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Prescription and Over-the-Counter Drug Use and its Relationship to Involvement in Safety-Critical Events

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EXECUTIVE SUMMARY

BACKGROUND

There is a considerable body of research showing an association between driving under the influence of alcohol and an increase in crash risk.[1] Impairment by drugs, especially legal drug use, such as legal prescription (Rx) and over-the-counter (OTC) drug use, has only recently received attention. In fact, the National Highway Traffic Safety Administration (NHTSA) co-sponsored an entire workshop that focused on the effects of drugs in transportation.[2] Although the adverse effects of alcohol and illicit drug use while driving have been widely documented, less is known about the adverse consequences of driving while under the influence of Rx and OTC medications.

Operating a motor vehicle is a complex task requiring sustained attention, auditory and visual information processing, quick reflexes, memory, concentration, decision making, and spatial recognition.[3] Some Rx and OTC medications have been shown to adversely impact many of these critical components of driving. Although some medications have potential adverse effects that may diminish driving-related skills, on-road driving research is lacking for many medications, especially medication use among commercial motor vehicle (CMV) drivers. CMV drivers are typically required to maintain attention, concentration, and alertness for longer periods of time than non-professional drivers. Thus, they may be more vulnerable to the driving-related adverse effects associated with Rx and OTC medication use.

The Large Truck Crash Causation Study (LTCCS) found that approximately 30 percent of truck drivers involved in a one truck/one passenger vehicle crash had an associated factor of Rx drug use, and approximately 19 percent had an associated factor of OTC drug use.[4] At first glance these statistics appear noteworthy; however, there were several methodological considerations in the LTCCS that preclude establishing a causal relationship between Rx and OTC drug use and crash involvement. More data are needed to support this contention, including (i) the base rate of Rx and OTC drug use in non-crash-involved CMV drivers; (ii) when the drug was taken in relation to the crash; (iii) whether the drug has an effect on driving performance, attention, and/or decision making abilities; (iv) whether the illness itself or the drug contributed to these decrements; (v) whether the critical reason or primary contributing factor was related to the drug's adverse effect on performance, attention, and/or decision-making capabilities; and (vi) other mitigating factors (e.g., prior sleep before crash, alcohol or illicit drug use, distraction, etc.).

PROJECT SUMMARY

The current study used data from the National Truck Driving Study (NTDS) to conduct a comprehensive analysis of truck driver Rx and OTC drug use and their relationship to involvement in a safety-critical event (SCE). This project served as a pilot test on the feasibility of using naturalistic data in analyzing the risk of a SCE associated with Rx and OTC drug use while driving. The SCEs and baselines (BLs) recorded in the NTDS, along with drivers' daily activity register (noting activity and medication use), were used to address the following research questions:

1. What was the prevalence of Rx and OTC drug use among truck drivers?
2. Was there an association between Rx and OTC drug use and involvement in an SCE?

METHODS

Naturalistic Truck Driving Study

The data used in this study were collected in the FMCSA-sponsored NTDS[5] and developed into a hybrid data set of naturalistically collected video data and activity register data in several subsequent studies.[6; 7] The NTDS collected data from November 2005 to March 2007. A total of 100 drivers participated in the study and drove an instrumented vehicle for approximately 4 consecutive weeks. The instrumented vehicles were installed with a data acquisition system (DAS) that included a computer and hard drive, sensors, vehicle network, incident box, and five video cameras. The sensors, used to measure driver performance, included a front radar-based Eaton VORAD, a Global Positioning System (GPS), a lane-tracking system, a yaw rate sensor, and an X/Y accelerometer.

A more detailed description of the methods used to collect and reduce data in the NTDS can be found in Blanco et al.[5] Below is brief summary of the methods used in the NTDS. In addition to the performance measures collected in the NTDS, drivers self-reported their daily activities in an activity register. The activity register detailed the driver's daily activities and medication/caffeine use for the entire 4 weeks he or she participated in the study. Participants were instructed to record the amount of medication or caffeine used and the time of use. Of the 100 drivers with naturalistic driving data, 97 drivers completed daily activity registers.

SCEs and BLs, used to compare driver performance during SCEs and non-SCEs, were identified as part of the NTDS. Potential SCEs and BLs were identified using a software program that searched the naturalistic data for sensor values characteristic of unsafe or safe driving. Researchers reviewed the triggered video and sensor data to verify the occurrence of an SCE or BL. The SCEs included crashes, near-crashes, crash-relevant conflicts, and unintentional lane deviations.

The final hybrid NTDS data set for this study included:

- Data from 97 CMV drivers
- Daily activity register (including medication/caffeine use and activities performed)
- 6.2 terabytes of data (video and performance data) and 14,500 driving-hours of valid video data
- 2,867 SCEs, including:
  - 5 crashes
  - 60 near-crashes
  - 1,588 crash-relevant conflicts
  - 1,214 unintentional lane deviations
  - 16 illegal maneuvers
- 5,069 BL epochs

Medication Coding

To evaluate the relationship between Rx and OTC drug use and SCE risk in the NTDS, the following steps were taken (these steps involved new reduction not covered in Blanco et al.[5]: (i) OTC and Rx drugs were grouped according to therapeutic class and by a broader drug classification using the Physicians' Desk Reference (PDR) and Krueger et al.[8]; (ii) each drug's absorption and half-life elimination rates were identified (a half-life is the amount of time required for the drug's concentration to be reduced by one-half); (iii) each drug's first, second, third, fourth, fifth, sixth, and seventh half-lives were calculated; (iv) drugs that could negatively affect driving performance, attention, and/or decision-making abilities were identified; and (v) whether the drug was OTC or Rx was determined.

SCE Risk Analysis

Once the driver activity registers were coded, the data were analyzed several ways. First, the research team documented the prevalence of Rx and OTC drug use among truck drivers in the NTDS using descriptive statistics, tables, and plots. Second, the risk of drug use was calculated by comparing the number of SCEs and BLs that occurred within a drug's half-life to the number of SCEs and BLs not occurring within a drug's half-life (for the same half-life). Odds ratios (ORs) and corresponding 95 percent lower (LCL) and upper confidence limits (UCL) were calculated using logistic regression models that controlled for each driver. The variable tested (e.g., adverse reaction classification, etc.) was included in the regression model as a covariate. Each half-life was investigated separately with a new logistic regression model.

RESULTS

Prevalence of Rx and OTC Drugs

The 97 drivers with daily activity/medication registers recorded a total of 9,120 drug entries. Of these drug entries, 75.11 percent were OTC (6,850 entries) and 24.89 percent were Rx (2,270 entries). Although 73.20 percent (71 drivers) of the participants reported no use of Rx drugs, only 3.09 percent (3 drivers) of the participants had no OTC drug entries. Furthermore, the majority of drivers (52.58 percent) reported using OTC medication in over 90 percent of their shifts. Thus, OTC medication use was far more common among the drivers that participated in the NTDS than Rx drug use.

In terms of when drivers used medication, Rx and OTC drug use peaked in frequency between 7:00 a.m. and 9:00 a.m., with another small peak in the evening, from approximately 6:00 p.m. to 9:00 p.m. However, OTC medications were taken most often while on duty (28.61 percent of the entries), and Rx medications were reportedly taken most often while resting off duty (22.52 percent of the entries).

Regarding the types of medications used, the most frequently recorded Rx drug classification was cardiac medication (44.54 percent) and "other" (39.74 percent). The most frequently recorded OTC drug classification was stimulant-caffeine, which included coffee, soda, tea, energy drinks, and caffeine pills (78.57 percent). Of the reported drugs, 61.23 percent of the Rx

drugs had possible performance-deteriorating qualities, and only 1.07 percent of the OTC drugs had possible performance-deteriorating qualities.

SCE Risk Associated with Rx and OTC Drug Use

Noteworthy results that assessed the SCE risk associated with Rx and OTC drug use are presented below.

- ORs for Rx drug use, irrespective of therapeutic class or possible performance-deteriorating effects, ranged from 0.62 and 0.70 for all seven half-lives, but the ORs were not considered significant.
- ORs for OTC drug use, irrespective of therapeutic class or possible performance-deteriorating effects, showed a statistically significant protective effect for all seven half-lives and ranged from 0.46 to 0.66. However, this effect was eliminated when caffeine was excluded from the analysis (ORs ranged from 0.90 to 1.35).
- Potential performance-deteriorating drugs had ORs that ranged from 0.64 to 0.86 for all seven half-lives, but the ORs were not considered significant.
- Non-performance-deteriorating drugs were associated with a significant decrease in SCE risk for all seven half-lives (ORs ranged from 0.45 to 0.59). However, this effect was eliminated when caffeine was excluded from the analysis (ORs ranged from 0.76 to 1.06).
- ORs for caffeine use were associated with a significant decrease in SCE risk for half-lives 1 through 6 (OR = 0.62, OR = 0.58, OR = 0.57, OR = 0.66, OR = 0.51, and OR = 44, respectively).

CONCLUSIONS

The main objective of the current study was to conduct a comprehensive analysis of truck driver Rx and OTC drug use and their relationship to involvement in an SCE. This project served as a pilot study that showed the feasibility in using naturalistic driving data to assess the SCE risk associated with Rx and OTC drug use while driving. Although the results suggest that OTC drugs and non-performance-deteriorating drugs were found to have a protective effect with respect to SCE risk, the data, especially for Rx drugs, were limited given the small number of drug entries for specific classifications and the small number of drivers using each drug (e.g., a number of the drugs were only consumed by one or two drivers and may have only been used a few times). Once caffeine was removed from these analyzes, OTC drugs and non-performance deteriorating drugs were not associated with an increase or decrease in risk of an SCE. As caffeine was the only drug classification where a large number of drivers used the drug classification multiple times, this OR analysis was the only analysis performed on a specific drug classification. Drivers that used caffeine were found to be half as likely to be involved in an SCE compared to drivers that did not use caffeine. This result was consistent with previous research that showed the potential of caffeine to be an effective short-term countermeasure for driver fatigue.[9-13] This was especially relevant to CMV drivers as they often work long, irregular hours.

This current study examined Rx and OTC drug use for CMV drivers. Generally, CMV drug use was not associated with an increased risk of being involved in an SCE. However, as indicated

above, these results should not be considered definitive or representative given the small sample of drivers using specific classifications of medication. This project did show the feasibility of using a naturalistic approach to assess the risk associated with Rx and OTC use while driving. It is possible analyses on specific medications could be performed with a large sample of drivers using each classification of drug. This should be considered in all future naturalistic CMV operator studies as collecting this data would likely involve minimal cost.

The current research found that nearly 97 percent of CMV drivers in the NTDS used Rx and/or OTC drugs during their participation in the study. Of these drivers, all used an OTC drug at least once (mostly caffeine use), and 25 percent used at least one Rx drug. The frequency of Rx drug use was consistent with the results obtained by the LTCCS, where Rx drug use was present during 30 percent of one truck/one passenger vehicle crashes.[4] These results may suggest that Rx drug use showed up in 30 percent of the LTCCS crashes as this is the base rate of Rx drug use among CMV drivers. However, OTC drug use was far more common in the NTDS than the 19 percent present in the LTCCS. This is likely because caffeine was not considered an OTC drug in the LTCCS.

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LIST OF ABBREVIATIONS AND SYMBOLS

ACE	Angiotensin-converting enzyme
BL	Baseline
CL	Confidence limit
CMV	Commercial motor vehicle
CNS	Central nervous system
DAS	Data acquisition system
FDA	U.S. Food and Drug Administration
FMCSA	Federal Motor Carrier Safety Administration
g/dL	Grams per deciliter
GPS	Global Positioning System
LCL	Lower confidence limit
LTCCS	Large Truck Crash Causation Study
MEP	Medical expert panel
MOI	Monoamine oxidase inhibitor
NHTSA	National Highway Traffic Safety Administration
NSAID	Non-steroidal anti-inflammatory
NTDS	Naturalistic Truck Driving Study
OR	Odds ratio
OTC	Over-the-counter
PDR	Physicians' desk reference
Rx	Prescription
SCE	Safety-critical event
SSRI	Selective serotonin reuptake inhibitor
UCL	Upper confidence limit
VTTI	Virginia Tech Transportation Institute

CHAPTER 1. **INTRODUCTION**

The U.S. Food and Drug Administration (FDA) defines a drug as any substance that affects the structure and/or function of the user's body and is used to diagnose, cure, mitigate, treat, and/or prevent disease.[14] Prescription (Rx) drugs are only available with a doctor's authorization, and over-the-counter (OTC) drugs are considered available to the general public without a doctor's prescription.[14] This definition of OTC encompasses many chemicals that people frequently ingest, including vitamins, caffeine, cold/flu medications, herbal supplements, and pain relievers.

The majority of people in the U.S. use Rx and/or OTC drugs each year. The Centers for Disease Control and Prevention reported that 48.5 percent of Americans indicated using a minimum of one Rx drug each month.[15] Furthermore, Gurwitz[16] and Rosenbloom and Santos[17] reported that 90 percent of adults 65 years old or older use a minimum of one Rx drug each week. Although these statistics show many adults in the U.S. frequently use Rx drugs, OTC medication use is even more prevalent. The U.S. Food and Drug Administration (FDA) reports that 80 percent of adults in the U.S. use at least one OTC drug each day.[18]

The effects of performance decrements while driving under the influence of alcohol have been widely accepted since Borkenstein, Crowther, Shumate, Ziel, and Zylman[19] released their study on the relationship between alcohol and crash risk. Impairment by drugs, especially legal drug use (i.e., legal Rx and OTC use), has only recently received considerable attention. In fact, the National Highway Traffic Safety Administration (NHTSA) co-sponsored a workshop that focused on the effects of drugs in transportation.[2] There is now a considerable body of research showing an association between driving under the influence of alcohol and many illegal drugs and an increase in crash risk.[1] However, less is known about the adverse consequences of driving while under the influence of Rx and OTC medications.

Rx AND OTC DRUG USE AND DRIVING PERFORMANCE

Operating a motor vehicle is a complex task requiring attention, auditory and visual information processing, quick reflexes, memory, concentration, decision making, and spatial recognition.[3] Rx and OTC medications have been shown to influence many of these critical components of driving. Although some medications have potential adverse effects that lead to diminished driving-related skills, on-road driving research is lacking for many medications, especially research examining medication use among commercial motor vehicle (CMV) drivers. CMV drivers are required to maintain attention, concentration, and alertness for longer periods of time compared to people who do not drive for a living. Thus, they are more vulnerable to the possible adverse performance effects associated with Rx and OTC medication use.

This section outlines the current knowledge regarding the possible effects of Rx and OTC drugs on driver performance. The drugs outlined in this section follow the classifications outlined in Krueger et al.[8] These classifications include hypnotics and sedatives, stimulants, antihistamines, pain medications, psychiatric medications, cardiac medications, and supplements. The purpose of this literature review was to include studies that examined the effects of Rx and OTC medication use on actual driving performance. It was outside the scope of this project to review studies that examined crash risk associated with medication use solely with questionnaires or psychomotor

tests. For a more detailed literature review concerning the effects of psychoactive medications on CMV driver performance, see Krueger et al.[8] and Elvik.[1]

Hypnotics/Sedatives

Hypnotics/sedatives are central nervous system (CNS) depressants. Drugs in this classification include sedatives, hypnotics, tranquilizers, and antianxiety medications.[9] These drugs are designed to promote sleep and provide a calming effect on the user. Common adverse effects of hypnotics include sedation, dizziness, cognitive impairment, confusion, and decreased concentration and coordination. Specific types of drugs that are classified as hypnotics and sedatives include benzodiazepines, barbiturates, and non-benzodiazepines.

Most of the research pertaining to Rx and OTC drugs and driving performance has focused on the crash risk associated with the use of benzodiazepines. There are two major types of benzodiazepines: long half-life benzodiazepines and short half-life benzodiazepines. A half-life is the amount of time it takes the concentration of a chemical to be reduced by one-half.[8] Long half-life benzodiazepines remain in the body for much longer periods of time compared to short half-life benzodiazepines. The effects on the body associated with long half-life benzodiazepines typically last at least 9 hours (sometimes much longer). The effects on the body associated with short half-life benzodiazepines last less than 9 hours and usually peak 2 to 3 hours after ingestion.[20] Some examples of common long half-life benzodiazepines include diazepam (e.g., Valium®), lorazepam (e.g., Ativan®), chlordiazepoxide (e.g., Librium®), clonazepam (e.g., Klonopin®), prazepam (e.g., Centrax®), and alprazolam (e.g., Xanax®). Examples of short half-life benzodiazepines include temazepam (e.g., Restoril®), triazolam (e.g., Halcion®), quazepam (e.g., Doral®), estazolam (e.g., ProSom®), and flurazepam (e.g., Dalmane®).

Most of the research regarding benzodiazepines and driving showed statistically significant driving performance deterioration.[21-30] Most research has shown a 1.3 to 2.2 crash risk associated with the use of benzodiazepines, but some studies have found benzodiazepines increase crash risk by 3.9 times.[25] These results seem noteworthy, but most of this research only examined long half-life benzodiazepines. On-the-road research regarding short half-life benzodiazepines is limited; however, O'Hanlon and Volkerts[24] did not find significant driving performance deterioration with short half-life benzodiazepines.

In regards to CMV driving, the Large Truck Crash Causation Study (LTCCS) found benzodiazepines (behind antidepressants) were the second most common drug used among CMV drivers involved in a crash.[4] This finding, along with the results showing driving performance deterioration associated with benzodiazepines, led a medical expert panel (MEP) to recommend all current users of benzodiazepines be prohibited from operating a CMV until the benzodiazepine was eliminated from the driver's body.[20] Thus, the MEP recommended to the Federal Motor Carrier Safety Administration (FMCSA) that CMV drivers taking benzodiazepines wait a full 7 half-lives before operating a CMV, and long-term users of benzodiazepines (more than a month of concurrent use) wait 7 half-lives plus an additional week before operating a CMV. Thus, this means a CMV driver must wait at least 72 and 21 hours (sometimes longer) to drive a CMV after ingesting a long half-life and short half-life benzodiazepine, respectively.

Stimulants

Due to long working hours, limited opportunities to sleep, nighttime operations, and pressure to work overtime, CMV drivers do not routinely get the recommended eight hours of sleep a night. Hanowski, Hickman, Fumero, Olson, and Dingus[31] found that CMV drivers averaged 6.28 hours of sleep per 24-hour period. Some believe that CMV drivers regularly use stimulants to remain alert while operating a CMV. Thus, it was important to examine the effects of Rx and OTC stimulants on a driver's ability to safely operate a motor vehicle.

Stimulants are typically used to treat excessive sleepiness often associated with a lack of sleep, a sleep disorder, attention deficit hyperactivity disorder, and depression. The most common Rx stimulants are amphetamines (e.g., Adderall®), methylphenidate (e.g., Ritalin®), and modafinil (e.g., Provigil®). The most common OTC stimulant is caffeine. In fact, caffeine has been identified as the most widely used psychoactive chemical in the world,[32] and it is believed that 80 percent of adults in the U.S. use caffeine daily.[18] Similar to other drugs, stimulants have common adverse effects. Some of the common adverse effects associated with stimulants include headaches, sleep disturbances, loss of appetite, mood swings, and restlessness.

Research examining stimulants' effects on driving performance has largely focused on the illegal stimulant cocaine. However, some research has examined the effects of legal stimulants on driving performance, but these studies have produced conflicting results. For example, Drummer et al.[33] found that CMV drivers were at an increased risk of a crash when using stimulants. However, Drummer et al.[33] grouped all stimulants (legal and illegal) together in the analysis. Thus, the results do not provide the risk associated with using legal Rx and OTC stimulants. Other research found that low doses of stimulants other than cocaine may benefit drivers and lower crash risk.[9; 10] In other words, the use of stimulants other than cocaine may help drivers avoid crashes. Additionally, research found that drivers who use caffeine during circadian lows (between 2:00 a.m. and 6:00 a.m.) had fewer lane deviations compared to drivers that did not use caffeine and those drivers that had a 30-minute nap.[11-13]

Antihistamines

Many people experience symptoms associated with seasonal allergies and antihistamines have been the preferred treatment to relieve these symptoms. Antihistamines are typically used to relieve the following problems: itchy and water eyes, runny nose, sneezing, coughs, insect bites, rashes, hives, and motion sickness. Although antihistamines are successful at relieving these symptoms, the following adverse effects are common: sedation, drowsiness, confusion, and impaired motor function.

Antihistamines are categorized into two groups: first-generation antihistamines and second-generation antihistamines. First-generation antihistamines usually consist of diphenhydramine–hydrochloride. Traditionally, these drugs are used to relieve the symptoms associated with the common cold and allergies. The chemical properties of first-generation antihistamines may cause sedation and drowsiness. Thus, many people use first-generation antihistamines as a sleep aid.[8] Some common brands that include first-generation antihistamines are Benadryl®, Dramamine®, Tylenol®, Vicks®, and Alka-Seltzer®.

Second-generation antihistamines are relatively new and often labeled as "non-sedating" antihistamines. For many people, taking a drug that may cause drowsiness is not an option during working hours. For example, CMV drivers cannot afford to become sedated while operating a CMV. Thus, second-generation antihistamines are a preferred drug class to relieve seasonal allergy symptoms.[34-36] Some common second-generation antihistamines include loratadine (e.g., Claritin®), fexofenadine (e.g., Allegra®), and cetirizine (e.g., Zyrtec®).

Research on first-generation antihistamines has shown possible negative effects on driving performance.[37-40] For example, Weiler et al.[37] found diphenhydramine to be associated with an increased variability in following distance and an increase in the number of lane drifts. Conversely, research has shown that the second-generation antihistamines loratadine and fexofenadine generally do not have an effect on driving performance.[37; 38; 41] However, research examining the effects of cetirizine on driving performance has shown a possible association with increased deviations in lateral lane position at higher doses.[38] This suggests cetirizine may cause more sedation compared to other second-generation antihistamines that may be safe to use while driving.

Pain Medications

As the name implies, pain medications are typically used to relieve chronic and minor aches and pains associated with injuries, surgeries, and disease.[42] Pain medications include a wide variety of drug classes, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. Common Rx opioids, also called narcotic analgesics, include hydrocodone (e.g., Vicodin®), oxycodone (e.g., Percocet® and OxyContin®), fentanyl (e.g., Duragesic®), morphine (e.g., Astramorph® and Avinza®), and hydromorphone (e.g., Dilaudid® and Exalgo®). Common NSAIDs include aspirin (e.g., Bayer® and Excedrin®), ibuprofen (e.g., Advil® and Motrin®), and naproxen (e.g., Aleve®). Tylenol® is acetaminophen, but many other brands include acetaminophen, such as Vick's DayQuil® and NyQuil®, Robitussin®, Sudafed®, Excedrin®, Vicodin®, Lortab®, and Percocet®.

NSAIDs and acetaminophen alone generally do not have any adverse effects on driving skills. Thus, very little research has been published on the effects of NSAIDs and acetaminophen on driving performance. However, Verster, Veldhuijzen, and Volkerts[43] found that NSAIDs did not produce any significant changes in driving behavior. Unlike NSAIDs and acetaminophen, narcotic analgesics may cause sedation and dizziness. There has been some research on the effects of narcotic analgesics on driving performance with varying results.[43-45] Linnoila and Hakkinen[44] used a simulator to study the effects of codeine on driving performance. They found that participants taking codeine were more likely to get into a collision compared to participants who only consumed alcohol. Furthermore, Linnoila and Hakkinen found that participants who took codeine also drove off the road more frequently and did not follow instructions as well as participants that took no drugs, took diazepam, or alcohol alone. However, Verster et al.[43] did not find significant driving performance changes with the use of oxycodone, and Galski et al.[45] determined that opioid analgesic therapy did not impair cognitive performance, perception, or coordination on the simulated driving performance of 16 patients using Chronic Opioid Analgesic Therapy.

Psychiatric Medications

Psychiatric medications, also known as psychotropic medications, are Rx drugs used to alter the chemical structure of the brain or central nervous system (CNS). There are three categories of psychiatric medications, including antipsychotics, anxiolytics, and antidepressants. Antipsychotics are typically prescribed to treat psychotic thoughts, suicidal tendencies, and schizophrenia. Some common antipsychotic drugs include clozapine (e.g., Clozaril®), risperidone (e.g., Risperdal®), aripiprazole (e.g., Abilify®), olanzapine (e.g., Zyprexa®), quetiapine (e.g., Seroquel®), and ziprasidone (e.g., Geodon®). Possible driving-related adverse effects associated with antipsychotic medications include drowsiness, dizziness, blurred vision, muscle spasms, and restlessness. Anxiolytics are typically prescribed to treat anxiety; the most common anxiolytics are benzodiazepines (see description above). Antidepressants are prescribed to treat the symptoms associated with depression and personality disorders. There are three categories of antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MOIs). An example tricyclic antidepressant is desipramine. SSRIs include citalopram (e.g., Celexa®), escitalopram (e.g., Lexapro®), fluoxetine (e.g., Prozac®), paroxetine (e.g., Paxil®), and sertraline (e.g., Zoloft®). MOIs include isocarboxazid (e.g., Marplan®), phenelzine sulfate (e.g., Nardil®), tranylcypromine (e.g., Parnate®), and selegiline (e.g., Emsam®). Possible driving-related adverse effects associated with antidepressants include sleeplessness, drowsiness, agitation, and blurred vision.

Most of the research regarding psychiatric medications, other than anxiolytics (as outlined above), has centered on antidepressants. Wylie, Thompson, and Wildgust[46] found that patients taking antipsychotic medications (flupentixol and fluphenazine) for symptoms of schizophrenia showed decreased driving accuracy and reaction time on a driving simulator. Additionally, Neutel[25] examined the driving performance effects of antipsychotic medications and found no increased crash risk within 2 to 4 weeks of receiving the Rx.

Although there has been a fair amount of research on the effects of antidepressants on driving performance, the results have been inconsistent.[28; 39; 47-49] Ray et al.[28] performed a retrospective cohort study with 38,701 person-years of driving, focusing on drivers aged 65 to 84 years old. Ray et al. found drivers using cyclic antidepressants were approximately two times more likely to get into a crash compared to drivers not using cyclic antidepressants. Similarly, Ramaekers[47] summarized the literature on the effects of antidepressants on actual driving performance. Ramaekers found that sedating antidepressants showed similar lane-keeping performance as a driver with a blood alcohol concentration of 0.08 g/dL (the legal limit in the U.S.). However, the diminished driving performance was eliminated after one week of taking the sedating antidepressant. Ramaekers also found that non-sedating antidepressants did not result in any changes in driving performance. O'Hanlon and colleagues[39; 48; 49] studied the effects of a number of different antidepressants on driving performance. They found that venlafaxine (SSRI), dothiepin (tricyclic antidepressant), fluoxetine (SSRI), moclobemide (MOI), and brofaromine (MOI) had no adverse effects on driving performance.

Cardiac Medications

Cardiac medications are typically used to treat symptoms associated with high cholesterol, chest pain, high blood pressure, cardiac arrhythmias, heart failure, and blood clots. There are several

types of cardiac medications, including anticoagulants, antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, vasodilators, digitalis preparations, and statins. Although there are many different types of cardiac medications, many of them have similar adverse effects that could affect driving performance, including fatigue, weakness, insomnia, dizziness, and tiredness. No literature was found regarding the effects of cardiac medications on actual driving performance.

Dietary Supplements

Dietary supplements are a very large category of drugs. The FDA defines dietary supplements as any ingredient/chemical that can be ingested for additional or supplemental nutritional benefits.[50] They can include vitamins, minerals, herbs or other botanicals, amino acids, or other substances intended to supplement a diet for a nutritional benefit. They may come in the form of a concentrate, metabolite, constituent, or extract. Some commonly used supplements include multivitamins, anabolic steroids, ginseng, ginkgo biloba, St. John's Wart, amino acids, melatonin, glucosamine, fish oil, zinc, vitamins A, B3, B12, C, D, E, and K, hibiscus, iron, magnesium, and calcium. Although each supplement has its own driving-related adverse effects, some can cause the following: dizziness, irritability and aggression, insomnia, fatigue, sleepiness, blurred vision, weakness, and confusion. However, most of these adverse effects are very rare. No research was found regarding the effects of supplements on actual driving performance.

CMV DRIVING AND Rx AND OTC DRUG USE

There is very little research examining Rx and OTC use among CMV operators. However, the LTCCS found that almost 30 percent of the truck drivers involved in a one truck/one passenger vehicle crash had an associated factor of Rx drug use, and approximately 19 percent had an associated factor of OTC drug use.[4] At first glance these statistics appear noteworthy; however, there were several methodological considerations in the LTCCS that preclude a causal relationship between Rx and OTC use while driving and crash involvement. More data are needed to support this contention, including (i) the base rate of Rx and OTC drug use in non-crash-involved CMV drivers; (ii) when the drug was taken in relation to the crash; (iii) whether the drug had an effect on driving performance, attention, and/or decision-making abilities and the direction of the effect; (iv) whether the illness itself or the drug contributed to these decrements; (v) whether the critical reason or primary contributing factor was related to the drug's adverse effect on performance, attention, and/or decision-making capabilities; and (vi) other mitigating factors (e.g., prior sleep before crash, alcohol or illicit drug use, distraction, etc.).

PROJECT SUMMARY

The current study used the data collected in the FMCSA-sponsored National Truck Driving Study (NTDS)[5] to conduct a comprehensive analysis of CMV driver Rx and OTC drug use and its relationship to involvement in a safety-critical event (SCE). Given the small sample size and limited Rx entries, this project should be viewed as a pilot test regarding the feasibility of using naturalistic data in analyzing Rx and OTC drug use and their association with SCEs. The SCEs

and baselines (BLs) recorded in the NTDS, along with drivers' daily activity registers (noting driver activity and medication use), were used to address the following research questions.

1. What was the prevalence of Rx and OTC drug use among truck drivers?

2. Was there an association between Rx and OTC drug use and involvement in an SCE?

CHAPTER 2. **METHODS**

DATA COLLECTION

The data used in this study were collected in the FMCSA-sponsored NTDS[5] and developed into a hybrid data set of naturalistically collected video data and activity register data in several subsequent studies.[6; 7] The NTDS collected data from November 2005 to March 2007. A total of 100 drivers participated in the study. The drivers were from four different fleet companies—three of the fleet companies were line-haul operations (out-and-back), and the fourth fleet company was a long-haul operation (typically out for 1 week at a time). Two of the companies were based in Virginia and two were based in North Carolina. The companies and drivers participated in the study voluntarily and, as with any study that used volunteers, the companies and drivers may not be representative of the general CMV population. For example, it is possible the participating companies were more proactive with respect to safety than the general population of CMV fleets and drivers (or vice versa).

The data were collected continuously as participants drove the instrumented trucks during their normal revenue-producing deliveries. In the NTDS, once a driver had completed his or her participation, a different participating driver was assigned to the instrumented truck. Each driver operated an instrumented truck for approximately 4 weeks. The instrumented trucks were installed with a data acquisition system (DAS), including a computer and external hard drive, sensors, vehicle network, incident box, and five video cameras. The sensors, used to measure driver performance, included front radar-based Eaton VORAD, a Global Positioning System (GPS), a lane-tracking system, a yaw rate sensor, and an X/Y accelerometer. The five video cameras recorded the driver's face, steering wheel, forward roadway, the left side of the truck looking backward, and the right side of the truck looking backward (Figure 1). More information on the DAS and sensors can be found in Blanco et al.[6]

Figure 1. Photo. Five camera images multiplexed into a single image.

SCEs and BLs were identified as part of the NTDS. Potential SCEs and BLs were identified using a software program that searched the naturalistic data for sensor values characteristic of unsafe or safe driving. Researchers reviewed the triggered video and sensor data to verify the occurrence of an SCE or BL. The SCEs included crashes, near-crashes, crash-relevant conflicts, and unintentional lane deviations. Table 1 below provides definitions for each SCE type.

Table 1. SCE trigger definitions.

Event Type	Description
Crash	Any contact with an object, either moving or fixed, at any speed, including another vehicle, roadside barrier, object on or off of the roadway, pedestrian, cyclist, or animal.
Near-crash	Any circumstance that requires a rapid, evasive maneuver (e.g., hard braking, steering) by the subject vehicle (SV) subject vehicle or any other vehicle, pedestrian, cyclist, or animal to avoid a crash.
Crash-relevant Conflict	Any circumstance that requires a crash-avoidance response on the part of the SV, any other vehicle, pedestrian, cyclist, or animal that was less severe than a rapid evasive maneuver (as defined above) but greater in severity than a normal maneuver. A crash avoidance response can be braking, steering, accelerating, or any combination of control inputs.
Unintentional Lane Deviation	Any circumstance where the SV crosses over a solid lane line (e.g., onto the shoulder) where no hazard (e.g., guardrail, ditch, vehicle, etc.) was present.

Participants were asked to detail their daily activities in an activity register for the entire 4 weeks each participated in the study. Each activity register corresponded to a 24-hour period, on a midnight-to-midnight timeline. A sample page of the activity register is shown below in Figure 2. Drivers noted on-duty period and off-duty period activities using activity codes. There were 15 possible activity codes. The first six activity codes were classified as on-duty activities and the last nine were classified as off-duty activities. Each activity code, with duty period classification and description, is provided in Table 2.

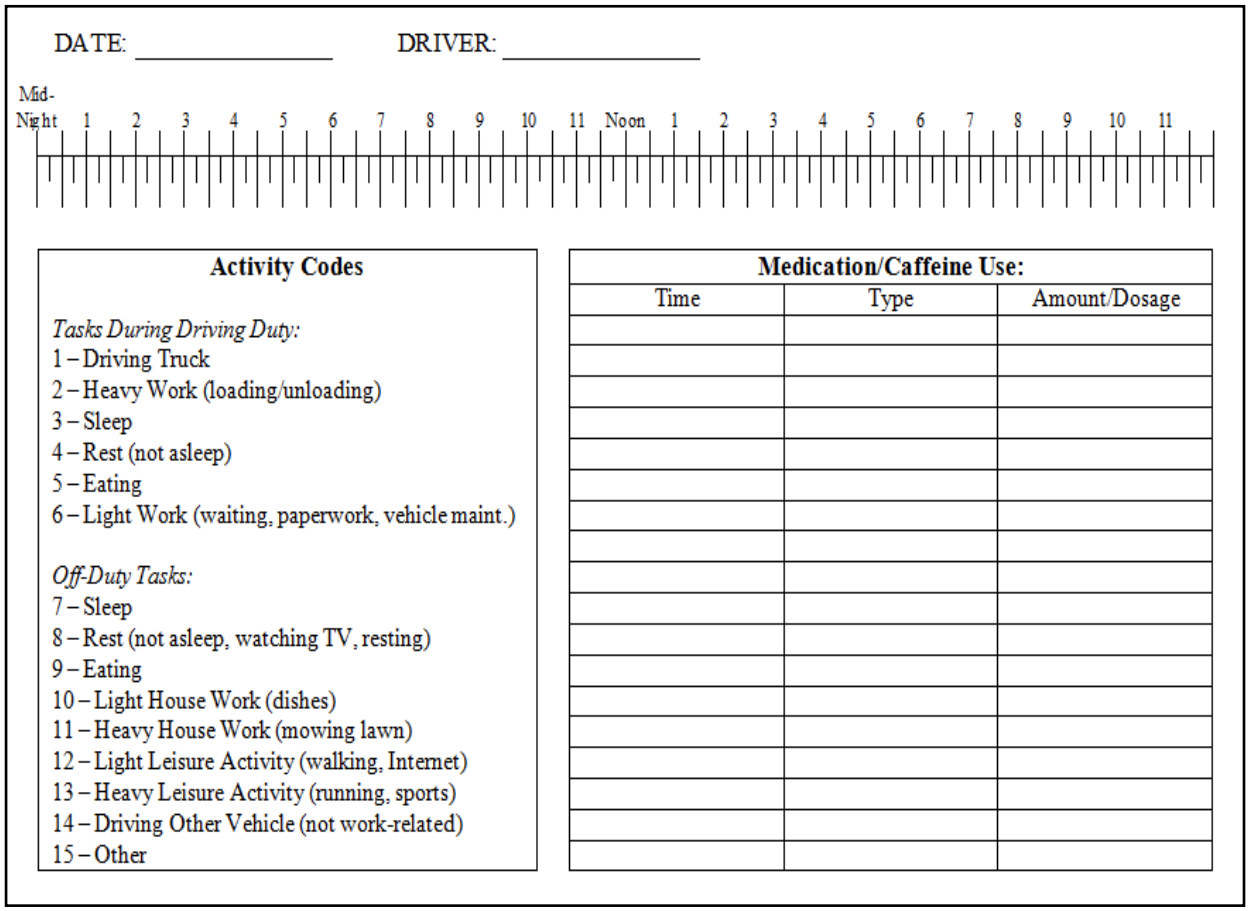


Figure 2. Illustration. Daily activity register sheet used to record activities.

Table 2. Activity code descriptions.

Activity Code	Description
1/Tasks During On Duty	Driving Truck
2/Tasks During On Duty	Heavy Work (Loading/Unloading)
3/Tasks During On Duty	Sleep
4/Tasks During On Duty	Rest
5/Tasks During On Duty	Eating
6/Tasks During On Duty	Light Work
7/Off Duty	Sleep
8/Off Duty	Rest (Not Asleep, Watching TV, Resting)
9/Off Duty	Eating
10/Off Duty	Light House Work (e.g., Dishes)
11/Off Duty	Heavy House Work (e.g., Mowing Lawn)
12/Off Duty	Light Leisure Activity (e.g., Walking, Internet)
13/Off Duty	Heavy Leisure Activity (e.g., Running, Sports)
14/Off Duty	Driving Other Vehicle (Not Work Related)
15/Off Duty	Other

Participants disclosed their activities on the 24-hour timeline on the top part of the daily activity register by marking the beginning and end of the activity on the timeline. Figure 3 displays an example of a completed activity register timeline. Three drivers had missing activity register data and were not included in the analyses.

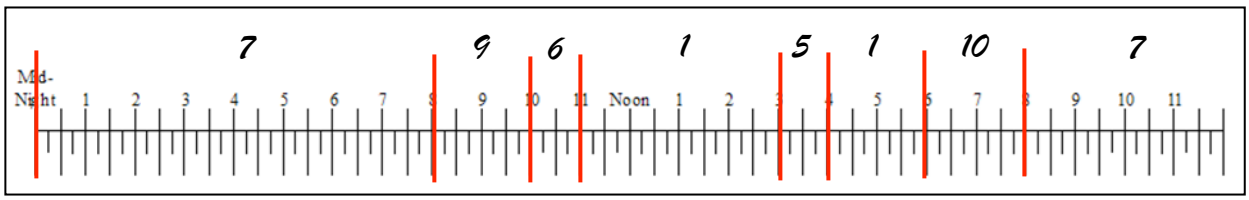


Figure 3. Illustration. Timeline with activity codes.

As seen in Figure 2, the daily activity register included a section for medication/caffeine use. Participants were instructed to record the medication or caffeine use, the time of use, and the amount. In addition to the three drivers with missing activity register data, three drivers did not have any medication or caffeine use entries.

As part of their participation in the study, drivers also completed various questionnaires. The questionnaires collected information on their demographic characteristics, health conditions and habits, and sleep hygiene. The complete list of questionnaires can be found in Blanco et al.[5] Of the 97 drivers with naturalistic and activity register data, 96 drivers provided demographic information.

HYBRID ACTIVITY REGISTER

Blanco et al.[6] created a hybrid data set of the NTDS video data and activity register data. This reconciled the two data sets into one data set. The steps taken to verify video data and develop the hybrid data set were extensive and can be read about in more detail in Blanco et al.[6] A general overview is provided here. The video data were collected when the truck's ignition was initiated. The video data, along with speed information, were used to verify or update the time of driving activities marked in the activity register. In Blanco et al.,[6] the drivers' daily activity registers were adjusted to ensure all SCEs occurred during a marked driving period. In Soccolich et al.,[7] the activity registers were adjusted to ensure all previously selected BLs occurred during a marked driving period. BLs and SCEs, by definition, must occur during driving. Therefore, it was important to update the activity registers to reflect BLs and SCEs that occurred only during driving. The activity register also provided information about which activities took place between driving episodes.

The final NTDS included:

- Data from 97 CMV drivers
- Daily driver activity registers (including medication/caffeine use and activities performed)
- 6.2 terabytes of data (video and performance data) and 14,500 driving-hours of valid video data
- 2,867 SCEs
  - 5 crashes
  - 60 near-crashes
  - 1,588 crash-relevant conflicts
  - 1,214 unintentional lane deviations
  - 16 illegal maneuvers
- 5,069 BL epochs

Rx AND OTC DRUG CODING

The medication entries listed in the NTDS included the following information: name of the drug, dose, date and time taken, basic drug classification, and the activity performed when the drug was ingested. Although these data were detailed, additional information was needed for each drug to adequately determine the SCE risk. The research team performed the following steps to assess the SCE risk associated with Rx and OTC drug use (these steps involved new reduction not covered in Blanco et al.[5]). The complete medication data coding protocol is located in Appendix A.

1. Found each drug's information in the Physician's Desk Reference (PDR) electronic library (www.pdr.net) or in the PDR handbook. If the drug was not listed in the PDR's electronic library or handbook, the authors identified the drug's information in other peer-reviewed medication electronic libraries (e.g., Medscape.com and Rxlist.com) or peer-reviewed scholarly articles.

2. Identified the drug's therapeutic class (Appendix B).

3. Grouped each drug into broad classifications based on Kruger et al.[8] Table 3 shows the drug classifications and the corresponding therapeutic classes.

Table 3. Drug classifications.

Classifications	Therapeutic Class
Antihistamines	Antihistamine
Cardiac Medications	ACE inhibitor, calcium channel blocker, selective $beta_1$-blocker, Angiotensin II receptor antagonist/thiazide diuretic, HMG-CoA reductase inhibitor, nicotinic acid, K^+-sparing diuretic/thiazide diuretic, fibric acid derivative, $alpha_1$-blocker
Vitamin/Herbal Supplements	Vitamin, natural/herbal supplement
Other	$Alpha_1$-antagonist, aluminum/magnesium hydroxide, aminopenicillin, anticholinergic bronchodilator, biguanide, corticosteroid, corticosteroid/$beta_2$ agonist, cough suppressant/expectorant, decongestant, fluoroquinolones, H_2-blocker, leukotriene receptor antagonist, proton pump inhibitor, purine antagonist antimetabolite, semisynthetic ampicillin derivative, thiazolidinedione, thyroid replacement hormone, type II 5 alpha-reductase inhibitor
Pain Medication	5-Aminosalicylic acid derivative, analgesic, NSAID, opioid analgesic, salicylate
Psychiatric Medication	Aminoketone, selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, thienobenzodiazepine, selective norepinephrine reuptake inhibitor
Sedative/Hypnotics	Sleep-Producing Agent, benzodiazepine, ethanol
Stimulant – Caffeine	Caffeine
Stimulants	Selective norepinephrine reuptake inhibitor, sympathomimetic amine, wakefulness-promoting agent

4. Determined when the drug was active in the driver's body. This required a researcher to review the pharmacokinetic properties for each drug to identify the absorption rate (T_{max}) and half-life elimination rate ($T_{½}$). The absorption rate (T_{max}) is the amount of time required for the drug to reach maximum concentration. The half-life elimination rate ($T_{½}$) is the amount of time required for the drug's concentration to be reduced by one-half. These two rates allowed researchers to approximate how long each drug was producing effects in a driver's body. However, researchers were not able to find reliable absorption and elimination rates for some drugs (e.g., vitamin/herbal supplements). In these cases, the absorption rate was coded as zero minutes, and the elimination rate was calculated by dividing the dosage instructions by 3. For example, a given supplement required one dose per day (i.e., every 24 hours). In this example the half-life elimination rate was calculated to be 8.0 hours. Although this calculation may not provide the most accurate elimination rate, it does provide a general estimation. The absorption rate and half-life elimination rate for each drug entry are shown in Appendix C.

5. Calculated when the drug's chemical properties were active in the driver's body. It is generally accepted that after five half-lives a drug's effects are negligible. After five half-

lives approximately 96.88 percent of the drug has been eliminated. However, Metzner et al.[20] recommended CMV drivers wait seven half-lives after using a benzodiazepine before operating a CMV. After seven half-lives, approximately 99.22 percent of the drug has been eliminated. Based on the Metzner et al.[20] recommendation for CMV operators, it was determined to use seven half-lives in the current project. To calculate these half-lives, the researcher added the absorption rate to the time the drug was ingested. This provided an estimation of when the drug's chemical properties affected the driver. The half-life elimination rate was added to this time. This represented the first half-life. The second half-life was calculated by adding the half-life elimination rate to the end time of the first half-life. The following half-lives were calculated using the same method. For example, at 8:00 a.m. a driver ingested a drug with an absorption rate of 60 minutes and a half-life elimination rate of 120 minutes. The first half-life in this example was between 9:00 a.m. and 11:00 a.m., the second half-life was between 11:00 a.m. and 1:00 p.m., the third half-life was between 1:00 p.m. and 3:00 p.m., and so forth.

6. Identified known adverse reactions that could negatively impact driving performance. Researchers identified the known adverse reactions (i.e., side effects) for each drug and compared them to a predefined list of conditions that could negatively impact driving performance. The predefined list included abnormal thinking, ataxia, aggression, blurred vision, confusion, decreased attention, decreased coordination, diplopia, dizziness, drowsiness, dyskinesia, fainting, fatigue, hallucinations, light-headedness, nystagmus, sedation, slowed reaction time, somnolence, suicidal tendencies, unsteadiness, vertigo, and weakness. The drug was coded as a performance-deteriorating drug if one of these adverse reactions was possible. Appendix D shows the possible performance-deteriorating drugs and their respective adverse reactions.

7. Determined if the drug was available OTC or by Rx only. Researchers looked up each drug entry using the FDA's website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Based on the dose ingested by the driver, the website indicated if the drug was available OTC or if a prescription was needed. If a drug was not listed on the website, additional Internet research was required. Appendix B lists the drugs considered Rx and OTC.

SCE RISK ANALYSIS

The data were analyzed in several different ways. First, drug use was investigated using descriptive statistics, tables, and plots. Researchers determined how many drivers were using drugs and the distribution of drug entries per driver. The correlation between Rx drug entries and OTC drug entries was measured to determine if drivers had similar usage of Rx and OTC drugs. Drug use was plotted across time of day, and the frequency of drug use by activity type was tabulated. Tables describing the frequency and percentage of different drug types and drug reactions were also included.

The risk of drug use was calculated by comparing SCEs and BLs that occurred within a drug half-life to SCEs and BLs not occurring within a drug half-life (for the same half-life period). Odds ratios (ORs) and corresponding 95 percent lower confidence limits (LCL) and upper confidence limits (UCL) were calculated using logistic regression models that controlled for each

individual driver. The variable to be tested (e.g., adverse reaction, classification, etc.) was included in the regression model as a covariate, and the results are presented by variable, across all seven half-lives. Each half-life was investigated separately with a new logistic regression model.

CHAPTER 3. **RESULTS**

As the current project was a pilot test of the feasibility in using naturalistic data to analyze Rx and OTC drug use, the following results should be considered with caution. Although there were thousands of individual drug entries, many medications were only used by one or two drivers. Moreover, medications can affect people differently. Thus, it was not possible to make generalizations based on such a small sample.

PREVALENCE OF DRUG USE AMONG CMV DRIVERS

Drivers recorded Rx and OTC drug use on their activity register with the time of use and the amount. Ninety-seven drivers completed activity registers, and 94 (97 percent) reported at least one incident of Rx or OTC drug use. Of the 9,120 drug entries recorded by the drivers, 75.11 percent were OTC (6,850 entries) and 24.89 percent were Rx (2,270 entries). Of the 97 drivers with activity register data, 73 percent (71 drivers) had no Rx drug entries in their activity register; thus, the results for Rx drugs should be considered exploratory in nature given the small sample size. Table 4 details the distribution of the remaining 26 drivers. The maximum number of Rx drug entries per driver was 390 entries (approximately 13 per day).

Table 4. Distribution of Rx drug entries per driver in one month.

Rx Drug Entry Count	Number of Drivers
0	71
1 to 50	12
51 to 100	7
101 to 150	3
151 to 200	2
201 or more	2

OTC drug use was far more common. Of the 97 drivers with activity register data, 3 percent (3 drivers) had no OTC drug entries in their activity register. Table 5 details the remaining 94 drivers' distribution of OTC drug entries. The maximum number of OTC drug entries per driver was 423 entries (approximately 14 per day). As Table 5 illustrates, OTC drug use was very common among the drivers.

Table 5. Distribution of OTC drug entries per driver in one month.

OTC Drug Entry Count	Number of Drivers
0	3
1 to 50	40
51 to 100	32
101 to 150	14
151 to 200	5
201 or more	3

The correlation between Rx and OTC drug use was examined in the next analysis. Each driver's percentage of Rx drug entries and OTC drug entries was calculated. These percentages were plotted using a scatterplot (Figure 4), and the correlation was measured using a Pearson

correlation. The scatterplot shows a slight correlation between OTC and Rx entries, with a correlation coefficient of 0.2249.

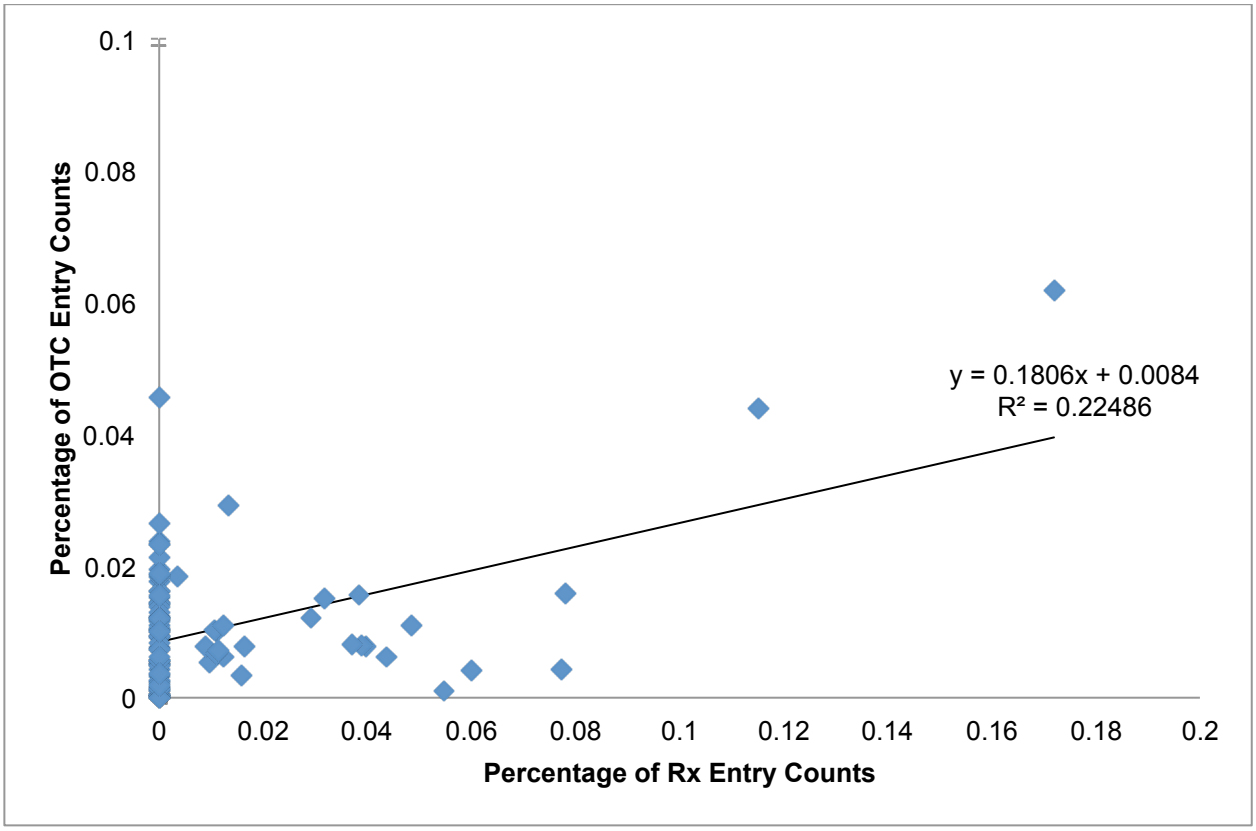


Figure 4. Graph. Scatterplot of Rx drug entry count percentage and OTC entry count percentage.

The next analysis considered what percentage of shifts, including the on-duty time and off-duty time, had reported Rx or OTC drug use. Again, 71 of the 97 drivers reported zero shifts with Rx drug use. Four of the remaining 26 drivers reported Rx drug use in 50 percent or fewer of their shifts. The remaining 22 drivers reported Rx drug use in over 50 percent of their shifts. Five drivers reported Rx drug use in all (100 percent) of their shifts. The distribution of drivers with varying levels of shifts with Rx use is displayed in Table 6.

Table 6. Percentage of drivers' shifts with Rx drug use.

Percentage of Shifts	Number of Drivers
0% – 10%	71
11% – 20%	0
21% – 30%	1
31% – 40%	2
41% – 50%	1
51% – 60%	0
61% – 70%	0
71% – 80%	1
81% – 90%	4
91% – 100%	17

Three drivers reported zero shifts with OTC drug use. Nineteen of the 94 remaining drivers reported OTC drug use in 50 percent of less of their shifts. The remaining 75 drivers reported OTC drug use in more than 50 percent of their shifts. Twenty-six drivers reported OTC drug use in all (100 percent) of their shifts. The distribution of drivers with varying levels of shifts with OTC drug use is displayed in Table 7. As shown in Table 7, the majority of drivers (51) reported OTC use in over 90 percent of their shifts.

Table 7. Percentage of drivers' shifts with OTC drug use.

Percentage of Shifts	Number of Drivers
0% – 10%	5
11% – 20%	5
21% – 30%	3
31% – 40%	4
41% – 50%	5
51% – 60%	1
61% – 70%	2
71% – 80%	6
81% – 90%	15
91% – 100%	51

Drivers noted the time of drug use in their activity register. Rx and OTC drug entry counts over the hours of the day are shown in Figure 5. Rx and OTC drug use peaked in frequency between 7:00 a.m. and 9:00 a.m. with another small peak in the evening from approximately 6:00 p.m. to 9:00 p.m.

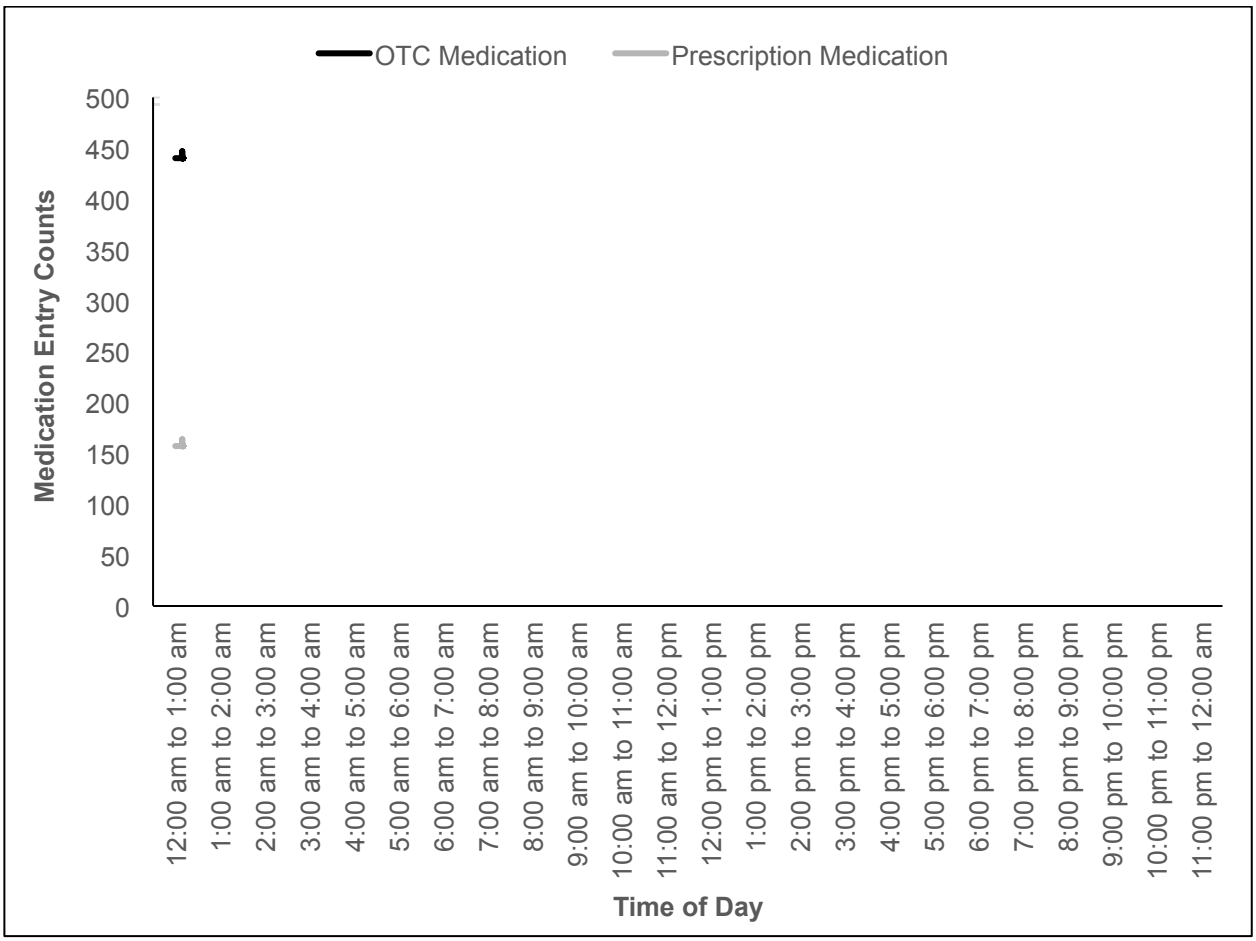


Figure 5. Graph. Rx and OTC drug use by time of day.

The driver activity at the time of drug ingestion was matched using time data and drug data. Table 8 shows the percentage of Rx and OTC drug entries marked during various activity codes. The activity codes were defined by their duty status and the activity description. The OTC medications appeared to be taken most often while driving the truck (28.61 percent of entries during activity code 1). The Rx medications were reportedly taken most often while resting off duty (22.52 percent of entries during activity code 8).

Table 8. Percentage of Rx and OTC drug use across activities.

Activity Code	Activity Description	Percentage of Rx Entries	Percentage of OTC Entries
1	On Duty – Driving Truck	9.62%	28.61%
2	On Duty – Heavy Work (e.g., loading/unloading)	0.21%	1.41%
3	On Duty – Sleep	4.76%	2.16%
4	On Duty – Rest	7.40%	6.09%
5	On Duty – Eating	2.75%	6.64%
6	On Duty – Light Work	8.77%	11.94%
7	Off Duty – Sleep	9.51%	4.77%
8	Off Duty – Rest (e.g., not asleep, watching TV, resting)	22.52%	14.31%
9	Off Duty – Eating	14.80%	9.14%
10	Off Duty – Light House Work (e.g., dishes)	2.01%	2.54%
11	Off Duty – Heavy House Work (e.g., mowing lawn)	0.32%	0.94%
12	Off Duty – Light Leisure Activity (e.g., walking, Internet)	5.07%	3.28%
13	Off Duty – Heavy Leisure Activity (e.g., running, sports)	0.42%	0.19%
14	Off Duty – Driving Other Vehicle (not work related)	3.07%	4.37%
15	Off Duty – Other	8.46%	3.28%
16	Off Duty – Left Blank – Potential Rest Off Duty	0.11%	0.14%
17	On Duty – Left Blank – Potential Work On Duty	0.11%	0.09%
18	On Duty – Left Blank – Potential Rest On Duty	0.11%	0.12%

Each drug entry was evaluated for possible driving-performance-deteriorating impacts (e.g., no, yes, or unknown). Table 9 below details the number and percentage of entries in the performance-deteriorating categories. Of the reported drugs, Rx drugs had possible performance-deteriorating qualities in 61.23 percent of entries, and OTC drugs had possible performance-deteriorating qualities in just 1.07 percent of entries. Approximately a third of the Rx drug entries (34.85 percent) and 98.93 percent of OTC drug entries had no performance-deteriorating qualities.

Table 9. Rx and OTC drug entries with possible performance-deteriorating effects.

Impact Performance	Number of Rx Entries	Rx Percentage	Number of OTC Entries	OTC Percentage	Overall Entries	Overall Percentage
Yes	1,390	61.23%	73	1.07%	1,463	16.04%
No	791	34.85%	6,777	98.93%	7,568	82.98%
Unknown	89	3.92%	0	0.00%	89	0.98%
Total	**2,270**	**100.00%**	**6,850**	**100.00%**	**9,120**	**100.00%**

Each drugs' possible driving-related adverse reactions (e.g., drowsiness) were noted by researchers during the medication coding process. Some drugs had no driving-related adverse reactions. The number and percentage of possible driving-related adverse reactions are shown in Table 10. Drugs could have up to six adverse reactions listed; therefore, the rows in the table below do not sum to the total number of Rx or OTC entries. Of the OTC entries, 6,777 entries (98.93 percent) had no driving-related adverse reactions, and 791 of the Rx entries (34.85

percent) had no driving-related adverse reactions. The most common possible driving-related adverse reaction in Rx drugs was dizziness (44.27 percent of entries). The most common possible driving-related adverse reaction in OTC drugs, although minimally observed in the entries, was drowsiness (0.79 percent of entries).

Table 10. Known driving-related adverse reactions in Rx and OTC drug entries.

Adverse Reactions	Number of Rx Entries	Rx Percentage	Number of OTC Entries	OTC Percentage	Overall Entries	Overall Percentage
Asthenia	35	1.54%	0	0.00%	35	0.38%
Blurred Vision	28	1.23%	4	0.06%	32	0.35%
Dizziness	1,005	44.27%	30	0.44%	1,035	11.35%
Drowsiness	48	2.11%	54	0.79%	102	1.12%
Fatigue	483	21.28%	0	0.00%	483	5.30%
Lightheadedness	57	2.51%	0	0.00%	57	0.63%
Sedation	6	0.26%	4	0.06%	10	0.11%
Slowed Reaction Time	0	0.00%	4	0.06%	4	0.04%
Somnolence	284	12.51%	0	0.00%	284	3.11%
Tiredness	57	2.51%	0	0.00%	57	0.63%
Unsteadiness	1	0.04%	4	0.06%	5	0.05%
Vertigo	135	5.95%	0	0.00%	135	1.48%
Weakness	8	0.35%	0	0.00%	8	0.09%
Unknown	89	3.92%	0	0.00%	89	0.98%
N/A	791	34.85%	6,777	98.93%	7,568	82.98%

The Rx and OTC drug entries were also grouped into broader drug classifications. Table 11 shows the number and percentage of the drug classifications. As some medications were a combination of different drugs, drugs could be classified into multiple categories. Thus, the columns below do not sum to the total number of entries. The most frequently recorded Rx drug classifications were cardiac medication (44.54 percent) and “other” (39.74 percent). The most frequently recorded OTC drug classification was stimulant–caffeine (78.57 percent). See Appendix B for a list of drugs and their classification.

Table 11. Rx and OTC drug classifications.

Classification	Number of Rx Entries	Rx Percentage	Number of OTC Entries	OTC Percentage	Overall Entries	Overall Percentage
Antihistamine	56	2.47%	108	1.58%	164	1.80%
Cardiac medication	1,011	44.54%	27	0.39%	1,038	11.38%
Vitamin/herbal supplement	0	0.00%	958	13.99%	958	10.50%
Other	902	39.74%	87	1.27%	989	10.84%
Pain medication	135	5.54%	400	5.78%	535	5.65%
Psychiatric medication	221	9.74%	0	0.00%	221	2.42%
Sedative/hypnotic	33	1.45%	4	0.06%	37	0.41%
Stimulant - caffeine	0	0.00%	5,382	78.57%	5,382	59.01%
Stimulant	78	3.44%	56	0.82%	134	1.47%
N/A	0	0.00%	6	0.09%	6	0.07%

Rx AND OTC DRUG USE AND RISK OF AN SCE

The probabilities of an SCE while driving under an Rx and OTC drug were compared across the categories of therapeutic classification, adverse reactions, classification, and performance-deteriorating quality. The drug entries were compared to the list of SCEs. For the first half-life, a drug entry was marked as containing an SCE if an SCE occurred between the active-in-body time and the first half-life end time. For the following half-lives, a drug entry was marked as containing an SCE if an SCE occurred between the end time of the previous half-life and the end time of the half-life of interest. The number of drug entries containing an SCE was then compared to the number of drug entries not containing an SCE. Drug categories with similar risk were expected to have similar rates of entries containing an SCE. The OR calculations, controlling for driver, indicated overall drug use was associated with a lower risk of an SCE for the first six half-lives (Table 12). Drug use was not associated with an increase or decrease in risk of an SCE in the last (seventh) half-life. Significant ORs are denoted with an "*" in Table 12.

Table 12. SCE risk for any Rx and OTC drug.

Half-Life	SCEs in Half-Life for any Drugs	SCEs Not in any Drugs' Half-Life	BLs in Half-Life for any Drugs	BLs Not in any Drugs' Half-Life	OR	LCL	UCL
1	810	1,934	1,960	2,957	0.6319*	0.4113	0.9707
2	852	1,892	2,167	2,750	0.5715*	0.3611	0.9045
3	851	1,893	2,130	2,787	0.5882*	0.3907	0.8857
4	771	1,973	1,919	2,998	0.6105*	0.3992	0.9337
5	639	2,105	1,747	3,170	0.5508*	0.3541	0.8568
6	540	2,204	1,580	3,337	0.5175*	0.3140	0.8527
7	579	2,165	1,404	3,513	0.6692	0.4341	1.0315

Rx Drug Use versus No Drug Use

Table 13 evaluates the risk of an SCE associated with Rx drug use compared to no drug use (no Rx or OTC drugs). The ORs for all seven half-lives were very similar, ranging between 0.6222 and 0.7037, but the ORs were not considered statistically significant. The use of Rx drugs was not associated with an increase or decrease in risk of an SCE in all seven half-lives.

Table 13. SCE risk for any Rx drug.

Half-Life	SCEs in Half-Life for Rx Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Rx Drugs	BLs Not in Drugs' Half-Life	OR	LCL	UCL
1	383	1,934	881	2,957	0.6647	0.3538	1.2487
2	357	1,892	834	2,750	0.6222	0.3255	1.1891
3	335	1,893	763	2,787	0.6464	0.3429	1.2186
4	304	1,973	719	2,998	0.6425	0.3368	1.2256
5	299	2,105	713	3,170	0.6315	0.3345	1.1922
6	315	2,204	742	3,337	0.6428	0.3384	1.2209
7	291	2,165	671	3,513	0.7037	0.3767	1.3147

OTC Drug Use versus No Drug Use

Table 14 evaluates SCE risk associated with OTC drug use compared to no drug use. For all seven half-lives, the ORs were significant and showed the use of OTC drugs were associated with a decrease in the risk of an SCE. Significant ORs are denoted with an "*" in Table 14.

Table 14. Risk of an SCE for any OTC drug.

Half-Life	SCEs in Half-Life for OTC Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for OTC Drugs	BLs Not in Drugs' Half-Life	OR	LCL	UCL
1	541	1,934	1,375	2,957	0.6016*	0.4022	0.8997
2	636	1,892	1,632	2,750	0.5664*	0.3637	0.8821
3	670	1,893	1,716	2,787	0.5748*	0.3902	0.8468
4	605	1,973	1,487	2,998	0.6182*	0.4110	0.9300
5	428	2,105	1,283	3,170	0.5024*	0.3333	0.7572
6	315	2,204	1,039	3,337	0.4590*	0.2870	0.7341
7	377	2,165	934	3,513	0.6550*	0.4309	0.9956

As mentioned above, caffeine accounted for approximately 79 percent of all OTC drug used. Thus, caffeine may have influenced the association between OTC drugs and risk of an SCE. Table 15 shows the SCE risk associated with non-caffeine OTC drug use compared to no drug use. For all seven half-lives, the ORs were not statistically significant. The use of non-caffeine OTC drugs was not associate with an increase or decrease in risk of an SCE for all seven half-lives.

Table 15. Risk of an SCE for non-caffeine OTC drug.

Half-Life	SCEs in Half-Life for Non-Caffeine OTC Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Non-Caffeine OTC Drugs	BLs Not in Drugs' Half-Life	OR	LCL	UCL
1	69	1,934	236	2,957	0.9443	0.5889	1.5152
2	81	1,892	273	2,750	1.0977	0.6285	1.9194
3	83	1,893	237	2,787	1.0684	0.6519	1.7513
4	74	1,973	259	2,998	0.9042	0.6006	1.3605
5	104	2,105	318	3,170	0.9470	0.6406	1.3986
6	83	2,204	249	3,337	1.3495	0.8278	2.1978
7	117	2,165	273	3,513	0.9960	0.6357	1.5601

SCE Risk of Performance-deteriorating Drugs

The next analysis used similar methods as those above to determine if drugs with performance-deteriorating adverse effects were associated with an increased risk of a SCE when compared to no drug use. Table 16 shows the resulting ORs and CLs. The ORs for all seven half-lives were not significant and did not show an association with an increased risk of an SCE for drugs with potentially performance-deteriorating adverse effects.

Table 16. SCE risk for any Rx and OTC drugs with performance-deteriorating adverse reactions.

Half-Life	SCEs in Half-Life for Performance-Deteriorating Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Performance-Deteriorating Drugs	BLs Not in Drugs' Half-Life	OR	LCL	UCL
1	291	1,934	608	2,957	0.7318	0.3726	1.4374
2	271	1,892	611	2,750	0.6447	0.3205	1.2968
3	255	1,893	541	2,787	0.6940	0.3482	1.3832
4	240	1,973	533	2,998	0.6842	0.3434	1.3633
5	233	2,105	517	3,170	0.6787	0.3451	1.3349
6	251	2,204	591	3,337	0.6430	0.3244	1.2748
7	271	2,165	509	3,513	0.8639	0.4810	1.5518

Non-performance-deteriorating drugs were also compared to no drug use. The ORs for all seven half-lives were statistically significant and ranged from 0.4520 to 0.5903 (Table 17). Non-performance-deteriorating drug use was associated with a significantly lower risk of an SCE compared to no drug use. This significant result was likely due to caffeine use. Significant ORs are denoted with an "*" in Table 17.

Table 17. Risk of an SCE for any Rx and OTC drugs with non-performance-deteriorating adverse reactions.

Half-Life	SCEs in Half-Life for Non-Performance-Deteriorating Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Non-Performance-Deteriorating Drugs	BL Not in Drugs' Half-Life	OR	LCL	UCL
1	618	1,934	1,652	2,957	0.5720*	0.3775	0.8667
2	677	1,892	1,858	2,750	0.5296*	0.3369	0.8326
3	722	1,893	1,909	2,787	0.5568*	0.3744	0.8281
4	653	1,973	1,681	2,998	0.5903*	0.3888	0.8962
5	492	2,105	1,474	3,170	0.5027*	0.3285	0.7691
6	369	2,204	1,236	3,337	0.4520*	0.2753	0.7421
7	386	2,165	1,129	3,513	0.5548*	0.3353	0.9178

Table 18 shows the SCE risk associated with non-caffeine, non-performance deteriorating drugs compared to no drug use. For all seven half-lives, the ORs were not statistically significant. The use of non-caffeine, non-performance deteriorating drugs were not associate with an increase or decrease in risk of an SCE for all seven half-lives.

Table 18. Risk of an SCE for any non-caffeine Rx and OTC drugs with non-performance-deteriorating adverse reactions.

Half-Life	SCEs in Half-Life for Non-Caffeine, Non-Performance-Deteriorating Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Non-Caffeine, Non-Performance-Deteriorating Drugs	BL Not in Drugs' Half-Life	OR	LCL	UCL
1	188	1,934	236	2,957	1.063	0.726	1.556
2	180	1,892	655	2,750	0.763	0.491	1.186
3	170	1,893	611	2,787	0.777	0.528	1.142
4	177	1,973	618	2,998	0.887	0.634	1.241
5	181	2,105	637	3,170	0.873	0.634	1.202
6	151	2,204	527	3,337	0.795	0.562	1.124
7	144	2,165	537	3,513	0.926	0.661	1.298

Drug Classifications

Drugs were labeled with up to three of the ten classifications. For consistency and simplicity, many drugs in the NTDS were classified as "other." These drugs did not fit into any of the other classifications. Some examples of the therapeutic classes labeled as "other" included decongestants, H_2-blockers, proton pump inhibitors, biguanide, corticosteroid, semisynthetic ampicillin derivatives, and aminopenicillin (see Appendix B for all drugs classified as "other"). Each classification was tested for a relationship with involvement in an SCE using a logistic regression. The logistic regression model controlled for each driver. Of the 10 classifications, caffeine was the only one where a large number of drivers used the drug classification multiple times. Thus, only the analysis related to caffeine is presented. As shown in Table 19, drugs classified as caffeine stimulants were associated with a decreased risk of SCE involvement for half-lives 1 through 6 (OR = 0.6204, OR = 0.5818, OR = 0.5745, OR = 0.6572, OR = 0.5076, and OR = 0.4385, respectively). The OR for the seventh half-life was not significant, but it was in the same direction (less than 1). Significant ORs are denoted with an "*" in Table 19.

Table 19. Risk of an SCE for caffeine stimulant drugs.

Half-Life	SCEs in Half-Life for Caffeine Stimulant Drugs	SCEs Not in Drugs' Half-Life	BLs in Half-Life for Caffeine Stimulant Drugs	BLs Not in Drugs' Half-Life	OR	LCL	UCL
1	480	1,934	1,183	2,957	0.6204*	0.4159	0.9254
2	574	1,892	1,434	2,750	0.5818*	0.3751	0.9023
3	599	1,893	1,535	2,787	0.5745*	0.3932	0.8394
4	545	1,973	1,260	2,998	0.6572*	0.4383	0.9855
5	333	2,105	988	3,170	0.5076*	0.3411	0.7552
6	232	2,204	801	3,337	0.4385*	0.2732	0.7038
7	260	2,165	671	3,513	0.6287	0.3870	1.0216

CHAPTER 4. **DISCUSSION**

The main objective of the current project was to conduct a comprehensive analysis of CMV driver Rx and OTC drug use and their relationship to involvement in an SCE using the NTDS data set. This project was designed to address the following questions: (i) what was the prevalence of Rx and OTC drug use among CMV drivers, and (ii) was there an association between Rx and OTC drug use and involvement in an SCE?

CONCLUSIONS

This project served as a pilot study that illustrated the feasibility of using naturalistic driving data to assess the risk of an SCE associated with Rx and OTC drug use while driving. Results from this study showed that Rx drug use, in general, was not associated with an increased or decreased risk of involvement in an SCE. However, OTC drug use was associated with a decreased risk of being involved in an SCE, in large part due to caffeine. Non-caffeine OTC drug use was not associated with an increased or decreased risk of involvement in an SCE. Given the small sample of drivers using specific classifications of medication, the results should be viewed with caution. The data, especially for Rx drugs, were limited given the small number of drug entries for specific classifications and the small number of drivers using each drug. As caffeine was the only drug classification where a large number of drivers used the drug classification multiple times, this should be considered the only reliable and valid analysis regarding risk of an SCE.

The current research found that 97 percent of CMV drivers in the NTDS used Rx and/or OTC drugs during their participation in the study. Of these drivers, all used an OTC drug at least once (mostly caffeine use), and 25 percent used at least one Rx drug. The frequency of Rx drug use was consistent with the results obtained by the LTCCS where Rx drug use was present during 30 percent of one truck/one passenger vehicle crashes.[4] However, OTC drug use was far more common in the NTDS than the 19 percent present in the LTCCS. This was because caffeine was not considered an OTC drug in the LTCCS. These results may suggest that Rx drug use showed up in 30 percent of the LTCCS crashes as this is the base rate of Rx drug use among CMV drivers.

Prevalence of Rx and OTC Drug Use among CMV Drivers

Results from this study showed that nearly all (97 percent) CMV drivers reported the use of at least one Rx and/or OTC drug during their one month of participation. Of these drivers, only 27 percent reported Rx drug use. Given the small sample size, it is premature to make associations with the general population. However, the results suggest that CMV drivers may take fewer Rx drugs compared with the 48.5 percent of the general population that take at least one Rx drug in the past month.[15] Conversely, 97 percent of the drivers reported OTC drug use at least once during the month; however, many of the drivers reported using OTC drugs at least once a day. Most of these drug entries were caffeine (78 percent of all OTC drugs). These results were similar to the FDA's statistic that 80 percent of adults in the U.S. consume caffeine every day.[18]

Drivers reported using Rx drugs in 17 percent of their shifts and OTC drugs in 53 percent of their shifts. The use of Rx and OTC drugs peaked between the hours of 7:00 a.m. to 9:00 a.m. and then again between 6:00 p.m. and 9:00 p.m. These times seem to correspond with drug use

during breakfast and dinner (similar with medications requiring two doses per day). Furthermore, caffeine is often consumed in the morning after waking. Additional results found that the majority of drivers use Rx medications while off duty. This practice may indicate that drivers use caution to limit the adverse reactions of drugs. Conversely, results showed that most drivers were on duty driving when taking OTC drugs. This result may indicate that many drivers use caffeine while driving to possibly combat sleepiness and/or fatigue.

Association between Rx and OTC Drug Use and Involvement in an SCE

Results from this project showed that Rx drug use, in general, was not associated with an increased or decreased risk of being involved in an SCE. However, OTC drug use, in general, was associated with a decreased risk of SCE involvement in all seven half-lives (ORs ranging from 0.46 to 0.66). This decrease in risk was due to caffeine. The protective benefit was eliminated when caffeine was excluded from analyzes. Additionally, results showed that Rx and OTC drugs with adverse reactions that may negatively impact driving were not associated with an increased risk of SCE involvement. However, Rx and OTC drugs without adverse reactions that may negatively impact driving were found to be associated with a deceased risk of SCE involvement in all seven half-lives (ORs ranging from 0.45 to 0.59). The protective benefit was again eliminated when caffeine was excluded from analyzes. Again, these results should be viewed with caution given the small sample size of specific drug use and the number of drivers that used each drug (e.g., a number of the drugs were only consumed by one or two drivers and may have only been used a few times).

Stimulants

Previous research regarding the use of Rx and OTC stimulants showed a decreased risk of crash involvement.[9-13] For example, research found that drivers who use caffeine during circadian lows (between 2:00 a.m. and 6:00 a.m.) had fewer lane deviations compared to drivers that did not use caffeine or those drivers that had a short 30-minute nap.[11-13] Results from this study support the conclusions from previous research. Caffeine while driving was found to be associated with a decreased risk of SCE involvement in all seven half-lives (ORs ranging from 0.44 to 0.66).

The results pertaining to caffeine use were especially promising for CMV drivers. Due to long working hours, limited opportunities to sleep, nighttime operations, and pressure to work overtime, CMV drivers do not routinely get the recommended 8 hours of sleep a night. Caffeine may be a good short-term countermeasure to combat fatigue when rest/sleep is not possible. However, reliance on caffeine to fight fatigue should not be the primary countermeasure. Sleep is the best method to fully recover from fatigue and sleepiness.

LIMITATIONS

Although the data mined in this project were comprehensive, there were several factors limiting the conclusions for determining the risk of an SCE associated with Rx and OTC drug use while operating a CMV. These limitations are listed below.

- There were 9,120 drug entries recorded by the drivers, but a number of the drugs were only consumed by one or two drivers and may have only been used a few times.

Additional data from other drivers using the same drug are needed to fully understand the link between these drugs and the risk of being involved in an SCE. Moreover, additional data are needed to perform analyses at the therapeutic class level.

- The majority of drugs in the current study had a range listed for their absorption and half-life elimination rates. Thus, different people are known to absorb and eliminate drugs at different rates. The data coding protocol for this project required using the lower end of the range. It is possible these rates were not accurate for the drivers that participated in this project.
- Medication usage data were self-reported by the participants. As with any self-report study, there is a possibility the drivers were not completely honest and/or forgot to report their medication use.
- The drivers' reported dosage of medication was not used to determine how long a drug was active in their bodies. Researchers only used dosage information to assist in determining the exact drug consumed.
- Drug companies are required to note all adverse effects determined to be associated with a drug, even if it is very rare or not serious. In many cases, these adverse effects are experienced by less than 5 percent of the people who use the drug. Thus, a drug may have been labeled as performance deteriorating, but it is possible that many of the drivers did not experience the performance-deteriorating effects.
- It was not possible to determine if the medications influenced SCE risk or if the disease/symptoms influenced SCE risk. And, it is possible the medication alleviated a condition, thus improving driving performance.
- Polydrug use was not examined. It is possible that using more than one medication at a time influenced SCE risk.
- It is possible that other driver factors that were not collected mitigated the results of drug use on SCE risk.

FUTURE RESEARCH

Although there is a growing body of research examining the effects of Rx and OTC drug use on crash risk, more research is needed. Listed below are areas for future research to better understand the prevalence and impact of Rx and OTC drug use on CMV crash risk.

- A larger CMV naturalistic driving data set including drivers' medication use is needed. The current study included self-reported medication use from 97 drivers, but many medications were only used by one or two drivers.
- More detailed information regarding the reason for medication use is needed. This additional information may assist in determining the risk associated with the illness itself versus the risk or protective benefits associated with the medication.
- A questionnaire could be used to determine if any adverse reactions were experienced by the driver. Although a medication may potentially cause dizziness or fatigue, it is possible that a driver did not experience those adverse reactions.

APPENDIX A. MEDICATION CODING PROTOCOL

This project will use VTTI's Naturalistic Truck Driving Study (NTDS) data set to conduct a comprehensive analysis of truck driver Rx and OTC drug use and its relationship to involvement in a safety-critical event (SCE). The SCEs and BLs recorded in the NTDS will be used to determine the following:

1. Prevalence of Rx and OTC drug use among truck drivers.
2. Relationship between Rx and OTC drug use and involvement in an SCE.
3. Correlates that predict crash involvement when using Rx and OTC drugs.

This document specifies the protocol coding the medication register associated with the NTDS data set. For each medication listed in the activity register, you will identify the following:

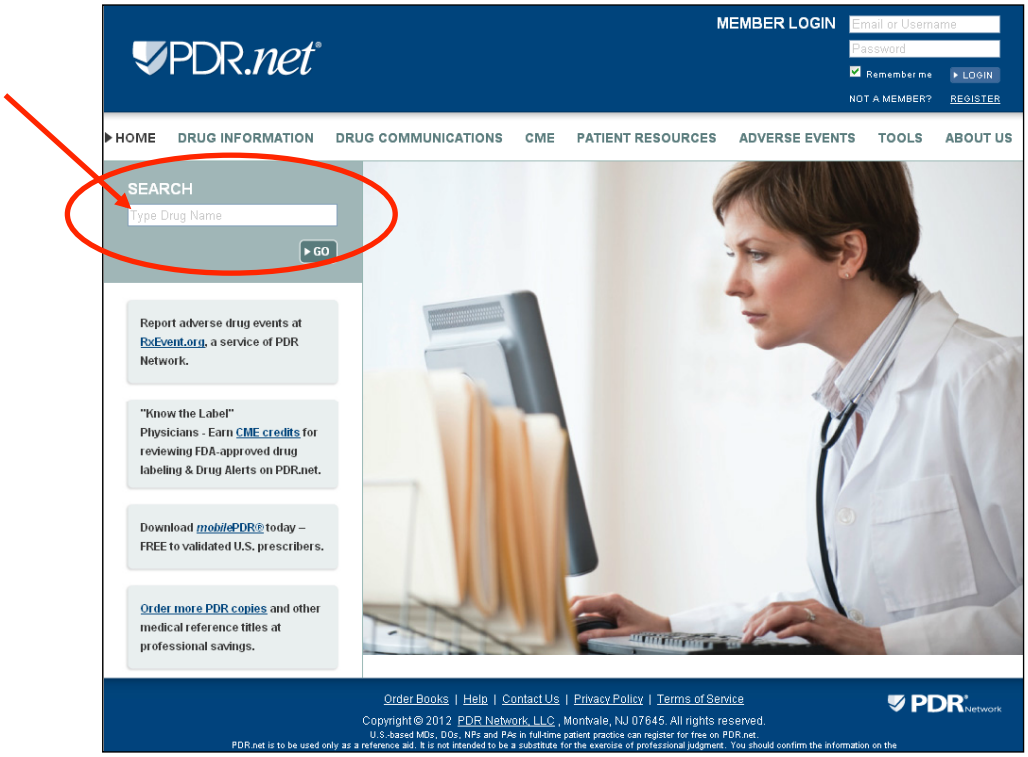
- If the medication was a Rx drug or OTC
- The therapeutic class of the medication
- The drug's classification
- The absorption and elimination rate of the drug
- The window of time that the drug was active
- If the drug could have impacted driving performance
- Adverse reactions that are pertinent to driving

STEPS FOR MEDICATION DATA CODING

1. **Open Activity Register database**
   a. P:\451141\Working\Documents\Medication Reduction\8Truck Medication_Reduction.xls

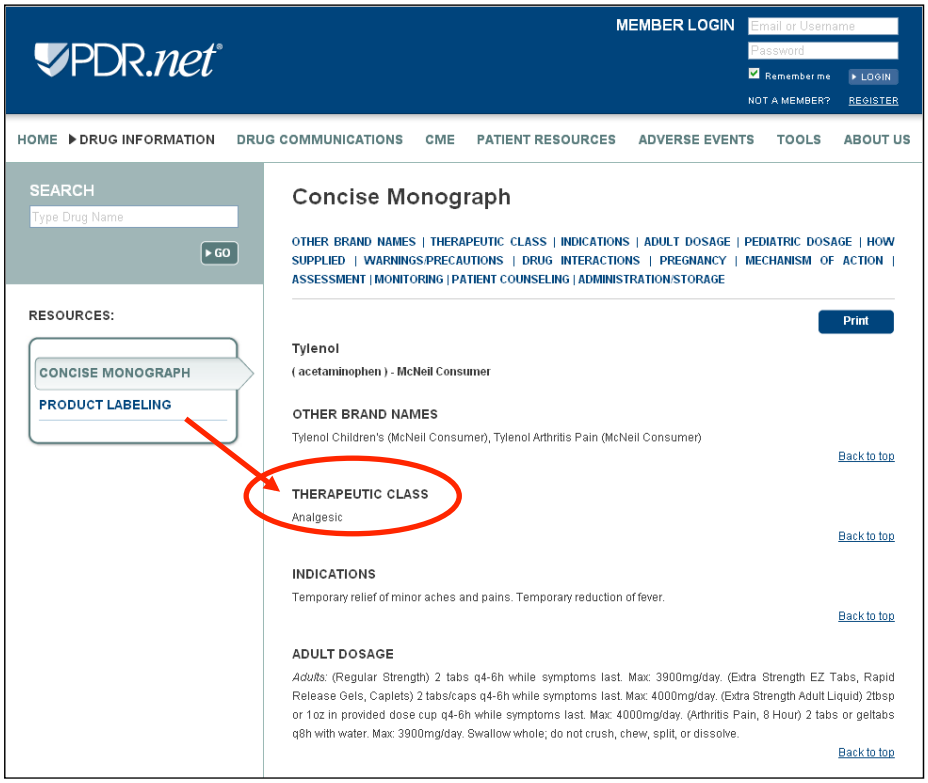
2. **Sign out driver on signout tab**
   a. Enter your initials next to the next driver on the list
   b. Enter the data you sign out that driver
   c. Go to the tab for the driver you signed out.

3. **Review each row for medications taken and classify according to the PDR:**
   a. Look at the information in Column E titled "Details"
   b. Open the known medication Excel database located here: Medications.xls
   c. Look for the medication in the database. If it is listed, enter the information into the medication reduction database. YOU MAY NOW SKIP TO STEP 4 C.
   d. If the drug is not already listed in the known medication database, open an internet browser and go to pdr.net
   e. Enter in the drug name from Column E into pdr.net



f. If your search turns up multiple options for the drug (e.g., search for Tylenol and the results produce Tylenol 8 Hour Caplets, Tylenol Allergy, Tylenol Arthritis, Tylenol Cold, etc.) and you cannot deduce which option was taken by the driver, review the dosage taken by the driver. Then review each option to see what medication is available in the dosage used. If this does not prove helpful in deducing which medication was taken, please choose the most basic option. In the example above, you would choose Tylenol 8 hour Caplets.

g. In Column H titled "Therapeutic Class from PDR" enter the Therapeutic Class as identified in the PDR or on pdr.net



h. Vitamin/herbal medications and supplements may not be found using the PDR or pdr.net. For these medications, please put "Herbal medication and Supplement" in Column H and Column I.

i. Next, you need to categorize drugs into the following classifications (see Table 1) based on the therapeutic class. Put the classification in Column I.

j. Not all therapeutic classes are listed in Table 1. *If you do not see a drug's therapeutic class listed, please make a note in the comments section of the reduction log and notify Matt Camden.*