The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning (DSP) with CNS-D drugs.

Stewart Oxley

Bachelor of Business, Bachelor of Psychology (Honours)

Submitted to the School of Psychology at the University of Newcastle in partial fulfilment of the requirements for the degree of Doctorate in Clinical and Health Psychology

September, 2014
I hereby declare that the work submitted in this thesis is the result of original research and has not been submitted for a university degree or other similar qualification to any other University or Institution.

Stewart Oxley

September 2014
I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of this thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

I hereby certify that the work in this thesis has been done in collaboration with the following researchers and carried out at Calvary Mater Newcastle Hospital and the University of Newcastle. My collaborators included:

Tharaka L. Dassanayake (MBBS, MPhil, PhD)1,6, Gregory Carter (FRANZCP, PhD)4,5, Ian Whyte (FRACP, FRCP (Edin), FAACT, FACMT)2,5, Alison Jones (MD, FRACP)3,5,7,8, 9, Gavin Cooper (B Mathematics, B Computer Science)1, Patricia T. Michie (PhD, FASSA)1,4.

1. School of Psychology, The University of Newcastle, NSW, Australia
2. Discipline of Clinical Pharmacology, School of Medicine and Public Health, Faculty of Health, The University of Newcastle, NSW, Australia
3. Graduate School of Medicine, University of Wollongong, NSW, Australia
4. Centre for Translational Neuroscience and Mental Health Research, University of Newcastle, NSW, Australia
5. Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, NSW, Australia
6. Department of Physiology, Faculty of Medicine, University of Peradeniya, Sri Lanka
7. Exec Dean Faculty of Science, Medicine and Health University of Wollongong
8. Researcher - Illawarra Health and Medical Research Institute
9. Conjoint professor, School of Medicine and Public Health, University of Newcastle

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Synopsis

Background

Hospital treated deliberate self-poisoning (DSP) has become a major concern for developed countries as 90% of all deliberate self-harm is DSP (Carroll, Metcalfe, & Gunnell, 2014). A major concern for hospital treated DSP is the capacity of individuals to perform daily activities, such as driving, after being medically discharged. One study found that, at discharge, individuals admitted to hospital for DSP with central nervous system non-depressant (CNS-ND) drugs outperformed those admitted for DSP with CNS-D drugs across several neuropsychological measures (Dassanayake, Michie, et al., 2012). A self-controlled case series that linked the New South Wales (NSW) Roads and Traffic Authority CrashLink database and the NSW Admitted Patient Data Collection from 2001–2008 found that patients were at increased risk of motor vehicle accident (MVA) within 3-days, 7-days, and up to 1-month after ingestion of CNS-D drugs (Dassanayake, Jones, et al., 2012). Based on this evidence the authors were concerned that patients medically fit for discharge were still suffering cognitive and psychomotor impairments no longer attributable to pharmacological properties.

At present the experimental literature reviewed in this thesis suggests that single and multiple therapeutic doses of central nervous system depressant (CNS) drugs (benzodiazepines, z-drug, antidepressants, opioids, and antipsychotics) have the capacity to impair simulated or actual driving ability in both healthy volunteers and patients diagnosed with various psychiatric disorders (e.g., anxiety; van Laar, Volkerts, & van Willigenburg, 1992). Evidence of a dose-response relationship suggests that supratherapeutic doses of CNS-D drugs can result in greater impairment. Examination of the epidemiological literature, again reviewed in this thesis, into the influence of CNS-D drugs on risk of motor vehicle accident (MVA) found that receiving or dispensing a prescription of CNS-D drugs up to 1-month prior increased the risk of MVA. Again a dose-response relationship suggests increasing the dose of CNS-D drugs increases the risk of MVA (Chang et al., 2012).
Despite evidence suggesting that patients discharged from hospital after DSP with CNS-D drugs have impaired cognitive and psychomotor function, no longitudinal cohort study has been conducted to support this claim. However, other factors could account for extended risk of MVA (4-weeks). These factors include, personality (Schwebel, Severson, Ball, & Rizzo, 2006), insight (Anstey, Wood, Lord, & Walker, 2005), vocational, financial, and/or interpersonal concerns (Selzer, 1969).

Methodology

This thesis reports a longitudinal cohort study that included patients admitted to hospital for DSP with CNS-ND or CNS-D drugs. Both groups provided self-assessment information of their cognitive and driving capabilities and performed neuropsychological tests that examined cognitive flexibility, cognitive efficiency, working memory, visual attention and visuomotor skills, the capacity to inhibit responses, and decision-making at discharge, day-7 and day-28 after discharge. The aims of the present study was to: compare the neurocognitive impairment (difference in means) at baseline (at discharge from hospital) for CNS-D and CNS-ND ingestion groups; compare the recovery of neurocognitive function (difference in means over time) over three time points (discharge, day-7, and day-28), in both CNS-D and CNS-ND groups; and to develop explanatory models for the recovery of neurocognitive function over time.

Results

This study replicated Dassanayake, Michie, et al. (2012), finding that the CNS-ND drug group had significantly faster completion times at discharge than the CND-S drug group for the primary measure of cognitive flexibility (Trail-Making Test B [TMT-B]). CNS-D and CNS-ND groups did not significantly differ across cognitive efficiency, visual attention and visuomotor skills test, working memory, inhibition, and decision-making. TMT-B completion times by the CNS-ND group remained stable over time (day-7 and -28) while completion times of the CNS-D group significantly improved at each time point. Compared to discharge, the both CNS-ND and CNS-D group showed significant improvement in visual attention and visuomotor skills test, and inhibition.
The CNS-D showed significant improvement in cognitive efficiency and working memory. Finally, more pre-DSP covariates were significant in the first month after discharge. Pre-DSP covariates included: a psychiatric diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; atypical antipsychotic medication; age; and intelligence.

**Conclusion**

The limited explanatory power of post-DSP variables could be explained by the lack of fidelity of information collected post-DSP. Additionally, there were concerns that ‘the right’ information was not collected, for example whether individuals were accessing psychological support in the month after discharge as such support has been show to improve cognitive functions (Brewin & Smart, 2005). Based on the results from the present study, future research should examine whether personality and/or driving style (Poó, Taubman-Ben-Ari, Ledesma, & Díaz-Lázaro, 2013), using a measure such as the Multidimensional Driving Style Inventory (Taubman-Ben-Ari, Mikulincer, & Gillath, 2004), influences risk of MVA. Further research should also examine insight (self-awareness) using visual analogue scales that target specific behaviour related to driving and require individuals to consider the level of support that they may need to complete a task, such as driving (Toglia & Kirk, 2000).

**Implications**

The present study had several limitations related to data collection measures (e.g., personality, driving style, psychotherapy, and social support) and assessment protocol (e.g., self-assessment at each time point). Even still, this research has found supporting evidence (Dassanayake, Michie, et al., 2012) that DSP with CNS-D drugs impairs performance after the patient has been deemed medically fit to be discharged. Given this, medical professionals may need to reconsider discharge protocols and the information provided to patients about their capacity to perform daily activities, such as driving, and their period of risk to themselves and the community.
Thesis Structure

According to the instructions for the Clinical and Health Doctorate thesis as set out by the University, School of Psychology, the thesis has been structured as follows:

Thesis Abstract

Chapter 1 - Extended Literature Review

Chapter 2 – Journal article for submission to Journal of Clinical Psychopharmacology

Chapter 3 – Extended Discussion

Appendices:

1. Glossary

2. Supplementary data

3. Instruments (questionnaires and measures)

4. Ethics Variation

5. Offsite Assessment form

6. Staff Information Sheet

7. Participant Information Sheet

8. Consent Form

9. Journal of Clinical Psychopharmacology Manuscript Instructions

10. Private Facility Letter
Chapter 1. Extended Literature Review

Structure of the Literature Review

The first chapter is divided into eight sections including several subsections. The first section of this chapter outlines the research investigating attempted suicide by deliberately ingesting central nervous system depressant (CNS-D) drugs and its influence on cognitive and psychomotor function. The second section describes a theoretical model of driving and includes the three mechanisms (i.e., operational, tactical, and strategic) thought to underpin this daily activity and how each functions to accomplish this task. The third section takes the three mechanisms of driving and shows how they relate to specific cognitive and psychomotor functions (i.e., attention, executive functions, reasoning and planning) relevant for driving and explains how deficits in these particular areas can influence driving performance. The fourth section of the extended literature review discusses a driving assessment protocol for examining prescription medication. In line with discussed protocols, the fifth section of this chapter contains a systematic review and meta-analyses of the experimental literature for benzodiazepines, z-drugs, antidepressant, opioids, and antipsychotic medication and the influence on driving performance. Similarly, the sixth chapter contains a systematic review of epidemiological studies that examined the risk of motor vehicle accident (MVA) over a 1-month period of taking CNS-D drugs. The seventh section of chapter one examines alternative explanations for the prolonged influence of therapeutic doses of CNS-D medication. The eighth and final section, enumerates the relevant evidence from the previous sections, points out the gaps in the research, and summarises the research question pertinent to the longitudinal cohort study.

Deliberate Self-Poisoning Literature

Attempted suicide by deliberately ingestion of drugs has become a growing concern in developed countries (Kessel, 1965) as 90% (median; range 46.8-100%) of all deliberate self-harm is
deliberate self-poisoning (DSP; Carroll et al., 2014). DSP can be considered to be the consumption of two or more times the Defined Daily Dose (the assumed average maintenance dose per day for a drug used for its main indication in adults; WHO Collaborating Centre for Drug Statistics Methodology, 2009) of a substance with the intention of self-harm.

DSP with central nervous system depressant (CNS-D) drugs is clinically important. Commonly ingested CNS-D drugs include benzodiazepines, newer “z-drugs” used as hypnotics, sedative antidepressants, antipsychotics, and opioids. Each year, CNS-D drugs account for over 122,000 hospital treated DSP admissions in the US (Substance Abuse and Mental Health Services Administration, 2010a, 2010b); 45,000 in the UK (Mid 2010-2011; National Institute of Health, 2012) and 12,500 in Australia (Mid 2009-2010; Australian Institute of Health and Welfare, 2012).

In Australia, following a CNS-D DSP, patients are usually discharged in less than 48 hours (Australian Institute of Health and Welfare National Hospital Morbidity Database, 2011). Clinical assessments include a brief clinical interview and a physical and basic bedside cognitive examination that requires individuals to have a normal level of consciousness, orientation, obey commands, and speak coherently with the clinician before discharge. Patients are not administered neuropsychological tests to assess whether these patients have any other impairment in cognitive and psychomotor function.

One study that investigated the cognitive and psychomotor functions of individuals admitted for DSP with CNS-D drugs at discharge found that this group performed substantially less well than a control group who were admitted for DSP with central nervous system non-depressant drugs (CNS-ND), such as paracetamol and non-sedating antidepressants (Dassanayake, Michie, et al., 2012). Results showed that the CNS-D drug groups performed poorly relative to CNS-ND drug group, demonstrated by increased reaction times and impulsivity, and inefficient problem solving and working memory. Based on this evidence the authors were concerned that the impairment of cognitive and psychomotor functions caused by CNS-D drugs may extend beyond discharge and
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Impaired daily activities, such as driving. To investigate these concerns they conducted a study to determine if the period following treatment for DSP from a CNS-D drug, was linked to an increased risk of a MVA (Dassanayake, Jones, et al., 2012). Data linkage between the New South Wales (NSW) Roads and Traffic Authority CrashLink database and the NSW Admitted Patient Data Collection from 2001–2008 was used to determine whether patients were at increased risk of MVA within 3-days, 7 days, and up to 1-month after ingestion of CNS-D drugs (Dassanayake, Jones, et al., 2012). This study found that patients admitted for DSP with CNS-D drugs were at increased risk of MVA up to 1-month after being discharged. This evidence raised the question that impairments produced by DSP with CNS-D drugs may have a longer influence on cognitive and psychomotor performance, important for daily activities such as driving, than that attributable to pharmacological properties.

A Model of Driving

Numerous models have attempted to explain the structures that underpin the complex cognitive operations involved in driving (for a review see; Michon, 1985, 1989; Ranney, 1994). Michon (1985) proposed a hierarchical model of driving consisting of three dynamically integrated levels of functionality that best explained driving-related tasks: 1) operational processes manipulate and control inputs (e.g. steering) for stable driving; 2) tactical/manoeuvring processes manage safe interactions with the environment and other vehicles; 3) strategic processes consist of higher level reasoning (e.g. planning a route).

Operational processes are considered to be automatised action patterns that experienced drivers perform intuitively because of practice, irrespective of the initial task complexity or situation (e.g. obstacles or hazards; Ranney, 1994). Tactical/manoeuvring processes are activated when more complex traffic situations occur (e.g. determining whether a gap was sufficient to overtake or enter the traffic stream) and shift the driver’s attention from a state of automatised operational processing into controlled tactical processes. Tactical processes are the criteria derived
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from the general goals set at the strategic level (e.g. to arrive at dinner with friends by 7pm), but are adaptable based on the situation. Operational processes are hypothesised to occur in milliseconds as opposed to tactical processes, which are made and executed within a few seconds, whilst strategic processes, which are not time-dependent, occur over a longer period. Integration of this model into driver-behaviour models (Salvucci, 2006) has assisted in the design of human research studies (Amick, Grace, & Ott, 2007; Stolwyk, Charlton, Triggs, Iansek, & Bradshaw, 2006) suggesting that this hierarchical model possesses some ecological validity.

**Deficits in Cognitive and Psychomotor Function that Underpin Driver Performance**

Research suggests that cognitive and psychomotor functions such as attention and information processing speed, and executive functions such as working memory and planning, underpin operational, tactical, and strategic processes that facilitate driving. Hence, deficits in these faculties may be associated with poor driving performance (Anstey et al., 2005). Attention is a cognitive faculty that facilitates the capacity to engage cognitive and psychomotor resources, including executive functions such as working memory, to process external and internal stimuli. Attention can be categorised as automated, for routine practised tasks, or controlled, for complex tasks that engage more mental resources. In this respect, attention forms the basis for numerous daily functions, including driving. For example, attention enables the ability to process information speedily in order to react in a timely manner to a threatening situation and to adopt appropriate motor responses (Ranney, 1994). Reaction time is crucial to driver response (e.g. applying brakes; Zhang et al., 2007), with delayed reaction times predicting poor driving performance (Anstey et al., 2005). Thus an ability to attend and respond appropriately to the environment is important for driving performance, tasks reflected by tactical processes (Michon, 1985).

Executive functions include cognitive faculties such as goal formation, planning and implementing plans, inhibition, mental flexibility, working memory, and the initiation and
monitoring of action (Lezak, Howieson, & Loring, 2004; Smith & Jonides, 1999). The executive function, working memory, is the ability to continually synthesise internal and external information to assist decision-making (i.e. the appropriateness of specific actions, and assisting the performance of these actions; tactical processes). Importantly, deficits in working memory have been associated with poor driving performance (Fitten et al., 1995) and increased risk of MVAs (Lee, Lee, Cameron, & Li-Tsang, 2003).

Strategic processes in driving include the capacity for higher-level reasoning and planning (Michon, 1985, 1989; Ranney, 1994). These functions are relevant for driving performance, in particular navigation (Odenheimer et al., 1994). Navigating to a particular destination may require modification of route in transit due to unforeseen circumstances (e.g., road works), thus the capacity to retrieve information to adapt is crucial. The ability to use information for higher-order reasoning and planning has been examined by neuropsychological tests (Trail-making Test; Reitan, 1986) that have been shown to be suitable proxies for driving performance (Classen, Wang, Crizzle, Winter, & Lanford, 2013; Ott et al., 2013), suggesting that the capacity to retrieve information for higher order reasoning and planning is important for driving performance.

**Driving Assessment Protocol**

In 2008, both the National Highway Traffic Safety Administration (NHTSA; Kay & Logan, 2011) and the International Council on Alcohol, Drugs & Traffic Safety (Walsh, Verstraete, Heustis & Morland, 2008) from the U.S. recommended that specific drugs and drug categories that impaired driving performance should be assessed using a standardised protocol. In response, the International Council on Alcohol, Drugs & Traffic Safety (Walsh, Verstraete, Heustis & Morland, 2008) advocated for a driving assessment protocol that incorporated pharmacological, toxicological, and epidemiological evidence as well as standardised behavioural assessments (essential driving ability domain model). The goal of this proposed assessment process was to provide a list of medications that are “safe” for use when driving that would better inform consumers and clinicians and would
provide better regulatory assistance to the National Transportation Safety Board (U.S.).

Figure 1 shows how each of the components of the driving assessment protocol interconnects. Pharmacological and toxicological research provides information on drugs or drug class features, while epidemiological data identifies the pattern associated with certain types of drug use, in this case those drugs that increase the risk of injury or death as a result of a MVA. Standardised behavioural assessments, such as those used in experimental research, investigate the cognitive, perceptual, and psychomotor effects of drugs (e.g. reaction time and executive function). This tiered protocol has been adopted for this literature review to examine both epidemiological and experimental evidence that CNS-drugs impair driving performance.

In summary, based on the model of Michon (1985) automated, tactical, and strategic processes are required to drive effectively. These processes appear to be underpinned by several cognitive and psychomotor functions (e.g. attention, executive functions, and working memory). The driving assessment protocol provides a framework to structure evidence that certain drugs and/or drug classes have the capacity to impair cognitive and psychomotor functions and as a consequence interrupt the key processes responsible for driving.

The next two sections of this thesis include a systematic review and meta-analysis of experimental literature, and a systematic review of epidemiological studies that investigated whether therapeutic dosage of z-drugs impaired driving performance and increased the risk of MVA. The purpose of these two sections is to examine the literature on CNS-D drugs and their ability to influence the performance of daily activities such as driving over a period of 1-month. If the evidence shows that CNS-D drugs impair driving performance at the therapeutic level, then an argument could be made that doses that exceed the therapeutic level, such as consumed in DSP, would cause additional impairments to driving performance for extended periods post-overdose.
Figure 1. Driving Assessment Protocol - Interrelation of the pharmacological and toxicological, epidemiological and behavioural assessments proposed by the NHTSA panel (from Kay & Logan, 2011).
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Chapter 1. Extended Literature review

Experimental evidence of exposure to CNS-D drugs and driving performance

Using the same criteria as Dassanayake, Michie, Carter, and Jones (2011), PubMed and Embase databases were selected to locate material related to CNS-D drug use and driving performance. The first set of search terms consisted of the EMTREE/MeSH terms ‘benzodiazepine derivative’, ‘zaleplon’, ‘zopiclone’, ‘zolpidem’, ‘zolpidem tartrate’, ‘eszopiclone’, ‘antidepressant agent’, ‘opiate agonist’, and ‘antipsychotic’. The second set included the EMTREE/MeSH terms ‘traffic accidents’, ‘traffic safety’ and ‘car driving’ and the general search term ‘driving’. By selecting the ‘explosion’ option (Embase only), the search also incorporated terms that are subtopics (e.g. individual drugs in a particular class of drugs) of each of the above EMTREE/MeSH terms. The articles that contained at least one term from each of the above sets of search terms were extracted for consideration for inclusion in the review. The reference lists of the eligible articles were searched for any other relevant literature.

Study selection inclusion criteria were:

(i) Published between January 1946 and 30 June 2013

(ii) Experimental design

(iii) Drugs assessed must include benzodiazepines, z-drugs, antidepressants, opioids or antipsychotics.

(iv) Single dose or multiple doses

(v) Participants engaged in an actual or simulated driving test (studies that examined cognitive/ psychomotor function by laboratory tests were excluded)

(vi) Testing within 1-month of start of study period

(vii) English language
Figure 2. Selection process for experimental studies of exposure to drug followed by driving simulator or driving test.
The initial search retrieved 2068 articles. Exclusion of the papers that did not meet the inclusion criteria is shown above in Figure 2. One thousand nine-hundred and eighty two studies were excluded because the studies failed to include a CNS-D drug, did not include a simulated or real driving test, did not include original data, were not published in English, had a study duration greater than 1-month, were not original research (e.g. reviews, meta-analysis). Eighty-six articles were retained and divided into particular drug classes (benzodiazepines and z-drugs [n= 57], antidepressants [n= 23], opioids [n= 3] and antipsychotics [n= 3]) and grouped according to whether participants were healthy volunteers or patients (with a diagnosed psychiatric illness), and whether they were administered a single or multiple dose/s.

**Systematic review results: experimental studies**

Primary outcome measures were standard deviation of lateral position (SDLP) or tracking error severity index (TESI; percentage of time spent off the road), standard deviation of speed (SDS), and brake reaction time (BRT) or reaction time (RT). Secondary outcome measures included number of collisions, headway maintenance, mean lateral position or lateral position, emergency decision making, car following performance, mean deviation from target, and road exits. In addition, some experimental studies recorded whether individuals were able or unable to complete the driving task. Terminate of driving tests were for safety reasons and attributed to the substance consumed. All studies were double-blind placebo-controlled unless otherwise specified.

**Benzodiazepines and z-drugs**

**Single dose studies in healthy volunteers.** A single dose of diazepam has been administered to healthy individuals in 27 studies. Linnoila and Hakkinen (1974) found that diazepam (10mg) administered 30-mins before testing caused more neglected instructions and collisions than a no drink or drug group. Diazepam (10mg) was also found to significantly increase SDLP compared to all other conditions (incl. diazepam 5mg) an hour after consumption. Takahashi
et al. (2010) found that while diazepam (5mg) increased BRT 4-hours after dosage, it was not significantly different to placebo, suggesting that a single dose of 5mg of diazepam is insufficient to significantly influence driving performance.

When driving ability after a single dose of diazepam (10mg), lormetazepam (2mg), and mephinolol (10mg) were compared, diazepam significantly delayed reaction time across all time points (1-, 2-, and 3-hours) but only impaired correct tracking executions after one hour (Willumeit, Ott, Neubert, et al., 1984). Willumeit, Ott, Neubert, et al. (1984) also found that lormetazepam (2mg) impaired RT and correct tracking executions in the first two hours after administration. One study administered diazepam (15mg younger, 10mg older) to 18 healthy volunteers (nine young, nine old) and conducted a driving test (1.5- and 4-hours after dosage) during the day and at night (Vanakoski, Mattila, & Seppala, 2000). This study found that both groups had significantly longer RTs and impairments to global driving performance, and committed significantly more simple tracking errors in day-time testing than the placebo condition. Diazepam (15mg) given to 12 healthy individuals also prolonged reaction time 1.5-hours after administration compared to placebo (Kuitunen, 1994). Finally, Mattila, Vanakoski, Kalska, and Seppala (1998) compared two benzodiazepines (oxazepam 30mg and diazepam 15mg) and found that only diazepam 15mg produced a significant difference to placebo in reaction time but no time after dose was reported.

A comparison between alprazolam (1mg) slow release (XR) and immediate release (IR) revealed that after 4-hours both formulations increased SDLP compared to placebo, with the increase for IR twice that of XR. In addition, ten driving tests were terminated (7-IR [39%], 3-XR [17%]; Leufkens, Vermeeren, Smink, van Ruitenbeek, & Ramaekers, 2007). In another study involving alprazolam (1mg), SDLP and SDS significantly increased compared to placebo when tested 1-hour after administration (Verster, Volkerts, & Verbaten, 2002). Six alprazolam driving tests were terminated.

Lorazepam (2mg) administered as either capsule or foam tablet significantly increased TESI
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and RT up to 6-hours after baseline (Mattila, Kuitunen, & Veilahti, 1993). Twelve hours after dose, flurazepam (15mg) and temazepam (20mg) resulted in significantly more participants hitting bollards (posts) while driving through passable gaps than placebo. Flurazepam also significantly impaired manoeuvring skills compared to placebo (Betts & Birtle, 1982).

Z-drugs (zaleplon, zopiclone, zolpidem and eszopiclone) have been used in studies that administered a single dose to healthy volunteers. Mattila et al. (1998) administered zolpidem (15mg) and zopiclone (7.5mg) to 12 healthy subjects, and found that both drugs significantly impaired TESI compared to placebo after 1- and 3.5-hours. Additionally, zolpidem significantly impaired TESI compared to all active treatments over the same timeframe. Several other studies compared zolpidem and zopiclone after a night time dose, with mixed results. Bocca et al. (1999) found that 10-hours after dosage zopiclone (7.5mg) and flunitrazepam (1mg), but not zolpidem (10mg), increased mean lateral position. A later study using the same drug, dose, and after dosage found that zopiclone (7.5mg) and zolpidem (10mg) significantly impaired SDS, and participants’ ability to enter road exits compared to placebo, while flunitrazepam (1mg) did not significantly impair performance (Bocca et al., 2011). Another study found that 10-hours after compared zopiclone (7.5 mg) and zolpidem (7.5mg) both impaired SDS, while two (8%) zolpidem driving tests were terminated (Leufkens, Lund, & Vermeeren, 2009). In a different study, 4-hours after administration, zolpidem (10/20mg) significantly increased SDLP and SDS compared to zaleplon (10/20mg) and placebo and resulted in three (10%) zolpidem driving tests being terminated (Verster, Volkerts, Schreuder, et al., 2002). Also, zolpidem (10mg) increased the number of collisions, standard deviation from speed limit, and standard deviation from ideal route compared to placebo 2-hours after dose. One final study examining zopiclone (7.5mg) and zolpidem (10mg) 10-hours after dose failed to show any impairment to driving (number of collisions), but there was a trend for zolpidem to increase the number of collisions (Meskali, Berthelon, Marie, Denise, & Bocca, 2009).
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Zopiclone has also been compared to other z-drugs and benzodiazepines in a single dose given to healthy volunteers. Zopiclone increased tracking errors and prolonged reaction time 1.5-hours after administration compared to placebo, while cyclopyrrolone suriclone (.4mg) did not impair performance compared to placebo at any time point (Mattila, Vanakoski, Mattila-Evenden, & Karonen, 1994). Zopiclone (7.5mg) and triazolam (.25mg) demonstrated the capacity to impair performance by increasing RT and tracking errors 1.5 hours after administration (Kuitunen, 1994). In the same study, six driving tests were terminated (two evening [7%], four night [14%]) and while zaleplon did not impair performance at either dose compared to placebo, one driving test had to be stopped (20mg, night [4%]). Vermeeren et al. (2002) found that 10-hours after dosage, one zopiclone (7.5mg) driving test was terminated. Finally, one study found that 10-hours after dosage, zopiclone (7.5mg) significantly impaired SDS and resulted in one zopiclone driving test being terminated (Leufkens & Vermeeren, 2009). Based on this evidence, it appears that zopiclone impairs driving performance after a single dose.

Other single dose studies found that driving performance was not impaired 10-hours after temazepam (20mg; Leufkens & Vermeeren, 2009), eszopiclone (3mg; Boyle, Trick, Johnsen, Roach, & Rubens, 2008), midazolam (15mg; Hindmarch & Subhan, 1983), and 3-hours after mexazolam dosage (1mg; Silveira, Vaz-Da-Silva, Dolgner, & Almeida, 2002).

Multiple dose studies in healthy volunteers (1-9 days). Numerous studies have examined the influence of multiple doses of benzodiazepine on the driving ability of healthy individuals. One 2-day study of 18 healthy males found that 10 hours after nocte dosage both Lormetazepam (1mg) and oxazepam (50mg) significantly increased SDLP compared to placebo and one (3%) oxazepam driving test was terminated (Volkerts, van Laar, van Willigenburg, Plomp, & Maes, 1992). But significant impairment of driving performance by oxazepam could be explained by the dose, as 50mg is usually administered over 3-4 doses rather than as a single dose. Another 3-day study of 12 healthy volunteers found that lormetazepam (1mg nocte) failed to impair the driving ability (time of
driving test after dosage unspecified; Ludice et al., 2002). Five hours after the second dose (bedtime [10:30pm] and night [3:30am]) zopiclone (7.5mg) impaired SDLP compared to zaleplon (10/20mg) and placebo (Vermeeren, Danjou, & O'Hanlon, 1998). Finally, a 7-day study of 12 healthy individuals found that lormetazepam (2mg nocte, 10pm) failed to impair driving performance at any time (time of driving test after dose unspecified; Willumeit, Neubert, Ott, & Hemmerling, 1983). In the same study, flurazepam (30mg nocte) produced significant tracking errors and prolonged reaction times when driving. The lack of active metabolites in lormetazepam could explain why it failed to impair next day driving performance (Willumeit, Ott, Neubert, et al., 1984).

The ability of flurazepam to impair driving performance has been demonstrated in two other studies when multiple doses were administered to healthy adults. One 4-day study of 24 healthy volunteers found that compared to flunitrazepam (2mg), triazolam (.5mg) and placebo, flurazepam (30mg) impaired driving performance 9-hours after dose on the final day (Laurell & Tornros, 1991). A 3-day study of 23 healthy volunteers found that 10-hours after the final dose flurazepam (30mg) significantly increased SDLP and SDS unlike chlorpheniramine (8/12mg), terfenadine (60mg), and placebo (Vermeeren, Ramaekers, Van Leeuwen, & O'Hanlon, 1998). In the same study, flurazepam also significantly increased RT compared to placebo and resulted in two (4%) driving tests being stopped. Based on this evidence, it appears that flurazepam impairs next-day driving performance up to 1-week when administered daily to healthy individuals.

Lorazepam has also demonstrated capacity to impair driving performance when administered to healthy participants in multiple doses. One 4-day study of 12 healthy females found that lorazepam (1mg t.i.d) resulted in significantly poorer performance across a number of driving skills such as parking, three-point turn, slalom, and braking, when tested 30 minutes after the morning dose on the final day (Hindmarch & Gudgeon, 1980). Significantly impaired driving (SDLP) on the final day of a 7-day study (3-hours after dosage) was recorded when 18 healthy
volunteers were administered lorazepam (1.5mg b.i.d; van Laar, Volkerts, & Verbaten, 2001). In addition, one (8%) lorazepam driving test was terminated. Another 7-day study of 16 healthy volunteers that conducted final day testing (time after dose unspecified) found that lorazepam (.5mg mane, .5mg midi, 1mg nocte) resulted in significantly more errors due to clumsiness and disinhibition (Mercier-Guyon, Lejay, & Choay, 1999). Finally, one 9-day study of 18 healthy volunteers found that 3-hours after dosage on day 2 and 9 both lorazepam (.5mg t.i.d) and suriclone (.2mg t.i.d) significantly increased SDLP. Both drugs significantly impaired headway maintenance (the ability to maintain distance with a lead vehicle) on day 2, while only lorazepam significantly impaired the outcome measure on day-9 (O'Hanlon, Vermeeren, Uiterwijk, van Veggel, & Swijgman, 1995). Also, lorazepam resulted in nine (25%) driving tests being stopped. This evidence suggests that lorazepam tolerance does not occur, even after 9-days.

Three studies found that diazepam, administered over multiple doses, impaired driving outcome measures. One 8-day study of 9 healthy volunteers, administered diazepam (25mg), diazepam-controlled release (20mg) and placebo, who were tested on day-1 (1.5- and 3-hours) and -8 found that TESI and reaction time were only significantly increased on day-1 (Mattila, 1988). One 9-day study of 48 healthy volunteers administered diazepam (15mg), buspirone (20mg), and placebo found that diazepam, taken 1 hour prior resulted in significantly impaired performance across several measures (SDLP, speed, headway control, and emergency decision-making) on day-1 and -8 (Moskowitz & Smiley, 1982). At the same dose, diazepam (5mg t.i.d) significantly impaired SDLP of 16 healthy volunteers compared to ondansetron (1-and 5mg b.i.d) and placebo on day-1 and -8 of an 8-day study (tested 1 hour after evening dose; O'Hanlon et al., 1995). One possible explanation for the diazepam results is that the dose given to participants exceeded the DDD (World Health Organization, 2013) of 10mg/day (2.5; Mattila, 1988; 1.5; Moskowitz & Smiley, 1982; 1.5; O'Hanlon et al., 1995).

Four other benzodiazepines have been administered to healthy individuals over multiple
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days. One study of 18 healthy volunteers found that nitrazepam (5mg nocte) and brotizolam (.25mg nocte) both significantly impaired BRT compared to placebo (9.5 hours after dosage) on day-1 of a 3-day daily dosing study (Tornros & Laurell, 1990). A study with the same number of participants, timeframe, and testing regime found that on day-3 nitrazepam (5mg) resulted in significant delay in BRT compared to triazolam (.25mg) and placebo (Laurell & Tornros, 1986). Finally, one 7-day study of 10 healthy volunteers found that clobazam (20mg nocte) impaired reverse parking on the final day (time of testing after dose unspecified; Hindmarch, Hanks, & Hewett, 1977).

**Single dose studies in patients.** Several studies investigated the impact of benzodiazepines on driving ability in patients with a variety of psychiatric diagnoses. Dureman and Norrman (1975) examined the influence of diazepam (5, 10, 15mg) and chlorazepate (10, 20, 30mg) on driving performance for 34 patients classified as neurotic currently taking either medication against 42 controls. There was no difference in steering precision and BRT 1-hour after administration, but the study did not mention the patient’s driving results and did not conduct an ANOVA to compare all the drug dosage groups. Partinen, Hirvonen, Hublin, Halavaara, and Hiltunen (2003) found that zolpidem (10mg) administered 5.5 hours prior produced significantly greater lane position deviations than temazepam (20mg) and placebo for 18 female patients diagnosed with insomnia. In contrast, another study found no difference between eszopiclone (3mg) and placebo BRT scores when administered 10 hours prior for 23 patients diagnosed with insomnia (Boyle et al., 2008). Finally, one study of 17 women diagnosed with insomnia found that flunitrazepam (2mg) and zolpidem (10mg) administered 10 hours prior did not significantly increase SDLP compared to placebo, but one flunitrazepam driving test was terminated (Vermeeren, O'Hanlon, Declerck, & Kho, 1995).

**Multiple doses in patients (1-28 days).** Benzodiazepine and z-drugs have been tested in multiple doses with patients diagnosed with various psychiatric disorders to determine whether they influence driving performance. One 2-day study of 24 females who ceased using hypnotics 2-years
prior to the study found that compared to placebo, flunitrazepam (2mg) resulted in significantly increased SDLP for up to 17 hours (O’Hanlon, 1984). When compared to temazepam (20mg), a 7-day study of 32 patients diagnosed with sleep disorders found that flunitrazepam (2mg) resulted in greater steering control errors on day-1 and -7 (10-hours after dose; Schmidt, Brendemuhl, & Ruther, 1986). Similarly, one 13-day study of 11 women diagnosed with insomnia study found that temazepam (20mg) or placebo resulted in minimal impairment of SDLP, but 16-hours after each dose of nitrazepam (10mg) SDLP was significantly impaired (O’Hanlon & Volkerts, 1986). Based on this evidence it appears that flunitrazepam and nitrazepam impairs driving performance when compared to temazepam and placebo.

Diazepam was used in three studies that involved individuals with diagnosed psychiatric disorders. Biehl (1979) found that diazepam (10mg) significantly impaired BRT compared to clobazam (20mg) and placebo in 24 male students with high neurotic scores, although the time between dose and testing was not specified. In addition, two (4%) driving tests were terminated with diazepam. An observer-blinded patient (n= 9, anxiety disorder) versus control (n=13) study that examined the influence diazepam (multiple doses across 1-day = 5-20mg) on driving ability (trained observer checklist) found that patients taking diazepam performed worse than healthy controls (testing times after dosage varied; de Gier, Hart, Nelemans, & Bergman, 1981). One 28-day study involving 24 outpatients, diagnosed with generalised anxiety disorder tested 1.5-hours after the last dose of the week found that diazepam (5mg t.i.d) significantly impaired SDLP and SDS compared to buspirone and placebo (end of week-1 to the end of week-3; van Laar et al., 1992). In addition, for diazepam two (4%) driving tests were terminated. The results from this last study are particularly important as they suggest that diazepam tolerance can take up to 3 weeks to develop in a clinical population.

The benzodiazepines used as hypnotics, lormetazepam and flurazepam, were administered in multiple doses in three studies. One 8-day study examined driving performance 10-hours after
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dosage of lormetazepam (1mg), zolpidem (10mg) zopiclone (7.5mg) on day-2 and -8 for 23 patients diagnosed with insomnia (Staner et al., 2005). Lormetazepam significantly increased the SDS while zopiclone significantly increased the number of collisions compared to placebo, but zolpidem did not impair performance compared to placebo. Another 8-day study examined the influence of lormetazepam (1, 2mg) and flurazepam (30mg) 10- and 16-hours after dosage on 16 patients diagnosed with insomnia (tested days 2,4,7; Brookhuis, Volkerts, & O'Hanlon, 1990).

Lormetazepam produced no impairment at either dose compared to placebo at any time point, but compared to placebo, flurazepam produced significant impairments to SDLP and SDS. In the final study, flurazepam (15, 30mg) given over 2-days to 24 female former hypnotic users (ceased use 2-years prior to the study) impaired SDLP at each testing period (morning [10-hour] and afternoon [16-hours]; O’Hanlon, 1984). Hence, evidence that lormetazepam and zolpidem impair driving is equivocal, while support exists for the capacity of zopiclone and flurazepam to impair driving performance when administered over several days for patients.

Finally, loprazolam, lorazepam, and medazepam have demonstrated the capacity to impair driving performance when administered over multiple days. One 2-day study testing on the second day 10-hours after dosage, found that loprazolam (1, 2mg) significantly increased SDLP in 16 former hypnotic drug users, and demonstrated a dose-response relationship (O’Hanlon, 1984). A 15 day study found that lorazepam (2mg) significantly increased SDLP in 18 individuals diagnosed with anxiety who were tested 4-hours after the morning on day-8 and 15 (O'Hanlon et al., 1995). In this study 10 (14%) driving tests were stopped because of excessive SDLP. Finally, Moore (1977) found that 14 males with anxiety that required hospitalisation produced minor driving errors when administered with medazepam (5-30mg) for three weeks compared to placebo. However, the time of testing after dose was not specified.

Antidepressants

Single dose in healthy volunteers. Six studies have found that a single dose of
amitriptyline resulted in reduced driving performance. One study involving 17 healthy male
volunteers found that, compared to placebo, 4-hours post-dose amitriptyline (25mg) significantly
increased SDLP and reduced car following performance. (Iwamoto et al., 2008). In a similar design
with 12 healthy volunteers, Kuitunen (1994) found amitriptyline (50mg) increased tracking errors
and RT at 1.5- and 4-hours post-dose compared to placebo. At the same dose (50mg), BRT was
significantly impaired at 2-hours post-dose but not at 5-hours for 9 female volunteers (Hindmarch,
Subhan, & Stoker, 1983). Another study using 9 female volunteers found that 50mg of amitriptyline
resulted in increased mean deviation from target (participants required to use a steering wheel to
follow an arrow in the simulation), but time after dose was not stated (Hindmarch, Harrison, &
Shillingford, 1988). Based on this evidence, a single dose of amitriptyline has the capacity to impair
driver ability to maintain position in the road and to react to stimuli up to 4 hours after
administration.

The selective serotonin reuptake inhibitors (SSRIs), paroxetine (10-mg; Iwamoto et al.,
2008) and zimeldine (200mg; Hindmarch et al., 1983), did not impair driving performance, nor did
the tetrahydroisoquinoline nomifensine (100mg) or tricyclic antidepressant lofepramine (70-mg and
140-mg; Hindmarch et al., 1988). However, the antidepressants mianserin (30mg) and tianeptine
(37.5mg) caused significant but marginal delays to BRT, and one individual given mianserin
(30mg) was unable to complete the driving test (Ridout & Hindmarch, 2001). But the analogue
drug, mirtazapine (15mg), failed to influence driving performance (Kuitunen, 1994). These results
show that some antidepressants (cyclic e.g. mianserin and amitriptyline) but not others, specifically
SSRIs, can impair driving performance.

**Multiple doses in healthy volunteers (1-22 days).** Tricyclic antidepressants administered
over multiple doses also showed a capacity to impair performance. For example, for 20 male
volunteers amitriptyline (25mg t.i.d) significantly increased SDLP for up to 5-hours on day-1 of a
1-day study and resulted in 1/3rd of driving tests stopped (O’Hanlon, 1984). Using the same drug
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and daily dose, an 8-day study found that amitriptyline significantly increased SDLP at 1.5 and 5 hours post-dose only on day-1 and resulted in the termination of 7 driving tests (11%; Robbe & O'Hanlon, 1995). Amitriptyline (.8mg/kg b.i.d) has also resulted in increased steering errors 2-hours after the morning dose of a single day study for 20 healthy volunteers (Landauer, Milner, & Patman, 1969).

Other tricyclic antidepressants delivered similar results, with doxepin (25mg t.i.d) resulting in increased SDLP 2-3 hours for 20 healthy volunteers after the final dose on day-1 (O’Hanlon, 1984; Ramaekers, van Veggel, & O’Hanlon, 1994). For 40 males imipramine (25mg t.i.d) increased the number of errors compared to placebo when the results were collapsed over 7-days (Clayton, Harvey, & Betts, 1977). The same drug, dose, and timeframe increased SDLP 2.5 hours after dose on day 1 in 12 healthy volunteers, and resulted in one (4%) driving test being stopped (van Laar, van Willigenburg, & Volkerts, 1995). Finally, dothiepin (75mg nocte day-1 to-8; 150mg nocte day-8 to -22) administered over 22-days to 16 healthy volunteers had no influence on SDLP or headway variability (distance between lead and follow car; Ramaekers, O'Hanlon, & Muntjewerff, 1995).

Studies that administered tetracyclic antidepressants found that these drugs have the capacity to impair driving performance. For 20 healthy volunteers mianserin (10mg t.i.d) administered 2.5-hours prior increased SDLP on day-1 (O’Hanlon, 1984) and day-8 of two 8-day studies that administered 30mg to 18 healthy volunteers (Ramaekers, Muntjewerff, van Veggel, Uiterwijk, & O’Hanlon, 1998; Ramaekers et al., 1994). One 7-day study of 37 healthy volunteers mianserin significantly increased SDS 2-hours after dosage on day-7 (O'Hanlon, Robbe, Vermeeren, van Leeuwen, & Danjou, 1998). Mianserin also resulted in several driving tests being stopped (5 driving tests [3%]; O'Hanlon et al., 1998; 2 driving tests [3%]; Ramaekers et al., 1998; 1 driving test [3%]; Ramaekers et al., 1994). Conversely, oxaprotiline (25mg t.i.d) failed to result in any change to driving performance in 20 healthy volunteers on day 1 (O’Hanlon, 1984).

Two 7-day studies administered mirtazapine (30mg) to 18-health volunteers and found that
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it resulted in significantly increased SDLP up to 18-hours after dosage over 7-days (Ramaekers et al., 1998; Wingen, Bothmer, Langer, & Ramaekers, 2005). One 8-day study of 19 healthy volunteers found that 15mg was sufficient to result in a significant increase in SDLP and subjective sleepiness for 8-days (Sasada et al., 2013). One participant (2%) administered mirtazapine fell asleep and was unable to complete their driving test (Wingen et al., 2005). Also, one 7-day study of 32 healthy volunteers that were administered the mirtazapine analogue, esmirtazapine (4.5mg), found that it caused significant impairment to SDLP 11-hours after a single dose but not after repeated doses (Ramaekers et al., 2011).

Several other drugs were tested after multiple administrations with mixed results. The SSRI paroxetine did not produce any change in SDLP performance but it did result in the termination of three (5%) driving tests (40mg mane), but three (5%) placebo driving tests were also stopped in this study (Robbe & O'Hanlon, 1995). Similarly, nefazodone did not influence SDLP or SDS, but one (4%) driving test was stopped after 200mg of nefazedone (van Laar et al., 1995). The monoamine oxidase inhibitors (MAOIs), brofaromine (75mg b.i.d) and moclobemide (200mg, b.i.d; Ramaekers et al., 1994), serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine (75mg, b.i.d; O'Hanlon et al., 1998) and milnacipran (50mg; Richet, Marais, Serre, & Panconi, 2004), SSRIs escitalopram (20mg; Wingen et al., 2005), and fluoxetine (20mg, NOCTE; Ramaekers et al., 1995), the serotonin antagonist reuptake inhibitor, trazodone (25mg; Sasada et al., 2013), and bicyclic antidepressant, viloxazine (50mg, t.i.d; Clayton et al., 1977), failed to influence driving performance after single or multiple dose/s administered over 1-22 days to healthy individuals.

Multiple doses in patients (9-30 days). Only three studies examined the influence of multiple doses of antidepressants on patient’s driving ability. A non-randomised control study of 40 patients diagnosed with depression (20 reboxetine and 20 mirtazapine depressed: doses were variable) were compared to 10 healthy matched controls (age and gender; Brunnauer et al., 2008). At baseline, patients produced significantly more accidents (simulator) than controls. By day-14, a
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significant decline in accidents in the patient group meant that there was no significant difference between patients and controls. However, the timing of testing after medication was not specified.

A 15-day study of 7 patients with chronic neuropathic pain taking amitriptyline (25mg) found that SDLP significantly increased 13 hours after dosage on day-2 compared to placebo, analogous to the effects caused by a blood alcohol content (BAC) of 0.5 mg/ml, but the impairment disappeared after 2-weeks (Veldhuijzen et al., 2000). Finally, Shen et al. (2009) conducted a randomised controlled trial that examined 28 patients diagnosed with major depression. Half were administered mirtazapine (30mg nocte) for 1-month, while the other half remained untreated for 9-days. Road positioning for the treatment group improved from their baseline score, and there was a significant reduction in crashes at 1-month compared to their baseline, but one (1%) driving test was stopped. The authors attributed the improvement in the treatment group to the circadian pattern in depressed mood (lower affect in the morning) although no mood variation was noted in the study.

Opioid (single dose)

Three experimental studies examined the influence of a single dose of opioid medication on driving performance. One study of 70 professional drivers administered codeine (50 mg; others conditions included alcohol alone or in conjunction with codeine) found that it produced more collisions in a simulator than the placebo group 30-minutes after dose (Linnoila & Hakkinen, 1974). When administered codeine alone 60% of participants believed that they had been given alcohol. Another study of 16 healthy volunteers found that mean lateral position results for participants administered 20mg of codeine/paracetamol (20/400mg) were significantly worse than the placebo group 1-hour after dose (Amato et al., 2013). The final study involving 18 healthy volunteers tested 1-hour after dosage did not produce any significant difference between experimental and placebo groups despite participants reporting that they required more effort to complete the driving test when given oxycodone/paracetamol (10/650mg; Verster, Veldhuijzen, & Volkerts, 2006).

Collectively these results suggest that opioids have some negative influence on driving performance
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including subjective reports of cognitive impairment, but the limited number of studies that administered opioids makes firm conclusions difficult.

**Antipsychotic (single and multiple doses)**

Three experimental studies were found that included prescription antipsychotic medication in conjunction with driving tests. One study examined the influence of suriclone (.4mg) and zopiclone (7.5mg) alone and in conjunction with chlorpromazine (50mg) on 12 healthy volunteers (Mattila et al., 1994). Simulator driving test results showed significantly increased TESI and RT when participants were administered chlorpromazine combined with either suriclone or zopiclone at 6–hours post-dose compared to placebo and chlorpromazine alone. This evidence suggests that the use of cyclopyrrolones in combination with antipsychotics impairs driving performance.

Two non-randomised controls studies examined the influence of antipsychotic medication on driving performance for individuals diagnosed with schizophrenia. The first study of 38 participants (22 schizophrenia patients; 16 controls) found that patients (15 on flupenthixol decanoate and 7 on flunphazine decanoate for 3-months: doses were variable) were significantly worse at driving (accuracy, RT, and red light recognition) than controls, irrespective of medication type (time of testing unspecified; Wylie et al., 1993). The second study of 80 participants diagnosed with schizophrenia revealed that those taking amisulpride had significantly fewer accidents than those taking haloperidol or flupenthixol, while individuals taking quetiapine had significantly fewer accidents than haloperidol (time of testing unspecified; Brunnauer, Laux, & Zwick, 2009). These two studies suggest that individuals diagnosed with schizophrenia who are medicated underperform compared to controls, while the type of medication has shown to modify the level of performance. However, underperformance could also be the result of the cognitive deficits that the patients with schizophrenia exhibit (Reichenberg & Harvey, 2007).

Based on very limited evidence, antipsychotic medication may worsen performance when taken in combination with other medication and driving performance appears to be influenced by
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the type of antipsychotic medication taken. However, the very limited driving studies involving participants prescribed antipsychotic medication (in particular double-blind placebo controlled trials) makes drawing firm conclusions about the impact on driving difficult.

Dose-response relationship

Five experimental studies (four single, one multiple dose) demonstrated a dose-response relationship on driving performance for benzodiazepines and z-drugs, antidepressants, and opioids.

Of the single dose studies, one found that 10mg of diazepam (compared with 5mg) caused significant impairment of SDLP 1-hour after dosage when administered to nine driving instructors (O'Hanlon, Haak, Blaauw, & Riemersma, 1982). In line with this, one study of 30 healthy volunteers that tested zolpidem, (10, 20mg) found that 4-hours after dose only 20mg significantly impaired SDLP and SDS (Verster, Volkerts, Schreuder, et al., 2002). One study of 16 healthy volunteers found that tianeptine, showed a dose-response trend with a marginal delay of BRT after a single dose at 37.5mg, but not at 12.5mg (Ridout & Hindmarch, 2001). One study of 18 healthy volunteers tested 1-hour after dosage found a significant impairment of SDLP and SDS after 10/650 oxycodone/paracetamol, but not 5/325mg (Verster et al., 2006). The only multiple dose study found that at 200mg, the antidepressant nefazadone resulted in the termination of one driving test (no driving tests terminated for 100-mg; van Laar et al., 1995).

Meta-analysis: experimental studies (z-drugs)

The experimental literature found by the systematic review was examined to determine whether a meta-analysis was possible. To be included in a meta-analysis the studies had to have the same study design (randomised double-blind placebo-controlled experimental study), drug class, outcome measure, dose regime, and time between dose and driving test. To synthesize heterogeneous studies, we used a random effects model analysis (Dersimonian-Liard correction) to calculate the pooled estimate, as this method does not assume that each component study of the meta-analysis is derived from the same population and does not compromise statistical validity.
However, the random-effects approach does produce wider confidence intervals than the fixed-effects approach, resulting in reduced precision. Only z-drugs satisfied the inclusion criteria, analysis of other drugs classes was not feasible because of the insufficient number of studies that met the criteria.

Five randomised double-blind placebo-controlled experimental studies investigated the influence of z-drugs on healthy volunteers’ driving performance (SDLP) 10-hours after being administered a single dose of zaleplon (10mg; Vermeeren et al., 2002), zopiclone (7.5mg; Bocca et al., 2011; Leufkens et al., 2009; Leufkens & Vermeeren, 2009; Ramaekers et al., 2011; Vermeeren et al., 2002), and/or zolpidem (10mg; Bocca et al., 2011; 7.5mg; Leufkens et al., 2009). Figure 1 shows that the meta-analysis found no heterogeneity between studies (Cochran Q = 5.03; p=0.656 I² = 0.0%). The meta-analysis (using Cohen’s d) detected a pooled moderate to large effect size of 0.69 (95% CI, 0.49-0.90) and a z-score analysis of standardised mean difference (SMD) between z-drugs and placebo was 6.56 (p<0.001, against a null value of SMD= 0). This evidence suggests that driving 10 hours after taking z-drugs impairs driving performance (SDLP) and that this impairment is significant compared to no medication.
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Conclusion: experimental studies

A meta-analysis and systematic review of the experimental literature investigating the influence of prescription medication on driving performance found that certain types of prescription medication (e.g., benzodiazepines, z-drugs, antidepressants, opioids, antipsychotics) can significantly impair driving performance. A meta-analysis of studies that administered a single dose of a z-drug (zopiclone, zolpidem, or zaleplon) 10-hours prior to a driving test found that z-drugs significantly impaired driving performance (SDLP) compared to placebo. The systematic review of experimental studies found that single and multiple doses of benzodiazepine and z-drugs impaired driving performance in healthy volunteers and patients. Drugs that impaired performance included diazepam (4-hours after a single dose healthy volunteers; 1.5-hours after dosage on day-21 in patients diagnosed with anxiety) lormetazepam (10-hours after dosage on day-8 for patients with
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insomnia), alprazolam (1 hour after dosage on day-9 for healthy volunteers), lorazepam (3-hours after dosage for healthy volunteers; 4-hours after dosage on day-15 for patient diagnosed with anxiety), nitrazepam (9.5-hours after dosage on day-3 for healthy volunteers; 16-hours after dosage on day-13 for patients diagnosed with insomnia), flurazepam (9 hours after dosage on day-4 for healthy volunteers; 16-hours after dosage on day-2 for patient diagnosed with insomnia), flunitrazepam (9-hours after a single dose for healthy volunteers; 17 hours after dosage on day-2 for females that used hypnotics), loprazolam (10-hours after dosage on day-2 for former hypnotic drug users) zopiclone (10-hours after a single dosage for healthy volunteers; 10 hours after dosage on day-8 for patients diagnosed with insomnia) and zolpidem (10-hours after a single dose for healthy volunteers; 5.5-hours after single dose for patients diagnosed with insomnia).

Only tetra and tricyclic antidepressants impaired driving performance: drugs included amitriptyline (5-hours after the final day-1 dosage for healthy volunteers; 13-hours after dosage on day-14 for patient diagnosed with neuropathic pain), miansein (2.5-hours after dosage on day-8 for healthy volunteers), and mirtazapine (18-hours after dosage on day-7 for healthy volunteers). While the opioids, codeine (30-minutes after single dosage for healthy volunteers) and oxycodone (1-hour after single dosage for healthy volunteers), and antipsychotics flupenthixol decanoate, flunphazine decanoate, haloperidol, chlorpromazine in combination with cyclopyrronolones demonstrated the capacity to impair driving performance, but given that very limited studies have used opioids and antipsychotics, it is difficult to make firm conclusions. Finally a dose-response relationship was reported for the benzodiazepine, diazepam, the tricyclic antidepressant tianeptine, and the opioid oxycodone. Together this evidence suggests that specific medication can influence the driving performance of healthy individuals and patients.

**Epidemiological evidence of exposure to CNS-D drugs and risk of MVA**

Using the same strategy as Elvik (2013), the terms “drugs” and “accident risk” were used in several databases, including the TRANSPORT literature database, PubMed, Sciencedirect
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(searching journals Accident Analysis and Prevention, Drugs and Alcohol Dependence and Journal of Safety Research) and SafetyLit.

**Study selection inclusion criteria were:**

(i) Published between 1976 and 2013

(ii) Cohort, case-control, case crossover, or case-series design

(iii) Explicitly identified estimation of risk of MVA (e.g. odds ratio [OR], standardised incidence ratio [SIR], relative risk [RR]) within 1-month of prescription or dispensation of medication.

(iv) Drugs assessed must include antidepressants, antipsychotics, benzodiazepines, opioids, or z-drugs.
Initially screened for relevance (n=117)

Excluded:
37 – no CNS-D drugs
69 – no estimation of risk, no original data, not in English, > 1-month time point, wrong study design

Retained articles (n=11)

1 – sample overlap
1 – re-analysed data from previous paper

Included Studies (n=9)

5 - cohort
2 – case control
2 – case crossover

Figure 4. Selection process for epidemiological studies of exposure and risk of MVA
Systematic review results: epidemiological studies

The initial search retrieved 117 articles. The selection process of the eligible studies is summarized in Figure 3. Thirty-seven articles were excluded because the drugs assessed were unrelated to the criteria. Sixty-nine articles were excluded because there was no estimation of risk, the language was not English, the time point exceeded 1-month, or were not original research studies (e.g. reviews, meta-analyses). Eleven articles were retained. From these articles a further 2 were removed because in more recent publications, one examined the same cohort while the second re-analysed the data from a previous paper. As shown in Tables 1-3, nine articles remained that included three types of epidemiological study designs: case-control studies, that examined the frequency of exposure to medication in drivers involved in MVAs versus the frequency of those who were not; case-crossover studies, where the case acted as their own control and time periods of non-exposure were compared to time periods of exposure; and cohort studies, where a group of people with differing exposure to prescription medication were followed for a period of time for MVAs.

Five cohort studies, shown in Table 1 examined benzodiazepines (hypnotics, anxiolytics, and unspecified), z-drugs (hypnotics with a short and long half-life), antipsychotics (unspecified), opioids (unspecified) or antidepressants (unspecified, cyclic, SSRI, and tricyclic), and other sedatives (unspecified). Three cohort studies (including a self-controlled case series) measured exposure as the first month following a prescription of benzodiazepines other sedative, antipsychotics, opioids, or antidepressants (Gibson et al., 2009; Neutel, 1995; Ray, Fought, & Decker, 1992), while two cohort studies measured exposure as the 2–week period after dispensing a prescription of benzodiazepines (hypnotics, anxiolytics, nitrazepam, flunitrazepam), z-drugs (zopiclone and zolpidem), or opioids (unspecified; Engeland, Skurtveit, & Morland, 2007; Gustavsen et al., 2008). Two case-control studies, shown in Table 2 (Hemmelgarn, Suissa, Huang, Boivin, & Pinard, [1997] only presented in Table 2 as Hebert, Delaney, Hemmelgarn, Levesque,
and Suissa [2007] re-analysed data in a case cross-over study), examined benzodiazepines (short and long half-life, hypnotics, anxiolytics, unspecified), z-drugs, antidepressants (SSRI, SNRI, cyclic, tricyclic, unspecified), or antipsychotics (unspecified; Chang et al., 2012; Orriols et al., 2012). One case–control study defined exposure as involvement in a MVA and registered in a national insurance database over a 1-month period (Orriols et al., 2012). The other case control study defined exposure as individuals registered in a national insurance database and receiving a prescription that coincided with the start of the study (Chang et al., 2012). Finally, two case crossover studies, shown in Table 3, examined benzodiazepines (short and long half-life) or z-drugs (zopiclone, zolpidem; Hebert et al., 2007; Yang, Lai, Lee, Wang, & Chen, 2011). Exposure was defined as: dispensing a prescription within 7-days prior to MVA (Hebert et al., 2007); 1-month after first prescription of medication (Gibson et al., 2009); and hospitalised due to MVA with 1-month of prescription (Yang et al., 2011). Estimators of risk are expressed in the form of; odds ratio (OR), adjusted odds ratio (AOR), relative risk (RR), incidence risk ratio (IRR), or standard incidence ratio (SIR).

**Benzodiazepines and Z-drugs**

Eleven epidemiological studies calculated the risk of being involved in a MVA associated with benzodiazepines and/or z-drugs (four cohort, two case control, and three case cross-over studies), as described below.

**Benzodiazepines. 1-day.** One case-control study showed that, compared to controls (outpatients not receiving treatment for MVA), those who received treatment for MVA had increased odds of receiving a prescription for benzodiazepines 1-day (1.62; 95% CI, 1.39-1.88: Chang et al., 2012). This same study found that benzodiazepines used as anxiolytics (1.63; 95% CI, 1.40-1.91) and benzodiazepines used as hypnotics (1.56; 95% CI, 1.17-2.08) also increased the odds of MVA compared to controls (Chang et al., 2012). Two studies, one case control (Chang et al., 2012) and one case cross-over (Yang et al., 2011), found that benzodiazepines with both a long and
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short half-life increased the odds of MVA compared with controls and control periods. The case control study found that, compared to controls, the odds of MVA were elevated for benzodiazepines with a long (1.91; 95% CI, 1.47-2.49) and short half-life (1.59; 95% CI, 1.35-1.87: Chang et al., 2012). Likewise the case cross-over studies found that, compared to three control periods (3-, 6-, and 9-months prior), receiving a prescription 1-day prior for benzodiazepines with a long (1.74; 95% CI, 1.26-2.40) and short half-life (1.13; 95% CI, 1.04-1.23) increased the odds of MVA (Yang et al., 2011).

7-days. One case control study found that, compared to controls, receiving a prescription for benzodiazepine 7-days prior increased the odds of MVA (1.64; 95% CI, 1.43-1.88; Chang et al., 2012). The same study found that, compared to controls, benzodiazepines used as anxiolytics (1.70; 95% CI, 1.47-1.96) and hypnotics (1.44; 95% CI, 1.09-1.91), and benzodiazepines with a long (1.89; 95% CI, 1.50-2.38) and a short half-life (1.63; 95% CI, 1.40-1.89) also increased the odds of MVA. A different case-control study found that, compared to controls (individuals that filled one prescription in the previous year), the odds of being involved in a MVA were increased 7-days after dispensing a prescription of benzodiazepines with a long half-life (1.45; 95% CI, 1.12–1.88: Hebert et al., 2007). However, the same study found that the odds of being involved in a MVA were no greater than controls 7-days after dispensing a prescription of benzodiazepines with a short half-life (1.07; 95% CI, 0.91–1.26: Hebert et al., 2007). At the same time point, a case-crossover study found that, compared to three control periods (3-, 6-, and 9-months prior), receiving a prescription for benzodiazepines with a long (1.08; 95% CI, 1.02–1.14) and a short half-life 7-days prior increased the odds of MVA (1.08; 95% CI, 1.02–1.14: Yang et al., 2011).

One cohort study found that, compared to the previous 6-months of non-exposure, dispensing of benzodiazepines used as hypnotics (9.1; 95% CI 1.1-72.7) and anxiolytics (13.5; 95% CI 1.8-100.8) 7-days prior increased the odds of MVA (Neutel, 1995). Another cohort study found that, compared to a non-exposure period, dispensing a prescription of benzodiazepines used as
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Hypnotics (2.9; 95% CI, 2.5-3.5) and anxiolytics (3.3; 95% CI, 2.1-4.7) 7-days prior increased the risk of MVA (Engeland et al., 2007). Finally, a cohort study found that, compared to a non-exposure period, dispensing a prescription for the benzodiazepines, flunitrazepam (4.0; 95% CI, 2.4-6.4) and nitrazepam (2.7; 95% CI, 1.8-3.9) 7-days prior increased the incidence (SIR) of MVA (Gustavsen et al., 2008).

2-weeks. One cohort study found that, compared to a non-exposure period, the incidence (SIR) of MVA was elevated 2-weeks after dispensing a prescription for the benzodiazepines, flunitrazepam (3.1; 95% CI, 2.0-4.6) and nitrazepam (2.2; 95% CI 1.6-3.0; Gustavsen et al., 2008). The other cohort study found that, compared to a non-exposure period of 6-months, dispensing a prescription for benzodiazepines used as hypnotics (6.5; 95% CI, 1.9-22.4) and anxiolytics (5.6; 95% CI, 1.7-8.4) 2-weeks prior increased the odds of MVA (Neutel, 1995). Finally, one case cross-over study found that, compared to three control periods (3-, 6-, and 9-months prior), receiving a prescription for benzodiazepines with a long (1.05; 95% CI, 1.02–1.08) and a short half-life (1.01; 95% CI, 1.01–1.02) 2-weeks prior increased the odds of MVA (Yang et al., 2011).

3-weeks. One case cross-over study found that, compared to three control periods (3, 6, and 9 months prior), receiving a prescription for benzodiazepines with a long (1.04; 95% CI, 1.01-1.06) and short half-life (1.01; 95% CI, 1.00-1.02) 3-weeks prior marginally increased the odds of MVA (Yang et al., 2011).

1-month. Four studies investigated the influence of benzodiazepines on MVAs at 1-month. One cohort study found that, compared to the control period, the odds of MVA were elevated 1-month after receiving a prescription for benzodiazepine used as hypnotics (3.9; 95% CI, I .9- 8.3) and anxiolytics (2.5; 95% CI 1.2-5.2; Neutel, 1995). Another cohort study found that, compared to non-exposure, receiving a prescription for benzodiazepines 1-month prior increased the risk (RR) of MVA (1.3; 95% CI, .6-2.9: Ray, 1992). One final cohort study (self-controlled case series) found that, compared to a period of non-exposure, receiving a prescription for benzodiazepines 1-month
prior increased the risk of being involved in a MVA (1.94; 99% CI, 1.62-2.32: Gibson et al., 2009). A case-control study found that, compared to controls, the odds of being involved in a MVA were elevated 1-month after receiving a prescription for benzodiazepines (1.56; 95% CI, 1.38-1.75), benzodiazepines with a long (1.72; 95% CI, 1.43-2.07) and short half-life (1.56; 95% CI, 1.37-1.78), and benzodiazepines used as hypnotics (1.51, 95% CI, 1.19-1.94) and anxiolytics (1.60; 95% CI, 1.41-1.80: Chang et al., 2012). One case cross-over study found that, compared to the three control periods (3, 6, and 9 months prior), receiving a prescription for benzodiazepines with a long (1.03; 95% CI, 1.01-1.05) and short half-life (1.01; 95% CI, 1.00-1.01) 3-weeks prior marginally increased the odds of MVA (Yang et al., 2011).

**Z-drugs. 1-day.** A case-control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for z-drugs 1-day prior increased the odds of MVA (1.34; 95% CI, 1.03-1.75: Chang et al., 2012). One case crossover study found that, compared to the three control periods (3, 6, and 9 months prior), receiving a prescription 1-day prior for zopiclone (1.55; 95% CI, .98-2.45) and zolpidem (1.74; 95% CI, 1.25-2.43) also increased the odds of MVA (Yang et al., 2011).

**7-days.** A case-control study found that, compared to controls, receiving a prescription for z-drugs 7-days prior increased the odds of MVA (1.37; 95% CI 1.06-1.75: Chang et al., 2012). A case cross-over study found, compared to the three control periods (3, 6, and 9 months prior), receiving a prescription for zopiclone (1.08; 95% CI, 1.00–1.16) and zolpidem (1.08; 95% CI 1.03–1.13) 7-days prior also increased the odds of MVA (Yang et al., 2011). Finally, a cohort study found that, compared to the non-exposure period, dispensing a prescription of zopiclone (2.3; 95% CI 2.0-2.8) and zolpidem (2.2; 95% CI, 1.4-3.4) 7-days prior increased the incidence (SIR) of MVA (Gustavsen et al., 2008).

**2-weeks.** A case cross-over study found that, compared to the three control periods (3, 6, and 9 months prior), receiving a prescription for zopiclone (1.03; 95% CI, 0.99–1.08) and zolpidem
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(1.05; 95% CI, 1.02–1.07) 2-weeks prior increased the odds of MVA (Yang et al., 2011). A cohort study found that, compared to the non-exposure period, dispensing a prescription of zopiclone (2.0; 95% CI, 1.7-2.2) and zolpidem (2.1; 95% CI, 1.5-2.9) 2-weeks prior increased the incidence (SIR) of MVA (Gustavsen et al., 2008).

3-weeks. A case cross-over study found that, compared to the three control periods (3, 6, and 9 months prior), receiving a prescription for zopiclone (1.02; 95% CI 0.99–1.05) and zolpidem (1.03; 95% CI 1.01–1.05) 3-weeks prior increased the odds of MVA (Yang et al., 2011).

1-month. A cohort study (self-controlled case series) found that, compared to a period of non-exposure, receiving a prescription for long (1.37; 99% CI 1.05-1.79) and short half-life z-drugs used as hypnotics (1.06; 99% CI, .73-1.54) 1-month prior increased the incidence of MVA (Gibson et al., 2009). Finally, a case control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for z-drugs (1.42; 95% CI, 1.14-1.76) 1-month prior increased the odds of a MVA (Chang et al., 2012). A case cross-over study found that, compared to the three control periods, receiving a prescription for zopiclone (1.02; 95% CI, 0.99–1.04) and zolpidem (1.03; 95% CI, 1.01–1.04) 3-weeks prior increased the odds of MVA (Yang et al., 2011).

Antidepressants

Several studies found mixed results for the influence of first (tricyclic, cyclic) and second- (SSRIs, SNRIs) generation antidepressants on the risk of being involved in a MVA.

1-day. One case control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for antidepressants (1.70; 95% CI, 1.26-2.29), SSRIs (1.74; 95% CI, 1.15-2.6) or cyclic antidepressants (1.88; 95% CI, 1.23-2.90) 1-day prior increased the odds of MVA (Chang et al., 2012).

7-days. One case control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for antidepressants (1.71; 95% CI 1.29-2.26), SSRIs (1.80; 95% CI 1.22-2.65) or cyclic antidepressants (1.93; 95% CI, 1.29-2.87) 7-days prior increased the odds of
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MVA (Chang et al., 2012).

2-weeks. One cohort study found that, compared to non-exposure (6-months prior without prescription), receiving a prescription for antidepressants 2-weeks prior did not increase the odds of MVA (1.0; 95% CI, .4-2.6: Neutel, 1995).

1-month. For one cohort study, compared to non-exposure (6-months prior without prescription), receiving a prescription for antidepressants 1-month prior did not increase the odds of MVA (1.0; 95% CI, .5-2.1: Neutel, 1995). Another cohort study found that compared to non-exposure, receiving a prescription for antidepressants 1-month prior increased the risk (RR) of MVA (1.6; 95% CI, .5-4.8: Ray et al., 1992). One final cohort study (self-controlled case series) found that, compared to a period of non-exposure, receiving a prescription for tricyclic antidepressants (0.92; 99% CI, .73-1.16) or SSRIs (0.92; 99% CI, .75-1.12) 1-month prior did not increase the risk (IRR) of MVA (Gibson et al., 2009). One case control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for antidepressants (1.73; 95% CI, 1.34-2.22), SSRIs (1.72; 95% CI 1.20-2.47), or cyclic antidepressants (1.77; 95% CI 1.27-2.48) 7-days prior increased the odds of MVA (Chang et al., 2012).

Opioids

A cohort study found that, compared to a non-exposure period, dispensing a prescription of opioids 7 days prior increased the incidence (SIR) of a MVA (2.0; 95% CI, 1.7-2.4: Engeland et al., 2007). Another cohort study found that compared to non-exposure, receiving a prescription for an opioid analgesic 1-month prior did not increase the risk (RR) of MVA (1.1; 95% CI, 0.5-2.4; Ray et al., 1992). Finally, one cohort study (self-controlled case series) found that, compared to a period of non-exposure, receiving a prescription for tricyclic opioids (1.70; 99% CI, 1.39-1.12) 1-month prior did not increase the risk (IRR) of MVA (Gibson et al., 2009).

Antipsychotics
The three epidemiological studies that examined the relationships between antipsychotics and MVAs produced mixed results. One cohort study found that, compared to non-exposure (6-months prior without prescription) receiving a prescription for antipsychotics 7-days (0.7; 95% CI .2-2.9) and 14-days (.6; 95% CI .2-1.9) prior, failed to increase the odds of MVA (Neutel, 1995). Likewise, a case control study found that, compared to controls (outpatients not treated for MVA), receiving a prescription for antipsychotics 1-day (0.96; 95% CI .52-1.77), 7-days (0.97; 95% CI I.53-1.78) or 1-month (0.91; 95% CI .52-1.59) prior did not increase the odds of MVA at (Chang et al., 2012).

**Other sedatives**

A cohort study found that, compared to the non-exposure period (6 months prior to the reference date), receiving a prescription for “other sedative” drugs (unspecified) 2- (2.7; 95% CI, 1.5-5.0) and 4-weeks (2.2; 95% CI, 1.3-3.7) prior increased the odds of MVA (Neutel, 1995).

**Effects of age**

Pharmacokinetic and pharmacodynamic changes occur with increasing age, which could influence the ability of the elderly to metabolise medications and hence may result in extended impairment of functioning (McLean & Le Couteur, 2004; Schwartz, 2007). Of the nine studies found, three investigated the risk of a MVA for drivers aged 65 years and over (Hebert et al., 2007; Ray et al., 1992; Yang et al., 2011). One case cross-over study of older drivers (67-84 years) found that, compared to the non-exposure period, dispensing a prescription of benzodiazepines with a long (0.99; 95% CI, 0.81-1.21) or short (1.04; 95% CI, 0.92- 1.17) half-life 7-days prior did not increase the risk of MVA. One cohort study of older drivers (65-84 years) found that, compared to non-exposure, receiving a prescription of benzodiazepines (1.3, 95% CI, 0.6-2.9) and antidepressants (1.6, 95% CI, 0.5-4.8) 1-month prior increased the risk (RR) of MVA (Ray et al., 1992). One case crossover study found that, compared to the three control periods (3, 6, and 9-months prior),
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receiving a prescription 1-day prior for long (1.74; 95% CI, 1.26-2.40) or short half-life benzodiazepines (1.13; 95% CI, 1.04-1.23), zopiclone (1.55; 95% CI, 0.98-2.45), or zolpidem (1.74; 95% CI, 1.25-2.43) 1-day prior increased the odds of MVA (Yang et al., 2011). The same study found that, for long and short half-life benzodiazepines, zolpidem and zopiclone, receiving a prescription 7-days to 1-month prior marginally increased the odds of MVA. Limited conclusions can be made about age and risk of MVA because a limited number of studies examined the influence of dispensing or receiving a prescription for medication by older drivers on the risk of MVA and no study compared younger and older populations.

Dose-response relationship

Three out of the nine epidemiological studies examined whether there was a dose-response relationship; that is, whether risk of MVA increases with a larger dose. A dose-response relationship was found for benzodiazepines (Chang et al., 2012; Ray et al., 1992), cyclic antidepressants (Ray et al., 1992), antidepressants (Chang et al., 2012), and z-drugs (Chang et al., 2012). A cohort study found that, compared to non-exposure, having a prescription equivalent to 4mg of the benzodiazepine diazepam 1-month prior resulted in a risk (RR) of MVA of 1.1 (95% CI, 0.5-2.2), when the prescription was equivalent to 20 mg or more of the benzodiazepine diazepam the risk (RR) of MVA increased to 2.4 (95% CI, 1.3-4.4; Ray et al., 1992). The same study found that, compared to non-exposure, having a prescription for 25mg of the cyclic antidepressants amitriptyline 1-month prior resulted in a risk (RR) of MVA of 0.8 (95% CI, 0.3-2.7), while when the dose increased to 125mg the risk (RR) of MVA increased to 5.5 (95% CI 2.6-11.6).

The final study compared users to a non-user reference group. This case-control study found that the consumption of antidepressants equal to 0.6–1 DDD (1.63, 95% CI 1.00-2.65) or >1 DDD (2.33, 95% CI 1.42-3.83) increased the odds (AOR) of a MVA (Chang et al., 2012). Compared to the non-user reference group, a low dosage of benzodiazepines (0.1–0.5 DDD) demonstrated a capacity to significantly increase the odds (AOR) of a MVA (1.31, 95% CI, 1.03-1.66); the odds
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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(AOR) of MVA increased when the dose increased 0.6–1 DDD (1.66, 95% CI, 1.30-2.10) and the same pattern occurred when the dose was >1 DDD (2.09, 95% CI, 1.63-2.68). The same pattern was found for z-drugs with the odds (AOR) of MVA increasing from 1.20 (95% CI, 0.85-1.70) for 0.6-1 DDD to 2.11 (95% CI, 1.38-3.23) for >1 DDD. However, these results only suggest a dose response relationship as the confidence intervals overlap. Finally, antipsychotics did not provide evidence that would suggest a dose-response relationship in this study and was not examined in any other study.

Conclusion: epidemiological studies

The current systematic review of epidemiological studies found that the type of medication prescribed or dispensed up to 1-month prior dictated the risk of MVA. Being prescribed or dispensed a benzodiazepine and z-drug 1-month prior increased the risk of MVA. For antidepressants, two epidemiological studies (cohort and case crossover) found that being prescribed an antidepressant (tricyclic, SSRI) up to 1-month prior did not increase the risk of MVA. In contrast, a case control study found that being prescribed an antidepressant (SSRI, cyclic, unspecified) 1-month prior did increase the risk of MVA. Two epidemiological studies (cohort, case-crossover) found that being prescribed or dispensing opioids up to 1-month prior did not increase the risk of MVA. However, one cohort study found that receiving a prescription for an opioid 1-month prior did increase the risk of MVA. All epidemiological studies that investigated antipsychotics found that receiving a prescription up to 1-month did not increase the risk of MVA. One epidemiological study (cohort) found that receiving a prescription of sedative medication (unspecified) up to 1-month prior increased the risk of MVA. Finally, three studies found a dose-response relationship for benzodiazepines, z-drugs, and antidepressants (cyclic and unspecified), which means that as the dose increases so does the risk of MVA. Despite the limited number of epidemiological studies that satisfied the inclusion criteria, receiving a prescription of, or dispensing a benzodiazepine or z-drug 1-month prior, increased the risk of MVA. One possible explanation of
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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this increased risk of MVA 1-month after receiving or dispensing benzodiazepines or z-drugs is that patients fail to develop a tolerance for the medication which impairs driving performance. A meta-analysis was not possible due insufficient compatible epidemiological studies that measured the same drug classes at the same time points.

**Confound by indication**

Conclusions from both experimental and epidemiological studies presented in this literature review are qualified by the fact that they include individuals with diagnosed disorders, mostly psychiatric disorders. Results are susceptible to confound by indication because the poor driving performance could be explained by the symptomatology of, or cognitive impairments associated with, the diagnosed illness (Metzner et al., 1993; Silverstone, 1988) or by consuming medication that has been shown to impair driving performance in healthy volunteers or both. In this instance, the risk of MVA would increase. Conversely, the drug classes in this systematic review of epidemiological studies may have included individuals who had been prescribed medication for future events that may not have occurred within the 1-month time frame. For example, the SSRI sertraline has been shown to be effective in reducing symptomatology in women diagnosed with premenstrual syndrome or premenstrual dysphoric disorder (Freeman, Sammel, Lin, Rickels, & Sondheimer, 2011). Absence of symptomatology and therefore the consumption of a prescribed medication would tend to reduce the risk of MVA. One way to account for confound by indication factors is to record and then control for factors that would systematically bias results. Diagnosis, medication, and other psychosocial factors could bias results in both experimental and epidemiological research.
<table>
<thead>
<tr>
<th>Study (y; country)</th>
<th>Design (period)</th>
<th>Study Cohort</th>
<th>Study Cohort</th>
<th>Ascertainment of Exposure</th>
<th>Ascertainment of non-exposure</th>
<th>Outcome Measure (method or reporting)</th>
<th>Adjustment/stratification/controlled/variables</th>
<th>Duration</th>
<th>Drugs/drug classes</th>
<th>Risk (95% CI)</th>
<th>Dose response effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ray et al. (1992; USA)</td>
<td>Cohort with a case crossover component for drivers involved in crashes (Jan 1984–Dec 1988)</td>
<td>16 262 Tennessee Medicaid enrollees aged 65–84 y, holding a driving licence</td>
<td>Receiving prescription for a psychoactive drug. Subgroups: current use, indeterminate use, past use</td>
<td>No prescriptions for BDZs</td>
<td>MVA reported to Tennessee Department of Safety (no. of crashes per 1000 person years)</td>
<td>Age, sex, race, county of residence and calendar year</td>
<td>Case-crossover study adjusted for alcohol use and driving frequency</td>
<td>1-month</td>
<td>BDZ</td>
<td>RR 1.3 (0.6-2.9)</td>
<td>Yes</td>
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<td>Neutel (1995; Canada)</td>
<td>Cohort (Jan 1979–Dec 1986)</td>
<td>323 658 individuals &gt;20 y of age included in the Saskatchewan Health Databases</td>
<td>First 2–4wk following prescription of a BDZ hypnotic (n = 78 070) or an anxiolytic (n = 147 726), but not receiving any within 6 mo preceding index</td>
<td>Not received a prescription for a BDZ within 6 mo preceding a reference date (n = 97 862)</td>
<td>MVA related hospitalization following sale of indexed prescription (no. of hospitalization s)</td>
<td>Age, sex and other prescribed drugs</td>
<td>7-days</td>
<td>BDZ Hyp</td>
<td>OR 9.1 (1.1-72.7)</td>
<td>No</td>
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<td>2-weeks</td>
<td>BDZ Anx</td>
<td>OR 13.5 (1.8-100.8)</td>
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<td>BDZ Hyp</td>
<td>OR 6.5 (1.9 to 22.4)</td>
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<td>BDZ Anx</td>
<td>OR 5.6 (1.7 to 8.4)</td>
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<td>Other sedatives</td>
<td>OR 2.7 (1.5-5.0)</td>
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<td>Antipsy</td>
<td>OR .7 (.2-2.9)</td>
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<td>Antidep</td>
<td>OR 1.0 (4-2.6)</td>
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<td>BDZ Hyp</td>
<td>OR 3.9 (1.9 to 8.3)</td>
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<td>BDZ Anx</td>
<td>OR 2.5 (1.2 to 5.2)</td>
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<td>Antidep</td>
<td>OR 1.0 (5-2.1)</td>
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<td>Study (y; country)</td>
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<td>Engeland et al. (2007; Norway)</td>
<td>Registry based (Apr 2004–Sep 2005)</td>
<td>All Norwegians aged 18–69 y (3.1 million)</td>
<td>Drug dispensing information. Exposed periods: first 7 days/14 days after dispensing or period corresponding to no. of dispensed DDDS</td>
<td>Period other than the exposed period for the given drug</td>
<td>MVA that resulted in a personal injury (incidence rate)</td>
<td>Stratified for sex and age, adjusted for month of the year</td>
<td>7-days</td>
<td>BDZ Anx, BDZ Hyp, Natural opium alkaloids</td>
<td>SIR 2.9 (2.5–3.5), SIR 3.3 (2.1–4.7), SIR 2.0 (1.7–2.4)</td>
<td>No</td>
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<td>Gustavsen et al. (2008; Norway)</td>
<td>Registry based (Jan 2004–Sep 2006) (Apr 2004–Sep 2005)</td>
<td>All Norwegians aged 18–69 y (3.1 million)</td>
<td>Drug dispensing information. Exposed periods: first 7 days/14 days after dispensing</td>
<td>Period other than the period defined as exposed time</td>
<td>MVA entered in Road Accident Registry (incident rate)</td>
<td>Month of the year, other prescribed drugs, stratified for age and sex</td>
<td>7-days</td>
<td>BDZ Hyp, nitrazepam, flunitrazepam</td>
<td>SIR 2.7 (1.8–3.9), SIR 4.0 (2.4–6.4)</td>
<td>No</td>
<td>The degree of the MVA (e.g. injurious, non-casualty) not specified. Risk is higher in</td>
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<td>Study (y; country)</td>
<td>Design (period)</td>
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<td>Ascertainment of Exposure</td>
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<td>Gibson et al. (2009; UK) Cohort (Self-controlled case series: 1986–Nov 2004)</td>
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<td>Individuals aged 18–74 met with TA and were prescribed with sedative drugs during 1986–2004. Non-driving participants excluded case series (1986–Nov 2004)</td>
<td>Drug prescription information. Initial exposure: first 4wk after prescription. Extended exposure: reminder of the course of treatment</td>
<td>Period beyond the time window that spans 4wk prior to first prescription to 24 wk after last prescription (49821)</td>
<td>MVA documented in primary healthcare database</td>
<td>Age education, sex, other diseases, miles driven, marital status, ethnicity, residence</td>
<td>1-month</td>
<td>BDZ nonBDZ hyp short +/-2</td>
<td>IRR 1.94 (1.62–2.32)*</td>
<td>No</td>
<td>young drivers and male drivers</td>
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<td>nonBDZ hyp long +/-2</td>
<td>IRR 1.06 (0.73–1.54)*</td>
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<td>Tricyclic antidep</td>
<td>IRR 1.37 (1.05–1.79)*</td>
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<td>SSRIs</td>
<td>IRR 0.92 (0.73–1.16)*</td>
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<td>Opioids</td>
<td>IRR 0.92 (0.75–1.12)*</td>
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<td>IRR 1.70 (1.39–1.12)*</td>
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<td>Authors</td>
<td>Study Design (period)</td>
<td>Study population from which samples selected</td>
<td>Cases</td>
<td>Controls</td>
<td>Drug exposure ascertainment</td>
<td>Adjustment/stratification/controlled/variables</td>
<td>Duration</td>
<td>Subgroups/studied drug group</td>
<td>Risk (95% CI)</td>
<td>Dose response effects</td>
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<td>*Hemmelgarn et al.[25] (1997; Canada)</td>
<td>Nested case control (Jun 1990–May 1993)</td>
<td>Subjects aged 67–84 y who possessed a valid driving licence and resided in Quebec for at least 2 y</td>
<td>5579 drivers involved in injurious MVAs</td>
<td>55 790 drivers (10 per one case) who were at risk of but did not meet with accidents during the index date</td>
<td>Prescription records: exposed if index date included the period of prescription, not exposed if no BDZ use within 365 days preceding index date</td>
<td>Sex, age, locality of residence, history of previous injurious TA, chronic disease score, use of other CNS drugs</td>
<td>7 days</td>
<td>long and short +/-2 benzo</td>
<td>OR 1.45 (1.04, 2.03) OR remains high in first year of use short first week of use OR 1.04 (0.81, 1.34)</td>
<td>No</td>
<td>* Cohort reanalysed by Hebert et al. (2007; Canada): Long +/-2: clonazepam, diazepam, clorazepate, flurazepam, nitrazepam, chlordiazepoxide; Short +/-2: alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam</td>
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<td>Orriols et al. (2012; France)</td>
<td>Case control (July 2005-</td>
<td>Individuals reported by the French Police as 34896 at fault in a MVAs 37789 not at fault in MVAs</td>
<td>34896 at fault in a MVAs</td>
<td>37789 not at fault in MVAs</td>
<td>Involved in a MVA that were</td>
<td>Controlled for other drugs that impair driving</td>
<td>1-month</td>
<td>Antidep SSRIs SNRIs</td>
<td>OR 1.34 (1.22-1.47) OR 1.3 (1.16-1.46) OR 1.51 (1.01-1.67)</td>
<td>No</td>
<td>Case control and case crossover</td>
<td></td>
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<tr>
<td>Authors</td>
<td>Study Design (period)</td>
<td>Study population from which samples selected</td>
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<td>Controls</td>
<td>Drug exposure ascertainment</td>
<td>Adjustment/stratification/controlled/variable factors</td>
<td>Duration</td>
<td>Subgroups/studied drug group</td>
<td>Risk (95% CI)</td>
<td>Dose response effects</td>
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<td>May 2008)</td>
<td>being involved in MVA matched to National police database of injurious crashes (n=72,685)</td>
<td>registered in the National Health Care Insurance Database</td>
<td>Tricyclic</td>
<td>OR 1.05 (.81-1.36)</td>
<td>within the same study</td>
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<td>*Orriols et al. (2012; Fance)</td>
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<td>*Orriols et al. (2012; Fance)</td>
<td>Case crossover (July 2005-May 2008)</td>
<td>Involved in a MVA that were registered in the National Health Care Insurance Database</td>
<td>1-day</td>
<td>AD</td>
<td>OR .96 (.88-1.05)</td>
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<td>No</td>
<td>Only case control discussed and used in the meta-analysis</td>
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<td>Chang et al. (2012; Taiwan)</td>
<td>Matched case control (January 2000-December 2009)</td>
<td>NHIRD prescription dates (Antidep, antipsy, BDZ, z-drugs)</td>
<td>Tricyclic</td>
<td>SSRIs</td>
<td>OR .92 (.83-1.03)</td>
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<td>Yes</td>
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<td>Authors</td>
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<td>Adjustment/stratification/controlled/variable(s)</td>
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<td>BDZ short +/2</td>
<td>OR 1.63 (1.40-1.89)</td>
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<td>BDZ long +/2</td>
<td>OR 1.89 (1.50-2.38)</td>
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<td>BDZ Anx</td>
<td>OR 1.70 (1.47-1.96)</td>
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<td>BDZ Hyp</td>
<td>OR 1.44 (1.09-1.91)</td>
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<td>Tricyclic antidep</td>
<td>OR 1.93 (1.29-2.87)</td>
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<td>Antipsy</td>
<td>OR 1.14 (.83-1.55)</td>
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<td>OR 1.71 (1.29-2.26)</td>
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<td>1-month BDZ</td>
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<td>BDZ short +/2</td>
<td>OR 1.56 (1.37-1.78)</td>
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<td>BDZ long +/2</td>
<td>OR 1.72 (1.43-2.07)</td>
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<td>BDZ Anx</td>
<td>OR 1.60 (1.41-1.80)</td>
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<td>BDZ Hyp</td>
<td>OR 1.51 (1.19-1.94)</td>
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<td>Tricyclic antidep</td>
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<td>Antipsy</td>
<td>OR 1.09 (.83-1.43)</td>
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<td>Antidep</td>
<td>OR 1.73 (1.34-2.22)</td>
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<td>SSRI</td>
<td>OR 1.72 (1.20-2.47)</td>
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<td>Study (year; country)</td>
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<td>Ascertainment of exposure</td>
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<td>Outcome measure (method of reporting)</td>
<td>Adjustment/stratification/controlled variables</td>
<td>Cases</td>
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<td>Results: risk measure (95% CI)</td>
<td>Dose response effects</td>
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<td>Hebert et al. (2007; Canada)</td>
<td>Matched Case-crossover (June 1990-May 1993)</td>
<td>Individuals aged 67-84 in the province of Quebec computerized driver's license file of the Societe de l'assurance automobile du Quebec that filled a benzodiazepine prescription during 1990-1993</td>
<td>Dispensed a benzodiazepine prescription 7 days prior to MVA</td>
<td>People that filled only 1 script in the previous year</td>
<td>MVA in which at least 1 person, not necessarily the driver, sustained injury</td>
<td>Age, other drugs and diseases, sex,</td>
<td>5579</td>
<td>7-days</td>
<td>BDZ long +/2 BDZ short +/2</td>
<td>OR 0.99 (0.81–1.21) OR 1.04 (0.92–1.17)</td>
<td>No</td>
<td>Long +/2 clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam, nitrazepam: short +/2 alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam</td>
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<td>Yang et al. (2011, Taiwan)</td>
<td>Case-crossover (Jan 1997-Dec 2004)</td>
<td>Hospitalised due to MVA within 1-month of prescription (12,929)</td>
<td>12,929 (own controls - 3 time periods)</td>
<td>MVA that resulted in hospitalization during the study period</td>
<td>Age, sex, drug history</td>
<td>12929</td>
<td>1-day</td>
<td>zolpidem zopiclone BDZ short +/2 BDZ long +/2</td>
<td>OR 1.74 (1.25–2.43) OR 1.55 (.98–2.45) OR 1.13 (1.04–1.23) OR 1.74 (1.26–2.40)</td>
<td>Yes</td>
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<td>Study (y; country)</td>
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<td>Results: risk measure (95% CI)</td>
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<td>3-weeks</td>
<td>zopiclone</td>
<td>OR 1.03 (0.99–1.08)</td>
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<td>BDZ short +/-2</td>
<td>OR 1.01 (1.01–1.02)</td>
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<td>BDZ long +/-2</td>
<td>OR 1.05 (1.02–1.08)</td>
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<td>3-weeks</td>
<td>zolpidem</td>
<td>OR 1.03 (1.01–1.05)</td>
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<td>BDZ short +/-2</td>
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<td>1-month</td>
<td>zopiclone</td>
<td>OR 1.02 (0.99–1.04)</td>
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<td>BDZ short +/-2</td>
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<td>BDZ long +/-2</td>
<td>OR 1.03 (1.01–1.05)</td>
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Psychosocial risk factors for MVA

Psychosocial factors could also account for the increased risk of MVA over the 1-month time frame examined by the epidemiological studies included in the systematic review. Most importantly psychosocial factors could account for the elevated risk of MVA found in the first month for patients discharged after DSP with CNS-D medication (Dassanayake, Michie, et al., 2012). Psychosocial factors other than psychopathology (discussed previously) could include personality, insight, social maladjustment, and/or vocational or financial concerns.

Conger et al. (1959) found that individuals responsible for multiple MVAs over a 4.5 year period had similar personalities. These individuals, irrespective of intelligence or responsiveness, displayed significantly more impulsivity and aggressive behaviours, showed a lack of distress tolerance, and insight into their behaviour. Impulsive and aggressive behaviour, among others, have been found in socially maladjusted individuals (Tillmann & Hobbs, 1949), which suggests that habitual behaviours may influence how individuals behave when driving. In line with this, McFarland and Moseley (1954) found that measures of social maladjustment (e.g. marital discord, broken home, truancy, poor employment records, and repeated contact with social services) predicted which truck drivers would remain accident-free with 85% accuracy. More recently, personality traits such as sensation seeking (Schwebel et al., 2006), impulsivity (Cheng & Lee, 2012; Owlsley, McGwin, & McNeal, 2003), aggression and anger (Schwebel et al., 2006; Stephens & Groeeger, 2009) have been linked to risky driving behaviour. This evidence suggests that personality can influence driving behaviour and account for increased MVA risk at 4-weeks.

Self-regulatory behaviour, such as reducing speed and avoiding difficult driving situations, appears to be based on awareness of capacity (Anstey et al., 2005; Horswill, Anstey, Hatherly, Wood, & Pachana, 2011). Some older drivers have avoided car accidents because they engaged in self-regulatory behaviour after being made aware of their functional decline (Holland & Rabbitt, 1992). It is possible therefore; that individuals discharged from hospital after DSP with CNS-D
drugs may lack insight into their cognitive and psychomotor capacities that could influence future behaviour.

Vocational, financial, personal, or interpersonal crises have also been noted as factors linked to car accidents (Selzer, 1969; Selzer, Rogers, & Kern, 1968). Interpersonal crises thought to contribute to reduced driver performance have been identified as close as 6 hours prior to a car accident (Selzer, 1969). One explanation why social factors have been linked to car accidents is that they are often ongoing stressors that consume valuable cognitive resources, such as working memory or problem solving, which may have otherwise been used to avoid danger when driving (Eysenck, MacLeod, & Mathews, 1987). The propensity for these crises to be long-term concerns may explain the elevated accident risk rate 4-weeks after DSP with CNS-D drugs.

**Gaps in the research**

Despite experimental evidence indicating that therapeutic and supratherapeutic doses of CNS-D drugs impairs cognitive and psychomotor functions and epidemiological data suggesting that these impairments place individuals at increased risk of traffic accidents at least 1-month after discharge, no prospective longitudinal clinical evidence on recovery of cognitive and psychomotor functions exists. That is, the pattern of improvement/recovery of cognitive and psychomotor functions following a DSP using a CNS-D drug is unknown. Further, the neuropsychological tests useful in the clinical setting that accurately characterise the recovery pattern and can predict improvement in function commensurate with the general population are also unknown. One criticism of Dassanayake, Michie, et al. (2012) study is that the researchers failed to collect subjective data from participants about their regular driving habits and their insight into their cognitive abilities at discharge. The latter is important because it provides an indication of their level of insight into their capacity and whether they plan to take compensatory measures. An additional gap is that the researchers failed to assess response inhibition (e.g. Stop-signal Task). Inhibition is important for the regulation of complex behaviours, such as driving, and failure to
demonstrate cognitive control has been linked to accident risk (Jongen, Brijs, Komlos, Brijs, & Wets, 2011; Mantyla, Karlsson, & Marklund, 2009).

**Conclusion**

The elevated accident risk, primarily at 3- and 7-days after DSP with CNS-D drugs may be directly linked to DSP (Dassanayake, Jones, et al., 2012), while increased accident risk 1-month after DSP with CNS-D drugs could relate to psychosocial, psychiatric, or medication maintenance treatment variables. Nonetheless the authors concluded that, in line with current discharge procedures, clinicians should continue to warn patients about the residual cognitive and psychomotor functional impairments and that, despite being medically fit to be discharged, daily activities such as driving should be avoided for 48-72 hours. Evidence suggesting an increased risk of MVA existing up to 1-month after DSP with CNS-D drugs raises important clinical and medico-legal questions pertaining to the discharge protocol, but extending driving restrictions beyond 72 hours would be contentious until findings that support longer periods are obtained. Conducting a longitudinal study that compares CNS-D drugs with drugs not linked to impairment of cognitive and psychomotor functions, for example, central nervous system non-depressant drugs (CNS-ND), may provide insight into the factors that influence cognitive and psychomotor performance and explain the reason for elevated risk of MVA. However, for these explanations to translate at least one of these factors must differentiate the CNS-D group from the CNS-ND group. Chapter two provides details of a longitudinal study (1-month) that compares individual admitted to a tertiary care facility for DSP with CNS-D or CNS-ND drugs across several neuropsychological measures (e.g., attention, reaction times, working memory, cognitive efficiency and flexibility, inhibition, and decision-making) and psychosocial measures that examine psychopathology, insight, and significant life events to determine whether these factors might account for the increased accident risk up to 1-month after discharge.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Chapter 2: Journal of Clinical Psychopharmacology Article

Cognitive recovery after Hospital-treated Deliberate Self-Poisoning with central nervous system depressant (CNS-D) drugs: A longitudinal cohort study.

Running title: CNS-depressant overdose and cognition recovery over time

Manuscript for submission to the Journal of Clinical Psychopharmacology.
Abstract

Hospital-treated deliberate self-poisoning (DSP) using central nervous system depressant drugs (CNS-D) has been shown to result in impairments to several cognitive and psychomotor functions important for daily activities such as driving. Our aim was to replicate previous findings that showed patients admitted to hospital following DSP with CNS-D drugs had cognitive and psychomotor impairments at discharge. The second aim was to examine recovery of impairments in the first month (day-7 and -28) for both a CNS-D and a central nervous system non-depressant (CNS-ND) drug group. The final aim was to examine the influence of prior, concurrent, and post-DSP variables on recovery. The primary outcome measure, cognitive flexibility, replicated previous results: the CNS-D group were impaired at discharge compared with the CNS-ND group. CNS-D and CNS-ND groups did not significantly differ at discharge on other cognitive measures. Recovery of cognitive flexibility continued until day-28 in the CNS-D group whereas the CNS-ND group’s performance remained unchanged relative to discharge. Although not differing at discharge, working memory and cognitive efficiency showed slower recovery in the CNS-D than the CNS-ND group whereas recovery on other cognitive measures such as visual attention and inhibition was similar in both groups. More pre-DSP covariates influenced recovery in the first month after discharge such as age and intelligence, having a psychiatric diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; and atypical antipsychotic medication. Patients discharged after DSP with CNS-D drugs have impaired cognitive and psychomotor functions which can require up to 1-month to recover.
Introduction

Hospital-treated deliberate self-poisoning (DSP) has become a growing concern in developed countries as 90% (median; range 46.8-100%) of all deliberate self-harm is DSP. \(^1\) DSP can be considered to be the consumption of two or more times the Defined Daily Dose (DDD) of the assumed average maintenance dose per day for a drug used for its main indication in adults with the intention of self-harm.\(^2\) Studies from developed countries show that central nervous depressant (CNS-D) drugs, such as benzodiazepines, newer non-benzodiazepine hypnotics, sedative antidepressants, atypical antipsychotics, and opioids are among the most commonly used drug groups in DSP. CNS-D drugs accounted for over 122,000 hospital treated DSP admissions in the US in 2008;\(^3\), \(^4\) over 45,000 in the UK (mid 2010-2011);\(^5\) and over 12,500 in Australia (mid 2009-2010).\(^6\)

At present, there has been limited research investigating the post-discharge impact of DSP with CNS-D drugs on cognitive and psychomotor functions that underpin daily activities, particularly demanding activities such as driving. One cross-sectional study has examined the cognitive and psychomotor functions at discharge of ambulant individuals admitted to hospital for DSP with CNS-D.\(^7\) In this study CNS-D drug overdose patients were compared with central nervous system non-depressant (CNS-ND) e.g. acetaminophen or non-sedating antidepressants, overdose patients across three domains of cognitive function (i.e., visual attention and visuomotor skills, executive functions and working memory, and impulsivity and decision making). The primary measures were Trail-Making Test-A (TMT-A) and Test–B (TMT-B), because of their ease of administration, usefulness in a clinical setting,\(^8\) and demonstrated relationship to driver performance (in both clinical and elderly populations).\(^9\)-\(^11\) The CNS-D drug group performed poorly relative to the CNS-ND drug group across all domains of investigation.\(^7\)

Differences in visual attention and visuomotor skills by the CNS-D group were demonstrated by significantly longer completion times for TMT-A and reaction times for a Choice
Reaction Time task (CRT). For tasks linked to executive functions and working memory, the CNS-D group produced significantly longer TMT-B completion times, a significantly larger TMTB-A derived measure (TMT-B minus TMT-A completion times), recalled significantly less sets in the Letter Number Sequence task (LNS), and solved significantly fewer problems in the minimum number of moves for the Stockings of Cambridge Task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Poor performance across all domains, in particular TMT-B, by participants in the CNS-D group suggested that DSP with CNS-D drugs reduces competence to perform tasks that require cognitive flexibility and attentional-switching.

These results, and the noted relationship between TMT and driver performance raised questions about the discharge procedures of tertiary care facilities. Of particular concern is the long-term impact of a CNS-D drug DSP on patients daily functioning, in particular their capacity to drive, after being discharged.

In response to these findings, Dassanayake, Jones, Michie et al. conducted an epidemiological study designed to determine whether being discharged from hospital after DSP with psychoactive drugs produced an increased risk of a car accident. Data linkage between the New South Wales (NSW) Roads and Traffic Authority CrashLink database from 2001–2008 and the NSW Admitted Patient Data Collection was used to determine whether patients were at risk of a car accident within 3-days, 7-days and up to 1-month after ingestion of CNS-D drugs. Results showed that CNS-D individuals were 3.5 times at risk of a motor vehicle accident (MVA) after discharge, 1.9 times 7-days after discharge, and, surprisingly, 1.6 times 4-weeks after discharge compared to control periods of no hospital treatment for DSP.

While the findings from the first week post-discharge suggest an ongoing impairment of cognitive and psychomotor function, it is less clear why individuals who ingest CNS-D drugs are at increased risk of being involved in a car accident up to 4-weeks after ingestion. Given the risk of
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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safety to the individual, and to the wider community, it is important to investigate possible explanations of these results.

Psychosocial factors could explain the elevated risk of MVA up to 1-month after discharge; with those shown to influence driving performance including self-awareness, social maladjustment, vocational or financial concerns, and psychopathology.

Aims:

1. Compare the neurocognitive impairment (difference in means) at baseline (hospital discharge) for CNS-D and CNS-ND ingestion groups.

2. Compare the recovery of neurocognitive function (difference in means over time) over three time points (discharge, day-7, and day-28), for CNS-D and CNS-ND group.

3. To determine those variables that contribute to, and develop explanatory models of, the recovery of neurocognitive function over time.

Methods

Study Setting

This longitudinal study was carried out in the Department of Clinical Toxicology and Pharmacology at the Calvary Mater Newcastle (CMN) hospital from February 2013 to January 2014. CMN is the tertiary referral center for poisonings in the Hunter New England Region of New South Wales, Australia. The Department of Clinical Toxicology and Pharmacology admits all patients with self-poisoning, and the Hunter Area Toxicology Service (HATS) database records all admissions to the Department. This model of patient management has been previously described. Following a toxicology assessment, the consultation–liaison psychiatry team provides a mental health assessment and determine the discharge destination; either discharged home or transferred to a psychiatric facility for further assessment (from which they were either admitted as an inpatient or
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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discharged home). The Hunter New England Human Research Ethics Committee granted ethics approval for the current study.

Participants

Participants were patients aged 18-70 years old who had been admitted to the CMN following an DSP episode of one of four classes of CNS-D drugs (e.g., benzodiazepines, atypical antipsychotics, opioids or sedating antidepressants) or one of two classes of CNS-ND drugs (non-sedating antidepressants or acetaminophen). Individuals that consumed more than twice the DDD of CNS-D drugs were allocated to the test group or CNS-ND drugs to the control group. In cases where patients ingested both CNS-D and CNS-ND drugs, those that consumed more than twice the DDD of CNS-D drugs were included in the CNS-D group (irrespective of the dose of CNS-ND). A patient whose CNS-D drug dose was less than two times the DDD but whose CNS-ND drug dose was greater than two times the DDD was included in the CNS-ND control group.

Patients were excluded if their first language was not English, or if they had any cognitively impairing neurological illness, a history of head injury causing neurological damage, uncorrected vision or hearing impairment, or acute psychosis or aggression. This information was derived from their medical history and a semi-structured clinical interview conducted by the consultation–liaison psychiatry team.

Eligible patients were identified during toxicology ward rounds and were introduced to the study after they were deemed medically fit for discharge by the clinical toxicology and psychiatry teams. Patients willing to participate gave informed written consent and provided contact details to allow 7- and 28-day follow-up testing. Participants who were still inpatients in a psychiatric facility at 7-day follow-up were tested in those hospitals. Otherwise, the participants were contacted prior to both 7 and 28-day follow-up to determine their preferred location for testing. Follow-up testing was conducted at the participant’s home (53%), in the School of Psychology at the University of Newcastle (2%), in the Department of Consultation-Liaison Psychiatry at the CMN (41%), or a
psychiatric facility (4%). If participants were unable to attend testing on the day coinciding with 7 and 28-day follow-up period, the closest possible day was chosen (2-days before to 1-week after the time points).

**Demographic and clinical data collection**

Demographic data were collected at discharge (age, gender), with additional clinical data collected from the HATS database. These data included psychiatric diagnoses, level of consciousness, information about the drug(s)/toxin(s) taken and drug(s) prescribed; the dose and the amount consumed (including alcohol). Participants completed self-assessments related to insight and awareness of driving and cognition, measures of mood and psychosocial trauma and a short battery of neuropsychological tests. The schedule for the self-assessments and neuropsychological tests of cognitive function is shown below in Table 1.

Demographic predictor variables included mean (SD) age, and gender distribution (% of females). Clinical measures included: mean (SD) estimated IQ; co-ingestion of alcohol (N); mean (SD) drug ingestion (in DDD); stimulants use/day (None/Small = [<300mg]/Large [>300mg]/No Follow-up/Missing; assessed on day-7); discharged location (Home/ Mater Mental Health/ Maitland Mental Health/Other); follow-up location (Home/Hospital/University/Other); mean (SD) list of threatening life events; participants with diagnoses related to depression, substance abuse, relationships personality, and Schizophrenia/Schizoaffective/Bipolar disorders; mean (SD) number of psychiatric diagnoses; mean (SD) usual antidepressant/s, benzodiazepine/s; atypical antipsychotic/s, and/or opioids prescribed; usual antidepressant/s, benzodiazepine/s; atypical antipsychotic/s, and/or opioids prescribed post DSP (Removed, No change, Change; assessed on day-7); and mean (SD) level of consciousness (lowest recorded Glasgow Coma Scale, [GCS]). GCS assesses the level of consciousness based on eye-opening (4 levels), verbal (5 levels), and motor (6 levels) responses\(^2^3\). The three elements are considered separately as well as and the sum total score. The lowest possible GCS score (sum) is 3 (deep coma) and the highest is 15 (fully awake person).
Driving outcome measures recorded whether participants: planned on driving next week (Yes/No); lived Alone (Yes/No); licence status (None/Learner/Provisional/Full); licence type (None/Car/Multiple); number of years driving (< 1 year/1-5 years/6-10 years/11-15 years/16-20 years/ 21-30 year/ 31+ years); had an accident within last two years (Yes/No); kilometres driven per week (None/Less than 5/5-10/11-30/31-40/41-50/51+); and area of driving (None/Urban/Highway/Rural/Multiple). These data are shown below in Table 2.
<table>
<thead>
<tr>
<th>Test Schedule for Self-assessment and Neuropsychological Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-assessment</strong></td>
</tr>
<tr>
<td>Self-assessment of driving capacity</td>
</tr>
<tr>
<td>Self-assessment of cognitive capacity</td>
</tr>
<tr>
<td>List of Threatening Life Events (LOTL)</td>
</tr>
<tr>
<td>Depression Anxiety and Stress Scale 21 (DASS-21)</td>
</tr>
<tr>
<td><strong>Neuropsychological tests</strong></td>
</tr>
<tr>
<td>National Adult Reading Test (NART)</td>
</tr>
<tr>
<td>Trail-making Test A and B (TMTA and TMTB)</td>
</tr>
<tr>
<td>Letter Number Sequencing (LNS)</td>
</tr>
<tr>
<td>Big and Little Circles (BLC)</td>
</tr>
<tr>
<td>Choice Reaction Time (CRT)</td>
</tr>
<tr>
<td>Stop Signal Task (SST)</td>
</tr>
<tr>
<td>Stockings of Cambridge (SOC)</td>
</tr>
<tr>
<td><strong>Total Time (minutes)</strong></td>
</tr>
</tbody>
</table>
Self-assessments

Self-assessments (see Table 1) were included to obtain driving information from participants, to characterise the events preceding DSP, and driving and cognitive ability at discharge. Depression Anxiety and Stress Scale (DASS) was examined at three time points.

Self-assessment of driving and cognitive ability (duration ~ 5 minutes). Questions related to self-reported general driving ability and regular driving habits. They included several 10 cm visual analogue scales (0 cm equals poor, 10 cm equals excellent) designed for this study to obtain a self-appraisal of driving ability and cognitive capacity at discharge from DSP (Appendix 3).

List of Threatening Life events (LOTL; duration: ~ 2 minutes). Participants answered 12 yes/no questions related to significant life events, for example, death of a first-degree relative, including a child or spouse. Yes responses indicated the presence of a significant life event and the mean sum totals of yes and no responses for CNS-D and CNS-ND drug groups were compared. Sensitivity and specificity of the LOTL questionnaire has been shown to be high at 0.89 and 0.74 respectively for events in the last 6 months providing support for concurrent validity.

Depression Anxiety and Stress Scale (DASS-21; duration: ~ 2 minutes). The DASS-21 is a 21-item set of self-report scales designed to measure the negative emotional states of depression, anxiety and stress. The sum total of each emotional state was converted to a percentile score using a DASS calculator. The DASS-21 is based on a dimensional rather than a categorical conception of psychological disorder. Research supports the three factor structure of the DASS-21 across both clinical and non-clinical samples.

Neuropsychological tests

National Adult Reading Test (NART; duration: ~ 5 minutes). The NART requires participants to read a list of 50 irregularly spelled words (e.g. debt, psalm, and ache). A regression equation derived by Crawford, Parker, Stewart et al., Estimated IQ =128.50-0.84 (NART errors),
was used in the current study to estimate pre-morbid full-scale IQ and was included as a covariate (Estimated IQ) in the analysis of the neuropsychological measures instead of NART error scores.

Trail-Making Test (TMT; duration: ~ 5-10 minutes). The TMT is a timed test composed of two parts, A and B. Part A requires participants to connect irregularly positioned numbers, 1-25 in ascending order. In part B participants are required to connect numbers 1-13 in ascending order and letters A-L in alphabetical order, alternating between numbers and letters. Examiners correct individual participant’s connection errors, which add to the completion time. Both TMT-A and B examine attentional capabilities and visual search and visual-spatial faculties, as well as speed. In addition, TMT-B taps into cognitive flexibility, in this case, shifting between two conceptual sets. The derived value calculated by subtracting TMT-A from -B (TMTB-A) is thought to measure cognitive efficiency. TMT A and B completion times were modelled as continuous variables and as a categorical variables (based on the 10th percentile cut-off).

To reduce practice effects, Wagner, Helmreich, Dahmen et al. developed three parallel forms by flipping the original TMT-A and -B patterns horizontally, vertically, and diagonally to ensure that the parallel forms contained the same number of circles placed at equal distances from each other across versions. Figure 1 illustrates the pattern of movement with square 1 (top left representing the original version). Retest reliability of the three TMT-A and -B parallel forms ranged from 0.76 and 0.89 and between 0.86 and 0.94, respectively.
Figure 1. Schematic of the method of development of three new versions of TMT-A and -B
Letter Number Sequencing (LNS; duration: ~ 5 minutes). LNS tests working memory capacity. The examiner reads aloud a string of numbers and letters (e.g., V–1– J–5) and the participant must first recall the numbers in ascending order, and then the letters in alphabetical order (1–5–J–V). The test starts with a sequence of two items (one number and one letter), and the span increases until the subject fails all three sequences at a given length. The mean total number of correctly recalled sequences was compared between CNS-D and CNS-ND drug groups. LNS also examines the ability to simultaneously recall and organise stimuli of different and/or similar types. The LNS test has demonstrated high test-retest reliability and minimal practice effects when tested over three sessions. The LNS test has also demonstrated criterion validity by showing sensitivity in a clinical population with traumatic brain injury.

Cambridge Neuropsychological Test Automated Battery (CANTAB; duration: ~ 33 minutes). A selected set of CANTAB tests (Choice Reaction Time, Stop Signal Task and Stockings of Cambridge) were administered on a Paceblade SlimbookTM 110 Series 12.1 tablet PC. One obligatory training test, (i.e., Big/Little Circles [BLC], duration ~ 3 minutes) was administered initially to introduce the participants to the test system.

Choice Reaction Time (CRT, duration ~ 7 minutes). The CRT is a test of attention and psychomotor speed. An arrow-shape stimulus is displayed on the screen pointing to the right or the left. In response, the subject must press the corresponding button on a response-pad. The participant has to respond as quickly as possible without making mistakes. The outcome measure used was mean CRT (based on 100 trials).

Stop Signal Task (SST, duration ~ 20 minutes). SST is a measure of inhibitory control. It requires participants to press one of two buttons, left and right, to match left and right arrows displayed on a computer screen. Some trials (25%) require response inhibition, signalled by an auditory tone presented at variable intervals (the stop signal delay [SSD]) after the arrow stimuli. Participants are encouraged to respond as quickly as possible to the left or right arrows but to inhibit
their response on hearing the stop signal. An adaptive algorithm modifies the delay of the auditory tone throughout the test to ensure a 50% successful inhibition rate. The score is an estimate of the stop signal reaction time (SSRT) which is calculated by subtracting the SST SSD (50%) from the median SST reaction time on GO trials (GoRT). The default setting “last half”, which has been used in this study, calculates SSRT from the last half of the trial.

Stockings of Cambridge (SOC, duration ~ 10 minutes). SOC is a computerised version of the Tower of London task, which tests planning and spatial working memory. The goal of the task is to rearrange a set of three balls in a minimum number of moves to match a sample pattern. Therefore, participants have to plan their moves before starting to move the balls. The assessed task has 12 trials (2 x 2-move, 2 x 3-move, 4 x 4-move and 4 x 5 move problems). The scores included in this study are the number of problems solved in minimum moves; the mean number of the moves spent in solving an n-move problem (Mean-n-Moves), n being 2, 3, 4 or 5; and mean initial thinking time. The SOC was only administered at discharge due to evidence of substantial practice effects on planning tasks.

**Data Analysis: Planned between-group comparisons**

Demographic and Clinical Characteristics

Independent sample one-tailed t-tests (continuous variables) and $\chi^2$ tests (categorical variables) were utilised to compare demographics and clinical characteristics of the CNS-ND and CNS-D groups (Table 2-3). A Monte-Carlo simulation (confidence interval 95%) was used for analysis of categorical variables for small cell sizes. Alpha was set at 0.05.

A linear mixed models (LMM) approach was also used to determine the influence of time, group, and group by time (interaction) on DASS scores with appropriate contrasts to determine if mood changed over time.

Neuropsychological tests
The first stage of analysis used a LMM to construct a base model for each
europsychological dependent variable, that included time (discharge, 7-days, 28-days), group
(CNS-D, CNS-ND), and a group by time interaction, as well as the covariates of age, estimated IQ,
and gender based on previous research showing that each of these covariates contributed to
performance on the neuropsychological tests used in this study. While the primary outcome
measure was TMT-B completion times, measures from all neuropsychological tests except for SOC
were subjected to a similar analysis.

A LMM approach was chosen as the method for statistical analysis given the propensity for
missing data due to attrition at day-7 and day-28 follow-up dates. Correlation between time periods
due to the repeated measures design was modelled using a residual covariance matrix with
unstructured form (unless noted otherwise) and with restricted maximum likelihood (REML)
estimation. If age, estimated IQ and/or gender were not significant covariates in the initial analyses,
they were removed before proceeding to the next stage.

As the CANTAB SOC was administered at discharge only, analysis of covariance
(ANCOVA) was used to determine if the two groups differed on the number of problems solved in
the minimum number of moves. To explore the effects of problem difficulty, a group x difficulty
ANCOVA with repeated measures on problem difficulty (2, 3, 4, or 5 move problems) was used to
determine whether there were group and difficulty effects on other SOC measures: the number of
moves required to solve a problem and mean initial thinking time. Covariates of estimated IQ, age
and gender were fitted for both analyses. Only significant covariates were retained.

Stage 2 and 3 of the LMM analysis aimed to find the best explanatory models for each
neuropsychological variable to explain recovery over time using forward elimination procedures.
Stage two of the LMM process tested the significant contributors from demographic and clinical
characteristics associated with the DSP as predictors of neuropsychological test performance in two
steps. The first step assessed DSP presentation covariates, including the co-ingestion of alcohol,
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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sedative and non-sedative drugs, mean drug defined daily dose units, and level of consciousness (Glasgow Coma Scale score). The second step examined pre-existing conditions such as LOTL, psychiatric diagnoses grouped by depression, relationship, personality, substance abuse, or schizophrenia-related/bipolar symptomatology, number of diagnoses, type of drugs prescribed pre-overdose (benzodiazepine, antidepressants, atypical antipsychotics, opioids), and whether participants lived alone. At each step, only significant covariates were retained. Stage 3 took the stage 2 model of each neuropsychological variable and assessed covariates that may have influenced discharge and post-discharge performance. These included stimulants/day, change in drugs usually prescribed after discharge (using the same categories as in stage two), and self-reported mood based for each DASS subtest percentile scores. In the interests of brevity, only the final model is reported. Unstandardised coefficients of each significant covariate from the final model were examined to determine the direction of their influence on each test variable. Between-(at discharge only) and within-group least significance difference (LSD) contrasts were examined to test our aims that the CNS-D group are more impaired at discharge and take longer to recover in terms of neuropsychological test performance than the CNS-ND group.

Missing value assumption

Under the missing-at-random assumption even if the failure to attend a follow-up session was related to scores obtained in previous sessions then the direct likelihood approach used for LMMs provides an unbiased estimate of the means at each time point. Using a missing values variable a one-way ANOVA found that participants that failed to attend day-7 and -28 follow-ups did not significantly differ across TMT-A, TMT-B, TMTB-A outcomes relative to those participants that did attend day-7 follow-up. Finally, an independent samples t-test at day-7 comparing participants who did and did not attend day-28 follow-up found no significant difference across TMT-A, TMT-B, TMTB-A results. These analyses show that despite attrition, the results for TMT-A, TMT-B, TMTB-A of participants that failed to attend day-7, 28, or both did not differ.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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significantly from those that did attend day-7 and -28 follow-ups. Thus the observations are consistent with the missing-at-random assumption.

Secondary Analyses

To determine whether participants were aware of their cognitive capacity at discharge, the relationships between self-assessment of cognitive ability and driving and cognition were assessed using pooled within-group correlations of each neuropsychological measure with self-assessment variables.

Odds ratios comparing the proportions of individuals from the CNS-ND and CNS-D groups that fell within the bottom 10th percentile for TMT-A and TMT-B (Table 4) were also extracted. However, the small sample sizes precluded formal statistical analysis.

All data were analysed using IBM SPSS Statistics version 22 for Windows.

Results

Sample

Seventy-two patients were considered for eligibility (Figure 2), 3 were excluded because of intellectual disability and 2 for a history of aggressive behaviour, leaving 67 (28 CNS-ND and 39 CNS-D) who met the criteria for this study (Figure 2). Of these, 36 participated in testing at discharge; this included fifteen patients who ingested CNS-ND drugs (12 acetaminophen, 3 selective serotonin reuptake inhibitor), and 21 participants who ingested CNS-D drugs (9 atypical antipsychotics, 9 benzodiazepine, 3 opioids). Approximately half of the participants in the CNS-ND group (53.3%) and a third (28.6%) of the CNS-D group were diagnosed with a major psychiatric illness. Fifteen patients were tested on day-7, and 13 were tested on day-28, from the CNS-D group, while 9 patients were tested on both day-7 and 28 from the CNS-ND group. One participant’s day-7 data (CNS-ND) was removed because of alcohol withdrawal symptomatology that prohibited her from performing several tasks.
72 considered for eligibility

Excluded:
3 - intellectual disability
2 - aggressive
1 - wrong drug class

66 approached

28 CNS-ND
9 - no consent
3 - no glasses
1 - unable to attend follow-up

21 CNS-D
10 - no consent
2 - unable to attend follow-up
2 - testing interrupted
1 - no glasses
1 - unable to read
1 - left hospital before testing

38 CNS-D

15 Control Group
As shown in Table 2, the CNS-ND and CNS-D groups showed no significant difference across demographic clinical characteristics, or driving habits, with the exception of admission to hospital with a psychiatric diagnosis related to depression.
<table>
<thead>
<tr>
<th></th>
<th>CNS-ND Group (n=15)</th>
<th>CND-D Group (n=21)</th>
<th>Sig (p≤0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age - Mean (SD)</td>
<td>33.13 (14.16)</td>
<td>36 (10.70)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender distribution</td>
<td>2/13 (87)</td>
<td>5/16 (76)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Driving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving Next Week (Yes/No)</td>
<td>8/7</td>
<td>12/9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Live Alone (Yes/No)</td>
<td>2/13</td>
<td>5/15*</td>
<td>n.s.</td>
</tr>
<tr>
<td>Licence Status (None/Learner/Provisional/Full)</td>
<td>3/1/3/8</td>
<td>5/1/2/13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Licence Type (None/Car/Multiple)</td>
<td>13/10/2</td>
<td>5/14/2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Years Driving*</td>
<td>3/1/2/3/1/2/3/0/1/2/3/2</td>
<td>5/0/3/2/1/5/3/2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Accident within last 2 years (Yes/No)</td>
<td>1/14</td>
<td>4/17</td>
<td>n.s.</td>
</tr>
<tr>
<td>km/week (None/Less than 5/5-10/11-30/31-40/41-50/51+)</td>
<td>3/1/0/3/1/2/5</td>
<td>5/2/1/1/0/5/7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Area of driving (None/Urban/Highway/Rural/Multiple)</td>
<td>3/4/0/3/5</td>
<td>5/6/1/1/8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale - Mean (SD)</td>
<td>14.93 (.26)</td>
<td>13.81 (2.46)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Estimated IQ - Mean (SD)</td>
<td>108.06 (5.39)</td>
<td>109.54 (6.18)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Co-ingestion with Alcohol (N)</td>
<td>3</td>
<td>8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Drug ingestion (in DDD) - Mean (SD)</td>
<td>12.80 (13.78)</td>
<td>17.39 (20.18)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stimulants use/day (None/Small&quot;/Large&quot;/No Follow-up/Missing)</td>
<td>4/3/0/6/2</td>
<td>7/4/3/7/0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Discharged to (Home/ Mater Mental Health/ Maitland Mental Health/Other)</td>
<td>9/3/3/0</td>
<td>14/4/2/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Follow-up Location (Home/Hospital/University/Other)</td>
<td>7/3/0/0</td>
<td>6/7/1/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>List of threatening life events - Mean (SD)</td>
<td>3.13 (2.48)</td>
<td>3.36 (2.53)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Depression related diagnoses (No/Yes)</td>
<td>5/10</td>
<td>14/7</td>
<td>0.05</td>
</tr>
<tr>
<td>Substance Abuse related diagnoses (No/Yes)</td>
<td>8/7</td>
<td>10/11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relationship related diagnoses (No/Yes)</td>
<td>6/9</td>
<td>10/11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Personality related diagnoses (No/Yes)</td>
<td>12/3</td>
<td>11/10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Schizophrenia/Schizoaffective/Bipolar related diagnoses (No/Yes)</td>
<td>15/0</td>
<td>19/2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychiatric diagnoses - Mean (SD)</td>
<td>2.07 (0.70)</td>
<td>2.24 (0.94)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual antidepressant taken prior to admittance(No/Yes)</td>
<td>3/6</td>
<td>3/11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual benzodiazepine taken prior to admittance(No/Yes)</td>
<td>8/1</td>
<td>7/7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual atypical antipsychotic taken prior to admittance (No/Yes)</td>
<td>5/4</td>
<td>4/10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual opioids taken prior to admittance(No/Yes)</td>
<td>8/1</td>
<td>13/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual antidepressant medication post DSP (Removed, No change, Change)</td>
<td>0/8/1</td>
<td>1/12/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual benzodiazepine medication post DSP (Removed, No change, Change)</td>
<td>0/9/0</td>
<td>6/6/2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual atypical anti. medication post DSP (Removed, No change, Change)</td>
<td>0/8/0</td>
<td>1/13/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual opioid medication post DSP (Removed, No change, Change)</td>
<td>1/8/0</td>
<td>1/13/0</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

CNS-ND = central nervous non-depressant; CNS-D = central nervous depressant; DDD = defined daily dose; *1 participant failed to respond
\*None/Less than 1 year/1-5 years/6-10 years/11-15 years/16-20 years/21-30year/31+ years; '<300mg caffeine;≥ 300mg of caffeine; anti.= antipsychotic
Table 3 displays the means and standard deviations of the DASS percentiles scores for the CNS-D and CNS-ND groups. LMM analysis of the depression scale percentile scores revealed a significant time effect (p = 0.036). Group and group-by-time interaction were not significant. LSD contrasts of DASS depression scores over time revealed that only the contrast between discharge and day-28 was significant, showing that DASS depression percentile scores declined significantly between these times.

LMM analysis of the DASS anxiety scale percentile scores, shown in Table 3, revealed a significant time effect (p = 0.007), a group effect (p = 0.052), and group by time interaction that approached significance (p = 0.075). As the interaction approached significance, contrasts of simple effects of group (at each time point) and time (within each group) were examined. LSD between-group contrasts revealed that the CNS-D group had significantly higher anxiety at discharge (p = 0.017) and day-28 (p = 0.043). LSD contrasts within each group revealed that the CNS-ND level of anxiety at day-28 was significantly lower than at discharge (p = 0.005) and day-7 (p = 0.007). The CNS-D group’s level of anxiety at day-7 was significantly lower than discharge (p = 0.044).

Finally, Table 3 shows that the LMM analysis of the stress scale percentile scores produced a time effect (p = 0.021), but no significant group effect (p = 0.288), nor group by time interaction (p = 0.804). Contrasts of changes over time indicate that stress percentiles at days-7 and 28 were significantly lower than at discharge (p = 0.022, p=.013 respectively). That is, DASS stress percentiles scores declined significantly over time in both groups.
<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>n</th>
<th>Discharge M (SD)</th>
<th>n</th>
<th>Day 7 M (SD)</th>
<th>n</th>
<th>Day 28 M (SD)</th>
<th>Main effects and interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASS Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>93.52 (10.06)</td>
<td>9</td>
<td>91.88 (9.76)</td>
<td>9</td>
<td>85.20 (25.96)</td>
<td>p = 0.942 p = 0.036 p = 0.691</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>96.71 (9.63)</td>
<td>15</td>
<td>91.46 (12.29)</td>
<td>12</td>
<td>74.77 (29.73)</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td></td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>83.51 (26.30)</td>
<td>9</td>
<td>86.56 (11.58)</td>
<td>9</td>
<td>73.15 (33.10)</td>
<td>p = 0.052 p = 0.007 p = 0.075</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>98.03 (3.58)</td>
<td>15</td>
<td>87.56 (21.60)</td>
<td>13</td>
<td>84.69 (22.13)</td>
<td>p = 0.017. n.s. P = 0.043</td>
</tr>
<tr>
<td>LSD</td>
<td></td>
<td>p = 0.017.</td>
<td></td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>90.50 (12.86)</td>
<td>9</td>
<td>81.56 (28.62)</td>
<td>9</td>
<td>75.67 (22.05)</td>
<td>p = 0.288 p = 0.021 p = 0.804</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>96.04 (3.56)</td>
<td>15</td>
<td>87.18 (16.02)</td>
<td>13</td>
<td>80.42 (27.26)</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td></td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

*equal variance not assumed; LSD = Least Significant Difference; M = Mean; SD = Standard Deviation
CNS-ND = central nervous non-depressant; CNS-D = central nervous depressant; DASS = Depression Anxiety Stress Scale
Primary Analysis

For TMT-A (Table 4), the final model included a time effect \( (p = 0.001) \), no group effect \( (p = 0.633) \), and no group by time interaction \( (p = 0.177) \), as well as significant covariates of age \( (p = 0.002) \), prescription of atypical medication pre-DSP \( (p < 0.001) \) and average stimulants per day post-discharge \( (p = 0.003) \). Estimates of unstandardised coefficients for the primary covariates revealed that each increase of 10 years in age \( (p = 0.002) \) resulted in an increase of approximately 2.5 sec in TMT-A completion time. For the other significant covariates, being prescribed an atypical antipsychotic prior to DSP \( (p = 0.008) \) resulted in an increase of approximately 8 sec in TMT-A reaction time. Contrary to expectations, compared to participants who consume a large amount of stimulants per day, consumption of either none or a small amount per day resulted in approximately 10 sec reduction in TMT-A completion time. The between-group contrast at discharge showed no difference. LSD within-group contrasts across time indicated that the CNS-D group was significantly faster on both day-7 \( (p = 0.001) \) and day-28 \( (p < 0.001) \) compared to discharge, shown below in Figure 3, but there was no difference between day-7 and day-28. The CNS-ND group showed a similar pattern except that only day-7 had significantly faster TMT-A completion times compared to discharge \( (p = 0.007) \). In summary, while there was no evidence that the CNS-D group were significantly slower than the CNS-ND group at discharge, there was some evidence of a greater decline in TMT-A completion times over the follow-up periods for the CNS-D than CNS-ND group.

For TMT-B (Table 4), the final model included a time effect \( (p < 0.001) \), and a group effect \( (p = .049) \), as well as significant covariates of age \( (p = 0.006) \), and a diagnosed psychiatric illness related to schizophrenia, schizoaffective, or bipolar disorders (SSBP; \( p < 0.001 \)). Estimated unstandardised coefficients for the primary covariates revealed that each 10-year increase in the age of the participant resulted in an increase in TMT-B completion time of approximately 6.5 seconds. Examination of other covariates revealed that having a diagnosis of a psychiatric illness related to
SSBP disorders increased TMT-B completion time by approximately 39 seconds. Shown in Figure 3, the group contrast at discharge showed that the CNS-D group produced significantly slower completion times at discharge than the CNS-ND group \( (p = 0.048) \). LSD within group contrasts revealed that CNS-ND group performance did not change significantly over time but the CNS-D group was significantly faster on day-7 \( (p = 0.003) \) and day-28 \( (p < 0.001) \) compared to discharge, with day-28 being significantly faster than day-7 \( (p = 0.039) \). These results suggest that over time cognitive flexibility remained stable for the CNS-ND group, but improved significantly for the CNS-D group from discharge to day-28.

For TMTB-A (Table 4), the final LMM model included a marginal time effect \( (p = 0.058) \). Diagnosed psychiatric illness related to SSBP disorders \( (p < 0.001) \), and a change to atypical antipsychotic medication \( (p = 0.016) \) also significantly increased the derived measure TMTB-A. Estimated unstandardised coefficients for the other covariates indicated that being diagnosed with a psychiatric illness related to SSBP disorders resulted in approximately an 87-point increase in the TMTB-A derived measure. Compared to having atypical antipsychotic medication remain unchanged or reduced from participant’s medication regimen, participants newly prescribed atypical antipsychotic medication after DSP resulted in approximately 10- and 60-point increase in the TMTB-A derived measure, respectively. The between-group contrast at discharge showed no difference (Figure 3). LSD within-group contrasts for the CNS-ND group showed that CRT mean latencies at day-7 \( (p = 0.031) \) and 28 \( (p = 0.025) \) were significantly faster.
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than discharge (Figure 3), but there was no significant difference between day-7 and -28. The pattern for CNS-D was the same; day-7 (p < 0.001) and day-28 (p = 0.010) were significantly faster than discharge with no significant difference between days-7 and -28.

For LNS (Table 4), the final model included a time effect (p= 0.008) as well as significant covariates of estimated IQ (p = 0.005), and a change in antidepressant medication (p = 0.003). An increase in 5 IQ points resulted in approximately 1 extra correctly recalled sequence. Compared to participants newly prescribed antidepressant medication after DSP, having antidepressant medication remain unchanged or reduced from participant’s medication regimen resulted in approximately 4 and 8 fewer correctly recalled sequences, respectively. The group contrast at discharge showed no significant difference (Figure 3). LSD within-group contrasts for the CNS-ND group produced no significant changes over time, whereas the number of sequences recalled at day-7 (p = 0.015) and -28 (p < 0.001) by the CNS-D group were significantly higher than at discharge (Figure 3); day-28 was not significantly higher than day-7 (p = 0.065).

For SSRT (Table 4), the final model included a time effect (p < 0.001), no group effect (p = 0.798), and no group by time interaction (p= 0.107). The group contrast at discharge showed no significant difference (Figure 3). LSD within-group contrasts for the CNS-ND group showed that compared to discharge participants were significantly faster at day-28 (p = 0.005; Figure 3); there was no difference between discharge and day-7 or between day-7 and -28 performance. SSRT was significantly faster at day-7 (p < 0.001) and day-28 (p < 0.001) relative to discharge for the CNS-D group, with no significant difference between day-7 and day-28.

An ANCOVA of the primary SOC dependent variable of the number of problems solved in the minimum number of moves, shown below in Table 4, indicated that group approached significance (p = 0.078) while estimated IQ was a significant covariate (p = 0.038). The CNS-ND group exhibited a trend to solve problems in fewer moves than the CNS-D group. Analyses of the number of moves required to solve a problem as a function of problem difficulty (see Table 5)
found that group (p = 0.035), difficulty (p= 0.012) and estimated IQ were significant (p = 0.014).

The group by difficulty interaction was not significant. Analysis of initial thinking time revealed that group approached significance (p = 0.066), difficulty (p= 0.030) was significant, but the group by difficulty interaction was not significant. Of the covariates, only age was significant (p = 0.002).

Overall, the CNS-D group required more moves to solve problems irrespective of difficulty than the CNS-ND group, as well as a trend for the CNS-D group to have shorter initial thinking times suggesting that they engaged in less planning prior to the first move (see Figure 4).
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>n</th>
<th>Discharge M (SD)</th>
<th>n</th>
<th>Day 7 M (SD)</th>
<th>n</th>
<th>Day 28 M (SD)</th>
<th>Main effects and interactions</th>
<th>Primary covariates</th>
<th>Other covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group main effects: p-value</td>
<td>Time main effects: p-value</td>
<td>Group*Time main effects: p-value</td>
</tr>
<tr>
<td>TMT-A, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>29.14 (8.60)</td>
<td>9</td>
<td>22.27 (7.55)</td>
<td>9</td>
<td>24.64 (8.36)</td>
<td>0.633</td>
<td>0.001</td>
<td>0.177</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>34.40 (14.76)</td>
<td>15</td>
<td>24.53 (8.80)</td>
<td>13</td>
<td>21.46 (5.76)</td>
<td>0.049</td>
<td>&lt; 0.001</td>
<td>0.159</td>
</tr>
<tr>
<td>TMT-B, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>71.11 (25.50)</td>
<td>9</td>
<td>55.46 (16.81)</td>
<td>9</td>
<td>24.64 (8.36)</td>
<td>0.585</td>
<td>0.104</td>
<td>0.459</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>121.60 (84.95)</td>
<td>15</td>
<td>82.39 (65.61)</td>
<td>13</td>
<td>63.29 (25.36)</td>
<td>0.143</td>
<td>0.001</td>
<td>0.143</td>
</tr>
<tr>
<td>TMTB-A, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>41.97 (24.33)</td>
<td>9</td>
<td>33.19 (16.42)</td>
<td>9</td>
<td>25.04 (10.41)</td>
<td>0.633</td>
<td>0.001</td>
<td>0.177</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>87.20 (76.29)</td>
<td>15</td>
<td>57.85 (62.44)</td>
<td>13</td>
<td>41.85 (24.59)</td>
<td>0.143</td>
<td>0.001</td>
<td>0.143</td>
</tr>
<tr>
<td>CRT M Latency, ms</td>
<td></td>
<td>385.25 (126.25)</td>
<td>9</td>
<td>340.77 (102.88)</td>
<td>9</td>
<td>332.38 (85.75)</td>
<td>0.143</td>
<td>0.001</td>
<td>0.143</td>
</tr>
<tr>
<td>CNS-ND</td>
<td>21</td>
<td>355.63 (79.55)</td>
<td>15</td>
<td>285.24 (34.95)</td>
<td>13</td>
<td>302.87 (38.64)</td>
<td>0.764</td>
<td>0.008</td>
<td>0.353</td>
</tr>
<tr>
<td>LNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>15</td>
<td>10.67 (1.88)</td>
<td>9</td>
<td>11 (1.80)</td>
<td>9</td>
<td>11.33 (2.35)</td>
<td>0.143</td>
<td>0.001</td>
<td>0.143</td>
</tr>
<tr>
<td>CNS-D</td>
<td>21</td>
<td>9.43 (2.73)</td>
<td>15</td>
<td>11.2 (2.31)</td>
<td>13</td>
<td>11.77 (1.74)</td>
<td>0.798</td>
<td>&lt; 0.001</td>
<td>0.107</td>
</tr>
<tr>
<td>SSRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>13</td>
<td>192.4 (35.37)</td>
<td>9</td>
<td>164.01 (30.49)</td>
<td>9</td>
<td>160.83 (27.52)</td>
<td>0.764</td>
<td>0.008</td>
<td>0.353</td>
</tr>
<tr>
<td>CNS-D</td>
<td>18</td>
<td>212.09 (39.43)</td>
<td>14</td>
<td>158.88 (38.45)</td>
<td>13</td>
<td>147.37 (31.31)</td>
<td>0.798</td>
<td>&lt; 0.001</td>
<td>0.107</td>
</tr>
<tr>
<td>SOC -correct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-ND</td>
<td>13</td>
<td>8.62 (1.19)</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>0.078</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CNS-D</td>
<td>16</td>
<td>7.5 (2.42)</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>0.078</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

M= Mean; SD = standard deviation; Est. IQ= Estimated IQ; TMT= Trail making Task; LNS = Letter Number Sequence; CRT= Choice Reaction Time; SSRT= Stop Signal Reaction Time; med =medication; anti. = antipsychotics
CNS-ND = Central Nervous System Non-depressant Drugs; CNS-D = Central Nervous System Depressant Drugs; SOC -correct = mean problems solved in the minimum number of moves; antidepress. = antidepressants; NR = no result; NA = not applicable

Usual atypical taken prior to admit
Stimulants use/day
Schizo/Schizoffective/Bipolarrel
Normal attentional control
Schizo/Schizoffective/Bipolarrel
Usual atypical med. post DSP
Drug ingestion (in DDD)
Usual antidep. med. post DSP

Figure 3. Adjusted means ± SE on Neuropsychological outcomes for the CNS-ND and CNS-D groups at discharge, day-7, and day-28.
Table 5. Number of Moves and Mean Initial Thinking Time raw group means (unadjusted) as a function of difficulty

<table>
<thead>
<tr>
<th>SOC Measures</th>
<th>Number of Moves Required to Solve a Problem</th>
<th>Main effect</th>
<th>Covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 Moves (SD)</td>
<td>3 Moves (SD)</td>
<td>4 Moves (SD)</td>
</tr>
<tr>
<td>CNS-ND</td>
<td>2 (.00)</td>
<td>3.07 (.19)</td>
<td>5.25 (.95)</td>
</tr>
<tr>
<td>CNS-D</td>
<td>2.09 (.27)</td>
<td>3.41 (.69)</td>
<td>5.48 (1.01)</td>
</tr>
</tbody>
</table>

Mean Initial Thinking Time (ms)

| CNS-ND       | 9091.42 (5554.31) | 8611.38 (18493.18) | 10880.63 (18664.17) | 12644.90 (22338.25) | 0.030* | 0.066 | 0.177* | NR | 0.002 |
| CNS-D        | 7615.81 (5341.97) | 5690.22 (5832.71) | 6391.14 (3855.78) | 6795.14 (4115.82) | 0.030* | 0.066 | 0.177* | NR | 0.002 |

M= Mean; SE= Standard Error; * Greenhouse-Geisser correction used as Mauchley’s test of Sphericity was violated; SOC = Stockings of Cambridge
CNS-ND = Central Nervous System Non-depressant Drugs; CNS-D = Central Nervous System Depressant Drugs; SOC= Stocking of Cambridge; Est. IQ = Estimated IQ
Figure 4. Adjusted means ± SE for the Number of Moves and Mean Initial Thinking Time as a function of task difficulty (2, 3, 4 or 5 move problems)
Table 6 shows that no significant differences between the CNS-ND and CNS-D groups were found on subjective appraisals of driving ability or cognitive capacity.
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>CNS-ND Group (n=15)</th>
<th>CND-D Group (n=21)</th>
<th>Sig (p≤ 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driving at present - Mean (SD)</td>
<td>4.78 (2.93)</td>
<td>5.14 (3.22)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Driving at night - Mean (SD)</td>
<td>4.31 (3.13)</td>
<td>4.86 (3.00)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Driving on the highway - Mean (SD)</td>
<td>4.17 (2.97)</td>
<td>4.38 (3.35)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Driving in bad weather - Mean (SD)</td>
<td>3.69 (2.89)</td>
<td>4.09 (3.08)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Concentration - Mean (SD)</td>
<td>4.06 (1.88)</td>
<td>2.94 (2.42)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Express thoughts - Mean (SD)</td>
<td>4.24 (2.42)</td>
<td>3.92 (2.78)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Perform daily activities - Mean (SD)</td>
<td>6.24 (2.67)</td>
<td>5.84 (2.73)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Following instructions - Mean (SD)</td>
<td>5.55 (2.53)</td>
<td>5.63 (2.91)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

CNS-ND = central nervous non-depressant; CNS-D = central nervous depressant
Secondary Analysis

Correlations between subjective assessment and neuropsychological performance

Pooled within-group correlations at discharge examined the relationship between participants’ subjective assessment of their cognitive and driving ability, and neuropsychological performance at discharge. Subjective appraisal of ability to follow instructions ($r = -0.347; p = 0.044$) was negatively related to TMT-A completion time; those who rated their ability to follow instructions at higher levels produced faster TMT-A completion times. TMT-B was negatively related to participants’ subjective appraisal of concentration ($r = -0.348; p = 0.044$) and ability to follow instructions ($r = -0.404; p = 0.018$); once again those who rated their concentration and ability to follow instructions higher had faster TMT-B completion times. The same pattern emerged for the derived measure TMTB-A which was negatively correlated with concentration ($r = -0.332; p = 0.055$) and ability to follow instructions ($r = -0.377; p = 0.028$); a higher self-rating was associated a lower derived TMTB-A measure and better cognitive efficiency. Conversely, LNS was positively related to several measures; concentration ($p = 0.074; r = 0.310$), ability to express thoughts ($r = 0.355; p = 0.053$), and follow instructions ($r = 0.412; p = 0.013$). Participants who gave themselves a higher rating were able to recall more sets. Finally, subjective assessment of driving ability in bad weather was positively related to CRT mean latency ($r = 0.404; p = 0.041$), that is, participants who rated themselves more highly on driving ability in bad weather actually produced slower reaction times.

Interestingly, SOC and SSRT were unrelated to any subjective assessment variables, while subjective assessment of daily activities, and driving ability at present, at night, and on the highway failed to show any relationship with any neuropsychological variables.

Bottom 10th percentile on TMT-A and TMT-B measures

Based on the age-stratified 10th percentile cut-off, the odds of the CNS-D group (compared with the CNS-ND group) being more impaired than the CNS-ND group, at discharge, day-7, and -28 for TMT-A were 3.25 (95% CI, 0.65-.21.96), 1.97 (95% CI, 0.07-53.49), and .7 (95% CI, 0.01-38.69), respectively. For TMT-B, the odds of the CNS-D group being more impaired than the CNS-ND group...
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at discharge, day-7, and -28 were 1.16 (95% CI, 0.31-4.70), 9.95 (95% CI, 0.48-205), and 4.93 (95% CI, 0.23-106.89), respectively, however none of these risk estimates reached significance due to reduced sample size. Figure 5 shows the percentages of CNS-D and CNS-ND participants that produced completion time in the bottom 10\textsuperscript{th} percentile at discharge, day-7 and -28.
Figure 5. Percentage of individuals in the CNS-ND and CNS-D groups whose Trail-making Test-A and -B completion times fell in the bottom 10th percentile (according to age) at discharge, day-7, and day-28.
Discussion

With respect to the first aim, namely, to replicate the findings of Dassanayake, Michie, Jones et al. \(^7\), that those admitted because of DSP with CNS-D drugs have significant cognitive impairment at discharge compared to DSP with CNS-ND; only cognitive flexibility, measured by TMT-B completion times, was found to be significantly impaired at discharge (adjusted means) in the current study. No significant differences in performance were found between the CNS-ND and CNS-D groups at discharge for the other neuropsychological measures. While not significant, Figure 3 shows that the CNS-ND produced superior performances compared to the CNS-D group for cognitive efficiency (TMTB-A). Conversely, the CNS-D group produced a non-significant superior performance than the CND-ND group for one visual attention and visuomotor skills test (CRT mean latency). However, neither group demonstrated superior performance at discharge for tasks that involved visual attention and visuomotor skills (TMT-A) working memory (LNS), or inhibition control (SSRT).

While we did not find a significant difference in SOC problems solved in the minimum number of moves, consistent with Dassanayake, Michie, Jones et al. \(^7\), we did find support for previous research that this task was influenced by age.\(^{50}\) Similarly, although we did not replicate the group by difficulty interaction in the SOC mean number of moves task, we found evidence that, compared to the CNS-ND group, the CNS-D group required more moves to solve problems overall and took less time to plan their first move. In other words, compared to the CNS-ND group, the CNS-D group spent less time on spatial planning, which may have resulted in poorer decision-making.

For TMT-B, age was a significant covariate but not gender or estimated IQ. This result conforms to previous findings for TMT-B in healthy populations, that cognitive efficiency tasks are increasingly impaired with age but are not influenced by gender.\(^{49}\)
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With respect to the second aim relating to recovery over the course of the study, several patterns were revealed. While the CNS-ND group performance remained stable from discharge to 1-month follow-up, the CNS-D group improved at each time point for the primary measure TMT-B (cognitive flexibility). For cognitive efficiency (TMTB-A) and working memory (LNS) performance by the CNS-D group showed significant improvements by day-28 and -7, respectively. These results suggest that DSP with CNS-D drugs may impair several executive functions tasks linked to driving performance and that recovery of function may continue up to 28 days.

Compared to discharge, both the CNS-D and CNS-ND group showed significant improvements at day-7 for visual attention and visuomotor skills (TMT-A and CRT), and the capacity to inhibit responses (SSRT), however there were no significant improvements beyond this time point. This suggests that recovery of function following DSP with both types of drugs may impair performance for 7 days.

The final aim of this study was to determine which variables contribute to and develop explanatory models for recovery of neurocognitive function over time. Several covariates were found to be significant predictors from both pre- and post-DSP variables, but the majority were pre-DSP. The results suggest that the most influential factors on recovery from DSP with CNS-D drugs are individual characteristics. In the present study the largest effects were associated with having a psychiatric diagnosis related to schizophrenia, schizoaffective, or bipolar disorders, taking atypical antipsychotics, age, and intelligence. Post-DSP variables that influenced recovery were a change to medication (antidepressants and atypical antipsychotics) and whether participants consumed stimulants.

Although examination of DASS scores showed that over time each mood subscale percentile score declined for both CNS-D and CNS-ND groups, no subscale percentile score achieved significance as a predictor of neuropsychological performance suggesting that the
reduction in mood was not predictive of CNS-D recovery from DSP. However it should be noted that anxiety percentiles were significantly higher in the CNS-D group at day 28 (and at discharge).

Across the majority of the neuropsychological variables, participants who rated their cognitive ability higher produced better neuropsychological performance at discharge. SOC and SSRT were the only two neuropsychological variables unrelated to any subjective assessment variables. Given this evidence it suggests that, for the most part, participants who were more confident in their cognitive abilities performed better. In contrast, the one driving self-assessment variable (driving in bad weather) that was significantly associated with an objective measure (CRT latency) actually showed an inverse relationship indicative of a rather worrying disconnect between self-awareness about driving capacity and speed of response.

Examination of participants whose completion times on TMT-A and -B fell into the bottom 10\textsuperscript{th} percentile revealed that the CNS-ND group had members who met this criterion only at discharge, whereas several participants from the CNS-D group continued to produce completion times in the bottom 10\textsuperscript{th} percentile at day-7 and -28. At day-7 and -28 the CNS-D group were still almost 10 and 5 times more likely to be impaired on the TMT-B task than the CNS-ND group, respectively. The 10\textsuperscript{th} percentile cut-off limit was based on previous research linking poor performance on TMT-B with driving performance. Evidence suggests that TMT-B completion times that fall within the bottom 10\textsuperscript{th} percentile increase the risk of failing a driving test by 2.5 times,\textsuperscript{51} and the risk of MVA by 1.5 times.\textsuperscript{52} However, both papers sampled individual aged 65 and over, an age at which the risk of MVA could be elevated. Even so, an increase of risk of such magnitude equates to a blood alcohol level content (BAC) of 0.07, above the legal limit in most countries.\textsuperscript{53} Taken together the evidence suggests some individuals that DSP with CNS-D drugs may be impaired to such an extent that ability to perform tasks such as driving may be compromised for as many as 28 days after discharge.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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In addition to this replication, the present study found that the neurocognitive domains investigated: (1) visual attention and visuomotor skills; and (2) executive functions and working memory demonstrate a different pattern of recovery based on the drug used for DSP. The evidence suggests that, compared to CNS-ND drugs, participants DSP with CNS-D drugs take longer to recover the functions associated with these neurocognitive domains. Finally, the present study showed that more pre-DSP than post-DSP factors influence neuropsychological performance after discharge and that the pre-DSP factors relate to individual characteristics.

The results from this research appear to support the claim that TMT-B is an effective tool for differentiating neuropsychological performance in a clinical setting. Further, TMT-B completion times provide an indication that driving performance may be impaired for longer than first thought for individuals DSP with CNS-D drugs. Given that tertiary care facilities discharge individuals within 48 hours of DSP with CNS-D drugs, the instructions provided to individuals at discharge should take this extended period of recovery into consideration. Potential responses to these findings may include requiring patients to refrain from driving for a week post-discharge, or having them return to hospital or the roads and traffic authorities to retake some tests (TMT-B) before being allowed to drive again following DSP with CNS-D drugs.

The limited sample size for this study meant that some non-significant differences between the CNS-D and CNS-ND groups might have been the result of insufficient power to detect effects. Hence, additional covariates may have reached significance with a larger sample size. Despite this lack of power, the primary measure TMT-B replicated results produced by Dassanayake, Michie, Jones et al. That is, at discharge, participants admitted for DSP with CNS-D drugs were outperformed by those admitted for DSP with CNS-ND drugs. However, the limited sample size of the current study does not allow firm conclusions about the pattern of recovery for individuals that DSP with CNS-D drugs.
Future research should aim to replicate the findings of this study on a larger scale. A larger sample size would provide greater statistical power to explore additional covariates which may influence recovery, including whether pre-DSP covariates have greater influence on recovery more than post-DSP covariates. In addition, the small sample size precluded testing the pre DSP and post DSP covariates in blocks, the forward elimination procedure provided a solution, albeit compromised. In addition, future research should also assess patients’ self-assessments of cognitive and driving ability at multiple time points as this may change in light of re-engaging in daily activities such as driving.
References


3. Substance Abuse and Mental Health Services Administration OoAS. The DAWN Report: Emergency Department Visits for Drug-related Suicide Attempts by Young Adults Aged 18 to 24: 2008. 2010 [cited 2014 January]; Available from: [http://www.samhsa.gov/data/2k10/DAWN002/SuicideAttemptsYoungAdults.htm](http://www.samhsa.gov/data/2k10/DAWN002/SuicideAttemptsYoungAdults.htm)

4. Substance Abuse and Mental Health Services Administration OoAS. Emergency Department Visits for Drug-related Suicide Attempts by Adults Aged 25 or Older: 2008. 2010 [cited 2014 January]; Available from: [http://www.samhsa.gov/data/2k10/AdultSuicide/AdultSuicide.htm](http://www.samhsa.gov/data/2k10/AdultSuicide/AdultSuicide.htm)


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Chapter 3: Extended Discussion

Aims

The present study found that for the primary measure, TMT-B, individuals admitted because of DSP with CNS-D drugs have significant cognitive impairment at discharge compared to DSP with CNS-ND. This result formed part of the first aim and replicated the previous of Dassanayake, Michie, et al. (2012). The present study also found results that suggest neurocognitive functions recover differently for individuals who DSP with CNS-ND or CNS-D drugs. While the CNS-ND groups performance was stable over time, cognitive flexibility (TMT- B) for the CNS-D group showed significant improvement at each time point relative to the preceding time point while cognitive efficiency (TMTB-A) and working memory (LNS) performance showed significant improvements by day-28 and -7, respectively, relative to discharge. These results suggest that DSP with CNS-D drugs selectively impairs some neurocognitive functions and that the recovery of function may continue up to 28 days. DSP with CNS-ND and CNS-D drugs appeared to similarly impair the neurocognitive functions of visual attention and visuomotor skills (TMT-A and CRT) and inhibition (SSRT). Moreover, both groups failed to improve on these measures beyond day-7. Finally, LMM analysis produced explanatory models for recovery of neurocognitive function over time. Significant predictors included pre-, concurrent, and post-DSP variables, but the majority were pre-DSP variables. Based on this evidence the most influential factors included pre-existing variables such as having a psychiatric diagnosis related to Schizophrenia Schizoaffective, or Bipolar disorders, taking atypical antipsychotics, age, and intelligence. The concurrent variable was drug ingestion (in DDD) and post-DSP variables included changes to medication (antidepressants and atypical antipsychotics) and whether participants consumed stimulants (e.g., caffeine). Mood as measured by the DASS changed over the 28-day follow-up period, but did not account for changes over the same time period observed in cognitive flexibility in the CNS-D group.

In summary, analysis of the primary outcome measure, cognitive flexibility (TMT-B), found that the CNS-D group was impaired relative to the CNS-D group at discharge. Over the 28-day period
following admission for a DSP, the CNS-ND group’s TMT-B results remained relatively stable compared to the CNS-D group, and compared to the CNS-ND, the CNS-D group’s recovery of function was slower. These results suggest that, compared to CNS-ND drugs, DSP with CNS-D drugs produces greater and more longstanding impairment to the cognitive and psychomotor functions required to perform the TMT-B task.

Aside from a greater proportion of CNS-D participants having a diagnosis of depression, the CNS-ND and CNS-D drug groups, prior to discharge, did not significantly differ across demographic, clinical characteristics, or self-assessment of cognitive and driving abilities. These data, obtained via both self-report and from the HATS database, and the covariate analysis suggest that differences on TMT-B were not due to pre-existing, mood or other differences between the CNS-D and CNS-ND groups. Other than an indication that cognitive flexibility shows a slower recovery in the CNS-D group, the current study does not offer a compelling explanation for why these individuals are at increased risk of traffic accidents at least 1-month after discharge (Dassanayake, Jones, et al., 2012). The remainder of this discussion explores reasons why the current study may have failed to provide such insights. We begin by discussing limitations of the current study.

**Limitations**

**Limited Post-DSP Covariates**

Pre-DSP, clinical, and demographic data were extracted from the HATS database (Whyte, Buckley, & Dawson, 2002). This database contains demographic information about the patient, details of toxic exposure, information about clinical examinations and investigations, information from psychiatric assessment, outcome, discharge destination, and follow-up information. To improve reliability and validity of the information contained within the HATS database psychiatric staff conduct weekly inpatient presentations.

In contrast, at day-7, some post-DSP data were acquired based on self-report, specifically, participants were asked to recall whether their medication regime had increased, decreased, or remained the same. This form of data collection may be subject to multiple sources of error including
recall errors (i.e., participants forgetting their new medication, being unable to remember their previous medication, and/or being unsure of dosage changes) or not wanting to disclose the type of medication that they had been prescribed (social desirability). Following DSP, all participants were referred to their GP. If attended, this appointment may have included a medication review (addition, reduction, or change), a mental health plan to see a psychologist, and/or a referral to a psychiatrist. However, this referral was not enforced, and some participants may not have consulted their GP, and by extension, not all participants would have even received advice on their medication post-DSP. Having access to prescription and dispensing databases would have provided additional information about GP changes to medication in the context of DSP and whether individuals were dispensed the medication. Admittedly, database information does not indicate compliance but could have been validated against participant self-report.

Participants were also asked to self-report how many caffeine or stimulant drinks they consumed each day. Similar to self-report for medication, asking participants to self-report their daily consumption of such stimulants may result in errors. For example, participants may be unable to recall the amount of caffeine or stimulants drinks they consume or provided a social desirable response rather than their actual level of consumption. Unfortunately, beyond questioning family members or friends, or diary data, this source of data cannot be validated by an external objective measure.

Therefore, the current study gathered limited information post-DSP relative to pre-DSP, which may have restricted identification of relevant post-DSP factors. In addition, the results suggest that other important information was not collected during the post-DSP period. For example, the List Of Threatening Life events questionnaire showed that participants in the CNS-ND and CNS-D had, on average, an equal numbers of stressful events in their lives. However, participants were not asked whether they were receiving psychological or psychiatric support prior to DSP and/or in response to DSP, which may have influenced the psychological impact of any stressful life events. It should be noted that while the CNS-D group reported higher levels of anxiety at day-7 and -28 than the CNS-ND group, none of the mood variables had a significant impact on cognitive recovery. Nonetheless,
differing levels of support may have been influential in terms of cognitive recovery, as research suggests that psychotherapy can have a positive influence on cognitive functioning (Brewin & Smart, 2005; Butler, Chapman, Forman, & Beck, 2006; Mohlman & Gorman, 2005). For example, the cognitive technique ‘thought stopping’ has been shown to improve working memory in 60 university students (Brewin & Smart, 2005), while cognitive behaviour therapy improved executive functions in 10 individuals diagnosed with general anxiety disorder (Mohlman & Gorman, 2005). Based on this evidence, it is possible that any psychotherapy received by participants could influence the recovery of cognitive functions useful in daily activities for individuals admitted to hospital because of DSP with CNS-ND and CNS-D drugs.

Finally, participants in the present study were admitted to hospital because of DSP with CNS-D or CNS-ND drugs; generally the DSP was a response to the inability to overcome particular challenges in their life (Baumeister, 1990; Birtchnell & Alarcon, 1971). Being discharged from hospital often meant that patients would return to their social supports. The response of social supports to the DSP, if made aware, may have influenced how participants’ cognitive and psychomotor functions recovered. Two models, the main effect model and the stress-buffering model (not mutually exclusive), describe how social networks can influence psychological well-being (Cohen & Wills, 1985). The main effect model argues that social support has a beneficial effect irrespective of the presence of stress. The stress-buffering model argues that social support protects individuals from psychological distress during difficult times. Given this, a measure that assesses the influence of social support in difficult times may provide some insight into recovery.

**Social Desirability**

Self-assessment measures can result in socially desirable responses whereby individuals misrepresent themselves and distort their results. As such, social desirability is the tendency to respond in accordance with socially approved behaviours (Nunnally & Bernstein, 1994). Distortions in self-assessment measures have been shown to be more acute when individuals may incriminate themselves. In the present study individuals were asked to rate their cognitive and driving ability,
medication, stimulant use, and mood. Although responses to these measures may not be incriminatory, there is certainly the capacity for distortion, particularly for driving ability and medication use. One way to account for social desirability is to develop measures for the particular response of interest, such as the Driver Social Desirability Scale which has been designed to assess socially desirable responses in driving (Lajunen, Corry, Summala, & Hartley, 1997). Unfortunately this measure has had limited use and has been criticised for its inability to differentiate between social desirability bias or a highly prudent driving style (Poó et al., 2013). Irrespective of this criticism, self-assessment measures introduce the capacity for socially desirable responses, therefore future research should continue to assess social desirability to ensure these distortions are taken into consideration.

**Self-assessment protocol**

Post-DSP, participants were required to complete several neuropsychological measures and provide a self-assessment of their cognitive and driving ability, medication and stimulant use, and mood as assessed by the DASS.

At discharge, participants’ self-assessment of their cognitive and driving abilities and neuropsychological performance were examined. Pooled within-group correlations resulted in significant correlations between concentration and TMT-B, TMTB-A and LNS; following instructions and TMT-A, TMTB-A, and LNS; expressing thoughts and LNS; and driving in bad weather and CRT mean latency. However, this assessment was measured at discharge only, and therefore not able to detect change over time. Self-assessment of cognitive and driving abilities may be influenced by negative reinforcement (e.g., increased forgetfulness or a near miss while driving), which in turn has been associated with behaviour change in older drivers (Braitman & Williams, 2011). It is unknown whether such reinforcement would have influenced self-assessment of cognitive and driving ability in the present study, as visual analogue scales were not repeated over time.

**Ecological validity**

This present study did not include an objective measure of driving, such as an actual or simulated driving test. Inclusion of an actual or simulated driving test is in line with studies that
investigated the influence of therapeutic doses of drugs on driving ability (Chapter 1). Failure to include such a measure reduces the ecological validity of the results from the present study.

**Future Research**

**Personality and Driving Style**

Personality traits such as sensation seeking (Schwebel et al., 2006), impulsivity (Cheng & Lee, 2012; Owsley et al., 2003), aggression, and anger (Schwebel et al., 2006; Stephens & Groeger, 2009) have been linked to risky driving behaviour (Póó et al., 2013). Given the association found between personality traits and risky driving behaviour, it is possible that a measure that assessed driving style, such as the Multidimensional Driving Style Inventory (Taubman-Ben-Ari et al., 2004), may be able to isolate differences in driving styles between the CNS-ND and CNS-D drug groups and contributed to an understanding of why the CNS-D group were at greater risk of MVA up to 4-weeks after discharge, the primary motivation for this research. The personality and driving style of the CNS-D drugs group could dictate the level of risk of MVA, beyond those attributable to the pharmacological properties of the medication.

Dassanayake, Michie, et al. (2012) investigated impulsivity using an objective neuropsychological measure (Information Sampling Task; Cambridge Cognition Limited, 2012) in individuals who were admitted to hospital for DSP with CNS-D or CNS-ND medication and found that, at discharge, individuals in the CNS-D group were more impulsive than individuals in the CNS-ND group. Differences in the impulsivity of the CNS-D group could partially account for why the follow-up self-control case-series study found that individuals admitted for DSP with CNS-D medication were at greater risk of MVA up to 4-weeks after discharge. The present study investigated response inhibition but, unlike impulsivity, found no significant difference in the capacity to inhibit responses between the CNS-ND and CNS-D drug groups. This result suggests that DSP with CNS-ND and CNS-D drugs have similar influences on response inhibition.

**Insight**

In cognitive psychology, metacognition is believed to be composed of two parts, knowledge
and online awareness (Hacker, 1998). Knowledge includes the awareness about cognitive and psychomotor capabilities, task characteristics, cognitive processes and strategies. Online awareness includes the capacity to monitor performance while performing a task, and is linked to self-regulatory processes that facilitate adjustment to correct performance. This requires correctly accessing information from stored knowledge and accurately relating it to current performance.

According to Crosson et al. (1989), awareness is comprised of three hierarchical elements that form The Awareness Pyramid: intellectual, emergent, and anticipatory awareness. Intellectual awareness forms the base of the pyramid upon which emergent and anticipatory awareness sit, and provides information about the capabilities of a particular function. Emergent awareness derives knowledge about the capability of a particular function and monitors performance over time; by doing this, emergent awareness can detects deficits. When intellectual and emergent awareness are intact, a person may be able to recognise that a deficit exists but not be able to recognise errors that arise from the deficit, except through external feedback. Anticipatory awareness sits at the top of the pyramid and is able to predict when a problem will occur with a particular function based on the knowledge derived from intellectual and emergent awareness.

Self-rating scales, such as the visual analogue scales used in the present study, have been linked to self-awareness, in that they reflect the individual’s strength-of-belief in their own ability (Bandura, 1997). However, it has been argued that questions that ask about deficits may be more aligned with self-awareness because they require an individual to think about their present capabilities in relation to the task and whether they require assistance to perform a task (Toglia & Kirk, 2000). Therefore, the use of visual analogue scales in this study more than likely tapped into self-efficacy or strength-of-belief in the ability to perform a task, such as follow instructions. That is, the responses by participants suggest that correlates with neuropsychological measures do not reflect awareness per se but rather self-efficacy.

Bandura (1997) identified 3 levels of self-efficacy assessment: global, intermediate, and specific. One criticism of global self-assessment measures of self-efficacy are that they fail to account
for the specifics elements of the activities being performed. The questions presented on the visual analogue scales in this study required participants to answer questions about global rather than specific functions and as such, may explain why several analogue scales failed to demonstrate a link between self-efficacy and the neuropsychological measures.

Failure to find links between some cognitive and driving abilities and neuropsychological measures could also stem from deficits in awareness that resulted directly from the DSP. Faculties temporarily damaged by the DSP could have produced deficits in: self-knowledge, which resulted in false judgements about capabilities; online awareness, which meant that participants began tasks without planning or assessing (as suggested by the data from the Stocking of Cambridge task); task performance, which meant that participants were unable to monitor their performance and adjust accordingly; and self-evaluation, which resulted in participants operating on false beliefs about capabilities.

Finally, a greater number of correlations were found between neuropsychological measured and cognitive abilities as opposed to driving abilities. Given that we did not use an objective measure of driving such as an actual or simulated driving test, it is difficult to confirm links between subjective and objective measure. Comparing subjective and objective measures of driving is consistent with driving research into awareness where participants provide a self-assessment measure of their driving ability and then are given an objective driving test (simulated or on-road). Discrepancies between subjective and objective measures indicate whether participants have accurately appraised their driving ability. The current results suggest that the neuropsychological measures used in the present study had little association with participant self-efficacy of driving abilities. Future research into awareness should include an actual or simulated driving test at discharge and follow-up for patients admitted for DSP with CNS-D drugs. Also, including visual analogue scales after an actual or simulated driving test may have provided different results.

At present, research into awareness requires individuals to appraise their performance before or after an event (or in some cases, both before and after). One study required healthy participants to
provide a self-efficacy/awareness rating on a visual analogue scale before and after performing several tests designed to tap into cognitive capacities such as executive function, memory, attention, and visuoperception (Schoo, van Zandvoort, Biessels, Kappelle, & Postma, 2013). Overall, estimation errors were significantly higher before than after performing the task and were domain specific, suggesting that awareness of cognitive abilities was altered based on experience. This evidence also suggests that rating self-efficacy/awareness is derived from pre-existing beliefs about cognitive abilities but that current beliefs about performance can be changed following feedback after executing the task.

Mismatches between beliefs about performance and actual performance have been found in driving literature. One study of 158 male drivers aged 19-63 years found that some individuals who rated themselves as highly capable drivers were evaluated by an expert assessor as “unsafe” (Amado, Arikan, Kaca, Koyuncu, & Turkan, 2014). In this case, it appears that these drivers require increased feedback on performance to better align their awareness of driving capabilities with their actual driving capabilities. Discrepancy between awareness of driving performance and actual driving performance was also demonstrated in a study of 272 drivers aged 70+ years (Wood, Lacherez, & Anstey, 2013). Results from this study showed that drivers who made critical errors (defined as errors that required the driving instructor to take control of the vehicle), rated themselves no worse than the rest of the group. Together this evidence suggests that inflated self-assessment of driving ability can occur, which may explain why there was (i) no significant difference in self-assessment of cognitive and driving abilities in the present study despite objective indices suggesting some impairments in the two groups and (ii) no correlations between objective assessments of cognition and ratings of driving abilities. In addition, it may also explain the extended accident risk, in that individuals involved in a MVA may have over-estimated their capabilities following their discharge from hospital after DSP with CNS-D drugs. Therefore, future longitudinal cohort research should track changes in subjective and objective measures over time to examine if and how assessment and actual driving performance change over time.
Clinical/Legal implications

After being cleared by the toxicology team and assessed by the psychiatry team, patients admitted to tertiary care facilities for DSP with CNS-D drugs in Australia are discharged in less than 48 hours. The assessment process requires the patient to participate in a brief clinical interview and behavioural examination. If the patient is deemed suitable for discharge they are provided with several recommendations. At present, one of these recommendations is to abstain from driving for a set amount of time, usually 48-72 hours. The systematic review of experimental and epidemiological literature, and results from the present study, suggests that more than 72-hours after a DSP with CNS-D drugs may be required for cognitive and psychomotor functions to recover. This evidence raises clinical and medico-legal concerns pertaining to the discharge protocol for individuals admitted for DSP using CNS-D drugs and suggests that the discharge procedure requires further examination.

Current regulations

Developed countries have different laws for reporting individuals who are unfit to drive. In the United Kingdom, Canada, and the U.S., regulations exist for reporting impaired individuals to licensing authorities, while Germany, Belgium, and the Netherlands have no regulations (Brison & Bosco, 1997; Eggert, Thali, & Pfaffli, 2012). In Australia, health professionals must consider the implications of any diagnosis that could impair driving community (National Transport Commission, 2013). Considerations vary based on whether the condition is temporary or long-term. Unlike temporary conditions, long-term conditions, such as dementia, require health professionals to advise licensing authorities.

Duty of care

The distinction made between temporary and long-term conditions is a false dichotomy as conditions, such as DSP with CNS-D drugs, may vary as to how severely they can impair driving. Given the present research, health professionals may need to advise licensing authorities about a patient, particularly if a patient fails to show insight and acknowledge the need for behaviour modification, such as refraining from driving. In these instances the patient has failed to recognise
their impairment or chosen to ignore the advice provided by the health professional. In either case, there is potential for harm to befall themselves and/or the community if they began driving shortly after being discharged.

**Confidentiality**

When appealing to the patient’s sense of community fails, the health professional may be required to break clinician confidentiality. Breaking this confidentiality has several implications: firstly, the clinician-patient relationship may be irreparably damaged; secondly, the health professional’s decision may impact on their professional reputation with the community (Berger, Rosner, Kark, & Bennett, 2000; Love, Welsh, Knabb, Scott, & Brokaw, 2008).

If the clinician does decide to break confidentiality, they must take into consideration the implications for the client, such as losing independence, ability to work and provide for dependents, maintaining social contacts, and continuing involvement in personal interests and community activities (Love et al., 2008). These losses have implications for many patients in terms of emotional and physical well-being, quality of life, and evaluation of self-worth. Therefore the clinician may have to weigh up the added risk to the community, the burden placed on the client, and the impact the decision will have on their role as a health professional before discharging the patient.

**Conclusion**

Despite the small sample size, the present study found that the CNS-D group was outperformed at discharge by the CNS-ND group for the primary outcome measure, cognitive flexibility. The present study also found that some cognitive and psychomotor functions in the group of individuals admitted for DSP with CNS-D drugs exhibited slower recovery of cognitive and psychomotor function impairments over a 1-month period. Finally, analyses to create explanatory models for the recovery a neurocognitive functions found more significant pre-DSP covariates that concurrent and post-DSP covariates.

The imbalance between the number of pre-DSP and post-DSP covariates could be explained by several factors; sample size, validity of post discharge measures, not asking the “right” questions,
and socially desirable responses. Failure to detect more correlations between self-assessment of
driving abilities and neuropsychological measures could be explained by the present study not
including an objective measure of driving (e.g., actual or simulated).

At present factors that influence recovery after DSP with CNS-D requires additional research.
Multi-site recruitment would facilitate increased sample size and help overcome data collection
challenges (e.g., participant willingness to participate) challenges including a measure of personality
and or driving style to determine whether these factors could explain the extended risk of MVA found
in the CNS-D group previously (Dassanayake, Jones, et al., 2012). Self-assessments measures should
target specific elements related to deficits in cognitive and driving activities in light of DSP and be
repeated at each time point as ratings could change in light of feedback.

Based on the evidence from the present study and previous research (Dassanayake, Jones, et
al., 2012; Dassanayake, Michie, et al., 2012), individuals discharged from hospital after being
admitted for DSP with CNS-D drugs appears to have cognitive and psychomotor function
impairments that could reduce their capacity to perform daily activities such as driving. Given this,
medical practitioners would be advised to ensure that patients are made aware of these potential
deficits and how they could impair daily activities. In some cases, participants may fail to
acknowledge this information or agree to engage in compensatory strategies, such as refrain from
driving. In these situations medical practitioners may need to contact regulatory bodies to ensure that
the community is protected.
Chapter 3: Extended Discussion

References


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Chapter 3: Extended Discussion


Schwartz, J. B. (2007). The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clinical pharmacology and therapeutics, 82*(1), 87-96. doi: 10.1038/sj.clpt.6100226


The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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zolpidem on driving ability, memory functions, and psychomotor performance. *Journal of clinical psychopharmacology, 22*(6), 576-583.


Appendices

Appendix 1: Glossary

AOR       Adjusted Odds Ratio
ANCOVA    ANalysis of COVAiance
BRT       Brake Reaction Time
CANTAB    CAmbridge Neuropsychologival Test Automated Battery
CNS-D     Central Nervous System Depressant
CNS-ND    Central Nervous System Non-Depressant
CRT       Choice Reaction Time
DASS      Depression Anxiety Stress Scale
DSP       Deliberate Self-Poisoning
IQ        Intelligence Quotient
IRR       Incidence Risk Ratio
LMM       Linear Mixed Model
LNS       Letter Number Sequence
LOTL      List of Threatening Life events
LSD       Least Significant Difference
M         Mean
MAOI      MonoAmine Oxidase Inhibitors
MVA       Motor Vehicle Accident
NART      National Adult Reading Test
NHTSA     National Highway Traffic Safety Administration
NSW       New South Wales
OR        Odds Ratio
RR        Relative Risk
RT        Reaction Time
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

- **SD**: Standard Deviation
- **SDLP**: Standard Deviation of Lateral Position
- **SDS**: Standard Deviation of Speed
- **SE**: Standard Error
- **SIR**: Standard Incidence Ratio
- **SNRI**: Serotonin-norepinephrine Reuptake Inhibitor
- **SOC**: Stockings Of Cambridge
- **SSBP**: diagnosed psychiatric illness related to Schizophrenia, Schizoaffective, or BiPolar disorders
- **SSD**: Stop Signal Delay
- **SSRT**: Stop Signal Reaction Time
- **SSRI**: Selective Serotonin Reuptake Inhibitor
- **SST**: Stop Signal Task
- **TESI**: Tracking Error Severity Index
- **TMT**: Trail-Making Test
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

Appendix 2: Supplementary data

Supplementary table 1: Benzodiazepines and driving performance: experimental studies (BAC = blood alcohol concentration. RT = reaction time. BRT = brake reaction time. DDD = defined daily dose. SDLP = standard deviation of lateral position. SDS = standard deviation of speed, b.i.d. = twice a day, t.i.d. = three times a day)

<table>
<thead>
<tr>
<th>Study [Ref. No.]</th>
<th>a) Experimental design</th>
<th>b) Subjects</th>
<th>c) Treatment conditions: Drug, dose, duration of treatment if &gt;1 dose</th>
<th>d) Timing of test after dosing</th>
<th>e) Task</th>
<th>f) Outcome measures</th>
<th>g) Results</th>
<th>h) Comments/ Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linnoila and Hakkinen, 1974</td>
<td>Double-blind, placebo-controlled</td>
<td>70 professional drivers (19-22y) In 7 groups (10 each)</td>
<td>No drug or drink (Zero group) Placebo drug &amp; drink Alcohol 0.5g/kg Diazepam 10mg Diazepam 10mg + alcohol Codeine 30mg Codeine 30mg + alcohol</td>
<td>30 minutes</td>
<td>40-minute drive in a driving simulator</td>
<td>Steering wheel reversals, number of times brakes used, number of times clutch used, number of times turning signal used, Speed, BRT, number of neglected instructions, number of collisions, driving off the road</td>
<td>Diazepam: More neglected instructions and collisions. Codeine: Less steering wheel reversals and more collisions. Diazepam + alcohol: More steering wheel reversals, neglected instructions and collisions. Codeine + alcohol: More collisions (All comparisons with the Zero group)</td>
<td>No comparisons with placebo. Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.</td>
</tr>
<tr>
<td>O'Hanlon et al., 1982</td>
<td>Double-blind, placebo-controlled, 5-way crossover</td>
<td>9 healthy male driving instructors (24-34y)</td>
<td>Diazepam 10mg Diazepam 5mg Placebo control No-tablet control Early-morning control</td>
<td>1h</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP</td>
<td>Increased SDLP after 10mg diazepam than in other conditions.</td>
<td></td>
</tr>
<tr>
<td>Verster et al., 2002b</td>
<td>Randomised double-blind placebo controlled 2-way crossover</td>
<td>20 healthy volunteers (8 men, 12 women). Age (SD): 25.1±2.0y</td>
<td>Alprazolam 1mg Placebo</td>
<td>1h</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP SDS</td>
<td>6 subjects did not complete driving test after alprazolam. Both outcome measures significantly impaired after alprazolam.</td>
<td>The SDLP increase equivalent to that caused by alcohol at a blood concentration of 1.5g/l.</td>
</tr>
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<tr>
<td>Willumeit et al., 1984b</td>
<td>Double-blind, placebo-controlled, 8-way crossover</td>
<td>16 healthy volunteers (10 men, 6 women. 20-33y)</td>
<td>Lormetazepam 2mg Diazepam 10mg Mepindolol 10mg Placebo, with and without alcohol 0.6g/kg</td>
<td>1h, 2h, 3h</td>
<td>Driving simulator test (30 min)</td>
<td>Correct tracking executions with steering Reaction time</td>
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<tr>
<td>Mattila et al., 1998</td>
<td>Double-blind placebo controlled 5-way crossover (latin square)</td>
<td>12 healthy subjects (21-28y)</td>
<td>Placebo, Ethanol (0.65-0.95g/kg), Oxazepam 30mg, Diazepam 15mg, Zolpidem 15mg, Zopiclone 7.5mg</td>
<td>Baseline, 1, 3.5, and 5hrs after intake</td>
<td>Simulated driving (6mins)</td>
<td>Tracking and mixed reactions (TESI = tracking error severity index), Reaction errors and cumulative reaction times</td>
</tr>
<tr>
<td>Takahashi et al., 2010</td>
<td>Placebo controlled Randomised double-blind 3-way crossover</td>
<td>18 healthy volunteers (male 32-44y, M 37.1 SD 3.3y)</td>
<td>Tandospirone 20mg Diazepam 5mg Placebo</td>
<td>Baseline, 1h 4h</td>
<td>Driving simulator test</td>
<td>SDLP BRT Coefficient of variation</td>
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<tr>
<td>Vanakoski et al., 2000</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>9 young (22-24y) and 9 old (55-77y)</td>
<td>Young: Diazepam 15mg, alcohol 0.8g/kg, placebo Old: Diazepam 10mg, alcohol 0.7g/kg, placebo</td>
<td>1.5h before and 4h after</td>
<td>Driving simulator test</td>
<td>BRT, tracking errors (simple and complex), global driving performance</td>
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<tr>
<td>Mattila et al., 1994</td>
<td>Double-blind placebo-controlled 5-way crossover</td>
<td>12 healthy volunteers (6 men, 6 women. 19-32y)</td>
<td>Suriclone 0.4 mg Zopiclone 7.5mg Placebo, alone and together with 50 mg chlorpromazine</td>
<td>Before, and after 1.5h, 3.5h &amp; 6h</td>
<td>Driving simulator test</td>
<td>Tracking errors RT</td>
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<tr>
<td>(Kuitunen, 1994)</td>
<td>Double-blind placebo-controlled 6-way crossover</td>
<td>12 healthy volunteers</td>
<td>Diazepam 15 mg Amitriptyline 50mg Mirtazapine 15mg Diazepam + one other drug Placebo</td>
<td>Before, and after 1.5h &amp; 4.5h</td>
<td>Driving simulator test</td>
<td>Tracking errors RT</td>
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

**Appendices**

(Kuitunen, 1994) Double-blind placebo-controlled 6-way crossover 12 healthy volunteers Zopiclone 7.5 mg Triazolam 0.25mg Placebo Alcohol 0.8 g/kg Zopiclone / triazolam + alcohol Before, and after 1.5h & 4.5h Driving simulator test Tracking errors RT Drugs alone and in combination with alcohol increased RT in both times and tracking errors at 1.5h. Triazolam + alcohol increased tracking errors at 4.5h. NO other significant effects.

Otmani et al., 2008 Randomised double-blind placebo-controlled 4-way crossover 16 healthy volunteers (12 men and 4 females, 45–55y) Prolonged-release melatonin 2mg Zolpidem 10mg Both drugs Placebo 2h & 13h Driving simulator test (60min, light traffic) Number of collisions, standard deviation from the speed limit, standard deviation of absolute speed, standard deviation from ideal route Number of collisions, standard deviation from speed limit and standard deviation from ideal route increased with zolpidem and zolpidem-melatonin combination at 2h. No significant difference at 13h.

Mattila et al., 1993 Double-blind placebo-controlled 4-way crossover (Latin square) 12 healthy male and female volunteers, 23-30y Placebo, Lorazepam 2mg (capsule; LZ cap), 2x Lorazepam (1mg each) sublingual foam tablets, Ethanol (1g/kg body weight), 3mg for 2 robust participant (93 and 97kg) Baseline (10:30am), 2,4 and 6 h after dose Simulated driving (5mins) Complex and simple tracking. Simple and choice reaction task. Tracking and error percentage. Tracking error severity index (TESI) TESI score for both formulations were significantly different to baseline at each post-baseline. The same was found for RT except that no sig diff at 6h for LZ cap. Simulated driving test only 5 mins

Silveira et al., 2002 Randomised Double-blind placebo controlled two-way crossover 32 healthy subjects (18-37y) Mean (SD) age 23.6 (3.8) Mexazolam 1mg, placebo Pre-treatment and 3-hrs post-dose Sports Car GT (Electronic Arts) computer game, IBM computer 15 Laps of a predefined track Total time score (TTS) Best lap time (BLT) No sig. diff btw placebo and mexazolam scores for TTS and BLT. There was a stat sig. improvement bw placebo and pre and post mexazolam scores. Improvement attributed to learning effect induced by a repetition of the tests

Verster et al., 2002a Double-blind placebo controlled 5-way crossover 30 healthy volunteers (15 men, 15 women). Age (SD): 24.0±2.4y Zaleplon 10mg or 20mg Zolpidem 10mg or 20mg Placebo Middle of the night 4h Standardised highway driving test (~100km) SDLP SDS Zolpidem: SDLP and SDS significantly increased with both doses. Significant dose-response relationship. 3 subjects were removed from the driving test after zolpidem – excessive errors Zaleplon: No significant difference form placebo.

Leufkens et al., 2007 Double-blind placebo controlled 3-way crossover 18 healthy volunteers (9 men, 9 women. 20-45y) Alprazolam slow release (XR) 1mg Alprazolam immediate release (IR) 1mg Placebo 4h Standardised highway driving test (~100km) SDLP SDS SDLP: Increased with both alprazolam preparations. Increase with alprazolam IR is twice the increase caused by alprazolam XR. SDS: No change. 10 driving tests discontinued prematurely (7IR, 3XR).
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

**Appendices**

**Vermeeren et al., 1998a**
- Double-blind, placebo-controlled 7-way crossover
- 28 healthy volunteers (14 men, 14 women, 23-40y)
- Zaleplon 10/20mg > placebo
  - Placebo > zaleplon 10/20mg
  - Zopiclone 7.5mg > placebo
  - Placebo > zopiclone 7.5mg
  - Placebo > placebo
- Bedtime > 5h later
- 5h after 2nd dose
- Standardised highway driving test (~100km)
- SDLP
- Zopiclone: Increased after bedtime dosing and after middle of the night dosing. Worse in latter condition.
  - Zaleplon: No significant increase after either bedtime or middle of the night administration of any of the doses.
  - 7 driving tests terminated (4 Zopnight, 2 Zopeven, 1 Za20night).

**Boyle et al., 2008**
- Randomised double-blind placebo-controlled 2-way crossover
- 32 healthy volunteers (17 men and women, 19–47y)
- Eszopiclone 3mg Placebo
- Before and 9.00-10.25h after dosing
- Closed-circuit driving BRT
- No difference in change BRT from baseline either with placebo or eszopiclone.

**Bocca et al., (2011)**
- Double blind placebo-controlled 4-way crossover
- 16 healthy individuals (55-65y) mean age of 60.3y
- Zopiclone 7.5mg Zolpidem 10mg, Flunitrazepam 1mg Placebo
- 9am (10hrs after night dose)
- Driving Simulator (1hr - urban route with accident scenarios)
- SDLP, SDS, mean lateral position, mean speed, number of road exits
- Zopiclone and Zolpidem impaired SDLP, SDS, and road exits.

**Hindmarch and Subhan, 1983**
- Double-blind, placebo-controlled, 4-way crossover
- 7 healthy female volunteers (25-40y)
- Placebo Midazolam 15mg Alcohol 0.5g/kg Midazolam 15mg + alcohol
- 10h (i.e. following morning)
- Actual driving test BRT
- No impairment with midazolam, alcohol or midazolam alcohol combination.

**Vermeeren et al., 2002**
- Double-blind placebo controlled 3-way crossover
- 30 healthy volunteers (15 men, 15 women 21-45y)
- Zopiclone 7.5mg Zaleplon 10mg Placebo
- 10h
- Standardised highway driving test (~100km)
- SDLP
- Zopiclone: Significantly increased compared to zaleplon and placebo.
  - Zaleplon: No difference from placebo
  - 1 driving test terminated (Zopiclone).

**Meskali et al., 2009**
- Double-blind placebo-controlled 3-way crossover
- 16 healthy elderly volunteers (8 women, 8 men, 55-65y)
- Flunitrazepam 1mg Zolpidem 10mg Zopiclone 7.5mg Placebo
- 11pm
- Driving simulator test (urban route with accident scenarios)
- Number of collisions (of 5 accident scenarios per treatment)
- No significant increase with any of the drugs.
- Total number of collisions among 4 conditions compared with chi-square test.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<tr>
<td>Bocca et al., 1999</td>
<td>Double-blind, placebo-controlled 3-way crossover</td>
<td>16 healthy volunteers (9 men, 7 women, 20-30y) in 2 groups (9am &amp; 11am) of 8</td>
<td>Zolpidem 10 mg, Zopiclone 7.5 mg, Flunitrazepam 1 mg, Placebo single dose at 11pm</td>
<td>10h (9am group), 12h (11am group)</td>
<td>Driving simulator test (~90 min)</td>
<td>Mean variance of lateral position: Increased by zopiclone and flunitrazepam at 10h but not by zolpidem. No effect by any drugs after 12h. Mean variance of vehicle velocity: Not affected by any of the drugs.</td>
</tr>
<tr>
<td>Leufkens and Vermeeren, 2009</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>18 healthy elderly volunteers (10 women, 8 men, 55-75y)</td>
<td>Temazepam 20mg, Zopiclone 7.5mg, Placebo</td>
<td>10-11h</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP: Significant increase after zopiclone but not temazepam. SDS: Significantly higher with zopiclone than with temazepam. 1 driving test terminated (Zopiclone)</td>
</tr>
<tr>
<td>Leufkens et al., 2009</td>
<td>Placebo controlled double blind 5-way crossover</td>
<td>25 healthy volunteers (13 men, 12 female, M 31.4y, SD 7.5y)</td>
<td>Gaboxadol 15mg, Zopiclone 7.5mg, Zolpidem 7.5mg</td>
<td>10-11h</td>
<td>Standardised highway driving test (1 hour)</td>
<td>Zolpidem and Zopiclone significantly impaired SDLP and SDSP. 2 driving tests terminated (Zolpidem)</td>
</tr>
<tr>
<td>Ramaekers et al., 2011</td>
<td>Placebo controlled randomised double blind 4-way crossover</td>
<td>32 healthy volunteers (16 men, 16 women, M 33y, SD 9y)</td>
<td>Esmirtazapine 1.5 mg, 4.5mg single and multiple (7-days); Placebo; Zopiclone 7.5mg (active control) single dose</td>
<td>11hrs after nocte dose Day2 Day8 Day 8 (Zopiclone)</td>
<td>1hr standardised on-the-road highway driving test.</td>
<td>Esmirtazapine 1.5 mg no change single or repeated; 4.5mg driving impairment after single dose but not after repeated. Zopiclone 7.5mg (active control) increased SDLP.</td>
</tr>
<tr>
<td>Betts and Birtle, 1982</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>12 healthy volunteers, all women</td>
<td>Flurazepam 15mg, Temazepam 20mg, Placebo</td>
<td>12h</td>
<td>Actual driving test</td>
<td>Poor manoeuvring skills with Flurazepam. More hits on sides in passable gaps after both drugs.</td>
</tr>
<tr>
<td>Friedel et al., 1991</td>
<td>Non-blind study</td>
<td>60 university students (male, 22-26y) in 3 groups (20 each)</td>
<td>Diazepam ~7mg, Diazepam –14mg, Placebo</td>
<td>Not specified</td>
<td>Standardised driving tasks in a driving simulator</td>
<td>No significant effect of diazepam. Simulation closer to real-life driving. Wide individual variation may be due to complex tasks and perhaps too short practice sessions.</td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<tr>
<td>Dureman and Norman, 1975</td>
<td>Double blind, placebo controlled 3-way crossover (patients)</td>
<td>34 neurotic patients (19-31y, mean age 25y) and 42 control (19-29y)</td>
<td>Patient: Placebo, Diazepam 5mg, Chlorazepate 10mg, t.i.d (7-days). Controls: Placebo, Diazepam 5, 10 or 15mg, Chlorazepate 10, 20, or 30mg</td>
<td>Patients before the trial and after each drug period (non-specific). Controls 1 hour</td>
<td>Controls: no difference in steering precision or break reaction time irrespective of treatment or dose. No objective measures of driving for patients mentioned. No mention of ANOVA conducted for the controls group.</td>
</tr>
<tr>
<td>Partinen et al., 2003</td>
<td>Randomised double-blind placebo controlled 3-way crossover</td>
<td>18 insomniacs women (35-60y)</td>
<td>Temazepam 20mg Zolpidem 10mg Placebo Single dose at 2am Baseline and 5.5h after each dose</td>
<td>Driving simulator test (110km) Lateral position deviation Speed deviation Reaction time Time to collision</td>
<td>Greater lateral position deviation after zolpidem but not after temazepam. No drug effects on other measures.</td>
</tr>
<tr>
<td>Boyle, et al., 2008</td>
<td>Randomised double-blind placebo-controlled 2-way crossover</td>
<td>23 patients with primary insomnia (22 men, 10 women, 20-55y)</td>
<td>Eszopiclone 3mg Placebo Before and 9.00-10.25h after dosing</td>
<td>Closed-circuit driving BRT</td>
<td>No difference in change BRT from baseline either with placebo or eszopiclone.</td>
</tr>
<tr>
<td>Vermeeren et al., 1995</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>17 women (25-51y) with insomnia</td>
<td>Flunitrazepam 2mg Zolpidem 10mg Placebo</td>
<td>Standardised highway driving test (~100km) SDLP</td>
<td>No significant impairment by any of the drugs. 1 driving test terminated (flunitrazepam).</td>
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<tr>
<td>Volkerts et al., 1992</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>18 healthy male volunteers, 25-31y</td>
<td>Lormetazepam 1mg, Oxazepam 50mg Placebo X 2 nights (10pm)</td>
<td>Simulator: 12h (1st dose). On-the-road: 10h (1st dose), 10h &amp; 16h (2nd dose)</td>
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<tr>
<td></td>
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<td></td>
<td>Standardised highway driving test (100km) &amp; Model TS2 driving simulator test</td>
<td>On-the-road driving: SDLP Driving simulator: Number of correctly executed curve navigation manoeuvres (TC), reaction time</td>
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<tr>
<td>Mattila, 1998</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>9 healthy volunteers</td>
<td>Diazepam (DZ) 10mg Diazepam controlled-release (DZ-CR) 10mg Placebo daily @ bedtime Acute: Single dose Day 1 and 8 of 25mg DZ and 20mg DZ-CR.</td>
<td>Baseline, 1.5 and 3 hrs after Day1 and Day8 acute dose. (Simulated driving only at 3hrs) Simulated driving test (duration not spec.)</td>
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<tr>
<td>O'Hanlon et al., 1995</td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>16 healthy volunteers (8 men, 8 women, 25-43y)</td>
<td>Ondansetron 1mg b.i.d. Ondansetron 5mg b.i.d. Diazepam 5mg t.i.d. Placebo 1st evening + 7-days</td>
<td>1h after evening dose on day 1 and day 8 Standardised highway driving test (~100km)</td>
</tr>
<tr>
<td>Iudice et al., 2002</td>
<td>Randomised double-blind placebo-controlled 2-way crossover</td>
<td>12 healthy volunteers (5 men, 7 women. 27-38y)</td>
<td>Lormetazepam 1mg Placebo X 3 nights Baseline, morning after last dose of each treatment Simulated drive (~15km) in interacting traffic</td>
<td>Time length of run, number of infractions and speed exceedings, time to collision</td>
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<tr>
<td>Tornros &amp; Laurell 1990</td>
<td>Randomised double blind placebo controlled 3 way crossover design</td>
<td>18 healthy volunteers 20-35y</td>
<td>Brotizolam 0.25mg Nitrazepam 5mg Placebo x 3 nights</td>
<td>Acute: 12 participants test immediately after first ingestion. Then tested on 3rd day with the remaining 6 subjects 9.5hrs after 11pm dose Simulated driving task (2hrs and 20 minutes)</td>
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<td>Laurell and Tornros, 1986</td>
<td>Double-blind, placebo-controlled, 3-way crossover</td>
<td>18 healthy volunteers, 20-34y</td>
<td>Triazolam 0.25mg, Nitrazepam 5mg, Placebo at 11pm x 3 nights</td>
<td>9h after 1st &amp; 3rd dose</td>
<td>Simulated driving (~2.5h), Actual driving test (30 min)</td>
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<tr>
<td>Vermeeren et al., 1998b</td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>23 healthy women (24-45y)</td>
<td>Chlorpheniramine 8mg / 12mg nocte &gt; terfenadine 60 mg mane Flurazepam 30mg night &gt; placebo morning Placebo night &amp; morning X 2 cycles</td>
<td>30min after last morning dose (10h after last nightly dose)</td>
<td>Standardised highway driving test (~100km), Car following test (25km)</td>
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<tr>
<td>Hindmarch and Gudgeon, 1980</td>
<td>Double-blind placebo controlled 3-way crossover study</td>
<td>12 female volunteers (26-40y)</td>
<td>Clobazam 10mg, Lorazepam 1mg, Placebo t.i.d. x 3 days + 1 dose in morning of 4th day</td>
<td>0.5h after last dose</td>
<td>Multiple car driving manoeuvres</td>
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<tr>
<td>Laurell and Tornros, 1991</td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>24 healthy volunteers (20-32y, moderate drinkers)</td>
<td>Flunitrazepam 2 mg, Flurazepam 30 mg, Triazolam 0.5 mg Placebo, x 4 nights Alcohol after day 5 testing</td>
<td>9h after 4th dose and then 10 min after alcohol</td>
<td>Drive 20 km in the shortest time in a driving simulator</td>
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<td>Hindmarch, Hanks &amp; Hewitt et al., 1977</td>
<td>Double-blind placebo controlled 2-way crossover</td>
<td>10 volunteers (5 men, 5 women, mean age 27y)</td>
<td>Clobazam 20mg Placebo x 6 nights</td>
<td>morning following 6th dose (day 7)</td>
<td>Multiple car driving manoeuvres</td>
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<tr>
<td>Van Laar et al., 2001</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>18 healthy male volunteers (25-36y)</td>
<td>Lorazepam 1.5mg, Ritalinser 5mg Placebo b.i.d. X 7-days</td>
<td>3h after last dose</td>
<td>Standardised highway driving test (~100km)</td>
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Vermeeren et al., 1998b: Significant increase of SDLP and SDS with flurazepam compared to other 3 conditions. Significant delay in RT compared to placebo. Chlorpheniramine / terfenadine combinations: No significant impairment. 2 driving tests terminated (flurazepam).

Hindmarch, Hanks & Hewitt et al., 1977: Acute effect not examined. Negative effects on day 7 may be due to absence of drug effect or to tolerance.

Laurell and Tornros, 1991: Lack of tolerance to lorazepam after 1 week.
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<td>Willumeit et al., 1983</td>
<td>Double-blind, placebo-controlled, 3-way crossover</td>
<td>12 healthy volunteers (11 men, 1 woman, 21-30y)</td>
<td>Lorazepam 2mg Flurazepam 30mg Placebo</td>
<td>Morning after last dose</td>
<td>Driving simulator test (30 min) Correct tracking executions with steering, Reaction time Flurazepam: less correct tracking executions and prolonged reaction time compared to placebo. Lorazepam: no difference from placebo.</td>
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<tr>
<td>Ramaekers et al., 2011</td>
<td>Placebo controlled randomised double blind 4 way crossover</td>
<td>32 healthy volunteers (16 men 16 women, M 33y, SD 9y)</td>
<td>Esmirtazapine 1.5 mg, 4.5mg single and multiple (7-days); Placebo; Zopiclone 7.5mg (active control) single dose</td>
<td>11hrs after nocte dose 1hr standardised on-the-road highway driving test.</td>
<td>SDLP Esmirtazapine 1.5 mg no change single or repeated, 4.5mg driving impairment after single dose but not after repeated. Zopiclone 7.5mg (active control) increased SDLP.</td>
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<td>Mercier-Guyon et al., 1999</td>
<td>Randomised double-blind 2-way crossover</td>
<td>16 healthy male volunteers (29-44y)</td>
<td>Lorazepam 0.5mg morning, 0.5mg lunchtime, 1mg bedtime Captodiamine 50mg t.i.d. x 7-days</td>
<td>Before and after 7-day treatment. Time not specified -15-min drive in 900m circuit with different driving manoeuvres</td>
<td>Number of errors due to clumsiness (slalom task), excessive inhibition (braking too early, too conservative gap judging), disinhibition (braking too late, forcing passage when gap is too poor CVP 2D6 metabolizers more sensitive to impairing effects of esmirtazapine</td>
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<tr>
<td>O’Hanlon, et al., 1995</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>18 healthy volunteers (9 men, 9 women, 22-34y)</td>
<td>Lorazepam 0.5mg Suriclone 0.2mg Placebo t.i.d. x 9 days starting from midnight day 1</td>
<td>2-3h after afternoon dose of day 2 &amp; day 9 Standardised highway driving test (~100km)</td>
<td>SDLP: increase with both drugs on both days. Headway maintenance: impairment on both days with lorazepam and day 2 but not day 9 with suriclone. Nine driving tests terminated (Lorazepam).</td>
</tr>
<tr>
<td>Moskowitz and Smiley, 1982</td>
<td>Double-blind placebo-controlled</td>
<td>48 healthy volunteers (24 men, 24 women, 21-40y) in 3 groups (8 men &amp; 8 women each)</td>
<td>Buspirone 20mg Diazepam 15 mg Placebo daily for 9 days.</td>
<td>Before and 1h after day 1, 8 and 9 Driving simulator task (~ 30 min)</td>
<td>Numerous measures: Lateral position control Speed control Headway control Target (e.g. road sign) detection Emergency decision-making Day 1, postdose: Worst overall performance with diazepam and best performance with buspirone. Day 8, predose: No significant difference among groups. Day 8, postdose: Worst performance with diazepam and best performance with buspirone.</td>
</tr>
</tbody>
</table>

A paper that included Willumeit 1984ab argued that short-acting benzodiazepines without active metabolites lead to superior driving perf. over night-time hypnotics.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

### Appendices

| Multiple doses, patient | O'Hanlon, 1984b | Double-blind, placebo-controlled, 4-way crossover | 16 former hypnotic drug users, females aged 25-40y | Loprazolam 2mg  
Loprazolam 1mg  
Flunitrazepam 2mg  
Placebo  
On 2 nights at 10pm | 10-11h & 16-17h following 2nd dose | Standardised highway driving test (~100km) | SDLP | Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h). | Degree of impairment increases with plasma loprazolam concentration |
|---|---|---|---|---|---|---|---|---|---|
| | O'Hanlon, 1984 | Double-blind, placebo-controlled, 4-way crossover | 24 former hypnotic drug users, females aged 25-40y | Flurazepam 30mg  
Flurazepam 15mg  
Secobarbitone 200mg  
Placebo  
2 nights at 10pm | 10-11h & 16-17h after 2nd dose | Standardised highway driving test (~100km) | SDLP | Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h). |
| | Brookhuis et al., 1990 | Double-blind placebo-controlled 3-way crossover | 16 patients with insomnia (6 males, 10 females, 26-41y) | Placebo x 2 nights > Lormetazepam 1mg or lormetazepam 2mg or flurazepam 30mg x 8 nights > Placebo x 3 nights | 10h & 16h after 2 placebo doses (baseline), 2, 4 & 7 active drug doses and 1 & 3 resumed | Standardised highway driving test (72km) | SDLP | Driving speed | Flurazepam: Significant impairment during treatment period. Worse in the morning. Lormetazepam 1mg or 2mg: No impairment during treatment period. |
| | Biehl, 1979 | Double-blind placebo-controlled 3-way crossover study | 24 male students (18-24y) with high neuroticism score | Clobazam 20mg  
Diazepam 10mg  
Placebo morning for 3 days | On day 2, timing not specified | Driving in traffic | 29 variables of driving performance: Observer-rated items and objective measurements | Break reaction time delayed with diazepam compared to clobazam. No other differences. | Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared. Real driving |
| | O'Hanlon and Volkerts, 1986 | Double-blind, placebo-controlled 2-way crossover study | 11 insomniacs, women, 26-38y | Placebo 2 days > Temazepam 20mg or Nitrzepam 10mg x 8 days > placebo 3 days (dosing at 10pm) | 10h & 16h after day 2, 4, 6, 9, 11, 13 dose | Standardised highway driving test (~100km) | SDLP | Temazepam: Minimum or no impairment at 10h (morning). No impairment in afternoon (16h). Nitrzepam: Significant impairment with repeated doses. Worse in the afternoon. |
| | O'Hanlon, et al., 1995 | Randomised double-blind placebo controlled | 24 men and 36 women with anxiety (24-64y) in 3 groups | Lorazepam 2mg (n=18)  
Alpidem 5mg (n=19)  
Placebo (n=19)  
b.i.d. run-in, treatment and washout periods, 7, 8 & 6 days respectively | Day 1 before run-in, Day 8 & 15, 3-4h after morning dose | Standardised highway driving test (~100km) | SDLP | Significant increase in SDLP with both drugs on both days 8 and 15. Change is less with alpidem. Driving tests terminated = 2 Alpidem 10 Lorazepam | SDLP of patients were similar to those of healthy volunteers of the previous two studies |
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

### Appendices

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<td>Staner et al., 2005</td>
<td>Randomised double-blind placebo controlled 4-way crossover</td>
<td>23 patients (9 men and 14 women, 18-65y) with primary insomnia</td>
<td>Zolpidem (10 mg)</td>
<td>9-11h (7:30am - 9:30am), on day 2 &amp; day 8</td>
<td>Simulated driving in light traffic (~ 60 min)</td>
<td>Lateral position deviation</td>
<td>Zopiclone increased the number of collisions. Lormetazepam increased the speed deviation. No changes by zolpidem.</td>
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<tr>
<td>Schmidt et al., 1986</td>
<td>Randomised double-blind</td>
<td>32 (20 men, 12 women) outpatients with sleep disorders</td>
<td>Two groups (16 each) Flunitrazepam 2mg Temazepam 20mg 7 nights</td>
<td>Baseline, morning (10h) after day 1 &amp; 7 dose</td>
<td>Standard driving test (25km, ~ 60min)</td>
<td>Steering control</td>
<td>Better performance with temazepam and worse performance with flunitrazepam on both days.</td>
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<tr>
<td>Moore, 1977</td>
<td>Double-blind, placebo-controlled 2-way crossover</td>
<td>14 males with anxiety required hospital admission. (20-40y) mean age 30y</td>
<td>Medazepam 5-30mg /d (mean 16.5mg) Placebo x 3 weeks</td>
<td>At the end of 3 weeks. Time not specified.</td>
<td>30 min drive in a simulator, Actual driving test</td>
<td>Driving Simulator: BRT, speeding, forgetting indications, errors in steering and positioning Actual driving: major (dangerous) or minor (technical) driving errors</td>
<td>Increased minor driving errors while on medazepam.</td>
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<tr>
<td>Van Laar et al., 1992</td>
<td>Placebo-controlled (Drug treatment double-blind, placebo single-blind)</td>
<td>2 groups of 12 outpatients (6 men, 6 women. 18-50y) with generalised anxiety disorder</td>
<td>Placebo x 7-days &gt; drug treatment x 4 weeks &gt; placebo x 7-days Drug treatment = Buspirone 5mg t.i.d. x 1wk &gt;10mg mane, 5mg noon, 5mg nocte x 3wks; or Diazepam 5mg t.i.d. x 4wks</td>
<td>Evening of 7 day of each treatment week, 1.5h after last dose of drug or placebo</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP Standard deviation of speed (SDS)</td>
<td>Buspirone: No impairment in SDLP or speed control throughout treatment. Diazepam: Marked increase in SDLP after 1st week, remain significant up to end of 3rd week. Poor speed control after 1 week, normal thereafter. 2 Diazepam driving tests terminated.</td>
</tr>
<tr>
<td>de Gier et al., 1981</td>
<td>Observer-blinded, two-groups</td>
<td>9 patients with anxiety (45.6 ±9.6y) and 13 controls (40.6 ±8.4y) (all men) treated by same physician</td>
<td>Diazepam 5mg – 20mg/d. Duration of treatment not specified</td>
<td>Varying times</td>
<td>Driving in traffic (~ 60km)</td>
<td>Driving performance measured according to a checklist by a trained observer</td>
<td>Poor performance in patients taking diazepam.</td>
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Supplementary table 2: Antidepressants and driving performance: experimental studies (BAC = blood alcohol concentration. RT = reaction time. BRT = brake reaction time. DDD = defined daily dose. SDLP = standard deviation of lateral position. SDS = standard deviation of speed, b.i.d. = twice a day, t.i.d. = three times a day)

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<td>Iwamoto et al., 2008a, Iwamoto et al., 2008b</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>17 healthy male volunteers (30-42y)</td>
<td>Paroxetine 10mg Amitriptyline 25mg Placebo</td>
<td>Pre-treatment and 1h &amp; 4h postdose</td>
<td>Simulated driving with road tracking, car following and braking</td>
<td>SDLP Variability of headway BRT</td>
<td>1h: No differences between conditions. 4h: Amitriptyline increased SDLP and variability of headway. Paroxetine no effect. No differences in BRT.</td>
<td>Moderate positive correlation between SDLP and plasma amitriptyline concentration.</td>
</tr>
<tr>
<td>Kuitunen, 1994</td>
<td>Double-blind placebo-controlled 6-way crossover</td>
<td>12 healthy volunteers</td>
<td>15 mg of diazepam 50 mg of amitriptyline 15 mg of mirtazapine Diazepam + one other drug Placebo</td>
<td>Before, and after 1.5h &amp; 4.5h</td>
<td>Driving simulator test</td>
<td>Tracking errors RT</td>
<td>Increased tracking errors and prolonged RT at both times with amitriptyline and both drug combinations. Diazepam prolonged RT after 1.5h. No other significant effects.</td>
<td></td>
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<tr>
<td>Ridout and Hindmarch, 2001</td>
<td>Double-blind placebo-controlled 4-way crossover</td>
<td>16 healthy volunteers (10 men, 6 women, 21-44y)</td>
<td>Tianeptine 12.5 mg Tianeptine 37.5 mg, Mianserin 30 mg Placebo</td>
<td>1.5h, 3h, 4.5h &amp; 6h</td>
<td>Drive on a closed circuit at 30 miles/h</td>
<td>BRT</td>
<td>Mianserin delayed BRT significantly longer than other three conditions. Tianeptine 37.5mg causes a marginal delay. No effect by tianeptine 12.5mg. Driving test terminated -1 Mianserin.</td>
<td></td>
</tr>
<tr>
<td>Hindmarch et al., 1983</td>
<td>double-blind placebo-controlled 3-way crossover</td>
<td>9 healthy female volunteers (30-45y)</td>
<td>Amitriptyline 50mg Zimeldine 200mg Placebo</td>
<td>Before, 2h &amp; 5h postdose</td>
<td>Brake reaction during actual driving</td>
<td>BRT</td>
<td>2h postdose: Significant impairment only with amitriptyline. 5h postdose: no significant difference between treatments.</td>
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<tr>
<td>Ramaekers et al., 2011</td>
<td>Placebo controlled randomised double blind 4-way crossover.</td>
<td>32 healthy volunteers (16 men 16 women, M 33y, SD 9y)</td>
<td>Esmirtazapine 1.5 mg, 4.5mg single and multiple (7-days); Placebo; Zopiclone 7.5mg (active control) single dose</td>
<td>11hrs after noce dose Day2 Day8 Day 8 (Zopiclone)</td>
<td>1hr standardised on-the-road highway driving test.</td>
<td>SDLP</td>
<td>Esmirtazapine 1.5 mg no change single or repeated; 4.5mg driving impairment after single dose but not after repeated. Zopiclone 7.5mg (active control) increased SDLP. 2 participants dropped out Esmirtazapine.</td>
<td>Poor CVP 2D6 metabolizers more sensitive to impairing effects of esmirtazapine.</td>
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<td>Hindmarsh et al., 1988</td>
<td>Double-blind, placebo-controlled 5-way crossover</td>
<td>9 healthy female volunteers (28-55y)</td>
<td>Amitriptyline 50mg, Lofepramine 70mg, Lofepramine 140mg, Nomifensine 100mg, placebo, Single morning doses</td>
<td>Same day, time not specified</td>
<td>Tracking task in a driving simulator</td>
<td>Mean deviation from target</td>
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<tr>
<td>O'Hanlon, 1984</td>
<td>Double-blind, placebo-controlled, 5-way crossover</td>
<td>20 healthy male volunteers (22-32y)</td>
<td>Amitriptyline 25mg, Doxepin 25mg, Mianserin 10mg, Oxaprotiline 25mg, Placebo t.i.d. x 1-day</td>
<td>1:00h-2:15h after last dose</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP</td>
</tr>
<tr>
<td>Richet et al., 2004</td>
<td>Double-blind, placebo-controlled 4-way crossover</td>
<td>12 healthy male volunteers (18-30y)</td>
<td>Milnacipran 50mg, Milnacipran 50mg + alcohol Placebo Placebo + alcohol b.i.d. x 3.5 days (alcohol only after last dose)</td>
<td>2h (day 3.5)</td>
<td>Driving test with reactions to visual and auditory stimuli</td>
<td>BRT Driving performance evaluated by instructors</td>
</tr>
<tr>
<td>Landauer et al., 1969</td>
<td>Randomised double-blind placebo-controlled</td>
<td>21 healthy volunteers in 3 groups (6 men, 1 woman in each group) Mean age(SD) =22.3(1.2y)</td>
<td>Amitriptyline 0.8mg /kg night &amp; morning Amitriptyline morning only Placebo &gt; Alcohol after 1st test</td>
<td>2h after morning dose and 15min after alcohol (day 2)</td>
<td>Driving simulator test</td>
<td>Steering control (Proportion of steering errors to total correct responses)</td>
</tr>
<tr>
<td>Clayton et al., 1977</td>
<td>Randomised double-blind placebo-controlled</td>
<td>40 male volunteers (18-29y) in 4 groups (10 each)</td>
<td>Imipramine 25mg t.i.d. Viloxazine 50mg t.i.d. Placebo t.i.d. x 7-days No drug</td>
<td>Before, 2h after 1st dose, 7 doses (day 3), 21 doses (day 7)</td>
<td>Driving test with a slalom task and a gap estimation task</td>
<td>Number of errors in a weaving task Gap estimation</td>
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### Appendices

**Van Laar et al., 1995**

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<th>Study Type</th>
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<td>Double-blind placebo controlled 4-way crossover</td>
<td>Nefazodone 100mg &amp; 200mg</td>
<td>Imipramine 50mg Placebo b.i.d. x 7-days; 2.25h after morning dose on day 1 &amp; day 7</td>
<td>SDLP</td>
<td>No significant effect</td>
<td>Effect of TCA imipramine is in contrast to those observed in epidemiological studies.</td>
</tr>
<tr>
<td>Robbe and O'Hanlon, 1995</td>
<td>Paroxetine 20mg</td>
<td>Paroxetine 40mg morning Amitriptyline 50mg &amp; 25mg morning Placebo X 8 days</td>
<td>SDLP</td>
<td>No significant effect</td>
<td>No significant effect by drugs. Day 7: No significant effect of imipramine on SDLP in either group. SDS: No significant effect by drugs. 2 driving test terminated - 1 Imipramine, 1 Nefazodone200mg.</td>
</tr>
<tr>
<td>Ramaekers et al., 1994</td>
<td>Moclobemide 200 mg b.i.d. Mianserin 10 mg t.i.d. Placebo x 8 days</td>
<td>2.5h after 3rd daily dose on day 1 and day 8.</td>
<td>SDLP</td>
<td>Increased SDLP</td>
<td>Increased SDLP after mianserin on both days. No change with moclobemide. 1 subject withdrew from the Mianserin.</td>
</tr>
<tr>
<td>Ramaekers, et al., 1994</td>
<td>Brofangomine 50mg b.i.d. Brofangomine 75mg b.i.d. Doxepin 25 mg t.i.d. Placebo x 8 days</td>
<td>3h after 3rd daily dose on day 1 and day 8.</td>
<td>SDLP</td>
<td>No change with brofangomine.</td>
<td></td>
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<tr>
<td>O'Hanlon et al., 1998</td>
<td>Venlafaxine 37.5 mg b.i.d.</td>
<td>Venlafaxine 37.5 mg b.i.d. x 2-weeks; Mianserin 10 mg t.i.d. x 7-days Placebo t.i.d. x 2-weeks</td>
<td>SDLP</td>
<td>Increased after mianserin in all 4 test days. No significant effect with venlafaxine. SDS: Increased after mianserin (compared to placebo) on day 1. No other changes. 5 withdrawal mianserin, 3 withdrawal venlafaxine 75mg.</td>
<td>7 subjects withdrew due to adverse effects of venlafaxine or mianserin. Results may underestimate the actual effect.</td>
</tr>
<tr>
<td>Ramaekers et al., 2011</td>
<td>Esmirtazapine 1.5 mg, 4.5mg single and multiple (7-days); Placebo; Zopiclone 7.5mg (active control) single dose</td>
<td>11hrs after nocte dose Day2 Day8 Day 8 (Zopiclone)</td>
<td>SDLP</td>
<td>Esmirtazapine 1.5 mg no change single or repeated. 4.5mg driving impairment after single dose but not after repeated. Zopiclone 7.5mg (active control) increased SDLP.</td>
<td>Poor CVP 2D6 metabolizers more sensitive to impairing effects of esmirtazapine.</td>
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<td>Study</td>
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<tr>
<td>Wingen et al., 2005</td>
<td>Randomised double-blind placebo-controlled 3-way crossover</td>
<td>18 healthy volunteers (9 men, 9 women. 21-40y)</td>
<td>Escitalopram 10mg x 7-days &gt; 20mg x 8 days Mirtazapine 30mg x 7-days &gt; 45mg x 8 days Placebo x 15 days</td>
<td>10:30am (following the evening dose) on day 2, 9, 16</td>
<td>Standardised highway driving test (~100km)</td>
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<td>SDLP, SDS</td>
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<td>Mirtazapine: Increased SDLP day 2. No effect on day 9 or 16. Escitalopram: No effect on either SDLP or SDS. 1 driving test terminated Mirtazapine 30mg fell asleep.</td>
</tr>
<tr>
<td>Ramaekers et al., 1998</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>18 healthy volunteers (9 men, 9 women. 21-35y)</td>
<td>Mirtazapine 15mg x 7-days &gt; 30mg x 8days Mianserin 30mg x 7-days &gt; 60mg x 8days Placebo x 15 days</td>
<td>Morning following the evening dose (15-18h) on day 2, 8, 9, 16</td>
<td>Standardised highway driving test (~100km)</td>
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<td>SDLP</td>
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<td>Significant, but minor increase in day 2 &amp; 7 with mirtazapine. Marginally increased in day 8 with mianserin. 2 withdrew from Miaserin condition.</td>
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<tr>
<td>Ramaekers et al., 1995</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>18 healthy volunteers (10 men, 8 women. 21-45y)</td>
<td>Dothiepin 75mg night x 8days + 150mg night x 13 days Fluoxetine 20mg at night x 22 days Placebo at night x 22 days</td>
<td>14h after 1st, 8th &amp; 22nd dose</td>
<td>Standardised highway driving test (~100km), Car following test</td>
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<td>SDLP Headway variability</td>
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<td>No significant effects of either drug on SDLP or headway variability. 1 driving test terminated placebo.</td>
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<td>Sasada et al., 2013</td>
<td>Placebo controlled randomised double blind 3 way crossover</td>
<td>19 healthy volunteers 26-49yo, M 38.8y SD 6.8y)</td>
<td>Mirtazapine 15mg, Trazodone 25mg</td>
<td>930am after nocte dose Day 2 and 8</td>
<td>Simulated driving with road tracking, car following and braking</td>
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<td>Sig Mirtazapine SLDP score days Increased subjective sleepiness score.</td>
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**Multiple dose, patient**

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<td>Brunauer et al., 2008</td>
<td>Randomised comparative clinical study</td>
<td>40 depressed patients (18 women, 22 men. 25-57y) + 10 matched healthy controls</td>
<td>Long-term treatment with, Reboxetine (for 20 patients) Mirtazapine (for 20 patients)</td>
<td>Before, 7 days &amp; 2-weeks after initiation of treatment</td>
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<td>Number of collisions</td>
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<td>Before treatment: More collisions in patient groups. Day 14: Significant decline in collisions compared to baseline, with both drugs. Number of collisions similar in patients and healthy controls in day 14.</td>
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<td>Timing of dosing before testing is not specified.</td>
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<td>7 chronic neuropathic pain patients (4 men, 3 women. 42-58y)</td>
<td>Amitriptyline 25mg Placebo at night x 15 days</td>
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<td>Amitriptyline increases SDLP on day 2 but no significant effect on day 16. No difference in subjective assessment of driving quality. SDLP increase by amitriptyline after acute dosing is similar to that caused by BAC of 0.5g/l.</td>
</tr>
<tr>
<td>Shen et al., 2009</td>
<td>Randomised controlled trial</td>
<td>28 patients with major depressive disorder: 14 treated (12 women, 2 men. 29-67y), 14 no treatment (10 women, 4 men. 26-62y)</td>
<td>Mirtazapine 30mg night x 30 days</td>
<td>Computerised driving simulator test</td>
<td>Mirtazapine group: Improvement in road positioning in day 2, 9, 16, 30 compared to baseline. Significant reduction of crashes on day 30 compared to baseline. Untreated: No improvement of driving performance on day 2 or 9. Not tested beyond 9 days. Significant group difference on day 9. 1 Driving test terminated – Mirtazapine. Incomplete follow up of the untreated group.</td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

**Supplementary table 3:** Opioids and driving performance: experimental studies (SDLP = standard deviation of lateral position. SDS = standard deviation of speed)

<table>
<thead>
<tr>
<th>Study</th>
<th>a) Design</th>
<th>b) Subjects</th>
<th>c) Treatment conditions: Drug, dose, duration if &gt;1</th>
<th>d) Timing of test after dosing</th>
<th>e) Task</th>
<th>f) Outcome measures</th>
<th>g) Results</th>
<th>h) Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single dose, healthy volunteers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linnoila and Hakkinen , 1974</td>
<td>Double-blind, placebo-controlled</td>
<td>70 professional drivers (19-22y) In 7 groups (10 each)</td>
<td>No drug or drink (Zero group) Placebo drug &amp; drink Alcohol 0.5g/kg Diazepam 10mg Diazepam 10mg + alcohol Codeine 50mg Codeine 50mg + alcohol</td>
<td>30 minutes</td>
<td>40-minute drive in a driving simulator</td>
<td>Steering wheel reversals, number of times brakes used, number of times clutch used, number of times turning signal used, Speed, brake reaction times, number of neglected instructions, number of collisions, driving off the road</td>
<td>Diazepam: More neglected instructions and collisions. Codeine: Less steering wheel reversals and more collisions. Diazepam + alcohol: More steering wheel reversals, neglected instructions and collisions. Codeine + alcohol: More collisions (All comparisons with the Zero group).</td>
<td>No comparisons with placebo. Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.</td>
</tr>
<tr>
<td>Verster et al., 2006</td>
<td>Randomised double-blind placebo-controlled 5-way crossover</td>
<td>18 healthy volunteers (6 men, 12 women) mean (SD) age: 24.0 (1.6)y</td>
<td>Oxycodone / Paracetamol 5/325mg, 10/650mg; Bromofenac 25mg, 50mg; Placebo</td>
<td>1h</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP SDS</td>
<td>No difference between active drugs and placebo conditions in any of the measures. Significant dose-response relationship for oxycodone / paracetamol</td>
<td></td>
</tr>
<tr>
<td>Amato et al. 2013</td>
<td>Randomised double-blind placebo controlled 4 way crossover</td>
<td>16 Healthy adults (8 men, 8 women). Mean (SD) age 22.4 (2.7)y</td>
<td>20mg codeine/400mg paracetamol, 40mg codeine/800mg paracetamol, 60mg codeine/1200mg paracetamol, placebo</td>
<td>1h</td>
<td>Driving simulator 60mins</td>
<td>SDS SDLP Lateral Position</td>
<td>20mg dose, sig diff to placebo for Mean Lateral Position.</td>
<td></td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

**Supplementary table 4:** Atypical antipsychotics and driving performance: experimental (BAC = blood alcohol concentration. RT = reaction time. BRT = brake reaction time. DDD = defined daily dose. SDLP = standard deviation of lateral position. SDS = standard deviation of speed, b.i.d. = twice a day, t.i.d. = three times a day)

<table>
<thead>
<tr>
<th>Study</th>
<th>a) Design</th>
<th>b) Subjects</th>
<th>c) Treatment conditions: Drug, dose, duration if &gt;1</th>
<th>d) Timing of test after dosing</th>
<th>e) Task</th>
<th>f) Outcome measures</th>
<th>g) Results</th>
<th>h) Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose, healthy volunteers</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mattila et al., 1994</td>
<td>Double-blind placebo-controlled 5-way crossover</td>
<td>12 healthy volunteers (6 men, 6 women, 19-32y)</td>
<td>Suriclone 0.4 mg Zopiclone 7.5mg Placebo, alone and together with 50 mg chlorpromazine (CP)</td>
<td>Before, and after 1.5h, 3.5h &amp; 6h</td>
<td>Driving simulator test</td>
<td>Tracking errors (TESI), RT</td>
<td>No (CP) besides digit symbol substitution. Zopiclone CP and Suriclone CP combo sig. increased tracking errors sig. prolonged RT even at 6h post-dose compared to placebo and CP alone.</td>
<td></td>
</tr>
<tr>
<td>Multiple dose, healthy volunteers</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wylie et al., 1993</td>
<td>No Placebo Not blind</td>
<td>38 subjects:22 patients (21-62y) Mean age 45.7; 16 controls, (24-65y) Mean age 44.1</td>
<td>15 patients flupenthixol decanoate, 7 fluphazine decanoate. Participants on medication for 3 months prior to the study</td>
<td>Patients tested morning btw 1-10 days after last injection.</td>
<td>Driving simulator task</td>
<td>Median RT, accuracy, lights missed</td>
<td>Treatment groups were Sig. worse in driving accuracy, reaction time and lights missed btw control and patients. No diff btw treatment groups.</td>
<td></td>
</tr>
<tr>
<td>Brunnauer et al. 2009</td>
<td>Not blind No placebo</td>
<td>80 subjects 18-60y mean age 32.5. 4 groups (20 each group) schizophrenia diag. receiving monotherapy</td>
<td>Mean mg/day dose (SD) Haloperidol 8.8 (5.2), Flupenthixol 5.5 (3.1) Quetiapine 425 (127.0) Amisulpride 505 (148.8). Each participant was under steady-state plasma level conditions</td>
<td>NA</td>
<td>Driving simulator task</td>
<td>Percentage of accidents</td>
<td>Amisulpride sig better than haloperidol and flupenthixol. Quetiapine sig better than haloperidol.</td>
<td></td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

Supplementary Data References


The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices


The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices


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Appendices


Appendix 3: Instruments (questionnaires and measures)

Driving/personal information

1. General driving proficiency:
   i) Licence status (please circle)
      Learner     Provisional     Full     None (Go to Section 4)
   ii) Licence type (please circle, circle multiple if relevant)
       C= Car    R= Rider  LR= Light Rigid  MR=Medium Rigid
       HR= Heavy Rigid  HC= Heavy Combination  MC= Multi-Combination
   iii) Number of years of driving (please circle)
       less than 1  1-5  6-10  11-15  16-20  21-26
       30+
   iv) Accident within last 1-2 years (please tick) Yes      No

2. Regular driving habits:
   i) Number of km driven per week
       less than 5  5-10  10-20  30-40  40-50  50+
   ii) Area of driving (please circle, circle multiple of relevant)
       Urban     Highway     Rural
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

3. After discharge from hospital:

i) Are you likely to drive within the next week? (Please tick) Yes No

ii) Self-assessment

How would you rate your general driving ability at present? (place an X on the scale)

- Poor
- Average
- Excellent

How would you rate your ability to drive at night at present? (place an X on the scale)

- Poor
- Average
- Excellent

How would you rate your ability to drive on a busy highway/road at present? (place an X on the scale)

- Poor
- Average
- Excellent

How would you rate your ability to drive in bad weather at present? (place an X on the scale)

- Poor
- Average
- Excellent
4. Personal characteristics

i) Do you live alone? (please tick)  

Yes  No


ii) Self-assessment

How would you rate your level of concentration at present? (place an X on the scale)

Poor  Average  Excellent

How would you rate your ability to express your thoughts at present? (place an X on the scale)

Poor  Average  Excellent

How would you rate your ability to manage your daily activities such as washing yourself and preparing food at present? (place an X on the scale)

Poor  Average  Excellent

How would you rate your ability to follow instructions at present? (place an X on the scale)

Poor  Average  Excellent
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

Appendix 4: Ethics Variation

| Name: | Emeritus/Conjoint Professor Patricia Michie |
| Qualifications & position held: | BA(Hon), PhD  
Emeritus Professor in Psychology |
| Organisational unit & mailing address: | School of Psychology, Faculty of Science and Information Technology, University of Newcastle, University Drive, Callaghan NSW 2308 |
| Telephone and Fax: | Tel: (02) 4921 5936  
Fax: (02) 4921 6980 |
| Email address: | Pat.Michie@newcastle.edu.au |

2 TITLE OF PROJECT (as it appears on the approval notification)

Neurocognitive effects of sedative psychotropic drug overdose

3 APPROVAL DETAILS
What is the Hunter New England Human Research Ethics Committee reference number for the project?

08/08/20/5.07

What was the date of approval from the Hunter New England Human Research Ethics Committee.

05 September 2008

4 IS THIS RESEARCH BEING CONDUCTED AS

SINGLE CENTRE RESEARCH (ie only within Hunter New England Health)  X

MULTI CENTRE RESEARCH
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

If so, please name those sites for which approval from the Hunter New England Human Research Ethics Committee extends:


5 STUDENT RESEARCH

Is the research being completed as part or whole of a degree or qualification? Yes X No

If YES: Name of student: Stewart Oxley
Course of study: Doctorate of Clinical and Health Psychology
Principal supervisor: Professor Patricia Michie
Name of Institution: University of Newcastle

6 PROJECT STATUS

Has the project commenced? Yes X No

If YES, when did the project commence? (dd/mm/yy): 05 September 2008

If NO provide reasons:

7 RESEARCH PERSONNEL

Does the variation involve changes to the research personnel working on the project? Yes X No

This might include such instances as the addition of new investigators or research assistants to the research team, removing the names of those who are no longer working on the project, adding a student researcher and his/her project supervisor or perhaps a situation where the project supervisor for a student project is changing.

If YES, go to the next section (7.1)
If NO, go to Question 8

7.1 Addition of research personnel who are NOT students (leave blank if not applicable)
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

**Appendices**

For each new member of the research team who is not a student of the University of Newcastle, please provide the following details.

<table>
<thead>
<tr>
<th>Name:</th>
<th>Dr. Tharaka Dassanayake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifications &amp; employment position:</td>
<td>MBBS MPhil PhD Senior Lecturer, Department of Physiology</td>
</tr>
<tr>
<td>Organisational unit &amp; mailing address:</td>
<td>Faculty of Medicine, University of Peradeniya 20400 SRI LANKA</td>
</tr>
<tr>
<td>Telephone and Fax:</td>
<td>+94 81 2396300</td>
</tr>
<tr>
<td>Email address:</td>
<td><a href="mailto:tlag23@yahoo.co.uk">tlag23@yahoo.co.uk</a></td>
</tr>
<tr>
<td>Role on research project:</td>
<td>Supervisor</td>
</tr>
<tr>
<td>Experience relevant to the research project:</td>
<td>Dr. Dassanayake was the original student investigator on this project. He has completed his component of the project and has published several papers in peer-reviewed journals as part of his Doctorate of Philosophy qualifications.</td>
</tr>
</tbody>
</table>

*Copy table and repeat for each additional person as required.*

### 7.2 Addition of a student researcher

(leave blank if not applicable)

For each student researcher being added to the project, please provide the following details.

**Note:** If the student's supervisor is not already recorded as an investigator, ensure they are added by completing section 6.1.

<table>
<thead>
<tr>
<th>Name of student:</th>
<th>Stewart Oxley</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student No:</td>
<td>9608598</td>
</tr>
<tr>
<td>School/Faculty/Campus</td>
<td>School of Psychology, Faculty of Science &amp; IT/ Callaghan campus, University of Newcastle</td>
</tr>
<tr>
<td>Telephone and Fax:</td>
<td>0419015101</td>
</tr>
<tr>
<td>Email address:</td>
<td><a href="mailto:c9608598@uon.edy.au">c9608598@uon.edy.au</a></td>
</tr>
<tr>
<td>Course of study:</td>
<td>Doctorate of Clinical and Health Psychology</td>
</tr>
<tr>
<td>Principal supervisor:</td>
<td>Professor Patricia Michie</td>
</tr>
</tbody>
</table>

*Copy table and repeat for each additional student as required.*

### 7.3 Deletion of research personnel

(leave blank if not applicable)

For each person who is leaving the research team, please provide the following details.

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisational unit</td>
<td></td>
</tr>
<tr>
<td>Email address:</td>
<td></td>
</tr>
<tr>
<td>Previous role on research project:</td>
<td></td>
</tr>
<tr>
<td>Reason for leaving project</td>
<td></td>
</tr>
</tbody>
</table>

*(brief statement)*

*Copy table and repeat for each additional person as required.*
8 DETAILS OF PROPOSED VARIATION
Using Plain English, provide details of the proposed variation(s) to the research protocol. Where appropriate, present in terms of from the existing protocol to the new protocol.

(Attach the original of any documents that are new or revised as a result of the variation, eg advertisements, participant information sheets, surveys, clinical protocols. For revised documents, please highlight changes and identify them with VERSION # and DATE.)

The present prospective longitudinal study proposes to recruit patients admitted to hospital as a result of overdose from drugs with sedative (e.g. benzodiazepines, opioids, antipsychotic agents and sedative antidepressants) and non-sedative effects (e.g. paracetamol and non-sedative antidepressants) to perform neurocognitive tasks (e.g. memory, thinking, attention, planning, decision making) and provide subjective assessments about cognitive functioning at discharge and at two follow-up time points, at approximately 7 and 28 days after discharge.

9 JUSTIFICATION FOR VARIATION
Why is the variation necessary?

Previous research conducted as part of this project has demonstrated that at discharge, patients that have consumed drugs with a sedative effect (e.g. benzodiazepines, opioids, antipsychotic agents and sedative antidepressants) in quantities considered to be an overdose (two or more times the defined daily dose) perform poorer on neurocognitive tasks (e.g. memory, thinking, attention, planning, decision making) than patients that overdosed on drugs with non-sedative effects (e.g. paracetamol, non-sedating antidepressants). This suggests that patients overdosing on drugs with sedative effects may, at the point of discharge, be unable to perform daily tasks, such as driving. Unfortunately, the data gathered was only at the point of discharge, which means that the pattern of cognitive recovery from an overdose of drugs with sedative effects is unknown.

In response to this concern, Dassanayake et al. conducted an epidemiological study (data linkage - NSW Roads and Traffic Authority CrashLink database linked to New South Wales (NSW) Admitted Patient Database) comparing the 4-week post-discharge period to a control period, times where individuals were not affected by an overdose, to determine whether there was an increased rate of risk of a serious traffic accident. At each time point, 3, 7, and 28 days after ingestion, individuals were at an elevated risk of a serious traffic accident. This evidence suggests that post-discharge driving ability is compromised but does not inform us as to the pattern of cognitive recovery over this period.

Therefore, the purpose of the present prospective longitudinal study is to provide some insight into the pattern of cognitive recovery in an effort to guide clinician’s recommendation. Specifically, this study will help in the development of clinical guidelines to effect safer patient discharge after sedative drug overdoses, particularly in terms of timing of discharge by medical staff and guidance for activities to avoid on the day of discharge, or longer.

10 RESEARCH PARTICIPANTS
Does the variation involve recruiting new participant groups, or changing the way in which participants are to be recruited? Yes X No

If YES, provide full details using the following headings:
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

**Appendices**

**What is the participant group?**
Patients that have overdosed using drugs with sedative and non-sedative effects. That is, the participant group is from the same source and will meet the same selection criteria as the original ethics approval. We are now requesting approval to select a new cohort from the same source and carry out a longitudinal study of recovery of cognitive functions.

**What is the number of participants involved and what is the justification for choosing this number?**
The sample size calculator RMASS was used to calculate sample size required at discharge as it could integrate the G* power variables and data from previous neurocognitive testing. It suggested that **40 participants were required at discharge** which allows for a 20% attrition rate over the course of the study. This means that if the study experiences a 20% attrition rate, **28 participants will remain at the conclusion of the study**, sufficient to detect a moderate effect size.

**From where will the participants be recruited?**
(Identify any schools, hospitals, organisations, etc, that are to be involved.)
Calvary Mater Newcastle Hospital

**How and by whom will participants be approached to receive the invitation to participate?**
Patients that meet the criteria for participation will be approached at discharge by the clinical toxicologist or the clinical toxicology fellow at the Calvary Mater Hospital to introduce the topic of research, the study, and Stewart Oxley. At this point, patients that agree to proceed further will be advised that Stewart Oxley will return later to explain in detail what is required of them if they decide to participate.

**How much time will participants have to consider the invitation to participate?**
The patients will be introduced to the study and invited once they are clinically stable. Therefore for those who are discharged the day following admission, this will be done on the day of discharge. In this case they will have few hours to consider the invitation. Those who stay in the ward for a few days will most probably be invited the day before discharge so that they will have around 16-24 hours to consider the invitation.

**11 ETHICAL CONSIDERATIONS**
What ethical considerations, if any, are raised by the proposed variation? (Refer to the National Statement on Ethical Conduct in Research Involving Humans, section 1 and other sections relevant to the project.)

No- there are no new ethical considerations.

**12 GOVERNANCE CONSIDERATIONS**
Please advise if this variation will have any implications for governance such as changes to the site specific assessment form or the regulatory documentation, Yes X No

If Yes, please advise the change and the documentation affects (and submit accordingly.)

Participants will be offered three locations for the follow-up testing: The Calvary Mater Hospital, The University of Newcastle, or at their home. Testing at The University of Newcastle will be conducted in a testing room within the School of Psychology.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

If the follow-up testing is conducted in the private home of the participant, the student investigator, Stewart Oxley, will contact the Chief investigator Patricia Michie via mobile, prior to entering the participant's house and after leaving the participant's house. The duration between phone calls will be no longer than one and half hours. Safety clearance will be sought from the University Health Safety and Environment Team.

13 REVISED DOCUMENTATION

Please list all the documentation that needs to be revised and is being submitted with this application for variation (ensure that the version numbers and dated are also revised)

| Information Statement Version 5 |
| Consent Form Version 4 |
| Changes are highlighted in red |
14 DECLARATION
In signing this application, I declare that:

1. The research protocol conforms to the National Statement on Ethical Conduct in Human Research (2007), which I have read.

2. The required number of any documents that are new or revised as a result of the variation, are attached, eg advertisements, participant information sheets, consent forms, surveys, clinical protocols.

3. The variation will not be implemented prior to receiving approval from the ethics committee(s).

4. I make this application on the basis that the information it contains is confidential and will be used by Hunter New England Health for the purposes of ethical review and monitoring of the research project described herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any other purpose without my prior consent.

5. I agree to the title of my research being listed for reporting purposes as required by Hunter New England Health, NSW Health or the NHMRC

   YES [x]          NO [ ]

If you object to the title of your research being included could you please provide a valid reason for its omission from the reporting process.

__________________________________________

Signature of chief investigator/project supervisor: 

Date: 28 September, 2012

PLEASE ENSURE AN ELECTRONIC COPY OF THIS FORM AND ATTACHED DOCUMENTS IS SUBMITTED TO

HNEHREC@HNEHEALTH.NSW.GOV.AU
Appendix 5: Offsite Assessment form

OFFSITE VISIT/INTERVIEW SAFETY GUIDELINES

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1.0 INTRODUCTION

2.0 RESPONSIBILITIES

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2.2 Supervisor (Chief Investigator, Responsible Academic/Student Project Supervisor)
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3.1.2 Scheduling Home Visit Appointments
3.1.3 Scheduling Appointments in Workplaces
3.1.4 Scheduling Appointments in Public Areas
3.1.5 Organising Transport
3.1.6 Organising University Photo ID
3.1.7 Communication System
3.1.8 Personal Safety
3.1.9 Reimbursement/Cash Handling
3.1.10 Other Considerations
3.1.11 Risk Assessment Training

3.2 Offsite Visit Interview Procedure
3.2.1 Preparation for the visit
3.2.2 Travel/Transport Safety
3.2.3 Communication
3.2.4 On-site Safety
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3.2.6 Interviews in Public Areas

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3.3.1 Lost
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3.3.3 Car Accident
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3.3.6 Loss of Contact

4.0 RISK ASSESSMENT

4.1 Identify and assess the problem
4.2 Eliminate or control the risk
4.3 Review

5.0 REFERENCES

6.0 CHANGE HISTORY

7.0 APPENDIX

7.1 Offsite Visit Form
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

7.2 Offsite Visit Safety Checklist/Risk Assessment and Control Measures
7.3 Offsite Visit Appointment Scheduling Form
7.4 Offsite Visit Itinerary Form
1.0 INTRODUCTION

These guidelines are applicable to research activities, undertaken by University staff and students involving visits/interviews in private homes (home visits) and much of the guideline also applies to projects involving interviews in public areas or workplaces.

Personal safety is of concern for all involved, although it should be noted that the vast majority of people who participate in the Universities’ research by allowing staff/students into their homes or workplaces will pose no risk/threat to University staff or students.

This safety guideline provides a documented procedure to ensure all risks are identified, that appropriate precautions have been taken and all foreseeable hazards have been controlled. This guideline is intended to address all foreseeable hazards which may be involved with offsite visits/interviews.

The majority of research involving offsite visits/interviews would be viewed as low risk and therefore many of the issues included in this guideline will not be applicable to individual projects and this will be reflected when the risk assessment and control measures form (Appendix 7.2) is completed.

Offsite visits are regarded as a workplace activity and as such, the OHS Act applies:

• It is the duty of the employer to identify and assess hazards and if reasonably practicable eliminate the risks. If that is impracticable the risks must be controlled.
• It is the duty of the employee to ‘take reasonable care for the health and safety of people who are at the employees’ place of work and who may be affected by the employees’ acts or omissions at work’

2.0 RESPONSIBILITIES

2.1 Head of School

• Ensure a Offsite Visit Form (OVF) (Appendix 7.1) and a Offsite Visit Safety Checklist/Risk Assessment and Control Measures form (Appendix 7.2) are completed by the Project Supervisor and approved prior to the research start date.
• Ensure corrective action is implemented for all accidents or incidents involving fieldwork.

2.2 Supervisor (Chief Investigator/Responsible Academic/Student Project Supervisor)

• Complete an application for safety clearance, OVF and Offsite Visit Safety Checklist/Risk Assessment and Control Measures form for all research/student practicals involving offsite visits or other interview related projects.
• Ensure the completed OVF has been signed off by the Head Of School or Faculty Safety Committee and forwarded to the University Health Safety and Environment Team at least one month prior to the proposed start date for the research.
• Ensure the project does not commence until a safety clearance has been given.
• The Supervisor is responsible for the health and safety of all staff/students for the duration of the activity, and for ensuring that they have received any necessary briefing, training or induction prior to the work commencing.
• Ensure all incidents and accidents are reported to the appropriate authority by completing a Newcastle University Incident/Injury/Hazard Report Form.
• Ensure that appropriate procedures are followed in the planning and execution of the work.
• Responsible for the regular supervision of how offsite visits are being conducted and kept informed of research progress and if any problems arise during the course of any offsite work.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

2.3 Staff/Students Carrying out the Home Visits

- All persons carrying out home visits are under the obligation to work and behave safely in the field, and to protect their own health and safety.
- Report all accidents/incidents occurring in the field by completing a Newcastle University Incident/Injury/Hazard Report Form.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

3.0 PROTOCOLS

3.1 Preliminary Planning

3.1.1 Venue for Appointment
When a research project is in the initial planning stage, consideration should be given to the idea of asking participants to come to the University rather than receiving a visit. This is a safer option but will not be appropriate or workable for many projects for a variety of reasons.

3.1.2 Scheduling Home Visit Appointments
You may use the document template provided (Appendix 7.3) or prepare your own for this task. When you contact the participant to schedule the home visit you should ask a number of questions to gain some basic information in order to conduct a preliminary risk assessment. Important questions to ask include:

- Is there adequate on street parking available?
- Where is the entry door located (front, side, back)?
- How many people will be on the premises during the home visit? Who are they and what is their relationship to the participant? Will they be sitting in on the activity/interview?
- Do they own any pets? If so will they pose a risk? (E.g. vicious dogs, overfriendly large dogs) If they pose a risk can they be restrained or kept separate during the interview?

You should advise the participant you will ring them closer to the visit date to check they are still available for the home visit and to recheck their details.

3.1.3 Scheduling Appointments in Workplaces (offices, factory etc)
You may use the document template provided (Appendix 7.3) or prepare your own for this task. When you contact the participant to schedule the home visit you should ask a number of questions to gain some basic information in order to conduct a preliminary risk assessment. Important questions to ask include:

- Where is the location?
- Is there adequate parking available close by?
- Do you need to obtain permission from management?
- Will the interview be in working hours? If not, are others going to be present?
- Is there a required P.P.E. or dress standard (e.g. enclosed shoes)?
- Are you required to attend an induction or sign in? (This should include emergency response for the workplace)

3.1.4 Scheduling Appointments in public areas (café, museum, park etc)
You may use the document template provided (Appendix 7.3) or prepare your own for this task. When you contact the participant to schedule the home visit you should ask a number of questions to gain some basic information in order to conduct a preliminary risk assessment. Important questions to ask include:

- Where is the location?
- Is there adequate parking available close by?
- Do you need to obtain permission from management/relevant authority?
- Will the interview be in daylight hours? If not, are others going to be present?
- Is it an isolated area?

3.1.5 Organising Transport
Staff and students who travel on official University business must do so in accordance with the University Travel Policy and Procedures. All travel on official University business is subject to prior approval by an authorized Officer (e.g. Head of School/Division), with appropriate delegation. Where approval is given to travel by
motor vehicle, it is expected that staff will use a University vehicle or Faculty/School/Division vehicle if available. It should be noted University vehicles are fully insured, routinely serviced and registered with the NRMA for roadside assistance. A major reason for using a University vehicle for home visits is that they can’t be used to trace the driver (privacy). The University Motor Vehicle Index provides further information.

If you decide to use a privately owned vehicle you will need to ensure the following:
- The vehicle is registered
- The vehicle is fully insured
- The vehicle is routinely serviced and roadworthy
- A roadside assistance scheme such as NRMA is in place for the vehicle

More information on using privately owned vehicles and travel related rates/allowances.

Please note if you have an accident in a private vehicle you are not covered by the University for repairs.

3.1.6 Organising University Photo Identification
Students may use their student photo ID card to provide identification to home visit participants. Staff photo ID cards can be organized through the Health, Safety & Environment Team, ring 16846 or 16542 for further information.

3.1.7 Communications System
All staff/students undertaking offsite visits must have a Mobile phone with them at all times. If a School or Department phone is available it should be used, otherwise a private phone is acceptable. NOTE: If using a private phone do not take or make any personal calls or SMS during a visit.

In regard to home visits always check participant addresses in advance to see if they are in a mobile phone black-spot area. If they are, two people should carry out the home visit.

3.1.8 Personal Safety
The safest way to conduct home visits is to work in pairs. Two or more people must be present for all home visits for studies involving participants with a history of mental health problems, or covering issues that may be considered as provocative to some participants.

No home visits are to be conducted if a participant has a history of aggressive behaviour, violence or sexual harassment, or if you believe you will be at risk.

A duress alarm must be provided to anyone undertaking home visits on his or her own. This is a relatively cheap item, which will supply piece-of-mind and may prove invaluable if personal safety is ever threatened. They can be purchased from various outlets including the Post Office in the Shortland Union.

A Safety Awareness/Aggression Minimisation training course is offered by Organisational Development which is tailored for staff conducting home visits and similar activities

3.1.9 Reimbursement/Cash Handling
If study participants are to be reimbursed, a separate risk assessment must be conducted covering the cash collection, handling, storage and transfer procedures. All staff involved will also need to attend a cash handling safety training course and should contact the Health Safety and Environment Team on 16846 or 16542 for enrolment information.
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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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3.1.10 Other Considerations

- Participants who are minors (under the age of 18) should have an adult representative (such as parent) present during a home visit. If the participant will be alone, two people should attend the interview.
- Staff/students making home visits to participants of the opposite gender should ideally be accompanied by another staff member/student of the same gender as the participant. Where this is not possible, the home visit should at least be conducted in pairs.

3.1.11 Risk Assessment Training

Staff/students must be competent in carrying out risk assessments. They should constantly be on the lookout for hazards which may arise during the course of their work and be able to analyse and eliminate/control the risks they identify.

A Risk Analysis Training Course is available through Organisational Development.

Additional Risk Analysis Information

3.2 Offsite Visit/Interview Procedure

3.2.1 Preparation for the visit

- Find a reliable person who is happy to act as your contact. For students this should be their supervisor and for staff researchers a co-investigator or supervisor. It should be noted that a third party unconnected with the project acting as a contact could breach the assurance of confidentiality given to participants.

The contacts duties will include:
- Being available for the time you are out on the road
- Logging in your calls
- Ready to act, if you call in with a problem, use your nominated code word identifying a hazardous situation or if you miss a scheduled call.

- Prepare an itinerary. You can use the Itinerary template provided (appendix 7.4) or prepare your own. Give a copy of your completed itinerary to your contact and your Supervisor.

- Ensure your mobile is in working order and fully charged prior to leaving. Program in your contacts’ number and any emergency numbers such as NRMA road service

- Ensure you are familiar and comfortable with the vehicle you will be driving. Adjust the seat and mirrors and check to see if there are any blind spots you should be aware of. Before leaving visually check the tyres and make sure you have enough fuel.

- Ensure you have your street directory and any maps you may require.

3.2.2 Travel/Transport Safety

Staff/students must comply with Australian road rules and must wear a seatbelt. It is suggested that headlights be switched on.

For information on safe work driving including driver fatigue, alcohol and drugs, speeding, seatbelts etc go to the RTA website, this site also includes a safe driving policy, safer work driving checklist and a driver knowledge test.

Staff and students should also adhere to the University Guidelines and Regulations for Implementation of the Policy on Alcohol and Other Drugs and the University Travel Policy and Procedures.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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3.2.3 Communication
Have your mobile switched on and with you at times when you are out on a home visit. Ensure you adhere to whatever call-in schedule you have organized with your contact person. If you encounter any problem or issue when out on a home visit ring and let your contact back in the office know so it can be duly noted.

3.2.4 On-Site Safety
Park on the street in a spot where you can’t be parked in or obstructed from leaving. Watch out for slip/trip hazards both outside and inside the premises. For home visits check to see that any pets, which may pose a risk, have been restrained or kept separate during the visit. Introduce yourself and show your ID, remember to check that they still consent to the home visit before entering the premises. Ask them if any additional people (other than previously advised) are present in the premises. Familiarise yourself with your surroundings as you enter the premises, make sure you will remember the path back to the exit/entrance. Choose a seat where you don’t have your back to a doorway and where you can clearly see all doorways/s into the room. Keep your keys on you at all times. If possible sit opposite the participant with a table or similar object between you. If you need to sit next to the person sit side on. Make sure you keep all your personal documents, mobile phone, wallet etc secure at all times. Try to keep to your appointment times and don’t linger at any premises longer than you need to.

3.2.5 Interviews in Workplaces
Depending on the workplace, formal approval may need to be obtained from management prior to interviews taking place. It is also preferable to ask for/receive an induction for the work area and/or to be supervised to some degree by a member of staff for some workplaces.

3.2.6 Interviews in Public Areas
Ensure location chosen to conduct interviews is well known and not isolated. In many cases it would be appropriate to notify the relevant authority prior to the activity commencing and in some cases formal permission from the authority will be required.

3.3 Emergency Procedures

3.3.1 Lost
Always plan your trip before you set off by consulting your maps/street directory. If you become lost while driving to or from a visit, pull over in a safe area and check your map or street directory. Always carry a current street directory/map with you when you’re out on the road. If you still cannot locate where you are, drive to the next signposted street and recheck your maps. Other options include backtracking until you are in a familiar area or ringing someone you know who is familiar with the area for help. Ring your contact to let them know what’s happened if it is going to affect your visit schedule or you are at all worried.

3.3.2 Breakdown
If your vehicle breaks down when you are on the road ring the NRMA help line 131111. If possible try to pull off the road into a safe spot to wait for assistance. If you break down in the middle of the road put on your hazard lights and when safe to do so (no traffic approaching) exit the car and move to a safe spot well off the road. If passers-by offer to push the vehicle off the road, only do so if a break in the flow of traffic allows this exercise to be done safely. If/once your car is parked off the road in a safe place you should remain in the car (with the doors locked, if it is an unsafe area or you are at all worried). Ring your contact to let them know what’s happened and they will contact any study participants that will be affected to explain and reschedule their appointment if necessary. If you must leave the vehicle or it is towed ensure you remove all documents/material relation to the project. You may need to complete a University Incident/Injury/Hazard Form.
3.3.3 Car Accident
If you are involved in a car accident it is your responsibility to firstly inform the Police and then Facilities Management (if using a University Vehicle). Ensure you get the details of any other drivers involved (name, address, licence number, make, model, car colour, registration, insurance company and policy number). Ring your contact who will both notify your Supervisor and contact any study participants that will be affected to explain and reschedule their visit. If you sustain any injury or suffer any pain or discomfort from the accident you should notify your supervisor and seek medical help by reporting to a hospital emergency department or to the University Health Clinic. Ensure you complete a University Incident/Injury/Hazard form and a Motor Vehicle Claim form (kept in the glove-box of University vehicles or from the University Risk Manager 49215328) within 24 hours.

3.3.4 Medical Emergency
If a medical emergency arises while you are undertaking a visit, call for help on 000 and wait until help arrives. Ring your contact to let them know what’s happened so they can contact any study participants that will be affected to explain and reschedule their visit if necessary. Ensure you complete a University Incident/Injury/Hazard form within 24 hours.

3.3.5 Violent/Threatening Situation
If during a study visit you feel at all threatened:

- Monitor for signs of impending violence such as facial expression, verbal threats and increase in breathing rate
- Summon help if needed
- Try to appear calm, speak slowly, clearly and softly and use simple language
- Do not attempt to contradict the person if they are angry
- Do not move closer to, or touch them
- If possible, keep an object such as a table between you.
- Avoid body language such as crossed arms, hands on hips or shaking fingers
- Avoid direct eye contact
- If you can withdraw, step back slowly and retreat out of the premises
- If you cannot withdraw you are entitled to use reasonable force to protect yourself
- If you are injured seek medical assistance, notify your supervisor and contact the police. Ensure you complete a University Incident/Injury/Hazard Form within 24 hours.

3.3.6 Loss of contact
If the staff/student conducting the home visits fails to ring their contact at a Scheduled time, the contact should:

- Ring the mobile (they may have forgotten to ring in, be in a mobile black-spot or have a flat battery)
- Ring the last participant to ensure they have left
- Ring the next participant to see if they have arrived, ask the participant to get them to ring if/when they do arrive
- Ring the next participant on the list (they may have accidentally missed an appointment)
- Ring their home in case they’ve popped home or have been in contact with someone there
- Notify their supervisor of the situation
- Ring the police station closest to the area where they last rang in

4.0 RISK ASSESSMENT
It is best if a risk assessment is completed by more than one person. Consult with your co-workers, supervisor, Health, Safety & Environment Unit and/or other knowledgeable persons,
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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to get a balanced analysis of the risks and possible measures, which can be taken to eliminate or control them.

4.1 Identify and assess the problem
Consider all possible sources of information about possible hazards that may be involved with Visits. Conduct a preliminary off-site check with participants when you contact them to schedule their Appointment. Ask about access, people who may be present, whether they own pets etc. Refer to the safety checklist/risk assessment (Appendix 7.2).

4.2 Eliminate or control the risk
Once the hazards have been identified and the risks to those undertaking the visits assessed, you need to either eliminate or reduce the risks. Elimination is the best way to address the hazard. Consult with other staff/students working on the project and/or with the Health Safety and Environment Team about the best way to address the identified risks and hazards.

Eliminate the hazard

- If the risk is too high do not carry out a home visit and remove the participant from the study
- You have the right to refuse to make a home visit with a participant if you feel at risk
- Be aware that once at a participants home you can leave if a situation develops with which you are not comfortable

Substitute the hazard

- If possible allocate two staff/students for the visit
- If there is a perceived risk you can request the participant visit the University for the interview

Plan the procedures with safety in mind

- Always keep mobile phones switched on during a visit. The phone should have a programmed emergency number
- Train in risk management techniques so you can do a risk assessment when you arrive at a home or location. If the situation is too risky, e.g., exposed syringes, intoxicated participant, unleashed, snarling dogs, do not continue with the visit.
- Leave the address of where you are going, including expected arrival and return times, with an appropriate person (contact) who is:
  - Available during all working hours
  - Able to monitor departure and return times
  - Able to respond appropriately in the event that the staff/student does not meet those expected times.

- Carry identification with you which specifies you are working for the University
- Establish code words to be used on the telephone to alert co-workers/supervisors that the you are in a threatening position
- Establish a procedure where you phone in after each home visit at a predetermined time.
- Discuss with the police the best methods of contacting them in an emergency.
- Choose a safe place to sit in a participants home, such as opposite the participant with a table between you and near an external door

4.3 Review
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Having put in place ways to control hazards involved with study visits, review them regularly (Did it work? Did it create another hazard?) to ensure they are effective.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

5. REFERENCES


The University of Newcastle Use of Private Vehicles http://www.newcastle.edu.au/service/vehicles/privatevehicles.html

The University of Newcastle Risk Analysis Website http://www.newcastle.edu.au/service/ohs/riskanalysis/index.html


6. CHANGE HISTORY:

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>WRITTEN BY</th>
<th>CHECKED BY</th>
<th>AUTHORISED BY</th>
<th>REASON FOR CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melissa Musicka 14/07/05</td>
<td>Liz Pilgrim 26/10/05</td>
<td>Tina Crawford 26/10/05</td>
<td>Not Applicable – First Issue</td>
</tr>
<tr>
<td>2</td>
<td>Melissa Musicka 04/07/07</td>
<td>Liz Pilgrim 09/07/07</td>
<td>Tina Crawford 16/07/07</td>
<td>Updating information and including interviews in workplaces and public areas</td>
</tr>
</tbody>
</table>
APPENDIX 7.1 OFFSITE VISIT FORM

<table>
<thead>
<tr>
<th>Research Project Title</th>
<th>Neurocognitive effects of sedative psychotropic drug overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Investigator</td>
<td>Name: Em/Prof Pat Michie</td>
</tr>
<tr>
<td>Responsible</td>
<td>Address: School of Psychology, University of Newcastle</td>
</tr>
<tr>
<td>Academic/Student Project Supervisor</td>
<td>Telephone Number: 49215936 or 0404447305</td>
</tr>
<tr>
<td></td>
<td>Email Address: <a href="mailto:pat.michie@newcastle.edu.au">pat.michie@newcastle.edu.au</a></td>
</tr>
<tr>
<td>Masters Student</td>
<td>Name: Stewart Oxley (Prof Doc in Clinical and Health</td>
</tr>
<tr>
<td>Professional Doctorate</td>
<td>Psychology)</td>
</tr>
<tr>
<td>Student</td>
<td>Address: Unit 6/28 Railway Road, New Lambton 2305</td>
</tr>
<tr>
<td>PhD Student</td>
<td>Telephone Number: 0419015101</td>
</tr>
<tr>
<td>Honours Student</td>
<td>Email Address: <a href="mailto:Stewart.Oxley@uon.edu.au">Stewart.Oxley@uon.edu.au</a></td>
</tr>
<tr>
<td>Undergraduate Student</td>
<td></td>
</tr>
<tr>
<td>Alternate Contact for CI</td>
<td></td>
</tr>
</tbody>
</table>

School/Faculty: Psychology/Science and IT

Proposed Project Start Date: 15 November, 2012

Number of participants: Maximum of 40

Type of visit (home, workplace, public area): Home

Number of home visits per participant: Two at most for follow-up visits per participant – but not all testing will be done in the home – participants will be offered 3 possibilities for follow-up assessments – Calvary Mater Hospital or School of Psychology (UoN) or home.

Purpose of Home Visit:
To conduct follow-up testing approximately 7 and 28 after discharge.

Description of Study Participants (Do not list names):
Individuals who have been admitted to hospital after overdosing on either central nervous system depressant and non depressant drugs.

How are participants being recruited:
Participants are being recruited at the Calvary Mater Hospital at the point of being discharge.

What participant details are known prior to visit:
Name, Address, Phone Number, Medical History

List Staff/Students Conducting visit/s (include drivers license and mobile phone number)
Stewart Oxley, 12483899, 0418 015 101

Description of Transport to be used for visits:
- University Car Pool Vehicle: (Make/model/Registration)
- Private Vehicle: (Make/model/Registration)

REVIEWED BY: Faculty Safety Committee (optional) Date: ___/___/____.

AUTHORISED BY: Head of School Date: ___/___/____.

Name: __________________________ Signature: __________________________

______.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

Attach a completed copy of your Home Visit Checklist/Risk Assessment (appendix 7.2) to this form and submit both documents with your R2/E2 application to Health, Safety & Environment, Human Resource Services, The Chancellery.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

Appendices

APPENDIX 7.2 OFFSITE VISIT CHECKLIST/RISK ASSESSMENT AND CONTROL MEASURES

<table>
<thead>
<tr>
<th>VEHICLES/TRANSPORT</th>
<th>COMMENT/ACTION (note details of control measures if they differ from those suggested, not required if measure N/A)</th>
<th>IMPLEMENTED YES/NO or N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>All staff/students are familiar with the University Travel Policy and Procedure</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>A University car pool vehicle will be used for home visits</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>If using a University vehicle, undertake operation and safety familiarization of the particular vehicle before operating it for the first time</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Ensure Staff/students hold valid drivers licences for the class of vehicle. Licences are recorded and verified</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ensure Vehicle records of registration, insurance, servicing etc are maintained and regularly checked</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>A roadside assistance scheme such as NRMA is in place for the vehicle used</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Prior to leaving for visit, drivers will check fuel levels and visually inspect tyres</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Vehicles are routinely serviced and a fault reporting mechanism is in place</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>A first aid kit is kept in the car</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Any incident/accident on the road will be reported on a University incident form</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Do not attempt to put a vehicle in motion while under the influence of alcohol or any other drug</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Ensure work that involves driving is organized in a way, which minimizes fatigue. For periods of extended driving, schedule regular rest breaks</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Mobile phone use in cars is only by use of a hands free kit; avoid dialling unless the car is pulled over. Minimize call times while driving.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ensure all interviews (and therefore travel) are scheduled for daylight hours</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Take an up-to-date map on all visits to ensure you don’t get lost</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ensure your car is locked when not in use</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Keep to a speed that does not exceed the limit</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Wear a seatbelt</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Drive to the road and weather conditions. It is suggested that Drivers drive with their headlights on.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Do not leave valuables, laptops, handbags or money in the car especially if they are clearly visible to passers-by</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>If you breakdown, phone the NRMA for help and if possible remain in the car,</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

### Appendices

<table>
<thead>
<tr>
<th>KEEP THE DOORS LOCKED IF IN A SECLUDED OR UNSAFE AREA</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO OR N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OUTSIDE RESIDENCE (FOR HOME VISITS)</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO OR N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park on the street. Do not park in the driveway or any other place where you can be obstructed from leaving</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Prior to entering premises; Have set procedure where you establish your credentials with your University photo ID card and ensure the participant still consents to the home visit</td>
<td>I will present my student card to the participant. They will also recognise me from a previous assessment.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMUNICATION</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO OR N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have communication equipment such as a mobile phone with you for all visits</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Communication equipment is checked prior to leaving for visit (battery is charged)</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Communication equipment is switched on at all times off-site and programmed for back-to-base and emergency numbers</td>
<td>My supervisor Emeritus/Conjoint Professor Pat Michie will attend to the phone during visits</td>
<td>Yes</td>
</tr>
<tr>
<td>Leave records of visit addresses, scheduled arrival and departure times and registration number of vehicle with contact person</td>
<td>Emeritus/Conjoint Professor Pat Michie will have my contact information</td>
<td>Yes</td>
</tr>
<tr>
<td>Report movements to base as agreed in protocols (regular call-in on arrival or departure)</td>
<td>I will call Emeritus/Conjoint Professor Pat Michie prior to and after leaving the premises, or if there are any concerns. Time between calls will be no more than 1.5 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Procedures in place if contact is lost or staff/student fails to return when expected</td>
<td>Emeritus/Conjoint Professor Pat Michie???? Call police</td>
<td>Yes</td>
</tr>
<tr>
<td>Code words established for off-site staff/students to signify they are in a threatening position</td>
<td>Sorcha</td>
<td>Yes</td>
</tr>
<tr>
<td>Never give participants your personal phone numbers</td>
<td>My phone will be blocked</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OFFSITE VISIT SECURITY</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO OR N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best practice to work in pairs</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Only those assessed as low risk to receive a home visit</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Carry an official photo ID which identifies you as University staff/student</td>
<td>Student Card</td>
<td>Yes</td>
</tr>
<tr>
<td>Withdraw from any visit if you feel at risk</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Staff/students working alone or in isolated situations are provided with a duress alarm</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Ensure Mobile phone blackout areas are known and procedures are in place for alternative communication, or work in</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

### Appendices

<table>
<thead>
<tr>
<th>pairs</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be are aware of safety procedures in private premises e.g. Maintaining clear line of exit, keeping car keys and personal documents including itinerary secure and parking car to facilitate exit.</td>
<td></td>
</tr>
<tr>
<td>Leave premises if firearms or other weapons are seen. Police are notified</td>
<td>Yes</td>
</tr>
<tr>
<td>Be are aware or techniques to diffuse violence</td>
<td>Yes</td>
</tr>
<tr>
<td>Undertaking Safety Course</td>
<td>Yes</td>
</tr>
<tr>
<td>Any incident on private premises is documented in incident reports</td>
<td></td>
</tr>
<tr>
<td>Avoid walking in deserted places or taking shortcuts</td>
<td>Yes</td>
</tr>
<tr>
<td>Withdraw from neighbourhoods where there are signs of unrest or trouble</td>
<td></td>
</tr>
<tr>
<td>Avoid appearing lost and seek directions by telephone, from a business owner or official rather than a stranger</td>
<td></td>
</tr>
<tr>
<td>If being followed by car or on foot, cross road, walk in opposite direction and seek refuge in safe place</td>
<td>Yes</td>
</tr>
<tr>
<td>No home visit will be undertaken if a participant has a known history of aggressive behaviour, violence or sexual harassment</td>
<td>Yes</td>
</tr>
<tr>
<td>If reimbursement of participants is involved with this project all staff/students handling cash have attended Cash handling safety training</td>
<td></td>
</tr>
<tr>
<td>Sandra Dimmock has undertaken course</td>
<td>Yes</td>
</tr>
<tr>
<td>If reimbursement of participants is involved with this project the activity has been separately risk assessed and the assessment is attached to this form</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### WORKING ON OTHER PREMISES

<table>
<thead>
<tr>
<th>WORKING ON OTHER PREMISES</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO or N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>When entering sites such as flats/apartments be aware of the security and emergency procedures of those premises</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>When visiting workplaces, permission will be obtained from management prior to visit</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>When visiting workplaces an induction will be completed and/or some level of supervision will be arranged/provided</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>When conducting interviews in public areas ensure the location is not isolated</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

#### OTHER PROJECT SPECIFIC IDENTIFIED RISKS AND CONTROL MEASURES

<table>
<thead>
<tr>
<th>OTHER PROJECT SPECIFIC IDENTIFIED RISKS AND CONTROL MEASURES</th>
<th>COMMENT/ACTION</th>
<th>IMPLEMENTED YES/NO or N/A</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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<table>
<thead>
<tr>
<th>ADDITIONAL CHECKLIST FOR THE DAY OF THE VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gates easy to open. Pathway, stairs/steps, floor surfaces- level, non-slip, uncluttered</td>
</tr>
<tr>
<td>Check to see if any pets which may pose a risk have been restrained or separated from worker</td>
</tr>
<tr>
<td>Ensure that the Entry/exit door is clear of obstructions</td>
</tr>
<tr>
<td>Assess whether the lighting is adequate for walking and performing work</td>
</tr>
</tbody>
</table>
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

**APPENDIX 7.3 CHECKLIST: OFFSITE VISIT APPOINTMENT SCHEDULING FORM**

<table>
<thead>
<tr>
<th>Participant Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant already known to study co-coordinators</td>
<td>☐ YES ☐ NO</td>
</tr>
</tbody>
</table>

| File Number: |  |

| Appointment Date: | / / |
| Appointment Time: | Start Finish am/pm am/pm |
| Reconfirm Appointment (date) | / / |

| If home visit, number of people who will be present (do not list names): |  |
| Relationship to participant if known |  |
| Will they be sitting in on the interview/activity |  |

| Address: |  |
| Phone Number: |  |
| Email Address: |  |

| Location- nearest cross street (draw/photocopy map and attach if needed) |  |

| On Street Parking Available: | ☐ YES ☐ NO |

| Location of Door to enter: | ☐ FRONT ☐ SIDE ☐ BACK ☐ OTHER |

| Pets that pose a risk (dogs or other animals): | ☐ YES ☐ NO |

| Pets posing a risk will be restrained or separated during visit? | ☐ YES ☐ NO ☐ NOT APPLICABLE |

| Initial assessed risk (Only proceed if risk is considered low) | ☐ LOW ☐ MEDIUM ☐ HIGH |

**Note:** To avoid any breach of confidentiality/privacy this form is only for the use of the researcher/co-investigators/project supervisor and no third party should be given access to the information recorded.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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**APPENDIX 7.4 CHECKLIST: OFFSITE VISIT ITINERARY FORM**

<table>
<thead>
<tr>
<th>Appointment Time</th>
<th>Participant</th>
<th>Anticipated Finish Time</th>
<th>Call-in time +/- 30 minutes (Tick off when call received)</th>
<th>Any Comments to be noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Address:</td>
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<td>Phone Number:</td>
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<td>Phone Number:</td>
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</tbody>
</table>

**Note:** To avoid any breach of confidentiality/privacy this form is only for the use of the researcher/co-investigators/project supervisor and no third party should be given access to the information recorded.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Appendix 6: Staff Information Sheet

EMERITUS/ CONJOINT PROFESSOR PATRICIA MICHIE
SCHOOL OF PSYCHOLOGY
Faculty of Science and Information Technology
University Drive Callaghan
NSW 2308 Australia
TELEPHONE (02) 4921 5936
FACSIMILE (02) 4921 6980
Email: Pat.Michie@Newcastle.edu.au

UNIVERSITY STUDY: INFORMATION SHEET

Deliberate Self Poisoning (DSP) Study

This is an information sheet for staff at the Mater hospital designed to outline the study being conducted by Stewart Oxley as part of a Clinical and Health Psychology Professional Doctoral Degree Program (Prof Doc), and to explain the inclusion and exclusion criteria for patient participation, in an effort to facilitate the identification of potential participants:

What is the study about?
Certain drugs used to treat illnesses such as depression, anxiety, lack of sleep have a depressant effect on the central nervous system. Overdose of these sedative drugs may reduce brain and mental functions such as attention, planning, decision making etc. and may reduce the ability to carry out everyday activities such as driving. The purpose of this study is to find out whether people who overdose with sedative drugs are still affected even after leaving hospital. We plan to find out that by testing them with sensitive tests of brain function, and comparing them with patients who take overdoses of a non-sedating drug (e.g. paracetamol), at discharge and again 7 days and 28 days later. The findings of this study will assist in understanding the nature and the duration of brain dysfunction that occurs in sedative drug overdose. This will help clinicians decide when to discharge patients with sedative drug overdose and what instructions to be given on discharge, so that we can minimise the risk of such patients encountering unsafe situations.

Inclusion Criteria
Patients 18-70 years old
Taken two or more times the defined daily dose of either
   A) a non-sedating drug such as paracetamol or non-sedating antidepressants (e.g. SSRIs), or
   B) a sedating drug of any of the following types: benzodiazepines and newer non-benzodiazepine hypnotics, sedative antidepressants and atypical antipsychotics, and opioids.

Exclusion Criteria
Cognitively impairing neurological illness
A history of head injury causing neurological damage
Uncorrected vision or hearing impairment
Acute psychosis or aggression
First language not English.

Your assistance in identifying patients that could participate would be greatly appreciated.

Yours sincerely
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Emeritus/ Conjoint Professor Patricia Michie
Professor of Psychology
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Appendix 7: Participant Information Sheet

EMERITUS/ CONJOINT PROFESSOR PATRICIA MICHIE
SCHOOL OF PSYCHOLOGY
Faculty of Science and Information Technology
University Drive Callaghan
NSW 2308 Australia
TELEPHONE (02) 4921 5936
FACSIMILE (02) 4921 6980
Email:Pat.Michie@Newcastle.edu.au

PARTICIPANT INFORMATION SHEET

Pattern of cognitive recovery following high doses of medication

You are being invited to take part in a research study that is being conducted by the following researchers:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Em./ Con. Prof. Patricia Michie</td>
<td>BA (Hon), PhD Emeritus Professor in Psychology University Drive Callaghan Tel: 02 4921 5936</td>
</tr>
<tr>
<td>Prof. Alison Jones</td>
<td>Graduate School of Medicine University of Wollongong E-mail: <a href="mailto:alisonj@uow.edu.au">alisonj@uow.edu.au</a> Tel: 02 4221 5151</td>
</tr>
<tr>
<td>Prof Gregory Carter</td>
<td>Conjoint Professor, Psychiatry and Suicide Prevention Unit <a href="mailto:Gregory.Carter@newcastle.edu.au">Gregory.Carter@newcastle.edu.au</a> Phone (BH): 02 4921 1283</td>
</tr>
<tr>
<td>Prof Ian Whyte</td>
<td>Director, Department of Clinical Toxicology and Pharmacology Calvary Mater Hospital Email: <a href="mailto:Ian.Whyte@newcastle.edu.au">Ian.Whyte@newcastle.edu.au</a> Phone (BH): 02 4921 1269</td>
</tr>
<tr>
<td>Dr. Tharaka Dassanayake</td>
<td>MBBS MPhil PhD Senior Lecturer, Department of Physiology Faculty of Medicine, University of Peradeniya, Sri Lanka Tel: 02 4921 1283</td>
</tr>
<tr>
<td>Stewart Oxley</td>
<td>Research Clinical and Health Psychology candidate School of Psychology University of Newcastle Email: <a href="mailto:c9608598@uon.edu">c9608598@uon.edu</a> Phone (MB): 0479166781</td>
</tr>
</tbody>
</table>

What is the study about?

Certain drugs used to treat illnesses such as depression, anxiety, lack of sleep make you tired. Overdose of these drugs may reduce brain and mental functions such as memory, thinking, attention, planning, decision making etc. and may reduce the ability to carry out everyday activities such as driving. The purpose of this study is to find out whether people overdosed with sedative drugs are still affected even after leaving hospital. We expect to find out that by testing them with sensitive tests of brain function, and comparing them with patients who take overdoses of a non-sedating drug, paracetamol. With the findings of this study we can understand the nature and the duration of brain dysfunction that occurs in sedative drug overdose. This will help doctors to decide when to discharge the patients with sedative drug overdose and what instructions to be given on discharge, so that we can minimise the risk of such patients encountering unsafe situations.

We would like to invite you to take part in this study because you are between 18-70 years old and have taken either paracetamol or a sedative drug of any of the following types:
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), opioids and antipsychotics.

Voluntary Participation

Before you decide whether you wish to consent to become involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information carefully. Ask us if there is anything that is not clear or if you would like more information. At the end of this document you will find contact information for each of us.

What do I have to do?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you in any way and will not affect the care that you receive. If you decide to take part you will be asked to sign the attached consent form and return it. We will contact you to set up a meeting. During the study you are still free to withdraw at any time and without giving a reason. If you decide to withdraw you may direct that all data related to you be withdrawn and your blood samples disposed of.

If you decide to participate you will take part in few tests of mental functions such as memory, attention, decision-making etc. They are detailed as following:

1. Once you are fit enough to go home you will take several tests at the bedside or in a room within the Department of Clinical Pharmacology. The first tests require that you provide a subjective appraisal of your cognitive and driving ability, mood, and indicate whether a major life event has occurred. This should take approximately 15 minutes

2. This will be followed by tests that examine your reading, decision-making, and memory. They require you to respond verbally or to use paper and pen. Your verbal responses will either be recorded on a digital recorder or written in a booklet. This section of the test should take approximately 20 minutes

3. If you feel comfortable to continue, the final tests are computer-based, where you will respond to various signals and patterns presented on a computer screen by pressing a button or by touching the computer screen. This section of the test will take approximately 40 minutes. During the testing you can have as many breaks as you like.

4. Two follow-up sessions, 7 and 28 days after discharge, when we will re-test you on most but not all of the tests conducted at discharge. You can have this testing conducted at The Calvary Mater Hospital, The University of Newcastle, or at your home, according to your preference. Prior these re-test sessions, we will send reminder text messages about testing dates, time and locations. These follow-up test sessions will take approximately 60 minutes. At these follow-up sessions, we will ask you for details of any changes in your medication following discharge. In the event that we are unable to contact you at your preferred number to arrange follow-up sessions, we seek the details of an alternate contact number such as a home phone number or number of a family member, partner or friend. We will only use this alternate method if we have been unable to contact you after 3 attempts.

We also seek your permission to access your medical records regarding the clinical features of your present illness and treatment measures.

What are the risks and benefits of participating?

The outcomes of the tests we propose to conduct are unlikely to change your further treatment. However, if we feel your test results show something that needs further medical assessment, we will discuss that with you and make necessary arrangements for further
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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medical attention. For each follow-up test at 7 and 28 days after discharge, you will receive a $20 Coles or Woolworths gift voucher as reimbursement for your time. This will be mailed to you after the completion of each session.

Confidentiality
All data sheets and computerised data will be coded using a letter-digit code that cannot be traced back to you by reading the sample or data sheets. None of these data will be used for any other purposes. Your personal information will be accessed, used and stored in accordance with Commonwealth Privacy Laws and the NSW Health Records and Information Privacy Act 2002.

How will the information be used?
This study will be conducted as a part of the Clinical and Health Psychology Professional Doctoral Degree Program (Prof Doc) of Stewart Oxley, who is the student researcher on the study. The information gathered from you will only be used for this research study. The data will be analysed and the findings will be published in the form of journal papers and a doctoral thesis, and presented at scientific conferences. Individual participants will not be identified in any of these reports arising from the project. With the findings of this study, we will be able to understand the nature of brain and mental dysfunction caused by a sedative drug overdose. That understanding will contribute to clinical guidelines to decide on the timing of discharge of the patients with sedative drug overdose and the instructions given on discharge, so that we can minimise such patients encountering unsafe situations in the future.

Thank you for considering this invitation!

Yours sincerely

Emeritus/ Conjoint Professor Patricia Michie
Professor of Psychology

The Research Team

Prof. Patricia Michie
Emeritus/Conjoint Professor of Psychology
University of Newcastle

Phone (BH): 02 4921 5936

Prof. Alison Jones
Dean of Medicine,
Graduate School of Medicine
University of Wollongong

Phone (BH): 02 4221 5151

Prof Gregory Carter
Conjoint Professor, University of Newcastle
Director, Psychiatry and Suicide Prevention Unit

Phone (BH): 02 4921 1283

Prof Ian Whyte
Director
Department of Clinical Toxicology and Pharmacology
Calvary Mater Hospital

Phone (BH): 02 4921 1269
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Dr. Tharaka Dassanayake
MBBS MPhil PhD
Senior Lecturer, Department of Physiology
Faculty of Medicine, University of Peradeniya 20400
SRI LANKA

Phone (BH): +94 81 2396300
Phone (AH): 04 2217 2983

Stewart Oxley
Doctoral Clinical and Health Psychology candidate
School of Psychology
University of Newcastle

Phone (MB): 0479166781

Complaints about this research
This research has been approved by the Hunter New England Human Research Ethics Committee of Hunter New England Health (Reference Number 08/08/20/5.07).

Should you have concerns about your rights as a participant in this research, or have a complaint about the manner in which the research is conducted you may contact the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Professional Officer (Research Governance and Ethics), Hunter New England Human Research Ethics Committee, Hunter New England Health, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email HNEHREC@hnehealth.nsw.gov.au
Appendix 8: Consent Form

EMERITUS/ CONJOINT PROFESSOR PATRICIA MICHIE
SCHOOL OF PSYCHOLOGY
Faculty of Science and Information Technology
University Drive Callaghan
NSW 2308 Australia
TELEPHONE (02) 4921 5936
FACSIMILE (02) 4921 6980
Email:Pat.Michie@Newcastle.edu.au

CONSENT FORM

Pattern of cognitive recovery following high doses of medication

Researchers: Em./Con. Prof. Patricia Michie, Prof. Alison Jones, Prof. Greg Carter, Prof. Ian Whyte, Dr. Tharaka Dasssanayake, and Stewart Oxley

Consent statement

I agree to participate in the above research project and give my consent freely.

I understand that the project will be conducted as described in the Information Statement, a copy of which I have retained.

I understand I can withdraw from the project at any time and do not have to give any reason for withdrawing.

I consent to,

• The researchers accessing my medical records for the purpose of extracting the information necessary for the above mentioned research project
• Participate in tests of mental functions that involve verbal, pen and paper, and computer-based tests prior to leaving hospital
• Participate in two follow-up sessions, 7 and 28 days after discharge
• Provide details of any medication changes after discharge and prior to follow-up sessions

I understand that my personal information will remain confidential to the researchers.

I have the opportunity to have questions answered to my satisfaction.

Print Name:………………………………………………
Signature:…………………………………………… Date:……………………
Contact Details:…………………………………………

If we have difficulties contacting you, we would appreciate having the contact details of a family member, partner, or friend or home phone number if appropriate. We will only attempt to contact you using this alternate approach if we have been unable to contact you at the above number after 3 attempts.
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Alternate Contact Details:…………………………………………..

Appendix 9: Journal of Clinical Psychopharmacology Manuscript

Instructions

http://edmgr.ovid.com/jcp/accounts/ifauth.htm

SCOPE

The Journal of Clinical Psychopharmacology is a peer-reviewed journal intended for practicing clinicians and trainees interested in improving their knowledge and in keeping up with the changing world of clinical psychopharmacology. The scope of the Journal includes clinical trials and studies, side effects and other adverse reactions, drug interactions, overdose management, pharmacogenetics, pharmacokinetics, and the psychiatric effects of nonpsychiatric drugs. Problems of special populations (the elderly, children, adolescents, pregnant women, and minorities) are of particular concern.

Clinicians and researchers are invited to submit their findings and observations to the following sections: Original Contributions (clinically relevant investigations, and animal work with direct applicability to clinical care), Brief Reports (condensed research findings), and Letters to the Editors. Authors must submit manuscripts on-line through the journal’s Web site at http://jcp.edmgr.com/. See submission instructions on the next page under “Manuscript submission.” Authors who wish to submit Review Articles should first contact the Editorial Office.

Ethical/Legal Considerations: A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

Patient anonymity and informed consent: It is the author's responsibility to ensure that a patient's anonymity be carefully protected. Authors must verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. If consent was not written, explain why. Authors should mask patients' eyes and remove patients' names from
The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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figures unless they obtain written consent from the patients and submit written consent with the manuscript.

**Original Studies:** The Journal requires authors to affirm that all original studies submitted for publication have been carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

**Conflicts of interest:** Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading “Conflicts of Interest and Source of Funding:”. For example:

**Conflicts of Interest and Source of Funding:** A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” ([www.icmje.org/update.html](http://www.icmje.org/update.html)). Please note that authors may sign the copyright transfer agreement form electronically. For additional information about electronically signing this form, go to [http://links.lww.com/ZUAT/A106](http://links.lww.com/ZUAT/A106).

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Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for *Journal of Clinical Psychopharmacology* is $3,000. The article processing charge for authors funded by the Research Councils UK (RCUK) is $3,800. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open access.

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The influence of central nervous system depressant (CNS-D) drugs on driving performance and cognitive functions and recovery of cognitive functions following hospital treated deliberate self-poisoning with CNS-D drugs.

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Preparation of Manuscript: Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Brief Reports: Total length should be no more than 14 double-spaced pages including abstract, text, reference list (double-spaced), tables, and figures. Title Page is not counted.

Letters to the Editors: Total length should be no more than 6 double-spaced pages including text (no abstract), reference list (no more than 20 references/double-spaced), and only 1 table OR figure. Title Page is not counted.

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The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

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Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion except for letters. Define abbreviations at first mention in the text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). Do not identify the authors anywhere in the manuscript except on the title page.

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Journal article


Book chapter


Entire book


Software


Online journals


Database


World Wide Web


Figures:
A) Creating Digital Artwork
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1. Learn about the publication requirements for Digital Artwork:
   http://links.lww.com/ES/A42

2. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).

3. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.

Figure legends: Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page. Use scale markers in the image for electron micrographs, and indicate the type of stain used.
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**List of Supplemental Digital Content:** A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:
Supplemental Digital Content 1.wmv

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their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. In that case, supply the chemical name and a figure giving the chemical structure of the drug. If applicable, capitalize the trade names of drugs and place them in parentheses after the generic names. To comply with trademark law, include the name and location (city and state in USA/city and country outside USA) of the manufacturer of any drug or equipment mentioned in the manuscript. Use the metric system to express units of measure, and degrees Celsius to express temperatures. Use SI units rather than conventional units.

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Appendix 10: Private Facility Letter

EMERITUS/ CONJOINT PROFESSOR PATRICIA MICHIE
SCHOOL OF PSYCHOLOGY
Faculty of Science and Information Technology
University Drive Callaghan
NSW 2308 Australia
TELEPHONE (02) 4921 5936
FACSIMILE (02) 4921 6980
Email: Pat.Michie@Newcastle.edu.au

Pattern of cognitive recovery following high doses of medication

Dr Ian McDonald
Chair Medical Advisory Committee

My name is Stewart Oxley, I am professional Doctoral candidate in psychology at the University of Newcastle. I am writing you this letter as a means to outline my current study in order to be able to gain access to Maitland Private Hospital to continue my research on a participant that has been accepted into the facility for treatment. The information below outlines the study, explains what is required of the participant, and shows how the information will be used.

What is the study about?
Certain drugs used to treat illnesses such as depression, anxiety, lack of sleep make you tired. Overdose of these drugs may reduce brain and mental functions such as memory, thinking, attention, planning, decision making etc. and may reduce the ability to carry out everyday activities such as driving. The purpose of this study is to find out whether people overdosed with sedative drugs are still affected even after leaving hospital. We expect to find out that by testing them with sensitive tests of brain function, and comparing them with patients who take overdoses of a non-sedating drug, paracetamol. With the findings of this study we can understand the nature and the duration of brain dysfunction that occurs in sedative drug overdose. This will help doctors to decide when to discharge the patients with sedative drug overdose and what instructions to be given on discharge, so that we can minimise the risk of such patients encountering unsafe situations.

We would like to invite you to take part in this study because you are between 18-70 years old and have taken either paracetamol or a sedative drug of any of the following types: benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), opioids and antipsychotics.

What does the participant have to do?
Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you in any way and will not affect the care that you receive. If you decide to take part you will be asked to sign the attached consent form and return it. We will contact you to set up a meeting. During the study you are still free to withdraw at any time and without giving a reason. If you decide to withdraw you may direct that all data related to you be withdrawn and your blood samples disposed of.

If you decide to participate you will take part in few tests of mental functions such as memory, attention, decision-making etc. They are detailed as following:
Once you are fit enough to go home you will take several tests at the bedside or in a room within the Department of Clinical Pharmacology. The first tests require that you provide a subjective appraisal of your cognitive and driving ability, mood, and indicate whether a major life event has occurred. This should take approximately 15 minutes.

2. This will be followed by tests that examine your reading, decision-making, and memory. They require you to respond verbally or to use paper and pen. Your verbal responses will either be recorded on a digital recorder or written in a booklet. This section of the test should take approximately 20 minutes.

3. If you feel comfortable to continue, the final tests are computer-based, where you will respond to various signals and patterns presented on a computer screen by pressing a button or by touching the computer screen. This section of the test will take approximately 40 minutes. During the testing you can have as many breaks as you like.

4. Two follow-up sessions, 7 and 28 days after discharge, when we will re-test you on most but not all of the tests conducted at discharge. You can have this testing conducted at The Calvary Mater Hospital, The University of Newcastle, or at your home, according to your preference. Prior these re-test sessions, we will send reminder text messages about testing dates, time and locations. These follow-up test sessions will take approximately 60 minutes. At these follow-up sessions, we will ask you for details of any changes in your medication following discharge. In the event that we are unable to contact you at your preferred number to arrange follow-up sessions, we seek the details of an alternate contact number such as a home phone number or number of a family member, partner or friend. We will only use this alternate method if we have been unable to contact you after 3 attempts.

We also seek your permission to access your medical records regarding the clinical features of your present illness and treatment measures.

How will the information be used?
This study will be conducted as a part of the Clinical and Health Psychology Professional Doctoral Degree Program (Prof Doc) of Stewart Oxley, who is the student researcher on the study. The information gathered from you will only be used for this research study. The data will be analysed and the findings will be published in the form of journal papers and a doctoral thesis, and presented at scientific conferences. Individual participants will not be identified in any of these reports arising from the project. With the findings of this study, we will be able to understand the nature of brain and mental dysfunction caused by a sedative drug overdose. That understanding will contribute to clinical guidelines to decide on the timing of discharge of the patients with sedative drug overdose and the instructions given on discharge, so that we can minimise such patients encountering unsafe situations in the future.

Yours sincerely

Stewart Oxley
Doctoral Clinical and Health Psychology candidate
School of Psychology
University of Newcastle
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The Research Team

Prof. Patricia Michie
Emeritus/Conjoint Professor of Psychology
University of Newcastle
Phone (BH): 02 4921 5936

Prof. Alison Jones
Dean of Medicine,
Graduate School of Medicine
University of Wollongong
Phone (BH): 02 4221 5151

Prof Gregory Carter
Conjoint Professor, University of Newcastle
Director, Psychiatry and Suicide Prevention Unit
Phone (BH): 02 4921 1283

Prof Ian Whyte
Director
Department of Clinical Toxicology and Pharmacology
Calvary Mater Hospital
Phone (BH): 02 4921 1269

Dr. Tharaka Dassanayake
MBBS MPhil PhD
Senior Lecturer, Department of Physiology
Faculty of Medicine, University of Peradeniya 20400
SRI LANKA
Phone (BH): +94 81 2396300

Stewart Oxley
Doctoral Clinical and Health Psychology candidate
School of Psychology
University of Newcastle
Phone (MB): 0479166781

Complaints about this research
This research has been approved by the Hunter New England Human Research Ethics Committee of Hunter New England Health (Reference Number 08/08/20/5.07).

Should you have concerns about your rights as a participant in this research, or have a complaint about the manner in which the research is conducted you may contact the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Professional Officer (Research Governance and Ethics), Hunter New England Human Research Ethics Committee, Hunter New England Health, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email HNEHREC@hnehealth.nsw.gov.au