLP is measured in meters. Therefore, it appears that, at 1 Standard Deviation of Lateral Position, the 0.250 mg dose of Triazolam increased weaving in lane by the bus operators (1st SDLP) by approximately 3.6 inches at 30 MPH and 6.1 inches at 45 MPH.

Table 5-12 – SDLP Magnitude Estimate for 30 and 50 MPH at 0.250 mg Triazolam

No drug at 30 MPH --Log(SDLP) = -2.510+(0.071*13.4112) = SDLP = $e^{-1.5578}$ = 0.211 meters (8.3 inches)
0.250 mg Triazolam at 30 MPH, at 120 minutes Log(SDLP)=-2.510+(0.017*13.4112)+(0.003*120)= SDLP = $e^{-1.1978}$ = 0.302 meters (11.9 inches)
No drug at 45 MPH, SDLP, , = Log(SDLP) = -2.510+(0.071*20.1168)= SDLP = $e^{-1.08171}$= 0.339 meters (13.03 inches)
0.250 mg Triazolam 45 MPH, at 120 minutes Log(SDLP)=-2.510+(0.071*20.1168)+(.003*120)= SDLP = $e^{-.72171}$ = 0.486 meters (19.131 inches)

5.3 Driver Performance 2- Traverse Work Zone Obstructions

Study participants were examined as they traversed around barrels under no-drug and drug conditions. The intent of using barrels in the driving scenarios was to simulate work zones and the likelihood that a driver may have a safety critical event when under the influenced of Triazolam. These work zones consisted of several barrels that were

placed in the roadway safety-zone that partially or fully blocked the road to traffic traveling in that direction.

The hypothesis related to this analysis was that, if participants were impaired by Triazolam, they would drive a longer distance as they navigated the work zone areas because they were unable to control the motion of their vehicle as precisely as those who took a placebo. Therefore, any exaggerated lateral movement would equate to a longer distance traveled. The dependent measure used to address this hypothesis is the total distance, in meters, traveled in avoiding these obstructions. This measure was chosen to model the variations in driving behaviors of those under the influence of Triazolam and those who were not.

5.3.1 Work zone scenarios examined.

Of the total fifteen individual drives across all three experimental sessions there were seven drives that contained simulated work zone areas. However, four of the seven driving scenarios had simulated work zones on four lane roads (or two lanes in each direction); as shown in Figure 5-10. On these 4-lane roads, the work zone area only impeded driving in the rightmost lane of the two lanes in the participants' driving direction. Hence, the participants did not always return to the far right lane after passing these areas.

Figure 5-10: View of Four Lane Work Zone Area

This four-lane setup allowed participants to drive in the lane that was not blocked but there was not consistent behavior after the barrels were passed. In other words, drivers may move to the far right lane after having passed the barrels, but they may also stay in

the left lane. This inconsistent behavior prevented a good comparison among all drivers.

We chose to model the collision avoidance behavior on the three remaining scenarios where the simulated work areas were on a two-lane roads so that the driving lane was completely blocked by the barrels. This configuration forced the driver to move into the oncoming lane in order to avoid these obstacles (Figure 5-11). All of the two lane work areas were navigated approximately 80 to 120 minutes after the participants were administered the dose for the particular driving session. Two of the two-lane scenarios that were used in the model were on the third and fourth drives of the first experimental session and one scenario was on the third drive of the third experimental session. Each of these scenarios had similar posted speed limits of 30 mph; however the lengths of these areas were different (Table 5-13).

Table 5-13 - Scenario Drive Length (meters)

Session 1 Drive 3	Session 1 Drive 4	Session3 Drive 4
470	376	792

Figure 5-11. The Drivers' View of a Work Zone on a Two-Lane Road

5.3.2 Participants for work zone drives

There were 18 participants included in this analysis. This number of participants was chosen because of the necessity to have equal number of participants for the 3 dose conditions. Given that only 6 people took the high dose of Triazolam, 0.250 mg, during

the third experimental session, that number of participants was the sample size chosen for all 3 dose conditions. Six individuals were selected at random from the placebo and 0.125 dose condition so that an equal number of people were included from all three driving scenarios and who had received one each dose level. With 3 different driving scenarios and 18 participants, there were a total of 54 individual drives examined in this analysis.

Figure 5-12. BMI Distribution for Barrel Model

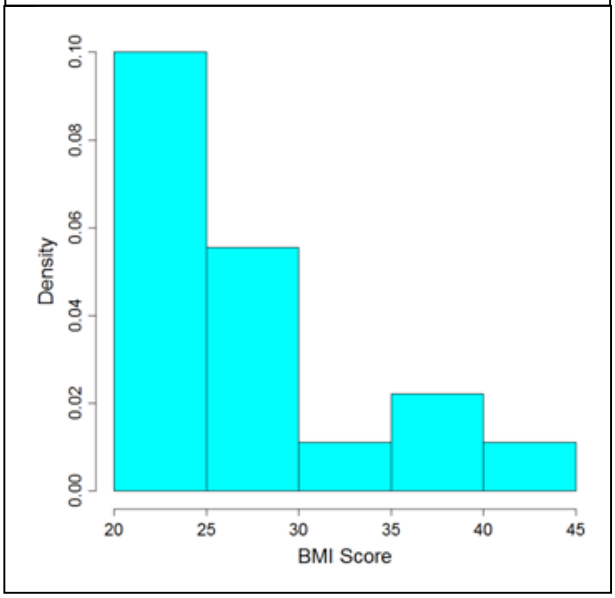


Figure 5-13. Driver Age and Experience for Barrel Model

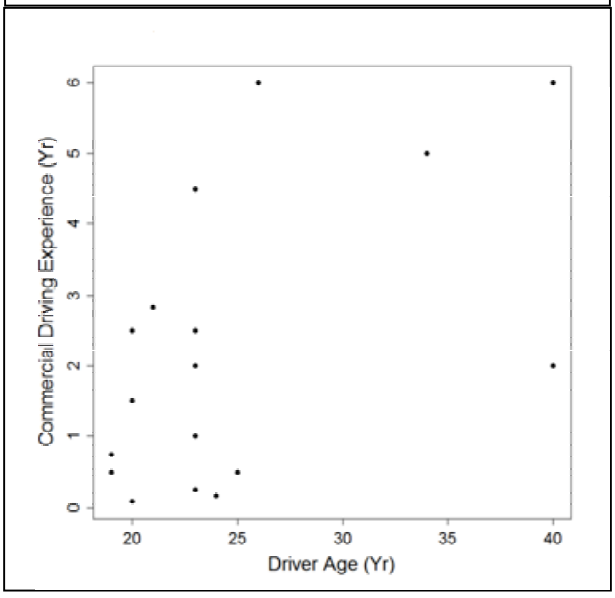


Figure 5-14. - Simulator Sickness Questionnaire (SSQ) Score by Drive

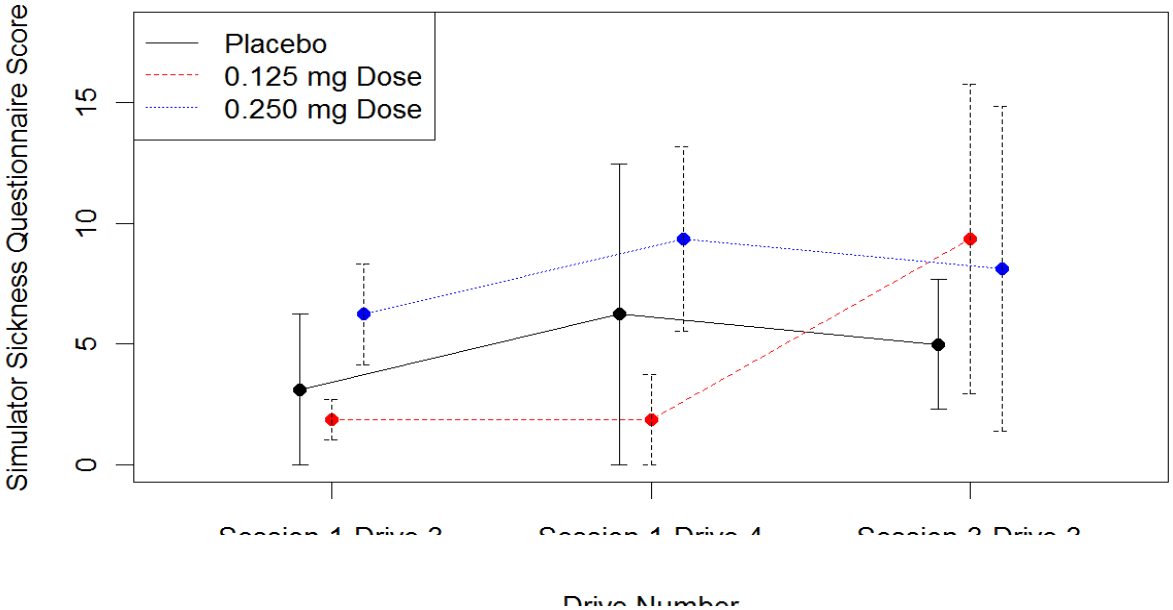
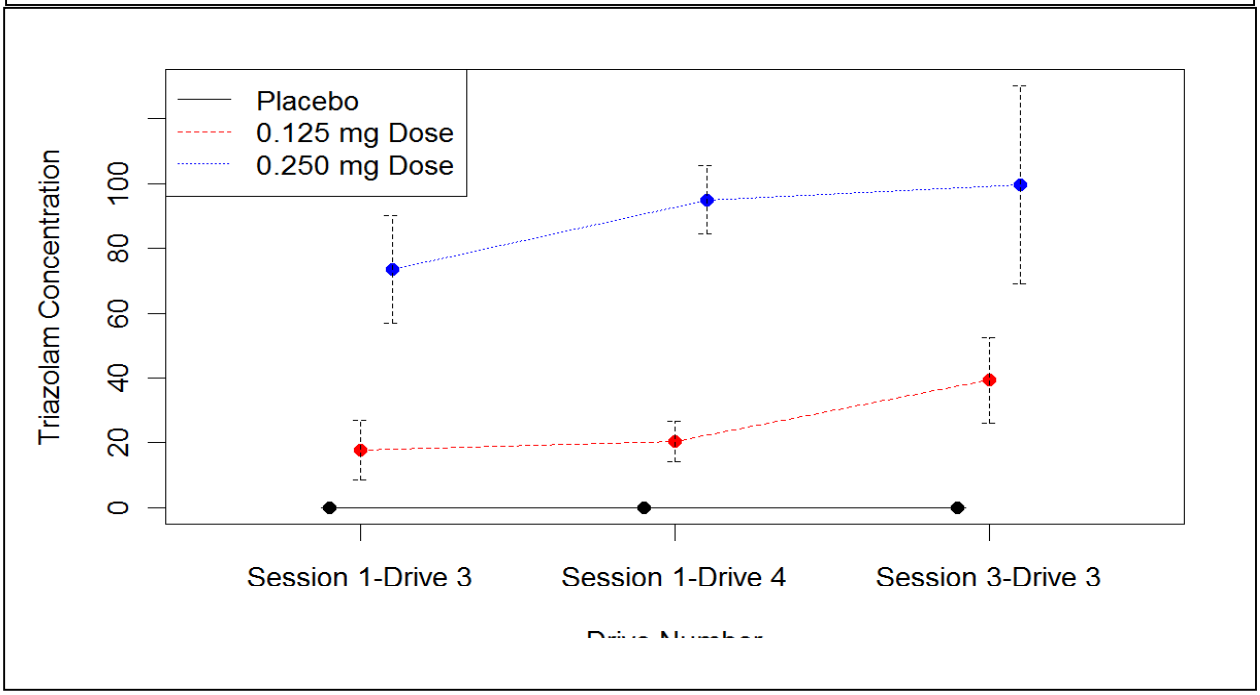


Figure 5-15. Triazolam Saliva Concentration (TSC) by Drive



5.3.3 Work zone independent variables

There were 9 fixed effects factors considered within this model. The primary factor of interest was the dose level. This factor had three levels representing the effect on total driving distance though the work zone: the placebo dose, the 0.125 mg dose of Triazolam and the 0.250 mg dose of Triazolam. Several other factors were considered within this analysis to account for any differences that may impact the interpretation of the effects of dose level.

There was a 3 level scenario factor that was included to account for the differences in the physical configurations of the three different work zone areas that were considered in this analysis.

The years as a commercial driver and the driver's age were also considered for use as independent variables, however there was a somewhat strong correlation between these variables (see Table 5-13) and BMI score so they were not included in order to avoid multicollinearity within the model.

A continuous variable for BMI score was included in the model because the interaction with Triazolam Saliva concentration was of interest. The score for the simulator sickness questionnaire (SSQ) and the interaction between the SSQ score and the Triazolam saliva concentration, were also included in the model.

Table 5-13– Correlation Between Driver's Age, Commercial Driving Experience and BMI Score for the Barrel Drive Study

Correlation			
	Age	Experience	BMI
Driver's Age	1	----	----
Commercial Driving Experience	0.54	1	----
BMI Score	0.30	0.40	1

The other variables included in the model were the dose order effect, BMI-dose interaction, SSQ score and driver index. The specific attributes for each of these factors were described in the model sections of the previous analyses.

5.3.4 Work zone distance driven model

Each subject had three observations associated with the three driving scenarios in this analysis. The linear mixed effects model was chosen to estimate the possible effects of Triazolam on the participants' total driving distance through the work zones. This type of model would account for the repeat observations on each participant. The model was developed using the statistical package R (V. 2.10.1) and the "nlme" package within that software. In order to model the random effects that were unique to the drivers, a random intercept was estimated for each of the drivers. After fitting the model and observing the residuals vs. fitted values, the response variable, distance traveled, was transformed by the log function to remove a slight mean-variance relationship in the residuals.

5.3.5 Work zone distance driven and steering entropy results

The model results showed that there were four significant factors that affected the total distance traveled when navigating the simulated work zones within the scenarios (see Tables 5-14 and 5-15.

There was a significant difference between those who had received the placebo and those who did not ($F(2, 28) = 5.09$, $p=0.01$). Those who had the doses of Triazolam administered to them traveled further around the barrels than those who did not. More specifically, those who had the 0.125 mg dose of Triazolam, ($t(28) = 2.87$) traveled further than those who had received the placebo. Those under the influence of the 0.250 mg dose ($t (28) = -1.01$, $p >0.2$) did not travel a distance that differed significantly from those participants who had received the placebo.

While the effect for those who had received the 0.250 mg dose is not significantly different from the placebo, it should be noted that the variance in distance traveled for those participants who received the 0.250mg is 1.5 times greater than those who had received the placebo. The increased variation of those who had received the 0.250 mg dose, coupled with the significantly different travel distance of the participants who had received the 0.125mg dose seems to indicate that those who had taken the Triazolam

had more difficulty choosing and or following the most efficient path around the barrel obstacles.

As one might expect, and upon visual observations of the drive paths of those under the influence, there was significant amount of variation between those who were under the influence of Triazolam and they tended to drift further out. It appears as if those under the influence of Triazolam, particularly those who had the 0.250 mg dose, had much more difficulty in navigating the work zone areas. For an example of the scenario drive paths see Figure 5-16. Those under the influence of Triazolam, especially those with those who were subject to the higher dose, exhibited more erratic driving behavior than those who were given the placebo. The participants under the influence seemed to go further into the opposite lane to avoid the barrel obstacles. Additionally, those who had taken the Triazolam seemed to move into the opposite lane earlier and return to the proper lane much later than those not affected by the drug.

The increased variability of drivers with the 0.250 mg dose, above those who had received the placebo or 0.125 mg dose, was confirmed and determined to be attributable to an increased steering work load. Drivers with the 0.25 dose had an increase in steering entropy ($F(2,28)=6.67$, $p=.004$), a measure of non-smooth steering with frequent small steering adjustments. The model was also adjusted for differences in the drive scenarios given that there was a higher steering entropy for the 2nd scenario (the short straight road) when compared to the 1st and 3rd drives.

Those drivers with a higher BMI also had significantly lower steering entropy ($F(1,11)=8.19$, $p<0.05$). There were no other significant differences observed.

5.3.6 Impact of Other Work Zone Variables

The scenario factor was shown to be significant ($F(2, 28) = 701000$, $p < 0.001$) with differences in the physical configuration of the work area sections having a highly significant effect on the distance traveled. This result was expected since the lengths of the different work areas were significant (see Table 5-13).

Dose Order seems to have a significant effect, $F(5,11)=3.29$, $p=0.046$. More specifically, Group E differed significantly from the other dose orders.

Table 5-14– ANOVA table for Work Area Distance Analysis

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	28	701000	<.0001
Scenario	2	28	27400	<.0001
Dose	2	28	5.09	0.013
BMI Score	1	11	0.31	NS
Triazolam Saliva Concentration(TSC)	1	28	1.03	NS
SSQ Score	1	28	2.12	0.156
Dose Order	5	11	3.29	0.046
Interactions				
BMI Score – TSC	1	28	2.37	NS
SSQ Score – TSC	1	28	2.75	NS

*Note: NS indicates Not Significant with p > 0.05

Table 5-15 – Effect Estimates for Work Area Distance Analysis

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value
(Intercept)	28	6.16	0.0002	26469	< 0.001
Session 1, Drive 4	28	-0.2240	0.0005	-475	< 0.001
Session 3, Drive 4	28	0.5200	0.0002	2218	< 0.001
BMI Score	28	-0.0001	0.0001	-0.554	NS
Dose: 0.125mg	28	0.0011	0.0004	3.148	0.004
Dose: 0.250mg	28	0.0001	0.0003	0.295	NS
Triazolam Saliva Concentration (TSC)	11	0.0001	0.0001	1.02	NS
SSQ Score	11	-0.0001	0.0001	-1.45	NS
Dose Order: B	11	-0.0001	0.0003	-0.32	NS
Dose Order: C	11	-0.0003	0.0002	1.36	NS
Dose Order: D	11	0.0004	0.0005	0.70	NS
Dose Order: E	11	-0.0006	0.0002	-2.40	0.036
Dose Order: F	11	0.0005	0.0003	1.47	NS
Interactions					
BMI Score – TSC	28	-0.0004	0.0001	1.54	NS
SSQ Score- TSC	28	-0.0008	0.0001	1.66	NS

*Note: NS indicates Not Significant at p > 0.05

Since all of the significant variables in the barrel traverse model are non-continuous factors, the x values can take on values of 0 or 1, whereas continuous variables, such

as SSQ score of Triazolam scores would be able to take on any value greater than or equal to 0.

Figure 5-16. Driver Paths for First Session, Third Drive by Dose Level

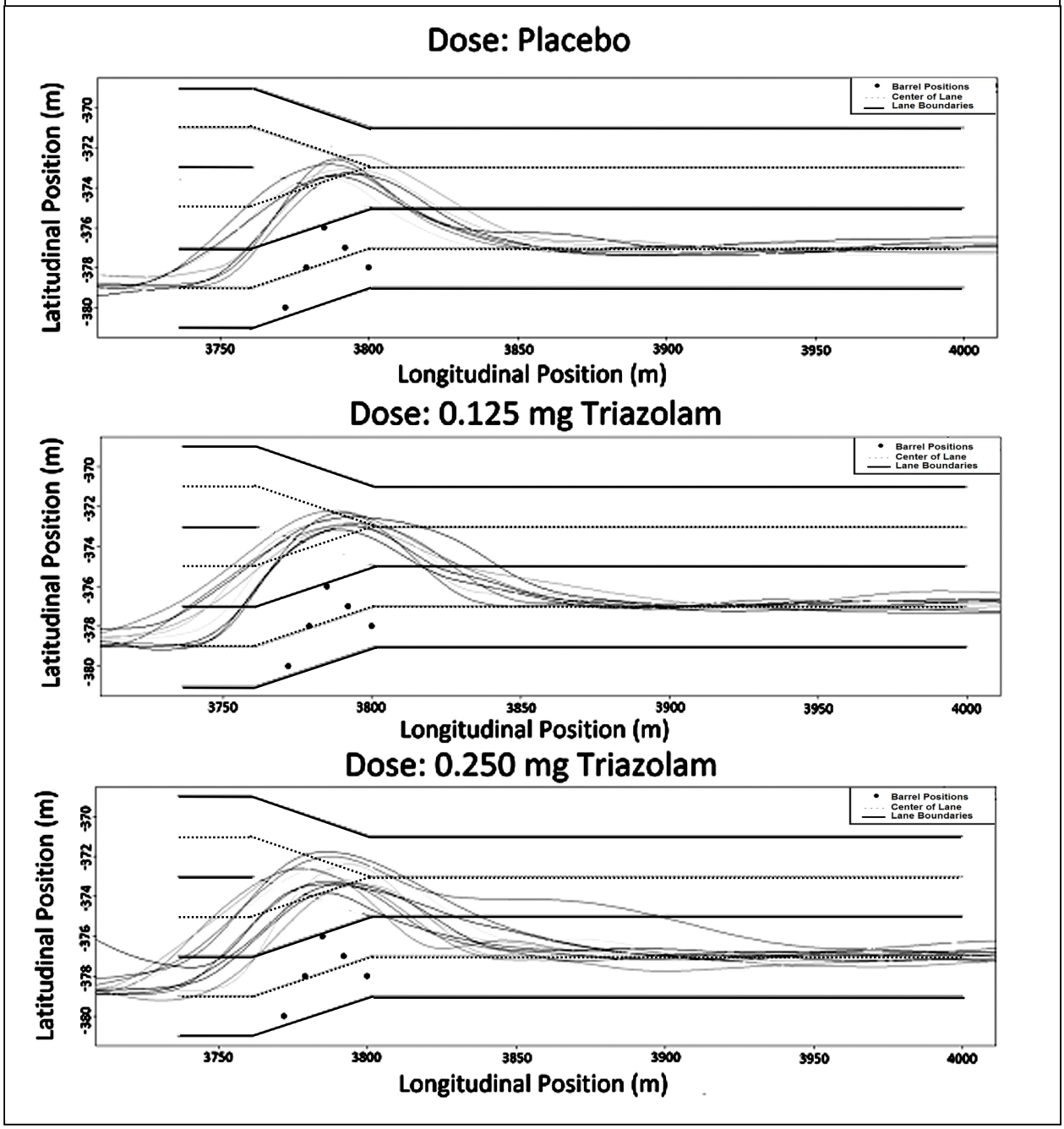


Figure 5-16 illustrates the paths taken by drivers traversing the five barrels (black dots) in the third drive of the first session. The dotted lines in the illustration are the centers of the lane (the dots not visible to the participant drivers) and the solid lines are visible lane markers. Participants drive from the left to the right. It can be seen that drivers with the 0.125 mg dose of Triazolam travel further north of the center line than drivers who have ingested the placebo dose. It can also be seen that there is more variance in the paths taken by drivers who have ingested the 0.250 dose than drivers under the 0.125 and placebo doses.

5.3.7 Work zone steering entropy model

The researchers also examined the steering entropy scores for drivers in the work zone segments. This was done to determine whether the data would confirm the observation of an apparent increase in variance in the lane paths taken by drivers who had taken the 0.250 mg dose of Triazolam.

Steering entropy is a measure of randomness in a driver's steering behavior. Steering entropy increases as the driver make more frequent and/or larger erratic steering movements. Due to impairment or inattention, the vehicle may drift away from the center of the lane, necessitating the driver to make a correction for this deviation. This sort or correction would then necessarily increase the steering entropy measure.

Steering entropy is a measure that has been used to examine increased workload (Nakayama, 1999). The steering angle and rate of change data of steering angle collected by the simulator enabled the steering entropy to be calculated. A related measure based on the entropy calculation is the 90% interquartile range, γ, since entropy is centered normally distributed with mean=zero and standard deviation=σ. This measure (γ) will give similar insights, compared to the traditional steering entropy, for drivers when a placebo baseline is not available across all drivers as is the case in this analysis.

Drivers with the 0.25 dose had an increase in steering entropy ($F(2,28)=6.67$, $p=.004$). The model was also adjusted for differences in the drive scenarios given that there was a higher steering entropy for the 4th drive in session 1 when compared to the 3rd drive in session 1 or the 4th drive in session 3. Participants with a higher Body Mass Index (BMI) also had significantly lower steering entropy ($F(1,11)=8.19$, $p<0.05$) than participants with lower BMI scores. There were no other significant differences observed.

In summary, drivers at the lower dose of Triazolam traveled further in traversing the barrels than drivers who had taken the placebo dose, swinging further into the neighboring lane. Drivers at the higher dose of Triazolam had more variance in their driving paths than either the placebo or the 0.125 dose group, indicating more degradation of steering control than either group.

5.4 Driver Performance 3 – Curve Following and Steering Entropy

Driver performance three was the ability of the participants to drive a long curve under drug and no-drug conditions, and to follow the curve smoothly. The measures examined were SDTP as a measure of weaving around the center lane of the curve, and steering entropy as a measure of steering randomness and steering reversals.

The steering entropy measure used for these analyses is the 90% inter-quartile range (γ) of the total steering entropy, as calculated via the method of Nakayama (2000). This metric is normally distributed with mean of zero and standard deviation of σ. Hence, this measure (γ) will give similar insights when the analysis includes drivers that withdrew from the study before a baseline was captured.

Both metric types, SDLP and Steering Entropy, were analyzed separately in this analysis using two types of modeling approaches. The first approach considered each of the three curves separately, referred to as the singular models. The second approach considered both left-hand curve drives together and the right-hand curve separately.

5.4.1 Curve following scenarios examined

For this analysis, the scenarios examined were the three driving scenarios that occurred on the third experimental drive across the three driving sessions. Each involved driving a 180^{o} curving exit off the highway, or on to the highway. The driving scenario on the first session involved a curve to the right. The two other scenarios on the second and third driving sessions involved a curve to the left. All of the curves in the scenarios examined were of the same length, radius and had the same speed limit of 55 mph. See Figure 5-17.

5.4.2 Participants

Of the 28 participants who participated in the study, there were 24 drivers who completed the second and third driving sessions. However, of these 24, only 22 had completed the curve drive on the first driving session. Two of the 24 participants drove the route incorrectly and did not drive the curve. For each driving session there were different distributions of dose level, see Table 5-16 and 5-17.

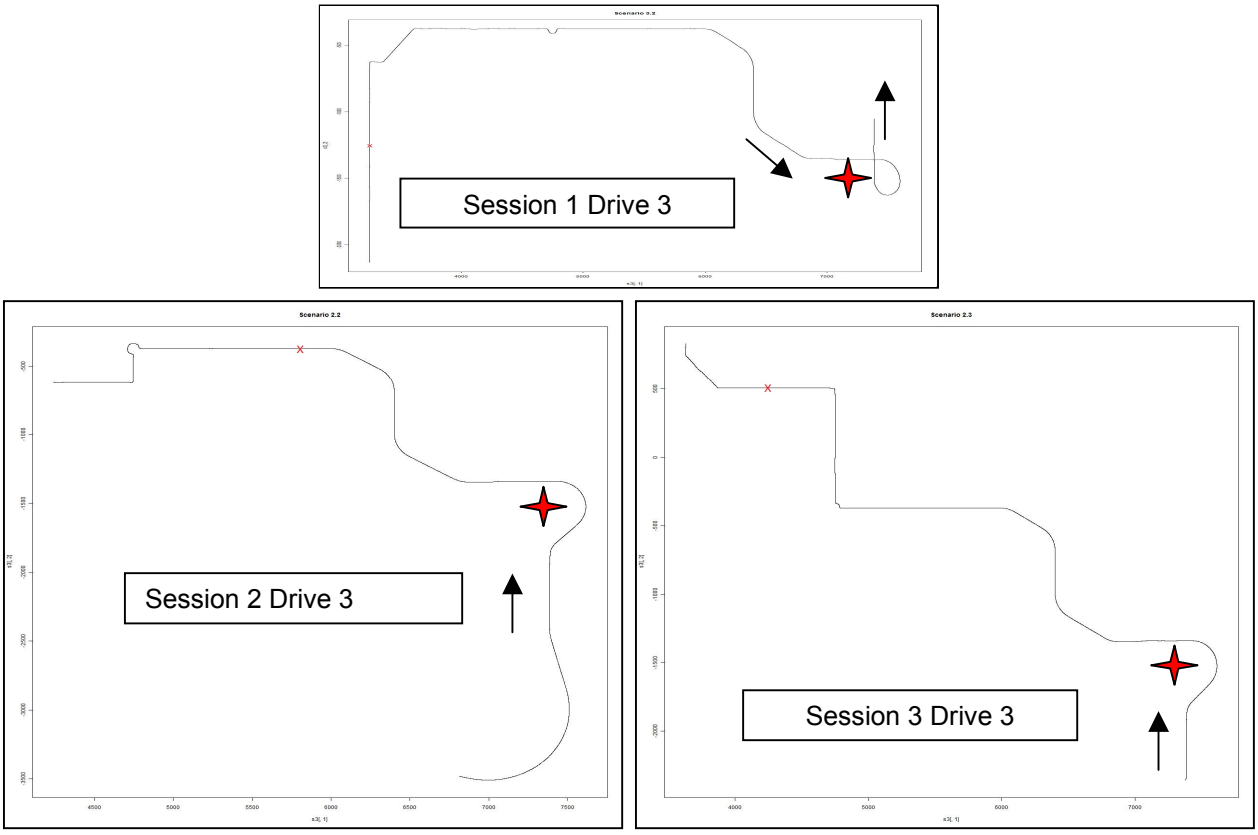
Table 5-16 – Dose Counts by Experimental Session

		Experimental Session		
		Session 1	Session 2	Session 3
Dose Count	Placebo	6	8	9
	0.125 mg Dose	8	7	9
	0.250 mg Dose	8	9	6

Table 5-17 - Number of participants included in each Drug Administration Order

	Dose Order Counts					
	A	B	C	D	E	F
1st Session	4	4	2	4	3	4
2nd& 3rd Sessions	5	4	2	4	4	5

Figure 5-16. Drive paths for Drive 3 on Sessions 1, 2 and 3. Arrows indicate the direction of travel.



5.4.3 Curve Following Independent Variables

There were a total of nine fixed effects considered in the models for both modeling approaches. The influence of dose level (fixed effect) on standard deviation of lateral position and the steering entropy measures was examined. Several other factors were included in the model to account for variables previously shown in the literature and the current study to significantly impact the results.

The explanatory variables considered were dose level, the participants body mass index (BMI) score, age, CDL experience, SSQ score, driver index, the interaction between dose level and the interaction between SSQ score and dose level. Since these variables are based on the driver, dose order (within-subject variable) was not included.

There were five effects examined in the combined model (analyzed using a linear mixed model on the second and third drive sessions): dose level, dose order, SSQ score, driver index and the interaction between SSQ and dose level. After fitting the model for the steering entropy measure, driver index was eliminated from the model due to its presence created numerical instabilities in the model-fitting algorithm.

The Triazolam saliva concentration of the study participants was not included in the model because there was a high correlation between the time variable and the Triazolam Saliva concentration (ρ=0.90), when taking the dose level into account. Thus, only the dose level or Triazolam saliva concentration variable could be included into the model, but not both, and after review of several models including one of these variables, the Triazolam saliva concentration variable was removed as an independent variable.

5.4.4 Model for Curve Following Analysis

Figure 5-16 illustrates the driving paths for the curve-following test on the 3rd drive of sessions 1, 2 and 3. The performance of the driver-participants driving the long curves identified in Figure 5-16 was studied. It can be seen that the curves on the 2nd and 3rd sessions are left-hand curves while the curve on session 1 is a right-hand curve.

Because two of the curves were left-hand turns and one was a right-hand turn, one approach used in the analysis was to include only the data from the left-hand curves on the second and third drive sessions. This approach was necessary due to (1) the unequal sample size between the left turning and right turning curves and (2) that driver behavior might change given the directionality of the curve being navigated.

The model chosen to analyze the data was a linear mixed effects model. The linear mixed effects model accounts for the within-subject effects of each participant having two drives over the two experimental sessions. The statistical software program that was used to fit the model was R (v. 2.10.1) using the “nlme” package. Observations within the left curves scenarios on the second and third driving session were repeated within subjects and therefore they could reasonably be correlated. In order to account for this, an unstructured correlation structure was used with the model. A random intercept was also included to account for the random effects associated with each driver. After fitting the model and observing the residuals vs. fitted values, SDLP and driver entropy variables were transformed by the log function to remove a slight mean-variance relationship in the residuals.

The second approach was to model each drive separately using a conventional linear regression model. This modeling allowed for more flexibility in model selection approaches and model adequacy diagnostics in addition to allowing for the analysis of driver behavior while traversing the right curves.

The continuous independent variables in these models were standardized by dividing the mean of the variable by two standard deviations as suggested by Gelman (2008). The reason for this standardization was to marginalize any possible multicollinearity between independent variables. The singular drive models were selected using a stepwise procedure and used the Akaike Information Criterion (AIC) (Akaike 1974) as the criteria for the final model selection. The AIC is a method of determining the "goodness-of-fit" among competing statistical models. This procedure was chosen due the fact that modeling each scenario separately reduced the sample size when compared to the linear mixed model approach, thus this reduction in sample size necessitated the removal of extraneous variables.

After the final model was selected using the stepwise procedure, the variance inflation factors were calculated. This metric allows for the direct detection of multicollinearity in the linear model, and was calculated using the procedure described by Fox and Manette (1992).

5.4.5 Results of the Curve Following Study

Figure 5-17 presents the results of the individual conventional linear regression model analysis. The results of the steering entropy measures are on the left side of the graphic and the SDLP results for the curve driving are on the right side of the graphic. The horizontal lines are the means of the data sorted by dose and the box plots are the standard error values.

The results of both approaches to analyze the effects of Triazolam on the steering entropy and SDLP of the study participants are inconclusive. The analyses of SDLP and steering entropy for the right-hand curve (session 1 drive 3) suggested that there is some effect of the dose of 0.250 mg on steering entropy and SDLP. However, the impacts on steering entropy and SDLP seem to be in opposite directions, as can be seen in the top boxes in Figure 5-17. The data indicates and the graphic portrays the SDLP (right block) as increased by the 0.250 mg dose while the steering entropy (left block) is reduced.

When analyzing the left curves scenarios (Session 2 and Session 3), the combined analysis suggest that there is no effect due to dose level. However, when analyzed separately, one of the two models does suggest there is an effect of dose level on steering entropy in session 3 drive 3 but there was no effect on SDLP.

5.4.5.1 Steering Entropy Linear Mixed Model

The analysis of the left turning curves (Sessions 2 and 3) showed that only dose order had a significant effect, see Tables 5-20 and 5-21. Additionally, only dose order C was significant at the $\alpha = 0.05$ level, $t(2.26)=0.017$.Because this model only accounted for the drives on the second and third drive sessions, dose orders C and F are the dose groups with no placebo level. Participants in the dose order C received the 0.125 mg dose and the 0.250 mg dose on the second and third experimental session, respectively. Additionally, dose order C was the least represented in the model with only 2 observations. Since dose order F (0.250 and 0.125 dosage on 2nd and 3rd

session) was not significant the significance findings of dose order C may actually be spurious

Figure 5-17 – Curve Steering Entropy and SDLP by Drive and Dose

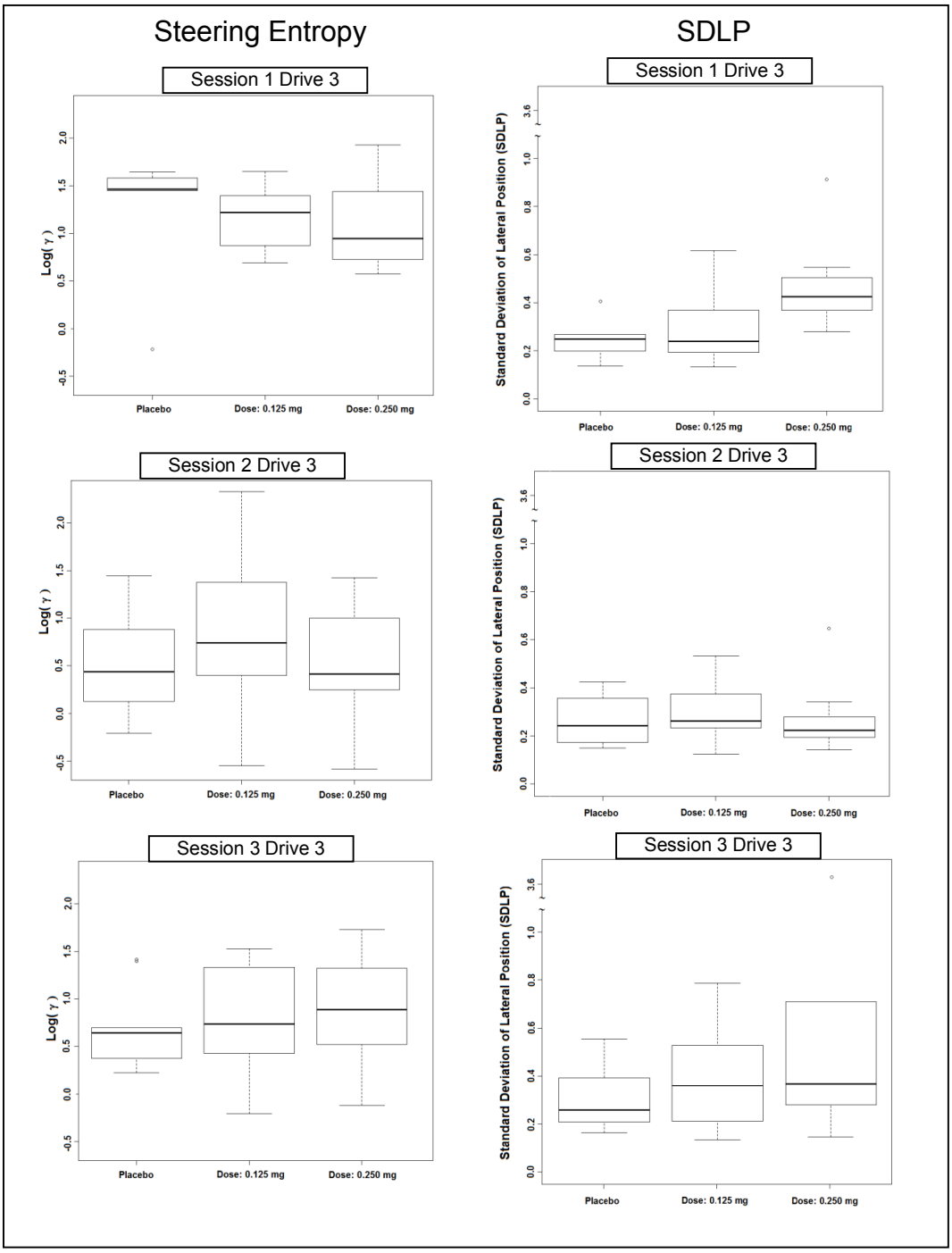


Table 5-20– ANOVA Table for Steering Entropy Left Curve Model

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	19	4.518	0.047
Dose Level	2	19	1.135	NS
Simulator Sickness Questionnaire Score (SSQ Score)	1	19	1.232	NS
Dose Order	5	18	1.796	NS
Interactions				
Dose Level – SSQ	2	19	0.371	NS

* Not Significant (NS): p > 0.05

Table 5-21 Effects Estimates for Steering Entropy Left Curve Model

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	19	0.547	0.250	2.125	0.047
Dose: 0.125mg	19	0.117	0.168	0.697	NS
Dose: 0.250mg	19	-0.135	0.177	-0.760	NS
SSQ Score	19	-0.012	0.011	-1.110	NS
Dose Order: B	16	0.141	0.366	0.387	NS
Dose Order: C	16	1.193	0.454	2.624	0.017
Dose Order: D	16	0.124	0.360	0.347	NS
Dose Order: E	16	0.367	0.371	0.990	NS
Dose Order: F	16	-0.035	0.346	-0.103	NS
Interactions					
SSQ Score - Dose: 0.125	19	0.010	0.014	0.706	NS
SSQ Score - Dose: 0.250	19	0.010	0.012	0.834	NS

Note* Not Significant (NS): p > 0.05

5.4.5.2 Steering Entropy Singular Linear Models

For the first session scenario, there were a total of four variables used in the model after performing the stepwise selection, Tables 5-22 and 5-23.These variables were dose level, age, CDI experience and SSQ score. There was no multicollinearity detected in this model, with all generalized variance inflation factors having values less than 3. However, only two variables were found to have significant effects estimates on steering entropy. There was a significant effect from the 0.250 mg dose level, $t(17)=-2.75$, $p=0.023$, which seemed to reduce the level of driver workload as the participants traversed the right-hand curve. The other significant variable was age and it too had a reducing effect on steering entropy.

For the second session drive model, Tables 5-24 and 5-25, a total of five variables were used in the model, dose, BMI score, CDI experience, driver index and the interaction between dose level and BMI score. Again, there were only two variables were found to

be significant, driver index and the interaction between a person's BMI score and the 0.125 mg dose level. There was no multicollinearity detected in this model, with all generalized variance inflation factors having values less than 5. The interaction between the BMI score and the 0.125 mg dose level was the only significant effect estimate for . The effect estimate suggests that those with higher BMI scores experienced a reduced level of driver work load. For driver index, only average driving ability, level 2,was significant. The effect estimate also suggests that those with average level experienced a reduced level of driver workload.

For the third session drive, tables 5-26 and 5-27, a total of four variables were used in the model: dose, BMI score, Age, and the interaction between dose level and BMI score. Three of the four variables were found to be significant, dose level, age and the interaction between a person's BMI score and the 0.250 mg dose level. There was no multicollinearity detected in this model, with all generalized variance inflation factors having values less than 3. There interaction between BMI and the 0.250 mg dose level was the only significant interaction for BMI score and dose level. The effect estimate suggests that those with higher BMI scores experienced an increased level of driver work load. For age, the effect estimate suggests that younger drivers experienced a lower workload. Finally, there was only one significant effect for dose level which was the 0.250 mg dose level. The effect estimate suggests that those who received the higher dose level experience a greater workload while navigating the curve.

Table 5-22 – ANOVA Table for Session 1 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	17	3.209	NS
Age	1	17	3.514	NS
CDI Experience	1	17	13.962	0.001
Simulator Sickness Questionnaire Score (SSQ Score)	1	17	2.156	NS

* Not Significant (NS): p > 0.05

Table 5-23 –Effects Estimates for Steering Entropy: Session 1 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	17	1.555	0.187	8.275	<0.0001
Dose: 0.125mg	17	-0.418	0.240	-1.738	NS
Dose: 0.250mg	17	-0.6799	0.269	-2.526	0.023
CDI Experience	17	0.417	0.222	1.875	NS
Age	17	-0.873	0.233	-3.737	0.002
SSQ Score	17	0.286	0.194	1.468	NS

Note* Not Significant (NS): p > 0.05

Table 5-24 – ANOVA Table for Steering Entropy: Session 2 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	15	0.913	NS
BMI Score	1	15	0.077	NS
CDI Experience	1	15	2.088	NS
Driver Index	2	15	4.242	0.034
Interactions				
BMI Score – Dose Level	2	15	4.135	0.037

* Not Significant (NS): p > 0.05

Table 5-25–Effects Estimates for Steering Entropy: Session 2 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	15	0.823	0.289	2.842	0.012
Dose: 0.125mg	15	0.354	0.327	-0.277	NS
Dose: 0.250mg	15	-0.057	0.315	1.081	NS
BMI Score	15	-0.131	0.476	-0.184	NS
CDI Experience	15	0.564	0.390	1.445	NS
Driver Index: 2 of 3	15	-0.984	0.386	-2.550	0.022
Driver Index: 3 of 3	15	0.467	0.347	0.135	NS
Interactions					
BMI Score - Dose: 0.125	15	-1.963	0.781	-2.513	0.024
BMI Score - Dose: 0.250	15	0.603	0.753	0.801	NS

Note* Not Significant (NS): p > 0.05

Table 5-26 – ANOVA Table for Steering Entropy: Session 3 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	17	4.098	0.035
BMI Score	1	17	1.376	NS
Age	1	17	14.007	0.002
Interactions				
BMI Score – Dose Level	2	17	5.663	0.013

* Not Significant (NS): p > 0.05

Table 5-27 –Effects Estimates for Steering Entropy: Session 3 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	17	0.540	0.148	3.627	0.002
Dose: 0.125mg	17	0.373	0.216	1.727	NS
Dose: 0.250mg	17	0.794	0.282	2.817	0.012
BMI Score	17	-0.308	0.263	-1.173	NS
Age	17	-0.820	0.219	-3.743	0.002
Interactions					
BMI Score - Dose: 0.125	17	0.624	0.396	1.577	NS
BMI Score - Dose: 0.250	17	2.696	0.812	3.317	0.004

Note* Not Significant (NS): $p > 0.05$

5.4.5.3 – SDLP Linear Mixed Model

When analyzing only the left curves using a linear mixed model none of the variables considered were found to have had a significant effect within the model, see Table 5-28 and 5-29.

Table 5-28– ANOVA Table for SDLP Left Curve Model

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	19	14.258	0.001
Dose Level	2	19	0.048	NS
Simulator Sickness Questionnaire Score (SSQ Score)	1	19	0.146	NS
Driver Index	2	16	0.360	NS
Dose Order	5	16	1.262	NS
Interactions				
Dose Level – SSQ	2	19	1.350	NS

* Not Significant (NS): $p > 0.05$

Table 5-29– Effects Estimates for SDLP Left Curve Model

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	19	-1.085	0.287	-3.77	0.001
Dose: 0.125mg	19	0.070	0.268	0.261	NS
Dose: 0.250mg	19	0.070	0.285	0.276	NS
SSQ Score	19	-0.006	0.017	-0.382	NS
Driver Index: 2 of 3	16	-0.157	0.281	-0.560	NS
Driver Index: 3 of 3	16	-0.214	0.267	-0.801	NS
Dose Order: B	16	-0.279	0.338	-0.824	NS
Dose Order: C	16	0.489	0.432	1.131	NS
Dose Order: D	16	0.249	0.331	0.751	NS
Dose Order: E	16	-0.292	0.378	-0.772	NS
Dose Order: F	16	-0.238	0.342	-0.697	NS
Interactions					
SSQ Score - Dose: 0.125	19	-0.001	0.021	-0.092	NS
SSQ Score - Dose: 0.250	19	0.024	0.018	1.265	NS

Note* Not Significant (NS): $p > 0.05$

5.4.5.4 SDLP Singular Linear Models

For the first session scenario, there were three variables used in the model after performing the stepwise selection, see Tables 5-30 and 5-31.These variables were dose level, age, driver index. There was no multicollinearity detected in this model, with all generalized variance inflation factors having values less than 3. Only dose level and driver index were found to be significant. The 0.250 mg dose level was the dose level that was significant. This estimate indicates that those who had received the 0.250 mg dose had higher SDLP compared to those who had received the placebo. For driver index, only the effect for the drivers in the top tier, level 3, was found to be significant. This estimate suggests that those in the better driver group had lower SDLP than the other groups.

For the second session drive only Two variables were used in the model, dose level and SSQ score, see tables 5-32 and 5-33. Of the two variables, only SSQ score was found to be significant. The estimate suggests that those experienced a high level of simulator sickness had a higher SDLP.

For the third and final session drive a two variables were used in the model, see Tables 32 and 33, dose level and age. Neither of the variables was found to be significant at the $\alpha = 0.05$ level nor were there any effect estimates found to be significant.

Table 5-30 – ANOVA Table for SDLP: Session 1 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	14	8.665	0.004
Age	1	14	0.706	NS
Driver Index	2	14	7.976	0.004

* Not Significant (NS): p > 0.05

Table 5-31 –Effects Estimates for SDLP: Session 1 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	14	-0.940	0.184	-5.105	<0.0001
Dose: 0.125mg	14	-0.210	0.190	-1.107	NS
Dose: 0.250mg	14	0.413	0.193	2.140	0.050
Age	14	-0.269	0.193	-1.395	NS
Driver Index: 2 of 3	14	-0.221	0.211	-1.044	NS
Driver Index: 3 of 3	14	-0.711	0.180	-3.945	0.001

Note* Not Significant (NS): p > 0.05

Table 5-32 – ANOVA Table for SDLP: Session 2 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	20	0.5574	NS
SSQ Score	1	20	5.2051	0.03

* Not Significant (NS): p > 0.05

Table 5-33 –Effects Estimates for SDLP: Session 2 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	20	-1.3731	0.1419	-9.672	<0.0001
Dose: 0.125mg	20	0.1303	0.2073	0.628	NS
Dose: 0.250mg	20	-0.0858	0.1971	-0.435	NS
SSQ Score	20	0.3887	0.1704	2.281	0.033

Note* Not Significant (NS): p > 0.05

Table 5-34 – ANOVA Table for SDLP: Session 3 Drive 3

Fixed Effect	df	Den df	F-value	p-value*
Dose Level	2	20	1.623	NS
Age	1	20	3.367	NS

* Not Significant (NS): p > 0.05

Table 5-35 –Effects Estimates for SDLP: Session 3 Drive 3

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	20	-1.357	0.232	-5.833	< 0.0001
Dose: 0.125mg	20	0.388	0.339	1.126	NS
Dose: 0.250mg	20	0.638	0.360	1.176	NS
Age	20	-0.551	0.300	-1.835	NS

Note* Not Significant (NS): $p > 0.05$

Table 5-36 is a summary table of the findings of the Singular Linear Models and Mixed Models for the curve following study. The data in Table 5-36 may be compared to the box plots in Figure 5-17. For Session 1 Drive 3, both the table and the box plot depict an SDLP that increases with dose paired with a Steering Entropy number that decreases with dose.

Table 5-36

Singular Linear Models						
Session and Drive	Dose .250	Direction	Other Var 1	Direction	Other Var 2	Direction
SDLP						
Session 1 Drive 3	p<.050	Increase	Driver Index 3	Decrease		
Session 2 Drive 3	NS		SSQ	Increase		
Session 3 Drive 3	NS		NS			
Steering Entropy						
Session 1 Drive 3	p.< .025	Decrease	Age	Decrease		
Session 2 Drive 3	NS		Driver Index 2	Decrease	BMI x Dose .125	Decrease
Session 3 Drive 3	p< .025	Increase	Age	Decrease		
Mixed Model - Left Curves Session 2 and 3						
SDLP	NS		NS			
Steering Entropy	NS		Dose Order C	Increase		

5.5 Driver Performance 4 - Stopping Event (Braking) Behavior

For this analysis, the several metrics chosen were different from the metrics chosen in previously to evaluate the behavioral effect of Triazolam on drivers. These metrics evaluate drug impact on drivers when they are confronted with stopping events such as a stop sign, stop light or cross-walks. The three previous behaviors evaluated elements of steering control.

1. Average braking duration, in seconds, was examined into order to see if those drivers under the influence of Triazolam behaved differently in their reliance on the vehicle's brakes compared to those who had received the placebo.
2. The time differential between the initial braking point and the point where the brake is depressed to its maximum point was examined as a surrogate variable for the driver's reaction to the imminent approach to the stopping point.
3. Additionally, the average deceleration and the maximum deceleration leading up to the stopping point were used to gauge the relative smoothness of the braking incidence as the driver approached the stopping point. The idea behind the choice of the variables is that those drivers who were able to decelerate more smoothly would indicate that they were better able to anticipate the arrival of the breaking point. Additionally, since the drivers are controlling a commercial vehicle commonly populated by people who are not in safety restraints, the level of deceleration is a safety issue. Rapid deceleration in such a situation could lead to unintended and unnecessary injuries to the passengers.
4. The distance to the stopping reference point at the driver's minimum speed was also examined. The minimum speed was chosen, rather than a full stop, since it did not preclude those drivers who did not come to a complete stop at the stopping point and allowed for the analysts to determine if the drivers exhibited a consistent behavior as they approached the stopping point.

5.5.1 Braking Event Scenarios Examined

For this analysis, three driving scenarios that occurred on the fourth drive of the three sessions were used. No other drives were chosen because they either (1) had no stopping events or (2) there were obstacles or driver distractions on those segments preventing a suitable stopping point from being collected. Additionally, within the remaining scenarios, the stopping points were chosen such that there were no obstructions or distractions directly preceding the arrival of the driver at the stopping points. Of the three scenarios, two required participants to make a left or right turn following the stop sign (i.e., first and third drive scenario). The other scenario (second) did not. The scenarios for this analysis consisted of data on the driver's behavior for the 150 meters leading up to the stopping point. A typical stopping event scenario is shown in Figure 5-18.

Figure 5-18 – Stopping Event Approach Example

5.5.2 Participants

Of the 28 participants who participated in the study, only 24 drivers completed all the drive scenarios being examined. These were the same 24 participants used in several other analyses described in this section. For each driving session there were different distributions of dose level, see Table 5-37. Note that in Session one only 23 drivers reached that stop sign. One driver took a wrong turn and did not complete that drive but did complete the remaining drives and sessions.

Table 5-37 – Dose Counts by Experimental Session

		Experimental Session		
		Session 1	Session 2	Session 3
Dose Count	Placebo	6	8	9
	0.125 mg Dose	8	7	9
	0.250 mg Dose	9	9	6

5.5.3 Stopping Event Independent Variables

The independent variables used for all models included: Dose level, simulator sickness questionnaire (SSQ) score, driver index, a scenario factor, the dose order and the interaction between dose level and the interaction between the driver's SSQ score and the corresponding dose level. BMI and the interaction of BMI and dose were not included in the model.

5.5.4 Stopping Event Models

Each subject had three observations that were associated with the three different driving scenarios in these analyses. Again, the model type chosen to estimate the possible effects of Triazolam on the participants stopping event behavior was the linear mixed effects model. This type of model accounted for the repeat observations on each participant. The models were again fitted using the statistical package R (V. 2.10.1) and the "nlme" package. In order to model the random effects that were unique to the drivers, a random intercept was estimated for each of the drivers. After fitting the model and observing the residuals vs. fitted values, the response variable and all of the dependent variables, except for average deceleration and maximum deceleration, were transformed by the log function to remove a slight mean-variance relationship in the residuals.

5.5.5 Stopping Event Results

The analyses of driver braking events shows that the effects of Triazolam alone on the behavior of the participants is relatively subtle. Of the five separate analyses, only two show significant effects due to Triazolam alone. These analyses included the time differential between the initial brake depression and the maximum brake depression (Tables 5-40 and 5-41) and average deceleration (Tables 5-44 and 5-44). Drivers on the drive they received the higher Triazolam dose (0.250 mg) significantly delayed the period between initial and maximum brake pressure. Drivers on the drive they received the lower Triazolam dose (.125 mg) had a higher average rate of deceleration than when they received the placebo or 0.250 mg dose.

Triazolam thus interacts in subtle ways with braking behavior absent its interaction with simulator sickness. Those effects are further examined in Tables 49 and 49.

All of the braking event analyses, however, revealed a significant interaction be Triazolam and simulator sickness.

5.5.5.1 Average Breaking Event Duration

This metric measures the average elapsed time from the moment of brake application to the moment when the driver reaches minimum velocity (stopped or minimum velocity considered equivalent in the analysis). There were no significant differences ($p<.05$) in average braking event duration for any of the independent variables considered (Tables 5-38 and 5-39). However, the t-Score for interaction between braking duration and SSQ ($t(41)=2.000$, $p =0.055$) was marginally significant and, consistent with other findings in

this section that drivers experiencing simulator sickness who received the 0.125 mg Triazolam dose stopped in a shorted period of time and had a higher average and maximum rate of deceleration than when they received the placebo dose.

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Table 5-38 – ANOVA Table for Average Breaking Event Duration

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	41	15.134	0.0004
Dose Level	2	41	0.411	NS
Simulator Sickness Questionnaire Score (SSQ Score)	1	41	0.112	NS
Driver Index	2	16	1.032	NS
Scenario	2	41	1.506	NS
Dose Order	5	16	0.718	NS
Interactions				
Dose Level – SSQ	2	41	2.036	NS

* Not Significant (NS): p > 0.05

Table 5-39 –Effects Estimates for Average Breaking Event Duration

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	41	0.637	0.163	3.89	0.0004
Dose: 0.125mg	41	0.284	1.047	0.27	NS
Dose: 0.250mg	41	0.283	1.118	0.25	NS
SSQ Score	41	0.025	0.074	0.33	NS
Driver Index: 2 of 3	16	1.677	1.336	1.26	NS
Driver Index: 3 of 3	16	-0.043	1.281	-0.03	NS
Session 2, Drive 4	41	0.953	0.856	1.11	NS
Session 3, Drive 4	41	-0.871	0.765	-1.14	NS
Dose Order: B	16	1.191	1.660	0.72	NS
Dose Order: C	16	-1.704	1.897	-0.90	NS
Dose Order: D	16	1.616	1.660	0.97	NS
Dose Order: E	16	0.272	1.694	0.16	NS
Dose Order: F	16	1.151	1.574	0.73	NS
Interactions					
SSQ Score - Dose: 0.125	41	-0.149	0.075	-2.00	NS (p=.055)
SSQ Score - Dose: 0.250	41	-0.104	0.077	-1.35	NS

Note* Not Significant (NS): p > 0.05

5.5.5.2 Time Differential between Initial Braking Incidence and Max Pedal Depression

There were four effects found to significantly affect time differential (Tables 5-40 and 5-41): dose level, the drive scenario factor, the dose order and the interaction between a participants SSQ score and the corresponding dose level received for that scenario. Only the 0.250 mg dose level showed a significantly higher time differential than the placebo group between the onset of braking and the maximum pedal depression ($t(41)=2.561$, $p=0.01$). On average, drivers when under the influence of the 0.250 mg dose took 1.3 seconds longer to reach maximum pedal depression than the same drivers when under the placebo dose.

There was also only one driving scenario effect that was significant different from the other two and this corresponded to the drive on the second session. As mentioned previously, the speed limit leading up to this stopping point was significantly higher, by 15 mph, than the other two and consequently the drivers braked earlier and more gradually when compared to the other two drives. Dose orders B ($t(16)=2.614$, $p=0.019$) and D ($t(16)=2.148$, $p=0.048$) were significantly different from dose order A. These corresponded to those drivers who received the placebo on the second driving session. Finally, there was a significant interaction between SSQ score and dose level for those drivers who received the 0.125 mg dose level, $t(40)=2.781$, $p =0.008$), resulting in a delay in reaching maximum braking for participants with a higher SSQ who received the 0.125 mg dose.

Table 5-40– ANOVA Table for Time Differential between Initial Braking and Max Braking Analysis

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	41	11.832	0.001
Dose Level	2	41	3.579	0.037
Simulator Sickness Questionnaire Score	1	41	0.158	NS
Driver Index	2	16	0.119	NS
Scenario	2	41	44.103	<0.0001
Dose Order	5	16	2.751	p=0.055
Interactions				
Dose Level – SSQ	2	41	5.194	0.010

* Not Significant (NS): $p > 0.05$

Table 5-41 – Effects Estimates for Time Differential between Initial Braking and Max Braking Analysis

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	40	0.824	0.239	3.439	0.001
Dose: 0.125mg	40	0.172	0.198	0.869	NS
Dose: 0.250mg	40	0.434	0.169	2.561	0.01
SSQ Score	40	-0.004	0.009	-0.398	NS
Driver Index: 2 of 3	16	0.085	0.181	0.468	NS
Driver Index: 3 of 3	16	0.013	0.168	0.080	NS
Drive 4, Session 2	40	1.413	0.159	8.854	<0.0001
Drive 4, Session 3	40	0.266	0.184	1.144	NS
Dose Order: B	16	0.641	0.245	2.614	0.019
Dose Order: C	16	-0.011	0.284	-0.038	NS
Dose Order: D	16	0.511	0.238	2.140	0.048
Dose Order: E	16	0.151	0.257	0.586	NS
Dose Order: F	16	0.052	0.250	0.211	NS
Interactions SSQ Score - Dose: 0.125	40	0.035	0.011	2.781	0.008
SSQ Score - Dose: 0.250	40	-0.013	0.009	-1.334	NS

Note* Not Significant (NS): $p > 0.05$

5.5.5.3 Distance from Stopping Reference at Minimum Speed

In looking at the behavior of the drivers as they approached the stop sign, only SSQ score was found to be significant factor, see Tables 5-42 and 5-43. The effect estimate indicates that those participants who experienced higher levels simulator sickness tended to stop further away from the reference point than the model predicts they otherwise would.

Drivers not experiencing simulator sickness, on averaged, stopped the bus (or reached minimum velocity) 14 meters, or about 45 feet, before the intersection. Given that the highest SSQ seen during the drives examined is 44.88, this translates to a maximum predicted difference of 4.3 meters, approximately 14 feet, further back from the stopping point of drivers not experiencing simulator sickness (Exp (2.64)=45) meters, (Exp(2.64+(.006*44))=18.25 meters).

Table 5-42– ANOVA Table for Distance from Stopping Reference at Minimum Speed

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	41	1478.8	<0.0001
Dose Level	2	41	0.426	NS
Simulator Sickness Questionnaire Score (SSQ Score)	1	41	10.191	0.003
Driver Index	2	16	2.335	NS
Scenario	2	41	0.591	NS
Dose Order	5	16	0.515	NS
Interactions				
Dose Level – SSQ	2	41	0.878	NS

* Not Significant (NS): p > 0.05

Table 5-43 – Effect Estimates for Distance from Stopping Reference at Minimum Speed

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	41	2.64	0.068	38.455	<0.0001
Dose: 0.125mg	41	-0.404	0.044	-0.917	NS
Dose: 0.250mg	41	-0.008	0.027	-0.311	NS
SSQ Score	41	0.006	0.001	3.192	0.002
Driver Index: 2 of 3	16	0.006	0.071	0.093	NS
Driver Index: 3 of 3	16	0.129	0.065	1.967	NS
Drive 4, Session 2	41	-0.261	0.027	-0.965	NS
Drive 4, Session 3	41	-0.260	0.028	-0.904	NS
Dose Order: B	16	0.061	0.084	0.731	NS
Dose Order: C	16	-0.089	0.106	-0.849	NS
Dose Order: D	16	0.012	0.085	0.141	NS
Dose Order: E	16	-0.035	0.089	-0.398	NS
Dose Order: F	16	-0.045	0.083	-0.545	NS
Interactions					
SSQ Score - Dose: 0.125	41	-0.002	0.003	-0.676	NS
SSQ Score - Dose: 0.250	41	-0.002	0.002	-1.312	NS

Note* Not Significant (NS): p > 0.05

5.5.5.4 Stopping Event Average Deceleration

For this model, three factors, SSQ score, driver index and dose level, were found to be significant, see tables 5-44 and 5-45. Drivers under the influence of the 0.125 mg dose have a higher rate of deceleration than when receiving the placebo dose. For SSQ score, t(41),=-2.437,p=0.019, the effects estimate indicates that those with higher SSQ scores are associated with a higher overall deceleration rate. Drivers with a Driver

Index of two have a significantly slower rate of deceleration than drivers with a Driver Index of one.

Table 5-44 – ANOVA Table for Average Deceleration

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	41	159.05	<0.0001
Dose Level	2	41	2.877	NS
Simulator Sickness Questionnaire Score (SSQ Score)	1	41	5.941	0.019
Driver Index	2	16	5.154	0.018
Scenario	2	41	0.427	NS
Dose Order	5	16	1.080	NS
Interactions				
Dose Level – SSQ	2	41	1.232	NS

* Not Significant (NS): p > 0.05

Table 5-45 – Effects Estimates for Average Deceleration

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	41	-0.862	0.068	-12.611	<0.0001
Dose: 0.125 mg	41	-0.114	0.047	-2.397	0.021
Dose: 0.250 mg	41	-0.038	0.045	-0.836	NS
SSQ Score	41	-0.004	0.001	-2.437	0.019
Driver Index: 2 of 3	16	0.187	0.061	3.100	0.006
Driver Index: 3 of 3	16	0.103	0.055	1.879	NS
Drive 4, Session 2	41	-0.041	0.048	-0.844	NS
Drive 4, Session 3	41	-0.021	0.051	-0.408	NS
Dose Order: B	16	0.073	0.079	0.931	NS
Dose Order: C	16	0.004	0.091	0.046	NS
Dose Order: D	16	-0.055	0.079	-0.696	NS
Dose Order: E	16	0.067	0.074	0.909	NS
Dose Order: F	16	0.079	0.075	1.052	NS
Interactions					
SSQ Score - Dose: 0.125	41	0.001	0.004	0.364	NS
SSQ Score - Dose: 0.250	41	-0.003	0.002	-1.202	NS

Note* Not Significant (NS): p > 0.05

The effects estimates indicates that drivers with a Driver Index Score of two have a 0.187 m/s^2 slower deceleration rate than those with a driver index score of 1. Finally,

despite not having a significant F statistic, there was a significant effect found for those drivers who had received the 0.125 mg dose, t(41)=-2.397, p=0.021. This estimate indicated that those drivers who had received the dose had a higher average deceleration rate than those who had received the placebo.

5.5.5.5 Maximum Deceleration

Table 5-46 – ANOVA Table for Maximum Deceleration

Fixed Effect	df	Den df	F-value	p-value*
(Intercept)	1	41	50.02	<0.0001
Dose Level	2	41	0.409	NS
Simulator Sickness Questionnaire Score	1	41	9.941	0.003
Driver Index	2	16	0.762	NS
Scenario	2	41	0.923	NS
Dose Order	5	16	1.064	NS
Interactions				
Dose Level – SSQ	2	41	1.649	NS

* Not Significant (NS): p > 0.05

Table 5-47 – Effects Estimates for Maximum Deceleration

Fixed Effects	df	Parameter Estimate	Std. Error	t-value	p-value*
(Intercept)	41	-3.898	0.551	-7.071	<0.0001
Dose: 0.125mg	41	-0.129	0.147	-0.871	NS
Dose: 0.250mg	41	-0.172	0.269	-0.638	NS
SSQ Score	41	-0.034	0.010	-3.153	0.003
Driver Index: 2 of 3	16	0.567	0.542	1.046	NS
Driver Index: 3 of 3	16	-0.043	0.527	-0.082	NS
Drive 4, Session 2	41	0.152	0.159	0.951	NS
Drive 4, Session 3	41	0.202	0.152	1.325	NS
Dose Order: B	16	0.175	0.665	0.263	NS
Dose Order: C	16	-0.363	0.830	-0.437	NS
Dose Order: D	16	0.167	0.672	0.249	NS
Dose Order: E	16	0.418	0.690	0.606	NS
Dose Order: F	16	1.236	0.661	1.871	NS
Interactions					
SSQ Score - Dose: 0.125	41	0.022	0.012	1.786	NS
SSQ Score - Dose: 0.250	41	0.009	0.017	0.543	NS

Note* Not Significant (NS): p > 0.05

For this model, only SSQ score was found to be significant factor, see tables 5-46 and 5-47. The effect estimate indicates that those participants experiencing higher levels of simulator sickness tended to have a higher maximum deceleration than the model predicts they otherwise would. Dose level was not found to have a significant effect on the maximum deceleration achieved by those under the influence of Triazolam.

5.5.5.6 Summary of Steering Studies

Table 5-48: Summary Table for Steering Analyses

Table	Study	DOSE	Direction	SSQ	Direction	SSQ x Dose	Direction	Other Variable 1	Other Variable 2
Table 39/39	Braking Duration Differential	N/S		N/S		SSQ x .125 mg p= .055	Faster stopping	N/S	N/S
Table 40/41	Initial to Max Braking Time Differential	0.25 mg p= .01	Delays time to max pressure	NS		SSQ x .125 mg p= .008	Delays time to max pressure	Session 2 Higher speed Delays time to max	Dose Order B&D Delays time to max pressure
Table 42/43	Stopping Distance Before Cross Street	N/S	N/S	SSQ p= .002	Stops further from cross street	N/S		N/S	N/S
Table 44/45	Average Rate of Deceleration	0.125 mg p= .021	more rapid average deceleration	SSQ p= .019	more rapid average deceleration	N/S		Driver Index 2 Less rapid deceleration	N/S
Table 46/47	Max Rate of Deceleration	N/S	N/S	SSQ p= .003	Higher max deceleration	N/S		N/S	N/S

Table 5-48 summarizes the speed control in stopping for a stop sign. The higher Triazolam dose increases the average time between when the driver begins to apply the brake and when the driver reaches maximum pressure (Table 40/41), and the lower dose increases the average rate of deceleration (Table 44/45). The Simulator Sickness effect is largely independent of the dose effect, with only one of the five studies finding a significant Dose x SSQ interaction. Drivers feeling the effects of simulator sickness delay applying maximum brake pressure, and have a higher average and maximum rate

of deceleration. In the one significant SSQ x Dose interaction, and also in the one interaction with a t-Score that approaches significance , the low dose of Triazolam interacts to potentiate the otherwise non-significant impact of simulator sickness on driver braking performance.

5.5.5.7 Deceleration and brake profile graphs

Figure 5-19. Average Deceleration and Brake Level by Dose and Drive

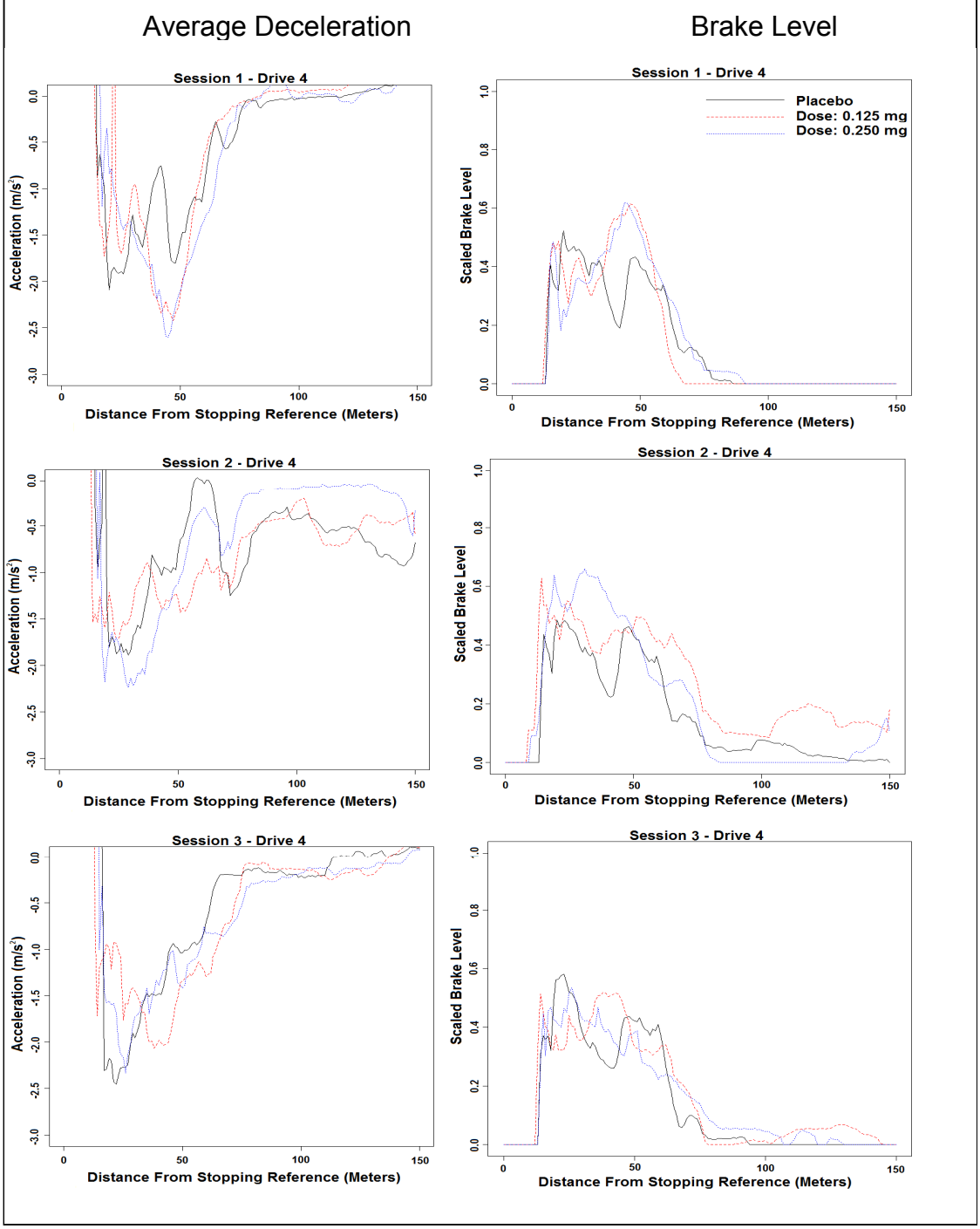
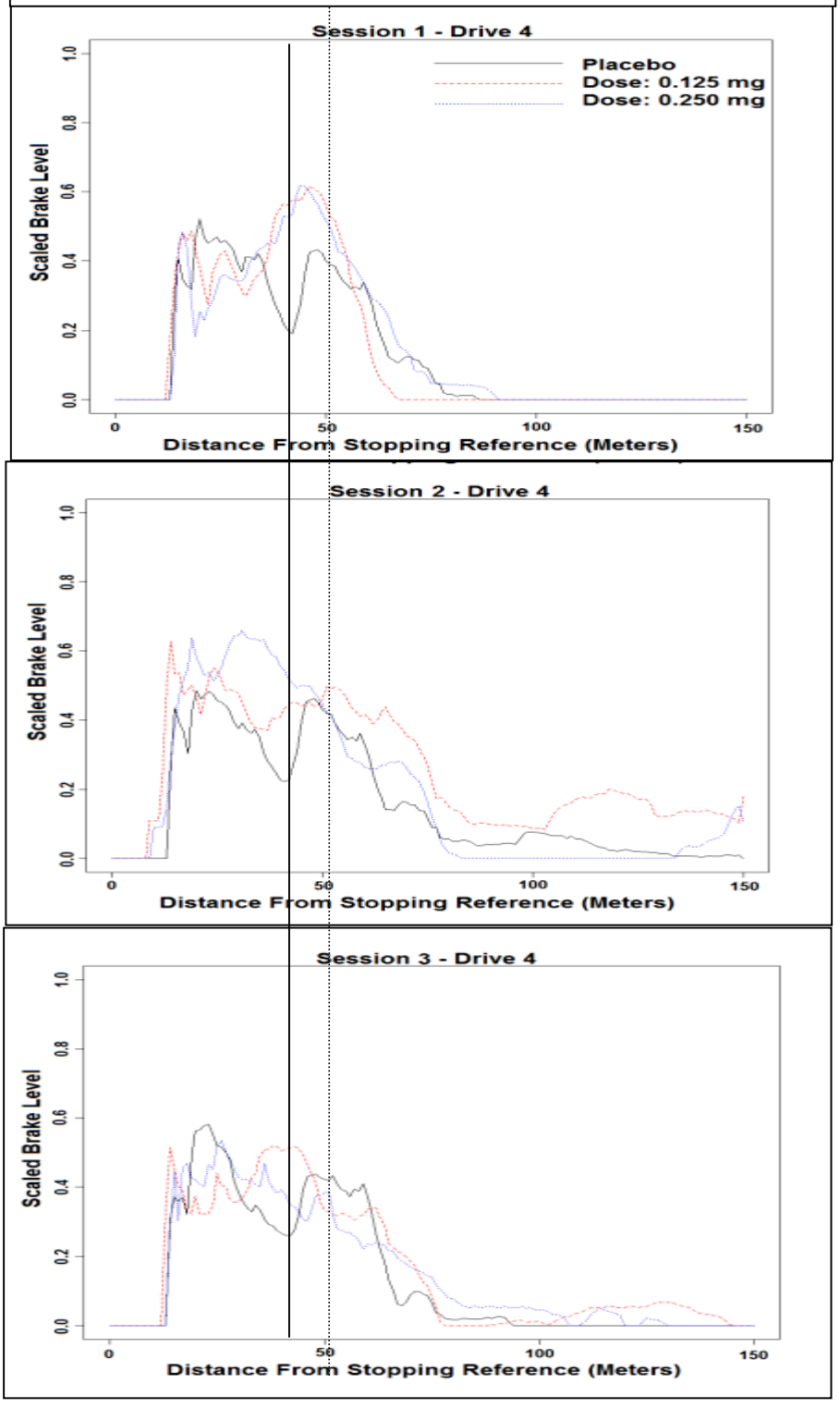


Figure 5-19 plots the average deceleration and brake level (surrogate for instantaneous deceleration in $m/s^{2)}$) for the braking scenarios in Session 1,2 and 3 by dose level.

Figure 5-20. Detail of braking profiles by scenario and dose.



The Average Deceleration chart (left side) is difficult to read because the speed limit approaching the stop sign in scenario two is higher than scenario one or three, resulting in different deceleration profiles.

However, the braking profile graph (right side of the graphic) is easier to examine visually, and seen in detail in Figure 5-20.

The braking profile of an experienced commercial driver reflects the need to stop the bus in a manner comfortable to the passengers and with an adequate safety margin given the initial speed. In scenario two, the stop sign is on a stretch of road with a speed limit of 50 MPH, whereas the stopping performance task in sessions one and three is on a stretch of roadway with a speed limit of 35 mph. Accordingly, in Figure 5-19, the drivers apply the brakes earlier in

session two than in the other two sessions. However, approximately 70 meters before the stop signs, the speeds of the bus are equivalent in all three scenarios and the braking profiles after 70 meters may be directly compared.

When experienced drivers reach a speed where they could apply emergency braking ("stomp on the brakes") in the event of an emergency, they "get off the brake". They then reapply brake pressure when it is necessary to reach a minimum speed, to "stop", typically stopping a bus length before the stop line. The drivers in the PATH project are "experienced" and their braking profiles from 50 meters before the stop sign may be compared,

The dotted line in Figure 5-20 aligns the plots at 50 meters before the stop sign. The solid line allows a visual inspection of the braking profile at about 42 meters from the stopping reference. The solid line in each of the graphs is the braking profile of the drivers receiving the placebo dose on that session. The red dotted line is the 0.125 mg group and the blue dotted line is the 0.250 mg group for that session.

It can be seen from a visual inspection of the graph at the solid line that drivers who have received the placebo dose in each of the sessions reduce barking pressure at approximately the 40 meter point. The same drivers, on sessions when they ingest the 0.125 or the 0.250 mg dose, are still at an elevated braking pressure at the 40 meter point. The ANOVA calculation and Effects Estimate seen in Tables 5-47 and 5-48 confirm the visual observation.

Table 5-49. ANOVA Table for the 40-Meter Braking Profile

40m Point Estimate – All Drive model
Linear mixed-effects model fit by REML
Number of Observations: 72 Number of Groups: 24

Fixed Effect	Num DF	Den DF	F-value	p-value
(Intercept)	1	41	15.125	0.0004
factor(dose)	2	41	3.599	0.0363
ssq.total	1	41	2.794	0.1023
factor(driver.index)	2	16	1.042	0.3756
factor(drive)	2	41	0.697	0.5041
factor(dose.order)	5	16	1.210	0.3488
factor(dose):ssq.total	2	41	3.549	0.0379

Table 5-50. Effects Estimate for the 40-Meter Braking Profile

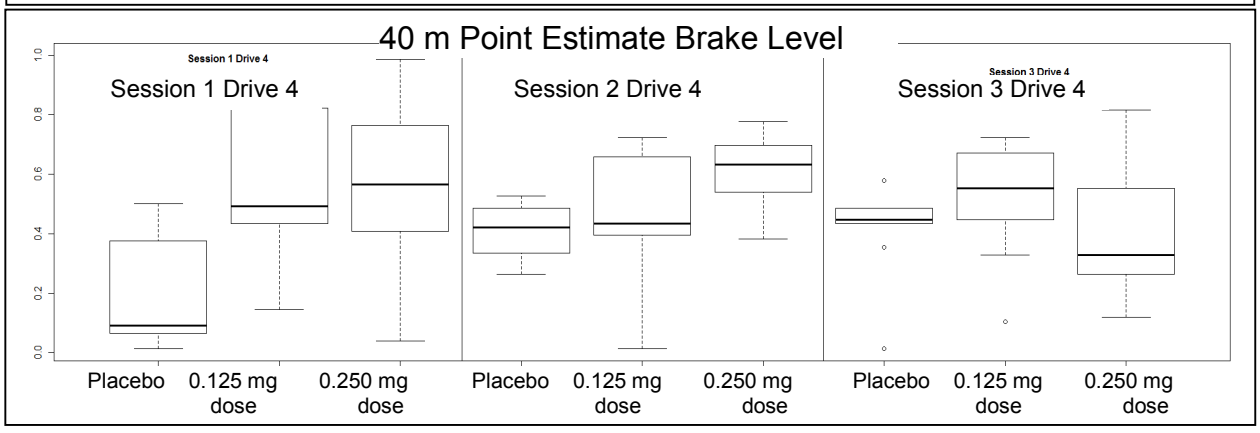
Fixed Effects	Value	Std.Error	DF	t-value	p-value
(Intercept)	0.322	0.083	41	3.889	0.0004
factor(dose)0.125 mg	0.136	0.063	41	2.163	0.0364
factor(dose)0.250 mg	0.147	0.069	41	2.129	0.0393
ssq.total	-0.004	0.003	41	-1.671	NS
factor(driver.index)2	0.046	0.062	16	0.738	NS
factor(driver.index)3	-0.050	0.059	16	-0.859	NS
factor(drive)V5_Drive4	0.066	0.060	41	1.102	NS
factor(drive)V7_Drive4	0.066	0.068	41	0.971	NS
factor(dose.order)B	0.031	0.082	16	0.374	NS
factor(dose.order)C	-0.051	0.123	16	-0.412	NS
factor(dose.order)D	0.075	0.077	16	0.968	NS
factor(dose.order)E	0.107	0.089	16	1.205	NS
factor(dose.order)F	-0.054	0.079	16	-0.680	NS
Interactions					
factor(dose)0.125:ssq.total	0.006	0.004	41	1.313	NS
factor(dose)0.25:ssq.total	0.010	0.004	41	2.615	0.0124

Note* Not Significant (NS): p > 0.05

The implication is that drivers under the effects of Triazolam do not have as fine control of the procedures for a safe and comfortable barking profile as they do when not under the influence of the benzodiazepine drug. The both levels of Triazolam have an impairing impact on this fine motor control, with the 0.250 mg dose creating a higher amount of impairment.

The box plot of the braking performance is seen in Figure 5-21.

Figure 5-21. Box plot for the 40-Meter Braking Profile Estimate



5.6 Discussion

5.6.1 Next-Day Effects on Steering

Due to the short half-life of Triazolam, there does not seem to be any residual narcotic effect that impairs the driver's ability to navigate a straight road the day after having taken Triazolam after a period of sleep. Although this study shows that the drug impairs the driving ability of a Commercial Motor Vehicle Operator using it, the outcomes suggest that a person who uses the drug on an occasional basis as sleep aid and also gets a full night's rest may not have impaired driving performance due to the drug's residual effects.

5.6.2 Standard Deviation of Lateral Position - SDLP

The findings of this study indicate that drivers under the influences of Triazolam drive more erratically than they do when not under the influence of Triazolam. More specifically, on the simplest driving performance test, the participants, when under the influence of the 0.250 mg dose of Triazolam, had a higher SDLP than the placebo group or the 0.125 mg dose. There was not a significant increase in SDLP seen from drivers on sessions when they received the 0.125 mg dose. This dose-dependent performance indicates that the drug at the higher dose impairs even over-learned simple driving performance but the lower dose may not impair that performance.

5.6.3 Traversing a Work Zone

However, in a more complicated task, traversing the barrels in a simulated work zone, drivers at the 0.125 mg dose did have significantly different drive paths through the work zone areas than the placebo group. The models indicated that the drivers on the 0.125 dose generally went further out around the barrels than the drivers when they received the placebo dose. This may indicate that those drivers under the influence were aware of the drug and its effect on their driving. Consequently, these drivers were more cautious than those who had received the placebo and resulted in those drivers giving the work zone areas a wider berth than they would were they not under the influence of Triazolam. Additionally, in that scenario, drivers when under the 0.250 mg dose had more variability in their path traces than they did when under the 0.125 mg or placebo conditions, and had a significantly elevated measure of steering entropy, indicating more erratic driving with frequent attempts to correct steering.

5.6.4 Curve Following Performance

The analysis of the driver behavior in navigating curves showed that Triazolam may have an effect on driver workload and SDLP while navigating curves. However, the effects estimated was not consistent across all the drives, so the results may be spurious and no real conclusions can drawn from these models.

5.6.5 Braking Performance

With respect to braking behavior, the reaction times (based on the time difference between the onset of braking and maximum brake depression) was significantly

affected for those under the influence of Triazolam. There was also an indication that the average deceleration for drivers after the 0.250 mg dose of Triazolam was higher than those who had received the placebo.

However, while the differences in average deceleration was statistically significant, in qualitative terms the higher average deceleration of those under the influence of Triazolam could not clearly be considered a safety hazard for passengers riding on the bus. The increase in average deceleration was small, only 0.114 m/s^2 greater for those under the influence of Triazolam. Finally, there was a dose-dependent change in the pattern of brake application. The participants, having ingested the placebo dose, reliably showed a pattern that included increasing brake pressure up to about 50 meters before the stop sign, then releasing brake pressure to about 40 meters before the stopping point, then gradually increasing brake pressure again to come to a comfortable stop. Participants, having ingested the 0.250 mg or the 0.125 mg dose, did not release brake pressure through this 50 to 40 meter mid-point, resulting in an overall higher maximum rate of deceleration and a ride that would have been less comfortable for passengers.

5.6.6 Estimates of Magnitude

These findings of impairment and increased variability of performance indicate that drivers having ingested a therapeutic dose of Triazolam are less predictable than when not under the influence of the drug. In a real world situation, this unpredictability could have serious safety implications since other drivers may not be able to anticipate the behavior of drivers under the influence of this drug.

On the straight driving test, the drivers that received the 0.250mg dose of Triazolam had more difficulty driving along a straight road. The models showed that over time, as the drug is absorbed from the gut and enters the blood stream, Triazolam progressively worsens the driver's ability to even drive along a straight road. Figure 5-22 illustrates the amount of weaving by drivers on the SDLP segment of session 2 drive 4. That SDLP segment is 597 meters long (1800 feet), with a 30 mph speed limit. One of the drivers with the 0.250 mg dose weaves so extensively that at one point the bus is 10 inches into the oncoming lane.

It is possible to use the findings from the SDLP model to generate estimates of the magnitude of weaving under varying conditions of speed. Table 5-10 confirms that SDLP, weaving in lane, increases as speed increases. Note that SDLP is a measure of the standard deviation of the collected data, standard deviation of lateral position. The computed SDLP value is the estimate for one standard deviation of lane weaving. One standard deviation covers the center 67% of the normal curve. The second standard deviation covers 28% of the normal curve, the 14% on either side of the center represented by one STD. The third standard deviation covers the remaining 4% of the normal curve, the 2% at either tail. As such, the SDLP measurement represents the expected weaving 68% of the time.

Using the data from Table 5-10, it is possible to estimate the expected weaving for one standard deviation, two standard deviations, and three standard deviations at normal

driving speeds. Those estimates are in Figure 5-22. Using estimates from Table 5-10, it can be calculated that drivers at the 0.250 mg dose at 55 MPH would frequently weave the bus into the adjacent lane perhaps as much as 30% of the time over the duration of the drive. At times, the estimates indicate the bus would be more than one yard into the neighboring, perhaps on-coming, lane.

Figure 5-22: Estimates of Lane Exceedance under Triazolam 0.250 mg

ESTIMATES OF MAGNITUDE OF LANE EXCEEDANCE FOR 0.250 mg TRIAZOLAM
at 80 Minutes Post Injestion for Speeds of 15 and 25 Meters per Second, Equivalent to 35 and 55 Miles per Hour

DOSE		Log SDLP Coefficient	SDLP Coefficient In Meters	SDLP Estimete in Feet	SDLP Estimete In Inches	Width 102 Inch Bus in Inches Center to Edge	Width Bus in Inches Plus SDLP	Width 12 Feet Road in Inches Center to Edge	Lane Available In Inches
			SDLP - 0.25 mg Triazolam - 1st StDev - 68% of Time						
mg	Coefficient	-2.51	0.0813	0.2666	3.20	51	54.20	72	17.801
0.00	15 mps (35 MPH)	-1.445	0.2357	0.7732	9.28	51	60.28	72	11.721
0.25	15 mps (35 MPH)	-1.205	0.2997	0.9830	11.80	51	62.80	72	9.204
0.00	25 mps (55 MPH)	-0.735	0.4795	1.5728	18.87	51	69.87	72	2.127
0.25	25 mps (55 MPH)	-0.495	0.6096	1.9994	23.99	51	74.99	72	**-2.993**
DOSE			**SDLP - 0.25 mg Triazolam - 2nd StDev - 27.2% of the Time**						
mg	Coefficient	-2.51	0.0813	0.2666	6.40	51	57.40	72	14.603
0.00	15 mps (35 MPH)	-1.445	0.2357	0.7732	18.56	51	69.56	72	2.442
0.25	15 mps (35 MPH)	-1.205	0.2997	0.9830	23.59	51	74.59	72	**-2.592**
0.00	25 mps (55 MPH)	-0.735	0.4795	1.5728	37.75	51	88.75	72	**-16.747**
0.25	25 mps (55 MPH)	-0.495	0.6096	1.9994	47.99	51	98.99	72	**-26.985**
DOSE			**SDLP - 0.25 mg Triazolam - 3rd StDev - 4.3% of the Time**						
mg	Coefficient	-2.51	0.0813	0.2666	9.60	51	60.60	72	11.404
0.00	15 mps (35 MPH)	-1.445	0.2357	0.7732	27.84	51	78.84	72	**-6.837**
0.25	15 mps (35 MPH)	-1.205	0.2997	0.9830	35.39	51	86.39	72	**-14.388**
0.00	25 mps (55 MPH)	-0.735	0.4795	1.5728	56.62	51	107.62	72	**-35.620**
0.25	25 mps (55 MPH)	-0.495	0.6096	1.9994	71.98	51	122.98	72	**-50.978**

Dose	Speed, Meters/Second	Speed, Miles/Hour	Pct Time Exceeding Lane By Dose and Speed	Pct Time	Minutes per Hour	
0.00	15 Meters/Sec	35 MPH	PCT of Time Exceeding Lane Width	**2.4%**	**1.42**	**Minutes/Hour**
0.25	15 Meters/Sec	35 MPH	PCT of Time Exceeding Lane Width	**7.5%**	**4.50**	**Minutes/Hour**
0.00	25 Meters/Sec	55 MPH	PCT of Time Exceeding Lane Width	**26.6%**	**15.95**	**Minutes/Hour**
0.25	25 Meters/Sec	55 MPH	PCT of Time Exceeding Lane Width	**38.1%**	**22.89**	**Minutes/Hour**

Figure 5-23 shows the actual tracks of drivers driving the SDLP straight segments on the 4th drive of the second experimental session. The red double-ended arrows are the width of the bus. The left edge of each of the graph is the edge of the road and the solid line in each graph is the median line between the drivers lane and the adjacent lane. The dotted lines are one meter from the center line.

The traces are grouped by Triazolam concentration. It can be seen that the amount of weaving in lane generally correlates with the Triazolam concentration. M2426, with a Triazolam concentration of 314 pg/ml, exhibits the largest SDLP. However, note that M2301, with a Triazolam concentration of 54 pg/ml, weaves ¾ of a meter and almost encroaches on the adjacent lane.

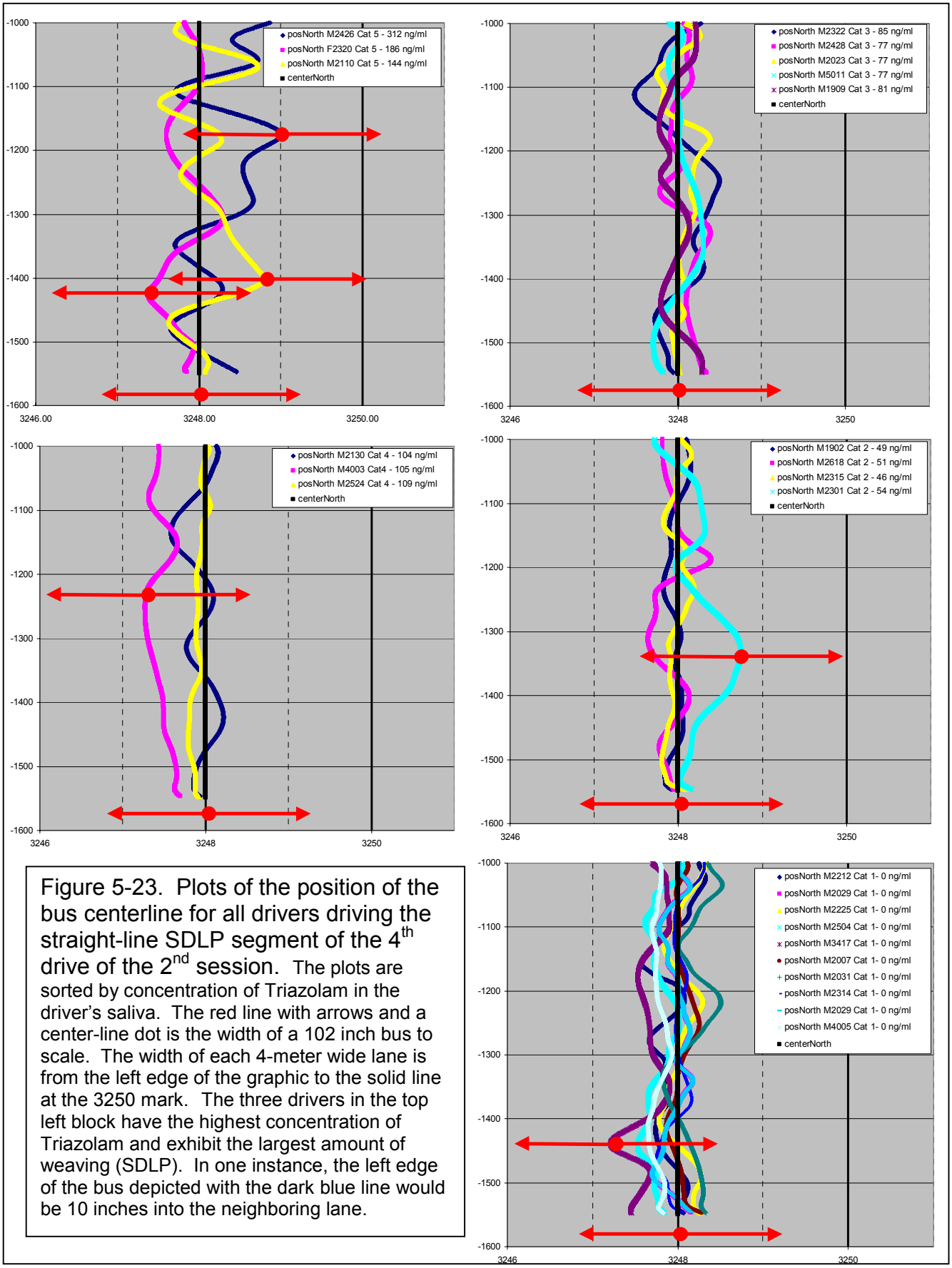


Figure 5-23. Plots of the position of the bus centerline for all drivers driving the straight-line SDLP segment of the 4th drive of the 2nd session. The plots are sorted by concentration of Triazolam in the driver's saliva. The red line with arrows and a center-line dot is the width of a 102 inch bus to scale. The width of each 4-meter wide lane is from the left edge of the graphic to the solid line at the 3250 mark. The three drivers in the top left block have the highest concentration of Triazolam and exhibit the largest amount of weaving (SDLP). In one instance, the left edge of the bus depicted with the dark blue line would be 10 inches into the neighboring lane.

6 DISCUSSION AND CONCLUSIONS

6.1 Goal of Project PATH

Project PATH was developed to meet the need for a standard and replicable research design and set of tasks useful for evaluating the impact of prescription medications on the driving performance of commercial motor vehicle operators. This study is the first iteration of that design development effort and is a successful proof of concept study. The research has produced statistically valid measures of driving impairment at therapeutic doses of Triazolam, the researched drug. The research has also yielded a set of psychomotor and driving performance tests that can be built into a tight research schedule. That research design recognizes the need to provide assurances that the driver-participant-subjects have an adequate recovery period between drug ingestion and their next performance of a safety-sensitive function. The research design incorporates next-day tests (and potentially second-day tests) that establish whether the participants have recovered pre-drug baseline performance.

6.2 Background

The National Transportation Safety Board (NTSB) has a long-standing requirement that the DOT-covered modes recognize the participation of prescription and over-the-counter (Rx/OTC) medications in the causation of accidents. The NTSB Safety Recommendations I-00-1 through I-00-4 (January 13, 2000)[50] provided a lengthy review of accidents investigated by NTSB in which Rx/OTC medications were involved. That document included specific recommendations to each mode for the establishment of comprehensive programs for the control of prescription and over-the-counter medications and for the establishment of a program of post-mortem toxicological testing for prescription medications and prohibited substances. Those recommendations were strengthened and continued in Safety Recommendations R-01-25 (January 23, 2002) reviewing two collisions at the Baltimore MTA, and in Safety Recommendation R-10-4 (August 10, 2010) investigating the Fort Totten WMATA accident with nine fatalities. In a 2009 letter[51] to the FTA Acting Administrator, the NTSB took notice of the FTA's responses to their recommendations. The NTSB recognized that "FTA has sought ways to identify the role of Rx/OTC medications in fatal transit accidents". It approved the FTA's plans to "perform a simulator study on operator impairment, develop Rx/OTC testing regulatory requirements and/or guidance recommendations, and apply Rx/OTC audit procedures to the Drug and Alcohol Compliance Audit Program."

The decision to develop project PATH reflects the growing understanding that prescription and over-the-counter medications commonly used by professional drivers, including benzodiazepines, may impair driving performance. Accordingly, there is a need for a procedure that defines the limits within which the medications may be used safely by professional drivers. Those procedures must assess impairment in the period following drug ingestion, and must repeat those tests after a period when the drug has presumed to have been eliminated from the driver's body. The first set of tests,

following drug ingestion, establish whether, and to what extend and under what conditions, the medication impairs driving performance. The second set of tests, after the expected wash-out period, establishes the period after which driving performance has returned to baseline, i.e. when it is again safe for the individual to perform as a professional driver.

Numerous studies have established links between prescription medications, driving performance, and elevated crash risk. Those "epidemiological" studies have primarily evaluated crash risk in the general driving population. NTSB has been the leader in the study of drug involvement on commercial motor vehicle collisions. Its 1990 study[52] assigning probable causes to 185 large truck collisions, found that only 31% of the accidents were caused by factors other than driver incapacity. This fatal-to-the-driver truck accident study established fatigue, drugs, alcohol or a combination of drugs and alcohol (see figure 6-1) as the primary cause of the accidents.

Figure 6-1: NTSB Probable Cause Assignments in Fatal-to-the-Driver Accidents

Fatal-to-the-Driver Accident Probable Cause Matrix						
Number Accidents	Physical Incapacity	Impairment Fatigue	Impairment Alcohol	Impairment Drugs	Both Drugs + Alcohol	All Other Causes
Investigated	20	59	15	33	8	58
Pct Distrib	10.81%	31.89%	8.11%	17.84%	4.32%	31.35%

The 1990 study ascribed a single probable cause to each of the accidents studied. More recent NTSB studies have ascribed Critical Causation Factors to accidents in a way that drug and alcohol use, fatigue and other factors could be cross-correlated for study. For instance, in the 2006 Large Truck Crash Causation Study (LTCCS), prescription drug use was a "associated factor" in 28.7% of the truck-initiated crashes and 33.9% of the car-initiated crashes.

In preparation for this study, the Cahill Swift PATH team performed a further (unpublished) analysis of the LTCCS data, analyzing the "Critical Factors" database against the "Drugs Found" database. The distribution of causal factors in the LTCCS accidents associated with the use of psychoactive prescription medications was significantly different ($p > 10^{-6}$) from the distribution of causes where no drug was found. This analysis found that there was a significant increase in the percentage of accidents ascribed to "driver performance" error when the driver used a psychoactive prescription medications compared to accidents when "no drugs" were found to have been used by the driver and in accidents when the drugs found were non-psychoactive. As seen in Figure 6-2, seventeen percent (17.7%) of accidents in which a psychoactive prescription medication was found were ascribed to "driver performance error" vs 7.6% of accidents in which "no drug" was found. There were smaller increases in accidents ascribed to "driver recognition" and "driver decision". Further, 31.5% of the accidents in which a benzodiazepine was found were ascribed to "driver performance" vs 7.6% of "no drug" accidents (data not shown).

Figure 6-2: Critical Causation Factors by Drug Use in the LTCCS

LARGE TRUCK CRASH CAUSATION STUDY
INCIDENCE OF DRUG USE BY CRITICAL CAUSATION FACTOR
PERCENTAGE DISTRIBUTION, PROBABILITY TESTS

Substance- NIDA and Psychoactive Rx/OTC Separated	No Driver Error	Physical Driver Factor	Driver Recognition Factor	Driver Decision Factor	Driver Performance Factor	Environment-Highway-Weather-Other	Chi Square Tests of Probability
NIDA Drug	17.5%	25.0%	30.0%	5.0%	17.5%	5.0%	Whole Table $p< 10^{-6, SIG}$
Psychoactive Rx/OTC	28.1%	9.4%	18.8%	20.8%	17.7%	5.2%	NIDA vs Psychoactive p=.0159, Sig
Non-Psychoactive Rx/OTC	54.6%	5.0%	14.9%	14.2%	5.0%	6.3%	Psychoactive vs. Non-psychoactive $p< 10^{-6,}$ SIG
No Drug Found	56.6%	3.1%	13.6%	13.9%	7.6%	5.2%	Psychoactive vs No Drug Found $p< 10^{-6}$, SIG

Benzodiazepines are among the most commonly used prescription medications. In the most recent National Roadside Survey of Alcohol and Drug Use by Drivers[53] (2007), 2.5% of the 7,719 drivers tested were positive for benzodiazepines, 4th in frequency of detection after THC (7.8%), Opiates (4.1%), and Cocaine (3.4%). In the 2009 "Drug Testing Index" published by Quest Diagnostics, the positivity rate for Benzodiazepines in the general workforce was 0.76%, an increase from 0.58% in the 2005. By comparison, the Benzodiazepine increase was during a period in which the positivity rate for Cocaine fell from 0.78% in 2005 to 0.29% in 2009[54].

The only direct report of Benzodiazepine use by safety-sensitive transit workers comes from an 1991 study[55] of drug and alcohol use by transit workers, who were promised anonymity for their estimates of use and for the results of their urine specimens. In the study, 0.79% reported daily use of "Tranquilizers like Librium, Valium, etc" and an additional 0.90% reported weekly but not daily use. The positivity rate was 0.26%, for benzodiazepines in the urine specimens, 5th after Cocaine (2.01%), Marijuana (1.08%), Opiates (0.77%), and Barbiturates (0.33%).

These data points imply that benzodiazepine use in the general civilian population (2.5% in the 1997 Roadside Survey) is approximately 4 times that in the labor force subject to non-DOT drug testing (0.76%), but usage in that labor force has grown steadily for a decade or more.

There are numerous reports of the contribution of prescription medications, including Benzodiazepines, in crash causation. The PATH team prepared a summary of literature reports associating accident rates and Triazolam drug use in preparation for this study.

6.3 Project Design Considerations

The following design considerations are built in and integral to the Project PATH experimental plan.

- Any experimental findings of drug impairment from research conducted on drivers drawn from the general public may not directly translate to the impacts that would be found with CMV drivers as subject-participants. Commercial motor vehicle operators are highly trained professionals and their professional skill set may counterbalance the impacting effects of drugs or counteract the impact in ways not applicable to general public automobile operators. Moreover, a 26,000 pound truck or a 40-foot bus loaded with passengers is a very different driving environment than a family sedan.
- The participants in Project Path should be drivers with a current CDL with passenger endorsements, i.e. commercial bus operators, or CDL truck drivers. There may be iterations of Project PATH in which the participants are not current bus or truck operators, but they should be at least former bus operators.
- The drug examined should be a prototype of its drug class, well-researched, used by the public and there should be enough epidemiological data to provide an estimate of usage in the general population, an incidence of use in the target population if possible, and an estimate of increased crash risk when used by the general public.
- The drug should only be administered in recommended therapeutic doses, not in supra-therapeutic doses. The drug should be administered in a randomized double-blind cross-over protocol so that all drivers get all doses. There must be a placebo comparison, and preferably at least two dose levels. It would be well to also have a direct comparison against the impact of alcohol on driving performance, preferably by having alcohol as an additional agonist.
- The drug must be considered to be generally safe to use within a wide range of ages, body styles and weights, and by persons taking concomitant over-the-counter drugs. The study leading to the final experimental design must also develop a list of drugs that would preclude a study applicant, taking a proscribed drug, from participating. However, for practical reasons and for scientific reasons, the study should accept applicants taking over-the-counter medications and prescription medications not on the proscribed list. The intake process should produce a full list of each OTC and non-proscribed prescription medication used by each participant, together with dosage, duration and frequency of use.
- There must be an adequate “wash-out” period between the drug ingestion and the next time the participant is scheduled to perform safety-sensitive duties. That wash-out period should be equivalent to a minimum of eight half-lives of the drug. A half-life is the time it takes the body to eliminate one-half of the ingested drug. Figure 6-3 implies that, for all practical purposes, this Project PATH design consideration limits the potential experimental drugs to those with a half-life of 8 hours or less.
- The first drive of each experimental day should be completed before the participant ingests the experimental dose for the day. That drive provides a baseline of performance that must be equalled after the wash-out period before the participant is qualified to next perform safety-sensitive duties.

- The period between drives in the experimental session should be spaced to bracket the expected peak action of the drug.

Figure 6-3: Wash-out periods of eight half-lives

Percent Remaining	# of half-lives	elapsed time 2 hr half-life	elapsed time 4 hr half-life	elapsed time 8 hr half-life
100.00%	0	0	0	0
50.00%	1	2	4	8
25.00%	2	4	8	16
12.50%	3	6	12	24
6.25%	4	8	16	32
3.13%	5	10	20	40
1.56%	6	12	24	48
0.78%	7	14	28	56
0.39%	8	16	32	64

- The apparatus used should be a high-fidelity driving simulator, preferably a bus or light truck simulator so that the vehicle dynamics are similar to a commercial motor vehicle. In addition to the simulator, the PATH team will need several rooms with computers where the psychomotor tests will be conducted and where the participants will rest between drives. Depending on the experimental design, the PATH team will need access to eye-tracking equipment and the computer resources that capture data from it.
- The project will utilize a series of standard psychomotor tests to provide objective measures of impairment of several of the driver skills that participant in safe driving. The psychomotor battery needs to be able to be accomplished in a time period that fits between the experimental drives.
- The project will need a continuous measure of the drug concentration in the system of participants. Depending on the time period between experimental drives, it might be possible to collect serial urine specimens but a more practicable option is to use serial saliva specimens. Additionally, participants should be asked to provide a blood specimen after the last experimental drive of each day, to provide a direct correlation between saliva and serum drug levels.
- The project data analysis should consider strategies that define the impact of the experimental drug on the Critical Causation Factors qualities identified in the Large Truck Crash Causation Study. Driver Performance was the factor most impaired by psychoactive prescription medication, followed by Driver Decision and Driver Recognition.
- The experimental analysis, in addition to evaluating the main effects of driving impairment by dose, should also consider the effects of driving impairment by saliva drug concentration. The analysis should also consider the modifying effect that the prescription and over-the-counter medications taken by the participants have on drug levels and impairment. The latter analysis is important in defining medications that may potentiate the primary drug impact and would act as a bar to performing safety-sensitive services under the effect of the concomitant medications.

6.4 Results – Types of Information Gathered

The PATH experimental vehicle was a high-fidelity bus simulator owned by the Paducah Area Transit System (PATS). The bus simulator is contained in a large tractor-trailer and consists of the front end of a Gillig 40-foot bus surrounded by seven large video-displays for a 360^{O} view of the road, passenger area of the bus and surroundings.

The experimental period spanned the time from August, 2006,when the project was first conceived, through a two-year initial development period, to the period from August 2008 to March 2009, when the Detailed Experimental Plan was completed and the project submitted to the Institutional Research Board (IRB) at the University of Iowa. IRB approval was received in July 2009 and recruitment commenced immediately. The experimental period extended from late September to Thanksgiving 2009. The period of data-cleaning, cataloging and verification extended through March 2010. Data analysis and report preparation has continued through the subsequent months.

During the period July through September, 2009, Project PATH recruited 41 applicants, of whom 34 applicants passed the physicals and the training drives and were accepted into the project. The training drives eliminated seven applicants who exhibited high levels of simulator sickness. Of the 34 enrolled participants, six dropped out for schedule-conflict reasons and did not complete the project and an additional four were de-enrolled by the PATH researchers after completing one or two of the three experimental sessions. Of those four, two were eliminated because their next-day saliva samples showed measurable levels of Triazolam after a wash-out period of 6 to 8 half-lives post ingestion. One was eliminated for having consumed alcohol after returning home and arriving for the next-day drive with a measurable breath alcohol level, and the other for chronic tardiness. Of the 24 participants who drove in all three experimental sessions, 18 completed all three (3) experimental sessions. Each experimental session consists of five experimental drives, four experimental drives on day one and one next-day drive. Due to mechanical problems with the simulator late in the experimental period, six of the participants drove the four same-day drives in the third experimental session but were excused from completing the next-day drive.

There are three classes of results reported in this Final Report of Project PATH. These are:

1. Data-gathering about and from the participants. This class of results analyzes the several repetitive paper-and-pencil surveys completed by the participants during and following the completion of the experiment. The written surveys consist of the “Simulator Sickness Questionnaire” administered after every drive; the “Simulator Realism Questionnaire” administered after the fourth drive of each of the three experimental sessions (while waiting for the project-provided and required ride home); and the “Sleep Quality Questionnaire” administered prior to the Next-day experimental drive. This class of results also includes the analysis of information collected about participants Such data includes their use of concomitant over-the-

counter and prescription medications, Body Mass Index data, Driving Style Index data, Triazolam saliva concentrations and other data used as control measures and explanatory variables.

2. Data gathered from the repetitive psychomotor test battery. Immediately before each of the 15-total experimental drives, participants completed a psychomotor test battery. The test battery consisted of a "Mood" scale, a "Sleepiness" scale, and six psychomotor tests. The psychomotor test battery gave a standardized measure of the drug impact across time and dose, against which data derived from the driving simulator was compared. Additionally, data from the information gathered by and from the participants could be analyzed to determine if there were consistent and significant interactions among individual participant characteristics and drug impact measures. Psychomotor test battery data was also analyzed to determine whether there were lingering performance changes or decrements after the wash-out period as compared with the first drive of the previous day. Psychomotor test battery data was also analyzed to chart the time course of the impairing effects of the Triazolam doses as compared to the placebo doses by time and psychomotor test.

3. Data gathered from the driving simulator. Custom software was written for the simulator by FAAC, Inc, the simulator manufacturer. The software routine collected a wide variety of participant-driver performance data, as well as data on the location of obstacles and the location, speed and direction of other virtual vehicles programmed into the simulator that participants interacted with.
   - Driver performance data was analyzed, first, to determine whether there were lingering performance decrements on the next-day drive after the wash-out period as compared to the first drive of the previous day.
   - Driver performance data was then analyzed to determine the drug impact by dose and time on four measures of driver performance.
     - Standard Deviation of Lateral Position (SDLP, also written as standard deviation of lane position is some publications). SDLP is a standard measure of the amount the driver is weaving in the lane while driving straight with no distractions.
     - Curve Following, a measure of the SDLP (weaving in lane) while a driver drives a curve of standard radius.
     - Barrel Obstruction, a measure of the driver's driving performance while maneuvering the vehicle around a set of road-construction barrels obstructing the driving lane.
     - Braking Profile, a measure of braking skill while stopping from driving speed at a stop light or stop sign.

4. Data gathered from the eye-tracking equipment. Driver-participants wore Mobile-Eye eye tracking equipment on all drives. The equipment recorded the center of the participant's gaze in x-y coordinates and also recorded the

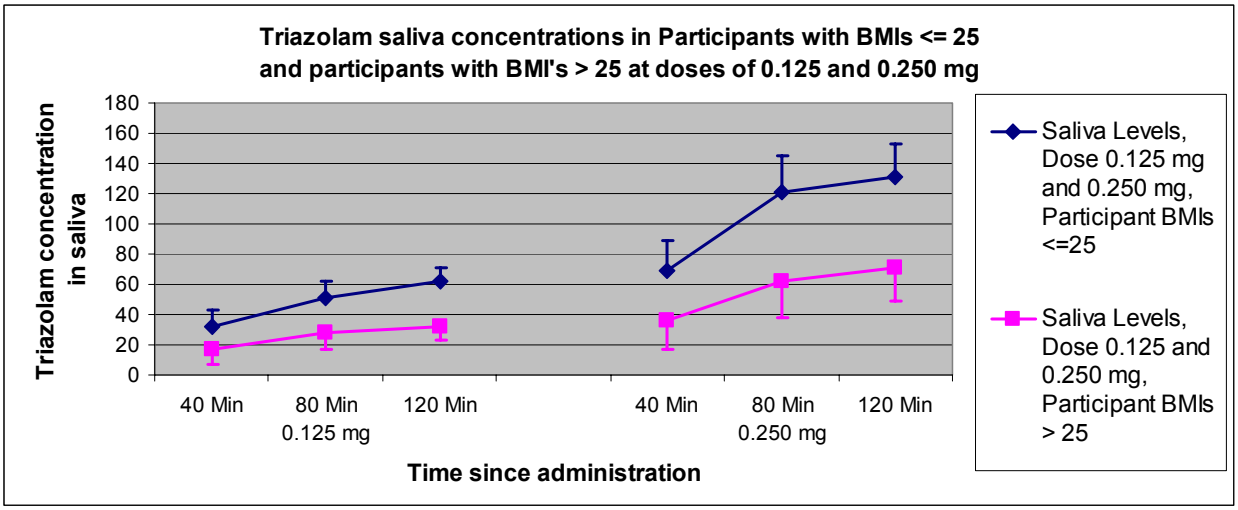
radius of the pupil of the driver's eye. It is anticipated that correlating information from the eye-tracker with driver performance and psychomotor data will do much to elucidate the connection between perception, performance and decision-making. However, the quality of each participant's eye-track record was affected by several variables, including drug dose. Consequently, the analysis of the eye-tracking information is complex and apparently will require a substantial effort of manual-counting of eye location on a frame-by-frame basis. Consequently, the report of the eye-tracking data will not be available to be included in this edition of the Project PATH report.

6.5 Results of the Project PATH Study

6.5.1 Data Gathered from Participants Medical Examinations and Triazolam Concentrations in Saliva Samples

1. Body Mass Index and Triazolam Saliva Concentrations – Unfortunately, participant height and weight was not recorded at the time of their physical examinations qualifying them to enter Project PATH. The purpose of the physicals was to assure that their liver functions were within normal ranges, indicating that participants would metabolize and eliminat the Triazolam within normal limits. Participant height and weight was gathered by Path Researchers during the close-out telephone interview after all participants had completed the project. Two of the 24 participants who completed the project could not be reached for that interview, so height and weight data was collected from 22 of the 24. The height and weight data was desired so that the Body Mass Index could be read from standard BMI tables and used as in index of the volume of body fluid in each participant, i.e. the volume on fluid in which the dose of Triazolam would dissolve.

Figure 6-4: Saliva Triazolam Concentration Highly Correlated with BMI

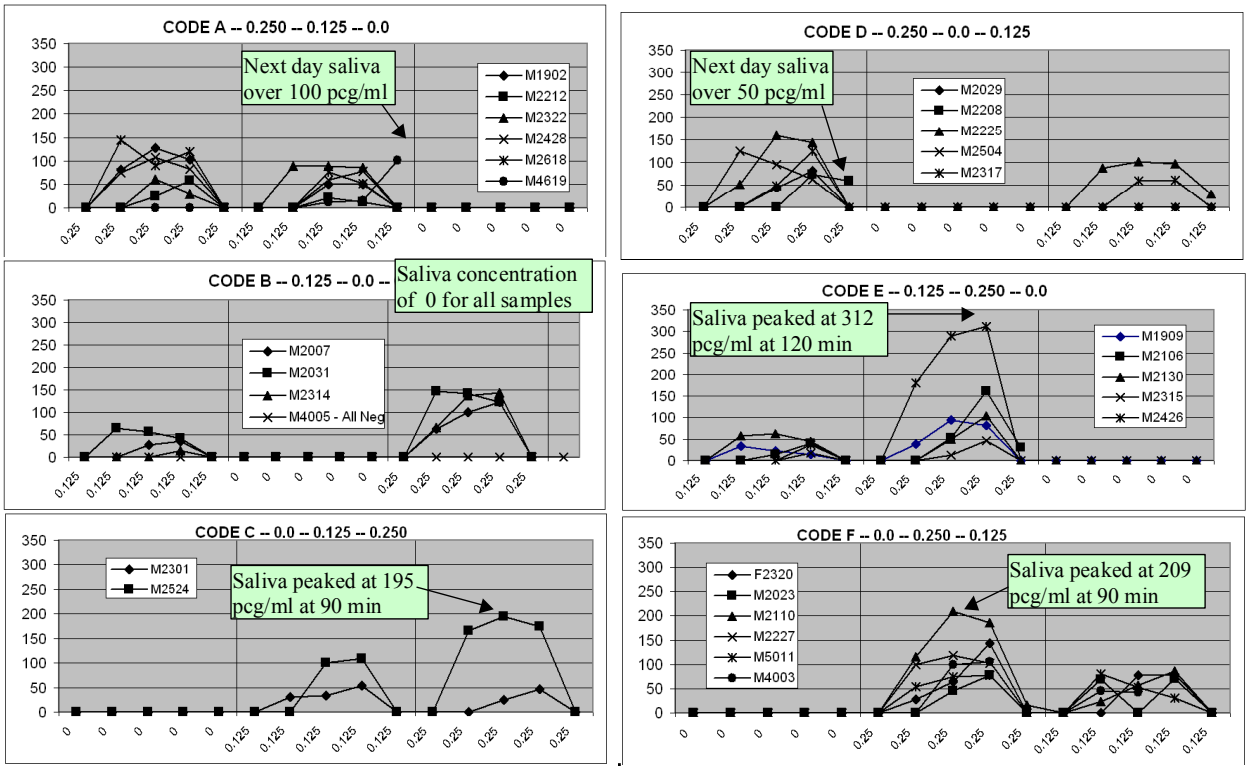


The BMI Index was graphed against the concentration of Triazolam by time to determine if the saliva concentrations were independent of Body Mass Index, or correlated with BMI. The results are shown in Figure 6-4.

The saliva concentration is highly correlated with BMI ($p < .01$), being consistently lower in participants with a higher Body Mass. If impairment is dose-dependent, it would be expected that participants with a higher BMI index might show less impairment than participants with lower BMI scores.

2. Saliva Triazolam Concentrations – Participants provided a 4 ml saliva specimen immediately following each experimental drive. The first saliva specimen of each experimental session was collected immediately before the participant took the first drive of the day. The experimental capsule, containing placebo, the 0.125 mg dose of the 0.250 mg dose, was ingested immediately following the first drive of the day. Thereafter, saliva specimens were collected immediately following each experimental drive, at 40 minutes, 80 minutes and 120 minutes post-ingestion, to provide a measure of Triazolam in the system at the time of the drive.

Figure 6-5: Triazolam saliva levels showing anomalous concentrations



It was assumed that saliva Triazolam concentrations would be relatively level after adjustment for BMI, but that was not the case. For participants receiving the 0.250 mg dose, Triazolam saliva levels ranged from a high of 312 picograms/ml to a low of 0 pcg/ml. Three participants exhibited what appear to

be higher than normal peak saliva concentrations at the 0.250 mg dose. A fourth participant had a zero-Triazolam saliva concentration across all doses and times. And four participants had measurable Triazolam saliva levels in the next-day specimens. Three of those four had low-to-moderate levels of Triazolam, but one participant had Triazolam saliva levels at 14 hours post-ingestion that were higher than any of his saliva concentrations in the 120 minutes following ingestion. The saliva concentration graphs are shown in Figure 6-5, arranged by the dose-order group into which the participant had been randomly assigned.

Figure 6-6: Saliva Triazolam concentrations at 80 minutes by BMI score and

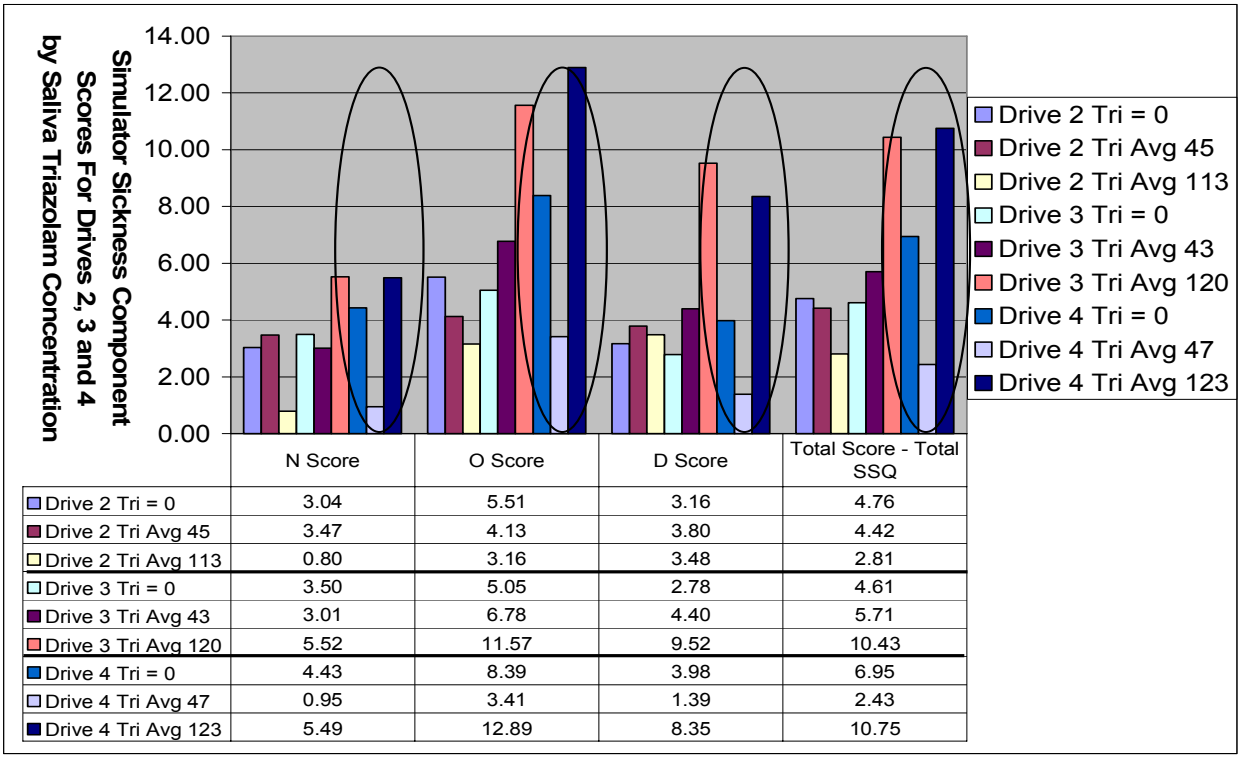
Subject ID	**Medications Taken by Driver Participants**	Highest Saliva Triazolam Concentration at .250 Mg Dose	BMI Score	BMI Index	Average Highest Saliva Level and Average BMI Score	Average of Hishest SSQ Scores	Average Driver Score
M2426	**Afrin Nasal Spray**	289	23	1			
M2110	Zyrtec, Cefaclor, Ibuprofen,Tylenol	209	24	1			
M2524	Acetaminophen	195	23	1			
M2031	N/A	142	24	1			
M2314	Aleve, Multi-vitamins, Vitamin D3, Fish Oil	137	22	1			
M1902	Multi-vitamins, Ibuprofen	127	23	1	120.33	18.388	8.3333
M2007	Tylenol, Centrum, Sudafed	100	20	1	22.25		
F2320	N/A	64	20	1			
M2322	Vitamin C	61	22	1			
M2130	Excedrin	49	22	1			
M2023	N/A	46	22	1			
M2212	Ibuprofen	25	22	1			
M2225	N/A	158	25	2			
M4003	Multi-vitamins, Ibuprofen, Tylenol, Nyquil	100	26	2			
M2504	Zyrtec	95	27	2	61.714		
M2029	N/A	43	28	2	26.571	15.227	8.7143
M2301	Ibuprofen, Motrin	24	27	2			
M2315	Ibuprofen, Zyrtec	12	25	2			
M4005	**Uknown Name of Benzodiazapine, Ibuprofen, Tylenol**	0	28	2			
M2428	Pepto-Bismol	108	30	3			
M1909	Advil liquid gell	95	39	3			
M2618	Tylenol	90	36	3	83.2	16.456	8
M5011	Coumadin, Simvastatin, Aleve	75	30	3	35.4		
M3417	Metformin, Zocor, Tylenol, Antacid	48	42	3			

3. Concomitant Prescription and OTC Medications and Saliva Triazolam Concentrations – Participants were required to list prescription and over-the-counter medications they were taking. Their medications may provide least a partial explanation for the anomalous saliva Triazolam readings. Of the participants with the three highest peak Triazolam levels, M2426, who had the highest readings, 298 picograms/ml (pcg/ml) at 80 minutes and 312 at 120 minutes, had a new prescription for Afrin nasal spray. M2110 had a prescription for Cefaclor, an antibiotic. There is no obvious explanation the elevated peak of M2524, who listed no concurrent medications. In the other direction, M4005, who had a prescription for a benzodiazepine with a name he couldn't remember, had negative (zero) saliva Triazolam concentrations across all doses.

The implication is that Afrin and Cefaclor compete for the same mechanisms that metabolize Triazolam and so slow its degradation and elimination. Contrariwise, in the case of M4005, the assumption is that his body has adapted to the on-going presence of a benzodiazepine (taken to assist with sleep) and metabolizes the drug extremely quickly. These explanations are conjectural, and do not explain the high peak concentration of 195 for M2524 or the low peak concentration of 12 for M2315. However, they do imply that the impact of one medication may strongly potentiate or diminish the impact of a second medication taken concurrently.

4. Sleep Quality Questionnaire – A "Sleep Quality" questionnaire was administered before each next-day drive. Participants reported improved sleep patterns on the night after they had taken the 0.250 mg dose, but not on nights after the 0.125 mg dose or the placebo dose. Since the doses were administered "double-blind" in a standard capsule, neither the participant nor the experimenter knew the dose of the capsule being ingested, so the Sleep Quality results are considered to be a reflection of the efficacy of the drug in improving sleep quality.

Figure 6-7: Average Simulator Sickness Component Scores by Triazolam Concentration



	N Score	O Score	D Score	Total Score - Total SSQ
Drive 2 Tri = 0	3.04	5.51	3.16	4.76
Drive 2 Tri Avg 45	3.47	4.13	3.80	4.42
Drive 2 Tri Avg 113	0.80	3.16	3.48	2.81
Drive 3 Tri = 0	3.50	5.05	2.78	4.61
Drive 3 Tri Avg 43	3.01	6.78	4.40	5.71
Drive 3 Tri Avg 120	5.52	11.57	9.52	10.43
Drive 4 Tri = 0	4.43	8.39	3.98	6.95
Drive 4 Tri Avg 47	0.95	3.41	1.39	2.43
Drive 4 Tri Avg 123	5.49	12.89	8.35	10.75

5. Simulator Sickness Questionnaire – The Simulator Sickness Questionnaire[56] (SSQ) quantifies the discomfort of simulator sickness into components consisting of

Nausea, Oculomotor Discomfort, and Disorientation. Figure 6-7 graphs the average simulator sickness scores for drives 2, 3 and 4 averaged from experimental sessions 1, 2 and 3. The ellipses are drawn to emphasize simulator sickness component scores on the 4th drive of the composite experimental session.

The general trend shown in Figure 6-7 is for Simulator Sickness scores to increase from drives 2 to 3 to 4. As the experimental session progressed, participant-drivers who were susceptible to Simulator Sickness experienced more discomfort on drive 4 than on drive 3 or 2.

Regression analysis indicates that simulator sickness scores are positively correlated ($p < .05$) with dose level, with saliva Triazolam concentration, and with BMI. However, when simulator sickness scores are examined closely, it can be seen that, on the fourth drive of each experimental session, drivers with low (but not zero) concentrations of saliva Triazolam who experienced simulator sickness experienced significantly less ($p < .05$) simulator sickness than drivers with higher concentrations of Triazolam in saliva or drivers with zero Triazolam concentration. The finding is most clear for Oculomotor simulator sickness on the fourth drive. On that drive there is the largest disparity between the Simulator Sickness scores for drivers with zero (0) Triazolam levels (Oculomotor 8.39), drivers with low to moderate Triazolam levels (Oculomotor 3.41), and drivers with higher average Triazolam scores (Oculomotor 12.89). The scores for moderate vs high Triazolam are significantly different ($p < .05$).

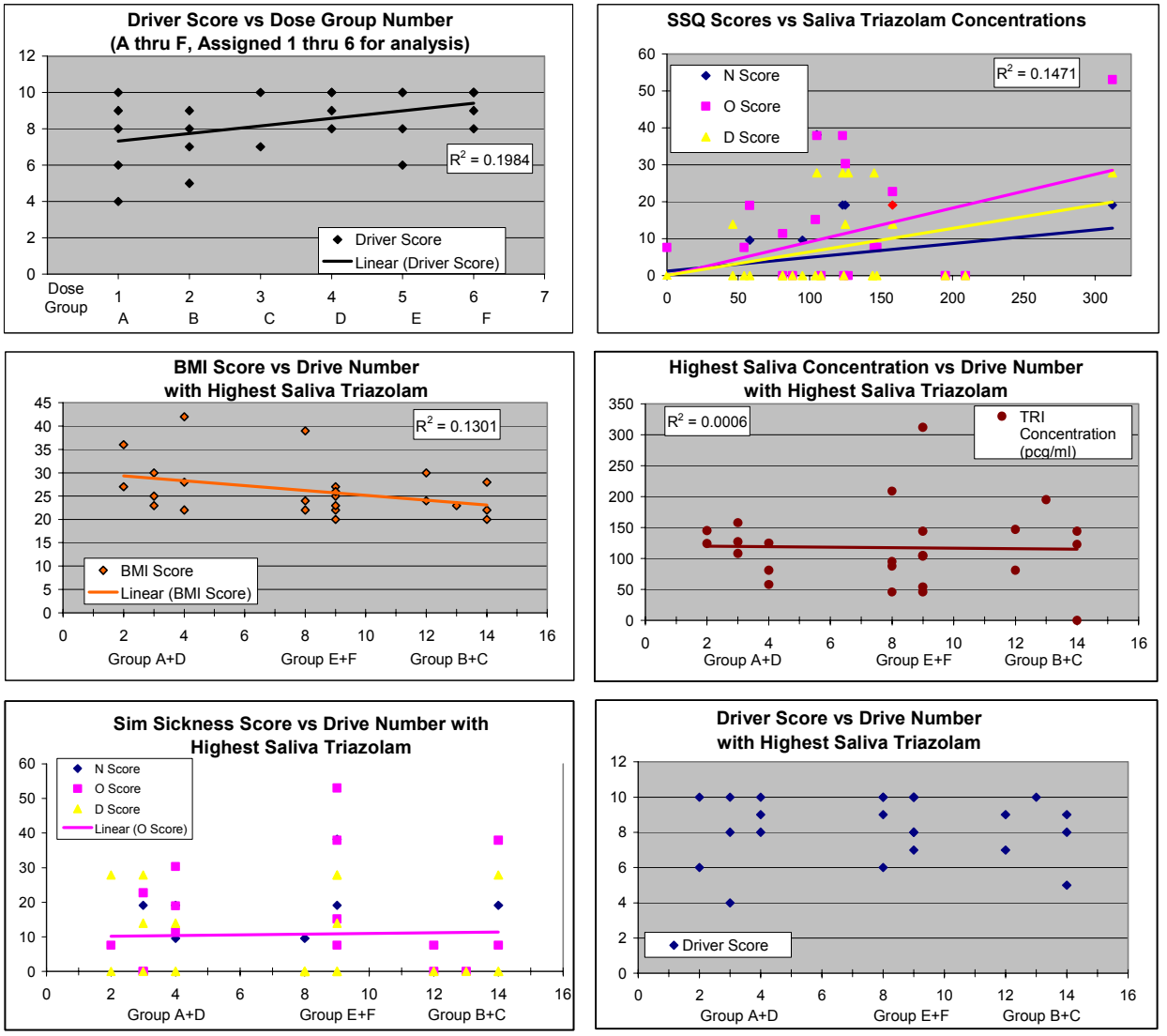
Fatigue and Difficulty Concentrating are the sub-scales within Oculomotor that show the most disparity in score between low and high Triazolam concentrations. The implication of this finding is participants with low saliva Triazolam levels experience significantly less Fatigue and Difficulty Concentrating on the last drive of the day than participants with zero Triazolam levels and participants with elevated Triazolam levels. Presumably, the low-dose of Triazolam is acting more as a stimulant than as a depressant as the drivers tire at the end of the experimental session.

6. Driver Score – It was of concern that each participant-driver's individual driving style and/or skill level might impact the main drug effect in unique ways. For instance, since the medication is a "tranquilizer", it seemed possible that it might have a differential effect on a driver who was fast and impetuous from its impact on a slower, cautious driver. For that reason, the PATH team devised a "Driver Score" rating system by evaluating the appropriateness of each driver's response to the four challenges built into the first drive of the first experimental session, before any of the experimental capsules had been ingested. The resulting numerical score ranged from 4 (poor response on each challenge) to 10 (appropriate response on each challenge).

6.5.2 Interaction of the Variables

Given the above data, there are likely to be interactions among and between the variables that may act to intensify, mitigate or cancel the main drug effect. That being so, the PATH team developed a series of graphs and cross-tabulations to study the potential interactions among the variables. The main results are shown in Figure 6-8.

Figure 6-8: Grouping of the Variables to Discern Potential Magnitude of Impact In the First, Second or Third Experimental Session



As can be seen from the top two graphs in Figure 6-8, several of the variables described above weakly but significantly correlated in a linear manner with other variables. For instance, in the top left graph, Driver Score (a putative measure of driver skill) correlated weakly with the Dose Group into which each driver had been randomly assigned. Dose groups D and F had drivers with the highest average driver score and the least inter-score variance. If driver score was an important variance in interaction with drug impact, drivers randomly assigned to Groups D and F might show the least

amount of impact (native skill counteracting drug impact). Moreover, since these groups have the least amount of variance in driver skill scores, and if skill is an importance variable, and if drug impact translated linearly against skill, these groups (D+F) should show the least amount of impairment and the least variance in individual impact.

However, the statement, that groups D and F should show the least amount of impairment (if driver skill opposes drug effect) is only true from the perspective of statistics, i.e. if Dose Groups D and F are considered together, or if each are considered separately.

If all dose groups are averaged together, the mean (and main) effect may overwhelm any antagonistic effects of driver skill and that resolution in the data would be lost. However, if dose groups are considered separately, or aggregated with similar dose groups, some of the variables may appear to have significant statistical power. For instance, on Figure 6-5, compare the saliva Triazolam levels of random groups A + D, that received the 0.250 mg dose on the first experimental drive, with random groups E + F which received the 0.250 mg dose on the second experimental session and groups B+C that received the 0.250 mg dose of the third experimental day. Groups E + F had participants who spiked the highest Triazolam levels. If the levels of impairment correlated with saliva Triazolam, it would be expected that Groups E and F would show the highest levels of impairment.

To test that hypothesis, the graphs in the second and third rows in Figure 6-8 aggregate data according the experimental drive (of a total of 15 experimental drives) on which the participant had the highest saliva Triazolam concentration. In most cases, this assignment is equivalent to whether the participant was assigned to a group that received the 0.250 mg dose on the first experimental day, the second experimental day or the third experimental day.

The data is more complicated because a few of the 24 participants had peak saliva Triazolam's on the day they received the 0.125 mg dose rather than the 0.250 mg dose. The data is even more complicated because a very few participants showed peak saliva Triazolam levels after the 40 minute drive, a few more peaked after the 80 minute drive, and some peaked after the 120 minute drive. Those data associations can be seen in Figure 6-8, where the x-axis number indicates the experimental drive (of 15) on which each participant provided a saliva sample with the highest Triazolam concentration.

From the graphs in Figure 6-8, the analysis would be that dose orders E + F might be expected to produce the most impaired participant-drivers. That is because to those groups were randomly assigned those participants who had the highest levels of Triazolam and experienced the most amount of Simulator Sickness. Groups E+F also had the participants with the lowest BMI. If the hypothesis is correct, the concatenation of those characteristics -- high saliva level, high simulator sickness and low BMI -- should concentrate the impairing effects of Triazolam to produce high levels of impairment. Moreover, as can be seen in Figure 6-8, these characteristics concentrate

on the third and fourth (but particularly drive 9, the fourth) drive of the second experimental session. Again, if the hypothesis is correct, the highest levels of impairment ought to be seen in the third and fourth drive on the second experimental session.

6.5.3 Summary

Three of the participant-subjects had high levels of saliva Triazolam, and the high concentrations, in two of the three instances, may arguably be ascribed to concomitant over-the-counter pr prescription medications. One employee exhibited surprisingly low levels of saliva Triazolam (0 pcg/mg for all doses) and that finding might also be ascribed to concomitant medication, in this case an unnamed benzodiazepine taken as a sleeping aid. When the variables that are considered to potentially impact driver performance are considered, they are seen to cluster in the second experimental day, and particularly drive four of session three, in a way that may concentrate the levels of impairment on the third and fourth experimental drives of Session two.

6.6 The Psychomotor Tests

Immediately before performing each of the 15 experimental drives (5 sessions x 3 days), each participant performed a short battery of computerized psychomotor tests. The purpose of the tests was to have a repetitive set of tasks that would measure some of the mood, motor and cognitive skills needed for safe driving in the minutes before each drive was performed. It was assumed that the psychomotor testing would provide a measure of the degree and time-course of any drug-induced impairment of driving-skills. The psychomotor measures could be correlated with, and help explain, any impairment of driving skills recorded in the driving simulator.

6.6.1 Results of the Psychomotor Tests

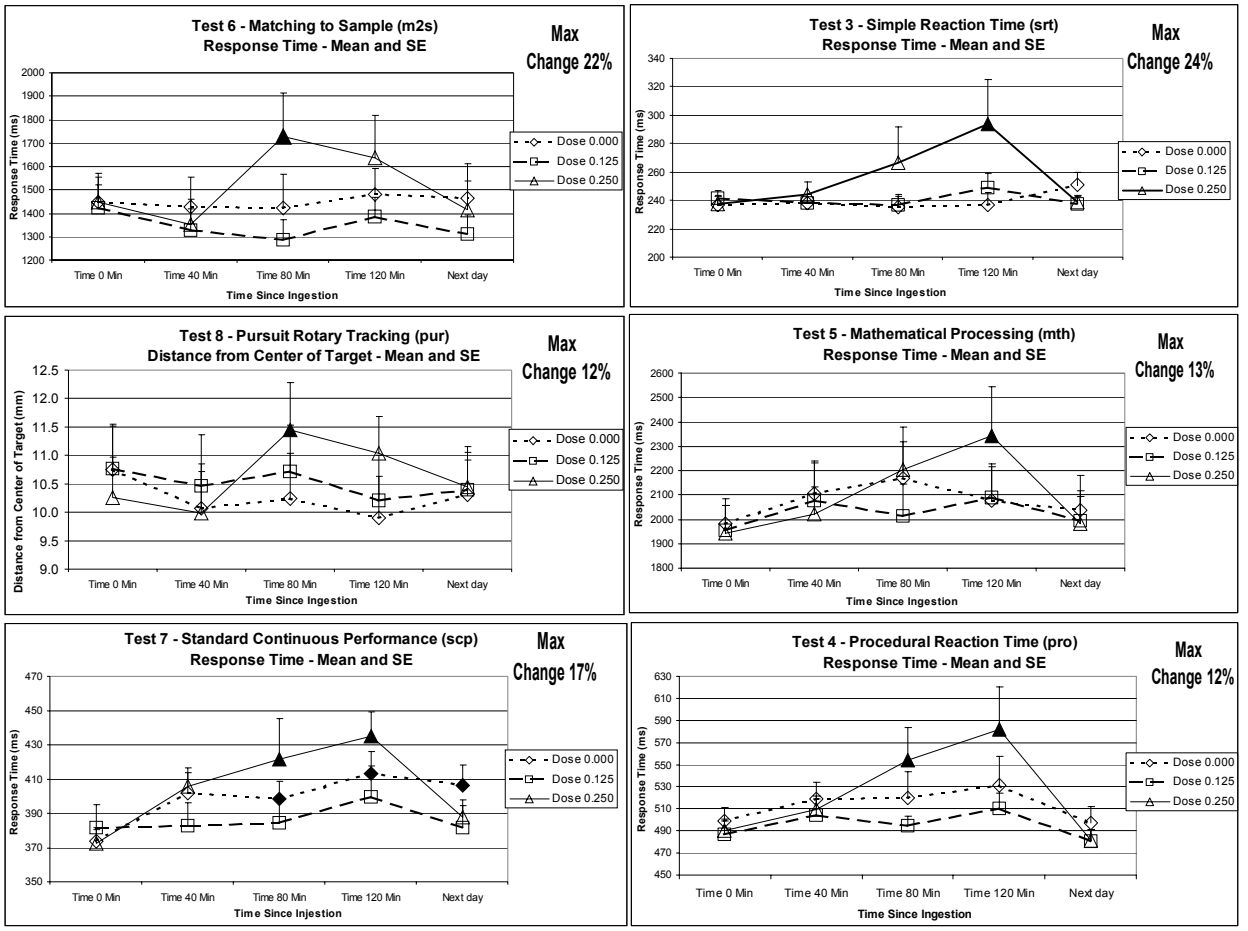
The psychomotor test battery selected for PATH is a sub-set of the large cadre of computerized routines available from the Center for the Study of Human Operator Performance (C-SHOP) at the University of Oklahoma. There were two classes of tests selected by PATH for this project. The first group of tests asked participants to rate their degree of Sleepiness, Fatigue, Vigor, Happiness, Depression, Anxiety, Anger and Restlessness on a scale from 0 (Not at all) to 3 (Somewhat) to 6 (Very Much). The second group of tests measured Psychomotor variables such as simple reaction time, stimulus discrimination, mathematical processing, matching to sample, and accuracy of tracking a moving “X” on the computer screen. These tests intend to measure underlying skills such as concentration, short-term memory, working memory, computational skills, eye-hand coordination, and decision-making skills such as whether to make or withhold a response.

There were no dose-related significant differences for the scores for Anxiety, Restlessness, Depression, Anger and Happiness. It would appear, from these self-assessments, that Triazolam does not impact or cause undesirable mood changes in

drivers. However, there were significant increases at 80 and 120 minutes in Fatigue and Sleepiness scores and reductions in Vigor scores recorded by participants on the sessions when they received the 0.250 mg dose of Triazolam compared to cross-over sessions when they received the 0.125 or the placebo (0.000 mg) dose. Interestingly, on the next-day psychomotor tests, participants on the sessions when they received the 0.250 mg doses recorded smaller sleepiness and fatigue scores then on the sessions when they received the placebo or the 0.125 mg doses. Thus, the psychomotor mood scores corroborate the participant's reports of improved sleep on the sessions when they received the higher Triazolam dose compared to sessions when they received the lower or placebo doses.

The dose-related time course of impairment on the six psychomotor tests is seen in Figure 6-9. Three aspects of these graphs stand out.

Figure 6-9: Time Course of Psychomotor Test Scores By Dose



1. The psychomotor tests scores of participants return to baseline on the next-day testing (with the exception of the scores of participants on the day they received the placebo dose).

2. Two of the psychomotor tests, Matching to Sample and Pursuit Rotary Tracking, show impairment peaks for the 0.250 mg dose at 80 minutes whereas the other four show impairment peaks at 120 minutes.

3. In three of the psychomotor tests, Matching to Sample, Standard Continuous Performance and Procedural Reaction Time, the average (Mean) reaction time of the participants on the days they received the 0.125 mg dose was improved relative to the days on which they received the 0.250 mg dose or the placebo dose. This observation holds true when Median (rather than Mean) reactions times are plotted (not shown).

4. The largest percentage changes from baseline (placebo dose at 0 minutes) are seen in Simple Reaction Time (SRT, 24%), Matching to Sample (22%), and Standard Continuous Performance (SCP, 17%). The performance required in SRT is one of pure reaction time. The participant clicks the mouse as soon as possible after the "X" appears on the screen. The performance required in Matching-to-Sample is one requiring short-term memory and the ability to distinguish between shapes that are similar. The participant is shown a 4x4 block of large colored pixels, some of which are blue and some of which are red. The screen blanks, then two 4x4 blocks are shown, one of which is the same as the stimulus and one slightly different. The participant clicks the left or right mouse button to identify the same stimulus. The performance in SCP is to make a go-no decision. The participant clicks the mouse if an "X" is shown on the screen but not if any other letter is shown.

   The importance of the skills behind these tests for safe driving can be easily imagined (but not tested scientifically or proved or disproved). Matching to Sample may tap the skill needed to recognize a threat situation from a non-threat situation as it emerges, for instance, a vehicle approaching from a cross street at a speed too fast for the approaching driver to stop at their stop sign. The Standard Continuous Performance Test may tap into the decision-making skill needed for an appropriate reaction to the perceived emerging threat. The Simple Reaction Time test may tap into the motor skills needed to rapidly move a foot from the gas pedal to the brake pedal or to initiate an evasive maneuver.

6.6.2 Individual Differences in the Psychomotor Reactions

It was important to determine whether any of the Intervening Variables discussed in body of this paper (Sections 6.5.1 and 6.5.2) would impact the results of the psychomotor testing. That is, were there any personal characteristics of the participants that would render individuals more or less susceptible to the Triazolam impairment.

The hypotheses developed in Section 6.5.1 are:

1. Participants with lower BMIs should be more impacted than participants with higher BMIs because they have relatively higher saliva Triazolam concentrations.
2. Persons with higher Driver Scores are more cautious and proficient drivers and the apparent drug effect may appear attenuated on high-skill drivers.
3. The random assignment of participants to dose groups resulted in some dose group having participants with lower than group average BMIs and higher than group average Driver Scores. Consequently, drug effect may be unequal by dose group.
4. Participants with higher saliva concentrations of Triazolam should be more impacted at the same dose level than participants with lower concentrations of Triazolam in their saliva. That is, saliva Triazolam concentration may be a better predictor of impairment than drug dose.
5. Participants taking certain Rx/OTC medications concurrently with the experimental Triazolam dose should be more impacted because they have much higher-than-average saliva Triazolam concentrations. Presumably, the concurrent medications are competing for the mechanism that metabolizes Triazolam, resulting in higher saliva (and presumably serum) concentrations.
6. Persons reporting higher levels of simulator sickness may perform less well in the simulator and less well on the psychomotor tests (any if there are carry-over of anticipation or lingering effects). However, the 0.125 mg dose appears to reduce the level of simulator-sickness in participants who experience SSQ and the result might be improved performance at the 0.125 mg dose compared to the 0.000 (placebo) or the 0.250 mg dose.
7. Persons receiving the 0.250 mg dose report improved sleep characteristics which might improve next-day performance.

Some of these hypotheses can be tested. The psychomotor test SCP, Standard Continuous Performance, was chosen for a closer data review. It is the only one of the psychomotor tests in which BMI score, Driver Score and Triazolam concentration had statistically significant regression coefficients (see Figure 4-17) and one of the two psychomotor tests on which the Mean Response Times were significantly elevated from baseline at both 80 and 120 minutes (Figure 6-9).

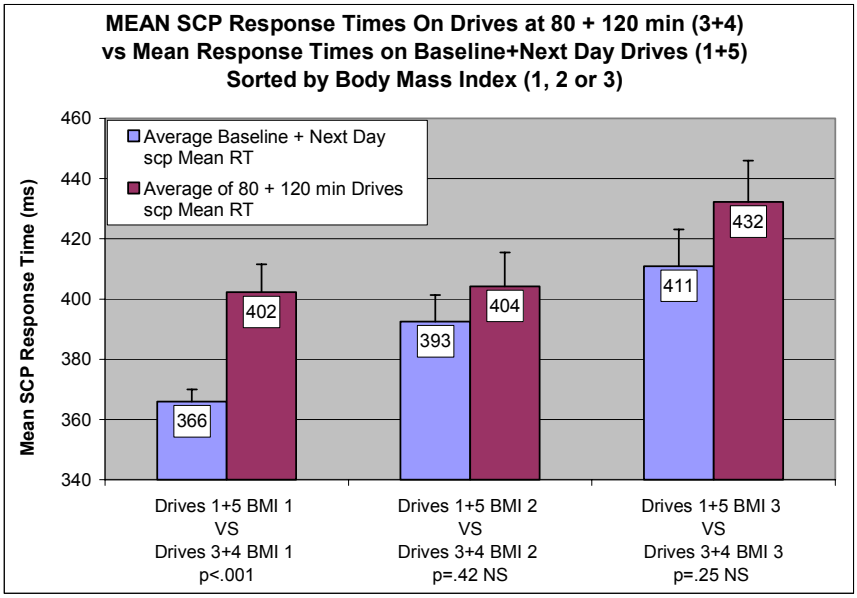
6.6.2.1 Hypothesis 1-

Because they have relatively higher saliva Triazolam concentrations, participants with lower BMIs should be more impacted than participants with higher BMIs.

Figure 6-10 compares the drug impact averaged for participants with a BMI Index of 1 (BMI 20 to 24), BMI Index of 2 (BMI 25 to 28), and BMI Index 3 (29 to 42). Figure 6-10 compares the mean response times on the scp test for the baseline and the next-day drives of sessions 1, 2 and 3 averaged together and compared to the mean response times on the scp test for drives 3 and 4 of sessions 1, 2 and 3 averaged together. Note that the average response times for drives 3 and 4 include participants at all dose levels rather than only participants who receive the 0.125 and 0.250 mg doses on those drives.

Figure 6-10 illustrates two points. First, as compared to the baseline and next-day average response times (drives 1 and 5 of sessions 1, 2 and 3), participants with BMI index scores of 1 on drives 3 and 4 significantly increased their mean response times ($p < .001$), from 366 to 402 ms on average. However, participants with BMI indexes of 2 and 3 did not show a significant increase in response times compared to their baseline and next day pooled and averaged response times. Second, because the baseline and next-day pooled response times correlated significantly with BMI Index, participants with the BMI Index of 3 still recorded the longest average response times on drives 3 and 4 regardless of dose.

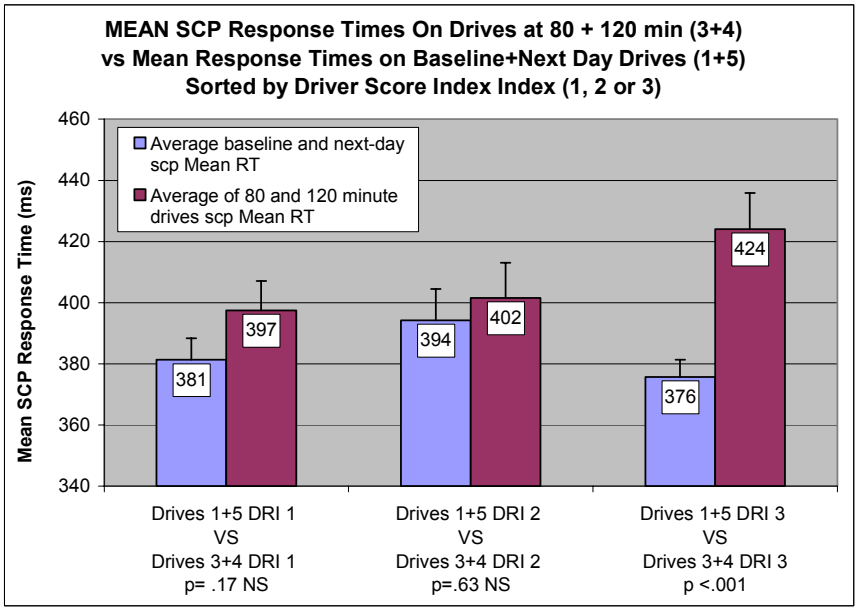
Figure 6-10: Effect of BMI on Drug Impairment



Thus, the hypothesis is confirmed, that the lower BMI drivers are more impacted at all dose levels that higher BMI drivers. But that impact is overlaid on the inherently slower baseline response times of the higher BMI drivers.

6.6.2.2 Hypothesis 2 -

Figure 6-11: Effect of Driver Score on Drug Impairment



Persons with higher Driver Scores are more cautious and proficient drivers and the drug effect may appear attenuated on high-skill drivers.

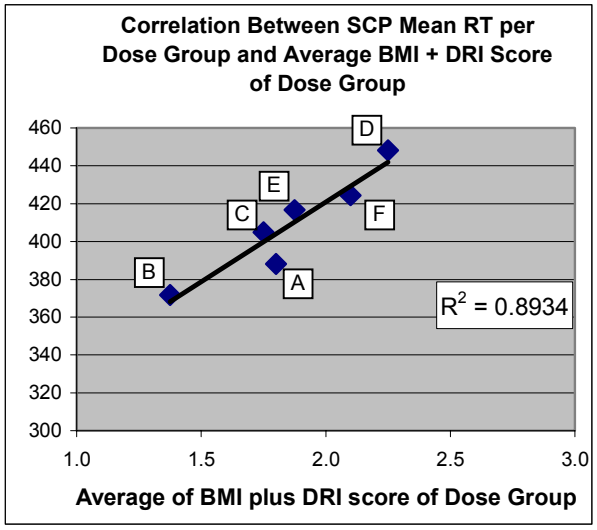
This hypothesis assumed that the higher skill levels of drivers who scored highest on the challenges of the first drive would ward off the impact of the Triazolam. This may not be the case, as seen in Figure 6-11. The largest

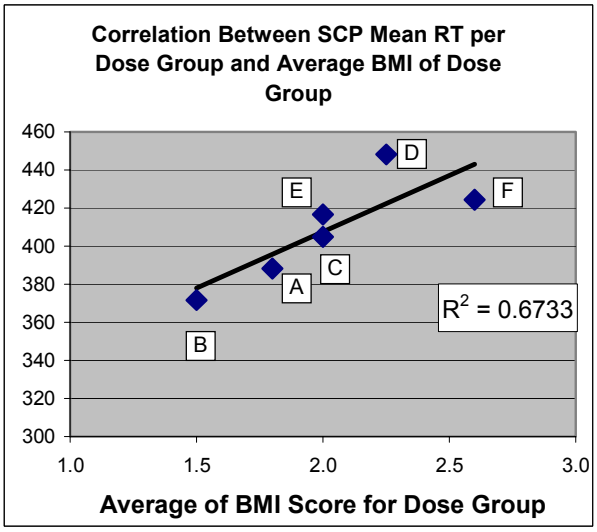
increase in reaction times was seen in the highest-scoring, most skilled drivers. On the SCP test, they went from having the lowest RTs on their baseline and next-day drivers to having the highest reaction times on drives 3 and 4. The increase in reaction times from baseline for participants with driver scores of 3 (DRI 3) were significant ($p<.001$) but the increases for participants with driver scores of 1 or 2 were not significant.

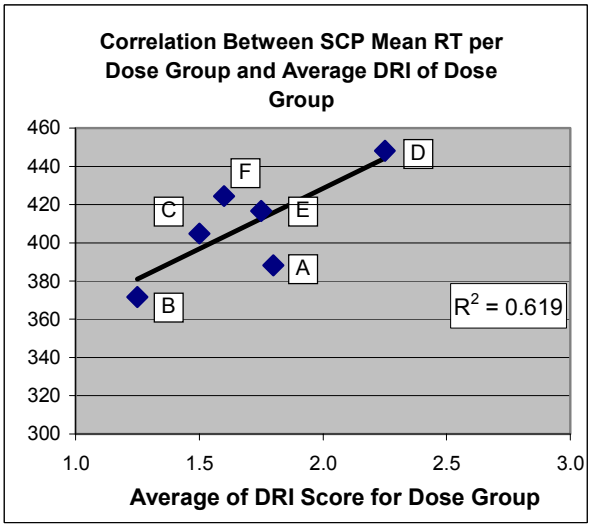
6.6.2.3 Hypothesis 3

Figure 6-12: Combined Impact of B MI and Driver Score on SCP Mean RT

Dose Group	Dose Order	Avg BMI+DRI	Avg BMI Score	Avg DRI Score	AVG scp RT
Dose Group A	0.250--0.125--0.000	1.80	1.80	1.80	388.15
Dose Group B	0.125--0.000--0.250	1.38	1.25	1.50	371.66
Dose Group C	0.000--0.125--0.250	1.75	1.50	2.00	404.89
Dose Group D	0.250--0.000--0.125	2.25	2.25	2.25	448.15
Dose Group E	0.125--0.250--0.000	1.88	1.75	2.00	416.63
Dose Group F	0.000--0.250--0.125	2.10	1.60	2.60	424.40







The random assignment of participants to dose groups resulted in some dose group having participants with lower than group average BMIs and lower than group average Driver Scores (DRIs), and some groups with higher than average BMIs and DRI. . Consequently, drug effect may be unequal by dose group, and concentrated in those dose groups.

In Figure 6-12, the Mean Reaction Time (RT) on the Standard Continuous Performance Test (SCP) for each of the six dose groups (A – F) is plotted against the average BMI for participants in that dose group, and also plotted against the average Driver Score for participants in that dose group. The results, shown in the lower graphs in Figure 6-12, yielded an acceptable and significant amount of linear regression. However, the upper graph in Figure 6-12 plots the mean RTs for each dose group against an average number constructed from pooling and averaging the BMI scores and the DRI scores for each dose group. It is much more linear and helps to account for the disparity in dose group mean response times for the pooled scores for drives 3 and 4 of sessions 1, 2 and 3.

From the column "Avg BMI+DRI" in Figure 6-12, it would seem that participants in Dose Group D would be expected to exhibit the most impairment, followed by participants in Dose Group F and E. However, most impairment will be seen in the session in which the participants receive the 0.250 mg dose. Dose Group D and Dose Group A received the 0.250 mg dose on Session 1. Participants in Dose Group A are the next to the least impaired on the SCP test. The average impairment on Session 1 will be an amalgam of the impairment of Dose Group D and A, and A may offset the impairment of D. Note also that Dose Groups B and C, whose participants are relatively less impaired by Triazolam, receive the 0.250 mg dose on Session 3. Participants in Dose Groups E and F receive the 0.250 mg dose in Session 2 and their high-levels of impairment may result in the 3rd and 4th drives of Session 2 showing the largest overall impairment.

6.6.2.4 Hypotheses 5-

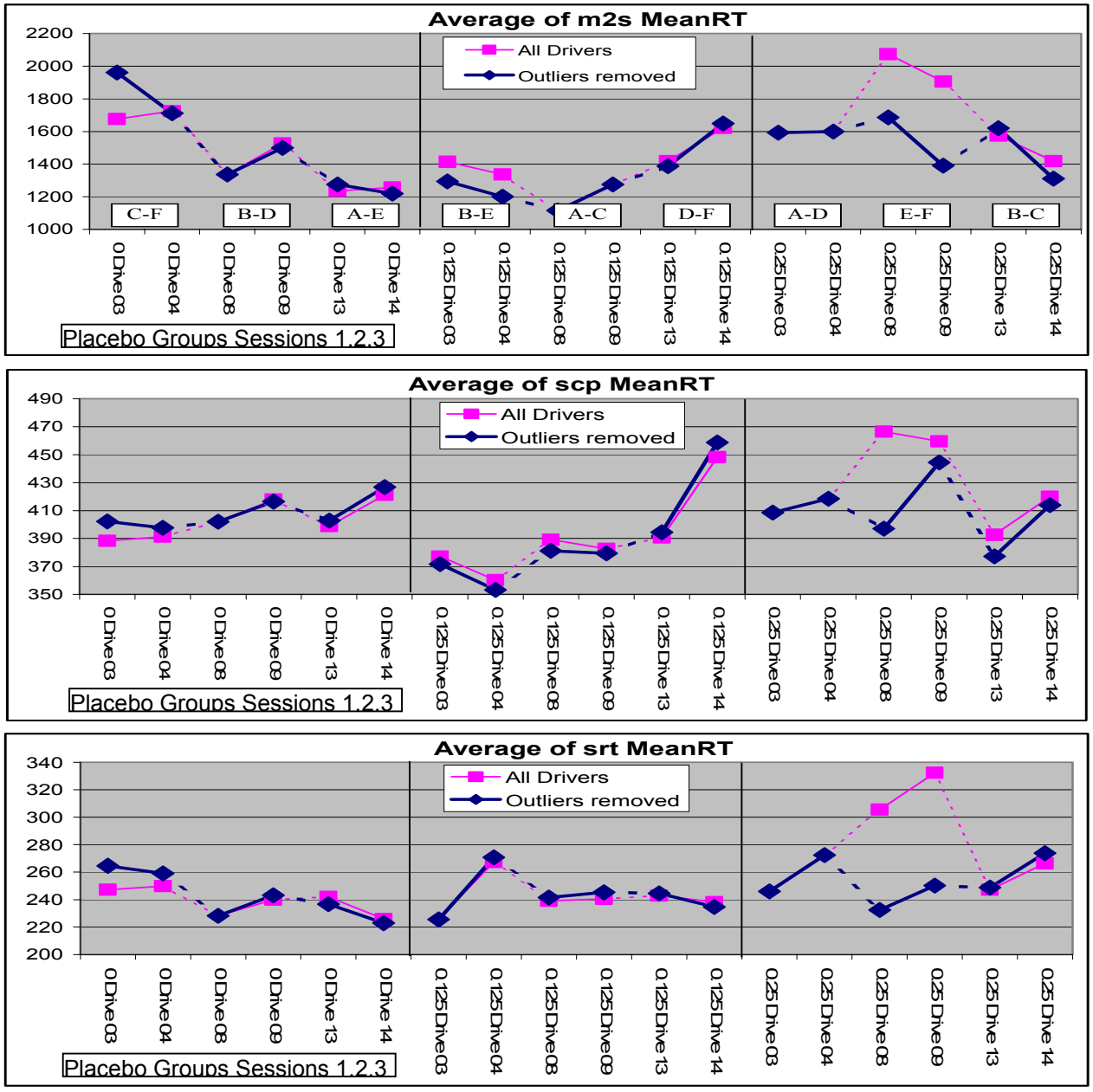
Participants taking certain Rx/OTC medications concurrently with the experimental Triazolam dose should be more impacted because they have much higher-than-average saliva Triazolam concentrations.

In Section Three, Figure 3-7 introduced the observation that three of the participants, M2426, M2110 and M2524, had higher than average saliva Triazolam levels at dose 0.250 mg. Section Four, Figure 4-17 and 4-18 compared impact of saliva Triazolam levels, BMI and Driver Score on the average reaction times for a truncated data set with the data from M2426, M2110 and M2524 removed against all participants (i.e. Truncated Data Set vs. Full Data Set).

When the scores of the three participants with the highest saliva concentrations were removed from the data set, the comparison demonstrated that the contribution of the Triazolam concentration to the increasing reaction times in the psychomotor tests dropped from highly significant ($p < .0001$) for the full data set, to just barely significant ($p < .05$) or insignificance for all tests in truncated data set.

Figure 6-13 graphs the mean response times for participants in the full and truncated data set for data at 80 and 120 minutes by dose group. M2426 and M2110 were randomly assigned to dose group F, receiving the capsules in the following Order: Session 1, placebo; Session 2 .250 mg, Session 3, 0.125 mg. M2524 was randomly assigned to dose group C: placebo, 0.125 mg, 0.250 mg. The impact of removing their 80 and 120 minutes data (drives 08 and 09) is obvious.

Figure 6-13: Comparison Reaction Times at 80 and 120 Minutes by Dose Group and Dose Level for the Full Data Set and the Truncated Data Set (with the data from the Outliers M2426, M2110 and M225 removed).



The impact of removing the Drive 08 and Drive 09 (Session 2, 80 and 120 minute) data of M2426 and M2110 from the full data set is obvious. The impact of dose level and Triazolam saliva level on reaction time is essentially eliminated. In Figure 6-14, it can be seen that values for the contribution of Triazolam saliva level in drug impairment on the three psychomotor tests drops from highly significant ($p < .0001$) to non significant or barely significant.

Figure 3-7 argued that the elevated saliva concentrations of two of these three participants may be caused by the medications they were taking concurrently competing for the mechanisms metabolizing Triazolam. Triazolam is rapidly absorbed and metabolized. Any mechanism that competes for the metabolizing enzymes will cause a rapid slowing of elimination and, hence, a rapid and unusual buildup of drug in the serum and saliva.

Figure 6-14: Summary Data from Figs 4-17 and 4.18 for Full and Truncated Data Set

Psychomotor test	Full Data Set		3 Outliers Removed	
	Coefficient	p.-val	Coefficient	p.-val
Scp mean rt -BMI	2.9	.01	.28	.004
Scp mean RT- DRI	9.3	.0003	8.2	.01
Scp mean rt - TRI	.39	**.0001**	.123	**.32**
M2s mean rt -BMI	17.5	.04	17	.06
M2s mean RT- DRI	38.2	.15	21	.16
M2s mean rt - TRI	3.5	**.0001**	1.5	**.19**
Srt mean rt -BMI	1.3	.32	1.3	.06
Srt mean RT- DRI	5.23	.19	2.1	.32
Srt mean rt - TRI	.56	**.0001**	.192	**.03**

As noted earlier, the Standard Continuous Performance Test (scp test) was chosen as the psychomotor test most applicable for intensive examination. It was selected because it was the only one of the tests that exhibits positive correlation with Body Mass Index, Driver Score and Triazolam concentration. In Figure 6-14, note that in the SCP test the probability value for TRI drops to NS after the "outliers" are removed. However, the P-Value for Simple Reaction Time (SRT) continues to be $p<.05$. The speculative implication is that decision-making requires higher levels of Triazolam to cause impairment, but simple reaction time tests are impaired at lower Triazolam concentrations.

6.6.2.5 Dose .125 and the Truncated Data Set

The other interesting observation from Figure 6-13 is that there are no changes in the reaction time data between the full and truncated data set for participants on the session they received the placebo dose and on the session they received the 0.125 mg dose. Figure 6-15 demonstrates that the Triazolam saliva levels of the three participants with the highest saliva levels at the 0.250 mg dose have normal and normally distributed saliva levels on the day they received the 0.125 mg dose.

Figure 6-15: Saliva levels for the full and truncated data sets.

Drive and Time	Partici-pant ID	Full Data Saliva Session 3 and 4 Dose .125	Ful Data Saliva Session 3+4 Dose .250	Partici-pant ID
Drive 3, 80 min	M2023	0	0	M4005
Drive 3, 80 min	M2029	0	12	M2322
Drive 3, 80 min	M2314	0	24	M2301
Drive 3, 80 min	M2315	0	25	M2315
Drive 3, 80 min	M2426	0	43	M2212
Drive 3, 80 min	M2504	0	46	M2504
Drive 3, 80 min	M4005	0	48	M2023
Drive 3, 80 min	M1909	22	49	M5011
Drive 3, 80 min	M2212	22	61	M1909
Drive 3, 80 min	M2007	28	64	M2029
Drive 3, 80 min	M2301	34	75	M2428
Drive 3, 80 min	M4003	43	90	M1902
Drive 3, 80 min	M1902	49	95	M2130
Drive 3, 80 min	M5011	53	95	M4003
Drive 3, 80 min	M2031	56	100	M2618
Drive 3, 80 min	M2110	57	100	M2031
Drive 3, 80 min	M2428	59	108	M2007
Drive 3, 80 min	M3417	59	127	M3417
Drive 3, 80 min	M2130	62	137	M2225
Drive 3, 80 min	M2618	76	142	F2320
Drive 3, 80 min	F2320	77	158	M2314
Drive 3, 80 min	M2322	88	195	M2524
Drive 3, 80 min	M2524	100	209	M2110
Drive 3, 80 min	M2225	101	289	M2426
Drive 4, 120 min	M2023	0	0	M4005
Drive 4, 120 min	M2029	0	29	M2322
Drive 4, 120 min	M2314	0	46	M2301
Drive 4, 120 min	M2315	0	46	M2315
Drive 4, 120 min	M2426	13	58	M2212
Drive 4, 120 min	M2504	14	62	M2504
Drive 4, 120 min	M4005	14	77	M2023
Drive 4, 120 min	M1909	17	77	M5011
Drive 4, 120 min	M2212	31	81	M1909
Drive 4, 120 min	M2007	35	81	M2029
Drive 4, 120 min	M2301	37	83	M2428
Drive 4, 120 min	M4003	42	103	M1902
Drive 4, 120 min	M1902	44	104	M2130
Drive 4, 120 min	M5011	49	105	M4003
Drive 4, 120 min	M2031	51	120	M2618
Drive 4, 120 min	M2110	54	122	M2031
Drive 4, 120 min	M2428	60	123	M2007
Drive 4, 120 min	M3417	70	125	M3417
Drive 4, 120 min	M2130	77	143	M2225
Drive 4, 120 min	M2618	79	144	F2320
Drive 4, 120 min	F2320	85	144	M2314
Drive 4, 120 min	M2322	86	175	M2524
Drive 4, 120 min	M2524	97	186	M2110
Drive 4, 120 min	M2225	109	312	M2426

From a pharmacological perspective, Figure 6-15 is highly suggestive of a mechanism competing for the metabolism of Triazolam. Assume substance A and B are competing for the same metabolic enzyme. If Substance A is in a substantial higher concentration or is more strongly attracted to the reaction site on the enzyme, it will crowd out and inhibit the metabolism of B. However, there will always be some available sites on the enzyme, and substance B will be metabolized at the rate constant of the available metabolic sites. That is OK if B is present in low concentrations, because the throughput rate is enough to metabolize B efficiently.

However, the throughput rate of B is a constant while A is present. So if B is available in a higher concentration, its metabolic degradation throughput rate is the same as when it is present at a low concentration. If the drug is also rapidly absorbed, metabolism falls behind absorption and the serum concentration reaches elevated levels.

This model explains the data seen in Figure 6-15, and supports the statement of M2524 at intake, (Figure 4-21) that he is taking no Rx or OTC medications. At the 0.125 mg dose level, M2426 and M2110 have low levels of Triazolam saliva but M2110 has the second highest concentrations at 80 and 120 minutes. However, on the day they took the 0.250 mg dose, M2426 went from almost lowest saliva Triazolam on the 0.125 dose to by far the highest Triazolam saliva and M2110

went from the middle of the pack to the second highest. Meanwhile, M2524's saliva Triazolam continued to be at the top of the cohort, as it had been at the 0.125 mg dose.

In summary, the impairment levels, correlated with the Triazolam saliva concentrations, support the Hypothesis 5 of competing metabolism, for two of the participants with the highest saliva Triazolam levels from the 0.250 mg dose, but not for the third. It seems probable that the Afrin nasal spray used by M2426 and the Cefaclor anti-bacterial used by M2110 are slowing the metabolism of Triazolam at the 0.250 mg dose and are responsible for their impaired reaction times at 80 and 120 minutes.

6.7 Summary of the Psychomotor Test Battery Data

The repetitive psychomotor tests provide insights into the time-course and individual aspects of the drug's impact. At a basic level, they are divided into two types. The Pursuit Rotary test and the Simple Reaction Time tests do not involve choices between alternatives. The other four tests involve choices. Of these, the Standard Continuous Performance (scp) is the only test that requires making a go-no go choice. It is also the only one of the tests in which all of the "Intervening Variables" make a significant contribution to the final drug impact. These are: Triazolam/Drug Dose, Body Mass Index, Driver Score, and Simulator Sickness score (SSQ p= .03 not shown).

At the dose level of 0.250 mg, when the participants with the three highest Triazolam concentration are removed from the database, only the Simple Reaction Test at dose level 0.250 mg continues to show significant ($p < .05$) impairment. At the 0.125 mg dose level, there is no change in average Triazolam saliva levels when the data points for participants with the highest saliva levels are removed from the data base. Likewise, there is no change in Mean Reaction Times for the SCP, SRT and M2S tests for participants receiving the 0.125 mg dose, even with the outliers removed.

The implication is that Triazolam at the higher therapeutic dose, 0.250 mg, reliably causes significant impairment in simple, non-choice tasks. However, impairment in tasks that require choice and "higher-level" processing may require high-levels of Triazolam in serum, reflected in saliva levels. Especially high levels of saliva Triazolam may be the result of OTC and prescription medications taken concurrently.

On the other hand, the saliva Triazolam levels, and the psychomotor performance scores, are very stable across all groups at the 0.125 dose level (see Figure 6-16 A and B). The implication is that impairment at the 0.125 mg dose is stable and not dependent on the participants who exhibit the highest Triazolam levels. The stable level of impairment associated with low doses may result in significant impairments in skills associated with tracking. In Figure 6-13, the stable RT impairments for the 0.125 mg dose seen for the 120 minute drives for the D-F dose groups may show up as driver performance impacts at the 0.125 mg dose in performances that require go-no dose decisions.

Figure 6-16A: Saliva Triazolam Concentrations for the Full and Truncated Data Set at 80 and 120 minutes

	Full Data Set		Truncated Data Set	
Drive	.125 mg dose	.250 mg dose	.125 mg dose	.250 mg dose
Drive 3, 8, 13 80 Minutes	41.1 pcg/ml	95.5 pcg/ml	39.5 pcg/ml	76.1 pcg/ml
Drive 4, 9, 14 120 Minutes	44.3 pcg/ml	106.1 pcg/ml	42.9 pcg/ml	89.2 pcg/ml

Figure 6-16B: Average RTs for three prototypical psychomotor tests for the full and truncated data sets

Dose	Psychomotor Test	Full Data Mean RT	Truncated Mean RT	Pct Change
Dose 0.125	Average of m2s MeanRT	1375.22	1334.94	-0.03
Dose 0.125	Average of srt MeanRT	242.48	243.54	0.00
Dose 0.125	Average of scp MeanRT	392.73	392.01	0.00
Dose 0.250	Average of m2s MeanRT	1718.08	1545.26	-0.10
Dose 0.250	Average of srt MeanRT	281.00	253.71	-0.10
Dose .025	Average of scp MeanRT	430.27	411.63	-0.04

6.8 Driver Performance in the Driving Simulator

As explained in Section 5 of this paper, much of the data analysis of drug impact on driver performance was conducted by Mr. Christopher Dietz under the supervision of Dr. Linda Boyle, Principal Investigator, at the University of Washington. Their primary statistical tool is the "R" statistical package and their analysis evaluates a level of interactions among the variables that is not possible using the statistical tools in Excel.

Project PATH participants completed 15 experimental drives in the high-fidelity bus simulator. The drives were conducted in three sessions of five drives. In each session, four drives were conducted at 40 minute intervals. The experimental sessions were scheduled for immediately after the last professional drive of the week for each of the drivers, with a requirement that there must be at least two days before the driver's next bus route. The randomly-assigned experimental dose was taken immediately following the first drive of each experimental session. The 40 minute between-drive interval was chosen to observe the early effects of the drug, at 40 minutes, and to bracket the expected time of maximum drug impact, reported in the experimental literature to be at approximately 90 minutes post dose. Each driver returned the next day to repeat the first drive of the previous day. The performance on the next-day drive was compared to the performance on first (pre-dose) drive of each session, to determine whether driver performance had returned to baseline or whether the drug impacts lasted longer than a normal period of sleep.

This section of the Discussion reviews the pre-dose to next-day findings, and the findings of the drug impacts on the first four drives on each of the three sessions. The analysis consists of the dose-related impact of Triazolam on four simple driving skills:

- Driving straight in lane vs. weaving in lane while driving straight;
- Following a smooth curve vs. weaving back and forth in lane while following a curve;
- Steering into the adjacent lane to avoid an obstruction; and
- Stopping at a stop light that is visible from a long distance.

Steering Entropy, a measure to quantify the number of small steering movements made by the drivers, is used to indicate steering control. The test segments of the drives were well integrated into each of the approximately 10-minute experimental drives. The contribution of the Intervening Variables identified in the psychomotor section of this discussion are included in each analysis.

6.8.1 Same-Day Next-Day Drive Comparisons

The "Standard Deviation of Lateral Position" (SDLP, also known as the Standard Deviation of Lane Position) is the driving performance measure used to determine whether the pre-dose driver performance had returned to baseline by the next-day drive. SDLP is a measure of the amount the driver weaves back and worth across the center line of the lane. It is calculated as the Standard Deviation of the amount of lateral distance from the center line over a stretch of straight road, rather than the average lateral deviation. The SDLP value is always positive and also occasional large deviations have less impact on the Standard Deviation than on the Average.

As explained in Section 5.1 of this paper, there were no residual effects of any of the Triazolam doses that were evident in the SDLP measures. This agrees with the finding in Figure 6-9, that the next-day psychomotor scores had returned to baseline at all dose levels. Tables 5-5 and 5-6 demonstrate that none of the measures on the next-day drive differed from the corresponding scores on the pre-dose, baseline drive. That is, there was no residual effects on SDLP between pre-drug and next-day SDLP measures for SDLP x dose, or for SDLP x BMI score, SDLP x Simulator Sickness (SSQ) score, SDLP x Driver Score, SDLP x Dose Order, and SDLP x dose with BMI interaction.

6.8.2 SDLP – Dose Impact on Weaving Back and Forth While Driving Straight

The analysis in Section 5 Table 5-10 and 5-11 determined that there was a significant drug impact on SDLP for the 0.250 mg dose that was correlated with time-since-dose administration. There were no significant dose-effects on SDLP for the 0.125 or the 0.000 (placebo) dose.

In Table 5-1, there were also interacting effects with dose order, and those participants assigned to Dose Order E and F had statistically lower SDLP scores and exhibited less weaving than participants randomly assigned to Dose Orders A, B, C or D. This finding

is in disagreement with the Dose-Order graph in Figure 6-12 for the psychomotor data. That chart shows that the increase in Reaction Time in the psychomotor tests correlates with the interaction of BMI and Driver Score, with Dose Groups E and F being the second and third most impaired on the psychomotor tests, after the participants assigned to Dose Group D.

The other finding from Table 5-10 and 5-11 is that speed is the most significant contributor to SDLP, more than dose over time. The coefficient for speed in Table 5-11 is 0.071 vs the coefficient for dose 0.250 of 0.003. The coefficients are multiplied by the corresponding values (speed in m/s and time in minutes-since-dose) to calculate the average impact across all drivers at that dose. The SDLP by speed estimates developed in Table 5-12 are presented in Figure 6-17.

Figure 6-17 SDLP interactions with dose and time per Table 5-7

Speed	Time (Minutes)	Dose	SDLP (meters)	SDLP (inches)
30 mph	120 minutes	0.000 mg	0.211 meters	8.3 inches
30 mph	120 minutes	0.250 mg	0.302 meters	11.9 inches
45 mph	120 minutes	0.000 mg	0.339 meters	13.03 inches
45 mph	120 minutes	0.250 mg	0.486 meters	19.13 inches

For this Discussion, it became useful to further to explore the interactions among dose, saliva Triazolam concentration, speed and dose group. This examination helps to explain the conditions under which Triazolam impacts driving performance in the simplest driving task, driving straight on a road with no traffic.

6.8.2.1 The Overall SDLP Effect

The calculations in Table 5-10 and 5-11 do not easily lend themselves to graphing because the raw values were converted in the R statistical package to their logarithms to normalize the distributions for calculation purposes. However, the raw data before conversion is useful for constructing a picture of the SDLP conclusions.

Figure 6-18 depicts the average SDLP values by drive and dose. The filled circles for the data points for the placebo (0.000 mg) and the 0.125 mg Triazolam doses indicate that none of the values are significantly different from the pre-dose (0 minute) values for drives at that dose. The open circles for the second, third and fourth drive on the day those drivers received the 0.250 mg dose indicate that the average SDLP values are significantly (p. <.05) higher than the initial SDLP (time 0, pre-dose) values.

Figure 6-18 graphs the averages for all drives and all doses. Consequently, it does not depict higher level of Lateral Deviation associated with the higher speeds, e.g. when SDLP was measured on a segment of the roadway with a speed of 45 MPH. Figure 6-18 also does not depict the lower level of Lateral Deviation associated with drives when SDLP was measured over a segment of the road with a speed limit of 30 mph.

The SDLP data was also graphed by driver speed by dose, as shown in Figure 6-19. Figure 6-19 shows the average driver speeds by dose for each of the twelve road segments on which SDLP was measured. These segments were chosen because there was no programmed traffic on these road segments. Since much of the programmed traffic were intended to pose challenges to the operators, it was determined to only consider SDLP measured on road segments with no traffic whatsoever. That limited the choices of road segments. In future experiments of this type, it is recommended that SDPL be calculated twice for each drive, on a higher speed road segment and also on a lower-speed road segment. That design will give a direct comparison of the drug impact on weaving in lane as influenced by speed.

Figure 6-18: Standard Deviation of Lateral Position for All Speed and Doses

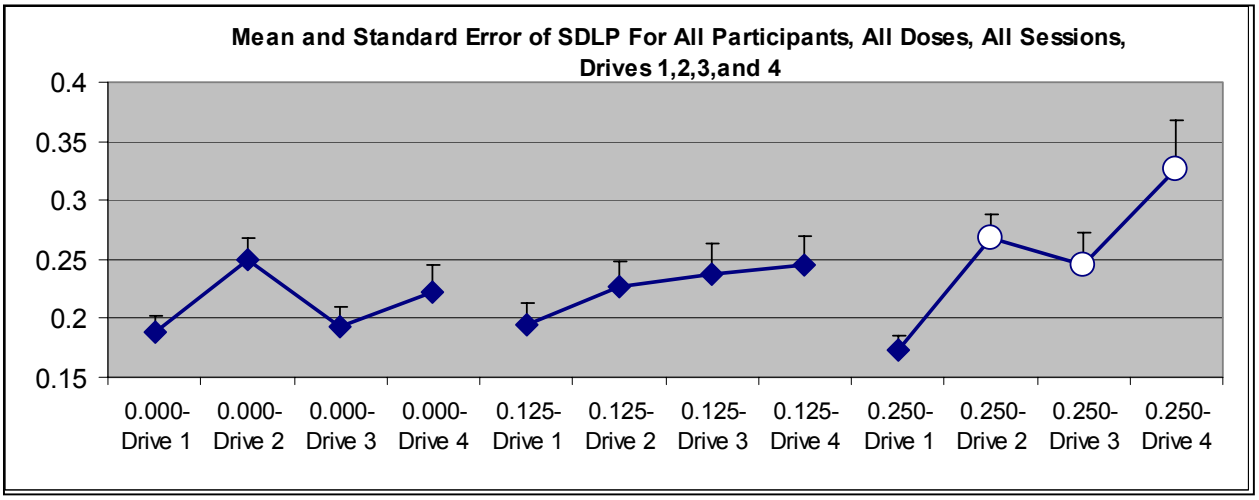
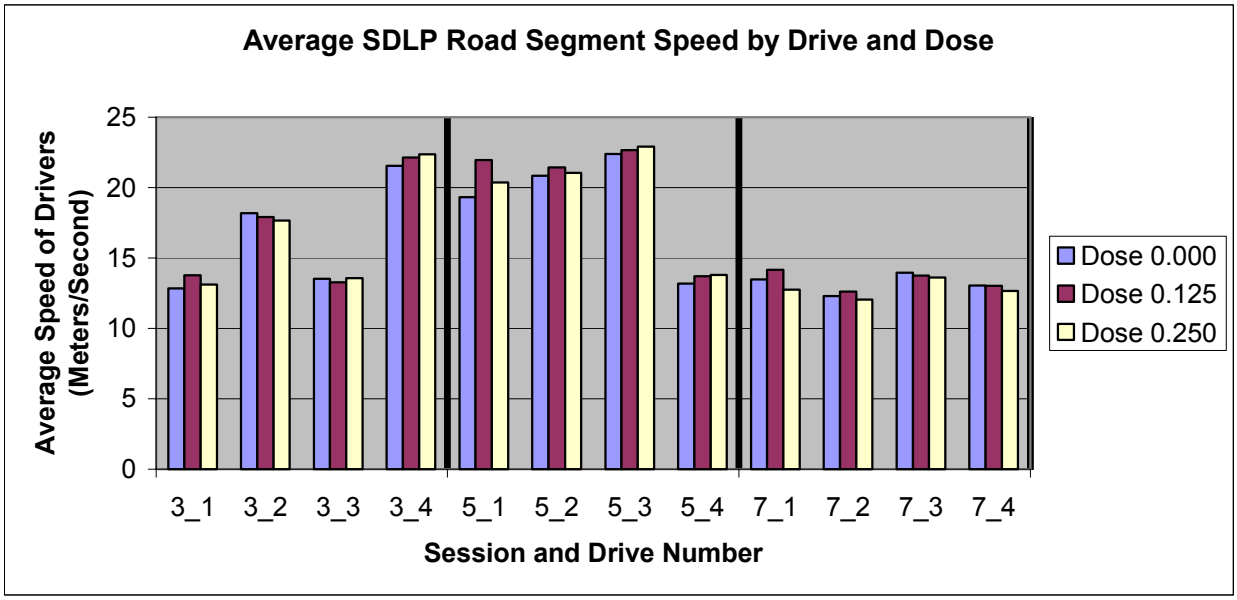


Figure 6-19: SDLP Road Segments by Average Driver Speed by Dose



In order to provide as direct a comparison as possible of the influence of driver speed on weaving and on drug effect, the SDLP data was sorted by speed and by drive number. The drive numbers used in Project PATH are shown below the columns in Figure 6-19. Session 3 was the first experimental session because Sessions 1 and 2 were the two training drives. Session 4 was the next-day drive after Session 3. Session 5 was the second experimental session and Session 7 was the third experimental session. Drive 7-4 was the last drive of Session 7, with Session 8, the last next-day drive being the last drive of the project for each of the participants.

It can be seen that the last drive of Session 3 and the first three drives of Session 5 were the four drives where SDLP was measured on the (virtual) road segments that had 45 MPH speed limits. The third drive of Session 3, the fourth drive of Session 5 and all of Session 7 drives were road segments with a 30 MPH speed limit. The road segment for Session 3 Drive 2 (3-2) has a 35 mph speed limit.

In Figure 6-20, SDLP for the higher speed-lane data was aggregated from the segments 3-4, and 5-2 and 5-3. SDLP for the lower-speed lanes was aggregated lanes 3-3, 5-4, 7-2, 7-3 and 7-4. Data from the pre-dose lane segments 3-1, 5-1 and 7-1 was kept aside for a non-drug baseline. The data is plotted in Figure 6-20.

Figure 6-20: Interactions of Drug Dose, Speed and SDLP

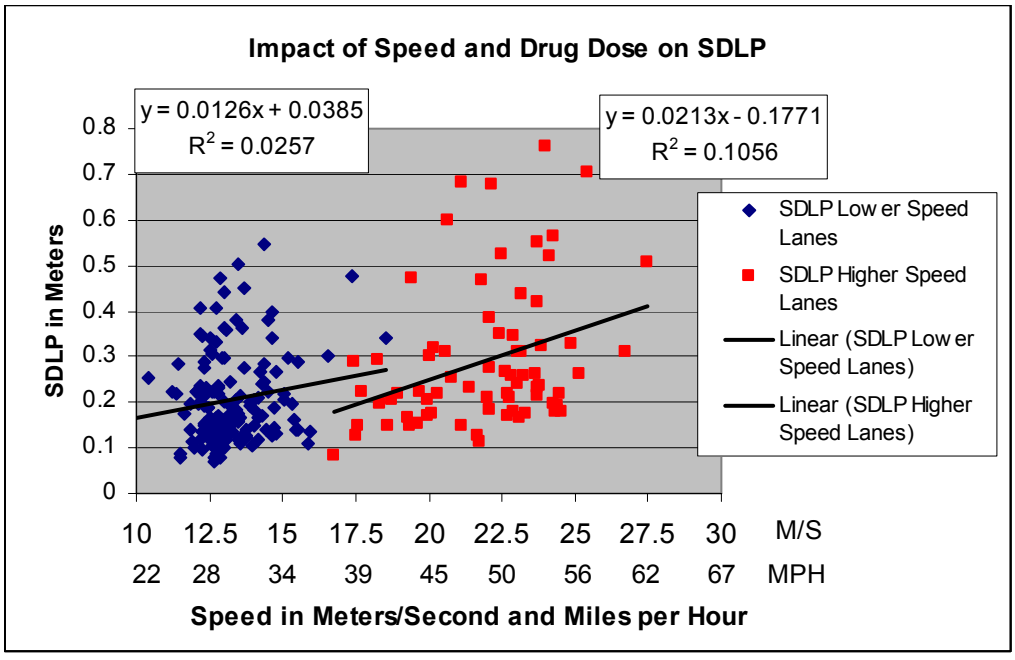


Figure 6-20 indicates that SDLP increased at the higher speed, and there is an implication that the rate of increase in SDLP with speed may be higher at higher speeds than at lower. In Figure 6-20, it is not possible to determine which of the points represented drivers who had received the placebo, the 0.125 or the 0.250 mg dose.

To further explore the relationships of SDLP, Triazolam dose and speed, the SDLP data was sorted by lane speed and linear regression calculations were performed to separate the contribution of speed, of Triazolam saliva concentration, and of the other intervening variables discussed earlier in the paper. These included BMI, Driver Score, and Simulator Sickness.

After sorting the SDLP data by speed and eliminating Drive 1, the pre-dose drive, from each of the three sessions, the data was again analyzed with the multiple linear regression capabilities of Excel. The analysis indicated that the SDLP data for the low-speed lane segments (30 mph) still included a significant contribution of speed. That is, the faster a person is driving at low speeds (roughly 20 to 40 MPH in this experiment), the more Lateral Deviation (weaving in lane) is created by the increment of speed regardless of drug contribution. The drug impact contribution is in addition to the speed contribution, and they are roughly equal within the low-speed range that these drivers drove given the speed limit constraints.

However, in the higher speed lanes (drivers in a 45 MPH lane), the no-drug SDLP is constant regardless of speed within the range of roughly 40 to 65 MPH. That means that, above a nominal speed of about 45 MPH, SDLP appears to be statistically constant regardless of speed in the range 45 to 65 MPH under no-drug conditions.

However, within the higher speed range, roughly 45 to 65 MPH, the amount of lateral deviation is highly influenced by Triazolam drug level. Within that range, SDLP increases at a rate consistent with triazolam drug level. The baseline (no drug) SDLP is .249 meters at 45 MPH. As the concentration of Triazolam increases post-dose, the amount of weaving in lane increases in proportion to drug concentration but without regard to speed of the vehicle. The zero-dose SDLP at and above 45 mph is calculated to be +/- 9.8 inches, while the SDLP for drivers with saliva Triazolam concentration of 200 pcg/ml is calculated to be 17.7 inches.

Given a 104 inch wide bus, there are 11 inches between the lane markers and the left and right side of the standard 144 inch driving lane. At any speed up to 45 MPH, the driver with no drug load does not encroach on the adjacent lane (SDLP +/ 9.8 Inches). However, the driver having ingested a normal therapeutic dose of Triazolam before coming on shift encroaches on the adjacent lane by almost 7 inches (+/- 17.7 inches) at 45 MPH.

The graphs and calculations for these estimates are found in Figure 6-21 on the following page.

Figure 6-21: Estimates of SDLP for Saliva Triazolam concentrations of 0 to 200 pc/ml and speeds from 15 to 25 meters/second (34 – 56 MPH).

SUMMARY OUTPUT

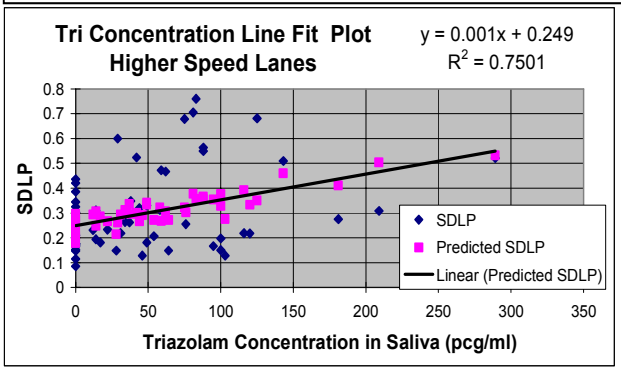
Regression of SDLP on Triazolam Concentration and Speed
Higher speed lanes on which SDLP was measured

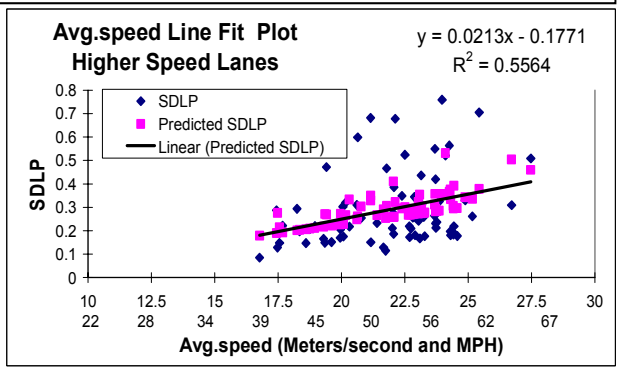
Regression Statistics	
Multiple R	0.43572
R Square	0.189852
Adjusted R Square	0.166369
Standard Error	0.140891
Observations	72

ANOVA

	df	*SS*	*MS*	*F*	*ignificance F*
Regression	2	0.320972	0.160486	8.084804	0.000701
Residual	69	1.369672	0.01985		
Total	71	1.690644			

	Coefficients	*Std Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*ower 95.0%*	*pper 95.0%*
Intercept	-0.073359	0.161633	-0.453865	0.651351	-0.395808	0.249089	-0.395808	0.249089
Tri Conc in Saliva	0.00084	0.000314	2.678262	0.009243	0.000214	0.001466	0.000214	0.001466
Avg.speed (m/s)	0.015053	0.007488	2.010345	0.048305	0.000115	0.02999	0.000115	0.02999





Estimated SDLP , Higher Speed Range, Impact of Triazolam Concentration plus Speed						
Tri Concentration	SDLP (m)	20 m/s	22.5 m/s	25 m/s	45 MPH	56 MPH
Tri Conc 0	0.249	0.249	0.302	0.355	9.8 in	14.0 in
Tri Conc 50	0.299	0.299	0.352	0.405	11.7 in	15.9 in
Tri Conc 100	0.349	0.349	0.402	0.455	13.7 in	17.9 in
Tri Conc 150	0.399	0.399	0.452	0.505	15.7 in	19.9 in
Tri Conc 200	0.449	0.449	0.502	0.555	17.7 in	21.9 in

Estimated SDLP, Higher Speed Range, Contribution of Speed Alone			
Avg Speed	SDLP (m)	MPH	SDLP (in)
15 m/s	0.142	34	5.61
17.5 m/s	0.196	39	7.70
20 m/s	0.249	45	9.80
22.5 m/s	0.302	50	11.90
25 m/s	0.355	56	13.99

6.8.2.2 Individual and Group Differences in SDLP, Dose and Experimental Session

An objective of this study has been to try to identify and understand the unique human factors that result in the extreme performance decrements seen in a few of the participants. Section 4.7 of this report reviewed the individual characteristics of the three "outlier" participants who had the highest concentrations of Triazolam in their saliva. It was assumed that the saliva concentration of Triazlam, in interaction with the Body Mass and Driver Skill Index of the participant, would predict and account for their psychomotor performance relative to other peers. These "outlier" participants, M2110, M2524 and M2426, contributed the most impaired psychomotor scores on the Reaction Time tests on the day they received the 0.250 mg Triazolam dose. By way of contrast, their psychomotor test scores were equivalent or better than the other participants on the day they received the 0.125 mg and the placebo doses. Moreover, their Mood scored were not different then the whole cohort of participants at any dose.

A review of the medical information provided by two of the three participants during enrollment provided a presumptive explanation for their elevated saliva Triazolam levels. M2426 has a current prescription for Afrin nasal spray, the metabolism of which might compete for the degradation of Triazolam. M2110 has current prescription for Cetachlor, an anti-biotic, and Zyrtec, an over-the-counter antihistamine. Either or both might compete for the metabolic sites where Triazolam is degraded. However, M2524 reported that he was taking no medications, so his outlier Triazolam levels and psychomotor scores remain unexplained.

Section 5.2.5 of this report demonstrated that the average SDLP measurements from two of the participant Dose Groups E and F were significantly lower (less impaired) than the averages of the other four Dose Groups. The PATH team examined the individual characteristics of the participants assigned to all dose groups and determined that the more interesting question was why the participants in Dose Groups A and D had higher SDLP scores than participants in the other four dose groups.

Figure 6-22: Participants with the highest SDLP scores, their Triazolam saliva levels and Dose Groups.

Simplified ID	dose.order	dose	Saliva	SDLP
M1902_3_2	A	0.25	81	0.399624
M2029_3_2	D	0.25	0	0.481816
M2029_3_4	D	0.25	81	0.705313
M2225_3_4	D	0.25	143	0.509193
M2314_7_4	B	0.25	144	0.404827
M2322_3_2	A	0.25	0	0.515271
M2322_3_4	A	0.25	29	0.599324
M2426_5_3	E	0.25	289	0.521151
M2426_5_4	E	0.25	312	0.396229
M2428_3_4	A	0.25	83	0.759823
M2504_3_4	D	0.25	62	0.467112
M3417_3_4	D	0.25	125	0.681663
M5011_5_3	F	0.25	75	0.679004
M2029_7_3	D	0.125	0	0.473198
M2029_7_4	D	0.125	0	0.546944
M2031_3_4	B	0.125	42	0.524085
M2225_7_2	D	0.125	87	0.450413
M2322_5_1	A	0.125	0	0.434143
M2322_5_2	A	0.125	88	0.550253
M2322_5_3	A	0.125	88	0.563968
M2428_5_3	A	0.125	59	0.472083
M2618_7_3	A	0	0	0.47439
M2322_7_4	A	0	0	0.502285
M2301_3_1	C	0	0	0.409557
M2301_3_4	C	0	0	0.420611
M2212_7_2	A	0	0	0.441921
M2023_3_4	F	0	0	0.436471
M1902_7_2	A	0	0	0.404699

Figure 6-22 shows the SDLP scores, doses, dose order (dose group) and participant IDs of the participants with the highest SDLP scores at the Triazolam doses of 0.250 mg, 0.125 mg and placebo. It is obvious that participants randomly assigned to Dose Groups A and D dominate the roster of highest SDLPs. There are 28 data points in Figure 6-22. Of these, participant M2322 has 6 of the highest SDLP scores and M2029 has 4 of the highest scores. In total, participants assigned to Dose Group A have 12 of the 28 highest SDLPs and participants assigned to Dose Group D have 8 of the highest scores. Participants assigned to the other four Dose Groups each have 2 of the highest SDLP scores.

In Chapter 4, the thesis was developed that participant impairment on the psychomotor battery was determined by their serum Triazolam concentration, which corresponded to each

individual's saliva Triazolam level. The impact of the Triazolam on their psychomotor performance was seen to be modified by their Body Mass Index and skill as a driver. The performance of individuals on the psychomotor battery was seen to be rational and explained by physical principals that could be measured.

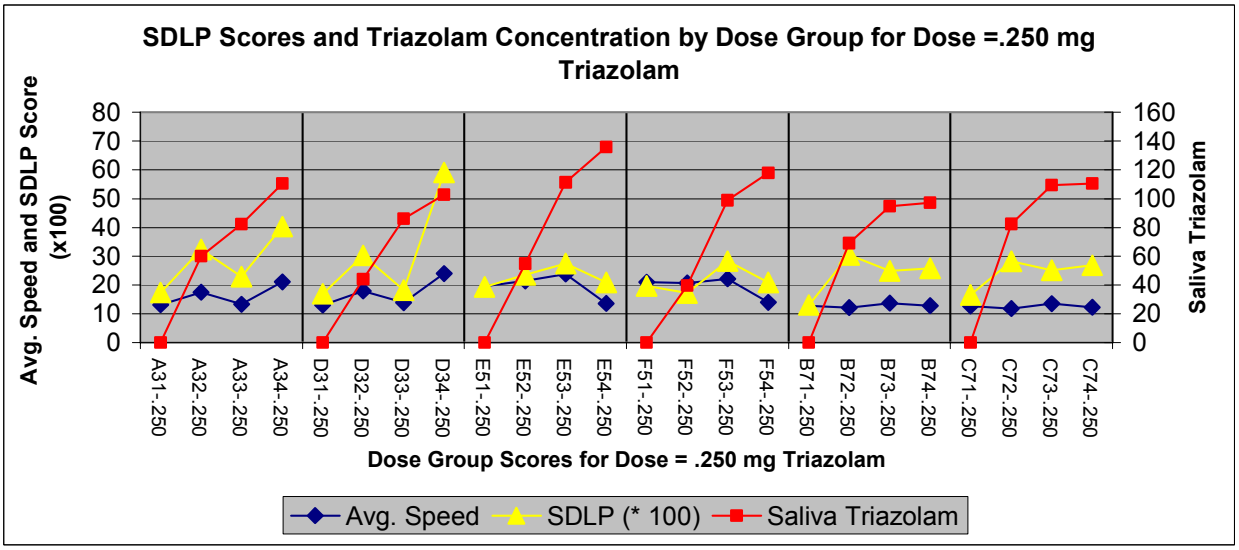
The question at hand is whether the driving performance, as measured by the Standard Deviation of Lateral Position, can similarly be explained as a combination resultant of Saliva Triazolam level, Body Mass Index and Driver Skill, and possibly the Simulator Sickness Quotient (SSQ). The answer appears to be that SDLP cannot be so easily explained on an individual basis.

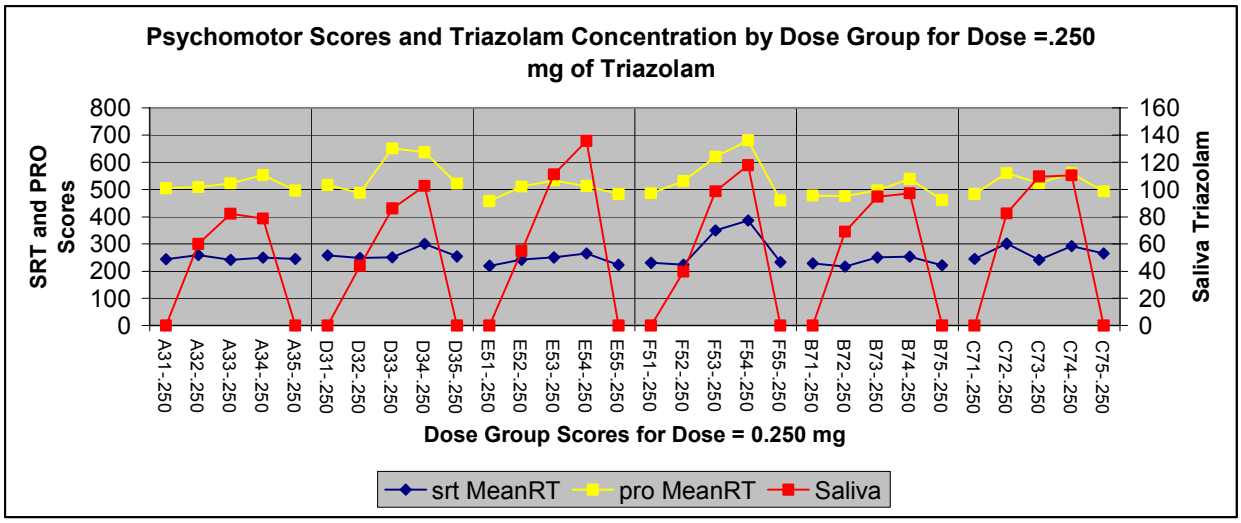
In Figure 6-21, the participants with the highest SDLP scores are M2428, M2029, M2322 and M3417. M2429 has the highest SDLP reading (.759 meters of weave) but his saliva Triazolam concentration is only 83 pg/ml. M2029 is next highest, with a SDLP of .705 meters and a saliva Triazolam of 81 pg/ml. M3417 has an SDLP of .681 and a saliva Triazolam of 125 pg/ml, and M2322 has a SDLP of .599 meters and a saliva Triazolam of 29 pg/ml.

By way of contrast, the three participants with the most impairment on the psychomotor tests and the highest concentrations of Triazolam in their saliva had comparatively lower SDLP scores. Of the three, only M2426 had an SDLP score among the top scores, .521 meters at a saliva Triazolam concentration of 289 pg/ml. The other two participants with the highest Triazolam concentrations, M2110 and M2524, were very little impaired in their driving ability at that concentration. M2110 recorded an SDLP of .339 at a Triazolam concentration of 186 pg/ml and M2524 had an SDLP of .236 meters at a saliva Triazolam concentration of 175 pg/ml.

Figure 6-23 A and B compare the pattern of SDLP scores by Dose Group against the pattern of psychomotor scores by Dose Group on the experimental sessions of which individuals in those Dose Groups received the 0.250 mg dose of Triazolam. Individuals assigned to Dose Groups A and D received the 0.250 mg Triazolam dose during the first experimental session. In Figure 6-23 A, it is clear that Dose Groups A and D had the highest recorded SDLP scores. However, in Figure 6-22B, it is seen that individuals in Dose Group A showed only low levels of psychomotor impairment while individuals in Dose Group D showed high levels of impairment. In Figure 6-23A, individuals in Dose Groups E and F received the 0.250 mg dose in their second experimental drive, and were the least impaired among any of the groups. However, in Figure 6-23B, individuals in Dose Group F show the most impairment in their psychomotor scores. Finally, individuals in Dose Groups B and C received the 0.250 mg dose on the third experimental session. Their SDLP scores and their psychomotor scores both indicate moderate levels of impairment. (Note that Figure 6-23B includes the psychomotor scores on the next-day testing as well as the scores on the day the 0.250 mg dose was received).

Figure 6-23 A and B: Comparison of SDLP against Triazolam saliva concentration and Psychomotor scores against Triazolam saliva concentration by Dose Group



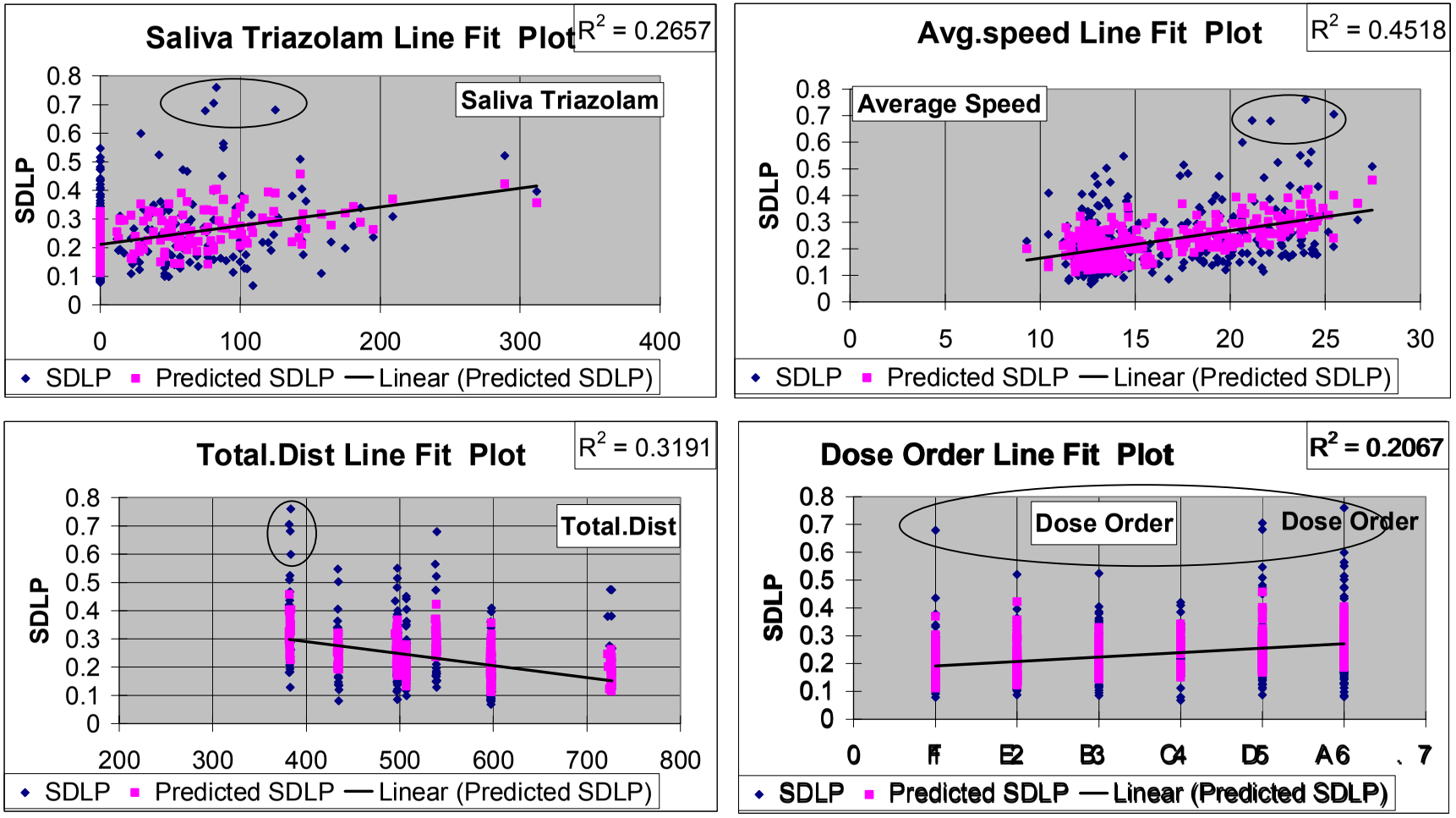


There appear to be no obvious answers to the questions posed by pattern of SDLP impairments seen for the Dose Groups, or for the reason that Dose Group F on the psychomotor testing (and to a lesser extent D) have psychomotor impairment scores higher than the other four groups.

Figure 6-24 presents the regression line fit plots for the four experimental variables that have statistical significance in the Excel multiple regression equation (P<.01) when regressed against SDLP. Dose Order accounts for the smallest amount of variance, followed by Saliva Triazolam concentration. SDLP increases at higher driving speeds and decreases when measured along a longer stretch of road.

However, from the regression calculation (not shown), these variable in combination account for approximately 30% of the total variance in the data ($F = 15.5$, $p<10^{-8}$, Adjusted $R = .284$). The intervening variables Body Mass Index, Driver Score and Optokenetic Score, shown to be useful in explaining psychomotor impairment, have no predictive power in the SDLP regression ($P = .68$, $.98$ and $.56$ respectively, not shown).

Figure 6-24 – Variables that contribute significantly to the generation of lane weaving (SDLP) in the driving simulator



Moreover, the review of medication indication provided no useful insights. We are left with the conclusion that idiosyncratic individual differences are responsible for the extremely high SDLP scores circled in Figure 6-24.

It would seem that, for some individuals, relatively low concentrations of Triazolam, when driving at higher speeds on short stretches of roadway, can result in weaving in lane of as much as +/1.75 meters.

6.9 SDLP While Driving Curves

The previous section described the variables that resulted in increased weaving and diminished steering control by drivers. Drivers exhibit more weaving on short stretches at higher speeds (higher SDLP scores), and Triazolam magnifies all of those factors.

This section discusses the findings of Section 5.4, SDLP and Steering Entropy while Driving Curves.

Steering Entropy, a measure defined by Natayama et al[52], is an index of the number of small steering corrections made by the driver and, hence, is a measure of the amount of steering work exerted by the driver. Drivers with a higher entropy score are making a higher number of small steering corrections.

A portion of the third drive of each experimental session required the participant to drive the simulated bus around a cloverleaf curve from a rural road to the highway. All three curves had the similar radius and speed limit to provide an equivalent driving scenario on which to measure steering control. However, the curve on the third drive of the first experimental session was a right-turning curve while the curves on the third drive of the second and third experimental session were left-turning curves. Drivers may use slightly-different techniques while drive left-turning curves as against right-turning curves since they are better able to see the edge of the road out of the driver's side window for the left-hand curve. Therefore, the curve-following data was analyzed separately for the two left-curves compared to the one right curve, and the data was also analyzed separately for each curve.

In this PATH project, the curve-following test utilizes a more standardized driving course than the SDLP straight-driving courses reported in Section 5.2 of this report. The data reported in Section 5.2, and summarized below in Figure 6-25, suggests that the participant performance may result from an adaptation to the Triazolam dosage.

In Figure 6-25, for the right-hand curve in Session 1 Drive 3, there is an inverse relationship between SDLP and Steering Entropy. That is, the drivers at the 0.250 mg dose have the largest SDLP (weaving) and the lowest Steering Entropy (small steering maneuvers). Both the SDLP and the Steering Entropy scores are statistically different ($p<.05$) from the dose 0.000 SDLP and Entropy scores. The participants who have

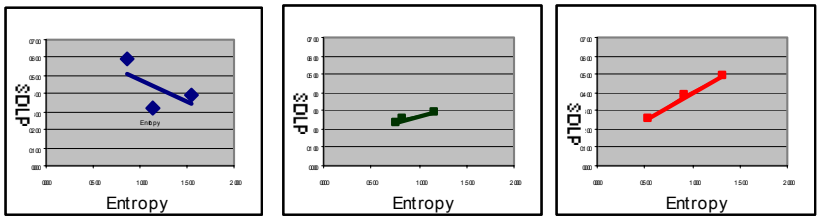
received the 0.250 dose are making large looping curves as they negotiate the turn. This is the classic profile for an inebriated driver.

The drivers negotiating the left-hand turn on Session 2 Drive 3 exhibit little impairment. The SDLP values for doses 0.000, 0.125 and 0.250 and essentially equal, as are the Steering Entropy scores. None of the scores are statistically significant. In contrast, the drivers negotiating the left-hand curve on Session 3 Drive 3 show a positive relationship between SDLP and Steering Entropy. The SDLP scores increase about by dose, but the .2 meter SDLP increase is not significant. Meanwhile, the steering entropy scores also increase significantly by dose, ($p<.05$ for dose 0.250 mg), indicating that the operators are making more small steering corrections.

Figure 6-25: Relationship between SDLP and Steering Entropy by Dose and Experimental Session

Relationship of Steering Entropy and SDLP for Curve Following

	Session 1 Drive 3 Right-Hand Curve		Session 2 Drive 3 Left-Hand Curve		Session 3 Drive 3 Left-Hand Curve	
	Steering Entropy	SDLP	Steering Entropy	SDLP	Steering Entropy	SDLP
Dose .000	1.555	0.391	0.823	0.253	0.540	0.257
Dose .125	1.137	0.317	1.177	0.289	0.913	0.379
Dose .250	0.875	0.590	0.766	0.233	1.334	0.487



The interpretation would be that, by the time the participants have entered the simulator for the third experimental session, all participants have driven in the simulator for ten experimental drives and have had either one or two sessions with Triazolam at 0,125 or 0.250 mg doses.

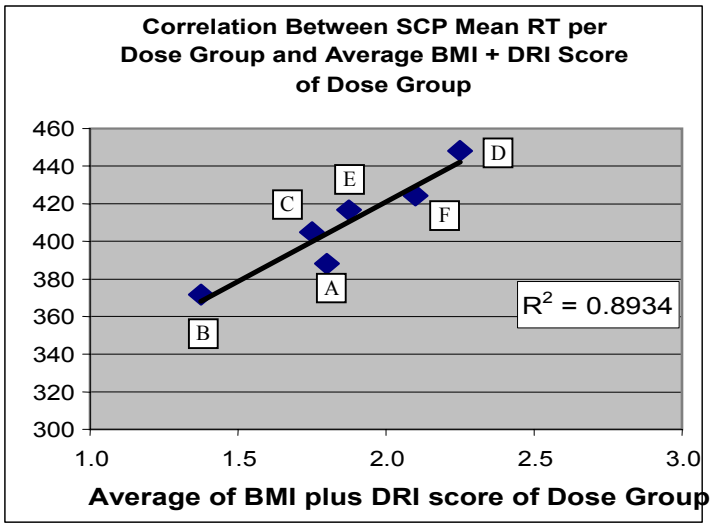
By the third experimental session, the implication would be that any dose-response relationship represents the drug effect on experienced uses rather than novice users. If that is the correct interpretation of the data from Session 3, the indication would be that even in experienced drivers and experienced uses, Triazolam at the 0.250 mg dose increases weaving in a curved lane by as much as 0.2 meters (7.8 feet). This even though drivers are performing an increased number of small steering adjustments to maintain lane position.

6.9.1 Influence of Driver Skill and Body Mass Index on Curve Following

Above in Section 6.8.2.2, the PATH team was not able to find a correlation between SDLP while driving straight and Body Mass Index or Driver Score (assumedly a surrogate for driver skill). However, the analysis of SDLP is complicated because the driving lanes on which SDLP was measured varied in length and speed limit.

The analysis of curve following SDLP and Steering Entropy is less complex because the driving distance and speed limits are equal and only the third drive in each of the three experimental session was studied.

In the analysis of Steering Entropy and SDLP reported in Section 5.4, participants assigned to Dose Order C were found to have a significantly higher Steering Entropy than drivers assigned to other Dose Groups (Table 5-21) while driving the left-hand curve in experimental sessions 2 and 3. Body Mass Index and Driver Scores were found to be significant modifiers of SDLP and Entropy for Session 3 Drive 3.

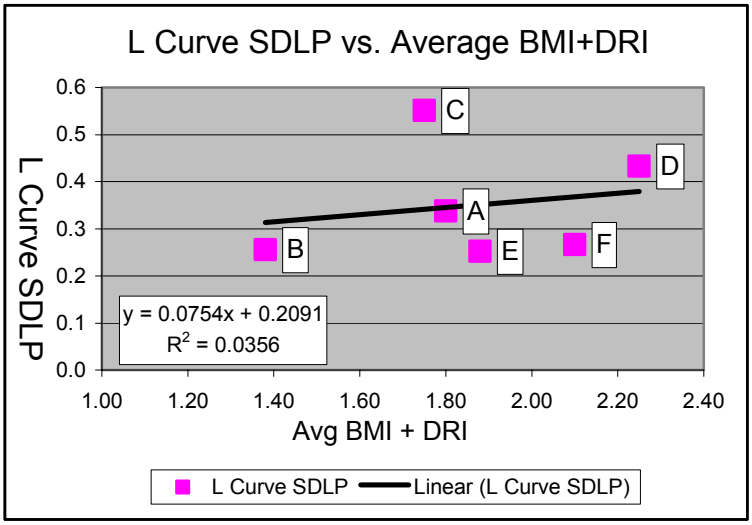


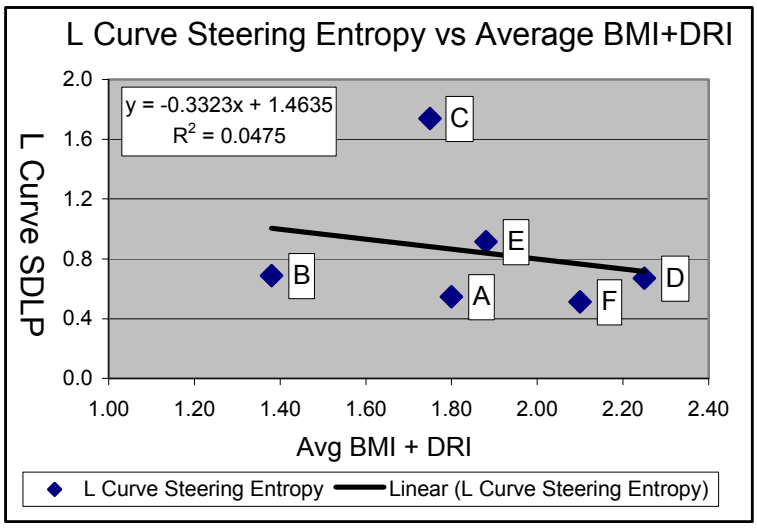
Earlier in Section 6.6.2.3, the Figure shown again to the left presented the correlation between Mean Response Time for the Standard Continuous Performance (SCP) psychomotor test and the composite BMI-SDLP scores calculated for each Dose Group. This graph supported the counterintuitive finding from the psychomotor testing, that impairment was greater in high Body Mass participants and high Driver Skill participants.

It was decided to test the hypothesis that impairment wold be predictably modified by Body Mass and Driver Skill in the curve-following driver tests. This was done by correlating the curve-following SDLP scores and the Entropy Scores against the composite Body Mass Index and Driver Score scores developed in that section.

In Figure 6-26, it can be seen that Left Curve SDLP and Left Curve Steering Entropy, correlated against composite BMI + Driver Score, both sort in the same order as the psychomotor scores graphed in Section 6.6.2.3.

Figure 6-26: Left Curve SDLP and Left Curve Steering Entropy Correlated Against Composite Driver Score and Body Mass Index





Group B, with the lowest BMI and Driver Score, shows the least SDLP and the most Steering Entropy, i.e. least impairment. Dose Group D, with the highest composite BMI and DRI score, shows the most impairment (highest SDLP and lowest Steering Entropy). Between those anchors, SDLP and Entropy scores sort in the order C-A-E-F. The psychomotor scores sort in order A-C-E-F. However, the SDLP and Entropy scores for Dose Group C are very elevated relative to their psychomotor scores so that fact that this group sorts before Group A rather than after Group A seems of little importance.

In summary, it seems that, in the relatively controlled driving situation over which lane following SDLP and Entropy were measured, driving performance is predicted from a composite score representing the interaction of driving skill and body mass index.

As with the findings in 6.6.2.3, the findings are counterintuitive. Dose Groups that contain drivers with the highest average Driver Score Index (most skillful) are also the Dose Groups that show the **most** drug impact rather than the least. Likewise, Dose Groups that contain drivers with the highest BMIs are also the Dose Groups with that show the **most** drug impairment rather than the least.

The disparate impact on the more skilled drivers is counterintuitive because one would expect the higher degree of driving skill to counteract the debilitating drug impact. The disparate impact on drivers with higher BMIs is counterintuitive because participants

with higher BMIs have lower saliva Triazolam concentrations, and presumably lower blood plasma levels. Common sensibly, they would be less impacted by the drug if the impact is related in a positive way to blood serum concentration.

Derry et. al.[57]. documented a possibly similar disparate impact of Triazolam on participants with higher BMIs. These researchers found that psychomotor test scores of obese participants following a second dose of Triazolam showed more impairment in the psychomotor test battery the normal-weight subjects. This was different than test results from one week earlier, when there had been no significant difference in psychomotor test scores by BMI following the first dose of Triazolam. In Derry's study, the psychomotor scores of the obese participants were significantly elevated in the second week relative to their scores of the first week, whereas the psychomotor scores of the normal-weight participants were significantly but less elevated on the return visit. Derry had no explanation for the basic question of why the psychomotor scores of the obese groups were not different from the beginning, since it had been hypothesized that the Triazolam dose would be more diluted in the higher BMI subjects and so result in less impairment.

However, the finding that curve-following SDLP is higher in drivers with higher Driver Scores is consistent with the PATH psychomotor score findings. In general, Driver Score was not a statistically significant variable in the PATH psychomotor test results. However, as seen in Figure 4-17 in this study, Driver Score was significantly correlated with the response times of the Standard Continuous Performance (scp) psychomotor test. Drivers with higher Driver Scores (presumably more skilled or more cautious) had higher SCP test (slower reaction time) scores ($p<.0001$). In Figure 4-18, the relationship between test score and BMI continued to be significant ($p=.01$) after removal of the "outliers", the three participants with the highest saliva concentration. This dispute the fact that the relationship between SCP and Triazolam saliva concentration dropped to NS after removing the "outliers". SCP, of all the psychomotor tests, shows the most stable relationships between BMI, Driver Score and test score.

In summary, the PATH data indicates that the impairing effects of Triazolam, measured in curve-following SDLP and psychomotor impairment on the Standard Continuous Performance (SCP) test, are more evident in higher-skilled drivers than in lower-skilled drivers, and more evident in drivers with higher Body Mass Indices than in drivers with lower BMIs.

6.10 Driver Performance Stopping for Stop Signs

The performance of drivers approaching and stopping at a stop sign or red light was measured on the fourth drive of experimental sessions one, two and three. The following characteristics of the stopping performance were calculated from the simulator data:

- Average braking duration – elapsed time from the moment of brake application to the moment when the driver reaches minimum velocity

- Time Differential between Initial Braking Incidence and Max Pedal Depression
- Distance from Stopping Reference at Minimum Speed
- Stopping Event Average Deceleration
- Maximum Deceleration
- 40-Meter Braking Profile

In the linear regression equations, drug dose was only a significant variable in tow of the six measures. These are Time Differential between initial and maximum braking and Maximum Deceleration. Drivers on the day they received the 0.250 mg dose took an average 1.3 seconds longer to reach maximum brake pressure than on the days theY received the placebo or 0.125 mg dose. Drivers, on the day they received the 0.125 mg dose, had a higher rate of maximum deceleration than on days they received the placebo or 0.250 mg dose.

The 40-Meter Braking Profile was the only measure that showed a drug impairment from both the 0.125 mg dose and the 0.250 mg dose of Triazolam. This test measures the brake pressure at a point 40 meters from the stop line. On the day drivers received the placebo dose, at 40 meters they had completed the initial braking maneuver and were applying relatively light peddle pressure. However, on the days they received the 0.250 mg or the 0.125 mg dose, they were applying strong brake pressure at 40 meters. Stopping a bus in a comfortable manner is a sophisticated maneuver requiring a variety of brake pressures at different points of the approach to the stop line. This careful control of brake pressure was seen in every driver on the day they received the placebo dose, but the careful control of the stopping maneuver was lost under drug impact at both doses.

Section 3.6 of this report discussed the response of the participants to the post-drive questionnaires that scored the “realism” of the simulator driving experience. “Feel when braking” is the simulator characteristic with lowest “realism” score (Figure 3-9). It is not surprising that, with the loss of proprioceptive feedback, control of deceleration would be diminished.

Additionally, simulator sickness (SSQ) was a significant factor in the stopping studies, and was more of an influence than in the SDLP studies. The linear regression equations identified SSQ as a significant variable in all six measures of stopping performance, but the effects, though consistent, were slight.

6.10.1 Impact of Driver Skill and Body Mass on Stopping Performance

In the discussion on curve following, the hypothesis was supported that impairment could be predicted, or at least explained, as a consequence of drug interaction modified by Body Mass Index and Driver Score. The effects of these intervening variables on impairment seemed counterintuitive – participants with higher BMI scores and Driver Scores appeared to be more impacted by Triazolam rather than less impacted. It was

desired to see whether that hypothesis would be born out in the performance of participants approaching bus stops.

However, in the analysis of driver performance approaching stop signs, that hypothesis does not seem to be born out.

The hypothesis is that drug impairment is modified in predictable ways by the Body Mass of the recipient (because the dose of drug is diluted in a larger volume of body fluid) and by the Driving Skill of the participant. The commonsense presumption would be that participants with large body masses who were well skilled drivers would be less impacted than drivers with less body mass who were not as well trained and skillful drivers. The counter intuitive presumption would be the reverse, that large, well-skilled drivers would be most impacted. That counterintuitive finding emerged from the review of the psychomotor testing and was reinforced by the review of SDLP.

However, the null hypothesis seems to he supported by the curve-following data – that there is no a priory predictor of impairment, or at least impairment by average group characteristics.

Figure 6-27: Hypothetical and Actual Ordering of Impairment by Dose Group for the Stopping Tests in the PATH project

Hypothesized Dose Group Order of Impairment							
Avg BMI+DRI	Hypothetical Order of Impairment by Dose Group	Braking Duration	Time Initial Braking to Max Braking (seconds)	Distance from Stopping Reference (meters)	Average Deceleration (meters/sec)	Maximum Deceleration (meters/sec)	40-meter Scaled Braking Level
1.38	**B**	6.22	4.33	14.89	-0.79	-3.72	1.18
1.75	C	0.34	2.25	12.82	-0.86	-4.26	1.23
1.80	A	1.89	2.28	14.01	-0.86	-3.90	1.09
1.88	E	2.48	2.65	13.61	-0.80	-3.51	1.18
2.10	F	5.98	2.40	13.48	-0.79	-2.70	1.17
2.25	**D**	9.52	3.80	14.27	-0.92	-3.77	1.17
		Actual Order of Impairmentfoe Each Stopping Measure					
		C	C	C	**D**	C	A
		A	A	F	A	A	**D**
		E	F	E	C	**D**	F
		F	E	A	E	**B**	**B**
		B	**D**	**D**	**B**	E	E
		D	**B**	**B**	F	F	C

In the top block of Figure 6-27, the hypothesized order of drug impairment by drug group is shown. Under the commonsense approach Group B should be the most impaired because it has, on average, the lowest Body Mass participants and the participants with the lowest average Driver Score. By the same reasoning, Group D should be the least impaired. The counterintuitive presumption has the order reversed.

In either case, Groups B and D should be far apart from each other in average level of impairment.

Figure 6-27 is calculated from the Fixed Effects Parameter Estimates in the linear regression tables in Section 5.5 of this report. The bottom block of the figure contains the Dose Group names for each of the six stopping measures, sorted from least to most level of impairment. It can be seen that there are no stopping measures where Dose Group B is the least impaired and D is the most impaired, and also none where the reverse is the case. In almost all cases, Dose Groups B and D are equally impaired.

So, as in the discussion of in Section 6.8.2.2, where there was no ready explanation for why certain participants were markedly impaired at low saliva Triazolam concentrations, there is no apparent explanation for the ordering on impairment levels by Dose Group on the stopping tests.

6.11 Conclusions

- It is possible to plan, develop and conduct a drugs and driver study in an academic setting which studies the impact of prescription medications on professional drivers, with full and careful review and approval by the Institutional Review Board. It is possible to recruit and screen participants and to conduct the experiment using modified commercial training equipment that can be purchased on the GSAdvantage website.

- A psychomotor test battery can be integrated into the study protocol and impairment on the psychomotor tests will be predictive of impairment on the driving tasks. Interestingly, the simplest psychomotor tasks appear to show drug impairment at lower concentrations of Triazolam than psychomotor tests that require choice behavior.

- The individual impact of drug on individuals is difficult to predict. Drug impact is modified in unexpected ways by the Body Mass of the driver and by the level of training and skill of the driver. The drug impact is also modified by concurrent medications being taken by the driver. That being said, there also appear to be idiosyncratic drug responses that are not explained by data gathered in this experiment.

- The measure Standard Deviation of Lateral Position (SDLP), a measure of weaving in lane while driving straight, is used to demonstrate diminishment of steering control. Group mean SDLP measurements are dose-dependent. The 0.250 mg Therapeutic dose of Triazolam increased lane deviation at all times by adding 6 to 10 inches of lane weaving. However, in impaired drivers, in addition to the additional 6-10 inches of weaving, the data indicated that there would be SDLP excursions of as much as 30 inches as frequently as 1 or 2 times an hour.

- At both dose levels studied, one impact of drug impairment is the loss of fine control of braking behavior. Drivers applied brake pressure more heavily and later in the stopping maneuver under both drug doses than after having received the placebo dose. Additionally, drivers exhibited a diminution of steering control while steering around construction barrels. The increase in SDLP, diminution of braking control and less exact steering control when avoidance maneuvers are required could contribute to an increased crash likelihood for drivers using Triazolam and driving.

- There appeared to be no carry-over effects of Triazolam on driving after a period of normal sleep. Drivers, returning for the next-day drive on the day after they had received the 0.250 mg dose, reported improved sleep the previous night relative to their normal sleep patterns. There were no reports of improved sleep on the next-day drives after having taken the 0.125 mg or placebo capsules.

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