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Investigating the Association Between Sedative Hypnotic Prescription Exposures and  
Motor Vehicle Crashes

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## **Abstract**

### Investigating the Association between Sedative Hypnotic Prescription Exposures and Motor Vehicle Crashes

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#### **Background**

Motor vehicle crashes occur daily and may be fatal for the driver, passengers or bystanders. Crashes have been shown to be associated with certain medical conditions and exposure to prescription medications that impair the ability to drive. We sought to create a linked, population-based longitudinal crash and medical care use dataset and to evaluate the relationships between prescription opioid and sedative hypnotic medication exposures and automobile crashes in Washington State.

#### **Methods**

Crash data from the Washington State Department of Transportation from 2002 to 2009 were linked to medical, pharmacy and administrative data from the Group Health Cooperative (GHC) for all eligible members. Continuous prescription exposures were defined based on fill records for opioids and sedatives. We estimated multivariate extended Cox regressions to investigate the association between police-reported crashes and prescription fills for opioids and sedative hypnotics. We also stratified our analyses by the length of continuous prescription fills.

## **Results**

A total of 676,694 subjects were included in the study. These individuals experienced 2.41 motor vehicle crashes per 100 person-years. Opioid prescription fills were associated with a hazard ratio of 1.37 (95% CI: 1.33 to 1.41). Stratifying opioid exposure by the length of continuous prescriptions resulted in a range of hazard ratios from 1.76 at 30 days (95% CI: 1.59 to 1.96) up to 11.33 at 120 days (95% CI: 9.18 to 13.98). Overall incident sedative prescriptions were associated with a hazard ratio of 2.23 (95% CI: 1.92 to 2.59). Stratifying continuous prescriptions by length revealed the highest risk group to be 121-240 days for all sedatives, trazodone and temazepam (overall HR: 6.84, 95% CI: 4.15 to 11.2). Zolpidem had no risk of crash in the first 30 days, yet risk climbed to a peak risk between 241-360 days (HR: 10.7, 95% CI: 3.9 to 29).

## **Discussion**

The risk of motor vehicle crash is increased in people who fill prescriptions for opioids and sedative hypnotics. The hazard ratios estimated are equivalent to blood alcohol concentrations in excess of double the legal limit to drive. Public health may be improved by reducing driving time when using these medications.

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## Chapter 1:

# Linking Health Maintenance Organization Medical and Pharmacy Records with Washington State Collision Data

## **Abstract**

### **Background**

Motor vehicle crashes occur daily and are events that may be fatal for the driver, passengers or bystanders. Crashes have been shown to be associated with certain medical conditions and exposure to prescription medications that impair the ability to drive. We sought to create a linked, population-based longitudinal crash and medical care use dataset in order to evaluate the relationships between prescription opioid and sedative hypnotic medication exposures and automobile crashes in Washington State. The purpose of this paper is to describe the development of the linked, longitudinal dataset and to present the findings from analyses to confirm the robustness of the linkage.

### **Methods**

Crash data from the Washington State Department of Transportation from 2002 to 2009 were linked to medical, pharmacy and administrative data from the Group Health Cooperative (GHC) for all eligible members. Correlations between injury reported crashes and medical care identified by diagnosis codes for acute pain, inflammation, contusion and motor vehicle crash injury, as well as prescription pain medications and muscle relaxants within 7 days of the crash report were investigated to evaluate the dataset linkages.

### **Results**

A study population of 676,705 subjects of driving age (21-79 years), residing in Washington State, and with at least one year of continuous health plan enrollment was identified from the GHC population of over 3 million during the eleven-year study period. Those individuals experienced 2.41 motor vehicle crashes per 100 person-years. Motor vehicle crashes were associated with medical care in 56% and prescription therapy in 33% of injury reported crashes (24% and 12% respectively for all crashes).

### **Discussion**

Linkage of state-level automobile crash data with medical data from an insured population generated a longitudinal repository of medication exposures and motor vehicle crash data. This database can be used to test hypotheses about the impact of medications on the ability of drivers to safely navigate the roadways. Roughly half of individuals involved in crashes sought medical care. It is possible that other drivers sought care after more than 7 days or used less traditional medical care (e.g. chiropractic care), which may not have been measured in this study. Even with these limitations, the longitudinal database is useful to examine relationships between medication exposures and motor vehicle crashes.

## Background

Motor vehicle crashes are commonplace in the United States. These events may cause significant or fatal injury, and also result in costs to individuals and to society.<sup>1</sup> There are many factors that may increase the likelihood of an individual driver to be involved in a motor vehicle crash. In 2002, the National Highway Traffic Safety Administration (NHTSA) commissioned a study to look at public and private databases in order to broadly investigate the association between motor vehicle crashes and multiple medications, medication interactions and drug-disease interactions in subjects over the age of 50 years.<sup>2</sup> This work was motivated by previously published research that investigated single drug or drug class associations with crashes and was centered on hypothesis generation for future work. Their main conclusion is that there exists a tangle of factors that impact an individual's ability to safely operate a motor vehicle. A recent systematic review evaluating pharmaceuticals and traffic safety concluded that large studies are needed to evaluate the association between pharmaceutical use and traffic crashes.<sup>3</sup>

Within Washington State there are over 100,000 law enforcement-reported traffic collisions annually. Safety legislation, enforcement, and changing norms such as improvements in road and vehicle safety have led to a steady decline in motor vehicle collisions since 2005. In 2005 there were 1,958 crashes per 100,000 state residents with 1,512 crashes per 100,000 reported in 2010, and a total of over 555,000 in the five years ending in 2010.<sup>4,5</sup> The incidence of motor vehicle crash fatalities in Washington State was 6.79 per 100,000 persons in 2010, down from 10.38 in 2005. These rates are below the national average of 10.63 per 100,000 from 2010 yet considerably higher than the best overall state rate of 3.97 per 100,000.<sup>6,7</sup> Drivers in the United States caused more than 32,000 crash related fatalities in 2010.<sup>7,8</sup> Continued efforts to reduce causes of traffic crashes and fatalities are of considerable interest to protecting public health.

We aimed to link medical and prescription records with motor vehicle crash data in order to evaluate the association between medical conditions or prescription drug exposures and motor vehicle crashes. Such linkages allow observational research to capture information about both the exposure of interest and a meaningful outcome as well as to compare the associations of several different exposures within a single population. Previous studies in Washington State have documented researchers' ability to link medical records with State Department of Transportation collision records.<sup>9,10,11</sup> These studies have utilized a publicly available algorithm for converting a subject's name and date of birth into a Washington State Driver's License number.<sup>12</sup> Our study sought to produce a linked, population-based longitudinal dataset to explore the association between prescription opioid and sedative hypnotic medication exposures and motor vehicle crashes.

We sought to link data from the Group Health Cooperative (GHC), a Washington State Health Maintenance Organization annually covering over 630,000 individuals, and the Washington State Department of Transportation (DOT) police-reported crash database. Furthermore, we sought to empirically confirm this linkage by matching collisions

recorded as injurious by the reporting officer with two potential markers of crash in the medical record, medical care encounters and prescriptions for pain and inflammation medications.

## **Methods**

### Setting

GHC's fully integrated health care system covered for over a half-million lives in Washington State. The GHC population closely resembled the underlying community within Washington State with respect to age, race, and gender. GHC membership has been stable; in 2001, 70% of GHC members >60 years of age had been enrolled in GHC for at least 10 years. Information on health plan enrollment, health care use including pharmacy utilization, laboratory values, diagnoses and procedures were recorded and maintained in GHC automated databases and were linked by a unique consumer number assigned to each enrollee. A fully integrated Electronic Medical Record (EMR) system that documents all patient care contacts has been in place at all GHC-owned clinics since 2005. The automated pharmacy database includes information on each prescription and over-the-counter medication dispensed since March 1977. Medical care and prescriptions dispensed to GHC enrollees are captured by the administrative database so long as they are reimbursed by GHC.

### Study Population

All adults aged 21 years or older as of January 1, 1999 or adults who reached 21 years of age during the study period while meeting all other inclusion criteria were eligible for the study. Inclusion criteria for all participants included: primary residence in Washington State, continuous GHC enrollment for at least 1 year between January 1, 1999 and December 31, 2009 with no more than a 60-day lapse in membership unless enrollment ended due to death, and participants must have also held prescription drug benefits with GHC. As we were primarily interested in active drivers, we excluded individuals aged over 79 years on January 1, 1999. Each subject's index date was defined by the first date of eligibility in GHC during the study period. Study end dates were recorded at disenrollment, death, or reaching 80 years of age during the study period. The minimum and maximum ages were determined by requirements of the Institutional Review Board. Requiring participants to hold their primary residence in Washington State sought to ensure a clean linkage with drivers license records from the State. And finally, the continuous enrollment criteria are set to facilitate a stable study population.

### Data

Staff at the Group Health Research Institute (GHRI) applied the study inclusion and exclusion criteria to the entire patient population at GHC in order to define the study population (Figure 1). Demographic characteristics, medical encounters, and prescription records were extracted from the electronic data warehouse for each study subject. Medical encounter ICD-9 codes and prescription medications were identified based on

the NHTSA analysis.<sup>2</sup> Each subject's Charlson Comorbidity Index was also calculated using an adapted algorithm that calculates the Index based on *International Classification of Diseases, Ninth Revision*, (ICD-9) codes from the GHC administrative database.<sup>13</sup> These scores were categorized into values of zero, one, two and three or greater.

The DOT maintained a crash database comprised of all police and state patrol reported crashes within the State of Washington. The database recorded pertinent information regarding the circumstances surrounding the crash, including the identity of the driver, date and time of the crash, officer-reported driver sobriety, blood alcohol level (when available), vehicle type, road type, road surface and lighting conditions, seat belt use, and officer-reported injuries and fatalities. Information on other passengers was also available but was not included in this study.

We utilized the driver's license number algorithm described by Gallian in 1991 in order to calculate each person's driver's license number.<sup>12</sup> This involves manipulating the subject's name and date of birth into an alphanumeric string and then using the string to calculate the final number in the string, which serves as a check digit. This algorithm was developed by IBM in the 1960's and is also used by the Canadian Province of Manitoba. The Driver License Number algorithm was applied to each member of the study population. This presumptive list of license numbers was provided to the Collision Data Center at the DOT. All crashes during the period from January 1, 2002 through December 31, 2009 where the primary driver in the crash was listed as matching one of the study driver's license numbers was returned in a total of four datasets, comprised of crashes reported on state, county, city and other roads (university campuses, tribal lands, etc). Crashes returned were matched with study participant demographic data. Crashes that occurred before or after each subject's study eligibility dates (index and end) were excluded from the analysis.

### Statistical Analyses

We attempted to demonstrate the quality of the linkage by examining medical care for injury and prescription patterns in the 7 days following a reported motor vehicle crash. We assumed that subjects reported as injured by the responding officer (injury, died at the scene, or died at hospital) would be likely to result in medical services in the time immediately post-crash. Medical care (ambulance, emergency department, outpatient visits and hospitalizations) with diagnoses related to injury (pain, lacerations, contusions, dislocations, as well as E-codes specific to crash) and prescriptions for medications typically used to treat acute pain that could be attributed to a motor vehicle crash were identified. The prescription records for each subject's crash were searched for a fill date within 7 days after the collision date in which the prescribed medication was either an opioid, non-steroidal anti-inflammatory (NSAID) or muscle relaxant as classified by a review of the relevant classes by generic name, linked to national drug code level data. A match of one or more prescriptions was coded as a prescription-crash match. Similarly, subject's medical encounter records for each crash were also searched for an encounter within 7 days after the collision date. A match to one or more encounters was coded as an encounter-crash match. Individual and combined correlations of medical care and

encounter-crash match. Individual and combined correlations of medical care and prescriptions with crashes recorded with driver injury were evaluated by calculating the Phi correlation coefficient, which is equal to the Pearson correlation coefficient when applied to two dichotomous variables.<sup>14</sup>

This study was reviewed and approved by the GHRI Institutional Review Board. All analyses were generated using SAS software for Windows, Version 9.3.

## Results

After application of inclusion and exclusion criteria, the study population included 676,705 individuals. The population averaged 41 years of age and 54% were female. Additionally, over 75% of the study population participated in the GHC Medical Centers delivery system, indicating they are fully managed lives and include complete capture of electronic medical records from GHC providers. The remaining 25% provided diagnosis and prescription records through administrative claims data. The complete demographic characteristics and prescription exposure proportions as well as the proportion experiencing at least one crash are listed in Table 1.

The DOT match returned a total of 131,452 unique crashes, which were matched to 106,686 individuals in the study population. Subject level chronologic eligibility restrictions removed 84,452 crashes, leaving 46,990 study crashes from 41,517 study subjects (Figure 2) during the study period. Of those individuals who experienced a crash, 4,607 (11%) experienced more than one crash during their follow-up period. Furthermore, Table 2 describes the crash frequencies of multiple crash drivers. Overall, the study population experienced 2.41 crashes per 100 person-years of study eligibility, with 0.48 of those crashes injuring the driver.

Of the 46,990 crashes, 5,830 (12.4%) were treated with prescription pain or muscle relaxant medications and 13,165 (28%) resulted in medical care, with a total of 14,314 (30%) seeking services from a healthcare provider. Reporting officers coded 9,590 crashes as including driver injuries. Of those crashes, 3,251 (33%) were associated with a prescription for a pain medication or muscle relaxants and 5,502 (56%) with trauma related medical care within 7 days after the collision date for a total of 5,911 (62%) receiving services from a healthcare provider (Table 3). Statistical tests of the correlations between injury crashes and subsequent services, all of which were statistically significant at the 0.05-level, were positive and are presented in Table 4.

## Discussion

This study sought to implement a linkage between medical, pharmacy and motor vehicle crash records in a large patient population in Washington State. Our goal was to generate a population-based longitudinal dataset for future exploration of associations between medical diagnoses and prescription exposures with motor vehicle crashes. We have linked these records utilizing a publicly available algorithm within an HMO population in Washington State. Over eleven years, adult drivers over the age of 21 experienced 2.41

motor vehicle crashes per 100 person-years. This compares with National rates of 1.79 per 100 U.S. residents in 2009.<sup>15</sup> Within those crashes, 0.48 per 100 person-years were recorded with injuries. This is also in line with the National rate for injury/fatality crashes in 2009 was 0.5 per 100 residents.<sup>15</sup> Additionally, over 10% of the individuals in the dataset crashed more than once during the study period indicating that the statistical methods for analyzing this dataset must account for repeated events.

Medical care and prescription medications for treating pain, inflammation and musculoskeletal problems were positively correlated with injury related crash, both individually and collectively. We empirically tested these correlations in order to establish the utility of our linked dataset and found moderate positive correlations that were all statistically significant. Ultimately however, medical care encounters and prescription drug usage were not strong indicators that an injurious motor vehicle crash has occurred in the past seven days in GHC patient medical records.

This study was somewhat limited in its ability to produce a meaningful demonstration of the dataset match via medical encounters or prescription drug utilization due to several factors. The coding of a crash as injury-related is a subjective decision made by the reporting officer. Thus classification may vary between officers and crash injury severity, especially among minor injuries. Some crashes may have occurred while the subject was on the job. Care for any work-related injuries would have been incurred by the State Department of Labor and Industries and would not be recorded in the GHC database if it occurred at an outside facility. Furthermore, not all crashes result in the use of traditional medical care. GHC offers patients direct web-based access to their healthcare providers, who can provide immediate consultation and diagnosis of common ailments such as minor aches and pains. Documentation of these interactions is not captured as a medical encounter in the administrative databases and thus virtual medical encounters are missing in our dataset. Additionally, some of the common sequelae of motor vehicle crash injuries can be successfully treated by chiropractic spinal adjustment and tissue massage therapy. These encounters would likely be missing from our dataset due to coding by Current Procedural Terminology (CPT) rather than diagnosis codes, which were used to capture encounters in our dataset. Some patients may have self-medicated with medications already on hand (prescription and/or over-the-counter) from similar conditions and many NSAIDs are available in over-the-counter formulations, which are not captured in the prescription claims database even when prescribed. Providers at GHC are nationally renowned for providing cost-effective medical care. One way to reduce prescription drug costs is to utilize over-the-counter treatments, when appropriate. Thus, pain and inflammation from many crashes may have in fact been treated by the order of a healthcare provider, but not captured in the prescription data records. This constellation of potential reasons for misclassified injuries and missing data leads us to believe that the dataset linkage is sound and the moderate correlations are actually attenuated by these factors.

A longitudinal repository of prescription exposures, medical diagnoses, and motor vehicle crash data has resulted from this study. The linkage between databases has been confirmed by examining the correlations between medical care and prescriptions with

injurious crashes. Many of the recorded exposures in our study population may put individuals at a higher risk of crash. Future research with this dataset will seek to investigate differences in risk of crash between prescription opioid and sedative hypnotic medication exposures, allowing direct comparisons of risk within a single study population. These comparative safety analyses will assess the relative associations of various medications with crashes in order to better inform medical providers, patients, and public policy makers on how to best limit or modify exposures to reduce crash risk.

## Chapter 2:

### Investigating the Association between Prescription Opioid Exposures and Motor Vehicle Crashes

## **Abstract**

### **Background**

Prescription opioid use is widespread throughout the world, with untoward effects that include injury, addiction, underemployment, morbidity, and mortality in the United States. These medications are associated with significant costs to society and increased risk of injury and motor vehicle crashes. We sought to investigate the association of the length of continuous opioid prescription dispenses on crash risk. We linked opioid prescription patterns among a large, longitudinal population-based cohort of insured adults at Group Health Cooperative (GHC) to police-reported crash data in Washington State.

### **Methods**

Our study population included all GHC enrollees aged 21 to 79 with at least one year of continuous enrollment. The study spanned from January 1999 through December 2009. We accessed medical, pharmacy and administrative data on all subjects, linked to motor vehicle crash data from the State Department of Transportation. We estimated multivariate extended Cox regressions to investigate the association between any, as well as stratified periods of continuous opioid prescription dispenses and motor vehicle crashes, controlling for age, gender and comorbidities at study entry.

### **Results**

A total of 676,694 subjects were included in the study. These individuals experienced 2.41 motor vehicle crashes per 100 person-years. Overall opioid prescription dispenses were associated with a hazard ratio of 1.37 compared to no opioid dispenses (95% CI: 1.33 to 1.41). However, stratifying opioid exposure by the length of continuous prescriptions resulted in a range of hazard ratios from 1.76 for 1-30 days (95% CI: 1.59 to 1.96) up to 11.33 for 91-120 days (95% CI: 9.18 to 13.98), decreasing to 1.11 (95% CI: 1.07 to 1.15) for continuous prescription dispense days exceeding one year.

### **Discussion**

The instantaneous risk of motor vehicle crash varied significantly during the first year of continuous opioid prescriptions. Peak risk of crash during the period from 91-120 days of continuous dispenses was associated with a hazard ratio equivalent to double the legal blood alcohol concentration for driving. The length of opioid exposure appears to play a role in the level of risk for motor vehicle crashes. Further research is warranted with regard to continuous opioid exposures of less than one year as well as other medications with properties similar to opioids.

## Background

Many factors may increase a driver's likelihood of being in a motor vehicle crash. In 2002, the National Highway Traffic Safety Administration (NHTSA) commissioned a study to look at public and private databases in order to broadly investigate the association between motor vehicle crashes and multiple medications, medication interactions and drug-disease interactions in subjects over the age of 50 years. This study was motivated by previously published research that investigated single drug or drug class associations with crashes and was centered on hypothesis generation for future work. One class of drugs identified in this study was the narcotic analgesics (opioids), which possess several possible side effects including drowsiness, dizziness, sedation, and delayed response times.<sup>2</sup> These same effects are also commonly associated with alcohol consumption, which is generally accepted as a causal factor in motor vehicle crashes both in the US and abroad.<sup>16,17</sup> Furthermore, these effects of prescription opioids manifest themselves regardless of age, yet prior studies investigating increased risk of crash have focused on the impact on older drivers.

Jick et. al. studied the association between exposure to five classes of potentially sedating drugs within three months of a crash and injury from a motor vehicle crash as evidenced by hospital discharge diagnosis in the late 1970's. However, this case-series only included a total sample of 244 subjects, the comparison groups were classified by chart review into either at-fault driver, passenger, or either unclassifiable or not at-fault driver, with a large proportion of subjects falling into the latter category, and the ascertainment of drug exposure allowed only a three month window. Overall, results from this study were not statistically significant across all five drug classes (at-fault driver RR of crash when exposed to a sedative: 1.3 for males, 1.4 for females).<sup>18</sup> Other previous studies involving prescription opioids have focused on elderly drivers as a higher risk population. A recent systematic review evaluating pharmaceuticals and traffic safety concluded that large studies are needed to evaluate the association between pharmaceutical use and traffic crashes.<sup>3</sup>

Although the association between crashes and prescription opioid use has been demonstrated, there is scant evidence investigating how the length of opioid exposure impacts this association.<sup>19</sup> Behaviors among prescription opioid users have unique differences depending on the duration of use.<sup>20,21</sup> Thus it is reasonable to expect differences in crash risk may exist between acute, short-term users of opioids and those using them on a long-term basis. Long-term users may exhibit both pain dysfunction and addictive behaviors, which may further influence crash risk.<sup>20</sup> We sought to use a population-based database to investigate and compare the association of prescription opioid use and the length of continuous dispenses with risk of police-reported motor vehicle crashes in a Health Maintenance Organization (HMO) population within Washington State. Elucidating differences in risk over time may foster improved medical and pharmacy care initiatives to improve public health and reduce motor vehicle crash risk.

## Methods

## Setting

Over 600,000 individuals were insured in the fully integrated Group Health Cooperative (GHC) health care system in Washington State in 2010. The GHC population closely resembled other residents of Washington State, with respect to age, race, and gender. Information on health plan enrollment, health care visits, pharmacy utilization, laboratory values, diagnoses, and procedures were recorded and maintained in an automated database. A unique consumer number assigned to each enrollee linked these health plan data.<sup>22,23,24</sup>

## Study Population

We performed a retrospective population-based cohort study of the GHC patient population. Eligibility for the study required subjects to be at least 21 years of age on January 1, 1999 or turned 21 during the study period while meeting all other inclusion criteria. Additional inclusion criteria included: primary residence in Washington State, continuous enrollment for at least 1 year between January 1, 1999 and December 31, 2009 unless they died, and drug benefits through GHC. Continuous enrollment was defined as no more than a 60-day lapse in enrollment. Subjects older than 79 years on January 1, 1999 were excluded. Follow-up ended at the earliest of: disenrollment, turning > 79 years of age, death, or the end of the study period (December 31, 2009).

## Data

We developed a linked dataset of GHC administrative, medical and pharmacy records with Washington State Department of Transportation motor vehicle crash records as described in detail elsewhere.<sup>25</sup> This longitudinal dataset of all GHC enrollees meeting our eligibility criteria included 46,990 crashes from 676,705 subjects with full crash level information regarding vehicle and driver status as well as medical encounter, diagnosis and prescription utilization. Each subject's age and Charlson Comorbidity Index<sup>13</sup> were calculated at their entry into the study.

### Exposure classification

Prescription opioid medications were defined using a free text query based on a complete list of brand and generic prescription opioid medication names. This query linked to a National Drug Code (NDC) table, which provided the dosage form level identifier necessary to identify medications in the GHC pharmacy database.

Duration of exposure was defined by collapsing individual dispenses into periods of continuous use. The start date was defined by the date of the first opioid prescription dispense. We utilized an 80% compliance factor multiplied by the days supply value of each prescription. The end date of a period of use was defined as the date of the last dispense plus the days supply (and the 80% compliance factor). Non-overlapping periods of use were evaluated as separate exposures, allowing subjects to transition between

exposed and non-exposed status throughout the duration of the study. Definition of acute opioid use required a prescription record or overlapping prescription records for an opioid with a days' supply less than 120 days. Periods of long-term opioid use were similarly defined but with total days supplied of 120 days or greater as previously elucidated.<sup>20,21</sup> Furthermore, we stratified periods of continuous opioid exposure in order to identify patterns of risk associated with various lengths of use under one year as well as more than one year of continuous use. Motor vehicle crashes were matched to periods of exposure and non-exposure for each person with a police-reported crash during the study period.

### Statistical Analyses

During the formation of the analytic sample we found zero individuals missing age at study entry, or Charlson score, but 11 subjects missing gender and a total of 3,912 (0.03%) prescription dispenses missing a days' supply. Therefore, a complete case analysis was deemed appropriate and the individuals without a gender along with the dispenses missing the days' supply variable were dropped from the analysis.

### Association with Crash

We sought to estimate the association between opioid prescription exposure and motor vehicle crash using a time-to-event model, which assumes that the instantaneous rate of crash is constantly proportional between the exposed and unexposed groups over time. However, by employing robust sandwich estimator standard errors in the model, we allowed for non-linearity of hazard ratios between the exposed and unexposed groups.<sup>26,27</sup> Within the study population, many (roughly 10%) individuals experienced more than one crash. In order to accommodate dependence between multiple crashes, we employed extended Cox regression models utilizing the Anderson Gill (AG) approach conditioned on previous crashes. The AG methodology uses an unrestricted risk set with common baseline hazard, a counting process estimation method for the risk intervals, and independent within-subject correlation. By conditioning on previous crashes, we account for the within-subject correlation thus relaxing the assumption of independence within subjects.<sup>28,29</sup>

We performed four separate regressions: any opioid dispense (binary), acute, long-term, and finally with six assigned dummy variables to account for different lengths of opioid exposures (1-30, 31-90, 91-120, 121-240, 241-360, >360 days). All models were adjusted for age (quadratic model), gender, and Charlson Comorbidity Index at study entry, categorized into zero, one, two and three or greater with zero serving as the reference group. We also translated our hazard ratio estimates into Blood Alcohol Concentration (BAC) equivalents using data from Peck et al.<sup>30</sup> The presence of other prescription medications (anti-seizure, Alzheimer's, anti-depressants) and additional medical diagnoses (neurologic and cardiovascular disorders) as well as police provided crash-level variables were not associated with both the exposure and outcome and were omitted from the final models.

This study was reviewed and approved by the Group Health Research Institute's Institutional Review Board. All analyses were generated using SAS software for Windows, Version 9.3.

## Results

Application of the inclusion and exclusion criteria along with the complete case analysis requirement resulted in 676,694 study subjects (see Figure 3). Selected baseline demographic characteristics and frequency counts of motor vehicle crashes are reported in Table 5. The median age in our study population was 41 years. Just over half (54%) were female, and most scored zero on the Charlson Comorbidity Index (94%). Study subjects were exposed to prescription opioids 8.4% of the time during the study. A total of 41,517 (6.13%) subjects experienced at least one crash, with 11% of crashes occurring in subjects who had two or more police-reported crashes during the study period.

We estimated the hazard ratio for any opioid use to be 1.37 (95% CI: 1.33 to 1.41, p-value <0.0001) (Table 6). Similarly, opioid use greater than 120 days (long-term use) including the entire study time horizon was associated with a hazard ratio of 1.28, controlling for age, gender and Charlson Comorbidity Index at baseline (95% CI: 1.24 to 1.32, p-value <0.0001). However, upon further stratification by periods of continuous prescription days, there was a clear pattern of excess risk peaking at approximately 120 days with a hazard ratio of 11.33 (95% CI: 9.18 to 13.98, p-value <0.0001) and then gradually declining over the study time horizon (Table 7). Evaluation of interaction terms between the gender and two age covariates for potential effect modification was not statistically significant and those covariates were not included in the final models. The opioid exposure levels estimated in our fully saturated model were translated to BAC equivalents and are presented in Table 8.

Figure 4 further demonstrates the dose-response relationship identified by stratifying prescription opioid exposure into discrete periods of continuous exposure. The slope of increasing risk reverses after 120 days of continuous dispenses and follows a linearly decreasing slope in order to reach the long-term risk of crash over the full study period.

## Discussion

Long-term opioid prescription patterns were associated with a 28% increase in the risk of motor vehicle crash. This estimate is lower than most previous publications on opioid exposures and motor vehicle crashes in the US, Europe and Australia. Those studies represent a mix of case-control and cohort studies most of which used only crash registries and were focused on injury-related crashes.<sup>10,31,32,33</sup> However, linking this risk to previous studies of BAC and relative risk of crash demonstrates that this risk is equivalent to opioid exposed drivers operating motor vehicles with a BAC of 0.06, which is approaching the legal limit for driving a motor vehicle.<sup>34</sup>

This research has built upon previous findings by also investigating the association of the length of opioid exposures with crash. During the first year of opioid exposure, the risk of

crash is significantly higher. We have found that the length of continuous opioid use in the first year of prescription exposure appears to follow an increasing dose-response relationship with crash through four months of exposure, where risk of crash peaks followed by a steady decrease in risk over the remainder of the first year of exposure and beyond. Furthermore, translating these crash risks into BACs demonstrates that prescription opioid use in the first year of continuous exposure is equivalent to driving at or above the legal limit for operating a motor vehicle (Table 8). The divergence in crash risk between acute and long-term exposures imparted by the exposure duration may be due to a combination of factors. First, differences in driving behaviors between patients exposed to 30 days or less versus 31-120 days of continuous opioids may exist due to underlying medical conditions and cautions of taking the medication. Additionally, tolerance to opioids accumulates over time during long-term opioid exposure and may manifest itself through psychological accommodation for sedation, euphoria and disorientation that can accompany opioid exposure. Over time, changes in overall driving time and accommodations from tolerance may result in differences reaction time and decision making behind the wheel.

As expected, males were at a higher risk for crash while increasing the number and relative severity of comorbidities (as measured by the Charlson Comorbidity Index) decreased crash risk, presumably by decreasing driving time. It is of interest to note that consistent with the decreasing trend in crash incidence within the State, the risk of crash due to opioids has decreased since Leveille et al published their odds ratio of 1.8 based on GHC data from 1987-88.<sup>10</sup>

This study has a number of important limitations. As with nearly all pharmacoepidemiology research, there is the possibility for confounding by indication. Medical conditions being treated by the drug exposures may be independently associated with crash, and our model estimates may be biased by such associations.<sup>35,36</sup> Second, our ascertainment of exposure in the retrospective analysis was based on prescription dispensing records at GHC and may not represent opioid use in the period preceding a crash, and we cannot estimate whether opioids were present in the patient's blood stream at the time of the crash. Third, while we have adjusted our models for comorbidities at study entry, the study occurred over an eleven-year period and thus potential misclassification of comorbidity at the time of crash or censoring cannot be ruled out. Fourth, this study was limited to residents of Washington State and crashes reported within the Washington State Department of Transportation database. It is likely that motor vehicle crashes for some study participants occurred outside the State, which could bias our results toward the null. The study was also limited to subjects over the age of 21, thus excluding younger drivers. However, this limitation should be expected to produce a more homogeneous population of drivers with regard to driving experience and thus a more stable estimate of crash risk. Finally, we were also limited to a single HMO population, which could impact this study's generalizability.

We report an association with motor vehicle crash for prescription opioids in a robust dataset of HMO administrative, medical and pharmacy records linked with State Department of Transportation crash records in Washington State. Our primary analysis

shows that acute prescription opioid use is associated with varying increased risk of experiencing a motor vehicle crash, which is similar to legal intoxication with alcohol. We have also found a suggestion that risk of crash changes over the length of exposure to opioids. Further research is warranted with regard to acute opioid exposures as well as other medications with properties similar to opioids.

### Chapter 3:

## Sedative Hypnotic Prescriptions and the Risk of Motor Vehicle Crashes

## **Abstract**

### **Background**

Few studies have evaluated the relative association of the various drugs within the broad sedative hypnotic medication class and motor vehicle crashes. We sought to employ a population-based database in Washington State linked to police-reported crashes to estimate the association between prescription dispenses for sedative hypnotic medications and motor vehicle crashes. We further wished to compare three commonly prescribed sedative hypnotic medications in a comparative safety framework.

### **Methods**

We accessed Washington State Group Health Cooperative enrollees medical, pharmacy and administrative data, linked to motor vehicle crash data from the Washington State Department of Transportation from January 2002 through December 2009. We estimated multivariate extended Cox regressions to investigate the association separately between new and prevalent sedative prescription dispenses and motor vehicle crashes, controlling for age, gender, co-prescription of opioid medications, and medical comorbidities. Additional models were also estimated to stratify by varying lengths of sedative prescription-time.

### **Results**

We identified 41,288 (6%) new sedative users and 2,338 (0.3%) prevalent sedative users. New users filling a sedative prescription were associated with a hazard ratio for crashes of 2.23 (95% CI: 1.92 to 2.59) relative to non-users. A large proportion of trazodone prescriptions in the prevalent user cohort resulted in a composite sedative HR of 1.52 (95% CI: 1.22 to 1.89). Among prevalent users, the risk of crash was highest with temazepam, HR: 4.11 and zolpidem, HR: 4.53. Stratifying continuous prescriptions by time revealed the highest risk group to be 121-240 days for all sedatives, trazodone and temazepam (overall HR: 6.84, 95% CI: 4.15 to 11.2) with the HR for temazepam reaching 12.5 (95% CI: 5.4 to 29). Zolpidem had a very low risk of crash in the first 30 days, yet risk climbed to a peak risk between 241-360 days (HR: 10.7, 95% CI: 3.9 to 29).

### **Discussion**

All three sedative hypnotics were associated with an increased risk of motor vehicle crash. New users of sedatives experienced a two-fold increased risk of crash. Two of the sedatives (temazepam and zolpidem) were associated with a more than four-fold increased risk of crash in prevalent users. Stratification by length of continuous prescription time revealed even higher risks, which varied by medication. It appears that society could benefit from increased counseling on driving habits for patients taking these medications and that during the selection of a sedative hypnotic treatment, consideration should be given to the length of treatment and patient's driving status.

## Background

The therapeutic class of sedative hypnotic medications contains a diverse group of chemicals with varying biochemical targets all focused on a variety of clinical indications.<sup>37,38,39</sup> Several of these medications are primarily indicated for the treatment of insomnia. As such, sedation is one of the more common outcomes from patients ingesting these drugs. Sedation, also a common side effect from alcohol consumption, is generally accepted as a causal factor in motor vehicle crashes both in the U.S. and abroad.<sup>16,17</sup> Motor vehicle accidents are estimated to add lifetime economic costs to society of \$82 billion in deaths and injury related costs.<sup>1</sup> However, little has been documented in the US to evaluate the relative association of the various drugs within the broad sedative hypnotic medication class and motor vehicle crashes. A recent systematic review evaluating pharmaceuticals and traffic safety concluded that large studies are needed to evaluate the association between pharmaceutical use and traffic crashes.<sup>3</sup> If such an association does exist, cautions regarding these medications must be strengthened in order to protect the general public as motor vehicle drivers cannot choose nor predict who they are on the road with at any given time.

The largest body of evidence regarding the risk of motor vehicle collisions and sedative hypnotics comes from Scandinavia and The Netherlands. However, none of this work provides the power to evaluate currently used medications comparatively. The largest study, a registry based cohort from Norway evaluated almost 13,000 collisions among the 3.1 million residents in 2004-2005 and examined the association with exposure to several drug classes including benzodiazepine hypnotics. This study found the standardized incidence ratio of crash when exposed to benzodiazepine hypnotics of 3.3 (95% CI: 2.1-4.7). For comparison, the SIR for calcium receptor antagonists (a common treatment for hypertension) was 0.9 (95% CI: 0.5-1.5).<sup>33</sup> A group of 18 elderly healthy subjects were studied by Leufkens and Vermeeren comparing temazepam, zopiclone and placebo treatment between 10-11 hours prior to a standardized driving test. In this study, zopiclone was found to affect driving performance, but temazepam's effect was similar to placebo.<sup>40</sup> Partinen and colleagues undertook a three-arm, double-blind, placebo controlled cross-over study of zolpidem and temazepam, studying the effect of taking these drugs after midnight on driving simulator ability the following morning. This was a small study (N=18) only including females and the primary outcome of time to simulated crash was not different between any of the groups. There was a statistically significant difference in groups in lane position deviation, where zolpidem produced greater deviations than either temazepam (0.135 meters of deviation, p=0.05) or placebo (0.117 meters of deviation, p=0.025).<sup>41</sup> Therefore, while it seems likely that an association between the sedative hypnotics and motor vehicle crashes exists, currently available research does not clearly elucidate relative differences between different medications. Furthermore, the largest cohort study has not been replicated to examine the validity or generalizability of its results beyond the Norwegian population.

The half-lives of insomnia treatments, some combined with delayed-release dosage forms, range from one to eleven hours<sup>42</sup>, meaning the drug is still measurable in the person's bloodstream between three and thirty-three hours after ingestion. Those

chemicals with longer half-lives have been associated with increased hangover effects during the morning following a sleep induced by the drug. These effects may produce slow reaction time and lack of appropriate judgment by someone operating a motor vehicle. We hypothesized that sedative hypnotics modify one's likelihood of crash by modifying two processes. First, all people have an internal psychological process that governs their decision of when to operate a motor vehicle. Some sedative hypnotics may have a significant modification of this process by effectively lowering one's ability to consciously or subconsciously inhibit driving activity. Second, depending on the timing of exposure, all sedatives may produce a modification of the probability of crashing once behind the wheel of a motor vehicle by increasing reaction times, altering decision making or simply causing general sedation.

Recent research has demonstrated that sedative hypnotic prescriptions may put people at an increased mortality risk of over three-fold compared to those not receiving sedatives.<sup>43</sup> As crashes are associated with both morbidity and mortality, one mechanism for this effect of hypnotics may be through motor vehicle crashes. We sought to use a population-based database to investigate risk of motor vehicle crash associated with prescriptions for the class of sedative hypnotics as well as compare individual sedative medications using a Health Maintenance Organization population linked to police-reported motor vehicle crashes in Washington State. We aimed to do so with a common measure of risk in a single population in order to establish a hierarchy of risk related to motor vehicle crashes between three common sedative hypnotic medications. Identifying high-risk prescriptions may improve public health by educating the prescribers and users of these medications about the particular types of exposures that could increase an individual's likelihood of crashing.

## **Methods**

### **Setting**

Group Health Cooperative (GHC) had a fully integrated health care system covering over 600,000 individuals in Washington State in 2010. The GHC population closely resembled the underlying community within Washington State, with respect to age, race, and gender. Information on health plan enrollment, health care visits, pharmacy utilization, laboratory values, diagnoses, and procedures were recorded and maintained in an automated database. These data were linked by a unique consumer number assigned to each enrollee.<sup>22,23,24</sup> The prescription drug formulary at GHC includes three sedative hypnotics: temazepam, trazodone and zolpidem. Over 21,000 GHC patients were utilizing these medications in 2008.

### **Study Population**

We performed a retrospective population-based cohort study on the GHC patient population. Inclusion criteria for the study included: age 21 on January 1, 1999 or turned 21 during the study period while meeting all other inclusion criteria, primary residence in Washington State, had continuous enrollment for at least 1 year between January 1, 1999

and December 31, 2009. We required that each participant could have no more than a 60 day lapse in membership unless enrollment ended due to death, held prescription drug benefits within the GHC system. Exclusion criteria included: age older than 79 on January 1, 1999. Subjects exited the study by either disenrolling from GHC, turning older than age 79, death, or reaching the end of the study period on December 31, 2009.<sup>25</sup>

## Data

We developed a linked dataset of GHC administrative, medical and pharmacy records along with Washington State Department of Transportation motor vehicle crash records. This longitudinal dataset of all GHC enrollees meeting our inclusion criteria included 46,990 crashes from 676,694 subjects with full crash level information regarding vehicle and driver status as well as medical encounter, diagnosis and prescription utilization over the entire study period. Each subject's age and Charlson Comorbidity Index<sup>13</sup> were calculated at their entry into the study.

### Exposure classification

Sedative hypnotic medications of interest were first identified within the GHC formulary. Subsequently, exposures were defined using a free text query based on a complete list of brand and generic medication names (trazodone (Desyrel®), temazepam (Restoril®), zolpidem (Ambien®, Ambien CR®)). This query linked to a National Drug Code (NDC) table, which provided the dosage form level identifier necessary to identify medications dispensed in GHC pharmacies.

Duration of exposure was defined by collapsing individual dispenses into periods of continuous use (episodes). The start date was defined by the date of the first opioid prescription dispense. We utilized an 80% compliance factor multiplied by the days supply value of each prescription. The end date of a period of use was defined as the date of the last dispense plus the days supply (and the 80% compliance factor). Non-overlapping periods of use were evaluated as separate exposures, allowing subjects to transition between exposed and non-exposed status throughout the duration of the study. Motor vehicle crashes were matched to the periods of exposure and non-exposure for each person with a police-reported crash during the study period.

Because differences may exist between new users (incident) versus long-term (prevalent) users of sedative hypnotics, we sought to investigate these groups separately. We used a two-year period (1999-2002) to categorize patients into two groups: sedative users and non-users. The non-user group was then utilized to identify incident prescription dispenses in the remaining years of the study. The patients associated with those prescriptions were categorized as incident users. Sedative users in the first two years of the study defined the prevalent sedative user group. The prevalent prescription dispenses were further stratified into periods of 1-30, 31-90, 91-120, 121-240, 241-360 and 361 or more concurrent prescription days.

## Statistical Analyses

During the formation of the analytic sample we found zero individuals missing age at study entry, or Charlson Comorbidity Index, but 11 subjects missing gender and a total of 3,912 (0.03%) prescription dispenses missing a days' supply. Therefore, a complete case analysis was deemed appropriate and the individuals without a gender along with the prescriptions missing the days' supply variable were dropped from the analysis.

#### Associations with Crash

We utilized Cox Proportional Hazards regression in order to estimate the hazard ratio and 95% confidence interval (CI) for sedative prescriptions using motor vehicle crash as the outcome. This approach used a non-parametric time-to-event model, which assumed that the instantaneous rate of crash is constantly proportional between the exposed and unexposed groups over time. However, by employing robust sandwich estimator standard errors in the model, we allowed for non-linearity of hazard ratios between the exposed and unexposed groups.<sup>26,27</sup> In order to accommodate dependence between multiple crashes, we employed extended Cox regression models utilizing the Anderson Gill (AG) approach conditioned on previous episodes via the count of prior crashes. The AG methodology uses an unrestricted risk set with common baseline hazard, a counting process estimation method for the risk intervals, and independent within-subject correlation. By conditioning on the number of previous crashes, we account for the within-subject correlation thus relaxing the assumption of independence within subjects.<sup>28,29</sup>

Within the incident and prevalent user groups we first defined all three sedatives of interest as a single composite exposure in order to estimate the overall association of sedatives with crashes. We then individually estimated the association for each medication. All models were adjusted for age (quadratic model), gender, prescription opioid dispenses, an interaction between the sedative and opioids, and Charlson Comorbidity Index at study entry, categorized into zero, one, two and three or greater with zero serving as the reference group. We also translated our hazard ratio estimates into Blood Alcohol Concentration (BAC) equivalents using data from Peck et al.<sup>30</sup> The presence of other prescription medications (anti-seizure, Alzheimer's, anti-depressants) and additional medical diagnoses (neurologic and cardiovascular disorders) as well as police provided crash-level variables were not associated with both the exposure and outcome and were omitted from the final models.

This study was reviewed and approved by the Group Health Research Institute's Institutional Review Board. All analyses were generated using SAS software for Windows, Version 9.3.

## **Results**

Application of the inclusion and exclusion criteria along with the complete case analysis requirement resulted in 676,694 study subjects in the full cohort (see Figure 3). Selected baseline demographic characteristics, medication exposures, and frequency counts of motor vehicle crashes for individual study cohorts are reported in Table 9. The median age in our study population was 41 years. Slightly over half (54%) of the cohort were

female, and most scored zero on the Charlson Comorbidity Index (94%). Study subjects were exposed to sedative hypnotics of interest for 2.5% and prescription opioids 8.4% of the time during the study. A total of 41,517 (6.13%) subjects experienced at least one crash, and 11% of subjects crashed more than once during the study period.

### Incident Users and Crashes

A total of 41,288 (6%) incident sedative prescription dispenses were identified from 2003-2009. Of those users, 27%, 31%, and 60% used temazepam, zolpidem, and trazodone respectively, with exposure-time accounting for 0.11%, 0.13%, and 0.50% of study time. The model coefficients for the four extended Cox regressions of new users are reported in Table 10. Overall incident sedative prescription dispenses were associated with an increased risk of crashes (HR=2.23; 95% confidence interval: 1.92 to 2.59, p-value <0.0001), adjusting for opioid prescriptions, an interaction term between sedatives and opioids, gender, age, and Charlson Comorbidity Index at study entry. Of the individual sedative medications, trazodone was associated with the lowest hazard at 2.15 (95% confidence interval: 1.83 to 2.51, p-value <0.0001), followed by temazepam HR: 2.91 (95% confidence interval: 1.97 to 4.30, p-value <0.0001) and zolpidem HR: 2.93 (95% confidence interval: 2.25 to 3.82, p-value <0.0001). Within these regressions, prescription opioid dispenses were associated with a hazard ratio between 1.64 (all sedatives) and 1.23 (zolpidem).

### Prevalent Users and Crashes

A total of 2,338 (0.3%) prevalent sedative prescription-filling subjects were identified from dispensing records between 1999-2002. Of those users, 31%, 87%, and 20% used temazepam, trazodone and zolpidem respectively, with exposure-time accounting for 0.04%, 0.21%, and 0.03% of study time. Overall prevalent sedative prescription dispenses were associated with an increased risk of crashes (HR=1.52; 95% confidence interval: 1.22 to 1.89, p-value 0.0002), adjusting for opioid prescriptions, an interaction term between sedatives and opioids, gender, age, and Charlson Comorbidity Index at study entry (Table 11). Of the individual sedative medications, trazodone was associated with the lowest hazard at 1.47 (95% confidence interval: 1.18 to 1.85, p-value 0.0008), followed by temazepam HR: 4.11 (95% confidence interval: 2.56 to 6.58, p-value <0.0001) and zolpidem HR: 4.53 (95% confidence interval: 1.95 to 10.5, p-value 0.0004). Within these regressions, prescription opioid dispenses associated with a hazard ratio between 1.46 (all sedatives) and 1.19 (zolpidem).

Stratification of the prescriptions of prevalent sedative fillers by continuous episode duration yielded a range of hazard ratios that peaked between 121-240 days of continuous prescription dispenses for all sedatives (HR: 6.84, 95% CI: 4.15 to 11.2), trazodone (HR: 7.51, 95% CI: 4.35 to 12.9) and temazepam (HR: 12.5, 95% CI: 5.37 to 29.1) but at between 241-360 days for zolpidem (HR: 10.7, 95% CI: 3.89 to 29.7) (Table 12). The lowest crash risk for all prescription dispenses was associated with continuous episodes lasting longer than 360 days, yet temazepam and zolpidem had two periods of shorter exposure (31-120 days for temazepam, 0-30 days for zolpidem) where no crashes

occurred resulting in hazard ratios of zero. The sedative hypnotic exposure level risks of crashes estimated in our fully saturated models were mapped to BAC level risks (Table 13). Prescription dispenses for all sedatives under one year were associated with a range of BAC between 0.09 and 0.15.

## Discussion

This study demonstrated that prescriptions for three different types of sedative hypnotic agents are associated with increased risk of motor vehicle crash. Overall, sedative hypnotic exposure was associated with an excess of a two-fold increased risk of crash in new users. Overall prevalent dispenses were associated with a smaller increased risk in aggregate. However, two of the sedatives (temazepam and zolpidem) were associated with a more than four-fold increased risk of crash in prevalent users. Furthermore, we were able to rank order these three medications with regard to risk of crash. Regardless of the type of prescription dispensed (incident or prevalent), zolpidem was associated with the highest instantaneous risk of crash among the three sedatives, followed by temazepam. Trazodone is indicated for use to treat both insomnia and depression, thus the underlying conditions for which study subjects were undergoing treatment may have varied compared to the other sedatives.

Upon stratifying prescription dispenses by the length of continuous exposure, specific patterns of risk within the first year of continuous dispenses were revealed. The increased risk of crash was immediately present for temazepam and trazodone yet zolpidem users did not crash with very acute exposures (<30 days). This was unexpected and may have been due to zolpidem users accounting for the smallest proportion of sedative use. Overall, we observed an increasing trend of exposure time to crash risk with a peak at either 4-8 or 8-12 months. These increasing risks may be the result of perceived familiarity with the effects of these medications over time. Furthermore, the decreasing risk over the length of the study may be due in part to subjects developing tolerance to the sedative properties or adjusting their driving behaviors. Translating these results to BAC equivalents demonstrates that prescriptions for sedative hypnotics are similar to alcohol intoxication, exceeding double the US legal limit to operate a motor vehicle.<sup>34</sup>

This study has a number of important limitations. As with nearly all pharmacoepidemiology research, there is the possibility for confounding by indication. Medical conditions being treated by the drug exposures may be independently associated with crash, and our model estimates may be biased by such associations.<sup>35,36</sup> Second, our ascertainment of exposure in the retrospective analysis was based on prescription dispensing records at GHC and may not represent sedative use in the period preceding a crash, and we cannot estimate the presence or absence of systemic sedatives at the time of the crash. Third, we are unable to ascertain the actual driving status of the study subjects, thus we do not know if any systematic differences exist between the exposed and non-exposed subjects with regard to actual driving behaviors. Fourth, while we have adjusted our models for comorbidities at study entry, the study occurred over an eleven-year period and thus potential misclassification of comorbidity at the time of crash or censoring cannot be ruled out. Fifth, this study was limited to residents of Washington

State and crashes reported within the Washington State Department of Transportation database. It is likely that some study participants crashed outside the State, which could bias our results toward the null. The study was also limited to subjects over the age of 21, thus excluding younger drivers. However, this limitation should be expected to produce a more homogeneous population of drivers with regard to driving experience and thus a more stable estimate of crash risk. Finally, we were also limited to a single HMO population and medication use within the medication formulary restrictions of that HMO, which could impact this study's generalizability.

Sedative hypnotic prescriptions appear to be associated with an increased risk of motor vehicle crash. Our results also suggest that this risk differs between individual sedatives possessing different chemical structures and mechanisms of action. However, this may be in part due to differing indications for use. Future research is needed to investigate the latency of use, tolerance to these medications, and the link between sedatives and fatal crashes as well as further investigation into the factors that influence crash risk related to the length of prescription exposure. Depending on an individual person's need to drive regularly combined with a need use one of these medications for sleep, the choice of a particular sedative will likely impact their risk of crashing. Prescribers, pharmacists, and patients should take care to discuss this increased risk and consider the implications of this analysis when selecting a sedative hypnotic medication. In the interest of the public safety on the roads and highways in the United States, all people using these medications should consider reasonable steps to ensure they limit their ability to drive under the influence of these medications.

Chapter 4:  
Summary of Findings and Implications

On average, over 278 motor vehicle crashes occur in Washington State every day with approximately 6 people experiencing a serious injury and at least one fatality.<sup>5</sup> Many factors contribute to increase the risk of crash including: road and lighting conditions, vehicle speed, alcohol, driver age, and driver awareness.<sup>2</sup> Many prescription medications carry side effect profiles that can change a person's awareness, cognition, or ability to react promptly and accurately while operating a motor vehicle. Drugs that produce sedation as an intended effect or side effect are particularly problematic in that their effects can mimic those of alcohol. This problem has been clearly demonstrated by comparing patients in a driving simulator after taking the sedating anti-histamine medication diphenhydramine with behavior on a newer non-sedating anti-histamine fexofenadine. Weiler and colleagues found that the consumption of the sedating anti-histamine were more likely to exhibit unstable driving compared to fexofenadine or alcohol.<sup>44</sup> Studying other medications that may increase the risk of crash and thus the crash rate in order to identify patterns that may be changed in order to reduce the number of crashes is in the direct interest of public health.

Epidemiology is the study of diseases within populations. This broad field of study has filled in many knowledge gaps of medical research by answering questions that are difficult to address with or cannot ethically be answered by randomized controlled trials.<sup>45</sup> Pharmacoepidemiology is a type of epidemiology focused on the impact of medication exposures on diseases. In order to avoid recall bias from subjects over long periods of time and to gain precision with regard to medication type, length of exposure, and dosage, this type of research relies on information stored in automated databases regarding medication histories.<sup>46</sup> Epidemiologic studies commonly utilize one of two designs: the cohort or case-control study. Each of these study designs has its own strengths and weaknesses and the choice of the study depends on the exposure and disease being studied as well as the available study population. The cohort study, as executed above, seeks to compare two groups that differ by the exposure of interest in order to investigate differences in the outcome of interest. This design is well suited to study less frequent exposures. However, these observational studies are limited to demonstrating associations between exposures and outcomes without the ability to prove causality. Generally, after controlling for confounding factors, increasingly strong estimates of association are accompanied with decreasing likelihood that the estimates achieved were arrived at by chance.

A robust cohort study relies on longitudinal data, typically including repeated measurements on subjects over time. Such data allows an individual subject to be tracked through time and their medication exposures and outcomes to be captured. However, these studies also require the application of the correct statistical analysis methodology in order to properly account for repeated records for the same subject and their correlation to estimate valid results from the study.<sup>47</sup> However, a further challenge for these studies is repeated outcomes for individual study subjects. Challenges with analyzing repeated outcomes data have been acknowledged and explored for more than 30 years.<sup>48,49,50</sup> For studies such as these where the length of medication exposure is varying and the event may recur over time, the conditional Cox regression model has been extended from traditional Cox regression, which allowed for a single event per subject.<sup>28,29</sup>

The studies described above have investigated the relationships between police-reported motor vehicle crashes and two frequently prescribed classes of medications within a population-based longitudinal database. And, while confounding (especially by indication) may remain in the statistical model results, the true value of this research lies not in the individual hazard ratios for a given drug but rather in the relative relationships between and the rank order of these medications. Therefore, even with residual confounding, the individual medications should have the same level of confounding and their relative relationships should produce valid relationships.

It is also important to appreciate that these estimates for are based on use as prescribed for medical conditions. The economic impact of non-medical prescription opioid use has been well documented in the literature.<sup>51,52,53</sup> Use of these medications for non-medical purposes may translate into effects on crash rates. Thus our estimates of risk may be biased by medication misuse/abuse. However, the exact impact of this bias is difficult to ascertain because our exposure is solely based on prescription fills. Therefore, assuming the exposure ascertainment is accurate, it remains impossible to distinguish whether those individuals characterized as exposed were using the medication as prescribed or if they were misusing the medication at the time of a crash. In order to properly ascertain the true impact of both opioids and sedatives, consistent blood testing of drivers involved in crashes would be required. Such levels are not currently required for sobriety testing and since many sobriety tests occur in the field, the implementation of blood sample collection may be unrealistic.

## **Results and Implications**

### *Prescription Opioids*

Our analysis of prescription opioid exposures revealed important new information about the risk of crash that has previously been attributed to opioids. While our non-stratified estimate of risk was similar (in fact slightly lower) to that of previously published estimates, the short-term risk of crash in patients who are exposed to opioids for relatively acute periods is substantial. The increasing risk of crash to a peak at approximately four months demonstrates that people who are treated for acute pain for a range of one to thirty days are likely driving less as they recover from the cause of the pain. However, those patients who are treated for slightly longer periods appear to return to more active driving habits yet are at a much higher risk of crash. Such a dramatic increased risk may be due in part to opioid dose-escalation, which was not investigated during our analyses.

The period of peak crash risk is followed by a slow decrease in risk out to the long-term estimate. We hypothesize that the slow decrease in risk is due to a combination of increasing influence of patients who drive very little or are unable to drive due to debilitating pain conditions as well as tolerance to the prescription opioid medication. In all, it is clear that medical and pharmacy practitioners as well as patients taking these medications are not adequately controlling driving habits in the presence of these

medications. Furthermore, given the relative relationship between the hazard ratio estimates and equivalent BAC, additional restrictions on driving under the influence of opioid medications may be warranted.

The possession of a prescription for a prescription opioid for a one to thirty day period, commonly associated with acute injuries and dental problems, is equivalent to the risk of driving with a BAC of 0.08%, the legal limit for operating a motor vehicle in the United States.<sup>34</sup> Given this association and the increased risk-BAC association for continuous prescriptions longer than 30 days but less than one year, action should be taken. Certainly warnings should be strengthened to include directly informing patients how their risk of crash equates with alcohol consumption. Stronger actions may also be warranted, up to coordination between medical providers or pharmacies and state drivers licensing offices to facilitate restriction of driving privileges for people receiving opioid prescriptions in the interest of public safety.

### *Sedative Hypnotics*

Interpretation of sedative hypnotics requires the consideration of two distinct groups. First, we consider people who are new or very transient (less frequently than every two years) users of these medications. This patient group may have historically used one of these medications, but it must have been at least three years prior, which would have removed any previous biochemical tolerance and allowed the person to potentially forget about the effects of the medication related to driving impairment. Thus, they are characterized as new users. Second, we will consider prevalent users of sedative hypnotics. These are people who have filled a prescription during the run-in period of the study and thus were expected to have recent experience with the medications and likely better appreciate the way the medication impacts their behavior and ability to operate a motor vehicle.

An accurate assessment and understanding of medication use based on prescription history is also required to interpret these findings. It is important to understand that prescriptions for sedative hypnotics are frequently written to be taken on an ‘as needed’ basis and that the interpretation of ‘as needed’ is different in the context of sedatives than it is with opioids. Taking an opioid ‘every 4-6 hours as needed’ may result in a person taking the drug in intervals that vary from 4 to say 12 or 24 hours. However, taking a sedative ‘as needed for insomnia’ may result in the person taking the drug once per week or month. We attempted to account for this extension of the potential length of exposure by capturing continuous prescription exposures under the assumption that if the patient is refilling a prescription regularly, it is being used regularly.

For the new user patient group, the risk of crash when adding a prescription for any sedative hypnotic, increases more than two-fold. This excess risk is equivalent to a BAC above the legal limit to operate a motor vehicle. Furthermore, it appears that trazodone may be the safest choice among the three medications studied. Although, given the overlapping confidence intervals of our estimates, a firm rank order is not possible due to a lack of statistical significance. Regardless of the statistical significance in the rank

order, the confidence intervals for trazodone were also the most narrow and thus associated with the lowest potential risk overall (the high end of the confidence intervals for temazepam and zolpidem were near a four-fold increased risk). These results suggest that when selecting a sedative for a new or transient user of these medications, using crash risk as the sole selection criteria, trazodone will mitigate additional crash risk.

Prevalent prescription history of these medications creates a more complicated landscape as the length of continuous exposure must be considered. Overall, when considering any length of exposure, again trazodone is the safest choice. In the case of prevalent users, there is statistical significance of rank ordering trazodone as safer than temazepam or zolpidem. However, even though zolpidem has a slightly higher hazard ratio we cannot clearly distinguish it as higher risk than temazepam. Evaluating the confidence intervals of the estimates for the highest risk sedatives also reveals that the risk associated with these medications may be considerably higher, which is demonstrated when we stratify the exposure by the length of continuous prescription-days.

Stratification of the sedative prescription fills by their length of continuous days revealed clear patterns of increasing risk of crash with increasing days. With trazodone and temazepam the risk of crash was immediate, yet zolpidem was associated with a lag in its risk increase. Continuous prescription periods between 4-12 months are associated with the highest risk of crash. Within that period, trazodone appears to again be the safest of the medications, followed by zolpidem and temazepam. However, the confidence intervals of the latter two almost completely overlap and thus distinguishing them on the basis of crash risk is not possible.

Similar to opioids, prescriptions for sedative hypnotics are strongly associated with motor vehicle crashes. Changes are needed to control the use of and strengthen the warnings related to these medications. Prescribers and pharmacists clearly need to improve their counseling and warnings to patients about the untoward effects of these medications. One regulatory step that could have immediate impact would be the re-classification of these drugs into a higher controlled substance schedule. Such an action can occur at either the individual state level or can be enacted federally by the Drug Enforcement Agency. Additionally, similar to prescription opioids, limitation of driving privileges during the possession of a prescription for these medications may be warranted. However, insomnia can be a much more transient disease and thus realistic enforcement of such restrictions may prove to be considerably more challenging.

## **Conclusion**

Many factors must be considered when initiating or continuing prescription medication therapies. The medical condition to be treated as well as the side effects and potential unintended effects should be included in the determination. In the case of opioids and sedative hypnotics, these studies have demonstrated that motor vehicle crash risk should be included as a factor in these decisions. Every time a prescription for one of these medications is filled in a pharmacy in the United States other drivers who may encounter the person receiving the medication on the road are being put at increased risk of crash.

In 2009 there were 10.8 million motor vehicle accidents in the United States and 33,808 deaths associated with those crashes.<sup>54</sup> Thus, roughly 3 people die for every 1,000 crashes. Adding injury-related care to mortality, the economic cost of motor vehicle crashes was estimated at \$82 billion in 2005.<sup>1</sup> Altering prescribing patterns and the driving behaviors of patients who require these medications should result in reduced morbidity and mortality with the potential for significant economic savings and improvement in public health. However, legislative intervention or cooperation between health care providers and licensing agencies may be required in order to reach a critical mass of change to more effectively control the use of these medications.

These studies have examined two drug classes for an association with crash and in doing so have also generated a rich population-based dataset that can be used in the future to study other medications as well as medical conditions that impact cognition and have a suspected association with motor vehicle crash risk. Additional studies that may be undertaken with this dataset include: evaluating injury and fatality related crashes, stratifying crashes by vehicle type, and stratifying analyses by driver age in order to evaluate differences in older drivers. Through the ongoing use of this database, we can further improve our understanding of avoidable risk factors associated with motor vehicle crashes and undertake research that provides actionable results for drivers around the world.

Table 1. Study Population Demographics

	N	%
<b>Demographic Characteristics</b>		
Sample Size	676,705	
Mean Age at index	41.37	41.37
Female	365,290	53.98
GHC Integrated Group Practice	510,494	75.44
<b>Charlson Score</b>		
Charlson Score 0	637,517	94.21
Charlson Score 1	25,702	3.80
Charlson Score 2	8,345	1.23
Charlson Score 3+	5,141	0.76
<b>Outcome</b>		
Crash	41,517	6.14
<b>Prescription Drug Use</b>		
Calcium Channel Blocker	19,053	2.82
Opioid	235,913	34.86
Anti-Seizure	31,669	4.68
Blood Glucose Control	34,106	5.04
Sedative	184,117	27.21
Anti-psychotic	30,263	4.47
Musculoskeletal Relaxant	87,419	13.72

Table 2. Multiple Crash Driver Frequencies

Crash Frequency	N (% of all drivers with a crash)
Any crash N=41,517	
0	635,188
1	36,910 (88.9)
2	3,945 (9.5)
3	530 (1.28)
4+	132 (0.32)

Table 3. Incidence of crashes and seeking subsequent services

	All Crashes N=46,990 % (SD)	Injury Crashes N=9,590 % (SD)
Medical Encounter alone	28% (0.45)	56% (0.50)
Prescription alone	12% (0.33)	33% (0.47)
Either	30% (0.46)	62% (0.49)

Table 4. Correlation coefficients for injury crashes and subsequent services

	Injury Crash Phi Correlation Coefficient	95% Confidence Interval		p-value
Medical Encounter alone	0.319	0.311	0.327	<0.0001
Prescription alone	0.315	0.307	0.323	<0.0001
Either	0.346	0.338	0.354	<0.0001

Table 5. Selected Characteristics of Prescription Opioid Study Cohort at Baseline, Exposures and Outcomes

Characteristic	Full Cohort N=676,694
Male sex	311,404 (46.0)
Age, median (IQR), years	41 (30-51)
<b>Charlson Comorbidity Index</b>	
0	94.21%
1	3.80%
2	1.23%
3+	0.76%
<b>Medication exposure time (% of total time)</b>	
All Opioid	8.4%
Acute Opioid (<120 days)	3.9%
Long-Term Opioid (120+ days)	8.0%
<b>Motor vehicle crash count ( % of those experiencing a crash)</b>	
0	635,188
1	36,910 (88.9)
2	3,945 (9.50)
3	530 (1.28)
4+	132 (0.32)

Table 6. Association between Opioids and Motor Vehicle Crashes model estimates

Parameter	Hazard Ratio	95% Confidence Interval		p-Value
Any Opioid	1.37	1.33	1.41	<0.0001
Age	0.95	0.94	0.95	<0.0001
Age^2	1.00	1.00	1.00	<0.0001
Gender (male)	1.46	1.43	1.49	<0.0001
Charlson 1	1.01	0.96	1.06	0.7053
Charlson 2	0.96	0.88	1.05	0.4336
Charlson 3+	0.87	0.76	1.00	0.0525

Table 7. Association between Continuous Episodes of Prescription Opioid Dispenses and Risk of Motor Vehicle Crashes

Parameter	Hazard Ratio	95% Confidence Interval		p-Value
<b>Duration of opioid episode</b>				
1-30 days	1.76	1.59	1.96	<0.0001
31-90 days	7.93	6.76	9.29	<0.0001
91-120 days	11.33	9.18	13.98	<0.0001
121-240 days	7.77	6.97	8.66	<0.0001
241-360 days	5.55	4.99	6.16	<0.0001
360+ days	1.11	1.07	1.15	<0.0001
Age	0.95	0.94	0.95	<0.0001
Age <sup>2</sup>	1.00	1.00	1.00	<0.0001
Gender (male)	1.46	1.43	1.49	<0.0001
Charlson 1	1.02	0.98	1.07	0.3040
Charlson 2	0.98	0.89	1.07	0.6953
Charlson 3+	0.88	0.77	1.01	0.0684

Table 8. Opioid Exposure Days-Blood Alcohol Concentration Crash Risk Translation

Duration of opioid exposure	Hazard Ratio	BAC Equivalents Range	
1-30 days	1.76	0.08	0.09
31-90 days	7.93	0.14	0.15
91-120 days	11.33	0.16	0.17
121-240 days	7.77	0.14	0.15
241-360 days	5.55	0.13	0.14
360+ days	1.11	0.05	0.06

Table 9. Selected Characteristics of Sedative Hypnotic Study Cohorts at Baseline, Exposures and Outcomes

Characteristic	New User Cohort N=646,236	Chronic User Cohort N=610,093
Male sex	301,604 (46.7%)	288,935 (47.4%)
Age, median (IQR), years	38.9 (27-50)	38.8 (27-49)
<b>Charlson Comorbidity Index</b>		
0	95%	95 %
1	3.5 %	3.4 %
2	1.1 %	1.1 %
3+	0.65 %	0.63 %
<b>Medication exposure time (% of total time)</b>		
Temazepam	14.3 %	14.6 %
Trazodone	67.9 %	76.2 %
Zolpidem	17.7 %	9.11 %
<b>Motor vehicle crash count ( % of those experiencing a crash)</b>		
0	607,156	572,579
1	36,951 (94.5)	33,174 (94.3)
2	1,978 (5.1)	1,858 (5.3)
3	127 (0.3)	125 (0.4)
4+	24 (0.06)	24 (0.07)

Table 10. New Sedative Users Association with Motor Vehicle Crashes\*

Parameter	Hazard Ratio	95% Confidence Interval		p-Value
A) All Sedatives	2.23	1.92	2.59	<0.0001
B) Trazodone	2.15	1.83	2.51	<0.0001
C) Temazepam	2.91	1.97	4.30	<0.0001
D) Zolpidem	2.93	2.25	3.82	<0.0001

\*All models adjusted for gender, age, Charlson Comorbidity Index at study entry, co-prescription of opioids, and the interaction between sedatives and prescription opioids.

Table 11. Prevalent Sedative Users Association with Motor Vehicle Crashes\*

Parameter	Hazard Ratio	95% Confidence Interval		p-Value
A) All Sedatives	1.52	1.22	1.89	0.0002
B) Trazodone	1.47	1.18	1.85	0.0008
C) Temazepam	4.11	2.56	6.58	<0.0001
D) Zolpidem	4.53	1.95	10.5	0.0004

\*All models adjusted for gender, age, Charlson Comorbidity Index at study entry, co-prescription of opioids, and the interaction between sedatives and prescription opioids.

Table 12. Association between Continuous Episodes of Sedative Hypnotic Dispenses and Risk of Motor Vehicle Crashes \*

Parameter	Hazard Ratio	95% Confidence Interval		p-Value
<b>A) All Sedatives</b>				
0-30 days	2.66	1.53	4.64	0.0006
31-120 days	2.11	1.16	3.82	0.0137
121-240 days	6.84	4.15	11.2	<0.0001
241-360 days	3.97	2.32	6.79	<0.0001
>360 days	1.09	0.89	1.34	0.3996
<b>B) Trazodone</b>				
0-30 days	3.54	1.96	6.37	<0.0001
31-120 days	2.87	1.63	5.06	0.0003
121-240 days	7.51	4.35	12.9	<0.0001
241-360 days	4.57	2.54	8.21	<0.0001
>360 days	1.19	0.95	1.49	0.1307
<b>C) Temazepam</b>				
0-30 days	3.17	1.23	8.18	0.0171
31-120 days	0.00	0.00	0.00	<0.0001
121-240 days	12.5	5.37	29.1	<0.0001
241-360 days	1.61	0.23	11.37	0.6352
>360 days	0.75	0.39	1.43	0.3851
<b>D) Zolpidem</b>				
0-30 days	0.00	0.00	0.01	<0.0001
31-120 days	2.79	0.34	22.9	0.3397
121-240 days	2.12	0.22	20.5	0.5147
241-360 days	10.7	3.89	29.7	<0.0001
>360 days	0.32	0.15	0.71	0.0045

\*All models adjusted for gender, age, Charlson Comorbidity Index at study entry, co-prescription of opioids, and the interaction between sedatives and prescription opioids.

Table 13. Prevalent Sedative Days-Blood Alcohol Concentration Crash Risk Translation

Parameter	Hazard Ratio	BAC Equivalents Range	
A) All Sedatives			
0-30 days	2.66	0.10	0.11
31-120 days	2.11	0.09	0.10
121-240 days	6.84	0.14	0.15
241-360 days	3.97	0.12	0.13
>360 days	1.09	0.05	0.06
B) Trazodone			
0-30 days	3.54	0.11	0.12
31-120 days	2.87	0.10	0.11
121-240 days	7.51	0.14	0.16
241-360 days	4.57	0.13	0.14
>360 days	1.19	0.06	0.07
C) Temazepam			
0-30 days	3.17	0.11	0.12
31-120 days	0.00	0.00	0.00
121-240 days	12.5	0.16	0.18
241-360 days	1.61	0.07	0.09
>360 days	0.75	0.00	0.00
D) Zolpidem			
0-30 days	0.00	0.00	0.00
31-120 days	2.79	0.10	0.11
121-240 days	2.12	0.09	0.10
241-360 days	10.7	0.16	0.17
>360 days	0.32	0.00	0.00

Figure 1. Study Enrollment Flow

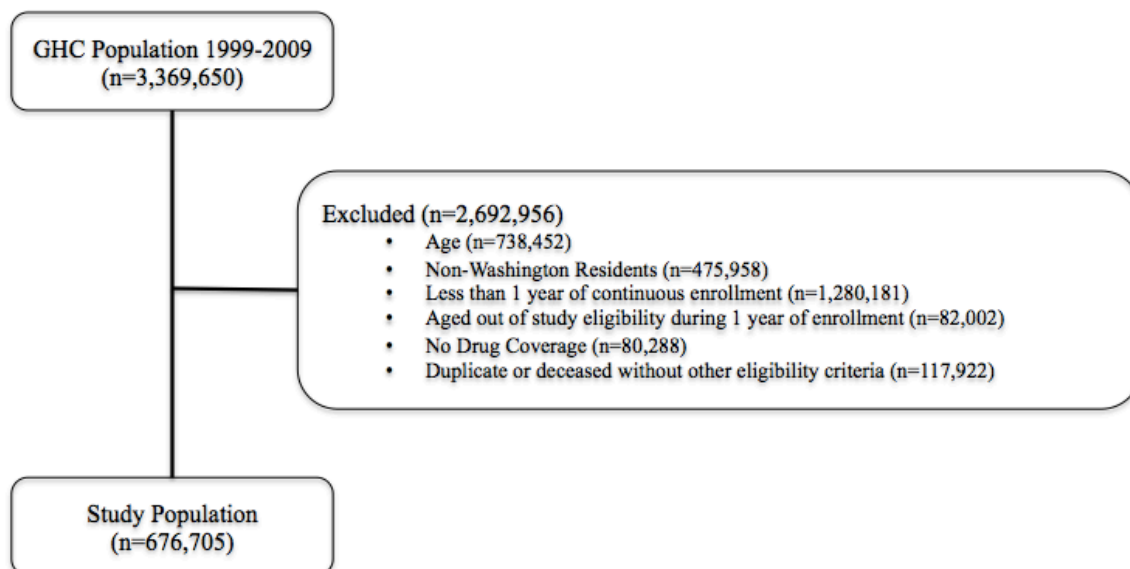


Figure 2. Crash Data Feed and Exclusion

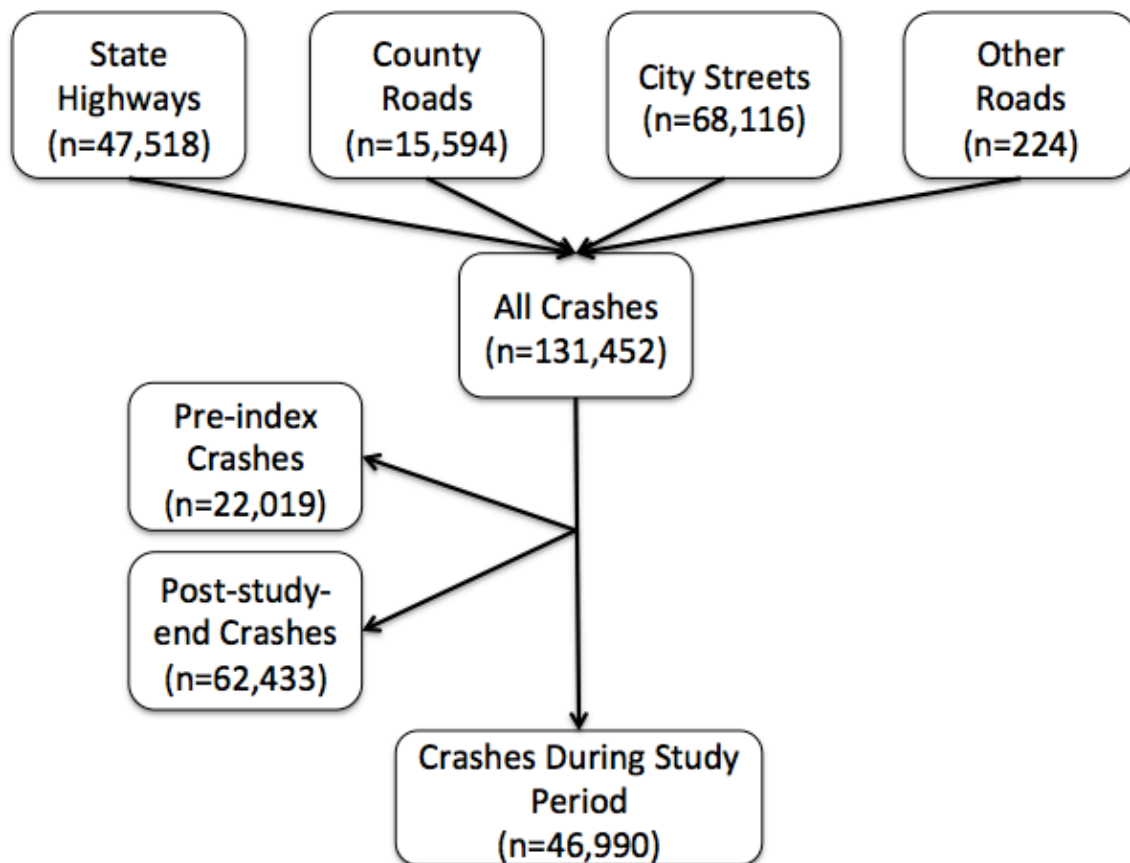


Figure 3. Opioid and Sedative Hypnotic Studies' Enrollment Flow

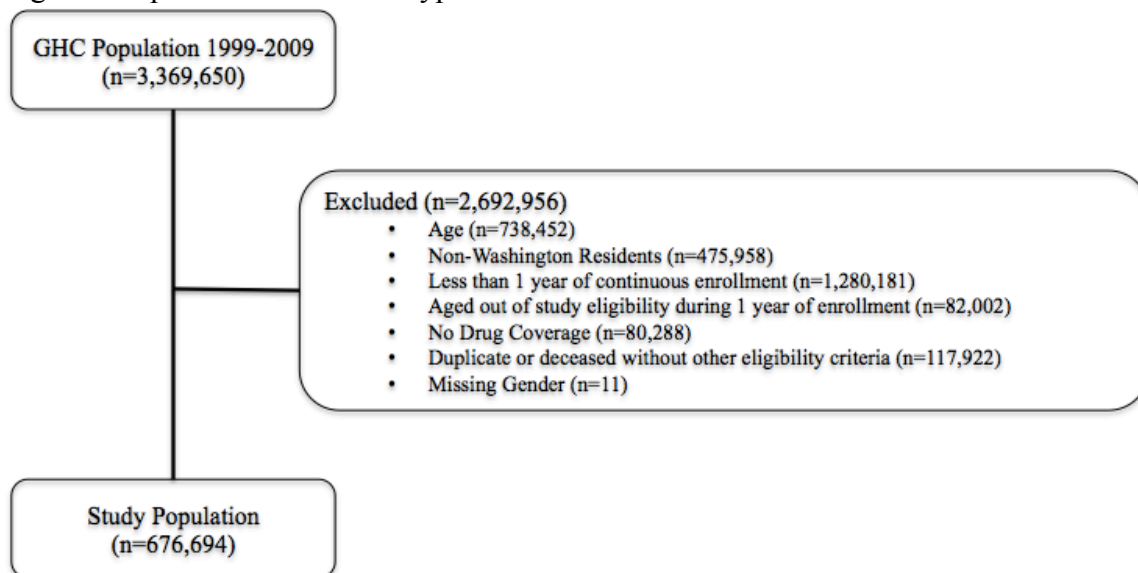
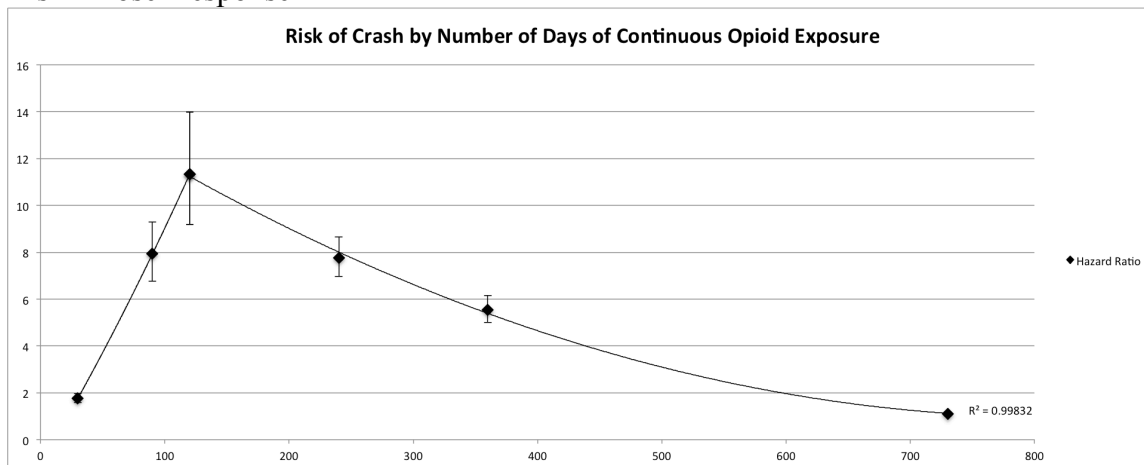


Figure 4. Relationship between Continuous Opioid Exposure and Motor Vehicle Crash Risk - Dose-Response



\*Error bars indicate 95% Confidence Intervals

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## CURRICULUM VITAE

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### EDUCATION

- 2012      **Doctor of Philosophy**, Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, Washington
- Dissertation:**                      The association between sedative hypnotic insomnia treatments and motor vehicle crashes.
- 2003      **Doctor of Pharmacy**, School of Pharmacy, University of Washington. Seattle, Washington.
- Externship Rotations:**              The Everett Clinic, Group Health Cooperative Administration, Premera Blue Cross, Harborview Medical Center, University of Washington Medical Center, Kindred Hospital, Kelley-Ross Pharmacy and, Homelink International Pharmacy
- 1999      **Bachelor of Arts, Cum Laude**, Chemistry and Philosophy, Carroll College. Helena, Montana.
- Thesis:**                                      Biological, Metaphysical and Ethical investigations into the National Bioethics Advisory Commission's Position on Human Cloning.

### PROFESSIONAL LICENSURE

- 2003              Registered Pharmacist, State of Washington

### PROFESSIONAL ACTIVITIES

#### **PHARMACY PRACTICE**

- 2003-present    Kelley-Ross & Associates, Inc., Seattle, Washington  
**Vice President, Technology Director, Privacy Officer, Pharmacist**

- Responsible for all aspects of technology for five pharmacies including deployment, troubleshooting, maintenance, development, policy and decision making
- Proactively design software solutions/interfaces with pharmacy software
- Design, maintain and enforce information security policies and procedures
- Provide primary patient care in both community and mail order settings

2004-2007    Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, Washington  
**Research Pharmacist**

- Agency for Healthcare Research and Quality (QHRQ) Health Information Technology Grant
- Primary focus: Computerized Prescriber Order Entry and its effects on medication errors, workflow and human factors.
- Role: Co-investigator
- Responsibilities: Study design, Administration, Prescription review, Time-motion analyses, Database design, Manuscript preparation and review

#### CONSULTING

2004-present    H Consulting limited, Seattle, Washington  
**President**

- Clinical Pharmacy Consulting
- Pharmacoeconomic Modeling
- Customized pharmacy system integration applications
- Cost-Effectiveness and Budget Impact Model Development and Evaluation

#### INTERNSHIPS

2000-2003    Kelley-Ross, Inc., Seattle Washington  
**Technology Solutions Specialist, Pharmacy Intern**

- Responsible for all aspects of technology for four community pharmacies including deployment, troubleshooting, maintenance, development, policy and decision making
- Proactively design software solutions/interfaces with pharmacy software
- Pharmacy compounding and dispensing intern

2000-2001    drugstore.com, Seattle, Washington  
**Pharmacy Intern**

- Drug Information Research, Weekly Literature Review, Writing, Editing and Posting Frequently Asked Questions for Patient Information
- Designed, developed and implemented an in-house Frequently Asked Question tracking database to provide pharmacists with the ability to keep answers up to date

1999-2000 Healthtek Pharmacy, Seattle, Washington  
**Pharmacy Intern**

- Compounding, OTC Patient Counseling, Dispensing
- Geriatric Services, Blister Packing, Drug Utilization Review

### POSTERS & PRESENTATIONS

**Hansen RN**, Joish VN, Sullivan SD. Folate Supplementation, Birth Weight, and Infant Mortality in the United States. Women's Health 2012: The 20<sup>th</sup> Annual Congress. March 16, 2012, Washington DC.

**Hansen RN**, Joish VN, Sullivan SD. Cost Benefit Analysis of Folate Supplementation and Birth Outcomes in the United States. 14th World Congress on Controversies in Obstetrics, Gynecology and Infertility. November 18-20, 2011, Paris, France.

Bloudek LM, **Hansen RN**, Liu L, Batty AJ, Varon SF, Lipton RB, Sullivan SD. Health Resource Utilization and Costs for Migraneurs in Scotland. International Society for Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 23, 2011, Baltimore, MD.

Bloudek LM, **Hansen RN**, Liu L, Batty AJ, Varon SF, Lipton RB, Sullivan SD. Headache Day Health states and Transition Probabilities for Patients With Chronic Migraine With and Without Headache Prophylaxis. International Society for Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 23, 2011, Baltimore, MD.

Globe D, Carlson JJ, Patel H, Colayco D, **Hansen RN**, Watanabe JH, Sullivan SD. Methodological Considerations for Cost-Effectiveness Analysis of OnabotulinumtoxinA in Patients With Neurogenic Detrusor Overactivity. International Society for Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 23, 2011, Baltimore, MD.

**Hansen RN**. Investigating the association between sedative hypnotic insomnia treatments and motor vehicle crashes. Harborview Injury Prevention Research Center. November 12, 2010, Seattle, WA.

**Hansen RN**, Oster G, Edelsberg J, Bobo M, Woody G, Sullivan SD. Economic costs of abuse and misuse of prescription opioids. International Society for Pharmacoeconomics and Outcomes Research 15th Annual International Meeting, May 20, 2010, Atlanta, GA.

**Hansen RN.** Executing Probabilistic Sensitivity Analyses in MS Excel using Visual Basic for Applications. Pharmaceutical Outcomes Research and Policy Program Retreat. May 3, 2010, Seattle, WA.

**Hansen RN,** Campbell JD, Sullivan SD. A Cost-Consequences Analysis of the Impact of A-Rated Anti-Epileptic Drug Switching: The Managed Care Plan Perspective. International Society for Pharmacoeconomics and Outcomes Research 14th Annual International Meeting, May 20, 2009, Orlando, FL.

**Hansen RN,** Campbell JD, Sullivan SD. Association of Anti-Epileptic Drug Switching and Seizure Related Events. American Epilepsy Society Annual Meeting, December 8, 2008, Seattle, WA.

**Hansen RN.** Problem Solving Through Contemporary Compounding: Application in Pediatric Patients. Pacific Northwest 28th Annual National Conference: Advanced Practice in Primary and Acute Care. October 2005, Seattle, WA.

Hollingworth W, Devine EB, Lawless N, **Hansen RN,** Wilson-Norton J, Tharp K, Sullivan SD. Evaluating the Impact of an ACPOE/CDS System on Outcomes: Using a Time and Motion Study to Measure Workload. Innovations Café. 2005 Annual Patient Safety and Health Information Technology Conference: Making the Health Care System Safer through Implementation and Innovation. Agency for Healthcare Research and Quality. June 2005, Washington DC.

Devine EB, Wilson-Norton JL, Lawless NM, **Hansen RN,** Kelly K, Te S, Wong C, Hazlet TK, Fisk AW, Sullivan SD. Evaluating prescribing errors pre- and post-CPOE in the ambulatory setting. 2005 Annual Patient Safety and Health Information Technology Conference: Making the Health Care System Safer through Implementation and Innovation. Agency for Healthcare Research and Quality. June 2005, Washington DC.

**Hansen RN.** Pharmacy Technology Update. Tri-State Pharmacy Conference. Washington State Pharmacy Association. June 2003, Coeur d'Alene, ID.

## **PUBLICATIONS**

**Hansen RN,** Oster G, Edelsberg J, Woody GE, Sullivan SD. Economic Costs of Non-Medical Use of Prescription Opioids. *Clinical Journal of Pain* 2011;27:194-202.

Devine EB, **Hansen RN,** Wilson-Norton JL, Lawless NM, Fisk AW, Blough DK, Martin DP, Sullivan SD. The impact of computerized provider order entry on medication errors in a multispecialty group practice. *Journal of the American Medical Informatics Association* 2010;17(1):78-84.

Devine EB, Hollingworth W, **Hansen RN**, Lawless NM, Wilson-Norton JL, Martin DP, Blough DK, Sullivan SD. Electronic Prescribing at the Point of Care: A Time-Motion Study in the Primary Care Setting. *Health Services Research* 2009;45(1):152-71.

**Hansen RN**, Campbell JD, Sullivan SD. Association between antiepileptic drug switching and epilepsy-related events. *Epilepsy and Behavior* 2009;15(4):481-5.

Devine EB, Wilson-Norton JL, Lawless NM, **Hansen RN**, Haney KK, Fisk AW, Sullivan SD. The impact of an Ambulatory CPOE System on Medication Errors. *AMIA Annual Symposium Proceedings* 2008:928.

Devine EB, Wilson-Norton JL, Lawless NM, **Hansen RN**, Hollingworth W, Fisk AW, Sullivan SD. Implementing an Ambulatory e-Prescribing System: Strategies Employed and Lessons Learned to Minimize Unintended Consequences. *Advances in Patient Safety: New Directions and Alternative Approaches*. Agency for Healthcare Research and Quality 2008. Rockville, MD, USA.

Hollingworth W, Devine EB, **Hansen RN**, Lawless NM, Comstock BA, Wilson-Norton JL, Tharp KL, Sullivan SD. The impact of e-prescribing on prescriber and staff time in ambulatory care clinics: a time motion study. *Journal of the American Medical Informatics Association* 2007;14(6):722-30.

Devine EB, Wilson-Norton JL, Lawless NM, **Hansen RN**, Hazlet TK, Kelly K, Hollingworth W, Blough DK, Sullivan SD. Characterization of prescribing errors in an internal medicine clinic. *American Journal of Health Systems Pharmacy* 2007;64(10):1062-70.

#### **WORKS IN PROGRESS**

**Hansen RN**, Boudreau DM, Ebel BE, Grossman DC, Koepsell TD, Sullivan SD. Linking Health Maintenance Organization Medical and Pharmacy Records with Washington State Collision Data.

**Hansen RN**, Boudreau DM, Ebel BE, Grossman DC, Koepsell TD, Sullivan SD. Investigating the Association between Acute and Long-Term Prescription Opioid Exposures and Motor Vehicle Crashes.

**Hansen RN**, Boudreau DM, Ebel BE, Grossman DC, Koepsell TD, Sullivan SD. Investigating the Association between Sedative Hypnotic Prescription Exposures and Motor Vehicle Crashes.

**Hansen RN**. Incorporating Health Technology Price Increases in Cost-Effectiveness Evaluations.

**Hansen RN**, Bloudek LM, Varon SF, Hayward E, Lipton RB, Sullivan SD. Cost-effectiveness of OnabotulinumtoxinA for Prophylaxis of Headache in Adults with Chronic Migraine in the United Kingdom.

### TEACHING

Value of Information. University of Texas – Austin, Department of Pharmacy Seminar. October 3, 2011.

Public and Private Reimbursement for Pharmaceuticals, Pharmacy 541, UW School of Pharmacy. February 2010-2012, Seattle, WA.

Application of Pharmacoeconomic Data to Formulary Decision-Making: Focus on Chronic Disease. Foundation for Managed Care Pharmacy Short Course. April 6, 2010, San Diego, CA.

Pharmacy Networking Best Practices for Independent Pharmacies. American College of Apothecaries Annual Meeting. May 2009, San Diego, CA.

Contracting for Pharmaceuticals: Medicare, Pharma, Corporate Payers and Pharmacies. Pharmacy 541, UW School of Pharmacy. February 2009, Seattle, WA.

Pharmacy Dispensing Technologies. Business Management Certificate Program, UW School of Pharmacy. October 2005, Seattle, WA.

### AFFILIATIONS

International Society for Pharmacoeconomics and Outcomes Research  
American College of Apothecaries  
Washington State Pharmacy Association

### SERVICE

Pharmaceutical Care Learning Center Renovation Committee, School of Pharmacy, University of Washington  
Technology Committee, American College of Apothecaries  
Technology Committee, Washington State Pharmacy Association  
Admissions Committee, PORPP, Department of Pharmacy, University of Washington  
Dean's Club, School of Pharmacy, University of Washington