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Running Head: IMPACT OF MEDICATIONS ON SAFE DRIVING

The Impact of Benzodiazepines and Opioid Analgesics on Safe Driving

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Abstract

Benzodiazepines are prescribed to relieve anxiety and aid sleep; opioid analgesics are prescribed to relieve severe or chronic pain. Both medications act as central nervous system depressants and can impair ones ability to drive safely. Currently, most epidemiological research has focused on the association between these medications and traffic crashes. Yet, the role of opioid analgesics and benzodiazepines on crash responsibility is still not properly understood. Therefore, we examined the impact of short, intermediate, and long half-life benzodiazepines and opioid analgesics on crash responsibility by drug half-life and driver age, using a case-control design with drivers aged 20 and over involved in fatal crashes in the U.S.A. from 1993-2006. Drivers (all with BAC=0) were classified as having no benzodiazepines detected versus short, intermediate, or long half-life benzodiazepines or no opioid analgesics detected versus present. Cases were drivers with at least one potentially unsafe driving action (UDA) in relation to the crash (e.g., speeding), a proxy measure for crash responsibility; controls had no UDAs recorded. Odds ratios (ORs) of any UDA by benzodiazepines half-life and opioid analgesic exposure were calculated, with adjustment for age, sex, other medication usage, and prior driving record. Compared with drivers not using benzodiazepines, drivers taking intermediate or long half-life benzodiazepines demonstrated increased odds of an UDA from ages 25 (Intermediate OR: 1.59; 95% CI=1.08, 2.33; Long OR: 1.68; 95% CI=1.34, 2.12) to 55 (Intermediate OR: 1.50; 95% CI=1.09, 2.06; Long OR: 1.33; 95%

CI=1.12, 1.57). Drivers taking short half-life benzodiazepines did not demonstrate increased odds of an UDA compared to drivers not using benzodiazepines. Compared with drivers not using opioid analgesics, odds of an UDA were increased from 25 (OR: 1.35; 95%: 1.05, 1.74) to 55 years of age (OR: 1.30; 95% CI: 1.07; 1.58) for a male driver, and from 25 (OR: 1.66; 95% CI: 1.32; 2.09) to 65 years of age (OR: 1.39; 95% CI: 1.17;1.67) for a female driver. Given the potential impact of these medications on driver safety, further experimental research is needed to better understand their effects on crash responsibility.

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Introduction

In 2006, there were over 40,000 fatal traffic collisions in Canada and the United States combined (Statistics Canada, 2008; National Highway Traffic Safety Administration, 2007b). This translates into approximately 13 fatalities per 100,000 licensed drivers in Canada and 21 fatalities per 100,000 licensed drivers in the United States (Statistics Canada, 2008; National Highway Traffic Safety Administration, 2007b). Factors that contribute to traffic crashes include environmental conditions (such as poorly designed roads, weather, or time of day) and vehicles involved (poor design, mechanical failure). However, research has shown that driver related factors have the greatest contribution to traffic crashes (Hendricks, Fell, & Freedman, 1999). Lack of experience, speeding, distracted driving can all result in poor driving that leads to a crash. Additionally, impairment related to drugs and alcohol can also contribute.

The impairing effects of alcohol are well established (Jones & Lacey, 2001). Other recreational medications, cannabis for example, have been shown to be associated with increased crash risk due to possible driver impairment (Bédard, Dubois, & Weaver, 2007). Drugs used for medicinal purposes to aid sleep, and relieve anxiety or pain, also have the potential to impair drivers and lead to fatal collisions since they are designed to depress brain function within the central nervous system (CNS). According to the National Highway Traffic Safety Administration in the United States, medications that depress the CNS including Narcotics (such as opioid analgesics) and benzodiazepines are found in approximately 15% of drivers

stopped for driving under the influence (DUI), the highest percentages for non-recreational drugs (Jones, Shinar, & Walsh, 2003). Currently, most epidemiological research has focused on the association of CNS depressants and traffic crashes, but their role as a causal factor is still not properly understood (Jones et al., 2003). Therefore, we chose to examine the role of two of the most prevalent CNS depressants (benzodiazepines and opioid analgesics) as a causal factor in fatal traffic crashes.

Benzodiazepine Overview

Benzodiazepine Uses and Prevalence

It is estimated that approximately 18% of Americans suffer from anxiety related disorders in a given year and 10-15% of Americans suffer from a sleep related disorder (Zammit, 2007; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Benzodiazepines, commonly known as tranquilizers and sleeping pills, are generally prescribed to treat anxiety or as sleep-aids, but can also be used as an anesthetic for outpatient surgery, to relax muscles, to relieve seizures, or to help with alcohol withdrawal. They can also be used recreationally, though use without a prescription is illegal in many parts of the world including Canada and the U.S.A. (Centre for Addictions and Mental Health, 2006). One year benzodiazepine use prevalence rates have been reported to range from 6.2% to 17.6% (Zandstra et al., 2002). While the prevalence of benzodiazepine use has declined over the past 10 years, benzodiazepines are the most frequently prescribed sedative-hypnotic for those 65 and over (Bogunovic & Greenfield,

2004; Centre for Addictions and Mental Health, 2006; Mamdani, Rapoport, Shulman, Herrmann, & Rochon, 2005). Further, a recent Canadian study demonstrated that as people age, benzodiazepine use for medicinal purposes increases (Beck et al., 2005).

Half-Life of Benzodiazepines

Benzodiazepines can be classified by half-life - the speed of elimination expressed in hours that it takes for half of the amount of benzodiazepine consumed to leave the body (Ashton, 2006). From a pharmacokinetic perspective, a benzodiazepine's half-life is important as it indicates the speed by which the medication affects the CNS and also the potential for cumulative effects with repeated doses (Birkett, 1996). It is common for benzodiazepine half-life to be dichotomized into two categories, short (half-life elimination < 24 hours) and long (half-life elimination ≥ 24 hours). Given the quick effect of short half-life benzodiazepines on the CNS they are typically used as Hypnotics (sleep-aids) while long half-life elimination medications, which work in a slower fashion, are used as a sedatives (anti-anxiety, known as Anxiolytics), but this is not always the case (Ashton, 1994). For example, Alprazolam has a half-life of 6-12 hours but is typically prescribed as an Anxiolytic. Benzodiazepines with the shortest half-lives can also be used as an anesthetic during outpatient surgery (e.g., midazolam). However, it is also important to understand that some benzodiazepines also produce active metabolites that can prolong the effect of the benzodiazepine. For example, the metabolic process for diazepam – which has a half-life of between 20-100

hours, produces the active metabolite desmethyldiazepam which has a half-life of 36-200 hours, thus increasing (by almost 100% in diazepam's case) the potential duration of the effect of the benzodiazepine (Ashton, 2006).

Impact of Benzodiazepines on the Central Nervous System

In pharmacological terms, benzodiazepines enhance inhibitory neurotransmitters that slow down CNS electrical signals (Ree & Cannard, 2006). It is this slowing down of the CNS electrical signals in the brain that can help to produce a calming effect. However, adverse effects can also occur and these include: over-sedation, drug interactions, memory impairment, paradoxical stimulant effects (i.e., the opposite effect of what is expected, hyperactivity for example), and depression. Both the intended and adverse effects can influence the CNS brain activity producing drowsiness, poor concentration, lack of coordination, and mental confusion, all of which can impair a person's ability to drive safely.

Prevalence of Benzodiazepines in Fatal Crashes

Despite the fact that benzodiazepines are labeled with warnings regarding their impact on a person's ability to drive safely, observational studies in Canada, Australia, and Europe, indicate that the prevalence of benzodiazepine use is approximately three to six percent among drivers involved in fatal crashes (Cimbura, Lucas, Bennett, Warren, & Simpson, 1982; Mercer & Jeffery, 1995; Drummer et al., 2003; Carmen, Gomez, Sancho, & Alvarez, 2002; Sjogren, Bjornstig, Eriksson, Ohman, & Solarz, 1997). Investigators have also studied the prevalence of benzodiazepine use in non-

fatal crashes in Australia, Asia, and Europe and found it to range between three and nine percent (Longo, Hunter, Lokan, White, & White, 2000; Lin, Lee, Pan, & Hu, 2003; Mura et al., 2003; Sjogren et al., 1997).

Experimental Studies – Benzodiazepines

Notwithstanding these data, an important research objective is to establish a causal link between the use of drugs and crashes. Some researchers have examined the impact of benzodiazepines on various driving-related tasks utilizing psychometric tests, driving simulators, and on-road driving courses (both open and closed circuit) (Drummer, 2002; van Laar, Volkerts, & van Willigenburg, 1992; Harrison, Subhan, & Hindmarch, 1985; Brookhuis, Volkerts, & O'Hanlon, 1990; Chung et al., 2005; Kozena, Frantik, & Horvath, 1995). Various experimental studies have shown that the benzodiazepine diazepam (also know by its brand name Valium) impairs coordination, and increases a driver's braking reaction time and their standard deviation of lateral placement (i.e., weaving) (Drummer, 2002). Studies have also examined the differences by benzodiazepine half-lives (i.e., short versus long). While shorter half-life benzodiazepines (such as oxazepam) affect driving skills shortly after consumption, they tend to have little to no impact the next morning which is particularly relevant given that they usually are prescribed as sleep-aids (Drummer, 2002). Conversely, longer half-life benzodiazepines have been shown to adversely affect driving in both morning after studies and in studies examining multiple doses spread over several days (Harrison et al., 1985; van Laar et al., 1992; Brookhuis et al., 1990; Drummer,

2002). For example, long half-life benzodiazepines such as flurazepam and diazepam have been associated with increased weaving and impaired speed control within one to three weeks following treatment initiation (van Laar et al., 1992; Brookhuis et al., 1990).

Observational Studies – Benzodiazepines

Analyses based on health record datasets provide further evidence that benzodiazepine use may be related to crashes. For example, drivers demonstrated increased odds of a crash during the time period of a current benzodiazepine prescription compared to an earlier time period when they did not have a current benzodiazepine prescription (Barbone et al., 1998). Barbone's study sample included approximately 20,000 drivers involved in a crash and the outcome was a first crash within the study period. Approximately 96% of the sample had a confirmed blood alcohol concentration (BAC) of zero. The odds of crash involvement were 100% higher for users of Anxiolytic type benzodiazepines (OR: 2.03; 95%CI: 1.4; 2.9) compared to when the drivers were not prescribed this medication. Interestingly, Barbone also examined benzodiazepines by half-life (short: < 6 hours, intermediate: 6-24 hours, and long: > 24 hours) and found that intermediate and long half-life benzodiazepines significantly increased the odds of a crash but short benzodiazepines did not. The contribution of benzodiazepines to hospitalizations due to a traffic injuries has also been examined (Neutel, 1995). Neutel found significant increases in hospitalizations due to a traffic injury for those drivers prescribed either Anxiolytics (OR:5.6; 95%CI: 1.7, 18.4) or

Hypnotic benzodiazepines (OR: 6.5; 95%CI: 1.9, 22.4), particularly for those benzodiazepines recently prescribed. It has also been demonstrated that as the frequency of benzodiazepine prescriptions increased (one script versus three or more, over a six month period), the risk of accident related (traffic or otherwise) medical encounters increased (Oster, Huse, Adams, Imbimbo, & Russell, 1990). In Tennessee Medicaid recipient drivers 65 years of age and older, Ray found a dose-response relationship. Increased doses of benzodiazepines (primarily long half-life benzodiazepines) were associated with increased odds of a crash with injury (Ray, Fought, & Decker, 1992). Further, older drivers whose exposure to long half-life benzodiazepines was recent had increased odds of a crash involving at least one hospitalization (OR: 1.45; 95%CI: 1.04, 2.03) (Hemmelgarn, Suissa, Huang, Boivin, & Pinard, 1997). However, those exposed to short half-life benzodiazepines did not demonstrate increased odds, regardless of exposure duration, a result which parallels those found in experimental research.

The main strength of these observational studies is the large samples they relied on. However, an important limitation is that they examined crash involvement rather than driver responsibility for crash initiation. For example, the outcome for Hemmelgarn's study was involvement in a crash resulting in injury (Hemmelgarn et al., 1997). A second limitation is the reliance on a proxy marker of exposure, such as a current prescription for benzodiazepine (Ray et al., 1992). Proxy exposure measures can lead to over-representation in the exposed group and under-representation in the non-exposed group (i.e., the

prescription was filled but not used). The third limitation is the population source of the health record. Data sources drawn from a specific sub-population, for example public health insurance (e.g., Medicaid recipient eligibility is determined by economic status), can limit the generalisability of results. A fourth limitation is in the classification of benzodiazepines. Most studies either group the benzodiazepines as a whole or divide exposure by benzodiazepine type (Anxiolytic, Hypnotic). For example, in both Oster and Ray's studies, benzodiazepines were grouped as a whole regardless of half-life (Oster et al., 1990; Ray et al., 1992). Alternatively, Neutel classed benzodiazepines as either Anxiolytic or Hypnotic – unfortunately the half-lives of their groupings overlapped considerably (2-250; 4-200 hours) (Neutel, 1995). A fifth limitation is the number of cases who used benzodiazepines in the data sources. While the samples may be large, the actual number of cases exposed to benzodiazepines may be too small to have sufficient statistical power. For example, Drummer examined Australian forensic reports of fatally injured drivers to determine if crash culpability increased under the influence of alcohol and drugs. While crash culpability was 27% higher when benzodiazepines were detected in the blood (no other drugs or alcohol) this increase did not achieve statistical significance - most likely due to the small number of benzodiazepine only impaired drivers. (OR:1.27; 95%CI: 0.5, 3.3) (Drummer et al., 2004). While Drummer's sample included almost 2000 drivers, only 34 tested positive for benzodiazepines alone.

Opioid Analgesics Overview

Pain Prevalence

According to the National Center for Health Statistics, an estimated 76.5 million (26%) Americans, aged 20 and over, reported suffering from pain lasting greater than 24 hours (National Center for Health Statistics, 2006). Of these, 56% reported suffering from pain lasting greater than 3 months (National Center for Health Statistics, 2006). Prevalence rates of chronic pain vary widely; partly due to different definitions of pain duration and also due to survey method employed (for example, self-report survey versus clinical examination) (Verhaak, Kerssens, Dekker, Sorbi, & Bensing, 1998). Regardless, prevalence rates vary from as low as two percent to as high as 40% (Verhaak et al., 1998; Mantyselka, Turunen, Ahonen, & Kumpusalo, 2003). Several conditions can be the source of pain and some include: cancer, osteoarthritis, fibromyalgia, and lower back pain. Often, prescription analgesics are used to help manage mild to severe acute and chronic pain associated with these conditions.

Prevalence of Prescription Analgesics

There are two classes of prescription analgesics: opiate and non-steroidal anti-inflammatory drug (NSAID) based. Prescription analgesic prevalence rates have been studied using both population-based surveys (Antonov & Isacson, 1998; Paulose-Ram et al., 2003; Turunen, Mantyselka, Kumpusalo, & Ahonen, 2005; Sawyer, Bodner, Ritchie, & Allman, 2006) and through examination of prescribing patterns found in pharmaceutical

databases (Eggen & Andrew, 1994; Blackburn, Downey, & Quinn, 1990). Regardless of method of study, prevalence rates for prescription analgesics tend to be between 8 – 10% (Turunen et al., 2005; Blackburn et al., 1990; Eggen et al., 1994; Sawyer et al., 2006; Antonov et al., 1998). Some studies break down prevalence rates by analgesic type (NSAID, opiate) (Eggen et al., 1994; Paulose-Ram et al., 2003; Sawyer et al., 2006). For example, Paulose-Ram examined self-reported prescription analgesic use that was captured in a representative sample of United States civilians (n=20,050) using the National Health and Nutrition Examination Survey (Paulose-Ram et al., 2003). While overall monthly prevalence of prescription analgesics was over 9%, the monthly prevalence rate for those on opiate based analgesics was 3.4% (Paulose-Ram et al., 2003).

Prevalence studies have demonstrated analgesic use increases with age. In 1994, Eggen and Andrew reported on analgesic prescriptions dispensed in a sample of the Norwegian population (Eggen et al., 1994). The overall user proportion of controlled analgesics during the one year period studied increased from 7.8% (aged 20-39) to: 12% for those aged 40-59, 15% for those aged 60-79, and 19.4% for those aged 80+ (Eggen et al., 1994). Comparable results by age were reported in Blackburn's study of a Canadian provincial pharmaceutical database where prevalence of use of mood modifying drugs (including analgesics) increased by age (Blackburn et al., 1990).

There is also evidence which suggests prescription analgesic use may differ by sex. For example, Antonov and Isacson found 12.2% of women reported prescription analgesic use compared with only 7.2% of men (Antonov et al., 1998). Eggen and Andrew reported female use of prescription analgesics was greater than males (8.9% vs. 6.8% $p<.0001$) (Eggen et al., 1994). Most analgesic users studied by Eggen and Andrew reported they consumed a little less than a month's worth of medication a year, however, approximately 15% of users reported consuming the medications on a weekly or even daily basis throughout the entire year studied. In these weekly to daily users, the proportion increased from 3.2% (aged 0-19) to 34.6% (aged 80+) in women, and 0.0% (age 0-19) to 26.8% (aged 80+) in men – both age and sex were statistically significant ($p<.0001$ for both age and sex) (Eggen et al., 1994).

The influences of other factors, such as the user's health and economic status, have also been examined in relation to prevalence rates. Turunen and colleagues performed a cross-sectional study of analgesic use in approximately 3300 Finns. Along with age and sex, Turunen also included indicators of: health (mood status and chronic disease presence), socioeconomic status (education and work status), and pain (frequency, duration, and intensity) (Turunen et al., 2005). A lack of formal education, unemployment, the presence of a chronic disease, a low mood score (indicating possible depression), and chronic, average to severe intensity, pain all significantly increased the odds of analgesic use. Even with these

additional factors accounted for, those participants aged 45 and older had twice the odds of consuming analgesics on a daily basis compared to those who did not (Turunen et al., 2005). On the other hand, older age did not significantly increase the odds of a person using opioid analgesics on an as needed basis. Also the odds of consuming analgesics did not significantly differ by sex when all variables were accounted for.

Antonov and Isacson examined analgesic use as reported in a structured interview of a probability sample (N=11,996) of all inhabitants of Sweden aged 18 – 84 years of age (Antonov et al., 1998). Poor health status (smoker, over-weight, poor self-perceived health, and poor physical function), pain severity, and a recent visit to a health care provider (physician or physical therapist) significantly increased the odds of prescription analgesic use in both men and women (Antonov et al., 1998). However, age did not significantly increase the odds of prescription analgesic use when health status, pain severity, and a visit with a health care provider were accounted for.

While both Turunen (Turunen et al., 2005) and Antonov (Antonov et al., 1998) look at several possible reasons for increased opioid use, neither authors' study discriminated between NSAID and opiate based prescription analgesics when querying participants. It is quite possible that along with age, sex, pain severity, and health status the type of analgesic prescribed can also influence prevalence rates. Sawyer et al's examination of medication use in community-dwelling older adults ($\geq$ 65 years of age) did discriminate between NSAID and opiate based prescription analgesics (Sawyer et al., 2006).

Approximately 31% of participants reported taking prescription analgesics at the time of the assessment - 25% reported taking a prescription NSAID and 8.5% reported using an opiate based analgesic (numbers do not add up due to some participants reporting multiple medication usage) (Sawyer et al., 2006).

Finally, opioid analgesic consumption is on the increase. According to the International Narcotics Control Board, in the United States of America consumption of the major opioid analgesics, including codeine, hydrocodone, morphine, oxycodone, and methadone increased by approximately 38% between the years 2001 and 2005. (International Narcotics Control Board, 2007)

Prescription Analgesics and Driving: Adverse Effects, Experimental, and Epidemiological Evidence.

Opioid analgesics can be used to help manage mild to severe acute and chronic pain. Colloquially known as "pain killers", common opioid analgesics include: codeine, hydrocodone (vicodin), methadone, and morphine. The route of administration varies, though it is typically either through oral (tablet, syrup) or parenteral (injection) forms. Along with pain management, opioid analgesics can also be used as a cough suppressant, for substance abuse withdrawal, and to aid anesthetic in surgery. According to the American Pain Foundation, the most common adverse effects of opioid based analgesics include nausea, sedation (sleepiness), and mental clouding (Altilio et al., 2007). Other adverse effects can include dizziness and memory

impairment (Altilio et al., 2007). These adverse effects can influence the CNS potentially impairing a person's ability to drive safely.

Current Evidence - Experimental

Using cognitive, laboratory, and on-road evaluations, researchers have examined the potential impact of opioid analgesics on driving ability (Bruera, Macmillan, Hanson, & MacDonald, 1989; Galski, Williams, & Ehle, 2000; Vainio, Ollila, Matikainen, Rosenberg, & Kalso, 1995; Byas-Smith, Chapman, Reed, & Cotsonis, 2005; Gaertner et al., 2006). In general, studies evaluating driving ability demonstrate small differences between opioid analgesic users and control groups. For example, Vainio and colleagues examined driving ability in cancer patients receiving long-term morphine analgesia (Vainio et al., 1995). Specifically, Vainio compared 24 cancer patients on a stable dose of slow-release morphine tablets with 25 cancer patients reporting no pain and who did not take regular analgesics. The psychomotor tests administered, were designed for professional drivers and measured basic non-verbal intelligence, vigilance, task concentration, divided attention, and fluency of motor reactions. While no significant differences were found between morphine and control groups, the authors reported that the morphine groups' responses were generally (but not statistically significantly) worse than the control groups. Given the relatively small sample size of this study, it is possible that the statistical comparisons lacked sufficient power to demonstrate a statistically significant difference. Regarding the neurological tests, the morphine group performed significantly worse on the test of balance

(i.e., increased body sway in cm) when eyes were closed (p=.028), but performed significantly faster on the finger-tapping test (p=.023) – however, while the association between medication and neurological tests was significant, one cannot rule out the effect that the pain itself may have had. Interestingly, the authors found moderate correlations between plasma concentrations of morphine and performance on the Q1 (test of attention capacity) and strong correlations between plasma concentrations and LL5 (test of concentration and structuring ability) errors performed.

Galski and colleagues performed a pilot study which evaluated the effects of Chronic Opioid Analgesic Therapy (COAT: greater than 6 month history of responsiveness to opioids for pain reduction and current use of a long acting opioid). They compared patients suffering from nonmalignant pain (e.g., osteoarthritis, fibromyalgia) (Galski et al., 2000) to historical control of 327 drivers, who had a history of stroke, traumatic brain injury, or anoxia. The historical control was divided into two groups: Driver's who had passed a behind the wheel test following rehabilitation (N=162); and driver's who had failed (N=165). Driving ability was measured with both a comprehensive battery of psychometric tests and with a one hour driving simulation that captured errors in braking, steering, accelerating, controlling speed, and signaling. The COAT patients equaled or exceeded both control groups' scores in all but one measure of driving-related ability. However, while COAT patients had faster completion times, they did so at the expense of accuracy. For example, on the Double Letter Cancellation Test (a test of visual scanning)

COAT patients committed twice as many errors compared to the control group who had passed their behind the wheel test (Galski et al., 2000).

In 2005 Byas-Smith compared driving ability between a convenience sample of those suffering from chronic pain under a stable opioid dosing regime, those suffering from chronic pain that chose not to use opioids, and a group of healthy normals. Driving ability was measured with both cognitive and on-road tests. While Byas-Smith found no statistically significant differences between the groups using attention-based tests, the normal group scored significantly faster compared to both chronic pain groups (opioid and non-opioid) on the Digit Symbol Substitution Test – which measures the speed by which visual information is processed and then translated into motor activity (Byas-Smith et al., 2005). The on-road test included both an obstacle course where speed and error rates were captured and a community drive where speeding, turning, stopping, and lane infractions were examined. For the obstacle course, Byas-Smith found no significant differences between the three groups in completion speed or error rate for the on-road obstacle course. During the community drive, only speeding infractions were recorded and there were no turning, stopping, or lane violations across the three groups. Speed exceedances ranged between 5 and 15 mph and there were no statistically significant differences between driver groups.

Another approach to assess the possible impairment of opioid analgesics was taken by Gaertner and colleagues (Gaertner et al., 2006). Their study compared driver related cognition and psychomotor performance

of 30 chronic non-cancer pain patients, currently treated with controlled release oxycodone, with 90 healthy volunteers whose scores were adjusted for an intoxication effect equivalent to $\geq$ 0.05 blood alcohol content (Gaertner et al., 2006). Volunteers were considered to be a representative sample of drivers from the German population. Each patient was assessed for performance under pressure, orientation, concentration, attention, and reaction time. Patients on oxycodone in general scored statistically significantly higher than the control group scores adjusted for the effect of alcohol. Compared with the control group, oxycodone patients had: significantly faster mean reaction times for the test of attention; scored better on the test of visual orientation, tachistoscopic perception with fewer wrong answers; better motor coordination represented by less time off track; and, a higher vigilance score with significantly fewer wrong answers. However, the authors found that daily oxycodone dosage correlated moderately with the number of wrong answers on the test of attention. Also, age was found to have a strong, positive, correlation with increased mean times and higher (poorer) scores of motor coordination and have a moderate correlation with reaction times for the test of visual orientation. Conversely, driving experience was shown to have a moderate negative correlation with reaction times on the test of visual orientation.

It should be noted that in all of the above listed studies, participants using opioid analgesic therapy received a stable treatment dose. One could hypothesize those patients on long term therapy (i.e., stable dosing) would be

at the least risk of driver impairment and consequently be responsible for the small effect sizes found in the studies described above. There is evidence to suggest that dosage state (increased versus stable) is associated with impaired driving ability. Bruera and colleagues examined the impact of prescription analgesics on cognition for those patients suffering from cancer pain (Bruera et al., 1989). Cognitive measures included finger tapping, arithmetic, memory for digits, and visual memory tests. Twenty patients were on a stable dosing regime and the other twenty had received an increased dosage of ≥ 30% within the past 3 days. Comparing the cognition change scores between the two groups demonstrated that the increased dosage groups' differences were significantly greater than the stable groups (Bruera et al., 1989) suggesting that increased dosing can result in the patient experiencing cognitive impairment.

Current Evidence – Observational

Similar to experimental evidence, most observational studies demonstrate small or non-significant differences between those drivers taking prescription analgesics and a variety of risks including intoxicated driving, involvement in a motor vehicle crash, and crash fatalities (Fishbain, Cutler, Rosomoff, & Rosomoff, 2002; Blomberg & Preusser, 1974; MacPherson, Perl, Starmer, & Homel, 1984; Holmgren, Loch, & Schuberth, 1985; Christensen, Nielsen, & Nielsen, 1990; Marquet et al., 1998; Gjerde, Beylich, & Morland, 1993; Honkanen et al., 1980; Skegg, Richards, & Doll, 1979; Ray et al., 1992; Leveille et al., 1994). In 2002, Fishbain et al conducted a structured evidence-

based review of studies from 1966 on containing epidemiological evidence regarding associations between opioid use with: (1) intoxicated driving, (2) motor vehicle crashes, and (3) motor vehicle fatalities (Fishbain et al., 2002). The quality of evidence was rated according to the Agency for Health Care Policy and Research Rating Scale I where evidence is rated between - (I) Meta-analysis of multiple-well designed studies (considered the strongest level) and (V) Case reports and clinical examples (considered the weakest level) (West et al., 2002). After assessing the evidence, the authors concluded that opioids were probably not associated with intoxicated driving, motor vehicle crashes, or motor vehicle fatalities (Fishbain et al., 2002).

Of the six studies Fishbain included which examined the association between opioid use and intoxicated driving, five compared opioid detection rates to general population reported prevalence of opioid use, and one reported differences in traffic convictions between methadone users and a driver control group. Of the five prevalence studies, opioids detected in drivers suspected of intoxicated driving were approximately one tenth of the estimated point prevalence for opioid use reported in two studies for the general population of the USA and Norway (Simoni-Wastila, 2000; Eggen et al., 1994). In the study which compared traffic convictions, no significant differences in the proportion of traffic convictions was found between drivers recovering from heroin addiction on methadone treatment and a matched (same sex, similar age) non-user of opioid analgesics control group (Blomberg et al., 1974). Given the low prevalence rate of opioid detection in drivers suspected of

driving under the influence, and the similar levels of traffic convictions found, Fishbain concludes that opioids are not likely to be associated with intoxicated driving.

However, these five studies were assessed as Type IV evidence – well designed non-experimental studies – and have limitations and inherent biases that need to be considered when evaluating the possible association between opioids and intoxicated driving (West et al., 2002). For example, sample selection for two of the five studies was based on drivers suspected of driving under the influence of alcohol by police officers (MacPherson et al., 1984; Holmgren et al., 1985). We cannot assume that drivers under the influence of opioid analgesics would exhibit the same characteristics as an inebriated driver. Another limitation of these studies is that the sample may not be representative of opiate users. For example, the sixth study regarding intoxicated driving and opiate use, rated by Fishbain as type II evidence (a well designed experimental study) consisted primarily of young males (mean age 27.1 years; 89% male) (Blomberg et al., 1974). Of the opiate analgesic groups' self reported miles driven in this study, approximately one third of miles driven per year were contributed by unlicensed drivers (Blomberg et al., 1974). It is quite plausible that this sample is representative of drivers recovering from heroin on methadone treatment, but would most likely not be representative of patients using opioid analgesics for other purposes, in particular pain relief.

In regard to the association between opioids and motor vehicle crashes, Fishbain reported on 11 studies of Type II (well-designed experimental study)

and III (well-designed quasi-experimental study) levels of evidence. Fishbain reported that ten of the eleven studies indicated opioids were not associated with motor vehicle crashes. For example, Christensen examined drug influence on Danish drivers (N=461) involved in motor vehicle crashes suspected of driving under the influence (Christensen et al., 1990). Opioids were detected in 38% of cases (N=173) suspected of driving under the influence, the second highest drug group after benzodiazepines (65%). However, of all drivers testing positive for opiates only 23% (N=40) were involved in a traffic crash versus 77% not involved in a crash ($p<.0001$) (Christensen et al., 1990). Marquet compared the presence of opiates in young French drivers (aged 18 – 35) injured in a motor vehicle crash with control group admitted to the same emergency units as drivers for non-traumatic reasons (Marquet et al., 1998). Of the drugs tested among injured drivers, opiates (with a 10.5% prevalence rate) were the second highest drug detected after cannabinoids. Yet, this prevalence rate was almost identical to the opiate prevalence rate for the non-trauma injury control group (10.4%) (Marquet et al., 1998). Given the evidence, Fishbain concludes that opioids are likely not associated with motor vehicle crashes.

Of the 10 (all type IV evidence) studies examined by Fishbain (Fishbain et al., 2002) addressing whether opioids are associated with motor vehicle crash fatalities, nine reported an opioid prevalence in fatally injured drivers between 0.3% and 3.9% (Fortenberry, Brown, & Shevlin, 1986; Mason & McBay, 1984; Cimbura et al., 1982; Garriott, DiMaio, Zumwalt, & Petty, 1977;

Gjerde et al., 1993; Williams, Peat, Crouch, Wells, & Finkle, 1985). The remaining two studies reported a 0% prevalence rate (Owens, McBay, & Cook, 1983; Budd, Muto, & Wong, 1989). For example, Owens and colleagues studied the incidence of alcohol and other drugs in North Carolina drivers killed in single car crashes for a one-year period (Owens et al., 1983). Of the 169 drivers meeting study criteria, 53% (n=90) of the fatally injured drivers were 30 years of age and under, and 83% of drivers were male. Approximately 67% of drivers tested positive for alcohol, 5.9% and 5.3% were THC or barbiturate positive respectively. None of the drivers tested positive for opiates. Budd and colleagues examined serum from autopsies of 102 fatally injured drivers over a six month period (Nov '85 thru April '86) and in a second study, 492 fatally injured drivers over a one-year period (May '87 thru May '88) from Los Angeles County (Budd et al., 1989). In the first study of 102 fatally injured drivers, approximately 64% (n=65) were positive for alcohol and/or drugs. Yet, only one case (0.9% of drivers) tested positive for opiates (codeine). In their second study of 492 fatally injured drivers, no cases tested positive for opiates.

Similar to Budd and Owens, others have found only small numbers of fatally injured drivers testing positive for opiates. Fortenberry and colleagues examined 1518 Alabama drivers fatally injured in a traffic crash found almost no opioid presence (Fortenberry et al., 1986). Less than 0.3% tested positive (N=4) for propoxyphene, an opioid analgesic. In Mason's study of 600 fatally injured North Carolina drivers, opioids were detected in 0.3% (N=3) cases (Mason et al., 1984). Given the results of the studies above, and that the other

studies examined reported an opioid prevalence well below North American standards, Fishbain concludes that the current evidence does not support an association between opioid use and vehicle crash fatalities (Fishbain et al., 2002).

While Fishbain's conclusions are generally supported by the epidemiological evidence, there are limitations of the studies that should be considered. For example, alcohol and other drug use in conjunction with opioid analgesics can also be an issue in interpreting associations between opiate use and traffic crashes or fatalities. Marquet found a significantly higher prevalence of opiates in male drivers, injured in a traffic crash, who also tested positive for cannabinoids compared to those drivers who tested negative for cannabinoids (Marquet et al., 1998). Christensen found that 54% (N=250) of their sample of drivers suspected of driving under the influence tested positive for two or more drug groups (Christensen et al., 1990). In a study of 159 fatally injured car drivers in Norway, Gjerde found that 12 (7.5%) were alcohol and drug positive (Gjerde et al., 1993). One of the 12 cases (representing 8.3% of those alcohol and drug positive) tested positive for therapeutic levels of Codeine and a BAC of 0.2 (Gjerde et al., 1993). MacPherson demonstrated that the combination of opioid analgesics (e.g., Codeine) and lower levels of alcohol (BAC < 0.115) were associated with increased crash risk (between 45 to 65%, $p < .01$) in young male Australian drivers compared to those testing positive for alcohol only (MacPherson et al., 1984).

It is also possible that analgesics are under-detected in epidemiological studies using serum (blood/urine) analyses. Like Marquet, Honkanen also examined the prevalence of drugs in drivers admitted to emergency room department (Honkanen et al., 1980). Along with urine and blood analyses, Honkanen also obtained self-report drug usage from the drivers. While no analgesics were detected in the serum analysis, 21% of drivers involved in traffic crashes reported using analgesics within the last week (N=41). Of these 41 drivers, nine reported using an analgesic within the past 24 hours (Honkanen et al., 1980). Walsh examined the prevalence of alcohol and other drug use among adults involved in motor vehicle crashes admitted to a trauma center (Walsh et al., 2004). This study found that if tested for alcohol use only, 45.2% would not have been identified for drug use.

Sometimes epidemiological studies can be limited by the size of the exposed group. Skegg and colleagues compared pharmacy prescriptions for 57 drivers involved in a crash (requiring hospital admission or resulting in death) with a randomly selected control group (N=1,425) matched on general practitioner, sex, and year of birth (Skegg et al., 1979). Of the 57 drivers involved in a crash, 7% (N=4) had received a prescription for minor analgesics versus 3.1% (N=44) of the 1425 control group members, resulting in a non-significant Relative Risk of 2.5. Unfortunately, Skegg's study was severely limited by the exposure sample and also the measure of exposure. Of the 57 drivers involved in crashes, 21 (37%) were driving cars, 22 (39%) motorcycles, and 14 (24%) bicycles. Further, the majority of the drivers involved in crashes

were males (N=44, 77%) with two thirds below 30 years of age (N=36, 63%). Skegg and colleagues contended that the power of their study was limited by the measure of medication exposure, a prescription filled within the last 3 months prior to the crash (Skegg et al., 1979).

Many epidemiological studies that indicate little or no association between opioids and unsafe driving have samples that are usually: a) comprised of younger drivers (Blomberg et al., 1974; Marquet et al., 1998; Maddux, Williams, & Ziegler, 1977; Skegg et al., 1979; Williams et al., 1985); or b) include a distribution that is positively skewed towards younger drivers (Mason et al., 1984; Honkanen et al., 1980; Owens et al., 1983; Cimbura et al., 1982; Williams et al., 1985); or c) do not indicate age of the drivers sampled (Budd et al., 1989). Additionally, in many of these epidemiological studies, females are under-represented – usually consisting of less than 20% of the drivers studied (Blomberg et al., 1974; Marquet et al., 1998; Maddux et al., 1977; Christensen et al., 1990; Skegg et al., 1979; Owens et al., 1983; Mason et al., 1984; Williams et al., 1985). It is plausible that the under-representation of both older and female drivers means that they are less involved in traffic-related incidents associated with opioid use. Yet, given that opioid prevalence has been demonstrated to be greater in females than males and has also been shown to increase with age (Eggen et al., 1994; Blackburn et al., 1990; Antonov et al., 1998), it is also plausible that the low reported prevalence of opioid analgesics and their minimal association with unsafe driving is driven by the characteristics of the sample. For example, less than 2% of fatally injured

drivers tested positive for opioid analgesics in Williams' study but the entire sample was comprised of male drivers between the ages of 15-34 – a sample we would expect a low prevalence of opioid analgesic use (Williams et al., 1985).

In studies that have examined older drivers at risk when using opiates, the results are inconclusive. Christensen did find drivers involved in a crash were significantly older, but as discussed earlier, did not detect a positive association between opioid use and traffic crashes (Christensen et al., 1990). In a sample of Tennessee Medicaid recipient drivers 65 years of age and older, Ray found no increased risk of involvement for an injurious crash for current users of opioid analgesics (relative risk = 1.1; 95% CI: 0.5; 2.4) (Ray et al., 1992). Leveille found a non-significant trend towards elevated risk of injury collisions in those drivers 65 and older as the probability increased that they were taking the medication on the day the crash occurred (Leveille et al., 1994). However, Leveille observed significantly higher odds (when adjusted for race, marital, education, and diabetic status) of an injurious crash (Adjusted OR: 1.8; 95% CI: 1.0; 3.4) in drivers who had filled their opioid prescription within the past 60 days (Leveille et al., 1994). It should be noted that the discrepancy between Ray and Leveille's studies may be due to differences in their exposure measure for opioids. Unlike Ray, Leveille included codeine-containing cough medications and these accounted for one of every five opioid prescriptions (Leveille et al., 1994).

Finally, studies have shown that the prevalence of opioid analgesic drugs detected in drivers is increasing. Drummer examined the prevalence of drugs, including opioids, in drivers killed in Australian road traffic crashes over a 10 year period (Drummer et al., 2003). The prevalence of opioids doubled from 3.4% (n=36) during the period of 1990-1993 to 6.6% (n=93) during the period of 1997-1999. Jonasson, through blood testing, also found that the prevalence of dextropropoxyphene, an opioid analgesic increased from 2.6% in 1992 to 4.3% in 1997 (Jonasson, Jonasson, Saldeen, & Thuen, 2000) in drivers suspected of driving under the influence of an intoxicating substance.

Purpose

Based on current evidence we set out to design a study that: a) examined the impact of both benzodiazepine and opioid analgesics exposure on driver error (versus crash involvement); b) was based on a representative data source with high external validity; c) measured drug exposure with standardized toxicological testing, and d) contained benzodiazepines representing all ranges of half-lives and all major opioid analgesics. Further, we wanted a data source with both the capacity and content to control for other factors that may contribute to crash initiation, such as age, sex, previous driving history, and other substances that may affect the CNS, such as alcohol and other medications. Specifically, we examined the contribution of both benzodiazepine and opioid analgesic exposure to driver error in fatal crashes in all U.S. fatal crashes from 1993 to 2006. Given both the experimental and

epidemiological evidence reviewed and the known effects of benzodiazepines and opioid analgesics on the CNS, we hypothesized that the odds of an unsafe driver action would be significantly increased for those drivers who were taking intermediate or long half-life benzodiazepines or opioid analgesics.

Methods

Data source

In 1975, the National Center for Statistics and Analysis of the National Highway Traffic Safety Administration, U.S.A., developed the Fatality Analysis Reporting System (FARS) (National Highway Traffic Safety Administration, 2006). This database contains fatal traffic crash information from the 50 states, District of Columbia, and Puerto Rico from 1975 to the present. Crashes included in FARS meet two criteria: 1) the crash involves a motor vehicle traveling along a traffic way customarily open to the public; and 2) the crash results in the death of a person (either an occupant or non-motorist) within 30 days of the crash.

Data are gathered from the following sources: police reports; vehicle registration and driver licensing files; state highway department data; vital statistics; death certificates, coroner, medical, emergency service, and hospital reports(National Highway Traffic Safety Administration, 2006). All data elements obtained from these sources are reported onto one of three forms (accident, vehicle, and person) by trained FARS analysts. The accident form contains crash information specific to the time, location, road and weather conditions, and overall vehicle information. More specific vehicle information,

such as: vehicle type, crash role, points of impact, the most harmful event, and drivers record and license status, is recorded on the vehicle form. Finally, a person form contains data for each person involved in the crash. Information recorded includes: age, sex, role, alcohol and drug involvement, injury severity, et cetera. In terms of drug involvement, the FARS database captures approximately 300 separate drugs with impairment potential which fall into one of 8 groupings (narcotic, depressant, stimulant, hallucinogen, cannabinoid, phencyclidine (PCP), anabolic steroid, and inhalant). Given, the quantity of information coded in the database, and number of crashes recorded, the FARS database allows for the control of numerous potential confounders, and calculation of crash estimates more easily generalized to all drivers involved in fatal crashes (Dischinger, Ho, & Kufera, 2000).

Data Assembly

Data Retrieval.

On an annual basis, the National Highway Traffic Safety Administration (NHTSA) updates the FARS data available via the FARS File Transfer Protocol (FTP) site (National Highway Traffic Safety Administration, 2007a). While the data is contained on three forms (Accident, Vehicle, Person) the data is captured in four datasets: Accident, Vehicle, Person, and Driver. For the years 1993 through 2003, data was downloaded from the FARS FTP site in structured query language (SQL) format. For data in SQL format, one yearly data file is provided containing all four levels of crash data (Accident, Vehicle, Driver, and Person). To allow analysis of this data, each crash data level was

extracted into its own data file (Accident, Vehicle, Person) by year. Between 2004 and 2006, the SQL format was no longer available; therefore data was downloaded in the available Statistical Analysis Software (SAS) format. For data in SAS format, each year's data was recorded in three data files (Accident, Vehicle, and Person). Given, the Driver information was contained in the Person file, driver data was extracted into a separate Driver file to allow merging of data between 1993 and 2006.

Preparation of Data for Merging

In preparation for merging yearly data together, consistent variable definitions were examined by year. As necessary, variable definitions were expanded to allow for definitions that changed across years. To be clear, variable elements were not changed, just the definition of a variable was expanded to allow the merging of data from all years available. For example, a variable that was originally coded with a one digit number, might have expanded into two digit coding, thus requiring us to expand the earlier definition to allow later years to reside under the same variable name.

Data Merge and Validation

After the all data variables were examined for consistency, the data merge began. Each component of the crash data level was combined into one yearly data set in three steps: first, variables from the accident file were added to the vehicle file to create a temporary Vehicle_Accident data file; second, variables from the driver file were added to the Vehicle_Accident file to create a temporary Vehicle_Accident_Driver file; third, variables from the

Vehicle_Accident_Driver file were added to the Person file to create the yearly data set. Next, all yearly data sets were merged into a master data set by sequential stacking starting with 1975 until a master dataset inclusive of all available years of FARS crash data (currently 1975 through 2006). Given collection of medication data by drug name began in 1993, data from 1993 - 2006 was extracted from the master dataset to form the analysis dataset. To validate the data merge, frequency reports were run for several years on various yearly characteristics such as Total Fatal Crashes, Traffic Crash Victims – Drivers, and Traffic Crash Victims – Passengers. These frequency reports were then compared to pre-existing reports contained in the FARS encyclopedia (National Highway Traffic Safety Administration, 2007b). All comparisons yielded exact matches.

FARS Variables Used

For our analysis we used data from the FARS database from 1993 to 2006. While fatal crash data has been recorded since 1975, more comprehensive collection of medication data began in 1993 allowing for analysis by medication type including benzodiazepines and opioid analgesics. We used the following FARS data: age, sex, drug test results (blood or urine), alcohol tests results (blood), type of vehicle driven, and the drivers' past driving record. To eliminate the influence of alcohol on driver error, only those drivers with a confirmed blood alcohol concentration of zero were included in the analysis.

Benzodiazepine Classification and Exposure

Twenty-two different generic benzodiazepines were recorded for one or more drivers in the sample. We classified benzodiazepines according to half-life duration. Typically, research has focused on grouping benzodiazepines into either short (< 24 hours) or long half-life (24 hours or more) groups. Given that approximately one third of short half-life benzodiazepines within our sample were those that are typically prescribed as an anesthetic for out-patient surgery (e.g., midazolam), we separated the short half-life category into a short and intermediate half-life groupings. Therefore, benzodiazepines were grouped as follows: ≤ 6 hours were classified as short; > 6 but < 24 hours as intermediate; and ≥ 24 hours as long. See Table 1 for benzodiazepines included in this analysis and the half-life classification assigned. Some benzodiazepines had overlapping half-life categories, for example tetrazepam (half-life range: 3-26). In such cases, these benzodiazepines were placed in the half-life grouping for which the majority of their range fell (therefore, tetrazepam was categorized as intermediate half-life). While there is pharmacodynamic variability within these classifications one main benzodiazepine accounted for most prescriptions in each category, therefore minimizing the possible effects of pharmacodynamic variation. For each driver, a maximum of three drug exposure results were provided (in no particular order). Given the limited number of drivers in the sample with just one benzodiazepine, we allowed each case to have more than one benzodiazepine as long as each benzodiazepine fell into the same half-life category. Therefore,

exposure was measured as either: No benzodiazepines detected, short half-life benzodiazepines, intermediate half-life benzodiazepines, or long half-life benzodiazepines detected.

Opioid Analgesics Classification and Exposure

All medications captured in the FARS database were classified as either opiod positive or negative according to section 1308.12 of the U.S. Code of Federal Regulations (U.S.Department of Justice - Drug Enforcement Administration, 2007). A total of 11 different opioid based analgesic medications were recorded for one or more drivers. Opioid containing medications included in the FARS sample are usually prescribed to treat pain (e.g., Codeine, Morphine), control heroin dependence (e.g., Methadone), or relieve coughing (e.g., Hydrocodone). See Table 1 for opioids included in this analysis. A maximum of three medication serum analyses were available for each driver, but we only considered those who tested positive for one opioid based medication. To reduce the potential bias of multiple drugs in a driver's system, those drivers with two or more positive results for opioid analgesics were excluded from the analysis.

Proxy Measures of Responsibility – Unsafe Driver Actions

A FARS analyst uses the police officer's crash narrative to determine the driver related factors for each crash (Blower, 1998). For every driver in the FARS database, up to three (four since 1997) driver-related factors are recorded. The majority of these driver-related factors (codes 20 – 59 inclusive) are considered unsafe driver actions (UDAs), that is, actions that contributed to

the crash (e.g., improper lane changing). Drivers for whom no UDAs were specified were assumed to not have contributed to crash initiation. In this study, cases were drivers with at least one UDA recorded in relation to the crash (e.g., weaving), controls were drivers who had no UDAs recorded. The full list is displayed in Appendix A.

Daniel Blower, Director of the University of Michigan Transportation Research Institute Center for National Truck and Bus Statistics, writes that the use of UDAs is preferred to traffic violations as a method for understanding the relative contribution of different drivers to a crash (Blower, 1998). This is because police officers are less likely to lay a charge for a traffic violation due to insufficient legal proof and therefore the use of traffic violations will lead to an incomplete picture of crash causes. Further, not all contributing factors are chargeable offences. On the other hand, the crash narrative contained in the police report and the source for the FARs analysts' UDA coding, allows the reporting officer to record their judgment therefore providing a more detailed picture of the factors contributing to the crash.

Further, Blower has tested the validity of the UDA coding by comparing crash configurations that allow inference of crash responsibility, such as head-on, rear-end, and opposite direction sideswipe collisions, with the UDAs reported in one truck and one passenger vehicle fatal vehicle crashes. Blower found that in crash types that strongly imply causation, the driver of the striking vehicle was assigned the majority of UDAs (Blower, 1998). Along with Blower's studies, researchers have successfully used UDAs as a measure of

"responsibility" (Perneger & Smith, 1991; Bédard & Meyers, 2004; Bédard et al., 2007). For example, Perneger used UDAs contained in the FARS dataset to demonstrate that driver errors often explain high rates of crash involvement and these driver errors were significantly associated with specific driver characteristics (alcohol for example) (Perneger et al., 1991).

Driver History

The FARS data set also includes variables containing the drivers' past three-year driving records. As it is important to control for high risk driving habits, we included these data in our analysis. Driving record variables include: number of accidents (crashes), number of recorded convictions for driving while impaired (DWI; includes both alcohol and drugs), speeding convictions (going too fast or too slow), other harmful moving violation convictions, and license suspensions and revocations. We excluded drivers aged less than 20 given that they would not have had sufficient opportunity (years) to acquire a driving history. Finally, we limited the vehicles included in our analyses to drivers of passenger vehicles, sport-utility vehicles and light trucks (pick-up trucks) only.

Analytical plan

Similar analyses plans were followed for both benzodiazepine and opioid analgesic medications. First, descriptive statistics were used to examine both demographic characteristics and most reported UDAs by benzodiazepine or opioid analgesic exposure groups. For benzodiazepines, exposure was categorized as follows: no benzodiazepines detected, short half-life

benzodiazepines only, intermediate half-life benzodiazepines only, and long half-life benzodiazepines only. For opioid analgesics, exposure was categorized as either: no opioid analgesics detected or opioid analgesic detected. Demographic characteristics and unsafe driver actions were formally compared by both exposure categories (benzodiazepines by half-life and opioid analgesics by presence) to the referent group using the Pearson Chi-square test (sex, unsafe driver actions) and One-way Analysis of Variance (age).

The main analysis included several logistic regression models. We first examined the difference in UDAs reported by each exposure medication (benzodiazepines or opioid analgesics) without adjusting for other factors. Next, we ran a model that included age, sex, prior driving record, other medications, and our exposure variable. Given that the relationship between a driver's age and committing an UDA could be quadratic (i.e., curvilinear versus linear), we also included the quadratic age term. To examine the interaction between age, sex, other medications, and the exposure variable, the third model included all two-way and three-way interaction of these terms. Finally, the last model included significant two-way and three-way interaction terms from the third model and all other terms (exposure variable, age, sex, other medications, and driver history).

Logistic regression allows the calculation of predicted odds (POs) and odds ratios (ORs). Essentially, POs are the probability of an event happening divided by the probability of an event not happening for a given combination of

explanatory variables. An odds ratio is the comparison by exposure of two POs. We used the logistic regression model to calculate POs of any UDA at selected combinations of the three interacting variables, and also calculate ORs of any UDA by benzodiazepine half-life and opioid analgesic exposure. Alpha was set at $p<.05$ and we report 95% confidence intervals. All analyses were done with SPSS version 15.

Results

Benzodiazepines

Of the 72,026 drivers with a blood alcohol content of zero, 2,200 (3%) tested positive for any benzodiazepine. Of these 1,550 cases tested positive for one or more of the same half-life Benzodiazepines as follows: 161 Short half-life; 369 Intermediate half-life; 1,020 Long half-life. These cases were included in the analyses. An additional 465 drivers tested positive for benzodiazepines which were unclassified by half-life and another 185 drivers tested positive for multiple benzodiazepines classified in more than one half-life category. These cases were not included in the analyses. In general, drivers exposed to benzodiazepines were slightly younger than non exposed drivers, but had a similar ratio of male:female drivers, they also were more likely to be on another medication aside from benzodiazepines, and had a worse driving record than those drivers with no benzodiazepines detected. Full results are displayed in Table 2.

For those drivers taking benzodiazepines, the most frequently reported medication classes were: depressants, narcotics, stimulants, cannabinoids,

and other (non FARS classified) drugs. Hallucinogens, PCP, steroids, and inhalants had the lowest reported prevalence. Overall, drivers taking benzodiazepines had higher positive test results for other medications than drivers with no benzodiazepines detected. Approximately one in six drivers (16.9%) with no benzodiazepines detected tested positive for another medication compared to 47%, 66%, and 58% of drivers taking short, intermediate, and long half-life benzodiazepines respectively.

The five most frequently reported UDAs by medication exposure group are reported in table 3. Overall, drivers exposed to either intermediate or long half-life benzodiazepines had an 11-14% higher reporting rate of any UDA compared to those not exposed. Specifically, there were significantly higher reports of "Failure to keep in proper lane/Running off road" and "Driving too fast" for those drivers' taking intermediate and long half-life benzodiazepines compared to drivers with no benzodiazepines detected. Those on short half-life benzodiazepines had a similar reported rate of any UDA compared with drivers not exposed.

The crude ORs of any potentially unsafe driver action occurring were 1.08 (95% CI=0.79, 1.49), 1.94 (95% CI = 1.53, 2.46) and 1.66 (95% CI = 1.45; 1.91) for those exposed to short, intermediate, and long half-life benzodiazepines respectively. After adjusting this association for age, sex, other medications, and driving record the ORs were 1.00 (95% CI=0.72, 1.39), 1.54 (95% CI = 1.21, 1.96), and 1.44 (95% CI = 1.25; 1.66) for those exposed to short, intermediate, and long half-life benzodiazepines respectively. We next

examined whether age, sex, and other medications (including depressants, narcotics, stimulants, cannabinoids, and other medications) interacted with benzodiazepine exposure. Sex did not significantly interact with the benzodiazepine exposure variable (Wald(3) = 5.0, p = .17) nor did the overall age term (Wald(3) = 5.0, p=.17). However, while age did not significantly interact with short (Wald(1) = .74, p = .39) or intermediate (Wald(1) = .34, p = .56) half-life benzodiazepines, age did significantly interact with long half-life benzodiazepines (Wald(1) = 3.96, p = .047). Given this significant interaction and that we expected age may be related to the half-life duration of benzodiazepines, the age by benzodiazepine interaction was included in the final model. Of the five medication categories examined, none interacted significantly with benzodiazepines. Given the low reported prevalence of Hallucinogens, PCP, Steroids, and Inhalants, these were combined into the Other medications category in the final model. Therefore, the final model included benzodiazepine exposure, driver sex, driver age, the quadratic driver age term, benzodiazepine exposure by age interaction, sex by age interaction, other medications, and previous driving record variables. The final ORs of an UDA occurring when age was centered at 45 years were 1.02 (95% CI=0.73, 1.42), 1.53 (95% CI = 1.20, 1.96) and 1.44 (95% CI = 1.25; 1.66) for those exposed to short, intermediate, and long half-life benzodiazepines respectively.

Younger age, male sex, and poorer driving records were associated with a higher risk of a reported UDA. In particular, one or more of either

"Previous Accidents", "Previous Other Convictions", or "Previous Speeding Convictions" increased the odds of an UDA by 15%, 11%, and 8% respectively. Linear increases were associated with reported UDAs for those with repeated offenses in the categories of "Previous Accidents", "Previous Speeding Convictions", and "Previous Suspensions". For example, as the number of repeated "previous suspensions" increased (1, 2, 3 or more) so did the odds of a UDA (33%, 42%, and 58% respectively). See Table 4 for more detail.

To examine the possible age by benzodiazepine exposure interaction, we generated predicted odds and odds ratios for selected ages (every 10 years, 25 through 75) (Aiken & West, 1991; Jaccard, 1998). These estimates show how the effects of benzodiazepines depend on age (see Figures 1, 2 and Table 5). For example, the odds ratio for a 25 year old driver using a long half-life benzodiazepine is 1.68 (95%: 1.34, 2.12) compared to 1.13 (95% CI: 0.84; 1.53) for a 75 year old driver. Overall, drivers taking intermediate and long half-life benzodiazepines demonstrated increased odds of an UDA from ages 25 (Intermediate OR: 1.59; 95% CI=1.08, 2.33; Long OR: 1.68; 95% CI=1.34, 2.12) to 55 (Intermediate OR: 1.50; 95% CI=1.09, 2.06; Long OR: 1.33; 95% CI=1.12, 1.57). As we can see from both Figures 1 and 2, younger drivers taking intermediate or long half-life benzodiazepines had the greatest increases in predicted odds and the largest odds ratios.

To further validate our analysis, we re-ran the final model (excluding any of the other medication terms), including only those cases that tested

positive for just one benzodiazepine only or no medications at all. Approximately 83% (N=58,562) of drivers not testing positive for benzodiazepines tested negative for other medications. Of those drivers testing positive for benzodiazepines, 53% of short (N=86), 32% (N=119) of intermediate, and 20% (N=200) of the long half-life cases were retained in the validation analysis. Similar trends were seen across benzodiazepine categories. While significance at the p=.05 level was not obtained for the intermediate half-life benzodiazepines (with the exception at age = 45, OR: 1.51, 95%CI: 1.02; 2.24) likely due to the much smaller sample size, a similar odds ratio pattern by age was demonstrated. For example, the odds ratio for those drivers taking intermediate half-life benzodiazepines ranged between 1.59 for 25 year olds to 1.40 for 75 year olds. For those drivers taking long half-life benzodiazepines, the results paralleled the analysis which included drivers on other medications; statistically significant increased odds of an UDA were seen from ages 25 (OR: 1.69; 95%: 1.05, 2.71) to 55 (OR: 1.61; 95% CI=1.13, 2.30). See Table 6 for the full results.

Given that research has shown that time of day can influence results for older drivers, we re-ran our analyses including time of day using the same intervals as Ray (6am – 12 pm; 1 pm – 7 pm; 8 pm – 5 am) (Ray et al., 1992). While time of day contributed significantly to the model and interacted significantly with age, it did not interact significantly with benzodiazepine presence.

Opioid Analgesics

In total, 72,026 drivers tested for both alcohol and drugs had a blood alcohol content level of zero. Of these, 2,109 (3%) tested positive for a single opioid analgesic (see Table 7) and form the basis of the analyses. An additional 380 (1%) cases tested positive for two opioid analgesics, and another 52 (0.2%) for three opioid analgesics; these cases were not included in the analyses. Regardless of medication status, drivers had a mean age of approximately 46 years of age and approximately two thirds were male. Approximately 60% of those drivers taking opioid analgesics were also taking at least one other medication compared to only 16% of those drivers testing negative for opioid analgesics. Depressants (27%), stimulants (16%), and cannabinoids (8%) were the most prevalent. Given that hallucinogens (.2%), PCP(.3%), and inhalants (0.05%) were the least prevalent medications these cases were combined with the other (non FARS classified) drug category with 20% of drivers taking opioid analgesics who also tested positive for these other medications. Drivers who tested positive for opioid analgesics had a worse driving record (higher percentage with previous crashes, DWI convictions, other driving convictions, speeding infractions, and license suspensions). Full results are displayed in Table 8.

Table 9 displays the top five most frequently reported unsafe driver actions. The group of drivers taking opioid analgesics had a 16% higher proportion of any unsafe driver action reported compared to the group of drivers on no opioid analgesics, χ^2 (1, N=71,592)= 86.2, p <.001. In particular,

drivers using opioid analgesics had significantly higher reported frequencies than non-opioid analgesic drivers for the following unsafe driver actions: "Failure to keep in proper lane" (41% greater, χ^2 (1, N=71,592)= 147.6, p <.001); "Driving too fast" (13% greater, χ^2 (1, N=71,592)= 4.1, p =.042); "Making Improper Turns" (40% greater, χ^2 (1, N=71,592)= 7.0, p =.008); and "Reckless vehicle operation" (20% greater, χ^2 (1, N=71,592)= 6.8, p =.009). While "Failure to properly yield" was the third highest unsafe driver action reported for those taking opioid analgesics it had a significantly lower reported frequency compared to those drivers on no opioid analgesics (33% less, χ^2 (1, N=71,592)= 27.9, p <.001).

Testing positive for the presence of an opioid analgesic increased the risk of performing an unsafe driver action by 57% (Unadjusted OR: 1.57; 95%CI: 1.43; 1.73). After adjusting this association for age, sex, other medications, and driving record the OR was 1.30 (95% CI = 1.18; 1.44). We next examined whether age, sex, and other medications interacted with opioid analgesic exposure. Sex (Wald Statistic = 4.8, p = .028), stimulants (Wald Statistic = 10.8, p = .001), and depressants (Wald Statistic = 5.0, p = .025) interacted significantly with the opioid analgesic exposure variable and were therefore retained in the final model. Given the quadratic age term interaction approached significance (Wald Statistic = 3.5, p = .061), we also included the age by opioid analgesics exposure and quadratic age by opioid analgesics exposure in the final model. Therefore, the final model included opioid analgesic exposure, driver sex, driver age, the quadratic driver age term,

opioid analgesic exposure by age interaction, opioid analgesics by age squared interaction, opioid analgesic exposure by stimulant medication interaction, opioid analgesic exposure by depressant medication interaction, opioid analgesic exposure by sex interaction, sex by age interaction, sex by age squared interaction, other medication, and previous driving record variables. The final ORs of an UDA occurring when age was centered at 45 years was 1.72 (95% CI = 1.45; 2.03) for those exposed to opioid analgesics.

Younger age, male sex, testing positive for other medications, and poorer driving records were associated with higher odds of a reported UDA. Risk was increased for those also testing positive for other medications with the exception of Narcotics. For each of the previous driver history variables, linear increases were associated with higher odds. For example, as the number of repeated offenses increased (1, 2, 3 or more) so did the odds of an unsafe driver action. Those drivers with "Previous Suspensions" had the greatest increased risk (33%, 38%, and 56% respectively). See Table 10 for more detail.

Given the significance levels in the final model for both the sex by opioid analgesic exposure term (Wald = 4.04, p = .045) and the quadratic age by opioid analgesic exposure term (Wald = 3.20, p = .074) in the final model, we generated predicted odds and odds ratios for selected ages (every 10 years, 25 through 75) by sex (Aiken et al., 1991; Jaccard, 1998). These estimates show how the effects of opioid analgesic depend on both age and sex (see Figures 3,4 and Table 11). For example, the odds ratio for a 25 year old using

an opioid analgesic, was 1.35 (95%: 1.05, 1.74) for a female driver, and 1.66 (95% CI: 1.32; 2.09) for a male driver. In comparison, at 75 years old the odds ratios were 0.94 (95% CI: 0.73; 1.22) for a female driver and 1.15 (95% CI: 0.91; 1.47) for a male driver. As can be seen in Figure 2, younger and middle-aged male drivers taking opioid analgesics had the greatest increases in predicted odds and the largest odds ratios.

To validate our analysis, we re-ran the final model, deselecting any case that had tested positive for any other medication. Included were 840 drivers from the opioid analgesic group and 58,549 drivers from the non opioid analgesic group. Similar patterns were seen to the analysis including drivers on other medications. For example, female drivers had significantly increased odd of an unsafe driver action from age 25 (OR: 1.69; 95% CI: 1.17; 2.44) through 55 (OR: 1.27; 95% CI: 1.12; 1.68). Male drivers had significantly increased odds of an unsafe driver action from age 25 (OR: 1.76; 95% CI: 1.27; 2.44) through age 65 (OR: 1.32; 95% CI: 1.04; 1.68). See Table 12 for all results. Regardless of sex, the highest odds ratios were seen at age 35 in both the original and validation analysis.

Discussion

Benzodiazepines

Depending on the age of the driver and type of medication exposure (benzodiazepine by half-life or opioid analgesic) the odds of an UDA increased by similar levels, 33% to 68% for drivers taking benzodiazepines, and 30% to

70% for drivers taking opioid analgesics compared to the respective control group drivers. In both medications' analyses, younger and middle age drivers were at the most risk. For example, drivers aged 25 had the highest odds of committing an UDA when exposed to either intermediate or long half-life benzodiazepines.

Effects of Age

The impact of benzodiazepines decreased with age but remained statistically significant for intermediate and long half-life benzodiazepines through middle age. Interestingly, benzodiazepine exposure did not significantly increase the odds of an UDA for drivers aged 65 and older which at first can appear counter to both Ray and Hemmelgarn's findings (Ray et al., 1992; Hemmelgarn et al., 1997). As Ray demonstrated, part of this may be explained by driver behavior. Ray's study showed that drivers 65 and older who were taking benzodiazepines (only) were at increased risk between the hours of 6 am and 12 pm (Relative Risk = 2.0, 95% CI: 1.3, 3.2) but not between 1 pm and 7 pm or 8 pm and 5 am (Ray et al., 1992).

It is also possible that our benzodiazepine analyses lacked sufficient statistical power for drivers 65 and older. Hemmelgarn and colleagues did not find increased risk for benzodiazepines with a half-life less than 24 hours, which is equivalent to our findings. However, they found that odds were increased for those taking long half-life benzodiazepines (Adjusted OR: 1.28, 95% CI: 1.12, 1.45). Our adjusted ORs are similar to those reported by Hemmelgarn (Adjusted OR for 65 year old: 1.22, 95% CI: 0.98; 1.54). Given

that we examined fatal crashes only and not those crashes resulting in non-fatal injuries, our sample of 205 drivers aged 65 and older exposed to benzodiazepines was considerably smaller than the 6,064 benzodiazepine exposed cases in Hemmelgarn's study and the 2,978 cases in Ray's study (Hemmelgarn et al., 1997; Ray et al., 1992).

Short Benzodiazepines

Drivers taking short half-life benzodiazepines (classified as <6 hour half-life), did not demonstrate increase odds of an unsafe driver action. This may be due to the fact that these medications are generally used for anesthesia in outpatient surgery and not to relieve anxiety or to aid sleep. One assumes that drivers would be warned about the possible side effects, post surgery, of the short benzodiazepines and therefore, if they still chose to drive, would demonstrate more vigilance than normal. Further, given this group's short half-life, the effects would most likely be minimal within a few hours after surgery. Interestingly, our overall results are similar to the dose-response results found in Barbone's study who also examined benzodiazepines by half-life (short: < 6 hours, intermediate: 6-24 hours, and long: > 24 hours) and found that intermediate and long half-life benzodiazepines significantly increased the odds of a crash but short benzodiazepines did not (Barbone et al., 1998).

Driver Behavior

The higher odds of an UDA with intermediate and long-acting benzodiazepines may be explained by the effect of these medications on driver behavior. Failure to stay in the proper lane was the number one UDA

across exposure categories. These results were especially prominent in the intermediate and long half-life benzodiazepines driver group who had approximately fifty percent more proportional cases cited for this particular unsafe driving action compared to drivers with no detected medications. Driving too fast was the second highest UDA cited for the intermediate and long half-life group. When compared with the non benzodiazepine group, the intermediate and long groups had 38% and 25% higher proportion of drivers cited respectively for this UDA. These results mirror experimental studies demonstrating that benzodiazepines significantly impair control of lateral position (i.e., weaving) and affect speed perception (O'Hanlon, Haak, Blaauw, & Riemersma, 1982; van Laar et al., 1992; Irving & Jones, 1992).

Opioid Analgesics

To date, epidemiological literature has focused on using prevalence rates to demonstrate minimal, or no associations between the use of opioid analgesics and safe driving. While prevalence rates remain relatively low in traffic crashes, the contribution of opioid analgesics to unsafe driver actions in fatal traffic crashes appears much greater than expected. Compared to drivers on no medications, those drivers testing positive for an opioid analgesic had the odds of an unsafe driver action increased by 30% to 74% depending on the driver's age and sex.

Effects of Age

While younger and middle-aged drivers had the highest odds of committing an unsafe driver action when exposed to opioid analgesics,

significantly increased odds were seen at all of the selected ages except 65 and 75 for females, and 75 for males. It should be noted that regardless of medication status, the predicted odds of an unsafe driver action aged 75 were 2.15 for females and 2.21 for males, among the highest of all age categories. Given that the predicted odds for drivers with no medication detected, aged 75, was 2.28 in females and 1.92 in males, the odds ratios were not significant.

Driver Behavior

The possible effects of opioid analgesics on driver behavior may explain the significantly higher odds of an unsafe driver action. The opioid analgesic group had a 16% greater proportion of reported UDAs compared to the no medication detected group. Of the Top 5 unsafe driver actions committed by drivers taking opioid analgesics, four were reported in significantly higher proportions when compared to drivers with no medication detected. The second, fourth, and fifth highest unsafe driver actions cited were: driving too fast for conditions; making improper turns; and erratic, reckless, careless or negligent vehicle operation respectively. Approximately 18% of drivers were cited for driving too fast, seven percent for improper turns, and six percent for erratic or reckless vehicle operation. While these proportional differences were similar to non opioid analgesics group, the differences were statistically significant. Of the top 5 unsafe driver actions reported for drivers on opioid analgesics, only failure to yield right of way, obey signs or other safety zone traffic laws was significantly lower than the non opioid analgesic drivers. Nearly

a 33% higher proportion of the non opioid analgesic drivers were cited for this unsafe driver action.

Failure to keep in the proper lane was the number one unsafe driver action reported for drivers taking opioid analgesics. Two of every five drivers were cited, approximately a 41% higher proportion cited compared to the no opioid analgesics detected group. Examples of failure to keep in proper lane include the vehicle crossing the centerline or the vehicle going straight in a turn lane (Tessmer, 2007). While minimal differences were found in the experimental literature between opioid analgesic drivers and non-medicated drivers, Byas-Smith found visual information was processed at half the speed of healthy normals, and Galski found twice as many visual scanning errors compared to the their cerebrally compromised control group (Byas-Smith et al., 2005; Galski et al., 2000).

Driving Record

Of interest, we found that drivers taking opioid analgesics had a poorer driving record compared to the non-medicated control group. In 2003, Fishbain after reviewing the current literature concluded, "that there was strong, consistent evidence for no greater incidence in motor vehicle violations/motor vehicle accidents versus comparable controls of opioid-maintained patients" (Fishbain, Cutler, Rosomoff, & Rosomoff, 2003). Our results demonstrated large, statistically significant, proportional differences in both categories. In terms of previous motor vehicle crashes, the opioid analgesic group had a 32% higher proportional number of previous crashes in the past three years

compared to the non opioid analgesic control group. In regard to the poorer driving record, those on opioid analgesics had a 38% higher proportional number of other traffic convictions, 12% higher proportional number of speeding violations, and 88% proportionally higher number of license suspensions in the past three years compared to the non opioid analgesic control group.

All Medications

Predicted Odds at Older Ages

Another important consideration when interpreting the study results is the possibility that the lower odds ratios for the older age groups may be due to the increased odds of an UDA for non-exposed drivers and not necessarily the decreased odds for exposed drivers. In Figures 2 and 4, we clearly see the well known u-shaped crash risk by age relationship in the drivers with no medications detected (McGwin, Jr. & Brown, 1999; Tay, 2006). Both younger and older drivers are at higher risk regardless of medication status. For example, while the predicted odds of an UDA for drivers aged 75 exposed to intermediate half-life benzodiazepines was 2.73, higher than any other age category for intermediate half-life benzodiazepines, the odds ratio was not significant given that for drivers with no medications detected, aged 75, the predicted odds were 1.89. Similar patterns are seen in the opioid analgesic analysis.

Important Study Limitations

Marker of Exposure

Our study has some important limitations. Our marker of exposure is dichotomous (present/absent) and therefore we do not know the route of administration, blood concentration level at time of crash, dosage received, or current dosing regime – all of which could influence this study's findings. Taking blood concentration as an example of this limitation, some drivers may have tested positive for either of these medications but have low concentrations that would not be expected to impair driving. The main consequence of this limitation is the potential underestimation of the risk posed by the benzodiazepine or opioid analgesic. Another example of this limitation is seen when considering dosing regimes for those taking opioid analgesics. Considering the literature, (Bruera et al., 1989; Galski et al., 2000; Vainio et al., 1995; Byas-Smith et al., 2005; Gaertner et al., 2006) we would expect those on stable dosing regimes on opioid analgesics to be safer drivers. If our sample consists of mainly those on stable dosing, then our results would represent an under-estimate of the potential risk associated with driving and non-stable opioid analgesic use. Conversely, if our sample had a higher proportion of drivers on a new dosing regime the results of the study would be an over-estimate of the associated risk of driving and stable opioid analgesic use. A similar bias could be seen with benzodiazepines. In terms of benzodiazepine use, experimental studies demonstrate that longer duration of use can reduce the adverse effects on driving performance as tolerance

increases. Therefore, this may lead to an underestimation of the increased risks for those beginning a new benzodiazepine prescription but an overestimation for long-term users.

Detection Methods

There is another important limitation of our study that needs to be considered especially given that the marker of exposure is dichotomous. The FARS database includes cases for all of the United States. Given that testing methods are determined at the state level we cannot comment on the accuracy of the tests and the possibility of bias introduced by test variation. Further, as the FARS data used in this study were collected every year since 1993, it is also possible that detection methods have become more sensitive over time. This may have introduced two sources of error. First, tests from earlier years may have less sensitivity (than recent ones) resulting in the classification of users of benzodiazepines or opioid analgesics as non-users; this would lead to an underestimation of the impairment effects of these medications. Second, newer testing methods may potentially result in the detection of traces of medications that would not necessarily be enough to result in driver impairment; this could lead to an under estimation of the effect of benzodiazepines and opioid analgesics.

Medical Conditions

Another limitation is that we do not know what medical conditions the benzodiazepines or opioid analgesics were prescribed for. It is possible that these medical conditions (e.g., cancer) and their symptoms (such as the pain

itself) are the causal agent for the impairment. For example, Sagberg examined the relative crash risk of involvement associated with various medical conditions. He demonstrated that at fault drivers who self-reported sleep onset insomnia, tiredness, and anxiety had increased odds of being at fault for a crash (OR = 1.87, p<.01; OR = 1.36, p = .03; OR = 3.15, p = .03 respectively) when controlling for age and annual driving distance compared with drivers without the particular medical condition (Sagberg, 2006). However, Sagberg reports that it is unclear as to whether medications may have been used during the time of the crash (Sagberg, 2006).

Sagberg also examined relative crash involvement risk associated with musculoskeletal and pain related conditions. Controlling for age and annual driving distance, Sagberg found no significantly increased odds of being at fault for a crash compared with those drivers without the particular medical condition or medication during the study time period (Sagberg, 2006). In 2006, Veldhuijzen examined the effect of chronic nonmalignant pain on highway driving performance (Veldhuijzen et al., 2006). Their study used both on-road and psychometric testing to measure driving performance differences between 14 chronic nonmalignant pain patients (not on medication) with 14 healthy controls. The primary outcome of the on-road test was standard deviation of lateral position (SDLP, i.e., the amount of weaving of the car within the traffic lane), which was measured continuously over a 100 km highway course. Drivers suffering from chronic nonmalignant pain performed worse than the healthy controls, having an approximately 20% higher mean SDLP. The

authors found a statistically significant group effect ($p = .007$) between the pain group and healthy controls. No statistical differences were found on mean speed, standard deviation of speed, or mean lateral position. Of interest, pain intensity and SDLP were not found to significantly correlate though this may be due to the small sample size. Further, while drivers suffering from pain did not score significantly different compared to the healthy controls, the direction of certain psychometric tests (measuring motor coordination, reaction, and divided attention) appeared worse than the healthy controls.

Charlton and colleagues examined the influence of chronic illness on crash involvement of motor vehicle drivers, including anxiety disorders (Charlton et al., 2004). Individuals with anxiety disorders can demonstrate a heightened alertness to threat and a tendency to worry which can have the adverse effects related to driving function including: decreasing working memory, increased distraction, and less attentional capacity available (Charlton et al., 2004). Further, the presence of chronic illness and co-morbidities increases the potential for polypharmaceutical effects. However, we did control for the influence and tested for possible interactions of medications that may contribute to impairment such as depressants, narcotics, and cannabinoids.

Enhancing Agents

While the FARS database screens for medications that have possible impairing effects such as narcotics, depressants, and hallucinogens it does not classify (but instead places them in a general other category) all medications

that may impair drivers or medications that may enhance the impairment effects of benzodiazepines or opioid analgesics. For example, omeprazole, a drug frequently used to treat ulcers and gastroesophageal reflux disease, is known to significantly reduce the elimination of certain benzodiazepines such as diazepam, potentially resulting in further impairment (Holt & Howden, 1991).

Possible Selection Bias

There is also the potential of selection bias in our sample. Of the 147,582 drivers between 1993 and 2006 with a blood alcohol level equal to zero, we analyzed only the 72,026 (49%) who were tested for drug use. This leaves 75,556 (51%) drivers who were not given a drug test. It is possible that several of these cases were taking benzodiazepines or opioid analgesics but their driving behavior did not warrant a drug test. If this is the case, including these cases would reduce the estimated risk posed by benzodiazepines and opioid analgesics.

Study Strengths

Some strengths of the study are worth noting. The use of unsafe driver actions as a proxy measure for crash initiation provides a better assessment of the putative causal relationship between benzodiazepines, opioid analgesics, and safe driving. Controlling for previous driver record and the driver's age and sex is a strength of the study, especially given the driving record differences found between medicated and non-medicated groups. Unlike many epidemiological studies, our sample had a relatively good proportional sex representation, with approximately 40% of drivers being female and also

contained drivers from all age groups. Given the size of our sample, we were also able to eliminate any drivers that tested positive for alcohol (a BAC > 0), thereby ruling out the effects of alcohol. Further, in the validation analysis, we isolated cases that tested positive for only one opioid analgesic or one benzodiazepine and no other medications, removing possible associations influenced by multiple medications or medications and alcohol.

Concluding Remarks

By using a proxy measure for crash initiation, moderating for driver characteristics such as age, sex, and driving record, and excluding drivers under the influence of alcohol or other medications, the results of our study, which suggest that benzodiazepines and opioid analgesics negatively affect safe driving, add to the current evidence.

For benzodiazepines, our results complement both the epidemiologic and experimental literature. Given the growing evidence regarding benzodiazepines and safe driving, the American Medical Association (AMA) recommends that patients of all ages be prescribed the shortest-acting benzodiazepine appropriate for their condition (Wang, Kosinski, Schwartzberg, & Shanklin, 2003). Those requiring longer-acting benzodiazepines should be advised of the possible impairment and associated risks while driving. Additionally, the AMA recommends that these patients should be advised to avoid driving, particularly during the initial phase of dosing (or adjustment) (Wang et al., 2003).

In terms of opioid analgesics, to date, there is limited evidence suggesting that opioid analgesics negatively affect safe driving. Nevertheless, given the potential side effects that may impair driving, the American Chronic Pain Association recommends warning the patient (and family of) against driving until a tolerance or baseline is reached (Covington, 2007). Brandman provides excellent suggested guidelines to optimize driving safety for the family physician, patient, and their family including driver safety vigilance, examining the possibility of outside help (e.g., other drivers might be available if the patient should not drive), and recognizing that certain accommodations (such as changing driver habits) will be necessary while under the influence of opioid analgesic medications (Brandman, 2005).

For both classes of medications, further work to clarify the specific nature of their impact on driving is required. Research to determine how the course of therapy (early on, long term), for each medication, influences the impact on driving would be beneficial. However, development of these medications should also continue, not only to increase their efficacy but also to lessen the side effects, especially those that impair driver safety.

Tables and Figures

Table 1: Benzodiazepines by half-life included in analysis (Adapted from: Ashton, 2007; BCNC, 2007)

Half-Life Category	Generic Name	Half-Life (Hours) [active metabolite]	N (%)
Short Half-Life			
	Midazolam	1.8 - 6	159 (98.8%)
	Triazolam	2	2 (1.2%)
	Total*		161*
Intermediate Half-Life			
	Alprazolam	6-12	297 (80.5%)
	Bromazepam	10-20	1 (0.3%)
	Clotiazepam	6-17	1 (0.3%)
	Estazolam	10-24	2 (0.5%)
	Loprazolam	6-12	2 (0.5%)
	Lorazepam	10-20	16 (4.3%)
	Lormetazepam	10-12	2 (0.5%)
	Oxazepam	4-15	14 (3.8%)
	Temazepam	8-22	45 (12.2%)
	Tetrazepam	3-26	1 (0.3%)
	Total*		369*
Long Half-Life			
	Chlordiazepoxide	5-30 [36-200]	51 (5.0%)
	Clobazam	12-60	2 (0.2%)
	Clonazepam	18-50	15 (1.5%)
	Delorazepam	60-200	3 (0.3%)
	Diazepam	20-100 [36-200]	815 (79.9%)
	Flurazepam	[40-250]	3 (0.3%)
	Ketazolam	30-100 [36-200]	3 (0.3%)
	Nitrazepam	15-38	1 (0.1%)
	Nordiazepam	36-200	583 (57.2%)
	Prazepam	[36-200]	1 (0.1%)
	Total*		1,020*

* Given some cases may have multiple BZDs per half-life category, totals indicates total number of cases with one or more of the particular half-life category.

Table 2: Descriptive statistics for drivers tested for Benzodiazepines with a BAC of zero

Demographics*	Benzodiazepines Absent (N = 69,826)	Short Benzodiazepines (N = 161)	Intermediate Benzodiazepines (N = 369)	Long Benzodiazepines (N =1,020)	χ^2/F **	*p* Value
Age, mean (SD), year	46.0 (19.3)	43.2 (18.4)	42.3 (15.6)	44.0 (16.3)	9.3	<.001
Male, # (%)***	45,235 (64.8)	107 (66.5)	233 (63.1)	638 (62.5)	2.9	.415
Other Medications						
Depressant, # (%)	759 (1.1)	5 (3.1)	30 (8.1)	101 (9.9)	777.2	<.001
Narcotic, # (%)	2,150 (3.1)	14 (8.7)	117 (31.7)	224 (22.0)	1942.8	<.001
Stimulant, # (%)	3,842 (5.5)	16 (9.9)	75 (20.3)	131 (12.8)	254.4	<.001
Cannabinoid, # (%)	2,689 (3.9)	9 (5.6)	33 (8.9)	66 (6.5)	44.4	<.001
Other Medications, # (%)	4,028 (5.8)	44 (27.3)	52 (14.1)	171 (16.8)	387.8	<.001
Any Other Medication, # (%)	11,270 (16.1)	75 (46.6)	245 (66.4)	589 (57.7)	1968.6	<.001
Driving Record – One or more in the past three years						
Crashes, # (%)	10,165 (14.6)	14 (8.7)	78 (21.1)	213 (20.9)	49.1	<.001
DWI, # (%)	1,164 (1.7)	5 (3.1)	30 (8.1)	81 (7.9)	310.9	<.001
Other Conviction, # (%)	10,933 (15.7)	26 (16.1)	107 (29.0)	191 (18.7)	56.0	<.001
Speeding, # (%)	13,173 (18.9)	39 (24.2)	113 (30.6)	204 (20.0)	36.7	<.001
Lic. suspension, # (%)	6,912 (9.9)	17 (10.6)	79 (21.4)	195 (19.1)	146.6	<.001
Any of the above, # (%)	27,322 (39.1)	68 (42.2)	218 (59.1)	506 (49.6)	107.1	<.001

Table 3: Unsafe Driver Actions – Top 5

	Benzodiazepines Absent (N = 69,826)	Short Benzodiazepines Present (N = 161)	Intermediate Benzodiazepines Present (N = 369)	Long Benzodiazepines Present (N=1,020)	χ^2	*p* Value
Driver related factor						
Failure to keep in proper lane, # (%)	20,146 (29%)	58 (36%)	154 (42%)	445 (44%)	138.5	<.001
Driving too fast for conditions or in excess of posted maximum, # (%)	11,267 (16%)	18 (11%)	81 (22%)	209 (20%)	26.0	<.001
Failure to yield right of way, obey signs or other safety zone traffic laws, # (%)	11,328 (16%)	35 (22%)	38 (10%)	113 (11%)	32.7	<.001
Making improper turn, # (%)	3,726 (5%)	1 (1%)	11 (3%)	45 (4%)	12.8	.005
Erratic, reckless, careless or negligent vehicle operation, # (%)	3,428 (5%)	5 (3%)	29 (8%)	53 (5%)	8.2	.044
Any UDA reported, # (%)	42,944 (62%)	102 (63%)	279 (76%)	741 (73%)	83.3	<.001

Table 4: Odds Ratios with 95% CI for the final model predicting Unsafe Driver Actions*

Variable, Referent	Adjusted OR		
Sex, Male	1.06 (1.03; 1.10)		
Age (decades)	0.44 (0.42; 0.47)		
Age^2	1.00 (1.00;1.00)		
Age x Sex	1.05 (1.03;1.07)		
Depressants, none detected	2.03 (1.73; 2.38)		
Narcotics, none detected	1.34 (1.22, 1.46)		
Stimulants, none detected	2.34 (2.20,2.57)		
Cannabinoids, none detected	1.11 (1.02,1.21)		
Other Medications, none detected	1.15 (1.08,1.23)		
	Short	**Intermediate**	**Long**
Benzodiazepine Exposure, no benzodiazepines detected*	1.02 (0.73; 1.42)	1.53 (1.20; 1.96)	1.44 (1.25; 1.66)
Benzodiazepine Exposure by Age Interaction, no benzodiazepines detected	1.09 (0.90; 1.31)	0.98 (0.83; 1.16)	0.92 (0.84; 1.01)
Prior Driving Record	**1**	**2**	**3 or more**
Accident, none	1.15 (1.1;1.2)	1.35 (1.2;1.5)	1.46 (1.2;1.8)
DWI, none	1.01 (0.9;1.2)	1.15 (0.8;1.7)	0.55 (0.2;1.4)
Other, none	1.11 (1.1;1.2)	1.16 (1.1;1.3)	1.21 (1.1;1.4)
Speeding, none	1.08 (1.0;1.1)	1.13 (1.0;1.2)	1.26 (1.1;1.4)
Suspensions, none	1.33 (1.2;1.4)	1.42 (1.3;1.6)	1.58 (1.4;1.8)

*Age centered at 45 years.

Table 5: Adjusted odds ratios of any UDA by Benzodiazepine exposure and driver age (No benzodiazepines detected is the reference category)

Exposure	Age					
	25	**35**	**45**	**55**	**65**	**75**
Short (95% CI)	0.87 (0.55;1.37)	0.94 (0.66;1.34)	1.02 (0.73;1.42)	1.11 (0.73;1.67)	1.20 (0.70;2.08)	1.31 (0.64;2.66)
Intermediate (95% CI)	1.59 (1.08;2.33)*	1.56 (1.18;2.06)**	1.53 (1.20;1.96)***	1.50 (1.09;2.06)**	1.47 (0.95;2.29)	1.44 (0.81;2.59)
Long (95% CI)	1.68 (1.34;2.12)***	1.55 (1.31;1.84)***	1.44 (1.24;1.66)***	1.33 (1.12;1.57)***	1.22 (0.98;1.54)	1.13 (0.84;1.53)

Note: Wald statistics are significant at the:

* p≤.05 level

** p ≤.01 level

*** p ≤ .001 level

Table 6: Validation Analysis: Adjusted odds ratios of any UDA by Benzodiazepine exposure and driver age (No medications detected is the reference category)

Exposure	Age					
	25	**35**	**45**	**55**	**65**	**75**
Short (95% CI)	0.75 (0.41;1.37)	0.91 (0.57;1.45)	1.10 (0.69;1.73)	1.32 (0.74;2.35)	1.59 (0.74;3.42)	1.92 (0.72;5.14)
Intermediate (95% CI)	1.59 (0.86;2.95)	1.55 (0.98;2.46)	1.51 (1.02;2.24)**	1.48 (0.93;2.35)	1.44 (0.77;2.69)	1.40 (0.62;3.20)
Long (95% CI)	1.69 (1.05;2.71)***	1.66 (1.16;2.38)***	1.64 (1.20;2.23)***	1.61 (1.13;2.30)***	1.59 (1.00;2.54)*	1.57 (0.85;2.89)

Note: Wald statistics are significant at the:
* p =.051 level,
** p ≤ .05,
*** p ≤ .01.

Figure 1: Predicted Odds of an Unsafe Driver Action by Benzodiazepine exposure and driver age, with all other variables set to their reference categories

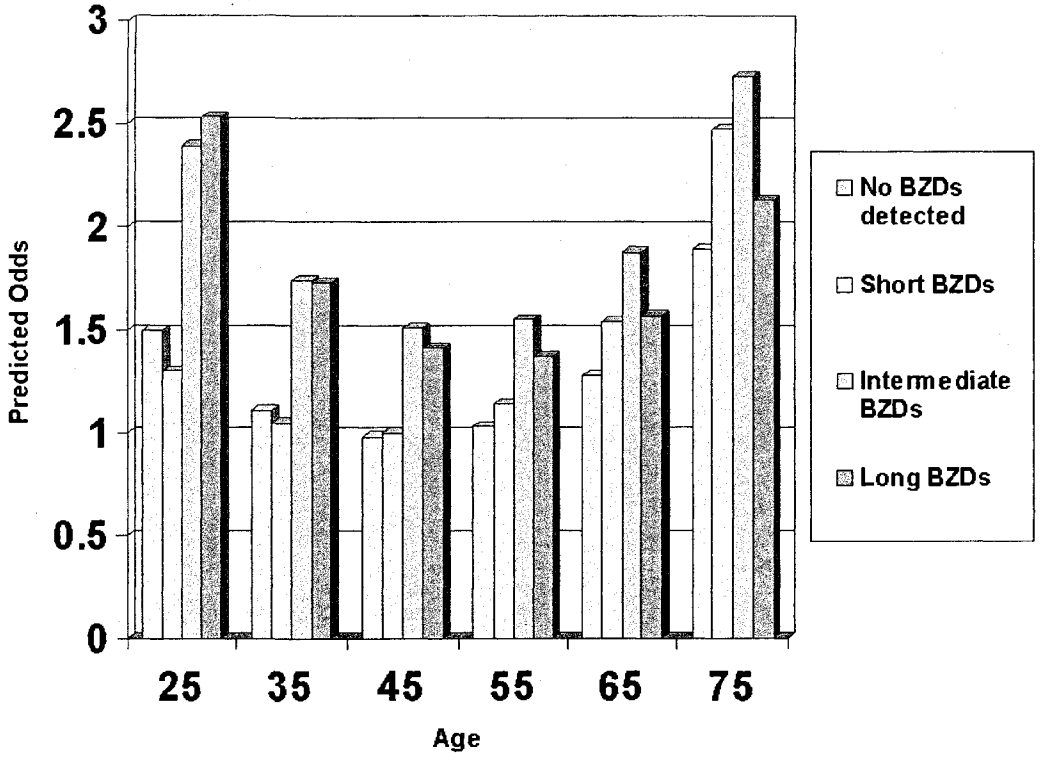
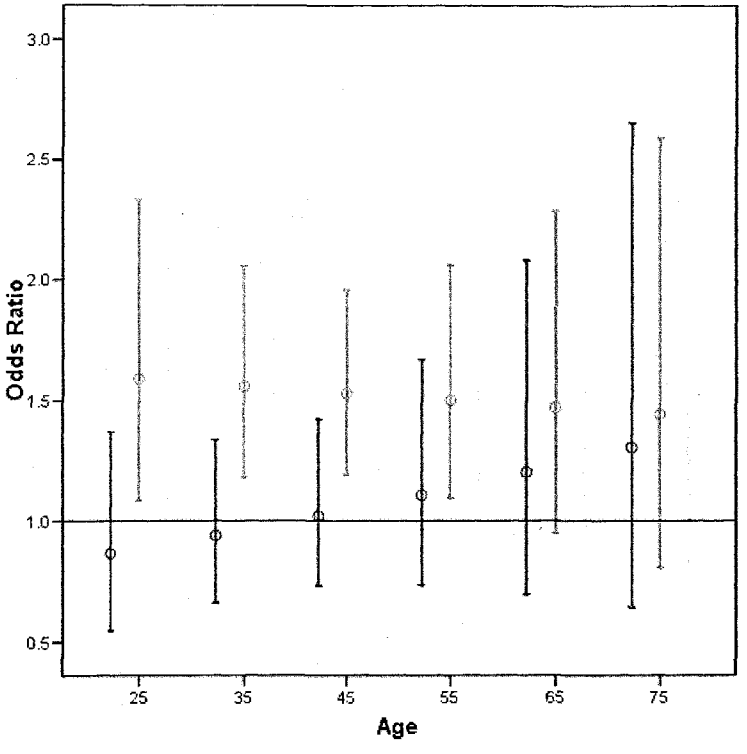


Figure 2: Odds ratios of an Unsafe Driver Action by Benzodiazepine exposure by driver age, with all other variables set to their reference categories



Legend

I Short: 95% CI

I Intermediate: 95% CI

Long: 95% CI

Table 7: Opioid Analgesic medications detected

Generic Name	Frequency of Opioid Analgesic Medications Detected			
	1	2	3	Total
	N (%)	N (%)	N (%)	N (%)
Morphine	393 (18.6%)	183 (24.1%)	37 (23.7%)	613 (20.3%)
Hydrocodone	360 (17.1%)	118 (15.5%)	18 (11.5%)	496 (16.4%)
Methadone	371 (17.6%)	79 (10.4%)	16 (10.3%)	466 (15.4%)
Opium	256 (12.1%)	89 (11.7%)	19 (12.2%)	364 (12.0%)
Codeine	142 (6.7%)	124 (16.3%)	35 (22.4%)	301 (10.0%)
Propoxyphene	257 (12.2%)	33 (4.3%)	5 (3.2%)	295 (9.8%)
Oxycodone	136 (6.4%)	67 (8.8%)	14 (9.0%)	217 (7.2%)
Acetominephen plus Codeine	107 (5.1%)	29 (3.8%)	6 (3.8%)	142 (4.7%)
Meperidine	062 (2.9%)	16 (2.1%)	2 (1.3%)	80 (2.6%)
Oxymorphone	14 (0.7%)	10 (1.3%)	2 (1.3%)	26 (0.9%)
Hydromorphone	5 (0.2%)	12 (1.6%)	2 (1.3%)	19 (0.6%)
Butorphanol	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Levorphanol	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Pentazocine	4 (0.2%)	0 (0.0%)	0 (0.0%)	4 (0.1%)
Totai	2,109 (100%)	760 (100%)	156 (100%)	3,025 (100%)
Totai Cases	2,109 (100%)	380 (100%)	52 (100%)	2,541 (100%)

Table 8: Descriptive statistics for drivers tested for Opioid Analgesics with a BAC of zero

Characteristic	No Opioid Analgesics Detected (N = 69,485)	Opioid Analgesics (N = 2,109)	$\chi 2$/ t	p-value
Age, Mean (SD),years	45.9 (19.3)	45.7 (16.5)	0.4	.672
Male, Number (%)	45,030 (64.8%)	1,314 (62.3%)	5.7	.017
Other Medications				
Depressant, # (%)	2,300 (3.3)	575 (27.3)	3,047.1	<.001
Narcotic, # (%)	194 (0.3)	51 (2.4)	274.6	<.001
Stimulant, # (%)	3,811 (5.5)	329 (15.6)	384.4	<.001
Cannabinoid, # (%)	2,715 (3.9)	161 (7.6)	73.7	<.001
Other Medications, # (%)	3,868 (5.6)	421(20.0)	753.2	<.001
Any Other Medication, # (%)	10,936 (15.7)	1,269 (60.2)	2,857.6	<.001
Driving Record – One or more in the past three years				
Crashes, No. (%)	10,096 (14.5%)	402 (19.1%)	33.6	<.001
DWI , No. (%)	1,202 (1.7%)	93 (4.4%)	82.8	. <.001
Other Conv. , No. (%)	10,859 (15.6%)	455 (21.6%)	54.4	<.001
Speeding , No. (%)	13,135 (18.9%)	444 (21.1%)	6.2	.013
Lic. Susp., No. (%)	6,847 (9.9%)	393 (18.6%)	173.6	<.001
Any of the above , No. (%)	27,207 (39.2%)	1,021 (48.4%)	73.4	<.001

Table 9: Unsafe Driver Actions – Top 5

	No Opioid Analgesics Detected (N = 69,485)	**Opioid Analgesics (N = 2,109)**	$\chi 2$	***p* Value**
Driver related factor				
Failure to keep in proper lane, # (%)	20,046 (29%)	866 (41%)	147.6	<.001
Driving too fast for conditions or in excess of posted maximum, # (%)	11,270 (16%)	377 (18%)	4.1	.042
Failure to yield right of way, obey signs or other safety zone traffic laws, # (%)	11,283 (16%)	252 (12%)	27.9	<.001
Making improper turn, # (%)	3,637 (5%)	138 (7%)	7.0	.008
Erratic, reckless, careless or negligent vehicle operation, # (%)	3,412 (5%)	130 (6%)	6.8	.009
Any UDA reported, # (%)	42,758 (62%)	1,508 (72%)	86.2	<.001

Table 10: Odds Ratios with 95% CI for the final model predicting Unsafe Driver Actions*

Variable, Referent	Adjusted OR		
Sex, Male	1.01 (1.01; 1.15)		
Age (decades)	0.96 (0.95; 0.97)		
Age^2	1.10 (1.09; 1.10)		
Age x Sex	1.06 (1.04; 1.08)		
Age^2 x Sex	0.99 (0.98; 1.00)		
Narcotic	1.05 (0.80; 1.39)		
Stimulant	2.41 (2.22; 2.62)		
Cannabinoid	1.10 (1.01; 1.20)		
Depressant	1.81 (1.64; 2.00)		
Other Medications	1.14 (1.06; 1.22)		
	Opioid Analgesic		
Opioid Analgesic Exposure, no opioid analgesic detected*	1.72 (1.45; 2.03)		
Opioid Analgesic Exposure by Sex Interaction, no opioid analgesic detected	0.82 (0.67; 1.00)		
Opioid Analgesic Exposure by Age Interaction, no opioid analgesic detected	0.96 (0.89; 1.03)		
Opioid Analgesic Exposure by Age^2 Interaction, no opioid analgesic detected	0.97 (0.94; 1.00)		
Opioid Analgesic Exposure by Stimulant Interaction, no opioid analgesic detected	0.62 (0.46; 0.83)		
Opioid Analgesic Exposure by Depressant Interaction, no opioid analgesic detected	0.76 (0.60; 0.97)		
Prior Driving Record	**1**	**2**	**3 or more**
Accident, none	1.15 (1.10;1.21)	1.34 (1.20; 1.50)	1.45 (1.17; 1.79)
Other, none	1.11 (1.05; 1.16)	1.15 (1.05; 1.27)	1.20 (1.05; 1.38)
Speeding, none	1.08 (1.03; 1.13)	1.12 (1.03; 1.22)	1.26 (1.12; 1.42)
Suspensions, none	1.33 (1.24; 1.44)	1.38 (1.23; 1.55)	1.56 (1.38; 1.76)
DWI, none	1.04 (0.90; 1.20)	1.13 (0.77; 1.65)	0.55 (0.22; 1.35)

*Age centered at 45 years.

Table 11: Predicted odds and adjusted odds ratios of any Unsafe Driver Action by Opioid Analgesic exposure, driver age, and sex

	Female Drivers			Male Drivers		
	Predicted Odds			Predicted Odds		
	No Opioid Analgesic Detected	Opioid Analgesics	Odds Ratio (95% CI)	No Opioid Analgesic Detected	Opioid Analgesics	Odds Ratio (95% CI)
Age						
25	1.43	1.94	1.35 (1.05;1.73)*	1.51	2.51	1.66 (1.32;2.09)***
35	1.14	1.62	1.42 (1.17;1.72)***	1.11	1.92	1.74 (1.47;2.05)***
45	1.06	1.49	1.40 (1.15;1.70)***	0.97	1.66	1.72 (1.45;2.03)***
55	1.17	1.52	1.30 (1.07;1.58)**	1.01	1.62	1.59 (1.34;1.90)***
65	1.51	1.72	1.14 (0.93;1.39)	1.28	1.78	1.40 (1.17;1.67)***
75	2.28	2.15	0.94 (0.73;1.22)	1.92	2.21	1.15 (0.91;1.47)

Note: Wald statistics are significant at the:

* $p \leq .05$

** $p \leq .01$

*** $p \leq .001$

Table 12: Validation Analysis: Predicted odds and adjusted odds ratios of any Unsafe Driver Action by Opioid Analgesic exposure, driver age, and sex

	Female Drivers	Male Drivers
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Age		
25	1.69 (1.17;2.44)**	1.76 (1.27;2.44)***
35	1.71 (1.31;2.24)***	1.78 (1.43;2.23)***
45	1.64 (1.25;2.15)***	1.71 (1.36;2.15)***
55	1.48 (1.12;1.96)**	1.55 (1.21;1.97)***
65	1.27 (0.96;1.68)	1.32 (1.04;1.68)*
75	1.03 (0.72;1.46)	1.07 (0.78;1.46)

* $p \leq .05$
** $p \leq .01$
*** $p \leq .001$

Figure 3: Predicted Odds of an Unsafe Driver Action by Opioid Analgesic exposure by driver age by sex, with all other variables set to their reference categories

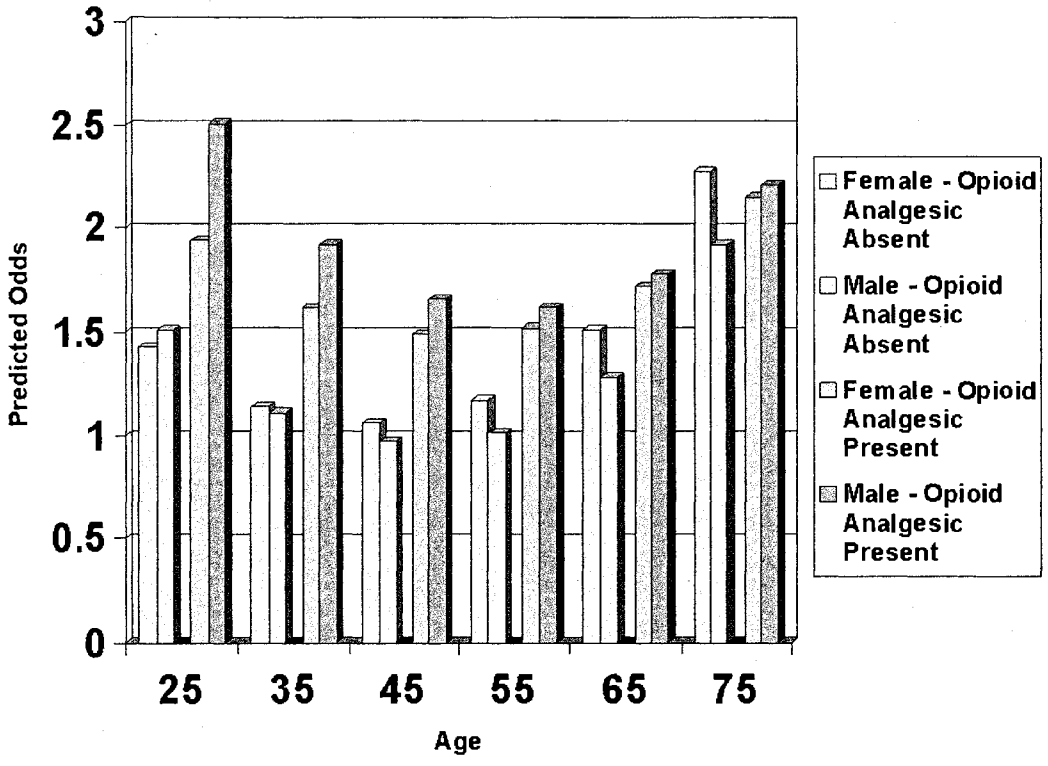
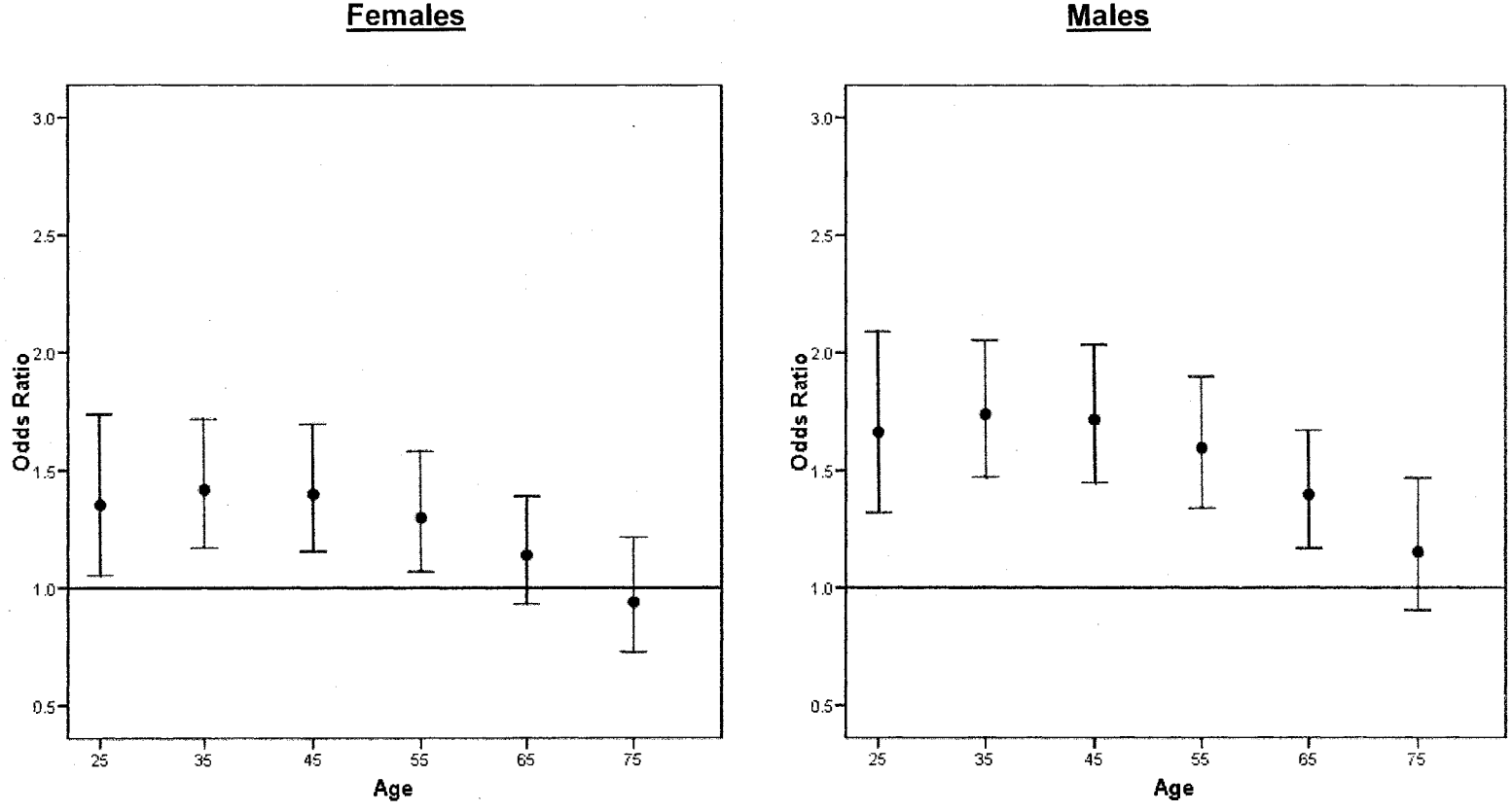


Figure 4: Odds ratios of an Unsafe Driver Action by Opioid Analgesic exposure by driver age and sex, with all other variables set to their reference categories



APPENDICES

Appendix A: Driver Related Factors

20 Leaving Vehicle Unattended in Roadway
21 Overloading or Improper Loading of Vehicle with Passengers or Cargo
22 Towing or Pushing Vehicle Improperly
23 Failing to [Dim Lights or, Since 1995] Have Lights on When Required
24 Operating without Required Equipment
25 Creating Unlawful Noise or Using Equipment Prohibited by Law
26 Following Improperly
27 Improper or Erratic Lane Changing
28 Failure to Keep in Proper Lane or Running off Road
29 Illegal Driving on Road Shoulder, in Ditch, on Sidewalk, on Median
30 Making Improper Entry to or Exit from Trafficway
32 Opening Closure into Moving Traffic or While Vehicle is in Motion (Since 2001)
33 Passing where Prohibited by Posted Signs, Pavement Markings, Hill or Curve, or School Bus Displaying Warning not to Pass
34 Passing on Wrong Side
35 Passing with Insufficient Distance or Inadequate Visibility or Failing to Yield to Overtaking Vehicle
36 Operating the Vehicle in Other Erratic, Reckless, Careless or Negligent Manner [or Operating at Erratic or Suddenly Changing Speeds, Since 1995]
37 High-Speed Chase with Police in Pursuit
38 Failure to Yield Right of Way
39 Failure to Obey Traffic Signs, Traffic Control Devices or Traffic Officers, Failure to Observe Safety Zone Traffic Laws
40 Passing Through or Around Barrier Positioned to Prohibit or Channel Traffic
41 Failure to Observe Warnings or Instructions on Vehicles Displaying Them
42 Failure to Signal Intentions
43 Giving Wrong Signal
44 Driving too Fast for Conditions or in Excess of Posted Speed Limit
45 Driving Less than Posted Maximum
46 Operating at Erratic or Suddenly Changing Speeds
47 Making Right Turn from Left Turn Lane or Making Left Turn from Right Turn Lane
48 Making Improper Turn
50 Driving Wrong Way on One-Way Trafficway
51 Driving on Wrong Side of Road [(Intentionally or Unintentionally) Since 1995]
52 Operator Inexperience
53 Unfamiliar with Roadway
54 Stopping in Roadway (Vehicle not Abandoned)
55 Underriding a Parked Truck

57 Locked Wheel
58 Overcorrecting (Since 1995)
59 Getting Off/Out of or On/In to a Vehicle

Appendix B: List of Abbreviations

BAC: Blood Alcohol Content.

CI: Confidence Interval.

CNS: Central Nervous System.

COAT: Chronic Opioid Analgesic Therapy.

DUI: Driving Under the Influence (of either alcohol or drugs).

DWI: Driving While Intoxicated (from either alcohol or drugs).

FARS: Fatality Analysis Reporting System.

FTP: File Transfer Protocol.

NHTSA: National Highway Traffic Safety Administration.

NSAID: Non-Steroidal Anti-Inflammatory Drug.

OR(s): Odds Ratio(s).

PCP: Phencyclidine of the chemical name Phenylcyclohexylpiperidine.

POs: Predicted Odds.

SDLP: Standard Deviation of Lateral Position.

SQL: Structured Query Language.

UDA(s): Unsafe Driver Action(s).

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