Psychoactive medications that act on the central nervous system and crash involvement for older drivers: A population-based study

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EXECUTIVE SUMMARY

Driving is a complex task where the driver continuously receives information, analyses it and reacts. Substances that have an influence on brain function or the mental processes involved in driving will clearly affect driving performance. Research has shown that driving under the influence of alcohol is an important risk factor for a crash (Borkenstein et al. 1974; Dunbar et al. 1985; Ross 1993). However, the role of drugs other than alcohol has not been well established. Current evidence indicates that several types of psychoactive medications have the potential to impair driving ability and increase the risk of crash involvement. A major limitation is that few studies have specifically examined their effects on older drivers despite the fact that the majority of the population using psychoactive medications are sixty year of age or older (Australian Bureau of Statistics 2009). In addition, within the "older" driver group, the use of such medications has been shown to increase with advancing age (Johansson et al. 1996). This has important implications for road safety.

The aim of this study is to estimate the association between psychoactive medications that act on the central nervous system and involvement in a motor vehicle crash for older drivers aged 60 years and older at the population level. By providing a population-based estimate of the magnitude of the problem it is proposed this will provide a greater insight into the relative importance of various medications to crash risk. These results will contribute to improved road safety by providing clinicians with the evidence-base to guide best practice in prescribing and counselling for older drivers as they continue to drive in Western Australia.

The specific objectives of this study are:

- To measure the incidence of hospitalised motor vehicle crashes for drivers aged 60 years and older taking psychoactive medications acting on the central nervous system from 2002 to 2008 in Western Australia;
- To determine the association between psychoactive medication use and hospitalisation crash risk for an older driving population from 2002 to 2008 in Western Australia;
- To develop clinical and policy recommendations to improve the safety for older drivers taking psychoactive medications as they continue to drive in Western Australia.

These objectives were met through the use of the Western Australian Data Linkage System. The Western Australia Data Linkage System (WADLS) was established in 1995 and is unique to Western Australia. It is one of only a small number of comprehensive, whole-population data linkage systems in the world and constitutes a powerful source for conducting health services and outcomes research on an entire population within an Australian setting.

A case-cross over study design was used where each subject acts as their own control thus eliminating confounding due to fixed characteristics (Orriols et al. 2009). Case-crossover studies are a modification of the case-control design; however, in the case-crossover design, only 'cases' or individuals with the outcome of interest are included. The case-crossover design is based on identifying the outcome of interest (motor vehicle crash) and assessing exposure to the transient risk factor of interest (psychoactive medication usage) in a chosen time period preceding the outcome. For this study, five control intervals were selected and exposure to the psychoactive medication usage in the time preceding the motor vehicle crash was compared with the five control intervals for the same individual.

The study involved the linkage of the Hospital Morbidity Data System (HMDS) and the Pharmaceutical Benefit Scheme (PBS) data at the Department of Health, Western Australia from 2002 to 2008 to ascertain the study population. The study drugs were classified into four groups:

- Benzodiazepines, which included hypnotics and sedative anxiolytics;
- Anti-depressants, which included tricyclic anti-depressants and selective serotonin reuptake inhibitors;
- Anti-epileptics; and
- Opioid analgesics.

The outcome of interest was a hospitalised motor vehicle crash. Matched analysis using conditional logistic regression was used to calculate the odds of having a crash requiring hospitalisation in association with psychoactive medication. The primary analysis involved 1: multipe (1:M) medication use during the hazard interval for any driver was compared with five control intervals. Subsequent analysis also examined 1:1 matching with each of the five control intervals.

The results of this research have provided a thorough description of the size and nature of psychoactive medication use and associated crash risk among older drivers aged 60 years and above in Western Australia from 2002 to 2008. The main findings are as follows:

Crash-related hospitalisations and psychoactive medication use

- Of the 629 individuals who had been prescribed psychoactive medication from 2002 to 2008, a total of 651 individuals were identified as having been admitted to hospital as a driver due to a motor vehicle crash.
- Among the hospitalised crash-involved drivers, the largest proportion of the cohort (43.6%, n=284) were prescribed an opioid analgesic, followed by benzodiazepines (37.9%, n=247). Drivers prescribed an anti-depressant represented 13.1% (n=85) of the cohort, while 5.4% (n=35) had been prescribed anti-epileptics.
- A fairly even distribution of usage of opioid analgesics was evident across all age groups: '60-69 years' (36.3%), '70-79 years' (32.4%) and '80 years and older' (31.3%). Benzodiazepine users were more frequently found to be aged 70-79 years (35.6%) and 80 years and over (36.0%) compared to those in the 60-69 years age group (23.9%). The majority of drivers who had been prescribed an anti-depressant were found among the 70-79 years age group (43.5%), while less than a quarter (23.5%) were aged between 60-69 years and one third (33%) were 80 years or older. Drivers with prescriptions of anti-epileptics were predominantly aged 60-69 years age (45.7%), compared to 22.9% of drivers aged 70-79 years, and 31.4% of those aged 80 years and above.
- A higher proportion of crash-involved females were found to have been prescribed all classifications of psychoactive medications compared to men (range: 55.3% – 67.1% versus 32.9% - 44.7%).
- Hospitalised crashes were more common among drivers who were not married or in a de facto relationship than married drivers across all classification of psychoactive medications (range: 51% - 58% versus 39% - 44%).
- Apart from one driver who had been prescribed an opioid analgesic (0.4%), all hospitalised crash-involved drivers were of non-Indigenous status.
- Over one quarter of all hospitalised drivers involved in a motor vehicle crash during the study period reported a chronic condition regardless of the type of medication prescribed.

- The majority of crash-involved hospitalised drivers across all medication groups lived in the metropolitan area (range: 69% - 75%). This was followed by rural Western Australia (range: 17% - 23%), then remote areas of Western Australia (range: 6 - 11%).
- The highest hospitalisation crash rates among older people were observed in 2003, with rates of 37 crashes per 100,000 population. Crash rates decreased in the following three years fluctuating between 30 and 32 crashes per 100,000 population but increasing again in 2007 to 36 crashes per 100,000 population.

Risk associated with psychoactive medication use

- Benzodiazepine usage was associated with a 5.3 increase in the likelihood of crashing (95%CI 3.60-7.77; p<0.001).
- An increased risk for a hospitalised crash while taking benzodiazepines was found for both males (OR 6.21; 95%CI 3.16-12.21; p<0.001) and females (OR 4.88; 95%CI 3.06-7.80; p<0.001).
- .An increased risk was also found for older drivers prescribed a benzodiazepine who reported a chronic condition (OR 3.97; 95%CI 2.94-8.10; p<0.001) as well as those who did not report a chronic condition (OR 5.95; 95%CI 3.75-9.45; p<0.001).
- The use of anti-depressants was associated with almost a two-fold increase in the likelihood of crashing (OR 1.8; 95%CI 1.02-3.27; p<0.044).
- Males had almost three times increased risk of crash involvement while prescribed anti-depressants (95%CI 1.08-6.93; p=0.03).
- Additionally, older drivers with a chronic condition had a significant increase in the likelihood of crashing when prescribed an anti-depressant (OR=3.36; 95%CI 1.32-8.53; p=0.01).
- The use of anti-epileptic medication was associated with a six time increase in the likelihood of crashing (95%CI 2.53-14.50; p<0.001). This result should be interpreted with caution due to the small sample size.
- Both males (OR=10.65, 95%CI 2.07-54.77; p=0.004) and females (OR=4.66; 95%CI 1.65-13.17; p=0.004) were at an increased risk for a hospitalised crash while exposed to anti-epileptics medication.
- An increased risk was also found for older drivers prescribed an anti-epileptic medication who reported a chronic condition (OR 14.46; 95%CI 1.64-127.80;

p=0.016) as well as those who did not report a chronic condition (OR 4.81; 95%CI 1.81-12.81; p=0.002)

- Opioid analgesics usage was associated with 50% increase in the likelihood of crashing (95%CI 1.00-2.33; p=0.05).
- Only women prescribed an opioids analgesic were at a significant increased risk for a hospitalisation crash (OR=1.76; 95%CI 1.05-2.95; p=0.03).

In conclusion, the findings of this study have identified a number of valid indicators that provide a sense of the size and nature of crash risk (requiring hospitalisation) among the older driving population due to use of psychoactive medication. The results have provided a benchmark against which to measure whether the future situation in Western Australia deteriorates, stabilises or improves. Therefore, this study not only provides current estimates of the degree of psychoactive medication use and crash risk, it also enables future trends to be assessed by replication of some or all of the methodology adopted in this research.

The following recommendations are based on the findings of this research.

Recommendation one

- The results of this study should be made available to clinicians and licensing authorities. Before prescribing medications, clinicians should determine whether and how often individual patients' activities require optimal alertness: for example, when driving a car. Clear directions and warnings should be given to patients rather than clinicians relying on package warnings to alert patients about drug effects on driving performance.

Recommendation two

- State and Federal governments should endeavour to identify new, more innovative approaches to dealing with drug-impaired driving. Evidence-based measures to reduce the risks to older drivers should continue to be developed and re-evaluated while still recognising their mobility needs and avoiding age discrimination issues.

Recommendation three

- Education campaigns should be developed and targeted at older drivers so that they become more aware of the possible impairment on cognitive function due to the usage of psychoactive medications as they continue to drive on Australian roads.

Recommendation four

- Standardised methodologies should be applied in repeated studies. There is a clear need for access to more comprehensive data to establish a definitive link between medication usage and crash risk for older drivers. Research to determine short and long term use of psychoactive medications on crash risk should continue. Emphasis should also be placed on newly emerging drugs with the potential for impairment.

Recommendation five

- National and international collaboration on future studies should be encouraged. There is a need for international scientific guidelines, procedures and methods of comparison for the conduct of drug impairment research. Collaboration between Australian States' and other countries' impaired-driving legislation could give valuable ideas as to which type of legislative measures would be most effective.

Recommendation six

- Information on the type and amount of psychoactive medications found in deceased or injured persons obtained by police, coronial services and public hospitals should be collected to provide more objective information to road safety researchers.

Recommendation seven

- There is a need for large, pharmaco-epidemiological studies, such as data linkage studies, to replicate the results of this study for all drivers as well as the older driver age group.

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1 INTRODUCTION

As Australians continue to live longer a gradual 'greying' of the population is being witnessed. The proportion of the population aged over 65 years has increased rapidly in Australia over past decades; representing approximately 13% of the total population at the current time (Australian Institute of Health and Welfare 2006). According to population projections, this will have doubled by the year 2021, rising steadily from 12.5% in 2000 to 25% in 2021 (Australian Institute of Health and Welfare 2001). Even more pronounced growth can be witnessed in the population aged 85 years and older with an expected four-fold increase in the proportion of people in this age group (Australian Bureau of Statistics 1999). Such predictions are diverting more attention to the economic, social and health problems that may be experienced by an increasing ageing population.

Driving is a complex task where the driver continuously receives information, analyses it and reacts. Substances that have an influence on brain function or the mental processes involved in driving will clearly affect driving performance. Research has shown that driving under the influence of alcohol is an important risk factor for a crash (Borkenstein et al. 1974; Dunbar et al. 1985; Ross 1993). However, the role of drugs other than alcohol has not been well established. Associated with the higher prevalence of medical conditions among the older population is the greater use of medications (Johansson et al. 1996). In addition, within the "older" driver group, the use of such medications has been shown to increase with advancing age (Johansson et al. 1996). Recent research has shown that the risk of being involved in a crash as the driver is significantly increased in users of psychoactive medications (Engeland et al. 2007). This has important implications for road safety.

The aim of this study is to estimate the association between psychoactive medications that act on the central nervous system and involvement in a motor vehicle crash for older drivers at the population level. By providing a population-based estimate of the magnitude of the problem it is proposed this will provide a greater insight into the relative importance of various medications to crash risk. These results will contribute to improved road safety by providing clinicians with the evidence-base to guide better prescribing and counselling for older drivers.

The specific objectives of this study are:

- To measure the incidence of motor vehicle crashes for drivers aged 60 years and older taking psychoactive medications acting on the central nervous system from 2002 to 2008 in Western Australia.
- To determine the association between psychoactive medication use and crash risk for an older driving population from 2002 to 2008 in Western Australia.
- Develop clinical and policy recommendations to improve the safety for older drivers taking medications that may impair cognitive function as they continue to drive in Western Australia.

These objectives will be met through the use of the Western Australian Data Linkage System. The Western Australia Data Linkage System (WADLS) was established in 1995 and is unique to Western Australia. It is one of only a small number of comprehensive, whole-population data linkage systems in the world and constitutes a powerful source for conducting health services and outcomes research on an entire population within an Australian setting. The WADLS combines seven core datasets which include inpatient hospital morbidity records dating back as early as 1966. The use of the WADLS enables retrospective studies to be conducted many years after exposure to the outcome of interest and minimises loss to follow-up by eliminating the burden on respondents and reliance on self-reported data. Using the WADLS also overcomes limitations due to sample size, loss to follow-up and ascertainment of accurate exposures and outcome measures (Holman et al. 1999).

Significance and benefits

The Western Australian Data Linkage System, which links over 30 datasets at an individual level for the entire Western Australian population of almost two million people, was used to examine the association between crash risk and the use of psychoactive medications that act on the central nervous system for older drivers. Datasets in the linked system include administrative health data from hospital admissions and death records. Data from the Commonwealth Pharmaceutical Benefit Scheme (PBS) has just recently been added and provides details on physician prescribed medication to Medicare-eligible persons. Therefore, using the Western Australian Data Linkage System, every older driver who had a prescription filled in Western Australia and had been involved in a motor vehicle crash between 2002 and 2008 was identified.

This project is one of the first population-based studies in Australia to examine the crash risk for older drivers who are taking medications that act on the central nervous system. The major strengths of this project are its large size, capturing an entire and relatively isolated population, the case-crossover study design, the use of objective, police-reported crash data and the use of the Pharmaceutical Benefits Scheme data. The identification of medications associated with an increased crash risk will provide clinicians with the evidence base to address the important issue of driving safety for this group. Such information would greatly improve the ability to identify drivers who pose a threat to public safety whilst maintaining the mobility of older drivers. This information is also essential to the development of strategic countermeasures and policy development. Future long-term benefits may include the reduction in the number of road-related deaths and injuries to older drivers particularly with the projected growth in the older driving population over the next decade.

2 LITERATURE REVIEW

2.1 Introduction

Advances in technology and health have provided Australians with a longer life than in the past. In general, older people are living more actively than previous generations of retired people with greater expectations of continued health and vigour. Possessing a driver's licence and driving a motor vehicle imply a higher degree of freedom and mobility and has been found to be a significant predictor of quality of life, functional independence and physical and mental health among older people (Metz 2000; Oxley & Whelan 2008). According to a recent report, one out of four drivers will be aged 65 and over by 2030 with estimates that over the next three decades fatal crashes could be as much as three times higher among older drivers unless there is active intervention (Lyman et al. 2002). These statistics have generated concern among road safety experts. While older drivers are involved in fewer crashes compared to other driver age groups, their crash risk is equivalent to that of young drivers when exposure is taken into account (Eberhard 2008; Li et al. 2003). They are also more likely to be responsible for these crashes (Langford et al. 2006). Furthermore, once involved in a crash their risk of being killed or suffering serious injury is two to five times greater than that of a younger person (Braver & Trempel 2004; Tefft 2008).

Psychoactive medications are chemical substances that act primarily on the central nervous system and can alter perception, mood, consciousness and behaviour. Psychoactive medications include for example; anti-depressants, opioid analgesics, anti-psychotics, hypnotic benzodiazapines and anxiolytic benzodiazepines. These medications are used to treat a large number of conditions that are common among the older population including insomnia, anxiety, pain, depression and psychosis (Australian Bureau of Statistics 2009). However, the therapeutic effects of these medications, such as sedation, may in fact, affect driving performance (Maes et al. 1999). To date, experimental laboratory-based, driving simulator and on-road driving studies have provided quite conclusive evidence that psychoactive medications can have detrimental effects on psychomotor and cognitive skills required for driving (Sansone & Sansone 2009; Verster et al. 2004). Epidemiological studies, despite reporting mixed results have also indicated increased probability of crash involvement for drivers taking some psychoactive medications (Barbone et al. 1998; Orriols et al. 2009; Sansone & Sansone 2009).

Evidence to date is limited for several reasons. Firstly, despite these medications being most commonly used by the older population, the majority of experimental studies have been conducted on small samples of young, healthy volunteers; meaning the findings may not apply to older drivers. These studies have also mostly assessed the effects of acute use of the medications on driving skills when many older drivers would be on stable regimes of medication. In addition, few epidemiological studies have either included or examined older drivers separately in their samples. Several of the studies that have examined older drivers however, are limited by small sample sizes, selection bias and have examined the effect of large groups of medications on crash risk rather than individual drugs. The focus of this review is to examine the association between different types of psychoactive medications and driving impairment or crash involvement for older drivers. In addition, limitations of past research that may be overcome by using a population-based study will be identified.

2.1.1 Cost of transport injuries in Australia

The total cost of injury in Western Australian was estimated to be approximately $2.9 billion in 2003 (Hendrie 2005). This figure represents both the direct and indirect monetary costs of injury in addition to the monetised value of loss of quality of life. Direct costs include non-medical and medical costs such as hospital, medical and rehabilitation costs related to the treatment of injury. Indirect costs refer to resultant disability, loss of life due to premature death and reduced productivity caused by injury. Additionally, unpaid household and voluntary community work undertaken by employed and non-employed persons represents a social cost to the community (Watson & Ozanne-Smith 1997).

Approximately 23% or $655.8 million of the total cost of injury was attributable to transport-related injuries followed by falls (19%) and self-inflicted injuries (19%). Transport injuries were one of the leading contributors to the cost of fatal injuries (27 %) (Hendrie 2005). Transport-related injury accounted for 20% of the $434 million health sector cost of injury. Additionally, it was one of the leading contributors to health system costs for all age and gender groups excluding females aged 60 years and over. With projections showing that the 65-and-over population is the fastest growing age group, it is estimated that the number of fatal crashes involving older drivers will continue to rise (Williams & Carsten 1989).

2.1.2 Use of psychoactive prescription medications in Australia

Psychoactive medications are widely prescribed and used among older people in Australia. From 2008 to 2009 in Australia, 196 million prescriptions were filled under the Pharmaceutical Benefit Scheme (PBS) (Medicare Australia 2009). In terms of the older population, the Stay on Your Feet WA project found that in 2004, 80% of Western Australians aged 60 years and over took prescribed medications on a regular basis (Milligan 2005). Psychoactive medications constitute a significant proportion of all prescriptions with one study reporting that 21% of prescriptions made by General Practitioners in Australia were for central nervous system and psychological medications (Britt et al. 2005).

Psychoactive medications are used to treat a large number of conditions that are common among the older population including insomnia, anxiety, pain, depression and psychosis. The Australian National Mental Health and Wellbeing Survey found that 16% of people aged 65 years and over reported symptoms consistent with a mental disorder in the past 12 months (Trollor et al. 2007). In addition, Australians aged 55 years and older have some of the highest rates of prescription drug use for health issues such as sleeping problems, anxiety and nervous tension (Australian Bureau of Statistics 2009).

Hypnotics are primarily used to treat insomnia and older people are considered the group at greatest risk of this disorder (Bain 2006). Examples include Flunitrazepam, Nitrazepam, Phenobarbitone, Temazepam and Zopiclone and these drugs are usually benzodiazapines or barbiturates. In Australia in 2004-2005, 11% of people aged 65 years and older had used sleeping tablets recently, a proportion much higher than in any other age group (Australian Bureau of Statistics 2006).

Anxiolytics are psychoactive medications used primarily to treat the symptoms of anxiety as well as panic attacks, tension and confusional states. Anxiolytics are usually benzodiazepines with the most commonly used being Diazepam (Hollingworth et al. 2010). The use of anxiolytics increases with age (Goldney & Bain 2006) and in Australia in 2004-2005, 3% of people aged 65 and over used anxiolytics recently, representing higher usage than any other age group (Australian Bureau of Statistics 2006).

Opioid analgesics are medications used to treat pain and examples include Codeine and Pethidine. Chronic pain is common among the older population with community based surveys suggesting that 40% of older people experience arthritis (Solomon et al. 2006). These psychoactive medications are frequently taken to relieve pain from musculoskeletal problems such as arthritis and back problems (Solomon et al. 2006).

Anti-depressants are used to alleviate mood disorders such as depression, for example the tricyclic anti-depressant, Amitriptyline Hydrochloride. The 2004-2005 National Health Survey reported 5% of respondents aged 65 years and over were taking anti-depressants (Australian Bureau of Statistics 2006). While the proportion of older people on anti-depressants was lower than for most other age groups, depression and anti-depressant use among the older population is still a major issue and recent reports indicate that anti-depressant use is rising among the elderly (Zhang et al. 2010).

Anti-psychotics are psychoactive medications used to manage psychoses such as schizophrenia, bipolar disorder and delusional disorder and are often used in older people with Dementia (Chahine et al. 2010). Anti-psychotics are often Phenothiazenes. Finally, anticonvulsant medications consist of a diverse group of pharmaceuticals that are used predominantly to control epilepsy/ seizures but are also used as mood stabilisers in conditions such as bipolar disorder.

2.4 Adverse effects of psychoactive medications

The wide range of psychoactive medications discussed above act on the central nervous system and both their intended effects and adverse side effects may impair driving ability. These medications have been associated with a myriad of physical, psychomotor and cognitive adverse side effects. Of additional concern are reports that older people often exhibit higher sensitivity to psychoactive medications and are more susceptible to their adverse effects, particularly cognitive effects (Chahine et al. ; Glass et al. 2005; Moore & O'Keeffe 1999; Nishtala et al. 2009).

Adverse effects that may impact on driving ability commonly listed for the psychoactive medications described above include:

- Sedation/ drowsiness
- Dizziness/ light headedness
- Headache
- Blurred vision
- Tremors
- Balance disturbance
- Muscle weakness
- Reduced co-ordination
- Confusion
- Memory impairment
- Lack of concentration
- Inattentiveness
- Indecisiveness
- Slowed visual processing
- Increased reaction time

(Chahine et al. 2010; Dubois et al. 2008; Glass et al. 2005; Hollingworth et al. 2010; Vermeeren 2004).

The normal physiologic decline in function that comes with ageing, the presence of chronic disease and the greater use of psychoactive drugs that may produce one or more of the listed adverse effects may in combination impact on the older driver's ability to operate a motor vehicle safely (Lotfipour & Vaca 2007). A meta-analysis of medication use and falls in people aged 60 years and over revealed that use of sedatives and hypnotic medications, anti-depressants and medications in the benzodiazepine class all significantly increased the likelihood of falls (Woolcott et al. 2009). It is quite possible that the psychomotor symptoms associated with falling may also pose safety concerns for driving.

Psychoactive medication and driving for older adults: existing evidence

Experimental studies that assess driving abilities through laboratory tests, driving simulators or on-road driving assessments have all provided important information on the potential impact of psychoactive medication use on road safety. However, they are unable to take into account the impact of 'real life' conditions including reacting to unexpected situations and interacting with other drivers and the road environment that translate to actual crash

involvement (Orriols et al. 2009). Epidemiological studies examining crash risk of various psychoactive medications, while limited have suggested a causal link between these medications and motor vehicle crashes (Barbone et al. 1998; Orriols et al. 2009; Sansone & Sansone 2009). Existing evidence from experimental and epidemiological studies on the association between each type of psychoactive medication and older drivers will be summarised and conditions that increase risk of driving impairment or crashes identified.

2.5 Anti-depressants

Anti-depressants possess many pharmacological properties that could potentially impair driving ability by causing sedation, cognitive difficulties, poor attention, indecisiveness, balance disturbance and psychomotor difficulties (Iwamoto et al. 2008; Sansone & Sansone 2009).

Several studies have examined the association between the use of sedating anti-depressants (including tricyclic anti-depressants) and driving impairment or crashes. An early cohort and case-crossover study conducted in the USA reported that the risk of injurious crash involvement in 65-84 year old drivers was significantly increased for current users of tricyclic anti-depressants (RR: 2.2; 95% CI 1.3-3.5). This risk was dose-dependent with results showing that doses of amitriptyline $\geq$ 125mg daily increased the risk of involvement in a crash by six times (Ray et al. 1992). Another USA-based case-control study of drivers aged 65 years and older reported similar findings with participants who were taking tricyclic anti-depressant experiencing increased odds of a motor vehicle crash of 2.3 (95% CI: 1.1-4.8) (Leveille et al. 1994). More recently, a population-based cohort study in Norway reported a slight but significant increase in crash involvement for drivers who had received prescriptions for sedating anti-depressants including tricyclic anti-depressants (standardised incidence ratio: 1.4) (Bramness et al. 2008). However, this study only included drivers aged 18-69 years. In contrast, a case-cross over study conducted in the UK showed no increased risk of crashes with the use of tricyclic anti-depressants but the analysis included drivers 18 years and older and did not focus on older drivers (Barbone et al. 1998).

Several studies have also examined the potential impact of tricyclic anti-depressants on driving performance. A review of studies measuring the effect of anti-depressants on actual

driving performance using a vehicular “weaving” test revealed that changes in performance after acute doses of sedating anti-depressants (including amitriptyline) were comparable to those seen in drivers with a blood alcohol concentration of 0.8 mg/mL or more (Ramaekers 2003). Driving performance returned to placebo levels after one week of treatment but it should be noted that the studies reviewed included only healthy drivers. Also, in a driving simulator-based study of young, non-depressed, Japanese men, significant impairment of car following, road tracking and vigilance was demonstrated four hours after administration of amitriptyline (Iwamoto et al. 2008).

The newer non-sedating or non-tricyclic anti-depressants including selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors are thought to produce less side effects. While a few studies have reported slight increased risk of crash involvement (Bramness et al. 2008) and reduced driving performance (De Las Cuevas & Sanz 2008), several have reported that non-sedating anti-depressants do not impair driving or increase crash risk (Barbone et al. 1998; Iwamoto et al. 2008; Ramaekers 2003).

A recent review by Sansone & Sansone (2009) concluded that there may be a small risk of driving impairment with anti-depressants but that the risk is elevated under specific conditions, the main one being advanced age. This may be due to older people responding differently or being more sensitive to anti-depressants and not adapting to the side effects as readily as younger people (Iwamoto et al. 2008; Sansone & Sansone 2009). Other conditions that increase risk include high doses of anti-depressants, the initial treatment phase and comorbid treatment with other medications, especially benzodiazepines (Sansone & Sansone 2009). Lastly, it is important to consider that data has shown depressive symptoms themselves increase crash risk, making it very difficult to determine whether demonstrated effects on driving are due to the medication or the illness itself (Wingen et al. 2006).

2.5 Opioid analgesics

Opioid analgesics are used to manage mild to severe acute and chronic pain, a condition common in the older population. These medications have been associated with side effects that could impair driving ability including nausea, sedation, mental clouding, dizziness,

memory impairment, reduced attention, slowed visual processing and increased reaction time (Hill & Zacny 2000).

Several studies that administered opioid medications to healthy opioid-naive volunteers have demonstrated dose-related impairments on psychomotor and driving ability tests (Zacny 1995). However, most chronic pain patients take opioid analgesics on a stable, long-term regime. A more recent study concluded that there were no significant differences in psychomotor performance or on-road driving ability between non-elderly patients with chronic pain managed with stable regimes of opioid analgesics and healthy volunteers (Byas-Smith et al. 2005). In addition, a structured review published in 2003 on whether driving is affected in patients on stable doses of opioids concluded that there was moderate evidence for no effect on psychomotor abilities but inconclusive evidence for effect on cognitive function in these patients (Fishbain et al. 2003). They also reported there was strong evidence that patients on stable doses of opioids did not demonstrate impairments in simulator, off-road or on-road driving assessments and were at no higher risk of traffic violations, convictions or motor vehicle crashes (Fishbain et al. 2003). This review however, did not include any studies of older drivers and included several studies of drug addicts on methadone treatment.

Very few studies have examined the impact of opioid analgesics on older drivers specifically and those that have provide inconclusive results. Leveille (1994) reported than in a USA-based case-control study of drivers aged 65 and over who had filled their prescription in the past 60 days, opioid analgesics were associated with a significantly elevated crash risk (OR: 1.8; 95%CI: 1-3.4). Another US study however, reported no increased risk for involvement in an injurious crash for 65-84 year old drivers (Ray et al. 1992). In addition, a recent Canadian case-control study found that testing positive for opioid analgesic medication was not associated with greater risk of an unsafe driving action prior to a fatal crash for older drivers but interestingly, was associated for younger drivers (Dubois et al. 2010). A Norweigan population-based study reported a significantly increased risk of crash involvement for opioid medication users within the first seven to 14 days of intake. While this study only included drivers aged 18-69 years, these results may suggest heightened risk during initial exposure to the drug (Engeland et al. 2007).

Overall, research suggests that there is no significant risk of driving impairment or crash involvement for *non-elderly* drivers on stable doses of opioid analgesics. This evidence however, may be confounded by polydrug use and the fact that pain itself has been shown to impair driving performance (Verster & Mets 2009). For older drivers however, the evidence is much less clear and more research is required to elucidate the overall effect of opioid analgesics on driving ability as well as whether older drivers experience increased risk during initial exposure to opioids and whether there are any dose-related effects.

2.6 Anti-psychotics

Quite limited evidence exists on the association between anti-psychotic medications and driving impairment and no published studies were located that focused on older drivers. Anti-psychotics may affect driving by producing side effects including sedation, impaired psychomotor and cognitive abilities and impaired reaction time (Wylie et al. 1993). One of the reasons it is so difficult to determine the effects of anti-psychotics on driving is that these medications are used to treat psychoses such as schizophrenia, bipolar disorder and delusional disorder. Cognitive and psychomotor impairments are key features of psychoses such as schizophrenia and often persist even during periods of remission or reduced psychotic symptoms (Brunnauer et al. 2009; Kagerer et al. 2003; Soyka et al. 2005). It is therefore difficult to determine whether effects on driving are due to the disorder or are a result of side-effects of the medication.

The majority of evidence comes from small clinical studies in Germany that have compared the psychomotor performance and driving ability of non-elderly, schizophrenic patients taking different anti-psychotic medications. In one non-randomised study, 49 schizophrenic patients' performance on psychomotor tasks thought to relate to driving fitness including peripheral vision, divided attention, sensorimotor function, reaction time, stress resistance and capacity to integrate information was tested (Kagerer et al. 2003). It was found that those treated with the anti-psychotic haloperidol (a conventional dopamine antagonist neuroleptic) showed considerable psychomotor impairment compared with patients who received an atypical neuroleptic medication including clozapine, amisupride, riperidone, quetiapine, olanzapine or ziprasidone (Kagerer et al. 2003). Since then, three more German studies have also reported that schizophrenic patients on atypical neuroleptic medication showed better test performance

on psychomotor and cognitive tests related to driving than patients on typical neuroleptics (such as haloperidol) (Brunnauer et al. 2004; Brunnauer et al. 2009; Kagerer et al. 2003). Driving simulator tests have also supported these findings (Brunnauer et al. 2009). However, Sokya (2005) also reported that although schizophrenic patients treated with atypical neuroleptics performed better on these tests related to driving than those treated with typical neuroleptics, schizophrenic patients overall, regardless of medication type still performed worse that healthy controls.

Whether these results translate to older drivers taking anti-psychotics is currently unknown and should be investigated through experimental and epidemiological studies.

2.7 Benzodiazepines

Benzodiazepines can have sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties and are used to treat a wide range of conditions. Benzodiazepines slow down central nervous system electrical signals and possible adverse effects that may influence driving ability include oversedation, memory impairment, poor concentration, lack of co-ordination and mental confusion (Dubois et al. 2008). Benzodiazepines can be classified by half-life or the time it takes for half of the amount on benzodiazepine consumed to leave the body in hours (Dubois et al. 2008). A short half-life is usually considered $\leq$ 6 hours, intermediate half-life 6–24 hours and long half-life $\geq$ 24 hours (Barbone et al. 1998). The half-life indicates how long a person may be affected by the medication and the potential for cumulative effects with repeated doses (Dubois et al. 2008). It is therefore, possible that benzodiazepines with different half-lives pose different risks for driving safety.

2.7.1 Benzodiazepines - general

Many epidemiological studies have examined the effects of the broad benzodiazepine group of medications on crash risk. A recent review of 11 epidemiological studies concluded that for the overall population, benzodiazepine users were at significantly increased risk of crashes compared to non-users (Rapoport et al. 2009).

Several studies have specifically examined the risk for older drivers and of seven epidemiological studies identified, four reported increased risk with benzodiazepine use. Two population-based studies in the USA both reported that benzodiazepine use was associated with crash involvement or at-fault crashes in drivers aged 65 and over (McGwin et al. 2000; Ray et al. 1992). Neutel (1998) also reported an increased risk of injurious crashes for drivers aged 60 and over, who used benzodiazepines in Canada. Interestingly, the risk was slightly lower for drivers aged over 60 than those under (Neutel 1998). A Canadian-based nested case-control study of drivers aged 67-84 years examined the use of long and short half-life benzodiazepines and injurious crashes (Hemmelgarn et al. 1997). They reported a significant increased risk of crash involvement within the first week of long half-life benzodiazepine use (rate ratio: 1.45, 95% CI: 1.04-2.03) and a slightly lower but significant increased risk with continuous use up to one year (rate ratio: 1.26, 95% CI: 1.09-1.45). Neither initiation nor continued use of short half-life benzodiazepines affected crash risk in this group (Hemmelgarn et al. 1997).

In contrast, an earlier case-control study in the USA reported no association between benzodiazepine use and injurious crash for older drivers (Leveille et al. 1994). A case-crossover study also found that benzodiazepine use increased the risk of crash involvement for younger drivers but that risk decreased with age and was not significant for drivers aged over 65 (Barbone et al. 1998). This finding may be due to an artefact of the case-crossover method. Similarly, a recent case-control study reported that benzodiazepine use did not increase the odds of crash responsibility for drivers aged 65 and over for short, intermediate or long half-life benzodiazepines (Dubois et al. 2008). However, drivers aged 25-55 years taking intermediate or long half-life benzodiazepines did experience increased odds of crash responsibility. Those taking short half-life benzodiazepines did not demonstrate increased odds (Dubois et al. 2008). This study only examined fatal crashes however and the authors acknowledge that the analyses may have lacked statistical power for drivers aged 65 and over (Dubois et al. 2008).

Overall, evidence indicates that benzodiazepine use does increase the risk of crashes in both older and younger drivers. Again however, it is difficult to determine whether these crashes should be attributed to the effects of the medication or the disorders they are prescribed for such as sleeping problems or anxiety. The findings point to certain factors that may increase

the risk of crashes including the use of intermediate and long half-life as opposed to short half-life benzodiazepines (Barbone et al. 1998). In addition, a dose-response relationship has been reported and risk may be higher during initiation of the medication and decrease as tolerance to the medication develops (Barbone et al. 1998; Hemmelgarn et al. 1997). While studies examining benzodiazepines in general provide useful data, this encompasses a very broad group of medications including anxiolytics and hypnotics that may exert quite different and specific effects on driving ability.

2.7.2 Anxiolytic benzodiazepines

The majority of anxiolytic medications used to treat anxiety and panic attacks are benzodiazepines. Acute exposure to anxiolytic benzodiazepines has been quite extensively shown to impair driving skills in healthy volunteers in laboratory, simulator and on-road assessments. For example, the common anxiolytic, alprazolam has been shown to cause serious driving impairment in healthy volunteers undertaking on-road driving tests one hour (Verster et al. 2002) and four hours (Leufkens et al. 2007) after administration of the drug. This impairment was shown to be double in long half-life as compared to intermediate half-life formulations (Leufkens et al. 2007). In addition, simulator tests of healthy males demonstrated that the anxiolytic, diazepam, significantly impaired harsh-braking performance as compared to another anxiolytic, tandospirone, four hours after administration (Takahashi et al. 2010).

While quite strong evidence exists for the acute effects of anxiolytic benzodiazepines, epidemiological studies examining chronic exposure have produced mixed results. An early study by Neutel et al. (1995) found an increased risk of hospitalisation due to a crash in drivers prescribed anxiolytic benzodiazepines. The increase was significant within four weeks of the prescription being filled (OR: 2.5, 95% CI: 1.2-5.2) and even higher within two weeks (OR: 5.6, 95% CI: 1.7-18.4) Older drivers were not examined separately (Neutel 1995). A recent Norweigan population-based study also reported a markedly increased risk of injurious crashes in users of the anxiolytic benzodiazepines - diazepam, oxazepam and alprazolam; (SIR: 2.9; 95% CI: 2.5-3.5) (Engeland et al. 2007). The risk of crash was more pronounced when an exposure period of seven days was utilised and decreased when a 14 day exposure period was used, possibly reflecting development of tolerance to the drug after the first week

of use. This study however, only included drivers aged 18-69 years (Engeland et al. 2007). A case-cross over study conducted in the UK also reported an increased risk of crashes in users of anxiolytic benzodiazepines; OR: 2.18 (95% CI: 1.52-3.13) when drivers of all ages were examined (Barbone et al. 1998). On further exploration, users of long half-life but not intermediate half-life anxiolytic benzodiazepines were at increased risk as well as those taking intermediate doses but not low doses. Numbers were too low to examine the effect of high doses (Barbone et al. 1998). This study also examined older drivers separately and observed that risk actually decreased with age with drivers 65 and over not experiencing any increased risk (Barbone et al. 1998). The low number of older drivers included in the study however, may have affected this result.

2.7.3 Hypnotic benzodiazepines

Hypnotics are most frequently used to treat sleeping problems and the majority of these medications are benzodiazepines. Hypnotics are usually prescribed for occasional use but it has been reported that older people more frequently use them long-term than other age groups (Gustavsen et al. 2008). Hypnotic benzodiazepines are administered before bedtime to encourage sleep. However, the effects that are desired during the night including sedation and reduced alertness may lead to residual sedation, reduced alertness, slowed reactions and impaired motor co-ordination the following day, which are of concern for driving safety (Vermeeren 2004; Verster et al. 2004).

A large number of experimental laboratory, driving simulator and on-road tests have investigated the residual adverse effects of hypnotics. Strong evidence indicates that most hypnotic medications do impair driving skills the next day (Leufkens & Vermeeren 2009; Vermeeren 2004; Verster et al. 2004). However, the degree of impairment and length of time of impairment varies considerably between the individual medications (Vermeeren 2004; Verster et al. 2004). Evidence from on-road driving studies also indicate that in contrast to other hypnotics, temazepam administered at its recommended dosage is unlikely to impair driving ability 10 hours later (Leufkens & Vermeeren 2009; Verster et al. 2004). Overall, hypnotics with long half-lives show more consistent and pronounced impairment in on-road studies than those with short half-lives and effects are dose-dependent (Verster et al. 2004). Impairment is also most pronounced during treatment initiation with tolerance developing

over time (Verster et al. 2004). It should be noted however, that the majority of evidence comes from studies conducted with young, healthy volunteers and it is believed that the residual effects of hypnotics may be more pronounced in older drivers (Verster et al. 2004).

Five epidemiological studies examining the association between hypnotic benzodiazepines and motor vehicle crashes were identified and two specifically examined older drivers. The first was the UK-based case-crossover study conducted by Barbone (1998). This study included the hypnotic medications flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam, temazepam and zopiclone and reported no increased risk of crashes for drivers aged over or under 65 years who used hypnotics (Barbone et al. 1998). However, analyses of hypnotics by half-lives showed that those with short half-lives (all cases were exposed to zopiclone) were significantly associated with crashes for all drivers (Barbone et al. 1998). Zopiclone is not a benzodiazepine but was included in the analysis as it acts on similar receptors to benzodiazepines. Although experimental studies have reported more severe driving impairment with longer half-life hypnotics, zoplicone specifically has consistently shown to exert residual effects on driving despite its short half-life (Bocca et al. 1999).

The Canadian study by Neutel (1998) showed a large, significant increase in injurious crash risk for users of the hypnotic – flurazepam aged over 60 (OR:3.4) and under 60 (OR: 6.1) (Neutel 1998). Earlier Neutel et al. (1995) also reported that the hypnotic benzodiazepines - traizolam and flurazepam were associated with significantly increased injurious crash risk two weeks (OR: 3.9, 95% CI: 1.9-8.3) and four weeks (OR: 6.5, 95% CI 1.9-22.4) after the prescription was filled. Older drivers were not examined separately (Neutel 1995). Similarly, Engeland (2007) also reported that 18-69 year old users of hypnotic benzodiazepines - flunitrazepam, nitrazepam and midazolam, had over three times the risk of crash involvement within seven days of prescription than controls. This risk decreased when the exposure period was increased to 14 days, reflecting possible development of tolerance to the drugs (Engeland et al. 2007). Finally, Gustaven (2008) examined the effects of specific hypnotics on crashes in 18-69 year old drivers in Norway and reported significantly increased risk for users of flunitrazepam (SIR: 4.0, 95% CI: 2.4-6.4) and nitrazepam (SIR: 2.7, 95% CI: 1.8-3.9). Exposure to the non-benzodiazepine hypnotics zopiclone and zolpidem also increased risk but resulted in a lower SIR (SIR: 2.3, 95% CI: 2.0-2.7) (Gustavsen et al. 2008).

Experimental and epidemiological evidence clearly demonstrates that hypnotics can produce residual impairing effects on driving and increase the risk of crash involvement. However, the effect of these medications on older drivers specifically has not been thoroughly investigated. In addition, each hypnotic medication has been shown to exert different degrees of impairment and for different lengths of time making it essential to investigate medications individually rather than grouping them together.

2.8 Limitations of past research

Although evidence indicates that several types of psychoactive medications have the potential to impair driving ability and increase the risk of crash involvement, a major limitation is that few have specifically examined their effects on older drivers. Despite the fact that the majority of the population using psychoactive medications are older (Australian Bureau of Statistics 2009), most experimental studies have been conducted using healthy, young volunteers and few epidemiological studies have included or analysed older drivers separately. It is not always appropriate to extrapolate findings from studies on young drivers to the older population because it has been reported that older people may respond differently to medications, are more sensitive to adverse effects and do not adapt as readily to side effects as younger people (Verster et al. 2004). The majority of studies have also examined the effects of acute treatment with medications whereas older people frequently undertake long-term chronic treatment with psychoactive medications, which may have quite different effects on driving (Verster & Mets 2009).

A number of experimental studies have assessed the driving abilities of older drivers using psychoactive medications through laboratory tests, driving simulators or on-road driving assessments. While such studies suggest potential impacts of medications on driving ability, they are unable to take into account the impact of real life conditions that translate to actual crash involvement for older drivers (Orriols et al. 2009). Therefore, epidemiological studies provide the optimal design to study the association between medication use and older driver crash involvement (Smink et al. 2005).

Recent epidemiological research has provided useful crash risk estimates by linking datasets including drug prescription, hospital admission due to motor vehicle crashes, police-reported

crashes and health insurance information (Barbone et al. 1998; Dubois et al. 2010; Engeland et al. 2007). However, these studies have provided mixed results. Reasons for this may include small sample sizes, selection bias, use of different outcome and exposure measures as well as failure to adjust for potential confounding factors. These confounders include health status, driving frequency, polydrug use, varying exposure to the medication and the effects of the medical condition itself on crash risk. Inadequate assessment of medication compliance has also been identified as a significant limitation of pharmaco-epidemiological studies (Dubois et al. 2010; Maes et al. 1999).

Another limitation of existing epidemiological research is the lack of statistical power. Despite large sample sizes, when drivers were divided into age and medication categories, the numbers of older drivers taking particular psychoactive medications were very small, resulting in wide confidence intervals and suggesting samples may have lacked the power to detect significant associations with crash risk (Barbone et al. 1998; Dubois et al. 2008; McGwin et al. 2000). In addition, the majority of studies grouped drugs according to therapeutic class, often for reasons of statistical power. For example, several studied the association between benzodiazepines and crashes (Rapoport et al. 2009). Benzodiazepines encompass a very broad range of medications including anxiolytics and hypnotics with short, intermediate and long half-lives and it has been demonstrated that each individual medication can exert quite different and specific effects on driving ability (Barbone et al. 1998; Hemmelgarn et al. 1997). Studies examining effects of broad groups of medications have provided mixed results possibly because each included different individual medications within their groupings and because risks associated with individual medications were averaged out when grouped together (Vermeeren 2004; Verster et al. 2004).

The proposed population-based case-crossover study examining older drivers specifically, will overcome several of these limitations. Large-scale whole-population studies eliminate selection bias, and their large sample sizes allow the examination of the association between individual medications and crash risk as well as any dose-response effects. Although such data linkage studies can only obtain information on how psychoactive medications were prescribed and not actual usage or compliance, this objective information is thought to provide far more accurate data than information obtained via participant self-report (Holland et al. 2003; McGwin et al. 2000). The most difficult confounding factor to control for when

examining associations between medications and crash risk is distinguishing the effects of the disease the medication is prescribed to treat, from the effects of the medication itself (Vermeeren 2004; Verster et al. 2004; Wingen et al. 2006). Case-cross over designs where each subject acts as their own control eliminate confounding due to fixed characteristics (Orriols et al. 2009).

2.9 Conclusion

Road crashes represent a significant cost to the Australian health care system. With projections showing that the 65-and-over population is the fastest growing age group, more attention is being diverted to the driving safety for older drivers. Older drivers involved in a crash are also more likely to be taking psychoactive medications that may impair the central nervous system and adversely affect their ability to safely operate a motor vehicle. However, very few epidemiological studies have focused on or examined older drivers separately. Epidemiological studies are essential to assess the effects of psychoactive drugs under "real" driving conditions. The proposed population-based study will address the limitations of past research through the use of the Western Australian Data Linkage System, which links over 30 datasets at an individual level for the entire Western Australian population of nearly two million people. Major strengths of the population-based study include the use of objective data and the use of a case-crossover design where each participant acts as their own control. With an ageing population, this information may be essential for clinicians to discuss issues of driving safety with at-risk patients and may also guide the development of policy and strategic countermeasures. The ultimate result of such actions may see a substantial improvement in the safety and mobility of older drivers.

3 METHODS

3.1 Research design

A retrospective population-based case-crossover study design was utilised to determine the association between psychoactive medication use and crash risk for older drivers in Western Australia (WA). Data was obtained through the linkage of the Hospital Morbidity Data System and the Pharmaceutical Benefit Scheme from 2002 to 2008 by the WA Data Linkage Unit at the Department of Health, Western Australia.

The case-crossover methodology was considered the most appropriate study design to assess the association in the risk of a rare outcome (motor vehicle crash) with exposure to a transient risk factor (use of psychoactive medications that act on the central nervous system) (Barbone et al. 1998). Case-crossover studies are a modification of the case-control design. In a case-control study, individuals with the outcome of interest (cases) are compared with similar individuals who do not have the outcome of interest (matched controls). However, in the case-crossover design, only 'cases' or individuals with the outcome of interest (motor vehicle crash) are included. Because each driver acts as their own control the design accounts for characteristics of the driver that may affect the risk of a crash but do not change over a short period of time, thereby eliminating possible confounding factors such as lifestyle, genetics, education, and chronic conditions from differences between individuals (Barbone et al. 1998; Gibson et al. 2009). One or more control intervals are selected and exposure to the risk factor in the time preceding the outcome is compared with exposure during one or more control periods in the same individual (Smeeth et al., 2006).

3.2 The Western Australian Data Linkage System

3.2.1 Background

The study uses the linked administrative data from the Western Australian Data Linkage System, which was established by the Department of Health WA and The School of Population Health at The University of Western Australia. This linkage system is unique in Australia and is one of only a small number of record linkage systems in the world. It records longitudinal data on the use of health services and vital events for the entire Western

Australian population. The WA Data Linkage System currently contains in excess of seven million records with the largest component consisting of the Hospital Morbidity Data System, which contains over seven million records. The register of births contains around 400,000 entries while the register of deaths contains approximately 200,000 entries. The Mental Health Information System contains data for just over 200,000 patients of mental health services and the Cancer Registry has information on over 80,000 registered cancers. Each individual patient record was linked by means of probabilistic matching. Linkages were based on six Automatch passes with surname, given name, date of birth, sex, and motor vehicle driver licence number and address as the principal matching fields. The average proportion of invalid links (false positives) and missed links (false negatives) have been estimated as 0.3% by an earlier validation study (Holman et al. 1999).

The main advantages of using the data linkage system in this study are:

- It is more time and cost-effective than studies relying on primary data collection.
- It avoids problems that result when individuals are lost to follow up or do not properly fill out a questionnaire.
- The privacy of the health and licensing records is fully protected and any data analysis is permitted only on totally de-identified data.
- The WA Data Linkage System is a dynamic system, which is constantly being revised and updated as new data are added to the system.

3.2.2 Databases

This study involved the linkage of the Hospital Morbidity Data System (HMDS) and the Pharmaceutical Benefit Scheme (PBS) from 2002 to 2008 to ascertain the study population.

The Hospital Morbidity Data System

International Classification for Diseases (ICD) codes for an ‘injury’ and an external cause code for a hospital admission as a driver aged 60 years and older involved in a motor vehicle crash were used to perform a de-identified extraction from the hospital morbidity records with a residential postcode specific to Western Australia as listed below.

ICD-10-AM (July 1, 1998–2010):	V40.0, V40.5, V41.0, V41.5, V42.0, V42.5, V43.0, V43.5, V44.0, V44.5, V45.0, V45.5, V46.0, V46.5, V47.0, V47.5, V48.0, V48.5, V49.0, V49.4 V50.0, V50.5, V51.0, V51.5, V52.0, V52.5, V53.0, V53.5, V54.0, V54.5, V55.0, V55.5, V56.0, V56.5, V57.0, V57.5, V58.0, V58.5, V59.0, V59.4, V86.0, V86.5.

Descriptive information such as age, gender, Indigenous status, postcode of residence, marital status and co-morbid health conditions for each hospitalised patient was also extracted for analysis.

Pharmaceutical Benefits Scheme

The Pharmaceutical Benefits Scheme (PBS) provides Medicare-eligible persons with access to prescription medications at a reasonable cost to the patient with subsidies for around 600 types of drugs in nearly 1500 formulations. The PBS does not include any medicines sold without prescription, public hospital dispensed medications or where the actual medication cost is below the PBS subsidy threshold. However, this would not impact on the medications of interest for this study.

The exposure to be investigated was a prescription for any psychoactive medication. The study drugs were classified into four groups:

- Benzodiazepines, which included hypnotics and sedative anxiolytics;
- Anti-depressants, which included tricyclic anti-depressants and selective serotonin reuptake inhibitors;
- Anti-epileptics; and
- Opioid analgesics.

Information extracted from the PBS database included the name of the drug, dose, quantity, and date the drug was dispensed. A complete list of psychoactive medications included in this study by classification are listed in Table 3.1.

Table 3.1: Medications by group and subgroup

Group	Sub Group	Medication Name
Benzodiazepines	*Hypnotics*	Clonazepam
		Flunitrazepam
		Nitrazepam
		Temazepam
	Sedative Anxiolytics	Alprazolam
		Bromazepam
		Diazepam
		Oxazepam
Anti-depressants	*Tricyclic Anti-depressants*	Amitriptyline Hydrochloride
		Dothiepin Hydrochloride
		Doxepin Hydrochloride
		Imipramine Hydrochloride
	Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram Hydrobromide
		Escitalopram Oxalate
		Fluoxetine Hydrochloride
		Sertraline Hydrochloride
		Fluvoxamine Maleate
Opioid Analgesics		Codeine Phosphate
		Codeine Phosphate with Paracetamol
		Dextropropoxyphene Napsylate
		Fentanyl
		Hydromorphone Hydrochloride
		Morphine Sulfate
		Oxycodone Hydrochloride
		Pethidine Hydrochloride
		Morphine Hydrochloride
		Tramadol Hydrochloride
Anti-epileptics		Carbamazepine
		Ethosuximide
		Gabapentin
		Phenytoin
		Topiramate
		Sodium valproate
		Lamotrigine
		Vigabatrin
		Phenytoin Sodium

3.3 Sampling methods

The sampling frame consisted of hospitalised drivers aged 60 years and older who were involved in a motor vehicle crash from June 2003 to December 2008 in Western Australia. These records were then linked to the PBS from January 2002 to December 2008 to identify those who had any psychoactive medications dispensed to them during the study period. A lookback period of six months of prescribed medications from the date of the first hospital admission was used in this study.

3.3.1 Selection of hazard (case) interval

According to Maclure & Mittleman (2000) the hazard (case) interval is defined as the time after a trigger (in this case psychoactive medication usage) in which an increased risk of the outcome (motor vehicle crash) is caused by that trigger (Maclure & Mittleman, 2000). The hazard interval can be as short as 10 minutes or as long as a year (Maclure & Mittleman, 2000).

Individual prescription periods using the defined daily dosage (DDDs) methodology for each medication were calculated based on data obtained from the PBS. These were used to assess exposure status for both case and control intervals. The duration and timing of the hazard (case) interval was determined using information relating to the induction period for each of the medications (may take 24-48 hours to get into the system), the prescription period and the amount of time it takes to be excreted from the body (Holman et al., class notes, 2009). These were determined based on an understanding of the pharmacokinetics of the drug and the causal biology of the outcome of interest as recommended by Holman (2009).

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. When the recommended dose refers to body weight, an average adult is considered to be a person of 70kg. A DDD is only assigned to drugs that already have an Anatomical Therapeutic Chemical (ATC) classification which is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway. It provides a global standard for classifying medical substances in drug utilisation and outcome research.

The prescription period (days) was calulated by multiplying the strength of the medication by the quantity dispensed and dividing this by the DDD. The half life ($t_{1/2}$)of the medication was

used to determine the time for the medication to be excreted from the body; this value was then added to the prescription period. The resulting number of days was then used to determine the hazard (case) interval for each medication in the PBS database.

$$\textbf{Prescription Period (days)} = \frac{\textbf{Strength of Medication x Quantity dispensed}}{\textbf{DDD}}$$

$$\textbf{Hazard Period (days)} = \textbf{Prescription period} + 4 \times t_{1/2}$$

For example, an older driver prescribed oxazepam 15 mg, for a period of 25 days with a DDD of 50mg results in a prescription period of 7.5 days. The half life of oxazepam is approximately 5-15 hours. Allowing a conservative approach of four times the half-life, oxazepam may be considered to be excreted from the body within 2.5 days. This resulted in a hazard (case) interval of 10 days (Holman, class notes, 2009). A full list of hazard intervals for each medication is found in Appendix A.

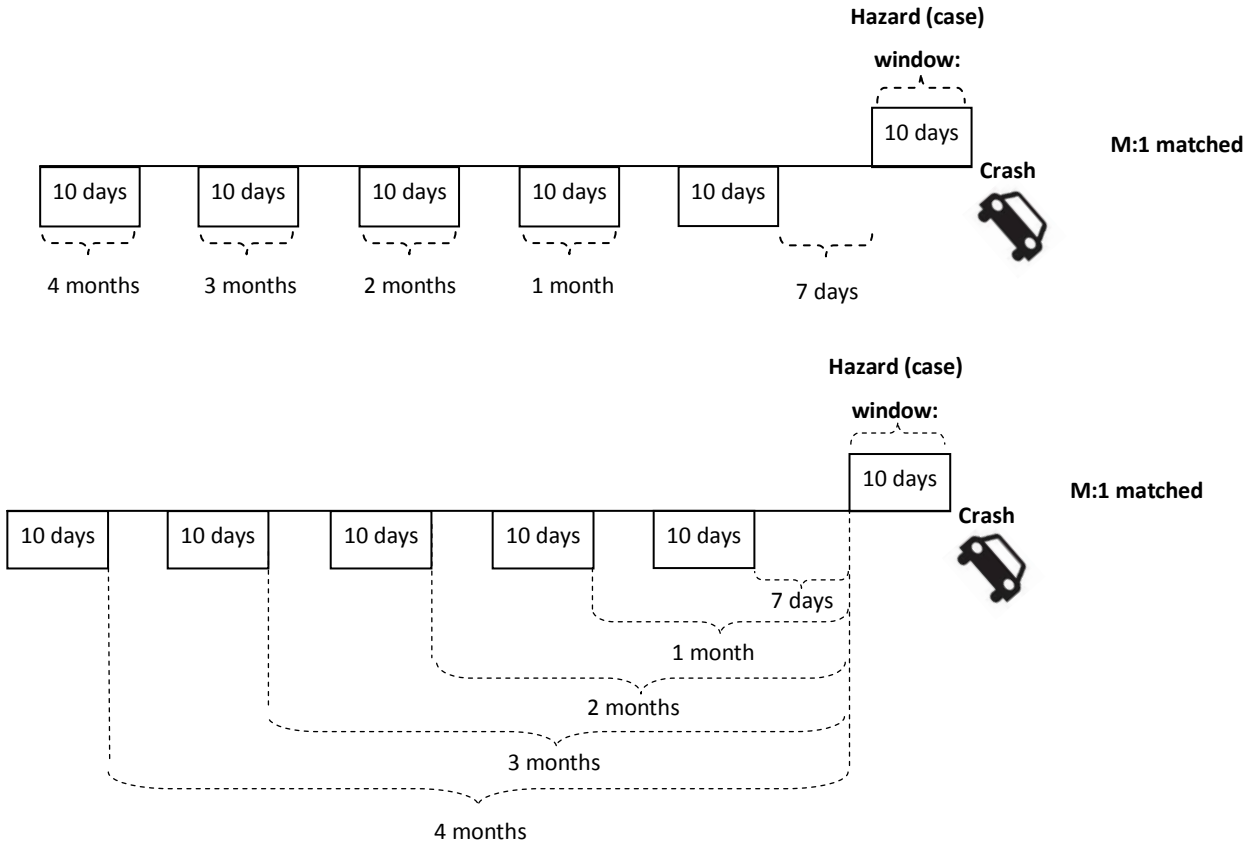
3.3.2 Selection of control intervals

Another important consideration in a case-crossover study is the number of control intervals to be selected. Mittleman (1999) found that the study power and the precision of the effect size improved based on the number of control intervals selected. Confidence intervals for risk estimates could be reduced by approximately 35% in going from one to four control periods and by 40% in going from four to >100 control periods unlike traditional case-control studies where there is little to be gained from going beyond four controls.

For this study, five control intervals were selected of the same duration as the unique hazard (case) interval calculated for each medication. Psychoactive medication usage was compared during the hazard interval at seven days, one month, two months, three months and four months prior to the closest date of prescription to the hospital admission crash date. The long duration of the control interval (same as hazard [case] interval) was intended to capture older drivers who might be exposed to a medication on a long term basis. Additionally, the use of lag periods between control intervals was also intended to account for long-term usage of a medication (Delaney & Suissa, 2008). Figure 3.1 provides an example of the selection of case hazard and control windows for the medication Oxazepam.

Figure 3.1: Case hazard and control window selection

Medication Name	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
Oxazepam	50 mg	15 mg	25	7.50	5-14 (hr)	20-56 (hr)	2	10.0



3.4 Statistical analysis

Plausibility checks were conducted and inconsistent data were cleaned prior to statistical analysis. Descriptive statistics were calculated for demographic variables such as age, gender, residential location, Indigenous status, marital status, and type of psychoactive medication prescribed.

Using the linked data, the annual incidence rate of hospitalised crashes for drivers over 60 years of age taking psychoactive medications (benzodiazepines, anti-depressants, anti-epileptics and opioid analgesics) were calculated based on the relevant Western Australian population data (Australian Bureau of Statistics 2008).

Residential location was defined as metropolitan, rural or remote based on patients' postcode at first hospital admission using the Western Australian's Hospital Department zones classification. Indigenous status was recorded if a patient was identified as having an Aboriginal or Torres Strait Islander heritage and marital status was classified as having a partner (married or de facto) or not. An unweighted co-morbidity score was assigned to each patient as the cumulative number of different co-morbid conditions identified from all hospital admissions up to one year before and including the index hospital admission for the crash. Comorbidity was classified as having one or more of the 17 conditions described by Holman et al. (1999). This was recorded into presence of a chronic condition or not.

Matched analysis using conditional logistic regression was used to calculated the odds of having a hospitalisation crash in association with psychoactive medication. The primary analysis involved 1: multipe (1:M) medication use during the hazard interval for an older driver compared with the five control intervals. Subsequent analysis also examined 1:1 matching with each of the five control intervals.

Four different models were undertaken: the first was based on benzodiazepine usage; the second, anti-depressant usage; the third, anti-epileptics usage; and the fourth was usage of opioid analgesics. Cases who had been admitted to hospital for more than one crash in a year were flagged and were accounted for only once in the model. Odds ratios, 95% confidence intervals and p values were calculated. Subgroup analysis based on gender and presence/absence of a chronic condition was undertaken using 1:M matching. The sample sizes based on age-group and location were too small for further analyses.

All data manipulations and analysis was undertaken using SAS 9.1 (SAS Institute Inc., Cary, NC).

3.5 Ethical implications

Ethical approval was obtained from both the Human Research Ethics Committee at Curtin University of Technology and the Department of Health WA Human Research Ethics Committee which is an independent committee appointed by the Minister for Health in Western Australia and the Commonwealth.

De-identified data obtained from the Data Linkage Branch of the Western Australian Department of Health were stored in a password-protected file that was only accessed by the Principal Researcher and the research assistant. All analyses were performed on the de-identified data set. De-identified files will be kept for seven years at the School of Public Health and destroyed after that period.

4 RESULTS

4.1 Demographic characteristics

There was a total of 44,171 prescriptions for psychoactive medications for 981 individuals aged 60 years who were hospitalised as the results of a crash between 2002 and 2008. After excluding those who did not meet the elegibility criteria (e.g. driver, motor vehicle crash) there was a total of 651 individuals in the cohort. Among the crash-involved drivers, the largest proportion (43.6%, n=284) were prescribed opioid analgesics, followed by benzodiazepines (37.9%, n=247). Drivers prescribed an anti-depressant represented 13.1% (n=85) of the cohort, while 5.4% (n=35) had been prescribed anti-epileptics.

Table 4.1 shows the breakdown by type of medication used and demographic characteristics for drivers' hospitalised for a motor vehicle crash.

4.1.1 Age

A fairly even distribution of usage of opioid analgesics was evident across all age groups: '60-69 years' (36.3%), '70-79 years' (32.4%) and '80 years and older' (31.3%). Benzodiazepines users were more frequently found to be aged 70-79 years (35.6%) and 80 years and over (36.0%) compared to those in the 60-69 years age group (23.9%). The majority of drivers who had been prescribed an anti-depressant were found among the 70-79 years age group (43.5%), while less than a quarter (23.5%) were aged between 60-69 years and one third (33%) were 80 years or older. Drivers with prescriptions of antiepileptics were predominantly aged 60-69 years age (45.7%), compared to 22.9% of drivers aged 70-79 years, and 31.4% of those aged 80 years and above (Table 4.1).

4.1.2 Gender

As can be seen in Table 4.1, the use of all medications among older drivers who were involved in a crash was higher among women, compared to men. The drugs prescribed most frequently to women were anti-depressants (67.1%), followed by benzodiazepines (64.8%), antiepileptics (60%) and opioid analgesics (55.3%).

4.1.3 Marital status

Similar distributions of drivers who were married (or in a de facto relationship) compared to non-married drivers were found across all medications, with those who were not married generally being involved more frequently in a crash than married drivers (range: 51% - 58% versus 39% - 44%) (Table 4.1).

4.1.4 Indigenous status

As shown in Table 4.1, apart from one driver who had been prescribed an opioid analgesic (0.4%), all crash-involved drivers were of non-Indigenous status.

4.1.5 Presence of chronic condition

Over one quarter of all drivers involved in a hospitalised motor vehicle crash during the study period reported a chronic condition regardless of the type of medication used. A large proportion of drivers had been prescribed anti-depressants (29.4%), followed by antiepileptics (28.4%), benzodiazepines (27.9%) and opioid analgesics (25.4%) (Table 4.1).

4.1.6 Residential location

The majority of crash-involved hospitalised drivers across all medication groups lived in the metropolitan area (range: 69% - 75%), followed by rural Western Australia (range: 17% - 23%), then remote areas of Western Australia (range: 6 - 11%) (Table 4.1).

Tabel 4.1: Characteristics of older drivers and motor vehicle crashes among drivers using medication that act on the central nervous system, 2002-2008

	Benzodiazepines		Anti-depressants		Opioid analgesics		Anti-epileptics	
All exposed individuals	n=247		n=85		n= 284		n=35	
	n	%	n	%	n	%	n	%
Age groups								
60-69	59	(23.9%)	20	(23.5%)	103	(36.3%)	16	(45.7%)
70-79	88	(35.6%)	37	(43.5%)	92	(32.4%)	8	(22.9%)
80+	89	(36.0%)	28	(33.0%)	89	(31.3%)	11	(31.4%)
Sex								
Male	78	(35.2%)	28	(32.9%)	127	(44.7%)	14	(40.0%)
Female	160	(64.8%)	57	(67.1%)	157	(55.3%)	21	(60.0%)
Marital status[1-4]								
Married/de facto	97	(39.3%)	36	(42.4%)	126	(44.4%)	15	(42.9%)
Not married	142	(57.5%)	48	(56.5%)	150	(52.8%)	18	(51.4%)
Indigenous/TSI								
No	247	(100.0%)	85	(100.0%)	283	(99.6%)	35	(100.0%)
Yes	0	(0.0%)	0	(0.0%)	1	(0.4%)	0	(0.0%)
Presence of chronic condition								
No	178	(72.1%)	60	(70.6%)	212	(74.6%)	25	(71.4%)
Yes	69	(27.9%)	25	(29.4%)	72	(25.4%)	10	(28.6%)
Residential location[5-6]								
Metro	184	(74.5%)	62	(72.9%)	204	(71.8%)	24	68.6 (%)
Rural	47	(19.0%)	16	(18.8%)	48	(16.9%)	8	22.9 (%)
Remote	15	(6.1%)	7	(8.2%)	31	(10.9%)	3	8.6 (%)

[1] Benzodiazepines; Missing: n=8 (3.2%)
[2] Anti-depressants; Missing: n=1 (1.2%)
[3] Opioid Analgesics; Missing: n=8 (2.8%)
[4] Anti-epileptics; Missing: n=2 (5.7%)
[5] Benzodiazepines; Missing: n=1 (0.2%)
[6] Opioid Analgesics; Missing: n=1 (0.2%)

4.2 Incidence rates for hospitalisation crashes

Annual incidence rates of hospitalised crashes among older people aged 60 years and older in Western Australia per 100,000 population are presented in Table 4.2. As there were only six months of crash data for 2002 and 2008 these rates are not shown. The highest hospitalisation crash rates among older people were observed in 2003, with rates of 37 crashes per 100,000 population. Crash rates decreased in the following three years fluctuating between 30 and 32 crashes per 100,000 population but increasing again in 2007 to 36 crashes per 100,000 population.

Tabel 4.2: Incidence rates for hospitalisation crashes, 2002-2008, Western Australia

Year	WA 60+ population (n)	Crashes (n)	Rate (per 100,000 population)	Std error	95%CI
2003	305,183	114	37.4	3.49	36.70-38.00
2004	316,577	102	32.2	3.19	31.60-32.80
2005	327,989	102	31.1	3.07	30.50-31.70
2006	337,165	100	29.7	2.96	29.10-30.20
2007	353,545	126	35.6	3.17	35.00-36.30

4.3 Risk associated with psychoactive medication use

4.3.1 Risk associated with benzodiazepine use

Benzodiazepine usage within the hazard period was associated with a 5.3 increase in the likelihood of crashing (95%CI 3.60-7.77; $p<0.001$). Analyses with paired matching to compare the hazard interval with an equivalent single control interval also showed significant associations between benzodiazepine use and the likelihood of a crash, similar in magnitude to the association with 1:M matching (Table 4.3).

Tabel 4.3: Risk of hospitalisation crash and use of benzodiazepines, 2002-2008

Type of matching	Odds ratio	*p*(0.05)	95%CI
1:M (multiple control intervals)	5.29	<0.0001	3.60-7.77
1:1 (7 days before drug prescription)*	5.36	<0.0001	2.82-10.21
1:1 (1 month before drug prescription)	3.44	<0.0001	2.04-5.82
1:1 (2 months before drug prescription)	7.11	<0.0001	3.54-14.29
1:1 (3 months before drug prescription)	7.11	<0.0001	3.54-14.29
1:1 (4 months before drug prescription)	6.19	<0.0001	3.27-11.69

**7 days before closest date of prescription to hospital admission crash date*

An increased risk for a hospitalised crash while taking benzodiazepines was found for both males (OR 6.21; 95%CI 3.16-12.21; p<0.001) and females (OR 4.88; 95%CI 3.06-7.80; p<0.001). An increased risk was also found for older drivers who reported a chronic condition (OR 3.97; 95%CI 2.94-8.10; p<0.001) as well as those who did not report a chronic condition (OR 5.95; 95%CI 3.75-9.45; p<0.001) (Table 4.4).

Tabel 4.4: Risk of hospitalisation crash and benzodiazepine use, using multiple control intervals by gender and chronic condition, 2002-2008

Benzodiazepines	Odds ratio	*p*(0.05)	95%CI
Sex			
Male	6.21	<0.001	3.16-12.21
Female	4.88	<0.001	3.06-7.80
Presence of chronic condition			
No	5.95	<0.001	3.75-9.45
Yes	3.97	<0.001	2.94-8.10

4.3.2 Risk associated with anti-depressant use

The use of anti-depressants within the hazard period was associated with almost a double increase in the likelihood of crashing (OR 1.8; 95%CI 1.02-3.27; p=0.044). Analyses with paired matching to compare the hazard interval with an equivalent single control interval showed varying results with significant associations between anti-depressants use and the likelihood of a crash for the seven days and four month control intervals (Table 4.5).

Tabel 4.5: Risk of hospitalisation crash and use of anti-depressants, 2002-2008

Type of matching	Odds ratio	*p*(0.05)	95%CI
1:M (multiple control intervals)	1.80	0.044	1.02-3.27
1:1 (7 days before drug prescription)*	2.43	0.05	1.01-5.86
1:1 (1 month before drug prescription)	1.78	0.17	0.79-4.02
1:1 (2 months before drug prescription)	1.00	1.00	0.49-2.05
1:1 (3 months before drug prescription)	1.56	0.30	0.67-3.60
1:1 (4 months before drug prescription)	3.17	0.01	1.27-7.93

**7 days before closest date of prescription to hospital admission crash date*

Males had almost a three times increased risk of crash involvement while taking of anti-depressants (95%CI 1.08-6.93; p=0.03). Also, older drivers with a chronic condition had an increase in the likelihood of crashing while taking an anti-depressant (OR=3.36, 95%CI 1.32-8.53; p=0.01) (Table 4.6).

Tabel 4.6: Risk of hospitalisation crash and anti-depressant use, using multiple control intervals by gender and chronic condition, 2002-2008

Anti-depressants	Odds ratio	*p*(0.05)	95%CI
Sex			
Male	2.74	0.03	1.08-6.93
Female	1.37	0.44	0.62-3.00
Presence of chronic condition			
No	1.21	0.63	0.55-2.66
Yes	3.36	0.01	1.32-8.53

4.3.4 Risk associated with anti-epileptics use

The use of anti-epileptic medication within the hazard period was associated with a six time increase in the likelihood of crashing (95% CI 2.53-14.50; p<0.001). Analyses with paired matching to compare the hazard interval with an equivalent single control interval also showed significant associations between the use of anti-epileptics and the likelihood of a crash, similar in magnitude to the association with 1:M matching (Table 4.7).

Tabel 4.7: Risk of hospitalisation crash and use of anti-epilectics, 2002-2008

Type of matching	Odds ratio	*p*(0.05)	95%CI
1:M (multiple control intervals)	6.06	<0.0001	2.53-14.50
1:1 (7 days before drug prescription)*	7.5	0.01	1.72-32.80
1:1 (1 month before drug prescription)	6.5	0.01	1.47-28.80
1:1 (2 months before drug prescription)	3.6	0.02	1.25-11.30
1:1 (3 months before drug prescription)	5.0	0.01	1.49-17.27
1:1 (4 months before drug prescription)	6.5	0.01	1.47-28.80

**7 days before closest date of prescription to hospital admission crash date*

Both males (OR=10.65, 95%CI 2.07-54.77; p=0.004) and females (OR=4.66; 95%CI 1.65-13.17; p=0.004) were at an increased risk for a hospitalised crash while exposed to anti-epileptics medication. An increased risk was also found for older drivers who reported a chronic condition (OR 14.46; 95%CI 1.64-127.80; p=0.016) as well as those who did not report a chronic condition (OR 4.81; 95%CI 1.81-12.81; p=0.002) (Table 4.8). However these results should be interpretated with caution due to the small sample size.

Tabel 4.8: Risk of hospitalisation crash and anti-epileptics use, using multiple control intervals by gender and chronic condition, 2002-2008

Anti-epilectics	**Odds ratio**	***p*(0.05)**	**95%CI**
Sex			
Male	10.65	0.004	2.07-54.77
Female	4.66	0.004	1.65-13.17
Presence of chronic condition			
No	4.81	0.002	1.81-12.81
Yes	14.46	0.016	1.64-127.80

4.3.5 Risk associated with opioid analgesics use

Opioid analgesics usage within the hazard interval was associated with a 1.5 increase in the likelihood of crashing (95%CI 1.00-2.33; p=0.05). (Table 4.9).

Tabel 4.9: Risk of hospitalisation crash and use of opiod analgesics, 2002-2008

Type of matching	Odds ratio	*p*(0.05)	95%CI
1:M (multiple control intervals)	1.53	0.05	1.00-2.33
1:1 (7 days before drug prescription)*	1.48	0.15	0.87-2.51
1:1 (1 month before drug prescription)	1.29	0.35	0.76-2.20
1:1 (2 months before drug prescription)	1.82	0.04	1.01-3.30
1:1 (3 months before drug prescription)	1.35	0.28	0.79-2.31
1:1 (4 months before drug prescription)	1.57	0.11	0.91-2.72

**7 days before closest date of prescription to hospital admission crash date*

Only women who were taking opiods analgesics were at a significant increase risk for a hospitalisation crash (OR=1.76; 95%CI 1.05-2.95; p=0.03) (Table 4.10).

Tabel 4.10: Risk of hospitalisation crash and opiods analgesics use, using multiple control intervals by gender and chronic condition, 2002-2008

Opioid analgesics	Odds ratio	*p*(0.05)	95%CI
Sex			
Male	1.17	0.66	0.57-2.40
Female	1.76	0.03	1.05-2.95
Presence of chronic condition			
No	1.38	0.20	0.84-2.26
Yes	2.05	0.09	0.90-4.68

5 DISCUSSION

The role of alcohol in traffic crashes has been firmly established but for drugs other than alcohol, particularly prescribed medications, there is limited current, evidence-based information. Past research has found that psychoactive medications prescribed to older drivers may impact on their driving performance and crash involvement (Oxley et al. 2004). Furthermore, polypharmacy (using several drugs at the same time) is more common among older people compared to younger age groups, and within the older driver group the use of such medications has been shown to increase with advancing age (Johansson et al. 1997; Oxley et al. 2004). However, results from epidemiological and experimental studies provide conflicting evidence regarding crash risk and the use of psychoactive medications among drivers. Also very few epidemiological studies have focused on or examined older drivers separately.

Opioid analgesics, benzodiazepines, anti-depressants and antiepileptics were the psychoactive medications that were predominantly prescribed to older drivers in this study. These results are similar to an Australian study of 3,398 fatally injured drivers in three states, which found that opioids (4.9%) and benzodiazepines (4.1%) were more frequently detected than other psychoactive drugs (2.7%) (Drummer et al. 2003). DeGier (1999) recently reviewed studies conducted in Europe and concluded that benzodiazepines were the most frequently detected drug other than alcohol in drivers of all ages. Interestingly, there are few studies which found that opioid analgesics were a common drug prescribed among drivers involved in a crash (Barbone et al. 1998; McGwin et al. 2000).

The overall results of this study confirm the findings of previous studies that several classes of psychoactive medications that act on the central nervous system can affect motor vehicle crash risk in older drivers (Drummer et al. 2003; Walsch, De Gier et al. 2004). A significant increase in the risk of crashing for drivers aged 60 and older was found for those taking antiepileptics medication ($p<0.01$), benzodiazepines ($p<0.01$), anti-depressants ($p=0.044$) and a marginal association was found for opioid analgesics ($p=0.05$). While it is difficult to specifically establish if crash risk was increased due to psychoactive medication usage or the underlying health issue for which the medication was prescribed the strength of the association particularly for benzodiazepine usage was high. Excess risk of greater than 5.0 are rare in epidemiological studies and may be considered a strong association. The results of this

study are also plausible as the usage of medications particularly benzodiazepines and antidepressants may make for less skillful drivers by increasing reaction time in dealing with the unexpected while driving.

The broad benzodiazepine group of medications has been frequently found to be associated with elevated crash risk in previous studies (Hemmelgarn et al. 1997; Leveille et al. 1994; Longo et al 2000b; Neutel et al. 1998; Ray et al. 1992). In this study, older drivers exposed to benzodiazepines were five-times more likely to crash (95%CI 2.8-10.2). According to Vinson et al., (1995) this is similar to the risk associated with driving with a blood alcohol level at the legal limit. The results are also similar to the findings of an American study (McGwin et al. 2000) which reported a similarly increased risk of 5.2 for benzodiazepine use for at-fault crashes in drivers aged 65 and over. Our study also found that both older male drivers, female drivers and those reporting a chronic condition had a significantly increased risk of crashing when exposed to benzodiazepines. These results are similar to the findings of a Canadian cohort study (Neutel 1998). However, our study did not differentiate between hypnotic and sedative anxiolytic benzodiazepines. It is probable that different risks may be associated within these groupings.

The findings of this study also support previous research which found that older drivers were almost twice as likely to be involved in a crash while taking antidepressants (Leveille et al. 1994; Bramness et al 2008). It has been suggested that patients may develop a tolerance to the sedating effects of the anti-depressant drugs over time (Ramaeckers, Muntjewerf and O'Hanlon 1995), and that treatment may cure the affective symptoms which can impair driving ability thus reducing the crash risk in medication users (Brunnauer, Laux and Geiger 2006). Also the newer non-sedating or non-tricyclic anti-depressants including selective serontonin reuptake inhibitors are thought to produce less side effects which may explain the lower risk of crashing for this group. Future research should look at these medications separately to provide a more accurate estimation of crash risk. Our study also found that males and those who reported a chronic condition were at an increased risk of crashing. Wingen et al. (2006) reported an increase in crash risk for older drivers with a chronic condition.

There are inconclusive results regarding crash risk for opioid analgesics on older drivers. Two epidemiologic studies reported that older drivers using opioid analgesics have significantly elevated crash risks (Engeland et al. 2007; Leveille 1994), while other epidemiological studies found no evidence to support the hypothesis that testing positive for opioid analgesic medication significantly increased crash risk for older drivers (Dubois et al. 2010; Ray et al 1992). Despite opioid analgesics representing the psychoactive medication most frequently dispensed among older hospitalised drivers involved in a crash, only a marginal association with crash involvement was found ($p=0.05$) in this study. This may be due to the fact that individuals may have been on long term opioid analgesic therapy and is supported by research that did not find any driving impairments in simulator, off-road or on-road driving assessments on individuals on stable long-term medication therapy (Vester & Mets, 2009). However, the majority of these studies did not include older drivers and further research is warranted. Our study also found that women reported a significant increased risk for crash involvement.

There is limited research into the impact of anti-epileptics usage and crash risk and the results of this population-based study found a significant increased risk of crashing. However, these results should be intepretated with caution due to the small sample size and wide confidence intervals.

The Western Australian record linkage methodology is powerful in that it makes available comprehensive information on a total population. The extent of the information allows an overview of the health experience of the population of interest under study. It has the advantage of detecting small differences due to its increased power because of the inclusion of a large number of cases and the provision of reliable and valid information. The use of the linked databases also possess advantages in terms of minimising loss to follow up and decreasing various forms of information bias. Furthermore, the study also possesses strong external validity. A recent study by Clark et al. (2010) found Western Australia to be representative of the broader Australian population in terms of key socio-demographic and health economic indicators, thus making conclusions drawn from this study to be generalisable to the rest of Australia. The use of high quality, objective data was also a strength of the study as it is considered to be more objective and accurate than those obtained via participant self-report measures (Holland et al. 2003; McGwin et al. 2000).

The use of a case-crossover study is particulary attractive for pharmacoepidemiology studies as it can address a number of limitations of other research designs. First, it overcame many of the difficulties of selecting an appropriate control group. Possible counfounding effects from differences between older drivers were eliminated and the focus of the analysis was on the transient use of psychoactive medications. Five control intervals were utilised which increased study power and improved the precision of the parameter estimates (Maclure & Mittleman 1999; Delaney & Suissa, 2008). However, a case-crossover design does not account for time-varying confounders such as 'over the counter' drugs unless they are known or measured which was not possible in the administrative databases used in this study. Also, the assumption of transient exposure inherent to the case-crossover study may not be met when medications are prescribed long term. This may actually underestimate risk as exposure periods of the medication would be the same at the time of the crash as during control periods. Long term medication use also increases with age and the risk profile between long and short term users may be quite different. According to Delaney & Suissa (2008) this can be addressed with the use of longer control intervals or lag periods between control intervals. Misclassification of exposure can also occur when the interval is either too long or too short. However, the use of hazard (case) and control intervals specific for each medication in this study which was based on the DDD, strength and quantity of the medication prescribed is unique to this study and thus minimises these biases. It is well known that factors such as the strength and quantity of medication are very important when determining risks associated with the use of psychoactive medication (Vermeeren, 2004). It must be stated however, that the fact that the medications were dispensed does not guarantee consumption by the individual at therapeutic levels and within the specified time frame.

Other limitations of this study was the presence/absence of co-morbidities was based on hospital records thus representing the more serious forms of chronic conditions. Also the study was limited to hospitalised crashes again, representing the more serious level of crash severity.

Lastly, as advocated by McEvoy et al. (2005); Maclure & Mitteman (2000) and Redelmeier & Tibshirani (1999) the positioning of the control windows should be targeted to the driving times of the individual. Unfortunately, it was not possible to ascertain if the individual was driving during the control intervals. In addition, it was assumed that all older drivers had the

same driving patterns in both the exposed and unexposed periods. Since an individual could not be involved in a crash if they did not drive the results of this study may underestimate the risks of driving associated with the use of psychoactive medications. Additionally, the data do not indicate whether the driver was at fault in the crash; it may be that the crash was caused by someone else. Drivers are also vulnerable to other distractions that could offset the potental risk due to medication usage. Finally, small numbers of several medication categories of interest precluded analysis for these medications. However, that should not detract from the value of the study as hospital admissions due to crash involvement is an important public health problem as these crashes can have a significant impact on an individual's quality of life and associated health care costs. Despite these limitations the results of this study contribute to a better understanding of the multiple factors influencing this ongoing public health problem.

6 CONCLUSION AND RECOMMENDATIONS

Since the number of older drivers is expected to increase significantly in the near future, issues related to safety for this group while ensuring their mobility needs are met is paramount. Limitations of current studies and areas for further considerations have been identified and recommendations made. The findings of this study will provide road injury researchers, licensing authorities, medical practitioners and other stakeholders with comprehensive, in-depth information on road crash risk for older drivers taking psychoactive medications which act on the central nervous system. Such information is essential for future research direction and essential to the development of evidence-based policy development.

Recommendations include:

- The results of this study be made available to clinicians and licensing authorities. Before prescribing medications, clinicians should determine whether and how often individual patients' activities require optimal alertness, for example, when driving a car. Clear directions and warnings should be given to patients rather than clinicians relying on package warnings to alert patients about drug effects on driving performance.

- State and Federal governments should endeavour to identify new, more innovative approaches to dealing with drug-impaired driving. Evidence-based measures to reduce the risks to older drivers should continue to be developed and re-evaluated while still recognising their mobility needs and avoiding age discrimination issues.

- Education campaigns should be developed and targeted at older drivers so that they become more aware of the possible impairment on cognitive function due to the usage of psycoactive medications as they continue to drive on Australian roads.

- Standardised methodologies should be applied in repeated studies. There is a clear need for access to more comprehensive data to establish a definitve link between medication usage and crash risk for older drivers. Research to determine short and long term use of psychoactive medications on crash risk should continue. Emphasis should also be placed on newly emerging drugs with the potential for impairment.

- National and international collaboration on future studies should be encouraged. There is a need however, for international scientific guidelines, procedures and methods of comparison for the conduct of drug impairment research. Collaboration between Australian States' and other countries' impaired-driving legislation could give valuable ideas as to which type of legislative measures would be most effective.

- Information on the type and amount of psychoactive medications found in deceased or injured persons obtained by police, coronial services and public hospitals should be collected to provide more objective information to road safety researchers.

- There is a need for large, pharmaco-epidemiological studies, such as data linkage studies, to replicate the results of this study for all drivers as well as the older driver age group.

7 REFERENCES

Australian Bureau of Statistics. 1999. *Older people: a social report*, cat. no. 4109.0, ABS, Canberra.

Australian Bureau of Statistics. 2006. *National Health Survey 2004-05: summary of results*, cat. no. 4364.0, ABS, Canberra.

Australian Bureau of Statistics. 2008. *Population by Age and Sex, Australian States and Territories, Jun 2008, TABLE 5. Time Series Spreadsheets, Estimated Resident Population By Single Year Of Age, Western Australia*, cat. no. 3201.0, ABS, Canberra.

Australian Bureau of Statistics. 2009. *Deaths, Australia, 2008*, cat. no. 3302.0, ABS, Canberra.

Australian Bureau of Statistics. 2009. *National Health Survey: summary of results 2007-2008*, Commonwealth of Australia, Canberra.

Australian Institute of Health and Welfare. 2001. *Residential Aged Care in Australia 1999-00: a statistical overview*, AIHW cat. no. AGE 19, AIHW, Canberra.

Australian Institute of Health and Welfare. 2006. *Australia's health 2006*, AIHW, Canberra

Bain, K. T. 2006. Management of chronic insomnia in elderly persons. *Am J Geriatr Pharmacother* 4 (2): 168-92.

Barbone, F., McMahon, A. D., Davey, P. G., Morris, A. D., Reid, I. C., McDevitt, D. G. and MacDonald, T. M. 1998. Association of road-traffic accidents with benzodiazepine use. *Lancet* 352 1331-1336.

Bocca, M. L., Le Doze, F., Etard, O., Pottier, M., L'Hoste, J. and Denise, P. 1999. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. *Psychopharmacology (Berl)* 143 (4): 373-9.

Borkenstein, R., Crowther, R., Shumante, R., Ziel, W. and Zylman, R. 1974. The role of the drinking driver in traffic accidents (the Grand Rapids Study). *Blutalcohol* 11 (Suppl. 1): 7-13.

Bramness, J. G., Skurtveit, S., Neutel, C. I., Morland, J. and Engeland, A. 2008. Minor increase in risk of road traffic accidents after prescriptions of anti-depressants: a study of population registry data in Norway. *J Clin Psychiatry* 69 (7): 1099-103.

Braver, E. R. and Trempel, R. E. 2004. Are older drivers actually at higher risk of involvement in collisions resulting in deaths or non-fatal injuries among their passengers and other road users? *Inj Prev* 10 (1): 27-32.

Britt, H., Miller, G. C., Knox, S., Charles, J., Pan, Y., Henderson, J., Bayram, C., Valenti, L., Ng, A. and O'Halloran, J. 2005, *General practice activity in Australia 2004-05*, AIHW cat. no. GEP 18, AIHW, Canberra.

Brunnauer, A., Laux, G., Geiger, E. and Moller, H. J. 2004. The impact of Anti-psychotics on psychomotor performance with regards to car driving skills. *J Clin Psychopharm* 24 (2): 155-60.

Brunnauer, A., Laux, G. and Geiger E. et al. 2006. Anti-depressants and driving ability: results from a clinical study. *J Clin Psychiatry* 67:1776-1781.

Brunnauer, A., Laux, G. and Zwick, S. 2009. Driving simulator performance and psychomotor functions of schizophrenic patients treated with Anti-psychotics. *Eur Arch Psychiatry Clin Neurosci* 259 (8): 483-9.

Byas-Smith, M. G., Chapman, S. L., Reed, B. and Cotsonis, G. 2005. The effect of opioids on driving and psychomotor performance in patients with chronic pain. *Clin J Pain* 21 (4): 345-52.

Chahine, L. M., Acar, D. and Chemali, Z. 2010. The elderly safety imperative and Anti-psychotic usage. *Harv Rev Psychiatry* 18 (3): 158-72.

Clark A., Preen D. B., DeGier, De Las Cuevas, C. and Sanz, E. J. 2008. Fitness to drive of psychiatric patients. *Prim Care Companion J Clin Psychiatry* 10 (5): 384-90.

Clark, A., Preen D. B., Ng, J. Q., Semmens, J. B. and Holman C. D. J. 2010. Is Western Australia representative of other Austrlalian States and Territories in terms of key socio-demographic and health economic indicators?. *Aus Health Rev* 34: 210-215.

De Gier J. J. 1999. Review of investigations of prevalence of illicit drugs in road traffic in different European countries. In: Group P (ed.). Road traffic and drugs; 1999, 13-60. Council of Europe, Strasbourg.

Delaney, J. A. C. and Suissa S. 2009. The case-crossover study design in pharmacoepidemiology. *Stat Methods Med Res* 18(1): 53-65.

Dubois, S., Bedard, M. and Weaver, B. 2008. The impact of benzodiazepines on safe driving. *Traffic Inj Prev* 9 (5): 404-13.

Dubois, S., Bedard, M. and Weaver, B. 2010. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. *Accid Anal Prev* 42 (1): 30-7.

Drummer, O., J. Gerostamoulos, H. Batziris, M. Chu, J. R. M. Caplehorn, M. Robertson, and P. Swann. 2003. The incidence of drugs in drivers killed in Australian road traffic crashes. *Forensic Sci Int* 134 (2-3): 154-162.

Dunbar, J. A., Ogston, S. A., Ritchie, A., Devgun, M. S., Hagart, J. and Martin, B. T. 1985. Are problem drinkers dangerous drivers? An investigation of arrest for drinking and driving, serum glutamyltranspeptidase activities, blood alcohol concentrations, and road traffic accidents: the Tayside Safe Driving project. *Brit Med J Clin Res Ed* 290 827-830.

Eberhard, J. 2008. Older drivers' "high per-mile crash involvement": the implications for licensing authorities. *Traffic Inj Prev* 9 (4): 284-90.

Engeland, A., Skurtveit, S. and Morland, J. 2007. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Ann Epidemiol* 17 (8): 597-602.

Fishbain, D. A., Cutler, R. B., Rosomoff, H. L. and Rosomoff, R. S. 2003. Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. *J Pain Symptom Manage* 25 (6): 559-77.

Gibson, J. E., Hubbard, R. B., Smith, C. J., Tata, L. J., Britton, J. R. and Fogarty, A. W. 2009. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol* 169 (6): 761-8.

Glass, J., Lanctot, K. L., Herrmann, N., Sproule, B. A. and Busto, U. E. 2005. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 331 (7526): 1169.

Goldney, R. and Bain, M. 2006. Prevalence of psychotropic use in a South Australian population. *Australas Psychiatry* 14 (4): 379-83.

Gustavsen, I., Bramness, J. G., Skurtveit, S., Engeland, A., Neutel, I. and Morland, J. 2008. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med* 9 (8): 818-22.

Hemmelgarn, B., Suissa, S., Huang, A., Boivin, J. F. and Pinard, G. 1997. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 278 (1): 27-31.

Hendrie, D. 2005, The cost of injury in Western Australia during 2003: an overview of total and health system costs, Western Australian Government, Perth, Western Australia.

Hill, J. L. and Zacny, J. P. 2000. Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. *Psychopharmacology (Berl)* 152 (1): 31-9.

Holland, C. A., Handley, S. and Fleetam, C. 2003, *Older drivers, illness and medication*, Road Safety Research Report No. 39, Department for Transport, London.

Hollingworth, S. A., Siskind, D. J., Nissen, L. M., Robinson, M. and Hall, W. D. 2010. Patterns of Anti-psychotic medication use in Australia 2002-2007. *Aust N Z J Psychiatry* 44 (4): 372-7.

Holman, C. D., Bass, A. J., Rouse, I. L. and Hobbs, M. S. 1999. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health* 23 (5): 453-9.

Iwamoto, K., Takahashi, M., Nakamura, Y., Kawamura, Y., Ishihara, R., Uchiyama, Y., Ebe, K., Noda, A., Noda, Y., Yoshida, K., Iidaka, T. and Ozaki, N. 2008. The effects of acute treatment with paroxetine, amitriptyline, and placebo on driving performance and cognitive function in healthy Japanese subjects: a double-blind crossover trial. *Hum Psychopharmacol* 23 (5): 399-407.

Johansson, K., Bronge, L., Lunberg, C., Person, A., Seidman, M. and Viitanen, M. 1996. Can a physician recognise an older driver with increased crash risk potential? *American Geriatrics Society* 44 1198-1204.

Kagerer, S., Winter, C., Moller, H. J. and Soyka, M. 2003. Effects of haloperidol and atypical neuroleptics on psychomotor performance and driving ability in schizophrenic patients. Results from an experimental study. *Neuropsychobiology* 47 (4): 212-8.

Langford, J., Koppel, S., Andrea, D. and Fildes, B. 2006. Determining older driver crash responsibility from police and insurance data. *Traffic Inj Prev* 7 (4): 343-51.

Legge, M., Gavin, A. and Cercarelli, L. R. 2004, *Reported Road Crashes in Western Australia 2001*, Road Safety Council of Western Australia, Perth, Western Australia.

Leufkens, T. R. and Vermeeren, A. 2009. Highway driving in the elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg, and placebo. *J Clin Psychopharmacol* 29 (5): 432-8.

Leufkens, T. R., Vermeeren, A., Smink, B. E., van Ruitenbeek, P. and Ramaekers, J. G. 2007. Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. *Psychopharmacology (Berl)* 191 (4): 951-9.

Leveille, S. G., Buchner, D. M., Koepsell, T. D., McCloskey, L. W., Wolf, M. E. and Wagner, E. H. 1994. Psychoactive medications and injurious motor vehicle collisions involving older drivers. *Epidemiology* 5 (6): 591-598.

Li, G., Braver, E. R. and Chen, L. H. 2003. Fragility versus excessive crash involvement as determinants of high death rates per vehicle-mile of travel among older drivers. *Accid Anal Prev* 35 (2): 227-35.

Longo, M. C., C. E. Hunter, R. J. Lokan, J. M. White, and M. A. White. 2000a. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part I: the prevalence of drug use in drivers, and characteristics of the drug-positive group. *Acc Anal Prev* 32 (5): 613-622.

Longo, M. C., C. E. Hunter, R. J. Lokan, J. M. White, and M. A. White. 2000b. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part II: The relationship between drug prevalence and drug concentration, and driver culpability. *Acc Anal Prev* 32 (5): 623-632.

Lotfipour, S. and Vaca, F. 2007. Commentary: Polypharmacy and older drivers: beyond the doors of the emergency department (ED) for patient safety. *Ann Emerg Med* 49 (4): 535-7.

Lyman, S., Ferguson, S. A., Braver, E. R. and Williams, A. F. 2002. Older driver involvements in police reported crashes and fatal crashes: trends and projections. *Inj Prev* 8 (2): 116-20.

Johansson, K., G. Bryding, M. L. Dahl, P. Holmgren, and M. Viitanen. 1997. Traffic dangerous drugs are often found in fatally injured older male drivers. *J Am Geriatr Soc* 45 (8): 1029-1031.

Maclure,M. and Mittleman, M. A. Case-Crossover designs compared with dynamic follow-up designs. *Epidemiology* (19) 2: 176-178.

Maes, V., Charlier, C., Grenez, O. and Verstraete, A. 1999, *Drugs and medicines that are suspected to have a detrimental impact on road user performance*, ROSITA Project, European Commission.

McEvoy, S.P., Stevenson, M.R. and Woodward, M. 2007. The prevalence of, and factors associated with, serious crashes involving a distracting activity. *Acc Anal Prev* 39 (3): 475-482.

McGwin, G., Sims, R. V., Vonne Pulley, L. and Roseman, J. M. 2000. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study. *Am J Epidemiol* 152 (5): 424-431.

Medicare Australia 2009, *Medicare Australia Annual Report 2008-2009*, Commonwealth of Australia, Canberra.

Metz, D. H. 2000. Mobility of older people and their quality of life. *Transp Policy* 7 (2): 149-152.

Milligan, R. A. K. 2005, Stay On Your Feet WA The 2004 falls prevention risk factor survey Perth Western Australia, Western Australian Government, Perth.

Moore, A. R. and O'Keeffe, S. T. 1999. Drug-induced cognitive impairment in the elderly. *Drug Aging* 15 15-28.

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

Neutel, I. 1998. Benzodiazepine-related traffic accidents in young and elderly drivers. *Hum Psychopharmacology* 13 (S2): S115 - S123.

Nishtala, P. S., Fois, R. A., McLachlan, A. J., Bell, J. S., Kelly, P. J. and Chen, T. F. 2009. Anticholinergic activity of commonly prescribed medications and neuropsychiatric adverse events in older people. *J Clin Pharmacol* 49 (10): 1176-84.

Orriols, L., Salmi, L. R., Philip, P., Moore, N., Delorme, B., Castot, A. and Lagarde, E. 2009. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf* 18 (8): 647-58.

Oxley, J., B. Corben, B. Fildes, M. O'Hare, and T. Rothengatter. 2004. *Older vulnerable road users - Measures to reduce crash and injury risk*. Melbourne: Monash University Accident Research Centre.10/3/10).

Oxley, J. and Whelan, M. 2008. It cannot be all about safety: the benefits of prolonged mobility. *Traffic Inj Prev* 9 (4): 367-78.

Ramaeckers, J. G., Muntjewerf, N. D., and O'Hanlon, J. F. 1995. A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 39:397-404.

Ramaekers, J. G. 2003. Anti-depressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiatry* 64 (1): 20-9.

Rapoport, M. J., Lanctot, K. L., Streiner, D. L., Bedard, M., Vingilis, E., Murray, B., Schaffer, A., Shulman, K. I. and Herrmann, N. 2009. Benzodiazepine use and driving: a meta-analysis. *J Clin Psychiatry* 70 (5): 663-73.\

Ray, W. A., Fought, R. L. and Decker, M. D. 1992. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am J Epidemiol* 136 (7): 873-883.

Redelmeier, D. A. and Tibshirani, R. J. 1997. Association between Cellular-Telephone Calls and Motor Vehicle Collisions. *N Engl J Med* 336: 453-458.

Ross, H. L. 1993. Prevalence of alcohol-impaired driving: An international comparison. *Acc Anal Prev* 25 777-779.

Sansone, R. A. and Sansone, L. A. 2009. Driving on anti-depressants: cruising for a crash? *Psychiatry (Edgmont)* 6 (9): 13-6.

Smeeth, L., Peter, T. D. and Cook, D. G. 2006. The use of primary care databases: case-control and case-only designs. *Fam Practice* 23(5):597-604.

Smink, B. E., Ruiter, B., Lusthof, K. J., Gier, J. J., Uges, D. R. A. and Egberts, A. C. G. 2005. Drug use and the severity of traffic accident. *Acc Anal Prev* 37 427-433.

Solomon, D. H., Avorn, J., Wang, P. S., Vaillant, G., Cabral, D., Mogun, H. and Sturmer, T. 2006. Prescription opioid use among older adults with arthritis or low back pain. *Arthritis Rheum* 55 (1): 35-41.

Sorock, G. S., Lombardi, D. A., Gabel, C. L., Smith, G. S. and Mittleman M. A. 2001. Case-crossover studies of occupational trauma: methodological caveats. *Inj Prev* 7: i38-i42.

Soyka, M., Winter, C., Kagerer, S., Brunnauer, M., Laux, G. and Moller, H. J. 2005. Effects of haloperidol and risperidone on psychomotor performance relevant to driving ability in schizophrenic patients compared to healthy controls. *J Psychiatr Res* 39 (1): 101-8.

Takahashi, M., Iwamoto, K., Kawamura, Y., Nakamura, Y., Ishihara, R., Uchiyama, Y., Ebe, K., Noda, A., Noda, Y., Yoshida, K., Iidaka, T. and Ozaki, N. 2010. The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers. *Hum Psychopharmacol* 25 (3): 260-7.

Tefft, B. C. 2008. Risks older drivers pose to themselves and to other road users. *J Safety Res* 39 (6): 577-82.

Trewin, D. 2003, *Socio-Economic Indexes for Areas: Australia 2001*, Australian Bureau of Statistics, Canberra.

Trollor, J. N., Anderson, T. M., Sachdev, P. S., Brodaty, H. and Andrews, G. 2007. Prevalence of mental disorders in the elderly: the Australian National Mental Health and Well-Being Survey. *Am J Geriatr Psychiatry* 15 (6): 455-66.

Vermeeren, A. 2004. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs* 18 (5): 297-328.

Verster, J. C., Volkerts, E. R. and Verbaten, M. N. 2002. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a randomized, placebo-controlled study. *Neuropsychopharmacol* 27 (2): 260-9.

Verster, J. C., Veldhuijzen, D. S. and Volkerts, E. R. 2004. Residual effects of sleep medication on driving ability. *Sleep Med Rev* 8 (4): 309-25.

Verster, J. C. and Mets, M. A. 2009. Psychoactive medication and traffic safety. *Int J Environ Res Public Health* 6 (3): 1041-54.

Vinson, D. C. Mabe, N., Leonard, L. L., Alexander, J. Becker, J. Boyer and Moll, J. 1995. Alcohol and injury. A case-crossover study. *Arch Fam Med* 4: 505–511.

Walsh, J. M., De Gier, J., Christophersen, S. and Verstraete A. 2004. Drugs and driving. *Traf Inj Prev* 5 (3): 241.

Watson, W. L. and Ozanne-Smith, J. 1997, *The cost of injury to Victoria*, Monash University Accident Research Centre, Melbourne.

Williams, A. F. and Carsten, O. 1989. Driver age and crash involvement. *Am J Public Health* 79 (3): 326-327.

Wingen, M., Ramaekers, J. G. and Schmitt, J. A. 2006. Driving impairment in depressed patients receiving long-term anti-depressant treatment. *Psychopharmacology (Berl)* 188 (1): 84-91.

Woolcott, J. C., Richardson, K. J., Wiens, M. O., Patel, B., Marin, J., Khan, K. M. and Marra, C. A. 2009. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 169 (21): 1952-60.

World Health Organisation 1975, International Classification of Diseases, Ninth Revision, WHO, Geneva.

World Health Organisation 1992, International Classification of Diseases and Related Health Problems, Tenth Revision, WHO, Geneva.

Wylie, K. R., Thompson, D. J. and Wildgust, H. J. 1993. Effects of depot neuroleptics on driving performance in chronic schizophrenic patients. *J Neurol Neurosurg Psychiatry* 56 (8): 910-3.

Zacny, J. 1995. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *Exper Clin Psychopharma* 3 (4): 432-466.

Zhang, Y., Chow, V., Vitry, A. I., Ryan, P., Roughead, E. E., Caughey, G. E., Ramsay, E. N., Gilbert, A. L., Esterman, A. and Luszcz, M. A. 2010. Anti-depressant use and depressive symptomatology among older people from the Australian Longitudinal Study of Ageing. *Int Psychogeriatr* 22 (3): 437-44.

Appendix A: Medication codes

Medication name	PBS Code	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
Benzodiazepines									
Alprazolam	2132F	1 mg	1 mg	50	50.00	12-15 (hr)	48-60 (hr)	2	52.00
	2130D	1 mg	250 microgm	50	12.50	12-15 (hr)	48-60 (hr)	2	14.50
	8118G	1 mg	2 mg	50	100.00	12-15 (hr)	48-60 (hr)	2	102.00
Bromazepam	4150K	10 mg	3 mg	60	18.00	20 (hr)	80 (hr)	3	21.00
	4151L	10 mg	6 mg	60	36.00	20 (hr)	80 (hr)	3	39.00
Clonazepam	1807D	8 mg	1 mg	5	0.63	20-50 (hr)	80-200 (hr)	6	6.63
	1808E	8 mg	2.5 mg	2	0.63	20-50 (hr)	80-200 (hr)	6	6.63
	1806C	8 mg	2 mg	200	50.00	20-50 (hr)	80-200 (hr)	6	56.00
	1805B	8 mg	500 microgm	200	12.50	20-50 (hr)	80-200 (hr)	6	18.50
	5339B	8 mg	2.5 mg	2	0.63	20-50 (hr)	80-200 (hr)	6	6.63
	5338Y	8 mg	2 mg	100	25.00	20-50 (hr)	80-200 (hr)	6	31.00
	5337X	8 mg	500 microgm	100	6.25	20-50 (hr)	80-200 (hr)	6	12.25
	5342E	8 mg	2.5 mg	2	0.63	20-50 (hr)	80-200 (hr)	6	6.63
	5341D	8 mg	2 mg	100	25.00	20-50 (hr)	80-200 (hr)	6	31.00
	5340C	8 mg	500 microgm	100	6.25	20-50 (hr)	80-200 (hr)	6	12.25
Diazepam	2558P	10 mg	10 mg	5	5.00	>100 (hr)	>400 (hr)	17	22.00
	3161J	10 mg	2 mg	50	10.00	>100 (hr)	>400 (hr)	17	27.00
	3162K	10 mg	5 mg	50	25.00	>100 (hr)	>400 (hr)	17	42.00
	3458B	10 mg	10 mg	5	5.00	>100 (hr)	>400 (hr)	17	22.00
	5073B	10 mg	10 mg	5	5.00	>100 (hr)	>400 (hr)	17	22.00
	5071X	10 mg	2 mg	50	10.00	>100 (hr)	>400 (hr)	17	27.00
	5072Y	10 mg	5 mg	50	25.00	>100 (hr)	>400 (hr)	17	42.00
Flunitrazepam	4216X	1 mg	1 mg	30	30.00	>24 (hr)	>96 (hr)	4	34.00
Nitrazepam	2732T	5 mg	5 mg	50	50.00	>24 (hr)	>96 (hr)	4	54.00
	2723H	5 mg	5 mg	25	25.00	>24 (hr)	>96 (hr)	4	29.00
	5189D	5 mg	5 mg	25	25.00	>24 (hr)	>96 (hr)	4	29.00

Medication name	PBS Code	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
	5359C	5 mg	5 mg	50	50.00	>24 (hr)	>96 (hr)	4	54.00
	5360D	5 mg	5 mg	50	50.00	>24 (hr)	>96 (hr)	4	54.00
Oxazepam	3134Y	50 mg	15 mg	50	15.00	5-14 (hr)	20-56 (hr)	2	17.00
	3135B	50 mg	30 mg	50	30.00	5-14 (hr)	20-56 (hr)	2	32.00
	3132W	50 mg	15 mg	25	7.50	5-14 (hr)	20-56 (hr)	2	9.50
	3133X	50 mg	30 mg	25	15.00	5-14 (hr)	20-56 (hr)	2	17.00
	5192G	50 mg	15 mg	25	7.50	5-14 (hr)	20-56 (hr)	2	9.50
	5193H	50 mg	30 mg	25	15.00	5-14 (hr)	20-56 (hr)	2	17.00
	5371Q	50 mg	15 mg	50	15.00	5-14 (hr)	20-56 (hr)	2	17.00
	5372R	50 mg	30 mg	50	30.00	5-14 (hr)	20-56 (hr)	2	32.00
Temazepam	2088X	20 mg	10 mg	50	25.00	10-20 (hr)	40-80 (hr)	2	27.00
	2089Y	20 mg	10 mg	25	12.50	10-20 (hr)	40-80 (hr)	2	14.50
	5221T	20 mg	10 mg	25	12.50	10-20 (hr)	40-80 (hr)	2	14.50
	5375X	20 mg	10 mg	50	25.00	10-20 (hr)	40-80 (hr)	2	27.00
	5376Y	20 mg	10 mg	50	25.00	10-20 (hr)	40-80 (hr)	2	27.00
Anti-depressants									
Amitriptyline Hydrochloride	2417F	75 mg	10 mg	50	6.67	9-46 (hr)	36-184 (hr)	4	10.67
	2418G	75 mg	25 mg	50	16.67	9-46 (hr)	36-184 (hr)	4	20.67
	2429W	75 mg	50 mg	50	33.33	9-46 (hr)	36-184 (hr)	4	37.33
Dothiepin Hydrochloride	1357K	0.15 g	25 mg	50	8.33	52 (hr)	208 (hr)	9	17.33
	1358L	0.15 g	75 mg	30	15.00	52 (hr)	208 (hr)	9	24.00
Doxepin Hydrochloride	1011F	0.1 g	10 mg	50	5.00	11-23 (hr)	44-92 (hr)	3	8.00
	1012G	0.1 g	50 mg	50	25.00	11-23 (hr)	44-92 (hr)	3	28.00
	1013H	0.1 g	25 mg	50	12.50	11-23 (hr)	44-92 (hr)	3	15.50
Escitalopram Oxalate	8700X	10 mg	10 mg	28	28.00	27-32 (hr)	108-128 (hr)	4	32.00
	8701Y	10 mg	20 mg	28	56.00	27-32 (hr)	108-128 (hr)	4	60.00
Imipramine Hydrochloride	2420J	0.1 g	10 mg	50	5.00	6-28 (hr)	24-112 (hr)	3	8.00
	2421K	0.1 g	25 mg	50	12.50	6-28 (hr)	24-112 (hr)	3	15.50
Citalopram Hydrobromide	8220P	20 mg	20 mg	28	28.00	33 (hr)	132 (hr)	5	33.00
	8702B	20 mg	10 mg	28	14.00	33 (hr)	132 (hr)	5	19.00
Fluoxetine Hydrochloride	1434L	20 mg	20 mg	28	28.00	24-72 (hr)	96-288 (hr)	7	35.00
Fluvoxamine Maleate	8174F	0.1 g	0.1 g	30	30.00	15.6 (hr)	62.4 (hr)	2	32.00
Sertraline Hydrochloride	2236Q	50 mg	50 mg	30	30.00	26 (hr)	104 (hr)	4	34.00
	2237R	50 mg	0.1 g	30	60.00	26 (hr)	104 (hr)	4	64.00

Medication name	PBS Code	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
	2242B	50 mg	20 mg	30	12.00	26 (hr)	104 (hr)	4	16.00
Opioid Analgesics									
Codeine Phosphate	1214X	0.1 mg	30 mg	2	0.40	4.5 (hr)*		1	1.40
Codeine Phosphate w Paracetamol	8785J	0.15 mg	30 mg	60	12.00	4.5 (hr)*		1	13.00
	1215Y	0.15 mg	30 mg	20	4.00	4.5 (hr)*		1	5.00
Dextropropoxyphene Napsylate	4081T	0.2 mg	0.1 mg	50	25.00	3.6-6.5 (hr)	14.4-26 (hr)	1	26.00
Fentanyl	8337T	1.2 mg	2.5 mg	5	10.42	3-4 (hr)	12-16 (hr)	1	11.42
	8338W	1.2 mg	5 mg	5	20.83	3-4 (hr)	12-16 (hr)	1	21.83
	8339X	1.2 mg	7.5 mg	5	31.25	3-4 (hr)	12-16 (hr)	1	32.25
	8340Y	1.2 mg	10 mg	5	41.67	3-4 (hr)	12-16 (hr)	1	42.67
Hydromorphone Hydrochloride	8421F	20 mg	10 mg	5	2.50	2-4 (hr)	8-16 (hr)	1	3.50
	8420E	20 mg	2 mg	5	0.50	2-4 (hr)	8-16 (hr)	1	1.50
	8423H	20 mg	0.5 g	1	25.00	2-4 (hr)	8-16 (hr)	1	26.00
	8422G	20 mg	50 mg	5	12.50	2-4 (hr)	8-16 (hr)	1	13.50
	8424J	20 mg	1 mg	1	0.05	2-4 (hr)	8-16 (hr)	1	1.05
	8541M	20 mg	2 mg	20	2.00	2-4 (hr)	8-16 (hr)	1	3.00
	8542N	20 mg	4 mg	20	4.00	2-4 (hr)	8-16 (hr)	1	5.00
Morphine Hydrochloride	2123R	0.1 g	5 mg	1	0.05	2-3 (hr)	8-12 (hr)	1	1.05
	2124T	0.1 g	10 mg	1	0.10	2-3 (hr)	8-12 (hr)	1	1.10
Morphine Sulfate	1653B	0.1 g	10 mg	20	2.00	2-3 (hr)	8-12 (hr)	1	3.00
	1654C	0.1 g	30 mg	20	6.00	2-3 (hr)	8-12 (hr)	1	7.00
	1655D	0.1 g	60 mg	20	12.00	2-3 (hr)	8-12 (hr)	1	13.00
	1656E	0.1 g	0.1 g	20	20.00	2-3 (hr)	8-12 (hr)	1	21.00
	2839K	0.1 g	20 mg	20	4.00	2-3 (hr)	8-12 (hr)	1	5.00
	2840L	0.1 g	50 mg	20	10.00	2-3 (hr)	8-12 (hr)	1	11.00
	8349K	0.1 g	10 mg	20	2.00	2-3 (hr)	8-12 (hr)	1	3.00
	8035X	0.1 g	5 mg	20	1.00	2-3 (hr)	8-12 (hr)	1	2.00
Oxycodone Hydrochloride	2622B	75 mg	5 mg	20	1.33	4-6 (hr)	16-24 (hr)	1	2.33
	8358H	75 mg	10 mg	20	2.67	4-6 (hr)	16-24 (hr)	1	3.67
	8386J	75 mg	20 mg	20	5.33	4-6 (hr)	16-24 (hr)	1	6.33
	8387K	75 mg	40 mg	20	10.67	4-6 (hr)	16-24 (hr)	1	11.67
	8464L	75 mg	5 mg	20	1.33	4-6 (hr)	16-24 (hr)	10	11.33
	8681X	75 mg	5 mg	20	1.33	4-6 (hr)	16-24 (hr)	1	2.33
Pethidine Hydrochloride	1829G	0.4 mg	0.1 g	5	1.25	3-4 (hr)	12-16 (hr)	1	2.25

Medication name	PBS Code	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
	5200Q	0.4 mg	0.1 g	5	1.25	3-4 (hr)	12-16 (hr)	1	2.25
Tramadol Hydrochloride	8455B	0.3 g	50 mg	20	3.33	4.5 (hr)*		1	4.33
	8611F	0.3 g	50 mg	20	3.33	4.5 (hr)*		1	4.33
	8523N	0.3 g	0.1 g	20	6.67	4.5 (hr)*		1	7.67
	8524P	0.3 g	0.15 g	20	10.00	4.5 (hr)*		1	11.00
	8582Q	0.3 g	0.1 g	5	1.67	4.5 (hr)*		1	2.67
	8583R	0.3 g			0.00	4.5 (hr)*		1	1.00
Anti-epileptics									
Carbamazepine	2419H	1 g	0.2 g	200	40.00	5-25 (hr)	20-100 (hr)	3	43.00
	2422L	1 g	0.1 g	200	20.00	5-25 (hr)	20-100 (hr)	3	23.00
	2426Q	1 g	0.2 g	200	40.00	5-25 (hr)	20-100 (hr)	3	43.00
	2427R	1 g	0.1 g	1	0.10	5-25 (hr)	20-100 (hr)	3	3.10
	2431Y	1 g	0.4 g	200	80.00	5-25 (hr)	20-100 (hr)	3	83.00
	5041H	1 g	0.1 g	1	0.10	5-25 (hr)	20-100 (hr)	3	3.10
	5039F	1 g	0.2 g	200	40.00	5-25 (hr)	20-100 (hr)	3	43.00
	5040G	1 g	0.2 g	200	40.00	5-25 (hr)	20-100 (hr)	3	43.00
	5038E	1 g	0.2 g	200	40.00	5-25 (hr)	20-100 (hr)	3	43.00
	5037D	1 g	0.4 g	400	160.00	5-25 (hr)	20-100 (hr)	3	163.00
Ethosuximide	1413J	1.25 g	0.25 g	200	40.00	60 (hr)	240 (hr)	10	50.00
Gabapentin	1834M	1.8 g	0.3 g	100	16.67	5-9 (hr)	20-36 (hr)	2	18.67
	8505P	1.8 g	0.1 g	100	5.56	5-9 (hr)	20-36 (hr)	1	6.56
	8559L	1.8 g	0.6 g	100	33.33	5-9 (hr)	20-36 (hr)	2	35.33
Phenytoin	1249R	0.3 g	50 mg	200	33.33	22 (hr)	88 (hr)	3	36.33
	1874P	0.3 g	0.3 g	200	66.67	22 (hr)	88 (hr)	3	69.67
	1873N	0.3 g	30 mg	200	20.00	22 (hr)	88 (hr)	3	23.00
Phenytoin Sodium	1873N	0.3 g	30 mg	200	20.00	22 (hr)	88 (hr)	3	23.00
	1874P	0.3 g	0.1 g	200	66.67	22 (hr)	88 (hr)	3	69.67
Topiramate	8164Q	0.3 g	50 mg	60	10.00	12-24 (hr)	48-96 (hr)	3	13.00
Sodium valproate	2294R	1.5 g	0.1 g	200	13.33	10-16 (hr)	40-64 (hr)	2	15.33
	2293Q	1.5 g	0.2 g	2	0.27	10-16 (hr)	40-64 (hr)	2	2.27
	2295T	1.5 g	0.2 g	2	0.27	10-16 (hr)	40-64 (hr)	2	2.27
	2289L	1.5 g	0.2 g	200	26.67	10-16 (hr)	40-64 (hr)	2	28.67
	2290M	1.5 g	0.5 g	200	66.67	10-16 (hr)	40-64 (hr)	2	68.67
	2289L	1.5 g	0.2 g	200	26.67	10-16 (hr)	40-64 (hr)	2	28.67

Medication name	PBS Code	DDD	Strength	Quantity	Prescription Period	Half Life	4 x Half Life	Days	Hazard Period
	2290M	1.5 g	0.5 g	200	66.67	10-16 (hr)	40-64 (hr)	2	68.67
Lamotrigine	2848X	0.3 g	25 mg	56	4.67	24-29 (hr)	96-116 (hr)	4	8.67
	2849Y	0.3 g	50 mg	56	9.33	24-29 (hr)	96-116 (hr)	4	13.33
Vigabatrin	2667J	2 g	0.5 g	100	25.00	2 (hr)	8 (hr)	1	26.00

Appendix B: Summary of studies included in literature review

Author	Methodology	Study Population	Sample Size	Study Period	Medication	Summary of Findings	Risk Association	Country
Pharmaco-Epidemiological Studies								
Barbone et al. 1998	2 population based databases	410 306 residents of Tayside, UK	19386 cases	Aug 1992 – Jun 1995	BZDs Anti-depressants Tranquillisers	Case-crossover study of drivers involved in MVC to determine odds of MVC while drug exposed compared with odds of MVC while unexposed. Users of anxiolytic BZDs & zopiclone were at increased risk of MVC.	✓	UK
Bramness et al. 2008	3 Population-based registries	3.1 million 18-69 years	3.1 million 18-69 years	Apr 2004 - Sept 2005	Anti-depressants	Standardised incidence ratios calculated by comparing incidence of MVC during exposure to anti-depressants with the incidence during non-exposure time. Results showed slight increased risk of MVC after being prescribed anti-depressants.	✓	Norway
Engeland et al. 2007	3 Population-based registries	3.1 million 18-69 years	3.1 million 18-69 years	Apr 2004 - Sept 2005	Opioids BZDs	Crash incidence among prescription drug exposed and unexposed subjects compared by standard incidence ratio. Results showed an increased risk of MVC involvement for drivers prescribed opiates and BZDs.	✓	Norway
Gustavsen et al. 2008	3 Population-based registries	3.1 million 18-69 years	3.1 million 18-69 years	Jan 2004 - Sept 2006	Hypnotics: Zopiclone Zopidem Flunitrazepam Nitrazepam	Standard incidence ratios calculated by comparing incidence of MVC in exposed person-time to incidence of MVC in unexposed person-time. Results showed users of these hypnotics had clear increased risk of MVC.	✓	Norway
Hemmelgarn et al. 1997	2 population databases	224 734 drivers 67 - 84 yrs from Quebec	5579 cases 55790 controls	Jun 1990 – May 1993	BZDs	Nested case-control design to determine association of BZD exposure and MVC. Results show new exposure to BZD is associated with increased risk of MVC. However, no risk was shown for long term users.	✓×	Canada
Epidemiological Studies								
Dubois et al. 2008	Blood & urine samples MVC registries Hospital records	72026 drivers > 20yrs involved in	1550 cases 69826 controls	1993 - 2006	BZDs	Case-control study to examine impact of BZDs on crash responsibility in fatal MVC. Compared with drivers not taking BZDs, drivers taking intermediate or long half-life	✓	Canada

Author	Methodology	Study Population	Sample Size	Study Period	Medication	Summary of Findings	Risk Association	Country
		fatal MVC but with BAC = 0				BZDs demonstrated increased odds of an unsafe driving action. Drivers taking short half-life BZD did not demonstrate UDA.		
Dubois et al. 2010	1 population data base	72,026 drivers of passenger type vehicles 20+ years	72,026	1993 – 2006	Opioids	Case-control study based on data from the Fatality Analysis Reporting System to examine the impact of opioid analgesics on drivers. Results showed that age differences exist between detection of opioid analgesics and crash-related unsafe driving actions: Cases had one or more crash-related unsafe driving actions (UDA) compared to controls who had none. Female drivers aged 25-55 and male drivers aged 25-65 who tested positive for opioid analgesics had increased odds of engaging in UDA compared to drivers who tested negative. Testing positive for opioid analgesics for older drivers was not associated with greater risk of an UDA.	×✓	U.S.A. (all 50 states plus the District of Columbia and Puerto Rico)
Leveille et al. 1994	Records from health maintenance organisation Crash data	Older drivers enrolled in health maintenance organisation	234 cases 447 controls	1987 - 1988	Anti-depressants Opioid analgesics BZDs Antihistamines	Population based matched case-control study of older drivers involved in MVC to evaluate risk for injurious MVC related to psychoactive drug use. Found no evidence of dose-related response & little association with increased risk for use of BZDs or antihistamines. Increased risk was found with use of opioids and anti-depressants.	×✓	USA
McGwin et al. 2000	Crash database Telephone interviews	39687 drivers	Drivers 65+ years 447 cases 454 controls	Jan 1 – Dec 31 1996	NSAIDs ACE inhibitors Anticoagulants BZDs Insulin Beta blockers Diuretics	Population based case-control study to identify medical conditions and medications associated with at fault MVC. 3 classes of medications were positively associated with MVC: NSAIDs, ACE inhibitors and anticoagulants. BZDs showed elevated risk.	✓	USA
Neutel 1995	3 population health databases	78,000 adults receiving BZD hypnotics, 148,000 adults receiving BZD anxiolytics , 98,000 controls	324,000	1979-1986	BZD hypnotics, BZD anxiolitcs	Cohort study investigating the risk of hospitalisation for traffic-related accidents after a first prescription for BZD was filled showed that subjects taking both medications had higher ORs. Younger age groups (20-39 yrs) were found to be at highest risk.	✓	Canada

Author	Methodology	Study Population	Sample Size	Study Period	Medication	Summary of Findings	Risk Association	Country
		All subjects 20+ years						
Neutel 1998	Health database linking hospital records with prescription records	409081	225796 cases 97862 controls	1979 - 1986	BZDs	Cohort study to examine the differences in crash risk after BZD use in older adults (60+) compared with younger people. Results showed that significantly increased risk of MVC with new users of BZD and a lower risk with repeat users which may suggest a level of tolerance. No difference was found between older and younger drivers.	✓	Canada
Ray et al. 1992	Medical database, driver's license files, police reports	16,262 Medicaid enrolees aged 65-84 who were drivers	16,262	1984-1988	BZDs cyclic anti-depressants opioid analgesics antihistamines	Retrospective cohort study to investigate whether commonly used psychoactive drugs increase the risk of involvement in MVC for driver >65 years. Results showed significant risk of injurious crash involvement for current users of BZD & cyclic anti-depressants	✓	U.S.A.
Experimental Studies								
Bocca et al. 1999	Driving simulator On-road driving test Computerised psychomotor tests	16 healthy volunteers	16 healthy volunteers		BZDs: Zolpidem Zoplicone Flunitrazepam	Double-blind crossover study to investigate the residual effects of 3 BZDs. Testing was conducted at different times following drug intake. Results showed driver impairment for 2 drugs but not zolpidem.	✓×	France
Brunnauer et al. 2004	Computerised psychomotor tests	120 schizophrenic inpatients	120 schizophrenic inpatients		Anti-psychotics	Naturalistic non-randomised design investigated the effects of neuroleptic monotherapy on psychomotor functions related to car driving skills in schizophrenic patients. Patients treated with atypical neuroleptics or clozapine showed a better test performance on skills related to driving ability when compared with patients on typical neuroleptics.	✓	Germany
Brunnauer et al. 2009	Computerised psychomotor tests Driving simulator	80 schizophrenic inpatients	40 using atypical Anti-psychotics, 20 using partial atypical Anti-psychotic 20 haloperidol		Anti-psychotics	Naturalistic non-randomised study to investigate schizophrenic inpatients regarding psychomotor functions related to driving skills and simulated driving behaviour. Patients treated with atypical Anti-psychotics showed better test performance in psychomotor measures and driving simulator performance.	✓	Germany

Author	Methodology	Study Population	Sample Size	Study Period	Medication	Summary of Findings	Risk Association	Country
Byas-Smith et al. 2005	On-road driving Closed road driving Computerised psychomotor tests	215 chronic pain patients 50 Healthy volunteers	21 opioid-using patients 11 nonopioid-using patients 50 healthy volunteers		Analgesic opioids	Psychomotor skills and driving skills were tested in 3 groups: one group of healthy volunteers and 2 pain patient groups (opioid analgesic users and non-users). No significant differences in driving skills were found among the groups.	×	USA
Iwamoto et al. 2008	Driving simulator	17 healthy males	17 healthy males received acute doses of paroxetine, amitriptyline, and placebo		Anti-depressants: Paroxetine Amitriptyline	Randomized, double-blind, placebocontrolled, 3-way crossover study to assess the effects of anti-depressants on driving performance. Acute doses of amitriptyline significantly impaired driving performance. Paroxetine impaired neither driving performance nor cognitive function.	✓×	Japan
Kagerer et al. 2003	Computerised psychomotor tests	49 schizophrenic inpatients	29 used atypical neuroleptics, 20 used haloperidol		Anti-psychotics	Naturalistic, non-randomised study to evaluate the effects of atypical neuroleptics in comparison with conventional dopamine antagonist (haloperidol) on psychomotor skills. Haloperidol treated patients demonstrated remarkably reduced psychomotor performance compared with patients treated with atypical neuroleptics.	✓×	Germany
Leufkens et al. 2007	On-road driving test Computerised psychomotor tests	18 healthy volunteers	18 healthy volunteers		Anxiolytic BZD: Alprazolam – extended release Alprazolam – immediate release	Double-blind, placebo-controlled, three way crossover study to compare the effects of alprazolam extended release and alprazolam immediate release on driving ability. Both formulations severely impaired driving performance. Impairment with alprazolam extended release was about half that observed with alprazolam immediate release.	✓	Netherlands
Leufkens et al. 2009	On-road driving test	18 healthy elderly drivers	18 healthy elderly drivers		Hypnotic BZD: Temazepam Zopiclone	Double-blind, 3-way crossover study to evaluate the residual effects the morning after evening doses of temazepam and zopiclone on driving performance. Zopiclone moderately impaired driving but driving performance did not differ between Temazepam and placebo.	✓×	Netherlands

Author	Methodology	Study Population	Sample Size	Study Period	Medication	Summary of Findings	Risk Association	Country
Sokya et al. 2005	Computerised psychomotor test	40 schizophrenic patients, 19 healthy controls	20 patients used haloperidol, 20 patients used risperidone, 19 healthy controls		Anti-psychotics: Haloperidol Risperidone	Non-randomised clinical study to evaluate the effects of an atypical neuroleptic (risperidone) in comparison to a conventional dopamine antagonist neuroleptic (haloperidol) on psychomotor performance related to driving. There was remarkably reduced psychomotor performance in both groups of schizophrenic patients compared to healthy controls.	✓	Germany
Takahashi et al. 2010	Driving simulator	18 healthy males	18 healthy males		Anxiolytic BZD: Tandospirone Diazepam	Double-blinded, three-way crossover trial to assess the effects of two anxiolytics on driving performance. Acute doses of diazepam significantly impaired the harsh-braking performance as compared to acute doses of tandospirone.	✓×	Japan
Verster et al. 2002	On-road driving test Computerised psychomotor test	20 healthy volunteers	20 healthy volunteers		BZD: Alprazolam	Randomised, double-blind, placebo controlled crossover study to examine effects of alprazolam on driving ability. Results showed significant driver impairment.	✓	Netherlands