Cooper, Lisa and Meuleners, Lynn and Duke, Janine and Jancey, Jonine and Hildebrand, Janina. 2011. Psychotropic Medications and Crash Risk in Older Drivers: A Review of the Literature. Asia-Pacific Journal of Public Health. 23 (4): pp. 443-457.

Psychotropic medications and crash risk in older drivers – a review of the literature

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. The role of drugs other than alcohol, particularly medications, has not been well established and there is limited current evidence-based literature. By 2030, one out of four drivers will be aged 65 years, 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.[1] These statistics plus the increasing number of older drivers on the road has generated concern among road safety experts. While older drivers are involved in fewer crashes compared with other driver age groups, their crash risk is equivalent to that of young drivers when driving exposure is taken into account.[2-4] They are also more likely to be responsible for these crashes.

Additionally, the older population has a higher prevalence of medical conditions and thus, a greater prevalence of medication use.[5-6] Older drivers involved in a crash are more likely to be taking medications that can impair central nervous system functioning and impact on driving ability.[5] Furthermore, polypharmacy is more prevalent among the elderly than younger age groups and within the older driver group (65+ years), the use of such medications has been shown to increase with advancing age.[5] Therapeutic effects of these medicines such as loss of psychomotor coordination, balance disturbance and somnolence may have detrimental effects on driving performance.[7] Psychotropic medications include antidepressants, anxiolytic sedatives, benzodiazepines, some antihistamines, opioid analgesics, antiepileptics, antipsychotics and some medications for Parkinson's disease.[8-10] For the purpose of this review, only the commonly-researched medications of hypnotic and sedating benzodiazepines and antidepressants were examined. Past research has found that the use of psychotropic (or psychoactive) drugs may adversely affect the ability of the older driver to safely operate a motor vehicle.[10-13] However, many studies examining the relationship between these medicines and their impact on driver performance

and crash risk have often been limited in their findings due to different methodologies, small sample sizes and selection bias.

This comprehensive literature review examines Australian and international research, focussing on the association between sedating medications that act on the central nervous system and motor vehicle crash involving older drivers, 65 years and older. The identification of medications associated with an increased crash risk will provide clinicians and road safety stakeholders with the evidence base to address the important issue of safe driving for this group.

METHODS

A search of electronic databases (MEDLINE, PROQUEST and SCIENCEDIRECT) was conducted from March 2010 to April 2010. Reference lists of key articles were also viewed and searched for specifically. GOOGLE SCHOLAR was accessed via the internet for definitions and related articles. Key words searched included all possible versions of 'crash risk, 'road crashes' 'accidents' 'motor vehicle crash' 'road accidents' in combination with 'psychotropic medicines" (with such medications listed specifically including 'benzodiazepines', 'anxiolytics', 'antidepressants' and 'hypnotics'); and/or, 'older drivers', 'ageing population' and 'aged drivers'. Words and phrases were joined in order to explore appropriate available literature.

The inclusion criteria comprised a priority focus on older adults (65+years) who held a driving licence and were taking psychotropic medication, and studies that addressed at least one of the following research questions:

- What is the prevalence of psychotropic medications use amongst older drivers?
- What are the side effects of driving under the influence of psychotropic medications?
- What is the association between crash risk and psychotropic medications for older drivers?

Studies limited to involvement of illicit drugs and alcohol only; studies of injury risk other than road traffic crashes; non-English articles; and articles pre-dating 1979, were excluded.

RESULTS

A total of 1634 articles were screened; of these, 127 full-text articles were reviewed (Fig. 1). Six experimental studies and 16 epidemiological studies were reviewed in detail and their methodologies and main results are summarised in Tables 1 and 2. A total of 106 national and international articles were used in the literature review.

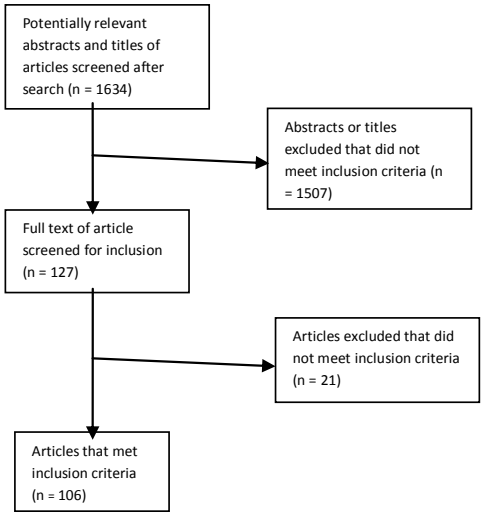

Figure 1. Flowchart of the process of article selection for inclusion in review

Prevalence of driving under the influence of Psychotropic Medications

Research on the prevalence of driving while under the influence of medications among the general population is limited, particularly in Australia. There is however, more research conducted on crash-involved drivers and drivers suspected of impaired driving.[14] Most of these study outcomes do not allow for comparison between countries due to different methodologies. However, Walsh et al.[15] estimates the prevalence of licit drugs affecting driver performance in European countries is between 5-10% of the general driving population, which is higher than the estimated illicit drug use (1-5%).[16]

Blood or urine samples of injured or killed drivers are used to determine the presence of drugs. De Gier[17] concluded that in Europe, benzodiazepines were the most frequently detected licit drugs other than alcohol. Studies of drivers stopped for suspicion of driving under the influence, reported benzodiazepines prevalence varied between 13-75%.[17] Similar findings were reported in Australia where approximately half the drivers tested positive for benzodiazepine use.[18] In a more recent 10-year Australian study of 3,398 fatally injured drivers in three states, Drummer and colleagues[8] reported the incidence of drugs other than alcohol and comprised opioids (4.9%), benzodiazepines (4.1%), and other psychotropic drugs (2.7%). They reported drivers with benzodiazepines at therapeutic concentrations and above, had a significant increase in driver culpability.[8, 16] Walsh and colleagues[15] confirm a lack of data on the prevalence of drug utilisation in the general driving population. They suggest, however, that the high prevalence of drug use found in collision-involved drivers supports the assumption that this is a serious road safety concern.

In an Australia-wide study, it was found to be as high as 10.6%. As many as 16.2% of the total sample population aged over 65 years (n=552) in the South Australian study (n=3015) were prescribed psychotropic medication.[19] This is consistent with results from a previous Sydney-based study on benzodiazepine use in the elderly which reported a prevalence of 16.6% using benzodiazepine on a long-term basis.[20] Such use is likely to increase with an ageing population.

Paradoxically, although elderly people living in the community have a lower prevalence of affective anxiety disorders than younger adults, they have a much higher use of psychotropic drugs.[20] This is possibly due to a higher prevalence of sleeping disorders and chronic physical illness among the elderly. Physical diseases and conditions reported to be associated with psychotropic drug use include cancer, heart disease, pulmonary disease, arthritis and musculo-skeletal pain.

Effects of Psychotropic Medications on Driving Performance

Benzodiazepines: Benzodiazepines possess sedative, hypnotic and anxiolytic actions and are the most frequently prescribed medication for the treatment of sleep and anxiety disorders.[7, 21] It is generally recommended in older adults, that benzodiazepines with a longer half-life be avoided due to residual sedative effects and an association with falls, motor vehicle crash and impaired memory.[22] Adverse effects of benzodiazepines on the central nervous system include drowsiness, confusion, dizziness, reduced motor coordination and impaired memory.[14, 21]

Antidepressants: Antidepressants are prescribed to treat affective disorders such as depression, panic disorders, phobias and obsessive-compulsive disorders.[7] Evidence suggests the sedating qualities of tricyclic antidepressants cause impairments in tasks related to driving skills for healthy individuals.[23-25] Certainly, the initial start up time or adjustment of prescription increases the risk of driver impairment while taking antidepressants.[25] This is also true for any rapid increase in dose or polydrug-use, particularly benzodiazepines.[25] The side effects of tricyclic compounds are more severe than the newer antidepressants which cause less impairment in tests of psychomotor function.[7, 23, 26] Side effects relating to driving impairment include drowsiness, blurred vision, dizziness, confusion and weakness. Adverse reactions may depend upon dosage and susceptibility to side effects may be related to age.[21]

Association of Psychotropic Medications and Crash Risk

Although it is difficult to measure the causal role of psychotropic drugs in motor vehicle crashes, their use increases the risk of crash involvement.[11, 27-28] Concentration, information processing, alertness, an ability to perceive hazards and identify risk-taking behaviour, decision-making and ongoing sensorimotor control are required at all times during the operation of a motor vehicle[29] and any impairment of driving often results in either traffic infringements or traffic crashes.

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.[30-31] However, the majority of these 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.

Experimental studies have shown adverse effects of many drugs on driving in controlled environments.[23, 32-36] It has been largely demonstrated that residual effects of benzodiazepine hypnotics impair memory, psychomotor performance and driving performance.[32, 35] Often a dose-dependent impairment of driving was demonstrated in these studies with higher risks during initial use compared to chronic use.[34, 37-38] Benzodiazepine anxiolytics were also found to be sedative and seriously deteriorated driving ability in two recent studies.[34-35]

Epidemiological studies, despite reporting mixed results have also indicated increased probability of crash involvement for drivers taking some psychoactive medications.[30, 39-40] Evidence is limited, however, for several reasons. Firstly, despite these medications being most commonly used by the older population, 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. Epidemiological data clearly indicate that hypnotic benzodiazepines have been detected in a significant percentage of drivers involved in road crashes.[37, 41-42] Vingilis and MacDonald[36] reported that benzodiazepine users are up to six times more likely to be involved in road crashes than non-users. Vermeeren[43] reported inconsistent findings of association with increased road crash risk in regards to hypnotics. This inconsistency related to the specific drug, dose administered and patient characteristics but agreed that hypnotics could increase

the risk of traffic crashes, whereas with anxiolytics, significantly increased risk in both the young and elderly drivers. This is supported by the findings of Ray et al.[44] that report increased risk of traffic crashes for elderly users of benzodiazepine anxiolytics. Conversely, no such association was found by Leveille et al.[45] Additionally, Hemmelgarn et al.[13], who made the distinction between long and short half-life benzodiazepines, reported an associated risk for elderly drivers who used long half-life benzodiazepines but not for benzodiazepines with a short half-life.

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.[46-47] Neutel[38] also reported an increased risk of injurious crashes for drivers aged 60 years and over, who used benzodiazepines in Canada. Interestingly, the risk was slightly lower for drivers aged over 60 years than those under.[48] 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.[49] 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.[49]

In contrast, an earlier case-control study in the USA reported no association between benzodiazepine use and injurious crash for older drivers.[45] 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.[39] 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.[50] 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.[50] 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.[50]

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.[39] 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.[39, 49] 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.

Walsh and colleagues'[15] research suggest that at high doses, almost all benzodiazepines will cause some impairment.[16, 51] Furthermore, an increased risk of crash occurs when taken above therapeutic doses or with alcohol.[16] Kelly et al.[14] reported findings from previous studies suggesting impairment may be limited to the early stages of benzodiazepine uptake,[16, 33, 41] supporting the theory that a tolerance level may negate the impairment affects of the drug. Some studies have found that impairing effects diminish over time, as patients develop tolerance. However, the majority of studies do find dose-related impairments in driving-related skills.[52]

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 ≥ 125mg daily increased the risk of involvement in a crash by six times.[47] 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).[45] 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).[53] However, this study only included drivers aged 18-69 years. In contrast, a case-crossover 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.[39]

The European Monitoring Centre for Drugs and Drug Addiction[51] reported an association with the use of tricyclic antidepressants and impaired driving performance. They found, however, no such impairment with new generation antidepressants.[16] Leville et al.[45] and Ray et al.[54] also reported this increased risk, particularly for older drivers (RR= 2.3).[16, 55] This was also supported by Bramness et al.[56] who found an increased risk for drivers who were taking antidepressants. He found a slightly higher risk for younger drivers.[55] In contrast to this, Barbone et al.[37] found no such relationship for drivers taking either selective serotonin reuptake inhibitors or tricyclic antidepressants. This could suggest the risk is specific to older drivers.[55] 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[53] and reduced driving performance,[57] several have reported that non-sedating anti-depressants do not impair driving or increase crash risk.[39, 58-59]

Psychotropic Medications, Crash Risk and the Older Driver

Scientific literature acknowledges that psychotropic medications can have a harmful effect on central nervous system responses, and thus, the psychomotor skills required for operating a vehicle.[5, 9, 11, 42] This is particularly true for older drivers who tend to experience adverse drug reactions more intensely.[5, 60] This is explained by reduced hepatic and renal function in the elderly along with a reduced ability to metabolise drugs efficiently.[60] Elderly drivers are more likely to have chronic medical conditions and more likely to be taking medications affecting driving performance than younger drivers.

The types of crash occurrence involving older drivers differ from those in younger age groups. The older driver is more likely to be involved in slow moving, right of way traffic crashes.[60] This suggests a difficulty with decision-making requiring perceptual and cognitive functions. Frailty is also associated with more adverse side effects[61] and may contribute to the older driver incurring more serious or fatal injuries when involved in road crashes[62]. With an ageing population, the number of drivers over the age of 65 years is certain to increase along with the increase in risk of serious or fatal motor vehicle crash. Historically, the elevated rate of motor vehicle crash involving older drivers has been attributed to the changes associated with ageing, such as visual impairment and delayed reaction time. However, recent literature has questioned this and suggested the intake of prescription and non-prescription psychotropic medicines may be an added causal factor.

DISCUSSION

While the current literature shows relatively limited knowledge of the prevalence of psychotropic drugs in road traffic compared to the knowledge regarding prevalence of alcohol in drivers, it is clear that driving under the influence of drugs is a worldwide problem. Research into the effects of prescription medication on drivers has not received the consideration it deserves. This is an emerging public health issue that has only in the past three decades been supported in some way by

research. Operating a vehicle while impaired by drugs, whether licit or illicit, is increasingly becoming a community concern. Attention needs to be focused on this issue so that evidence-based information can be used to provide guidelines and education for the community on the effects of drugs on driving.

It is evident from the literature that drugs are frequently detected in crash-involved drivers and that impaired driving is a significant cause of human trauma. However, results from laboratory, simulator and on-road tests indicate that the effect of medications on driver skills can vary between individuals depending on the interactions of age, gender, health condition and prescription use.[29] Medication effects will also be influenced by dosage, polypharmacy, tolerance levels and the time since intake.[14, 29] Understanding the degree of reduced driving capability caused by psychotropic medications presents a major challenge for road safety experts. The principal drugs of concern are those which can affect a person's ability to react to external stimuli, leading to impairment of driver skills.

It is apparent that high doses of psychotropic medications, polypharmacy and drugs used in combination with alcohol are all likely to produce a significant threat to road safety.[14] More knowledge about the traffic safety of therapeutic psychotropic medications is needed. The main concern seems to be with benzodiazepines and related sedative or hypnotic drugs, and to a lesser extent tricyclic antidepressants but this may be due to lack of research in these areas.[9]

Older drivers are more likely to sustain serious or fatal injury than younger drivers given the same crash conditions. While the safety of older drivers is important today, it will become even more important in the near future as the population ages. Public health initiatives to reduce the morbidity and mortality of older drivers should be vigorously pursued.

Limitations of Past Research

Although evidence indicates that several types of psychotropic medications have the potential to impair driving ability and increase the risk of crash involvement, a major limitation is that few have examined their effects specifically on older drivers. Despite the fact that the majority of the population using psychotropic medications are older,[63] most experimental studies have been conducted using healthy, young volunteers and few epidemiological studies have included or analysed older drivers separately.

A number of experimental studies have assessed the driving abilities of older drivers using psychotropic medications through laboratory tests, driving simulators or on-road driving assessments. While such studies suggest the potential impact of medications on driving ability, they do not take into account the impact of real life conditions that translate to actual crash involvement for older drivers.[55] Therefore, epidemiological studies provide the optimal study design to examine the association between medication use and older driver crash involvement.[64]

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.[37, 65] However, these studies have provided mixed results. Reasons for this may include small sample sizes, selection bias, and 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 and varying exposure to the medication. Inadequate assessment of medication compliance has also been identified as a significant limitation of pharmaco-epidemiological studies,[7] although this objective information is thought to provide far more accurate data than information obtained via participant self-report.[66-67] The most difficult confounding factor to control 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.[24, 43, 68] Case-cross over designs where each subject acts as their own control

represent an appropriate study design for future research in this area as they eliminate confounding due to fixed characteristics.[55]

Additionally, both epidemiological and experimental studies may not be able to accurately predict the effects of psychotropic drugs under "real" driving conditions. A non-exhaustive list of key experimental and epidemiological studies conducted since 1988 are summarised in Tables 1 and 2.

Recommendations

Based on this review, the following recommendations are made for future research:

- The impact of psychotropic medication use on driving performance and crash risk should continue to be investigated.
- National and international collaboration on future studies should be encouraged. This should be supported by the development of international scientific guidelines and procedures. Methodologies and core variables need to be standardised in repeated studies.
- Collaboration between Australian States' and other countries' impaired-driving legislation could give valuable insight into appropriate and potentially effective policy and legislative initiatives.
- Large-scale, whole-population, epidemiological studies, such as data linkage studies aimed at investigating the individual and combined role of psychotropic medications in the risk of road traffic crashes, particularly in the older driver age group. This pharmaco-epidemiological approach may be useful in identifying medications which pose a potential risk to traffic safety in populations with prescription and MVC databases.
- Education campaigns and community based interventions should be developed and targeted at older drivers so that they become more aware of the possible impairment of cognitive function due to medications and driving. Future research should include clarification of drug-induced driving impairment and risk perceptions related to impaired driving.

Conclusion

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. The literature supports the common sense approach that medication with strong sedative action taken in high doses has the highest potential for significant driver impairment. More research into chronic as well as acute use of psychotropic medication needs to be conducted on performance of driving related tasks. Emphasis should also be placed on newly emerging drugs with the potential for impairment. The findings of this review will provide road injury researchers and other stakeholders with comprehensive, in-depth information about Australian and international studies on road crash risk for older drivers taking medications which act on the central nervous system. Such information is fundamental for future research direction and essential to the development of evidence-based policy development.

(4576 words)

Table1.

SUMMARY OF KEY EXPERIMENTAL STUDIES

Formatted: Tab stops: 9.12 cm, Left

EXPERIMENTAL STUDIES

Author	*Study Design*	*Study Population*	*Sample Size*	*Study Period*	*Summary of Findings*	*Medication*	*P Value*	*Country*
Brunnauer et al. 2006	Computerised psychomotor tests	100 depressive in-patients	100	Jan 2004 – Mar 2005	Non-randomised, comparative clinical study to evaluate effects of antidepressants on psychomotor performance related to driving. Results showed significant impairment in more than 60% of patients and severe impairment in 16% who were regarded as unfit to drive.	Antidepressants: SSRIs NaSSAs TCAs SNRIs	$p<0.05$	Germany
Busto et al. 2000[3232323232323232323232323232323232323232323]	Double-blind crossover study Computerised psychomotor tests Blood samples		13 male volunteers		Double blind four way crossover study to compare pharmacokinetic & psychomotor performance on 3 BZDs. Results showed significant impairment for alprazolam and lorazepam but not bromazepam.	BZDs: Alprazolam Lorazepam bromazepam	$p<0.05$	Canada
Meskali et al. 2009	Double-blind crossover study Driving simulator		16 healthy drivers 55-65 yrs		Double-blind balanced crossover study to assess residual effects of common hypnotics & placebo on older drivers' performance. Results showed insignificant increase in collision rate however some results indicated risky driving behaviour.	Hypnotics: Zolpidem Zopiclone Flunitrazepam	$p<0.01$	France
Vanakoski et al. 2000	Double-blind crossover study	18 volunteers	9subjects 22-24 yrs		Double-blind, crossover, placebo controlled study to determine if alcohol and BZD use increases risk of night time driving.	Diazepam	$p<0.05$	Finland

	Driving simulator Computerised tests	9 subjects 55-77 yrs	Older drivers showed poor baseline results but were less sensitive to Diazepam. Psychomotor performance was unaffected by light conditions.			
Van Laar et al. 2001	Double-blind crossover study Computerised psychomotor test On-road driving	18 healthy volunteers	Double-blind, placebo controlled crossover study to investigate the subchronic effects of the drug on actual driving performance. Results showed impairment on lateral position control and sedation but had no effect on other parameters.	BZD anxiolytic: Lorazepam	$p<0.0001$	Netherlands
Verster et al. 2002	Randomised double-blind crossover study On-road driving test Computerised psychomotor test	20 healthy volunteers	Randomised, double-blind, placebo controlled crossover study to examine effects of alprazolam on driving ability. Results showed significant driver impairment	BZD: alprazolam	$p<0.0001$	Netherlands

Table 2.

SUMMARY OF KEY EPIDEMIOLOGICAL AND PHARMACO-EPIDEMIOLOGICAL STUDIES.

EPIDEMIOLOGICAL STUDIES								
Author	***Study Design & Source of Data***	***Study Population***	***Sample Size***	***Study Period***	***Summary of Findings***	***Medication***	***Statistical Results***	***Country***
Bramness et al. 2002	Case-control study NIFT Registry	90000 blood samples from drivers suspected DUID	11,577 818 case samples containing one BZD 10,759 controls containing only alcohol	1987-1998	Case-control study examining the relation between BZD concentrations and impairment in apprehended drivers found that impaired subjects had significantly higher blood levels of diazepam, oxazepam or flunitrazepam than those not impaired. Further, the blood concentration of BZDs was the only characteristic which was related to impairment.	BZDs: Diazepam oxazepam flunitrazepam	OR= 4.11[2.22-7.60]	Norway
Bramness et al. 2007	Cohort study NorPD NRAR NCPR	3.1 million 18-69 yrs	12865 involved in MVC	Apr 2004 - Sept 2005	Crash incidence among drug exposed and unexposed subjects compared by standard incidence ratio. Patients receiving carisoprodol were found to have increased risk of MVC involvement.	Carisoprodol Diazepam Salbutamol	SIR= 3.7 [2.9-4.8] SIR= 2.8 [2.2-3.6] SIR= 1.1 [0.6-1.8]	Norway
Bramness et al. 2008	Cohort study NorPD NRAR NCPR	3.1 million 18-69 yrs	3.1 million 18-69 yrs	Apr 2004 - Sept 2006	Standardised incidence ratios calculated by comparing incidence of MVC during exposure to antidepressants with the incidence during non-exposure time. Results showed slight increased risk of MVC after being prescribed antidepressants.	Antidepressants: Cyclic AD Non-sedating AD	SIR= 1.4 [1.2-1.6] SIR= 1.6 [1.5-1.7]	Norway

Drummer et al. 2004	Multi-centre case-control study VIFM Vic State Coroner's Office NSW State Coroner's Office Perth Coroner's Office WA Toxicology	3398 fatally injured drivers in VIC, NSW & WA	1694 cases 1704 controls	1990 - 1999	Multi-centre case-control study to assess effect of alcohol & drug use on culpability. With regards to culpability neither BZDs nor opiates showed association. Strongest link was with cannabis and amphetamines or combination of drugs. Older drivers & drivers <25yrs showed greatest culpability.	BZDs Opiates Other psychoactive medications	OR=1.27 [0.5-3.3] OR= 1.41 [0.7-2.9] OR= 3.78 [1.3-11]	Australia
Dubois et al. 2008	Case-control study FARS database NCSA database Blood & urine samples	72026 drivers 20+yrs involved in fatal MVC but with BAC = 0	1550 cases 69826 controls	1993 - 2006	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 BZDs demonstrated increased odds of an unsafe driving action. Drivers taking short half-life BZD did not demonstrate UDA.	BZDs: Short half-life Intermediate half-life Long half-life	 OR= 1.02 [0.73-1.42] OR= 1.53 [0.83-1.16] OR= 1.44 [1.25-1.66]	Canada
Engeland et al. 2007	Cohort study NorPD database NRAR database NCPR database	3.1 million 18-69 yrs	3.1 million 18-69 yrs	Apr 2004 - Sept 2005	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.	Opioids BZD tranquilisers BZD hypnotics NSAIDs	SIR= 2.0 [1.7-2.4] SIR= 2.9 [2.5-3.5] SIR= 3.3 [2.1-4.7] SIR= 1.5 [1.3-1.9]	Norway
Gustavsen et al. 2008	Cohort study NorPD database NRAR database NCPR database	3.1 million 18-69 yrs	3.1 million 18-69 yrs	Jan 2004 - Sept 2006	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.	Hypnotics: Zopiclone+ Zolpidem Nitrazepam Flunitrazepam	 SIR= 2.3 [2.0-2.7] SIR= 2.7 [1.8-3.9] SIR= 4.0 [2.4-6.4]	Norway

Hebert et al. 2007	Case-control & case-crossover study SAAQ	224 734 drivers 67 - 84 yrs	5579 cases 12911 controls	Jun 1990 – May 1993	Used both case-control & case-crossover approaches to compare results on same study population. The 2 designs produced different results. Case-control found increased risk of MVC for elderly users of BZD but case-crossover showed no association. Authors suggest case-crossover should be used for intermittent users rather than long term users.	BZDs	OR= 1.45 [1.12-1.88]	Canada
Hooper et al. 2010	Case-control study DoD MMR database CTS database MHSDMA database	Active duty military personnel	962 cases 2886 controls	Oct 2001 – Sept 2006	Case-control study design used to examine association between prescribed medications & fatal MVC in military population. Cases & controls were matched. Findings suggest association between antidepressant medication & fatal MVC.	Antidepressants Opioids BZDs	OR=3.19 [1.01-10.07]	USA
Longo et al. 2001	Cross-sectional study Blood samples from hospitalised patients	2500 injured drivers	2,500	Apr– Aug 1995 and Dec 1995 – Aug 1996	Cross-sectional study showed there was a significant linear relationship between BZD concentration and crash risk.	BZDs	2.7% drivers positive for BZD	Australia
McGwin et al. 2000	Case-control study Responsibility	39687 drivers	901 drivers 65+ yrs 447 cases 454 controls	Jan 1 – Dec 31 1996	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.	NSAIDs BZDs Antidepressants	OR= 1.7 [1.0-2.6] OR= 5.2 [0.9-30.0] OR= 0.3 [0.1-1.0]	USA
Movig et al. 2004	Case-control study Urine or blood samples Roadside interviews	350000 general population	110 cases MVC patients 816 controls Randomly	May 2000 – Aug 2001	Prospective observational case-control study to estimate the association between psychoactive drug use and MVC. Outcomes measures were OR & found increased risk for single use BZD, multiple drug use and drug-alcohol combinations.	BZDs Opiates	OR= 5.05 [1.82-14.04] OR= 2.35 [0.87-6.32]	Netherlands

	Hospital records		selected drivers					
Mura et al. 2003	Case-control study Blood & urine samples	Patients of ED rooms of 6 hospitals	900 cases Drivers involved in MVC 900 controls ED patients not involved in MVC	Jun 2000 – Sept 2001	Collaborative case-control study to determine prevalence of alcohol, licit & illicit drug use among drivers injured in MVC compared with control population. Outcomes confirmed high prevalence of use in population. Prevalence of medicines increased with age. BZDs most frequently observed medicine.	Opiates BZDs	OR= 8.2 [2.5-27.3] OR= 1.7 [1.2-2.4]	France
Smink et al. 2005	Cohort study? Exposed/unexposed? NFI TRC Screened blood samples	993 drivers	993	Oct 1998 – Sep 1999	Data linkage study that linked blood samples of crash-involved drivers to accident records. Results showed no clear association between the use of alcohol, illicit drug and/or medicinal drug use and the severity of an accident.	BZDs tricyclic antidepressants	No association	Netherlands
Smink et al. 2008	Cohort study? Exposed/unexposed? Injury Severity Score, blood + urine samples	106 injured car drivers	106	May 2000 – Aug 2001	Cross sectional study explored the relationship between the use of psychoactive substances and the injury severity in a group of crash-involved drivers. Results found no clear association between use of psychoactive substances and the severity of crash-related injury.	BZDs methadone, opiates tricyclics antidepressants	No association	Netherlands
Woratanarat et al. 2009	Case-control study Urine & blood samples, alcohol	1049 drivers in Bangkok: 200 cases recruited	1049	Feb-Nov 2006	Case-control study to determine the relationship between alcohol use, psychoactive drug use and road traffic injury showed that cases had significantly higher odds of an alcohol breath test, illicit	Illicit psychoactive drugs Non-illicit	OR= 3.4 [1.7-6.6] OR= 3.1 [1.5-6.3]	Thailand

	breath tests	from hospitals, 849 matching controls recruited from gas stations	and non-illicit psychoactive drugs.	psychoactive drugs

REFERENCES

1. Lyman S, Ferguson SA, Braver ER, Williams AF. Older driver involvements in police reported crashes and fatal crashes: trends and projections. *Inj Prev.* June 2002 2002;8(2):116-120.
2. Eberhard J. Older Drivers' "High Per-Mile Crash Involvement": The Implications for Licensing Authorities. *Traffic Inj Prev.* 2008;9(4):284-290.
3. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd; 2003.
4. Fildes BN. Future Directions for Older Driver Research. *Traffic Inj Prev.* 2008;9(4):387 - 393.
5. Oxley J, Corben B, Fildes B, O'Hare M, Rothengatter T. *Older vulnerable road users - Measures to reduce crash and injury risk.* Melbourne: Monash University Accident Research Centre;2004.
6. Gibson J, Hubbard R, Smith C, Tata L, Britton J, Fogarty A. 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.* 2009;169(6):761-768.
7. Maes V, Charlier C, Grenez O, Verstraete A. *Drugs and medicines that are suspected to have a detrimental impact on road user performance.* Ghent, Belgium: ROSITA Project, European Commission;1999.
8. Drummer O, Gerostamoulos J, Batziris H, et al. The incidence of drugs in drivers killed in Australian road traffic crashes. *Forensic Sci Int.* 2003;134(2-3):154-162.
9. Movig K, Mathisjssen M, Nagel P, et al. Psychoactive substance use and the risk of motor vehicle accidents. *Accid Anal Prev.* 2004;36(4):631-636.
10. Dubois S, Bédard M, Weaver B. The Impact of Benzodiazepines on Safe Driving. *Traffic Inj Prev.* 2008;9(5):404 - 413.
11. Engeland A, Skurtveit S, Mørland J. Risk of Road Traffic Accidents Associated With the Prescription of Drugs: A Registry-Based Cohort Study. *Ann Epidemiol.* 2007;17(8):597-602.
12. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Medicine.* 2008;9(8):818-822.
13. Hemmelgarn B, Suissa S, Huang A, Jean-Francois B, Pinard G. Benzodiazepine Use and the Risk of Motor Vehicle Crash in the Elderly. *JAMA.* July 2, 1997 1997;278(1):27-31.
14. Kelly E, Darke S, Ross J. A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. *Drug and Alcohol Review.* 2004;23(3):319-344.
15. Walsh JM, Gier J, Christophersen AS, Verstraete A. Drugs and Driving. *Traffic Inj Prev.* 2004;5(3):241.
16. Walsh JM, Gier J, Christophersen S, Verstraete A. Drugs and driving. *Traffic Inj Prev.* 2004;5(3):241.
17. De Gier JJ. *Review of investigations of prevalence of illicit drugs in road traffic in different European countries.* Strasbourg1999.
18. Longo MC, Hunter CE, Lokan RJ, White JM, White MA. 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. *Accid Anal Prev.* 2000;32(5):623-632.
19. Goldney R, Bain M. Prevalence of psychotropic use in a South Australian population. *Australas Psychiatry.* 2006;14(4):379-383.
20. Jorm A, Grayson D, Creasey H, Waite L, Broe G. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health.* 2000;24(1):7-10.

21. Galski T, Vocaturo L, Galski TM. Driving, Medical Illness, and Medications. In: Maria TS, John D, Douglas LC, eds. *Handbook for the Assessment of Driving Capacity*. San Diego: Academic Press; 2009:159-185.

22. Simoni-Wastila L, Yang HK. Psychoactive drug abuse in older adults. *Am J Geriatr Pharmacother.* 2006;4(4):380-394.

23. Brunnauer A, Laux G, Geiger E, Soyka M, Moller H. Antidepressants and driving ability: Results from a clinical study. *J Clin Psychiatry.* 2006;67:1776-1781.

24. Wingen M, Ramaekers J, Schmitt J. Driving impairment in depressed patients receiving long-term antidepressant treatment. *Psychopharmacology (Berl).* 2006;188:84-91.

25. Sansone R, Sansone L. Driving on antidepressants: cruising for a crash? *Psychiatry.* 2009;6(9):13-16.

26. Hindmarch I, Alford C, Barwell F, Kerr JS. Measuring the side effects of psychotropics: the behavioural toxicity of antidepressants. *J Psychopharmacol.* January 1, 1992 1992;6(2):198-203.

27. Hours M, Fort E, Charnay P, et al. Diseases, consumption of medicines and responsibility for a road crash: a case-control study. *Accid Anal Prev.* 2008;40(5):1789-1796.

28. Hebert C, Delaney JAC, Hemmelgarn B, Lévesque LE, Suissa S. Benzodiazepines and elderly drivers: a comparison of pharmacoepidemiological study designs. *Pharmacoepidemiol Drug Saf.* 2007;16(8):845-849.

29. Starmer GA, Mascord D. *Drugs and Traffic Safety.* Canberra: Federal Office of Road Safety;1994.

30. Sansone RA, Sansone LA. Driving on antidepressants: cruising for a crash? *Psychiatry (Edgmont).* Sep 2009;6(9):13-16.

31. Verster JC, Veldhuijzen DS, Volkerts ER. Residual effects of sleep medication on driving ability. *Sleep Med Rev.* Aug 2004;8(4):309-325.

32. Bocca M-L, Le Doze F, Etard O, Pottier M. Residual effects of zolpidem 10mg and zopiclone 7.5mg versus flunitrazepam 1mg and placebo on driving performance and occular accades. *Psychopharmacology (Berl).* 1999;143(4):373.

33. Busto U, Kaplan H, Wright C, Gomez-Mancilla B, Zawertailo L, Greenblatt D. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release. *J Psychopharmacol (Oxf).* 2000;20(6):628-635.

34. van Laar M, Volkerts E, Verbaten M. Subchronic effects of the GABA-agonist lorazepam and the 5-HT2A antagonist ritanserin on driving performance, slow wave sleep and daytime sleepiness in healthy volunteers. *Psychopharmacology (Berl).* 2001;154(2):189-197.

35. Verster J, Volkerts E, Verbaten M. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a randomized, placebo-controlled study. *Neuropsychopharmacology.* 2002;27(2):260-269.

36. Vingilis E, Macdonald S. Review: Drugs and Traffic Collisions. *Traffic Inj Prev.* 2002;3(1):1-11.

37. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet.* 1998;352(9137):1331-1336.

38. Neutel I. Benzodiazepine-related traffic accidents in young and elderly drivers. *Human Psychopharmacology.* 1998;13(S2):S115.

39. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet.* 1998;352:1331-1336.

40. Orriols L, Salmi LR, Philip P, et al. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf.* Aug 2009;18(8):647-658.

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

42. Meskali M, Berthelon C, Marie S, Denise P, Bocca M. Residual effects of hypnotic drugs in aging drivers submitted to simulated accident scenarios: an exploratory study. *Psychopharmacology (Berl).* 2009;207(3):461-467.

43. Vermeeren A. Residual Effects of Hypnotics: Epidemiology and Clinical Implications. *CNS Drugs.* 2004;18(5):297-328.

44. Ray WA, Gurwitz J, Decker MD, Kennedy DL. Medications and the safety of the older driver: is there a basis for concern? *Hum Factors.* 1992;34(1):33-47.

45. Leveille SG, Buchner DM, Koepsell TD, McCloskey LW, Wolf ME, Wagner EH. Psychoactive medications and injurious motor vehicle collisions involving older drivers. *Epidemiology.* 1994;5(6):591-598.

46. McGwin G, Sims RV, Vonne Pulley L, Roseman JM. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study. *American Journal of Epidemiology.* 2000;152(5):424-431.

47. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *American Journal of Epidemiology.* 1992;136(7):873-883.

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

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

50. Dubois S, Bedard M, Weaver B. The impact of benzodiazepines on safe driving. *Traffic Inj Prev.* Oct 2008;9(5):404-413.

51. European Monitoring Centre for Drugs and Drug Addiction. *Literature Review on the Relation between Drug Use, Impaired Driving and Traffic Accidents.* Lisbon: EMCDDA;1999.

52. Drug & Alcohol Services. *Benzodiazepines, Opioids and Driving: Summary of the Literature.* Adelaide: Drug & Alcohol Services of South Australia;2006.

53. Bramness JG, Skurtveit S, Neutel CI, Morland J, Engeland A. Minor increase in risk of road traffic accidents after prescriptions of antidepressants: a study of population registry data in Norway. *J Clin Psychiatry.* Jul 2008;69(7):1099-1103.

54. Ray WA, Thapa PB, Shorr RI. Medications and the older driver. *Clin Geriatr Med.* 1993;9(2):413-438.

55. Orriols L, Salmi L-R, Philip P, et al. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf.* 2009;18(8):647-658.

56. Bramness J, Skurtveit S, Neutel CI, Mrland J, Engeland A. Minor increase in risk of road traffic accidents after prescriptions of antidepressants: a study of population registry data in Norway. *J Clin Psychiatry.* 2008;69(7):1099-1103.

57. De Las Cuevas C, Sanz EJ. Fitness to drive of psychiatric patients. *Prim Care Companion J Clin Psychiatry.* 2008;10(5):384-390.

58. Iwamoto K, Takahashi M, Nakamura Y, et al. 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.* Jul 2008;23(5):399-407.

59. Ramaekers JG. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiatry.* Jan 2003;64(1):20-29.

60. Morgan R, King D. The older driver - a review. *Postgrad Med J.* 1995;71:525-528.

61. Nair B. Older people and medications: what is the right prescription? *Australian Prescriber.* 1999;22(6):130-131.

62. Hanrahan RB, Layde PM, Zhu S, Guse CE, Hargarten SW. The Association of Driver Age with Traffic Injury Severity in Wisconsin. *Traffic Inj Prev.* 2009;10(4):361-367.

63. Australian Bureau of Statistics. *Population by Age and Sex, Australian States and Territories, Jun 2009* Canberra: ABS;2009.

64. Smink BE, Ruiter B, Lusthof KJ, De Gier JJ, Uges DRA, Egberts A. Drug use and the severity of a traffic accident. *Accid Anal Prev.* 2005;37(3):427.
65. Bramness JG, Skurtveit S, Mørland J, Engeland A. The risk of traffic accidents after prescriptions of carisoprodol. *Accid Anal Prev.* 2007;39(5):1050-1055.
66. Holland C, Handley S, Fleetam C. *Older drivers, illness and medication.* London: Department for Transport;2003.
67. McGwin G, Sims R, Pulley L, Roseman J. Relations among Chronic Medical Conditions, Medications, and Automobile Crashes in the Elderly: A Population-based Case-Control Study. *Am J Epidemiol.* 2000;152(5):424-431.
68. Verster J, Volkerts E. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol.* 2004;92:294-304.

Fig 1

Appendix A1 A strategy framework for pedestrian and MMS safety**

	Policy/Law Makers	Urban Planners Road Designer	Schools (K-12)	Learner Driver Instructors
Environmental/technological Strategies				
Conduct walkability & safe route audits in areas of high pedestrian activity	✓	✓		
Reduce travel speed and traffic in high density pedestrian/ MMS areas*	✓	✓		
Develop guidelines for adequate crossing times for older pedestrians*	✓	✓		
Improve maintenance of sidewalks, surrounds, and street lighting*	✓	✓		
Develop safer access for older people at bus and tram stops*	✓	✓		
Pedestrian-friendly enforcement of pedestrian traffic laws e.g. warnings for violations as jaywalking.	✓			
Development of MMS registration system	✓			
Education & Behavioural Strategies				
Prioritise pedestrians/ MMS users on the transport hierarchy – cultural shift	✓	✓		
Legitimate walking as an active form of transport in a sustainable society	✓	✓	✓	✓
Raise awareness of pedestrian/ MMS users right of way traffic laws	✓		✓	✓
Raise awareness of vehicle speed & severity of pedestrian/ MMS users crash injury	✓		✓	✓
Raise awareness of older pedestrians reduced cognitive/ physical ability	✓		✓	✓
Raise awareness of the importance of pedestrian visibility and conspicuity	✓		✓	
Increase knowledge of risk & protective factors for pedestrian/ MMS users injury	✓		✓	✓
Increase knowledge of crossings (marked & unmarked)	✓		✓	✓
Comprehensive social marketing campaign for pedestrians/ MMS users.	✓			
Target group and key stakeholder community consultation	✓	✓		
Targeted information sessions with older adults	✓	✓		
Use driving simulator to educate			✓	✓
Increase knowledge of road rules and skills of mobility scooter users.	✓			
Increase stakeholders knowledge of environmental modifications	✓			

*Oxley & Fildes (2004) p.187 (J. Oxley, Fildes, et al., 2004)

** no attempt here to grade the quality of evidence of effectiveness for these interventions/actions.