Effects of Central Nervous System Depressant Drug Overdose on Cognitive Functions and Driving

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Declarations

Statement of originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library**, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Tharaka Dassanayake (Date)
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Dedication

...To my mother

Berney Dassanayake...
List of publications included as part of the thesis


Statement of contribution of others

Co-author statement

We, Patricia Therese Michie, Alison Linda Jones and Gregory Leigh Carter attest that Research Higher Degree candidate Tharaka Dissanayake contributed to the following papers/publications of which we are co-authors.

All authors designed the study. Tharaka did the literature search, evaluated the papers, performed meta-analyses and wrote the initial manuscript. All authors revised the paper.


Tharaka took the leading role in designing this project, collected all data and performed the statistical analyses. He wrote the two manuscripts that were revised by the all authors.

This study was jointly developed by Tharaka and other co-authors. Tharaka handled data acquisition. Tharaka and Patrick McElduff performed data analysis and interpretation. Tharaka wrote the first manuscript which was revised by all authors.
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Abstract

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Synopsis

Self-poisoning with pharmaceutical agents is very common across the world. Central nervous system depressant drugs (CNS-Ds) are among the most common substances taken in overdose in hospital-treated episodes of self-poisoning in Australia, the UK and the US. The majority of the patients with CNS-D overdose treated in hospitals in Australia and the UK are discharged within 24-48 hours of their admission, when they still could potentially have subclinical effects of those drugs.

This thesis systematically reviews published evidence on the effects of CNS-Ds on cognitive functions (Chapter 2), automobile driving and traffic accidents (Chapter 3, Paper 1), and presents original research conducted to examine the effects of CNS-D overdose on cognitive functions underpinning daily activities (Chapter 5, Paper 2), surrogate bedside tests of driving skills (Chapter 6, Paper 3) and risk of traffic accidents (Chapter 7, Paper 4) of patients discharged from hospital following treatment.

Comprehensive neuropsychological assessment shows that patients discharged after treatment for CNS-D overdose have significant residual impairments in multiple cognitive functions including visual attention and visuomotor skills, decision-making, and executive functions and working memory (Chapter 5). The impairments, as estimated by regression models, were equivalent to a ‘cognitive ageing’ of 10-20 years depending on the domain tested. Furthermore, executive dysfunction of the patients tends to worsen with increasing task demands.

Converging evidence from the neuropsychological assessment and epidemiological approach indicates that CNS-D overdose has deleterious effects on driving. In particular, the performance of Trail-Making Test B, when interpreted with
respect to its correlation with driving performance and traffic accident risk, suggests that nearly two-thirds of the patients with CNS-D overdose may be grossly impaired (≤10th percentile) at the time of discharge from hospital (Chapter 6, Paper 3). The epidemiological evidence (Chapter 7, Paper 4) shows that the traffic accident risk of these individuals increases by 3-4 times in the immediate post-discharge period, and remains nearly twice their baseline risk after one week following overdose.

In the concluding chapter (Chapter 8), we examine the impact of these impairments on daily activities that the discharged patients are expected and likely to carry out during the post-discharge period, and discuss the clinical implications in post-discharge management of patients treated for CNS-D overdose.
CHAPTER 1

Introduction

Many individuals in the community are prescribed psychoactive drugs with central nervous system depressant effects. The most widely prescribed central nervous system depressant drugs (CNS-Ds) in Australia are opioids, benzodiazepines, atypical antipsychotics and sedative antidepressants (Australian Government Department of Health and Ageing, 2009).

*Benzodiazepines* are used as anxiolytics, hypnotics and muscle relaxants. A single night-time dose is taken when they are used as hypnotics, whereas divided daytime dosing is preferred when used as anxiolytics.

*Opioid* medications are extensively used as analgesics (Australian Government Department of Health and Ageing, 2009; Hudson et al., 2008; Manchikanti and Singh, 2008; Parsells Kelly et al., 2008). Codeine-paracetamol combination preparations were among the top ten prescribed drugs (as indexed by the prescription counts) in Australia in 2007 (Australian Government Department of Health and Ageing, 2009).

*Atypical antipsychotics* represent a collection of structurally heterogeneous class of drugs. Their distinction from older antipsychotics is based on different clinical and preclinical criteria, however, one primary feature is that they cause minimal extrapyramidal effects in therapeutic doses (Burns, 2001). Atypical antipsychotics are increasingly preferred over typical antipsychotics in recent years primarily because of their favourable adverse effect profile (Demland et al., 2009;
Diatta et al., 2007). Australian Statistics on Medicines show that the use (as indexed by the number of defined daily doses used per 1000 population per day) of atypical antipsychotics quetiapine and olanzapine has steadily increased since year 2000 (Australian Government Department of Health and Ageing, 2004; 2007; 2009).

Antidepressants are classified according to their mode of action into tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NaRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and noradrenaline dopamine reuptake inhibitors (NDRI) (Shelton, 2003). Newer non-sedating antidepressants – predominantly SSRIs and SNRIs – have largely replaced TCAs (Australian Government Department of Health and Ageing, 2009; McManus et al., 2000).

1. Epidemiology of CNS-D overdose

CNS-Ds are among the most commonly ingested substances in self-poisoning in the developed world accounting for around 71,000 hospital-treated drug overdoses in the US (2006) (Coben et al., 2010), 39,000 in the UK (mid 2009 – mid 2010) (National Institute of Health, 2011). In 2008, analgesics (which included opioids), sedative/hypnotic/antipsychotic medications, and antidepressants were collectively responsible for 40% of all toxic substance exposures among adults in the US (Bronstein et al., 2009). Sedative/hypnotic/antipsychotic medications, opioids and antidepressants ranked first, second and third respectively in poisoning-related fatalities. Hospitalisations following intentional overdose of opioids (particularly
methadone) and benzodiazepines have been increasing markedly over last decade in the US (Coben et al., 2010).

Australian statistics follow the same pattern. During a one-year period from mid 2007 to mid 2008, there were 30,611 hospital separations following poisonings due to drugs, medications and biological substances. Of these, 12,000 were overdoses with benzodiazepines, antidepressants, opioids or atypical antipsychotics (Australian Institute of Health and Welfare National Hospital Morbidity Database, 2011). Atypical antipsychotic overdose has increased three-fold since 1998/99. This correlates with the steady increase in their use over the past decade. The admission statistics (from Jan 2000 – June 2009) to the regional Clinical Toxicology unit in Newcastle in the New South Wales is representative of the national trend. Benzodiazepines, SSRIs, atypical antipsychotics and opioids are the 2nd, 3rd and 4th and 7th commonest classes of drugs of overdose, respectively. Paracetamol is the most common drug taken in overdose (source: Hunter Area Toxicology Services Database, unpublished).

2. Effects of CNS-D overdose

The CNS-Ds discussed hitherto represent a group of pharmacologically heterogeneous agents. However, the common manifestation of overdose is decreased level arousal.

_Benzodiazepines_ potentiate the inhibitory action of gamma-aminobutyric acid (GABA) by binding and allosterically modulating the GABA-A receptors to open chloride channels of neurons (Stahl, 2000). In most cases overdose leads to mild to moderate sedation (Gaudreault et al., 1991), with low fatality rate when taken alone.
(Hojer et al., 1989). They are much safer in overdose than barbiturates that had been widely used previously as sedative hypnotics. However, large doses of benzodiazepines can cause deep coma and respiratory depression particularly in benzodiazepine-naïve individuals. This may in turn lead to hypoxic brain injury, sometimes leaving permanent neurocognitive deficits (Gaudreault et al., 1991).

Plasma benzodiazepine concentrations correlate poorly with the clinical outcome of intoxication and clinically have no value in management of overdose (Norman and Burrows, 1984). Toxicity of different benzodiazepines in overdose depends on the potency of the drug and its half-life (Buckley et al., 1995a; Isbister et al., 2004b; Serfaty and Masterton, 1993).

**Opioid** intoxication results from deliberate self-poisoning, or accidentally among recreational users of opioids such as heroin and methadone. Heroin and methadone are the commonest opioids taken in fatal overdose (Hall et al., 2000; Hickman et al., 2003; White and Irvine, 1999). Deaths are mainly due to respiratory depression that results in hypoxia. In one study conducted in Newcastle, Australia, opioids constituted 3.2% of self-poisoning related hospital admissions but accounted for 26.7% of deaths that were primarily attributable to drugs (Buckley et al., 1995b).

Neurological features of intoxication of *atypical antipsychotics* vary depending on the receptor affinity of individual drugs (Stahl, 2000). These include drowsiness, impaired consciousness and anticholinergic features including delirium. The drugs appear to be relatively safe in overdose with very low fatality rates (Bronstein et al., 2007; Bronstein et al., 2009; Ngo et al., 2008). As with benzodiazepines and opioids, patients who are on regular atypical antipsychotic treatment may tolerate relatively large doses with less toxic effects that drug-naïve
individuals. Although no comparisons have been made between different atypical antipsychotics, quetiapine seems to be the commonest drug taken in overdose (Balit et al., 2003; Ngo et al., 2008; Hunter Area Toxicology Services Database: unpublished).

The majority of the antidepressant overdoses involve non-sedating antidepressants such as SSRIs and SNRIs (McKenzie and McFarland, 2007; Rich and Isacsson, 1997; Townsend et al., 2001). Although TCAs have prominent sedative effects (Stahl, 2000), overdoses have become much less frequent, along with a decline in their therapeutic use. SSRIs are safer than TCAs in overdose, causing less morbidity and mortality (Baca-Garcia et al., 2002; Barbey and Roose, 1998; Graudins et al., 2002; Henry et al., 1995; Isbister et al., 2004a; Klein-Schwartz and Anderson, 1996; Peretti et al., 2000).

3. Effects of CNS-D overdose on cognitive functions and driving

Most of the patients hospitalised with CNS-D overdose are managed in emergency departments or less frequently in specialised clinical toxicology departments. The in-hospital management primarily consists of supportive care and monitoring for complications. Only a small minority develop complications of overdose such as seizures, respiratory depression or profound hypotension and subsequent hypoxic brain damage while the vast majority of the patients recover from acute toxicity without complications. The decision to discharge from the hospital is made by a physician team based on history and clinical examination.
This clinical assessment of recovery of the CNS functions however taps only into the domains of orientation (time, place and person), motor coordination (test of hand-eye coordination, gait) and basic self-care (feeding and toileting independently). No specific tests are carried out to assess recovery of higher cognitive functions (e.g. executive functions, working memory, complex visuomotor skills and attention) that are important in daily activities. It is expected that these functions return to normal as the drug effects wear off, however the time the patients spend in hospitals could be too short for a complete cognitive recovery: length-of-hospital-stay statistics, particularly those in the UK (National Institute of Health, 2011) and Australia (Australian Institute of Health and Welfare National Hospital Morbidity Database, 2011) indicate that the majority of the patients with CNS-D overdose are discharged from hospitals within 24–48 hours of admission. Any residual cognitive and psychomotor impairment at the time of discharge may impact on their daily activities such as driving, operating machinery and other domestic and workplace tasks during the post-discharge period.

In this thesis, we aimed to assess the effect of CNS-D overdose on cognitive functions underpinning daily activities and to examine whether CNS-D overdose is associated with impaired driving during the post-discharge period.

3.1. Empirical evidence

We conducted an extensive literature search to find out the published studies on CNS-D overdose and cognitive functions or driving. However, the search retrieved only two studies (Verwey et al., 2000; 2005). Both reported anterograde amnesia following benzodiazepine overdose in hospitalised patients, which improved from
day 1 to day 2 after overdose. Patients demonstrated poor word recall on day 1 relative to day 2. This observation is clinically important as anterograde amnesia may interfere with overdose patients remembering advice (e.g. to avoid driving on discharge) given within the first 24 hours after overdose. However, no previous study has assessed cognitive functions in patients with CNS-D overdose at the time of discharge, when these patients are deemed fit to return to the community to carry out their daily activities, including driving.

Although neurological features such as drowsiness, sedation, memory impairment are helpful in assessing the effects of CNS-Ds in a clinical setting, exploring the magnitude and the spectrum of subclinical effects of the drugs in a research setting would require more sensitive tests that tap into distinct cognitive domains. Even though evidence is lacking on the cognitive effects of CNS-D overdose, numerous experimental studies have examined the effects of CNS-Ds in therapeutic doses on distinct cognitive functions and driving, and a large body of epidemiological studies have looked in to the association between CNS-D use and traffic accidents. Before formulating the specific research questions, we reviewed this literature (Chapters 2 & 3) in order to characterise the spectrum, magnitude and the temporal nature of the effects of CNS-Ds (viz. benzodiazepines, opioids, atypical antipsychotics and antidepressants).

Chapter 2 delineates the cognitive framework of everyday functioning and reviews the experimental studies on the adverse effects of CNS-Ds on cognitive functions underpinning daily activities. Chapter 3 (Paper 1, Dassanayake et al., 2011) reviews the experimental studies on the effects of CNS-Ds on driving and the epidemiological studies on the association between CNS-Ds and traffic accidents.
References


2.1. **Cognitive functions underlying everyday activities**

Theoretical models and empirical evidence help to define the cognitive framework of everyday functioning. Many different cognitive functions (e.g. perceptual and psychomotor functions, attention, memory and executive functions) have been investigated for their association with everyday activities, particularly driving.

**Attention, perceptual and psychomotor functions:** *Attention* can be defined as the capacity of an individual to be receptive to external or internal stimuli and process stimulus information further. Attention span refers to the amount of information an individual can grasp at once (Lezak et al., 2004). A distinction is usually made between automatic versus controlled attention. With extended practice on certain tasks, attention to the task becomes effortless or automatic. However, more complex types of tasks require more mental resources and are said to require controlled attention and thus are more sensitive to clinical or other conditions that reduce attentional capacity. These complex forms of attention include:

- **Sustained attention or vigilance** - the ability to maintain attention over a sustained period of time.
- **Divided attention** - the capacity to attend to multiple cognitive tasks concurrently.
• **Selective attention** - the ability to focus on one stimulus or an internal process in the presence of many competing stimuli or thoughts.

• **Attentional switching or attentional set-shifting** - the ability to rapidly shift attention from one task to another in a multi-task situation.

Tests of attention often involve performing perceptual and psychomotor tasks. Commonly used neuropsychological tests of attention and psychomotor functions include digit-symbol substitution test (DSST, where the subject has to substitute a series of digits with matching symbols as quickly as possible) and reaction time (Lezak et al., 2004; Strauss et al., 2006). Another widely used psychophysical measure of perceptual processing capacity in psychopharmacological research is Critical Flicker Fusion (CFF) threshold (Curran and Wattis, 1998). A flickering light stimulus is presented at increasing flicker frequency until the subject is no longer able to perceive two successive stimuli. The flicker frequency at this point is called CFF frequency or CFF threshold.

**Memory:** Memory refers to encoding, and storage of mental representations and retrieval of information. It is commonly classified on a temporal scale into sensory memory (very transient memory traces that can be retrieved if accessed immediately), short-term / working memory and long term memory (Gazzaniga et al., 2002). Psychopharmacology research focuses mainly on the latter two aspects of memory. The working memory system represents a transient store that can retain information over a short period and perform mental operations on the contents. This system receives information either from the external environment (through sensory systems) or from long-term memory stores. Digit span is a commonly used neuropsychological test of working memory capacity. The subject listens to a random
sequence of digits and recalls them in the same sequence (i.e. digit span forwards) or
the reverse sequence (digit-span backwards) immediately after presentation. The
maximum number of digits recalled correctly (i.e. the digit-span) is a measure of
working memory capacity, although digit-span backwards is more consistently
nominated as a measure of working memory. Long-term memory stores information
for months, years or throughout the lifetime. Depending on the characteristics of
information stored, long-term memory is divided into two types, viz. explicit
(declarative) memory and implicit (non-declarative) memory. Explicit
memories of memories and knowledge that are consciously accessible. Explicit
memories of specific personal experiences from a particular time and place are called
episodic memories whereas factual knowledge about the world and more abstract
concepts constitute semantic memories. Implicit memory encompasses knowledge
that is inaccessible for conscious recollection, such as procedural knowledge and
classical conditioning.

Executive functions: Executive functions is a general term that encompasses a
number of functions including goal formation, planning, carrying out goal-directed
plans, inhibition, mental flexibility, as well as the initiation and monitoring of action
(Lezak et al., 2004; Smith and Jonides, 1999). These functions enable a person to
engage independently in society and behave in a purposive, goal-oriented manner.
Executive functions involve higher-level integration of multimodal information so
that deficits of executive functions may manifest as impairment in a wide spectrum of
daily functions. Control aspects of attention and working memory are also integral
components of executive functions.
2.1.1. Cognitive functions underlying activities of daily living

Scales of activities of daily living (ADL) evaluate an individual’s ability to carry out different day-to-day activities. Two widely used scales are,

1. Basic activities of daily living (BADL) (Katz et al., 1970): evaluates a set of activities necessary for basic self-care, viz. movements in bed, transferring from one seat to another, bathing, feeding, dressing and toileting.

2. Instrumental activities of daily living (IADL) (Lawton and Brody, 1969): evaluates more complex skills necessary for living independently in the community. The Lawton scale categorises the IADL into housekeeping, preparing food, doing laundry, managing finances, using the telephone, shopping, using transportation and handling medication.

BADL are mainly dependent on motor functioning and co-ordination whereas IADL are dependent more on cognitive functioning (Bennett et al., 2002; Boyle et al., 2002; Cahn et al., 1998).

Studies on healthy individuals (Grigsby et al., 1998) and patients with dementia (Boyle et al., 2002; Boyle et al., 2003) show that executive functions are strongly associated with functional status as indexed by IADL scores.

*Procedural memory* appears to be the most important form of memory in routine everyday tasks, including driving. Cognitively deteriorated patients may accomplish common household tasks that involve familiar objects using procedural knowledge although they cannot make semantic judgments of the objects they handle (Bozeat et al., 2002; Riddoch et al., 2002).

*Visual information processing* (Hill et al., 1995; Owsley et al., 2002) and *psychomotor speed* (Matsuda and Saito, 2005) are strongly correlated with IADL
especially when the task has to be accomplished under time constraints. Owsley et al. (2002) report that timed IADL (TIADL) correlate stronger with visual-information processing speed than other cognitive determinants such as memory and reasoning. Training in speed of processing appears to improve the TIADL performance (Edwards et al., 2005).

2.1.2. Cognitive framework of automobile driving: theoretical approaches

The integration of complex operations in driving has been explained by different cognitive models (Ranney, 1994). They propose that cognitive control processes operate in a hierarchical fashion in driving (Michon, 1985; 1989; van der Molen and Botticher, 1988). The hierarchical control models classify driving-related task processes into three different strata of functionality: 1) operational processes manipulate control inputs (steering, accelerator) for stable driving, 2) tactical (manoeuvring) processes manage safe interactions with the environment and other vehicles, 3) strategic processes consist of higher level reasoning and planning. This framework has been adopted by other workers in designing human research (Amick et al., 2007; Stolwyk et al., 2006) and driver-behaviour models (Salvucci, 2006).

The operational processes are largely automatised in experienced drivers (Ranney, 1994). These processes are skill based and involve automated schemata which consist of well-learned procedures (Lundqvist, 2001). Tactical processes are involved in more complex traffic situations (e.g. overtaking a vehicle, manoeuvring the vehicle in an intersection). It is theorised that in these instances, situational factors that increase uncertainty shift the driver’s attention from automatic operational
processes to more controlled tactical processes (Ranney, 1994). The operational and tactical processes are time-constrained whereas processes at strategic level (e.g. selecting a route to follow, parking the car) are less constrained by time.

Recent neuroimaging studies strengthen the theory of hierarchical involvement of neural substrates in driving. Walter et al. report a functional magnetic resonance imaging (fMRI) study where recordings were obtained during a simulated driving task (Walter et al., 2001). There was no traffic or unexpected events and the controllers only enabled steering and acceleration/deceleration, thus engaging only the operational processes. The task activated occipitoparietal and motor areas, but not prefrontal regions, indicating occurrence of visuomotor processing with minimal involvement of higher executive functions. In a different study Hirth et al. (2007) allowed drivers to watch videos with hazardous driving situations interspersed with uneventful driving scenarios. Simultaneously recorded fMRI data showed activation of visual association areas and right prefrontal cortex when drivers observed hazardous situations, suggesting visuomotor integration and involvement of executive functions in complex driving situations (Hirth et al., 2007). In another study on experienced taxi drivers, Spiers and Maguire report an fMRI study that showed specific activation of right lateral prefrontal cortex during the processing of road traffic rules (Spiers and Maguire, 2007). These findings suggest that in addition to visuomotor processing areas, prefrontal regions responsible for executive control are also active in complex tactical and strategic level driving tasks.
2.1.3. Neurocognitive correlates of automobile driving: behavioural evidence

Behavioural evidence suggests that driving performance depends on the integrity of many neurocognitive domains including visual attention, visuomotor skills, working memory and executive functions (Anstey et al., 2005; Ball, 1997; Bieliauskas, 2005; Panek et al., 1977; Reger et al., 2004; Withaar et al., 2000 for reviews). Correlational studies between neuropsychological and driving simulator test performance in patients with Parkinson’s disease have shown that deficits in executive functions such as working memory, planning and attentional set-shifting are associated with impairments of demanding task processes such as complex curve navigation, whereas impaired information processing, visual attention and visuospatial skills are associated with errors in simpler operational processes such as maintaining constant driving lane position (Amick et al., 2007; Stolwyk et al., 2006).

2.1.3.1. Visual attention and visuomotor skills

According to theoretical models, impaired information processing precludes timely, informed motor responses (Ranney, 1994). Simple reaction time (SRT) and choice reaction time (CRT) are simple tests used extensively in test batteries in driving research. Delayed reaction times have been found to predict poor driving performance (Anstey et al., 2005; Ball, 1997; Bieliauskas, 2005; Marshall et al., 2007; Panek et al., 1977; Reger et al., 2004; Withaar et al., 2000). Reaction time is a crucial factor in driving manoeuvres such as in applying brakes (Zhang et al., 2007),
and was found to be associated with a modest increase in accident risk (Margolis et al., 2002).

Visuospatial attention may be important in judging the relative position and movement of road-side obstacles, pedestrians and other vehicles. The driver has to simultaneously estimate the relative positions of the relevant objects in the visual field and predict their positions in the next fraction of a second, before manoeuvring the vehicle. Richardson and Marottoli (2003) tested a group of healthy elderly (72 years or above) individuals with a set of standard neuropsychological tests of cognition that included the letter cancellation test, which is a test of visual attention. Visual attention had a significant correlation with overall on-the-road driving performance and 25 driving manoeuvres (out of 36) including making turns in intersections, interacting with traffic and/or pedestrians, accelerator-to-brake reaction time and using directional signals.

Visual tracking is a test of visuomotor coordination. Tracking tasks have been integrated into computerised test batteries (Innes et al., 2007; Korteling and Kaptein, 1996). Simple tracking tasks have been improved to provide more complex divided attention tasks where the subject has to react to a random stimulus while tracking a previously delineated path. This is similar to a driving scenario where the driver has to attend to unexpected targets (e.g. pedestrians, vehicles) while maintaining the driver-lane. Increased cognitive workload in the divided attention task will either increase the tracking error or delay the reaction time to the novel stimulus, or both. Both these measures have been found to correlate with actual driving performance in patients with brain disorders (Fitten et al., 1995; Innes et al., 2007; Korteling and Kaptein, 1996).
Composite tests have been developed to specifically assess driving-related visual information processing skills. *Useful field of view* (UFOV) is a composite measure of pre-attentive visual processing, visual information processing speed, selective and divided visual attention in a traffic scene (Ball and Owsley, 1993). UFOV has been used by many workers, and impaired test performance was found to correlate with increased crash risk (Ball et al., 2006; Marcotte et al., 2006; Owsley et al., 1991; Rubin et al., 2007) and poor performance in driving tests (Hoffman et al., 2005; Marshall et al., 2007; Stav et al., 2008; Whelihan et al., 2005) and landmark / traffic sign identification (Uc et al., 2006). The *Motor free visual perception* (MFVP) test assesses visual perceptual skills in five areas: spatial relations, visual discrimination, figure-ground discrimination, visual closure, and visual memory. Test performance was predictive of on-road performance in healthy drivers over 55 years (Oswanski et al., 2007) and in patients after a stroke (Mazer et al., 1998). Owsley et al. (1998) report that drivers with reduced visual attention and visual processing speed were 2.2 time more likely to encounter a motor vehicle crash than those with normal visual functions (Owsley et al., 1998).

### 2.1.3.2. Working memory and executive functions

Hierarchical models of driving highlight that strategic processes require executive functions such as higher level reasoning and planning (Michon, 1985; 1989; Ranney, 1994). These processes include decision-making tasks such as selecting one from many possible routes, having provided the distance, speed limits and traffic congestion of each alternative (Walker et al., 1997). Long-term memory retrieval aids these decisions and is important in navigating through familiar areas.
(Lloyd et al., 2001). In contrast, tactical tasks (e.g. overtaking, manoeuvring vehicle in an intersection) appear to involve other executive functions such as shifting of selective attention, updating and monitoring of the contents of working memory and impulse inhibition.

Working memory deficits were found to be associated with poor driving performance (Fitten et al., 1995) and increased risk of motor vehicle accidents (Lee et al., 2003). In complex driving situations, working memory has to be updated rapidly and the information already in the store has to be utilised to judge the situation and bring about appropriate actions. Thus, even mild working memory deficits may potentially limit the driver’s capability of handling time-limited, complex driving situations.

Parasuraman and Nestor argue that in driving, selective attention is more important than sustained attention and divided attention (Parasuraman and Nestor, 1993; Parasuraman and Nestor, 1991). Selective attention deficits correlate strongly with road traffic accident involvement (Ranney, 1994). Impaired selective attention was also found to be associated with weaker driving performance in patients with Alzheimer’s dementia (Duchek et al., 1997; Parasuraman and Nestor, 1993; Parasuraman and Nestor, 1991).

### 2.1.4. Role of neuropsychological tests in predicting driving performance

Neuropsychological tests have been extensively investigated for their value as surrogate markers of driving performance.
The *Trail-Making Test* (TMT) is a simple objective test of cognitive and psychomotor functioning. The test has two parts: TMT-A and TMT-B. TMT-A involves connecting a set of numbers irregularly positioned on a paper with lines, in ascending order within the shortest possible time. The completion time is a measure of attention, visual scanning and visuomotor tracking. TMT-B involves tracking numbers in ascending order and letters in alphabetical order switching alternatively between two sets and thus also an index of cognitive flexibility and attentional set-shifting (Lezak et al., 2004; Mitrushina et al., 2005; Strauss et al., 2006). TMT-B is one of the most commonly used off-road-screening tests of driving fitness (Korner-Bitensky et al., 2006). The TMT-B has been shown to be able to predict on-the-road driving ability in healthy elderly individuals (Classen et al., 2008; Richardson and Marottoli, 2003), patients with Alzheimer’s disease (Grace et al., 2005) and patients rehabilitated following brain damage (Lundqvist et al., 1997; Marshall et al., 2007 review; Mazer et al., 1998; Schanke and Sundet, 2000). Richardson and Marittoli (2003) found a significant negative correlation of TMT completion time with 10 driving manoeuvres. TMT-B performance correlated strongly with complex manoeuvres (lane changing and responding to other vehicles and pedestrians), but only moderately with simpler tasks such as making a turn. Drivers with long test completion times were found to have increased crash risk (Ball et al., 2006; Stutts et al., 1998).

The *Wisconsin card sorting test* (WCST) is used to assess abstract thinking and cognitive ‘set-shifting’. *Stroop colour-word naming* test measures the ability to suppress an automatic response. Elderly drivers with a history of repeated crashes showed higher perseveration errors in WCST and longer completion times and more
errors on the Stroop task (Daigneault et al., 2002; Grillo and Mangone, 2007).

However, some other studies have found Stroop test performance does not predict on-the-road driving performance (Schanke and Sundet, 2000).

*Maze navigation tests* have been used to test planning ability and foresight (Lezak et al., 2004). Whelihan et al. (2005) report a moderate correlation ($r = 0.52$) between maze navigation with actual driving performance (Whelihan et al., 2005) in dementia. Studies that used a computerised version of the test have also shown that navigation time and navigation errors predict actual driving performance (Ott et al., 2008; Ott et al., 2003).

Attempts have been made to find out whether common applied clinical scales such as *Mini-Mental State Examination* (MMSE) are able to predict driving ability. Some studies report an association (De Raedt and Ponjaert-Kristoffersen, 2001; Hansen and Hansen, 2002; Stav et al., 2008), whereas some others do not (Grillo and Mangone, 2007; Ott et al., 2000). Except for the figure copy sub-test which was found to correlate with driving performance in healthy older individuals (Marottoli et al., 1994), MMSE is mostly weighted towards left hemisphere-based verbal tasks rather than visuospatial functions. MMSE scores in the middle range were found to correlate well with driving ability, but the correlation was poor towards the higher end of the scale (Fitten et al., 1995). In line with these observations, Withaar (2000) argues that significant driving impairment may occur with mild or no impairment in MMSE scores. Thus, at its best, MMSE may correlate with driving ability in individuals with gross cognitive deficits, but is an inadequate tool in predicting driving competence in those with subtle cognitive impairment.
In summary, domain-specific neuropsychological measures seem to be better predictors of driving performance. Such measures also provide more meaningful empirical evidence to understand the neurocognitive underpinnings of automobile driving. Researchers suggest that in a modern society, clinicians have to be more aware of the possible implications of neurocognitive impairment on driving, and be prepared to offer sound advice to their patients (Morgan and King, 1995; Weiss and Ratzon, 2007).

2.2. Acute neurocognitive effects of CNS-Ds

Acute neurocognitive effects of sedative drugs have been most extensively studied in healthy volunteers given therapeutic doses. Unless specified otherwise, all studies reviewed in this section are double-blind placebo-controlled crossover trials where drugs have been administered orally.

2.2.1. Benzodiazepines

The duration of the cognitive effects a benzodiazepine partly depends on its elimination half-life ($t \frac{1}{2}$). Both the short-half-life benzodiazepine temazepam (20mg) ($t \frac{1}{2}$ 8-22h) and an equivalent dose of the long-half-life benzodiazepine nitrazepam (10mg) ($t \frac{1}{2}$ 15-38h) showed impairment in psychomotor skills and memory when tested a few hours after dosing (Liljequist and Mattila, 1979), but the effects were persistent for several hours only after nitrazepam (Griffiths et al., 1986; Liljequist and Mattila, 1979). Similarly, the half-life-dependent distinction in the duration of cognitive impairment has been observed in studies that compared triazolam ($t\frac{1}{2} \sim 2h$)
with flunitrazepam (t½ 40-200 hours) (Mintzer and Griffiths, 1998), temazepam (15mg and 30mg) with flurazepam (15mg and 30mg, t½ of active metabolite 40-250h) (Roth et al., 1979) and intravenous midazolam (t½ 1.8-6hours) with diazepam (t½ 20-100 and its active metabolite t½ 36-200h) (Nuotto et al., 1992).

Short-acting benzodiazepine hypnotics triazolam and temazepam are known to cause acute cognitive impairment 2-3 hours post dose (Rush and Griffiths, 1996; Rush et al., 1993). However, neither triazolam (0.125mg and 0.25mg) nor temazepam (15mg and 30mg) caused impairment in attention, memory or psychomotor functions in elderly subjects with insomnia when tested 12-14 hours after dosing (Nakra et al., 1992).

2.2.1.1. Attention, perceptual and psychomotor functions

Benzodiazepines reduce CFF frequency (Hindmarch and Tiplady, 1994; King and Henry, 1992; Seppala et al., 1976) indicating that they can impair perceptual processing capacity of the central nervous system. They also are known to impair simple and choice reaction times (Blin et al., 2006; Hindmarch and Tiplady, 1994; Palva et al., 1979; Patat et al., 1987; Seppala et al., 1976), vigilance (Kleinknecht and Donaldson, 1975; Koelega, 1989; Preston et al., 1988; Unrug-Neervoort et al., 1992), visuomotor speed (as indexed by DSST performance) (Friedman et al., 1992; Greenblatt et al., 2005; Greenblatt et al., 1993) and visuomotor tracking (Hindmarch and Tiplady, 1994; Sellers et al., 1992). Many studies have found reaction time (King and Henry, 1992; Preston et al., 1988) and CFF frequency correlate strongly with the degree of sedation (Blin et al., 2006; King and Henry, 1992; Seppala et al., 1976) and thus some workers have used these measures as surrogate markers of the degree of
sedation caused by benzodiazepines (Weingartner et al., 1993). Electrophysiological studies also have demonstrated that early event-related potential (ERP) components such as N100 which is sensitive to cortical arousal and selective attention are affected by single oral doses of alprazolam (1mg) (Semlitsch et al., 1995) and lorazepam (2mg) (Curran et al., 1998).

2.2.1.2. Memory

Amnesic effects of benzodiazepines are well-documented (Barbee, 1993; Curran, 1991; Ghoneim and Mewaldt, 1990; King, 1992; Roth et al., 1984 for reviews). A single oral dose of a benzodiazepine can cause anterograde amnesia as they impede memory acquisition / encoding (Ghoneim et al., 1981; Loke et al., 1985; Patat et al., 1987; Preston et al., 1988; Unrug-Neervoort et al., 1992). Episodic memory (in contrast to semantic memory or implicit memory) is particularly affected (Coull et al., 1999; Curran and Birch, 1991; Danion et al., 1989). Hippocampus (Bird and Burgess, 2008; Squire et al., 2007) and prefrontal cortex (Blumenfeld and Ranganath, 2007; Buckner and Koutstaal, 1998) have been identified as the main regions responsible for episodic memory encoding and retrieval. The CA1 – located in the dorsal hippocampus – plays a major role in memory consolidation. Pyramidal cells of this region are innervated by GABA-A inhibitory interneurones (Klausberger and Somogyi, 2008) which are potential targets of benzodiazepines (Izquierdo and Medina, 1991; Savic et al., 2005). Similarly, prefrontal cortex is also rich in GABA-A neurones (Jones, 1993). Combined behavioural and positron emission tomography (PET) studies have demonstrated that compared to a placebo, single oral doses of diazepam (10mg) and triazolam (0.25mg/70kg body weight) cause reduced
performance in memory encoding tasks and attenuation of prefrontal cortex activity (Coull et al., 1999; Mintzer et al., 2006). Newer imidazopyridine hypnotics such as zolpidem have low affinity to GABA receptor subtypes found in hippocampus and other areas involved in learning and memory (Benavides et al., 1993; Schmid et al., 1995) and appear to cause less amnesic effects (Blin et al., 2006).

The extent of benzodiazepine-induced memory impairment correlates with the degree of sedation (Loke et al., 1985; Preston et al., 1988; Unrug-Neervoort et al., 1992). However, experiments that carefully controlled for the degree of sedation have shown that the amnesic effect of benzodiazepines is at least partially independent of their sedative effect (Curran et al., 1998; Gorissen et al., 1997). When comparable degrees of sedation (to that of those who received benzodiazepines) were induced in control groups using alternative methods such as 24-hour sleep deprivation (Gorissen et al., 1997) or sedative antihistamines (Curran et al., 1998), benzodiazepine and the control groups demonstrated a similar degree of sedation on subjective ratings and in objective measures of sedation. However, only the benzodiazepine groups demonstrated memory impairment. These findings indicate that amnesia caused by benzodiazepines is not simply a consequence of reduced arousal.

2.2.1.3. Executive functions and working memory

Neuropsychological studies have shown that a single 10mg oral dose of diazepam impairs working memory (Coull et al., 1995b) and executive functions such as planning, decision-making and shifting of selective attention (Coull et al., 1995a; b; Deakin et al., 2004). One study also observed disinhibitory effects on decision-making in a gambling task (Deakin et al., 2004). Impairment in the ability suppress an
automatic response (as tested by the Stroop task) and working memory has also been reported with 2mg of lorazepam (Meador et al., 2011).

Event-related potential (ERP) studies provide robust neurophysiological evidence for impaired working memory and executive functions caused by benzodiazepines. P300 (P3b) ERP waveform evoked by ‘oddball tasks’ showed amplitude reduction and latency prolongation after oral administration of benzodiazepines including diazepam 10mg (Ray et al., 1992), temazepam 10mg (Martin et al., 1992), alprazolam 1mg (Semlitsch et al., 1995) etizolam (Fukami et al., 2010) and oxazepam 30mg (Johannes et al., 2001). P300 latency prolongation signifies delayed working memory updating and stimulus classification (Polich, 2007) and amplitude reduction indicates reduced processing capacity of the working memory system (Kok, 1990). GABAergic inhibition of excitatory postsynaptic potentials of glutaminergic neurons is thought to be the reason for reduced amplitude and increased latency of P300 (Frodl-Bauch et al., 1999). The error-related negativity (ERN) is an ERP index of action monitoring and error detection (Holroyd and Coles, 2002). ERN amplitude reduction has been found with alprazolam 1mg (Riba et al., 2005), oxazepam 30mg (Johannes et al., 2001) and lorazepam 2.5mg (de Bruijn et al., 2004). Neural generators of ERN have been located in rostral anterior cingulate cortex (Carter et al., 1998; Garavan et al., 2002; Kiehl et al., 2000; Ullsperger and von Cramon, 2001), an area extensively innervated by inhibitory GABAergic neurones (Benes et al., 1992; Marcel et al., 1986; Vogt et al., 1992). Thus it is likely that benzodiazepines, through their GABAergic action, inhibit the activity of the neural generators of ERN. This reflects the detrimental effects of these drugs on error detection which is an essential component of action monitoring.
2.2.2. Antidepressants

Owing to their non-specific receptor affinity, TCAs tend to have more adverse neurocognitive effects compared to more selective newer antidepressants (Amado-Boccara et al., 1995; Hawley et al., 1997; Hindmarch, 1997; Thompson, 1991). Subjective ratings of the degree of sedation have been consistently greater with TCAs compared to placebo (Bye et al., 1978; Dal Pozzo et al., 1997), and newer antidepressants (Fairweather et al., 1996). A recent study corroborates this objectively: subjects showed poor performance in attention tests and increased daytime sleepiness (as measured by Multiple Sleep Latency Test) after night-time amitriptyline, but not after escitalopram (Doerr et al., 2010). TCAs also lower the CFF frequency (Kerr et al., 1992a; Ogura et al., 1983), indicating that they can reduce the perceptual processing capacity of the brain.

Improved information processing has been reported with citalopram (Fairweather et al., 1997; Nathan et al., 2000), sertraline (Hindmarch and Bhatti, 1988) and paroxetine (Kerr et al., 1992b; Ridout et al., 2003). Moclobemide, a reversible MAOI, also cause less cognitive impairment compared to TCAs in young (Allain et al., 1992; Fairweather et al., 1993; Siepmann et al., 2004; Tiller, 1990) and elderly (Hindmarch et al., 1992; Kerr et al., 1992a) volunteers.

2.2.2.1. Attention, perceptual and psychomotor functions

Psychomotor impairment caused by antidepressants can be viewed as a product of lowered levels of arousal and impaired attention and cognitive abilities. Sedative effects may also lead to poor sensory-motor coordination. Several
neuropsychological studies report impairment in many cognitive and psychomotor functions with TCAs. These include impaired attention (Kerr et al., 1992a; Weinstein et al., 1996) and visuomotor tracking (Kerr et al., 1992a; Kerr et al., 1996), and delayed CRT (Allen et al., 1991; Crome and Newman, 1978; Kerr et al., 1992a) and slowed finger-tapping (Lader et al., 1986). In contrast, studies with SSRIs report faster CRT with paroxetine (Ridout et al., 2003), sertraline (Hindmarch and Bhatti, 1988), fluvoxamine (Hasbroucq et al., 1997) and citalopram (Nathan et al., 2000) and increased finger tapping speed with citalopram (Lader et al., 1986).

2.2.2.2. Memory

TCAs with anticholinergic properties block M₁ and M₂ muscarinic receptors. Blockade of M₁ receptors of the cerebral cortex, hippocampus, and striatum is responsible for impairment of memory, cognitive and judgmental abilities. These memory disturbances are aggravated by sedative effects of the drugs. Memory impairment is more pronounced with TCAs with marked anticholinergic actions such as amitriptyline, imipramine and dothiepin (Danion, 1993; Frewer and Lader, 1993; Mattila et al., 1978; Sakulsripong et al., 1991).

Impairment of delayed recall has also been demonstrated with the SSRI paroxetine (Schmitt et al., 2001), potentially associated with its anticholinergic effects. However, many newer antidepressants including fluvoxamine (Curran et al., 1986), fluoxetine (Fudge et al., 1990), sertraline (Schmitt et al., 2001), bupropion (Carvalho et al., 2006), nefazodone (Frewer and Lader, 1993) and venlafaxine (Siepmann et al., 2008) do not affect memory functions. Citalopram was found to improve delayed recall but not immediate recall of lists of words in healthy
volunteers, and the authors suggest that it may enhance memory consolidation (Harmer et al., 2002). These findings draw parallels with an earlier study which indicated reduction of serotonin activity (through tryptophan depletion) may impair memory consolidation (Riedel et al., 1999).

2.2.2.3. Executive functions and working memory

Long term treatment with newer antidepressants is known to improve executive deficits in depression (Borkowska et al., 2007). However, research evidence is scarce on the acute effects of antidepressants on executive functions. A recent study did not show any adverse effect of either amitriptyline or escitalopram (an SSRI) on digit-span, a measure of working memory capacity (Doerr et al., 2010). Compared to healthy volunteers given paroxetine, those who were given amitriptyline showed reduced P300 ERP amplitude and increased latency, reflecting reduced capacity and slowing of attention and working memory processes (van Laar et al., 2002). These ERP changes appear to be mediated via the anticholinergic effects of amitriptyline, given the significant cholinergic involvement in the generation of P300 (Dierks et al., 1994; Hammond et al., 1987).

2.2.3. Opioids

Opioids bind to μ, κ, and δ receptors in the nervous system. The sedative effects are thought to be caused by action on κ receptors of the brain (Fine and Portenoy, 2004). The receptor affinity profile of opioids indicates that opioids do not directly affect neural circuits involved in cognitive processes. The empirical evidence
on their effects on specific cognitive domains is relatively inconsistent when compared with the neurocognitive effects of benzodiazepines and antidepressants (Ersek et al., 2004; Zacny, 1995 for reviews). This could be due to the wide variation in selectivity and potency of different opioid drugs (i.e. whether the drug is an agonist, a partial agonist or a mixed agonist-antagonist). Furthermore, relatively few studies on acute effects have been carried out in healthy volunteers. Opioids seem to be associated with impairments predominantly in attention, perceptual and psychomotor functions, which are closely dependent on the degree of arousal.

2.2.3.1. Attention, perceptual and psychomotor functions

CFF frequency had been tested after intravenous doses of morphine (10mg, 15mg) and dextropropoxyphene (100 mg, 200 mg) (Hanks et al., 1995; O’Neill et al., 1995). Dextropropoxyphene 200mg and both doses of morphine caused a significant reduction in CFF threshold when tested 4 hours after dosing. Digit-symbol substitution test (DSST) has also been used extensively to assess the effect of opioids on information processing speed. It has been found to be unimpaired in most of the instances with morphine, pethidine, codeine and methadone (Zacny, 1995), but impaired with a more potent opioid hydromorphone (Hill and Zacny, 2000; Walker and Zacny, 1999).

Auditory reaction time was found to be delayed in healthy volunteers after 10mg of IV morphine (Zacny et al., 1994a; Zacny et al., 1994b) and codeine 60mg (Stacher et al., 1986; Stacher et al., 1987). However visual reaction time was not found to be increased in healthy volunteers who received therapeutic doses of
morphine (Berman et al., 1993; Saddler et al., 1985) or codeine (Bradley and Nicholson, 1986).

2.2.3.2. Memory

A number of opioids (morphine, methadone, and meperidine) have been tested for their effect on memory. The results consistently show that they do not cause acute impairment in working memory, as indexed by digit span (Gritz et al., 1975; Kelley et al., 1978; Saddler et al., 1985). However, delayed recall of information is significantly impaired in healthy volunteers a few hours after intravenous infusions (Kerr et al., 1991) and injections (10mg and 15mg) (Hanks et al., 1995) of morphine. Similar results have been shown in palliative-care patients who received immediate release oral morphine preparations (Kamboj et al., 2005). These findings suggest that morphine may impair memory retention at therapeutic plasma concentrations.

2.2.3.3. Executive functions

Studies on acute effects of opioids on executive functions are scarce. However, long-term use of opioids may be associated with deteriorated executive functions (Gruber et al., 2007). Opiate abusers have shown increased deliberation time in a decision-making task although the decisions were as accurate as those of healthy controls (Rogers et al., 1999).
2.2.4. Atypical antipsychotics

Atypical antipsychotics have a higher affinity towards D₃ and D₄ dopaminergic receptors than typical antipsychotics. They act more selectively on mesolimbic dopaminergic pathways. Neurocognitive deficits and extrapyramidal effects are less due to sparing the mesocortical pathways and nigrostriatal pathways, respectively.

Acute cognitive and psychomotor effects of atypical antipsychotics are primarily mediated via anticholinergic and antihistaminergic effects. Sedative effects of atypical antipsychotics are attributed to high H₁ histaminergic receptor antagonism which is observed predominantly with quetiapine, olanzapine and clozapine. Clozapine and olanzapine are also potent M₁ muscarinic receptor antagonists and hence may cause memory deficits and other anticholinergic effects (Stahl, 2000).

However, very few studies so far have examined acute neurocognitive effects of these drugs. We found only one study on olanzapine (Beuzen et al., 1999), one on clozapine (Vollenweider et al., 2006) and none on quetiapine.

Beuzen et al. report a study where 12 healthy elderly (62-81 years old) volunteers were tested in a double-blind placebo-controlled crossover study (Beuzen et al., 1999). A 3mg dose of olanzapine impaired simple and choice reaction times, sustained attention, and visuomotor tracking on day 1 of treatment. The impairment was significant at 2 hours post-dose while the deficits in visuomotor tracking were evident at 4 hours. These deficits were persistent even after 8 hours; however, all returned to pre-dosing levels at 24-hours post-dose.

In a double-blind, placebo-controlled crossover study of 30 young healthy male volunteers (20-30 years old), each subject was given 30mg (20mg followed by
10mg after 90 minutes) of clozapine, and multiple cognitive testes from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered (Vollenweider et al., 2006). The drug impaired sustained attention as indexed by poor performance in a rapid visual information processing task. However, there was no impairment in spatial recognition memory or attentional set-shifting.

2.3. Conclusions

Although very little research has been conducted on the cognitive effects of CNS-D overdose, experimental evidence reviewed in this chapter shows that CNS-Ds, even in therapeutic doses could impair a multitude of cognitive functions underpinning daily activities.

Commonly, CNS-Ds seem to impair attention, visuomotor skills and the speed of information processing. Depending on the CNS receptor affinity of the drugs they could also interfere with higher cognitive domains such as memory, executive functions etc. Cognitive models of driving – backed by empirical evidence – indicate that these domains are crucial components of the cognitive framework of driving behaviour. While simple visuomotor skills underpin lower-level operational processes, higher-level executive functions seem to be crucial in complex interactions in the driving environment.

This review however, does not directly demonstrate whether any impairment caused by drugs is significant enough to adversely affect driving. The next chapter reviews the experimental evidence on the acute effects of CNS-Ds on driving and the epidemiological studies on CNS-D use and traffic accidents.
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Comparing the subjective, psychomotor and physiological effects of intravenous

Effects of Benzodiazepines, Antidepressants and Opioids on Driving: A Systematic Review of Epidemiological and Experimental Evidence

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ABSTRACT

Background: Many individuals in the community are prescribed psychoactive drugs with sedative effects. These drugs may affect their daily functions, of which automobile driving is a major component.

Objective: To examine the association of three classes of commonly used psychoactive drugs (viz. benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) with 1) the risk of traffic accidents (as indexed by epidemiological indicators of risk) and 2) driving performance (as indexed by experimental measures of driving performance).

Methods: A literature search for material published in the English language between January 1966 and January 2010 in PUBMED and EMBASE databases was combined with a search for other relevant material referenced in the retrieved articles. Retrieved articles were systematically reviewed, carrying out meta-analyses where possible. Twenty-one epidemiological studies (13 case-control and 8 cohort studies) fulfilled the inclusion criteria by estimating the accident risk associated with drug exposure (ascertained by blood/urine analysis or prescription records). Sixty-nine experimental studies fulfilled the inclusion criteria by testing actual or simulated driving performance after administering a single dose or multiple doses.

Results: Two meta-analyses showed that benzodiazepines are associated with a 60% (for case-control studies: pooled odds ratio [OR] 1.59; 95%CI 1.10, 2.31) to 80% (for cohort studies: pooled incidence rate ratio: 1.81; 95%CI 1.35, 2.43) increase in the risk of traffic accidents and a 40% (pooled OR 1.41; 95%CI 1.03, 1.94) increase in ‘accident responsibility’. Co-ingestion of benzodiazepines and alcohol was associated with 7.7-fold increase in the accident risk (pooled OR 7.69; 95%CI 4.33, 13.65).
Subgroup analysis of case-control studies showed a lower benzodiazepine-associated accident risk in elderly (>65 years) drivers (pooled OR 1.13; 95% CI 0.97, 1.31) than in drivers < 65 years of age (pooled OR 2.21; 95% CI 1.31, 3.73), a result consistent with age-stratified risk differences reported in cohort studies. Anxiolytics, taken in single or multiple doses during daytime, impaired driving performance independent of their half-lives. With hypnotics, converging evidence from experimental and epidemiological studies indicates that diazepam, flurazepam, flunitrazepam, nitrazepam and the short half-life non-benzodiazepine hypnotic zopiclone significantly impair driving at least during the first 2–4 weeks of treatment. The accident risk was higher in the elderly (> 65 years) who use tricyclic antidepressants (TCAs), however the evidence for an association of antidepressants with accident risk in younger drivers was equivocal. Sedative but not non-sedative antidepressants were found to cause short-term impairment of several measures of driving performance. Limited epidemiological research reported that opioids may be associated with increased accident risk in the first few weeks of treatment.

**Conclusions:** Benzodiazepine use was associated with a significant increase in the risk of traffic accidents and responsibility of drivers for accidents. The association was more pronounced in the younger drivers. The accident risk was markedly increased by co-ingestion of alcohol. Driving impairment was generally related to plasma half-lives of hypnotics, but with notable exceptions. Anxiolytics, with daytime dosing, impaired driving independent of their half-lives. TCAs appeared to be associated with increased accident risk at least in the elderly, and caused acute impairment in driving performance. Opioid users seemed to be at a higher risk of
traffic accidents; however experimental evidence is scarce on their effects on driving. The clinical and medico-legal implications of these findings are also discussed.

**BACKGROUND**

Many individuals in the community are prescribed psychoactive drugs with sedative effects, such as benzodiazepines, tricyclic antidepressants (TCAs) and opioids. The vast majority of those who are treated with these drugs are outpatients and are expected to carry out their daily activities in a similar manner to other individuals. However, these drugs can adversely affect the cognitive and psychomotor functions underlying daily activities, and some of those functions (e.g. reaction time, attention, visuospatial skills) are considered important in automobile driving.\(^{[1-3]}\)

The effects of drugs on driving safety have been previously examined using epidemiological and experimental study designs. The epidemiological studies examine this relationship in terms of traffic safety by measuring the association between use of sedative psychotropic drugs and the risk of traffic accidents, while experimental studies approach the question by examining whether administration of drugs is likely to impair driving performance. The focus of the present review is to explore the role of three classes of psychoactive drugs (viz. benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) in traffic safety by combining the evidence from epidemiological and experimental studies, because each type of study in isolation fails to establish drugs as a causative factor in traffic accidents.

The outcome of interest in epidemiological studies is traffic accidents (in most instances injurious or fatal accidents), which are a major outcome of immediate
practical significance. Being observational studies, they fall short of establishing a cause and effect relationship between drug use and traffic accidents, i.e. detection of a drug in a driver who met with an accident does not necessarily mean that the drug was a cause for the accident.[4] Accident responsibility studies attempt to overcome this limitation by establishing that the drug in question is more prevalent in drivers responsible for accidents than in those who are not responsible for accidents. Therefore the present review also focuses on accident responsibility studies.

The aim of experimental studies is to determine the effect of a single or of a few doses of drugs on driving performance, as tested in different actual driving tests[5–7] or driving simulator tests[8–10]. Experimental studies can eliminate many of the limitations of epidemiological studies, but mostly at the cost of compromising the ecological validity. Driving performance is frequently tested in a highly controlled environment where only certain components of driving behaviour are examined through specific driving tasks. Certain driving tests however have achieved a greater ecological validity within a controlled environment and have been also validated against surrogate markers of traffic safety. For example, in a standardized driving test developed by O’Hanlon and colleagues[5] in the early 1980s, the primary outcome measure is the driver’s ability to maintain the lateral position of the vehicle in the driving lane. Cognitive models of driving define such processes as ‘operational’ processes of driving, which are necessary for stable driving.[11-13] The degree of weaving of the vehicle (termed standard deviation of lateral position [SDLP]) was calibrated against different blood levels of alcohol, which is a known risk factor for traffic accidents.[5] Several recent reviews have comprehensively analysed the effects of different doses of commonly used benzodiazepine and non-benzodiazepine
hypnotics\textsuperscript{[14,15]} and antidepressants\textsuperscript{[16]} on this measure of lateral position control in highway driving. While impaired performance in the above driving test suggests the participant is unfit for highway driving, unimpaired driving performance does not necessarily mean that one is able to drive safely, particularly in complex driving environments where the driver has to respond to other vehicles, pedestrians, traffic signs and other roadside objects. According to cognitive models of driving, more complex processes which are necessary to interact with the external environment and to help make higher level decisions in driving are categorized as ‘tactical’ and ‘strategic’ level processes.\textsuperscript{[11-13]} Different actual and simulated driving tests have been used to tap these higher level aspects of driving and are reviewed in the present paper.

Many recent epidemiological studies\textsuperscript{[17-19]} and reviews of experimental studies\textsuperscript{[14-16]} emphasize the differences in the effects of individual drugs (even if they are in the same class of drugs). Accordingly, the present review will also focus on the level of individual drugs. In addition, we also focus on different subject factors (patients vs healthy volunteers, young vs the elderly) that are likely to modify drug effects on driving and traffic accidents.

**Objectives**

The broad objective of the present study was to systematically review the literature to find out whether three groups of commonly used psychoactive drugs (benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) are associated with increased risk of traffic accidents and impaired driving. More specifically we aimed to examine (i) whether use of each of these drugs is
associated with increased risk of traffic accidents (as indexed by risk estimates measured in analytical epidemiological studies); and (ii) whether experimental administration of these drugs causes impairment in driving performance (as indexed by quantitative measures of driving performance in an actual vehicle or a driving simulator).

**METHODOLOGY**

**Literature search strategy**

We conducted a literature search on the PUBMED and EMBASE databases for material published between January 1966 and 31 January 2010. The search was limited to human studies published in English. Two sets of search terms were used. The first set consisted of the EMTREE/MeSH terms ‘benzodiazepine derivative’, ‘zaleplon’, ‘zopiclone’, ‘zolpidem’, ‘zolpidem tartrate’, ‘eszopiclone’, ‘antidepressant agent’ and ‘opiate agonist’. 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, the search also incorporated the 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.
Inclusion criteria

Inclusion criteria for epidemiological studies were (i) cohort or case-control study design or variants such as case-crossover studies (survey designs and other descriptive studies were excluded); and (ii) explicitly stated exposure ascertainment (e.g., detection of drugs in body fluids, records of drug prescription) and outcome ascertainment (i.e., traffic accidents or subcategories such as ‘traffic accidents required hospitalization’ or ‘fatal traffic accidents’). The research methods of epidemiological studies were assessed based on the appropriate fields outlined in STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statements for case-control studies and cohort studies.

The inclusion criteria for experimental studies were (i) administration of a single dose or multiple doses of a relevant drug to at least one of the study groups; and (ii) implementation of an actual driving test or a test in a driving simulator (studies that examined cognitive/psychomotor functions related to driving by laboratory tests were excluded). The methodology of the experimental studies was evaluated under four categories: experimental design, selection of study samples, pharmacological manipulation and outcome measures.

The initial search retrieved 1271 articles. Exclusion of the papers that did not meet the inclusion criteria are summarized in figure 3.1. This initial literature search retrieved 15 epidemiological studies and 54 articles on experimental studies. A review of the reference lists produced an additional 6 epidemiological studies and 9 experimental studies. Thus, in total, 21 epidemiological studies and 69 experimental studies (in 62 papers) met the aforementioned inclusion criteria. Of the 21 epidemiological studies, 13 were case-control studies (table I) and 8 were cohort
studies (table II). Nineteen epidemiological studies investigated exposure to benzodiazepines, 6 to antidepressants and 7 to opioids. Of the 69 experimental studies, benzodiazepines and/or ‘z drugs’ were tested in 48 studies (Supplementary Table 1: see Appendix), antidepressants in 20 (Supplementary Table 2: see appendix) and opioids in three studies (Supplementary Table 3: see appendix).

Figure 1: Selection process of studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design (period)</th>
<th>Study population from which samples selected</th>
<th>Cases</th>
<th>Controls/Exposure</th>
<th>Adjustment stratification/Variables</th>
<th>Subgroups/Study drug groups</th>
<th>Results: risk measure (95% CI)</th>
<th>Comments/consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skagg et al.[20] (1979; UK)</td>
<td>Matched (Mar 1974-Feb 1976)</td>
<td>43117 people registered with 16 GPs</td>
<td>57 drivers who died or were hospitalized due to injuries from TA</td>
<td>1425 randomly selected people from GP registers</td>
<td>Prescription records: prescribed and dispensed with a tranquilizer within 12 wk before TA</td>
<td>Matched for sex, general practice enrolled, year of birth</td>
<td>All tranquilizers RR 5.2 (2.2 12.6) RR 4.9 (1.8 13.0)</td>
<td>No CI given for major tranquilizers as there were too few subjects</td>
</tr>
<tr>
<td>Honkanen et al.[21] (1980; Finland)</td>
<td>(Apr. May, Sep. Oct 1977)</td>
<td>Injured car drivers arriving at EDs in Helsinki</td>
<td>201 drivers arrived at ED within 6 h after TA</td>
<td>325 car drivers selected randomly at petrol stations</td>
<td>Serum analysis for BDZs</td>
<td>Matched for weekday, hour of day and location of accident</td>
<td>BDZs (mainly diazepam) More commonly detected in cases than in controls (p&lt;0.003) May have introduced a bias as the duration of holding the licence was shorter and blood alcohol levels higher in cases then controls</td>
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<td>Jick et al.[22] (1981; USA)</td>
<td>(Jan 1977-Dec 1978)</td>
<td>Patients (15-64 y) discharged from a Group Health Cooperative hospital with diagnosis of injury due to automobile accident</td>
<td>93 drivers ‘at fault’ of the accident, as recorded in clinical notes</td>
<td>Group 1: 83 passengers Group 2: 85, driver-status undetermined (45), not-at-fault drivers (13), drivers’ fault status unknown (27)</td>
<td>Prescription records: at least one prescription for sedative drug (major or minor tranquilizer, antihistamines, or opioid analgesic) within 3 mo of accident</td>
<td>Matched for sex At-fault drivers vs passengers (for use of any drug group)</td>
<td>Crude OR 1.0 Sex-adjusted OR 1.1 (0.6 2.2) Not included in meta-analysis because of (i) questionable accuracy of clinical notes in assigning at-fault status of drivers; (ii) no adjustment for alcohol (more cases drinking than controls); (iii) no direct comparison of drivers at fault and not at fault</td>
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<tr>
<td>Lagier[23] (1993; France)</td>
<td>(May 1989-Jul 1990)</td>
<td>Patients admitted to hospital after TA injury</td>
<td>Drivers responsible for accident</td>
<td>Drivers not responsible for accidents and pedestrians</td>
<td>Blood analysis for BDZs</td>
<td>Blood alcohol &lt;0.2 g/L OR 0.96 (0.8 1.2) Blood alcohol &gt;0.2 g/L OR 7.2 (3.4 15.2) Blood alcohol 0.2-0.8 g/L with no BDZs OR 2.03 (1.4 2.9) BDZ-alcohol combination increases risk compared with alcohol/BDZ alone</td>
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<td>Level[24] et al. (1994; USA)</td>
<td>Matched (1987-8)</td>
<td>Enrollees of Group Health Cooperative, Puget Sound</td>
<td>234 drivers aged &gt;65 y sought treatment for TA within 7 days of 447 drivers &gt;65 y matched for age, sex and county of residence, but not met with</td>
<td>Prescription records, current exposure: prescription within 60 days Race, marital status, education, miles driven, insulin or oral hypoglycaemic use for diabetes mellitus</td>
<td>BDZs: current exposure OR 0.9 (0.4 2.0) Past exposure OR 1.2 (0.5 2.7) Main BDZ triazolam (~50%) Exposure status was defined in relation to a given class of drugs. ‘Unexposed group’</td>
<td>Chapter 3</td>
<td>66</td>
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<td>Study (y; country)</td>
<td>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>Subgroups/studied drug groups</td>
<td>Results: risk measure (95% CI)</td>
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<td>accident</td>
<td>TA during the same calendar year</td>
<td>Past exposure: prescription 60 days–6 mo before</td>
<td>No exposure: no prescriptions within 6 mo</td>
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<td>Hemmelgarn et al. (1997; Canada)</td>
<td>Nested (Jan 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 crashes</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>
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<tr>
<td>Long t1/2 BDZs: current use</td>
<td>OR 1.28 (1.12, 1.45)</td>
<td>Long t1/2: clonazepam, diazepam, clorazepate, flurazepam, nitrazepam, chloridiazepoxide</td>
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<td>first week of use</td>
<td>OR 1.45 (1.04, 2.03)</td>
<td>OR remains high in first year of use</td>
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<td>Short t1/2 BDZs: current use</td>
<td>OR 0.96 (0.88, 1.05)</td>
<td>Short t1/2: alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam</td>
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<td>first week of use</td>
<td>OR 1.04 (0.81, 1.34)</td>
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<td>Study (y; country)</td>
<td>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>Subgroups/studied drug groups</td>
<td>Results: risk measure (95% CI)</td>
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<td>Barbone et al. [20] (1996; UK)</td>
<td>Case-crossover (Jan 1992 - Jan 1995)</td>
<td>410,306 residents in Tayside region, UK, who had been registered with a Tayside GP</td>
<td>19,386 persons ≥18 y who experienced a TA, Case period: same day of TA</td>
<td>18 wk</td>
<td>Intake of the drug on the day based on dispensed prescription records</td>
<td>Stratified for age, sex, severity of injury, breath alcohol, lighting, driver culpability</td>
<td>BDZs: all</td>
<td>OR 1.62 (1.24, 2.12)</td>
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<td>OR 2.18 (1.52, 3.13)</td>
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<td>OR 2.0 [p &lt; 0.05]</td>
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<td>OR 1.3 [p &gt; 0.05]</td>
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<td>OR 3.3 [p &lt; 0.05]</td>
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<td>OR 3.6 [p &lt; 0.05]</td>
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<td>Long et al. [4] (2000; Australia)</td>
<td>(Apr 1995 - Aug 1996)</td>
<td>2500 injured drivers from SA</td>
<td>Drivers culpable for TA</td>
<td>Drivers not culpable for TA</td>
<td>Detection of drugs in blood samples</td>
<td>Stratified for different drug concentrations in blood</td>
<td>BDZs alone: all levels</td>
<td>OR 2.0 [p &lt; 0.05]</td>
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<tr>
<td>Study (y; country)</td>
<td>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>Subgroups/studied drug groups</td>
<td>Results: risk measure (95% CI)</td>
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<td>McGwin et al.[29] (2000; USA)</td>
<td>(Jan-Dec 1996)</td>
<td>39,687 residents of Mobile County, AL, ≥65 y who had a driver’s license in 1996</td>
<td>244 at-fault drivers involved in TAs from 1 Jan 1996 to 31 Dec 1996</td>
<td>1. 182 not-at-fault drivers involved in crashes during same period 2. 475 drivers not involved in crashes</td>
<td>Self-reporting of medication use in a telephone interview</td>
<td>Age, sex, mileage of driving</td>
<td>BDZs only</td>
<td>OR 13.4 [p&lt;0.05]</td>
</tr>
<tr>
<td>Mura et al.[30] (2003; France)</td>
<td>(Jun 2000– Sep 2001)</td>
<td>Patients &gt;18 y admitted to EDs</td>
<td>900 drivers after TAs</td>
<td>900 patients admitted due to other reasons</td>
<td>Detection of drugs in blood samples</td>
<td>Matched for age, sex</td>
<td>BDZs only</td>
<td>OR 1.7 (1.2, 2.4)</td>
</tr>
<tr>
<td>Drummer et al.[30] (2004; Australia)</td>
<td>(1990–9; variable periods in different states)</td>
<td>Drivers killed in TAs in VIC, NSW and WA</td>
<td>Drivers culpable for crashes</td>
<td>Drivers not culpable for crashes</td>
<td>Detection of drugs in blood samples</td>
<td>Age, sex, no. of vehicles in crash, state of vehicle</td>
<td>BDZs only/Opioids only</td>
<td>OR 1.27 (0.5, 3.3)/OR 1.41 (0.7, 2.9)</td>
</tr>
<tr>
<td>Movig et al.[31] (2004; Netherlands)</td>
<td>(May 2000– Aug 2001)</td>
<td>Injured and non-accident-involved drivers in Tilburg</td>
<td>110 car or van drivers hospitalized after TA</td>
<td>816 drivers randomly selected from moving traffic (stopped for alcohol testing by police)</td>
<td>Positive blood/urine samples</td>
<td>Age, sex, blood alcohol concentration, concomitant drug exposure, season, time of day</td>
<td>BDZs/Opioids/Drug combinations</td>
<td>OR 5.05 (1.82, 14.04)/OR 2.35 (0.87, 6.32)/OR 6.1 (2.6, 14.1)</td>
</tr>
<tr>
<td>Study (y; country)</td>
<td>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>Subgroups/studied drug groups</td>
<td>Results: risk measure (95% CI)</td>
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<td>Dubois et al.[2]</td>
<td>(Jan 1993–Dec 2006)</td>
<td>Drivers &gt;20 y involved in fatal TAs between 1993 and 2006</td>
<td>Drivers responsible for TA (as indexed by unsafe driving actions)</td>
<td>Drivers not responsible for TA</td>
<td>Blood sample analysis for BDZs, categorized according to ( t_1 )</td>
<td>Age, sex, other medication use, driving history</td>
<td>Short ( t_1 ) (&lt;6 h): midazolam 98% Intermediate ( t_1 ) (6–24 h): alprazolam 80% Long ( t_1 ) (&gt;24 h)</td>
<td>OR 1.02 (0.73, 1.42) OR 1.53 (1.20, 1.96) OR 1.44 (1.25, 1.66)</td>
</tr>
</tbody>
</table>

**AL** = Alabama; **ED** = Emergency Department; **GP** = general practitioner; **NSW** = New South Wales; **OR** = odds ratio; **RR** = relative risk; **SA** = South Australia; **SSRIs** = selective serotonin reuptake inhibitors; \( t_1 \) = elimination half-life; **TCAs** = tricyclic antidepressants; **VIC** = Victoria; **WA** = Western Australia.
### Table II. Cohort studies on the roles of benzodiazepines (BDZs), antidepressants and opioids on the risk of road traffic accidents (TAs)

<table>
<thead>
<tr>
<th>Study (y; country)</th>
<th>Design (period)</th>
<th>Study cohort (n)</th>
<th>Ascertainment of exposure</th>
<th>Ascertainment of non-exposure</th>
<th>Outcome measure (method of reporting)</th>
<th>Adjustment/stratification/controlled variables</th>
<th>Subgroups/different drugs</th>
<th>Results: risk measure (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey et al. [93]</td>
<td>(1992, USA)</td>
<td>16,262 Medicaid enrollees aged 65–84 y, holding a driving licence</td>
<td>Receiving prescription for a psychoactive drug</td>
<td>No prescriptions for BDZs</td>
<td>Injuries 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>Current use of:</td>
<td>RR 1.5 (1.2, 2.0)</td>
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<td>Jan 1964–Dec 1988</td>
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<td>BDZs</td>
<td>RR 1.5 (1.1, 2.0), risk increases with dose</td>
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<td></td>
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<td>cyclic antidepressants</td>
<td>RR 2.2 (1.3, 3.5), risk increases with dose</td>
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<td>opioid analgesics</td>
<td>RR 1.1 (0.5, 2.4)</td>
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<td>BDZ + TCA</td>
<td>RR 2.1 (1.1, 4.2)</td>
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<tr>
<td>Neutel et al. [94]</td>
<td>(Jan 1989–Dec 1996)</td>
<td>75,587 individuals &gt;20 y of age included in the Saskatchewan Health Databases</td>
<td>First 4–6 wk following prescription of a BDZ hypnotic (n = 79,870)</td>
<td>Not received a prescription for a BDZ within 6 mo preceding a reference date (n = 97,862)</td>
<td>Traffic injury-related hospitalization following sale of index prescription (no. of hospitalizations)</td>
<td>Age, sex and other prescribed drugs</td>
<td>All trUCs</td>
<td>OR 3.1 (1.5, 6.2)</td>
<td>ORs are similar in young (&lt;60 y) and elderly (&gt;60 y) drivers; however, young age group is an independent risk factor for TAs</td>
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<td>Hypnotics (triazolam, flurazepam):</td>
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<td>within 4 wk</td>
<td>OR 3.9 (1.9, 8.3)</td>
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<td>within 2 wk</td>
<td>OR 6.5 (1.9, 22.4)</td>
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<td>Anxiolytics (oxazepam, lorazepam, diazepam):</td>
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<td>within 4 wk</td>
<td>OR 2.5 (1.2, 5.2)</td>
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<td>within 2 wk</td>
<td>OR 5.6 (1.7, 18.4), risk reduces with time since prescription</td>
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<td>Outcome measure (method of reporting)</td>
<td>Adjustment: stratification controlled variables</td>
<td>Subgroups: different drugs</td>
<td>Results: risk measure (95% CI)</td>
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<td>Engelund et al. [29] (2007; Norway)</td>
<td>Registry-based (Apr 2004–Sep 2005)</td>
<td>All Norwegians aged 18–89 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>TA that resulted in a personal injury (incidence rate)</td>
<td>Stratified for sex and age, adjusted for month of the year</td>
<td>BDZs: anxiolytics (diazepam, oxazepam, alprazolam) hypnotics (nitrazepam, flunitrazepam, midazolam) natural opium alkaloids</td>
<td>SIR 2.9 (2.5, 3.5)</td>
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<td>Bramness et al. [19] (2007; Norway)</td>
<td>Registry-based (Apr 2004–Sep 2005)</td>
<td>All Norwegians aged 18–89 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>TA that resulted in a personal injury (incidence rate)</td>
<td>Stratified according to sex and age, adjusted for month</td>
<td>Diazepam: first 7 days</td>
<td>SIR 2.9 (2.2, 3.2)</td>
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<td>SIR 2.5 (2.1, 3.0)</td>
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<td>SIR 3.3 (1.6, 5.8)</td>
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Table II. Contd

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<th>Adjustment/stratification/controlled variables</th>
<th>Subgroups/different drugs</th>
<th>Results: risk measure (95% CI)</th>
<th>Comments</th>
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<td>Bramness et al.⁶⁹¹ (2008; Norway)</td>
<td>Registry-based (Jan 2004–Sep 2006)</td>
<td>All Norwegians aged 18–69 y (3.1 million)</td>
<td>Drug dispensing information. Exposed period: no. of days corresponding to no. of dispensed DDD</td>
<td>Period other than the period defined as exposed period</td>
<td>TA that resulted in a personal injury (incidence rate)</td>
<td>Stratified according to sex and age, adjusted for month</td>
<td>Sedative antidepressants (TCAs, mianserin, mirtazapine):</td>
<td>all users</td>
<td>SIR 1.4 (1.2, 1.6)</td>
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<td>new users</td>
<td>SIR 1.0 (0.7, 1.4)</td>
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<td>Non-sedative antidepressants (SSRIs, MAOIs, SNRIs):</td>
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<td>SIR 1.6 (1.5, 1.7)</td>
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<td>new users</td>
<td>SIR 1.6 (1.3, 1.9)</td>
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<tr>
<td>Gustavsen et al.⁶⁹⁶ (2008; Norway)</td>
<td>Registry-based (Jan 2004–Sep 2006)</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>TA entered in Road Accident Registry (incident rate)</td>
<td>Month of the year, other prescribed drugs, stratified for age and sex</td>
<td>Zopiclone:</td>
<td>first 7 days</td>
<td>SIR 2.3 (2.0, 2.8)</td>
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<td>first 14 days</td>
<td>SIR 2.0 (1.7, 2.2)</td>
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<td>Zolpidem:</td>
<td>first 7 days</td>
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<td>first 14 days</td>
<td>SIR 2.1 (1.5, 2.9)</td>
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<td>Nitrazepam:</td>
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<td>SIR 2.7 (1.8, 3.9)</td>
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<td>first 14 days</td>
<td>SIR 2.2 (1.6, 3.0)</td>
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<td>Flunitrazepam:</td>
<td>first 7 days</td>
<td>SIR 4.0 (2.4, 6.4)</td>
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The degree of the TA (e.g., injurious, non-casualty) not specified. Risk is higher in young drivers and male drivers.
<table>
<thead>
<tr>
<th>Study (y; country)</th>
<th>Design (period)</th>
<th>Study cohort</th>
<th>Ascertainment of exposure</th>
<th>Ascertainment of non-exposure</th>
<th>Outcome measure (method of reporting)</th>
<th>Adjustment/stratification/ controlled variables</th>
<th>Subgroups/different drugs</th>
<th>Results: risk measure (95% CI)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Gibson et al. 2009; UK</td>
<td>Self-controlled case series (1986–Nov 2004)</td>
<td>Individuals aged 18–74 y met with TA and were prescribed with sedative drugs during 1986–2004. Non-driving participants excluded</td>
<td>Drug prescription information. Initial exposure: first 4 wk after prescription. Extended exposure: reminder of the course of treatment</td>
<td>Period beyond the time window that spans 4 wk prior to first prescription to 24 wk after last prescription</td>
<td>Motor vehicle crash documented in primary healthcare database</td>
<td>BDZs (all):</td>
<td>first 14 days</td>
<td>SIR 3.1 (2.0, 4.6)</td>
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<td>first 4 wk</td>
<td>IRR 1.94 (1.62, 2.32)</td>
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<td>extended use</td>
<td>IRR 2.38 (2.01, 2.81)</td>
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<td>diazepam first 4 wk</td>
<td>IRR 1.93 (1.54, 2.43)</td>
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<td>extended use</td>
<td>IRR 2.77 (2.20, 3.48)</td>
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<td>temazepam first 4 wk</td>
<td>IRR 1.56 (1.12, 2.17)</td>
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<td>extended use</td>
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<td>nitrazepam first 4 wk</td>
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<td>extended use</td>
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<td>zopiclone first 4 wk</td>
<td>IRR 1.03 (0.68, 1.55)</td>
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<td>zolpidem first 4 wk</td>
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<td>IRR 1.16 (0.60, 2.25)</td>
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<td>Opioids (all):</td>
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<td>IRR 1.70 (1.39, 2.08)</td>
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<td>IRR 1.29 (1.08, 1.54)</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>Codeine</td>
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<td>Morphine</td>
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<td>IRR 1.16</td>
<td>(0.81, 1.65)</td>
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<td>first 4 wk</td>
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<td>Dihydrocodeine</td>
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<td>Tramadol</td>
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<td>(0.73, 1.16)</td>
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<td>extended use</td>
<td>IRR 0.94</td>
<td>(0.77, 1.14)</td>
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</table>

Bachs et al. (2008; Norway)  
Registry-based: Jan 2004–Sep 2006  
All Norwegians aged 18–69 y (3.1 million)  
Drug dispensing information. Exposed period: first 7 days after dispensing codeine or tramadol  
Unexposed period: period not exposed to any CNS-imparing drugs  
TA that resulted in a personal injury (incidence rate)  
Adjusted for month  

DDD = defined daily doses; IRR = incidence rate ratio; MAOIs = monoamine oxidase inhibitors; OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio; SNRIs = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Meta-Analysis

The retrieved epidemiological studies were pooled for meta-analyses in the instances where adequate numbers of studies with required data were available. A random-effects model analysis (DerSimonian-Laird method) was employed to calculate the pooled estimates as it does not assume that each component study of the meta-analysis is derived from the same population, and hence allowed pooling statistically heterogeneous studies without compromising the statistical validity of the results. However, random-effects modelling generated wider confidence intervals (CIs) for the pooled estimate than fixed-effects modelling would do, thus compromising the precision of the pooled estimate. Subgroup analyses were planned in the instances where there was a severe statistical heterogeneity. However, this could be carried out only for the case-control studies on benzodiazepines (based on age), because there were too few studies in the other meta-analyses.

RESULTS

Epidemiological studies: risk of traffic accidents and use of benzodiazepines, antidepressants and opioids

The methodology and results of 13 case-control studies and 8 cohort-studies are summarized with the limitations specific to individual studies noted in tables I and II, respectively.

Two distinct sampling methods can be observed in epidemiological studies. Seven case-control studies ‘recruited’ cases from drivers who were
hospitalized\textsuperscript{[4,21,23,28,30]} or died\textsuperscript{[31,38]} after traffic accidents, whereas controls were recruited either from the victims of traffic accidents or randomly from the roadside.\textsuperscript{[21,30]} Drug exposure was ascertained by analyzing the blood or urine samples. The main advantage of this method is the availability of confirmatory evidence for the presence of the drug under question at the time of accident.

In other case-control studies (except one, where exposure was ascertained through an interview\textsuperscript{[27]}) and all cohort studies, both exposure and outcome ascertainment was registry-based. Accident involvement was ascertained from entries in hospital admission or general practice databases or road accident registries, and drug exposure was ascertained by means of prescription entries in drug prescription databases. Outcome ascertainment was based on motor registry data or medical records. The number of days for which the drugs are prescribed was usually considered the ‘exposed period’. Linkage of the two databases showed whether the patient was prescribed (and hence likely to be taking) the drugs at the time of the accident. The advantage of this approach is the ability to enlist large numbers of subjects, thus increasing the power of the study.

However, this registry-based approach has also introduced certain biases common to many of these observational studies. First, it introduces an exposure ascertainment bias. It is impossible to know whether patients had been actually taking the prescribed drugs during the designated ‘exposed period’ and had not been taking any leftover prescribed drugs or drugs obtained off-prescription during the ‘unexposed period’. Nevertheless, such false exposure ascertainment shifts the results towards null findings and hence does not threaten the validity of any detected positive association between drug use and traffic accidents. Second, only a certain percentage
of the outcomes (i.e. traffic accidents) are recorded in the databases. Particularly less serious accidents, which are likely to represent a significant proportion of all accidents, might have not been entered. For example, studies that recruited accident victims from hospitals\cite{4,21,23,28,30} only include injurious traffic accidents where the injuries were serious enough to seek medical assistance. Third, data on some important confounders may have not been recorded in the registries. Many studies did adjust the analyses or matched the samples for demographic variables (e.g. age, sex) but missed some other important confounders, such as underlying illnesses for which the drugs are prescribed (e.g. depression), which can also affect driving. Inevitably, this may have left a certain degree of residual confounding. Other limitations and potential biases specific to individual epidemiological studies are noted in tables I and II.

**Benzodiazepines and ‘z drugs’**

Of the three classes of drugs, benzodiazepines were the most extensively studied. Benzodiazepines have been studied in 12 case-control studies and 6 cohort studies. Of these, 1 case control study\cite{26} and 2 cohort studies\cite{18,37} have also examined the traffic accident risk of ‘z’ drugs. Based on these studies, we conducted three separate meta-analyses for case-control studies, cohort studies and accident responsibility studies.

1. *Case-control studies on benzodiazepine exposure and traffic accident risk* (figure 2): Of the 12 case control studies, 8 examined whether exposure to benzodiazepines is associated with increased odds of traffic accidents. Two studies\cite{26,30} did not report the exposure data and numbers of traffic accidents in exposed and unexposed periods.
so that those two studies could not be included in the meta-analysis. However, both these studies showed a significant association between benzodiazepine exposure and traffic accidents. The first was a case crossover study where, in a group of drivers involved in traffic accidents, the proportion exposed to benzodiazepines on the day of accident (i.e. the case period) was compared with the proportion exposed on a within-subject control period (i.e. same day of the week in up to 18 weeks prior to the accident date). The adjusted odds ratio (OR) for all benzodiazepines in this study was 1.62 (95% CI 1.24, 2.12), suggesting higher accident risk associated with benzodiazepine use. The second study reported that benzodiazepine exposure was associated with a 5-fold increase in the risk (adjusted OR 5.05; 95% CI 1.82, 14.04) of injurious traffic accidents.

The other six publications contained adequate data for analysis and were included in the meta-analysis (see figure 2). The studies showed a marked statistical heterogeneity (Cochran Q = 16.20; p = 0.006; I² = 69.1%). Nonetheless, the overall association between benzodiazepine exposure and traffic accident risk was significant (p = 0.014), showing that benzodiazepines are associated with a 59% increase in traffic accident risk (pooled OR 1.59; 95% CI 1.10, 2.31). A previous meta-analysis by Rapoport et al. in 2009 used the same set of studies; however, the authors included subject counts only for long-acting benzodiazepines in the Hemmelgarn et al. 1997 study in their analysis. We included the subject counts for all benzodiazepines in the Hemmelgarn et al. study because long/short half-life distinction has not been made in the other studies included in the current meta-analysis. Indeed, some other studies in the meta-analysis also included subjects
predominantly exposed to short-acting benzodiazepines (e.g. the majority of the subjects of the Leveille et al.[24] 1994 study were exposed to triazolam).

2. Cohort studies on benzodiazepine exposure and traffic accident risk (figure 3): Of the six cohort studies, two[18,19] included the same data sources used in a previous study[35] and thus those two articles were excluded. One other article was also excluded as it did not have enough information to calculate risk.[37] However, this study showed a significantly high incidence rate ratio (IRR) suggesting benzodiazepines are associated with increased traffic accident risk. The remaining three studies[32,33,35] were included in the meta-analysis (see figure 3). Similar to case-control studies, there was a significant heterogeneity among individual study results (Cochran Q = 6.65; p = 0.036; I² = 70%). Nonetheless, the overall effect of exposure on traffic accident risk was highly significant (p < 0.0001), with an 81% increase of accident rates in benzodiazepines users (pooled IRR 1.81; 95% CI 1.35, 2.43).

3. Case-control studies on benzodiazepine exposure and traffic accident responsibility (figure 4): Six case-control studies determined whether benzodiazepines are more commonly detected in the blood of drivers responsible for accidents than in the victims (i.e. drivers who were involved but not responsible for the accident or passengers). One of the studies was excluded because of inadequate data,[26] however, this study showed a significant association between accident responsibility and benzodiazepine exposure. The other five studies were included in the meta-analysis. In the selected studies, driver responsibility was ascertained using evidence of ‘unsafe driving actions’ at the time of accident,[31] information from police/researcher investigation findings[23] and comprehensive scoring systems based on drivers’ attempts to mitigate an accident[4,29] as well as subjective recall.[27] The
last study was the smallest and had the widest confidence intervals. There was a marginally significant heterogeneity among the studies (Cochran Q = 9.30; p = 0.054; I² = 57%). The overall effect (p = 0.034) showed benzodiazepines were significantly associated with a 41% increase in accident responsibility (pooled OR 1.41; 95% CI 1.03, 1.94).
Figure 2. Meta-analysis of case-control studies on benzodiazepines and traffic accidents. \( \chi^2 \) = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; Cochran Q = test statistic for heterogeneity of studies; df = degrees of freedom; \( I^2 \) = percentage of variation of study estimate due to heterogeneity (100% * [Q – df]/Q).
Figure 3. Meta-analysis of cohort studies on benzodiazepines and traffic accidents. **Cochran Q** = test statistic for heterogeneity of studies; **df** = degrees of freedom; **I²** = percentage of variation of study estimate due to heterogeneity (100%*[Q – df]/Q); **Z** = Z statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method.
Figure 4. Meta-analysis on accident-responsibility studies on benzodiazepines. $X^2$ = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; Cochran $Q$ = test statistic for heterogeneity of studies; df = degrees of freedom; $I^2$ = percentage of variation of study estimate due to heterogeneity ($100\% \times [Q - df]/Q$).
These three meta-analyses clearly confirm benzodiazepines, as a group, are associated with increased accident risk for drivers. However, different subgroup analyses in individual studies suggest several other drug and driver factors can modify this association. These confounding factors include age of drivers, therapeutic use (i.e. daytime use as anxiolytics and night-time use as hypnotics), half-life of the drug, drug dose, duration of benzodiazepine use and co-ingestion of other psychoactive substances. We conducted subgroup meta-analyses based on age and co-ingestion of alcohol but not for each of the above factors because the numbers of studies were limited.

1. Age

Two independent sets of evidence suggest benzodiazepine-associated traffic accident risk is lower in the elderly. First, we estimated the pooled ORs of the three case-control studies that only involved elderly (>65 years) drivers\textsuperscript{[24,25,27]} and three case-control studies that comprised drivers over a wider age range starting from 18 years.\textsuperscript{[20,21,28]} There was no significant statistical heterogeneity among the studies once the studies were subgrouped according to age (older group: Cochran Q = 2.15; $p = 0.34$; $I^2 = 6.9\%$, younger group: Cochran Q = 3.19; $p = 0.20$; $I^2 = 37.3\%$). The pooled OR of the older subgroup (OR 1.13; 95% CI 0.97, 1.31) was less than that of the younger subgroup (pooled OR 2.21; 95% CI 1.31, 3.73). Second, of the epidemiological studies that had participants across a wider age range, four have reported the age-stratified risk estimates for traffic accidents.\textsuperscript{[19,26,34,35]} Of these, three report lower risk in older groups than in younger groups,\textsuperscript{[19,26,35]} while one reported similar ORs in the young (<60 years) and the elderly (>60 years).\textsuperscript{[33]} One accident
responsibility study also report age-stratified risks, and found higher responsibility in young benzodiazepine users but not in their older counterparts.\textsuperscript{[31]}

2. Therapeutic use and dosing regimen

Anxiolytics are usually taken in single or multiple doses during the daytime; thus, it is possible that they increase accident risk irrespective of their short half-lives. Two cohort studies and one case-control study have categorized benzodiazepines as anxiolytics or hypnotics. All three showed increased risk with anxiolytics.\textsuperscript{[26,33,35]} Two cohort studies showed an increased risk in the groups using hypnotics,\textsuperscript{[33,35]} while the case-control study showed that, as a group, hypnotics did not significantly increase traffic accident risk.\textsuperscript{[26]} Hypnotics are taken at bedtime, and the following day adverse effects may depend on the duration of action of the individual drugs.

3. Half-life of drugs

Two studies have examined the effect of elimination half-life of benzodiazepines, one on the risk of traffic accidents on older (\textgreater{}65 years) adults\textsuperscript{[25]} and the other on accident responsibility.\textsuperscript{[31]} The first study categorized benzodiazepines into short (\textless{}24 hours) and long (>24 hours) elimination half-life drugs.\textsuperscript{[25]} Long but not short half-life drugs were associated with increased accident risk in the elderly. The second study categorized benzodiazepines into short (<6 hours, mainly midazolam), intermediate (6–12 hours) and long (>24 hours) elimination half-life drugs.\textsuperscript{[31]} New users of long and intermediate half-life benzodiazepines were at a significantly higher risk of accident responsibility, whilst those exposed to short half-life benzodiazepines showed no increased risk compared with controls.
Where individual drugs have been analysed, the accident risk is increased with the use of diazepam,\textsuperscript{[19,33,37]} even after 2–4 weeks into treatment, but not with oxazepam.\textsuperscript{[33]} Alprazolam was also more commonly detected in drivers responsible for an accident than in those who were not responsible.\textsuperscript{[31]} Although therapeutic use of each drug was not specified in the studies, these drugs are more often prescribed as anxiolytics.

Five studies report accident risks associated with several different benzodiazepine and non-benzodiazepine hypnotics. The long-acting benzodiazepines flunitrazepam,\textsuperscript{[18]} flurazepam\textsuperscript{[33]} and nitrazepam\textsuperscript{[18,37]} appear to increase the risk of traffic accidents. However, the medium half-life benzodiazepine hypnotics lorazepam\textsuperscript{[33]} and temazepam\textsuperscript{[37]} and the short-acting benzodiazepine triazolam\textsuperscript{[33]} were also found to increase the accident risk. No significant effect was observed with the very short-acting hypnotic midazolam.\textsuperscript{[31]} The short-acting non-benzodiazepine hypnotic zopiclone was examined in three studies. One case-control study showed a 4-fold increase in accident risk,\textsuperscript{[26]} while a large-scale cohort study reported a 2-fold increase in accident risk.\textsuperscript{[18]} The other study did not show a significant change in the accident risk with zopiclone.\textsuperscript{[37]} For the short-acting hypnotic zolpidem, the large-scale study reports a 2-fold increase in risk,\textsuperscript{[18]} while the other study reported no significant effect.\textsuperscript{[37]}

4. Duration of use

Five cohort studies have examined the traffic accident risk associated with benzodiazepine use during the first 1–4 weeks following prescription and all found an increased risk of traffic accidents.\textsuperscript{[18,33,35-37]} Two studies reported that the risk remained high with continuing use.\textsuperscript{[25,37]}

Chapter 3
5. Drug dose

Three epidemiological studies examined the dose-response relationship between benzodiazepines and traffic accidents. They showed that higher benzodiazepine doses are associated with greater accident risk\cite{26,32} and higher benzodiazepine concentrations in blood are associated with accident responsibility of drivers.\cite{4} The last study reported higher accident responsibility associated with therapeutic and supratherapeutic benzodiazepine concentrations but not with subtherapeutic concentrations.

Antidepressants

Antidepressants were examined in three case-control studies and three cohort studies. One study, where all antidepressants were considered as a single group, did not show a significant increase in traffic accident risk\cite{33} or accident responsibility.\cite{27} There were too few studies in each category with necessary data to perform a meta-analysis.

There is no clear distinction between sedative and non-sedative antidepressants in their association with traffic accidents in patient groups investigated in epidemiological studies. In younger populations, two studies show no significant increase in accident risk either with TCAs or selective serotonin reuptake inhibitors (SSRIs),\cite{26,37} while one reports an increased risk with both sedative and non-sedative antidepressants.\cite{36} However, in the elderly, the sedating antidepressants do appear to increase the traffic accident risk. Two epidemiological studies have studied antidepressants and accident risk in older drivers (>60 years). Both show that TCA use increased the risk,\cite{24,32} with one study demonstrating that the risk increases
with dose. However, these studies have not examined the effects of non-sedating antidepressants and thus there is insufficient data to make any evaluation of newer antidepressants.

**Opioids**

The risk of traffic accidents associated with prescription use of opioids has been examined in four cohort studies and one case-control study. Of the four cohort studies, two had overlap of data sources and one did not have adequate information to calculate risk. Therefore, a meta-analysis was not performed on epidemiological studies of opioids.

Therapeutic use of opioids (as a group) was associated with a higher risk of traffic accidents in young drivers. The effect on accidents in elderly drivers (>65 years) is inconsistent. Limited evidence suggests that codeine, dihydrocodeine and tramadol may be associated with increased accident risk at least during the first 4 weeks of use. In contrast to prescription-based studies, the detection of opioids in blood in drivers was associated neither with the accident risk nor accident culpability.

**Drug-alcohol interactions and drug interactions**

Drug-alcohol interactions are reported in three case-control studies. Benzodiazepine-alcohol combinations always showed a greater risk of traffic accidents and accident culpability. All three studies consisted of adult drivers over a wide age range, and determined benzodiazepine and alcohol exposure with
blood/urine sample analysis. In each study, the reported OR for benzodiazepine-alcohol combination was higher than that observed with either benzodiazepines or alcohol alone (table I). The three case-control studies were combined in a random-effects model meta-analysis (figure 5). The results show that benzodiazepines can increase the odds of traffic accidents by 7.7-fold (pooled OR 7.69; 95% CI 4.33, 13.65), suggesting a marked synergistic effect of alcohol-benzodiazepine combination on risk of traffic accidents. These studies do not specify the blood alcohol levels, but all three have included some participants with blood alcohol levels below the legal limits for driving.

One case-control study and one cohort study report combined effects of psychoactive drugs on traffic accidents, both in elderly drivers. In the case-control study, use of one drug was associated with a 30% increase in the accident risk, which further increased to 100% with the use of two or more drugs.\[24\] Similarly, the cohort study showed 110% increase in traffic accident risk if the driver is taking both benzodiazepines and TCAs.\[32\]
Figure 5. Meta-analysis of case-control studies on congestion of benzodiazepines and alcohol. $\chi^2$ = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; Cochran Q = test statistic for heterogeneity of studies; df = degrees of freedom; $I^2$ = percentage of variation of study estimate due to heterogeneity ($100\% \times [Q – df]/Q$).
Experimental studies: effects of benzodiazepines, antidepressants and opioids on driving performance

Appraisal of the methodology

Any methodological concerns specific to each study are noted against the respective studies in supplementary tables 1–3 (Supplemental Digital Content). Table III summarizes the different methodological approaches of the 69 experimental studies.

Experimental design

Of the 69 studies, 63 were double-blind, placebo-controlled studies, whereas six were of other designs. Of the 63 double-blind, placebo-controlled studies, 57 were within-subject crossover studies (where the same group of subjects were tested under different treatment conditions), thus ensuring maximum control over individual variations of driving performance. In many studies, attempts had been made to minimize systematic changes in performance across treatment conditions by providing adequate practice to participants and by randomizing treatment order. The participants were assigned into separate treatment or placebo groups in the other six double-blind, placebo-controlled studies (three randomized, three not specified).

Of the six experimental studies with other designs, the participants were patients in four studies.[40-43] Single groups of patients were tested before and after treatment in two of these studies, whereas a control group treated with an active drug was included in the other two. In the remaining two studies where healthy volunteers
were tested, one was a randomized, double-blind study in which lorazepam served as an ‘active-control’ drug,\[^{[7]}\] whilst the other one was a non-blind study.\[^{[44]}\]

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<th>Table III. Experimental study designs (both benzodiazepines and opioids were tested in one study. Some studies administered both actual and simulated driving tests)</th>
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Study samples

The participants in the majority of the studies were healthy volunteers. Although healthy volunteer studies examine the effect of a particular dose of a specific drug on driving performance, they cannot examine the interactive effects of the drugs and the conditions for which these sedative drugs are commonly prescribed (e.g. depression, insomnia, anxiety disorder, chronic pain) on driving. However, this ‘confounding by indication’ is accounted for in experimental studies that use patient groups experiencing insomnia,\[^{[5,45-50]}\] anxiety,\[^{[51-53]}\] depression\[^{[40,43]}\] and chronic pain.\[^{[42,54]}\]

Participants of almost all experimental studies were relatively young. Of the 69 studies, only four\[^{[55-58]}\] had elderly participants.

Pharmacological manipulation

Driving performance was tested after one or a few doses of drugs to examine the acute effects and/or after several days of administration to find out
subacute/subchronic effects. All drugs were orally administered (except one study where fentanyl was administered transdermally) in therapeutic doses. Adequate washout periods were ensured between treatment conditions in all crossover studies.

The driving impairment observed in drug-naive individuals with fixed, single/short-term dosing regimens of experimental studies does not portray the full spectrum of impairment that can occur in real-life situations. For instance, the effects of supratherapeutic doses (that might occur with deliberate self-poisoning) on driving may be much greater, whereas patients receiving long-term medication (especially benzodiazepines and opioids) show varying degrees of tolerance so that may not exhibit the same degree of impairment observed in drug-naive subjects in experimental studies.

Driving task and outcome measures

Forty-nine studies have carried out actual driving tests, while 21 have used driving manoeuvres performed in a driving simulator.

Actual car driving tests have a better ecological validity, but safety concerns in pharmacological experiments preclude testing actual driving in traffic. A standardized highway driving test developed by a research group in the Netherlands has been used in 31 experimental studies retrieved in the current review (see O’Hanlon[5] for technical details). The primary aim of the driving task is to maintain a constant lateral position and constant speed of 95 km/h. The main outcome measure, ‘SDLP’, indicates the degree of weaving of the vehicle from the intended path and, in turn, depends on steering control. A secondary outcome, ‘standard deviation of speed (SDS)’ is a measure of variability of speed and depends on accelerator control. The
driver sometimes has to interact with normal traffic (e.g. overtaking a slow vehicle); however, these segments are not included in calculating SDLP and SDS. Thus, the outcome measures do not directly reflect driving ability in normal traffic. Rather, the test examines the driver’s ability to operate the basic controls of the vehicle for stable highway driving at a constant speed.

Eight other actual driving experiments focus on more complex driving manoeuvres, albeit on a closed-course. These tasks include manoeuvring around bollards (slalom task), gap estimation, reversal and parking.[6,51,59-62] Brake reaction time was an outcome measure in seven studies on actual driving.[59,63-67] One limitation of these studies is that being closed-course tests, subjects may not have had the same safety concerns as in open-road driving.

Driving simulator tests offer a safe alternative to on-road driving. Some simulator studies have measured mean variance of lateral position and mean variance of speed which are comparable with SDLP and SDS, respectively. However, there are two main limitations in predicting actual driving performance based on simulated driving. First, the artificial quality of the driver-vehicle-environment interaction compromises the ecological validity of the tests. Although participants used at least some driving controls found in a real vehicle (i.e. steering, brake) in the tests, there is a wide variation of the nature of the driving scenes and the perceptual feedback generated by the vehicle. For instance, in the simplest simulator tests, subjects had to perform a continuous tracking task (with steering) and a secondary reaction time task (using a foot pedal) in response to relatively abstract visual stimuli,[10,68-70] whereas the most complex simulator tests employed more life-like driving scenarios and emulated the forces acting upon an actual moving vehicle.[44] Second, subjects
performing simulated driving tests may not consider the safety factor as much as those who undergo real driving tests, so that the driving errors in simulated driving tests may exaggerate the actual risk of driving errors in real-life driving.

Pooled estimates of SDLP for different doses of short- and long-acting benzodiazepines have been calculated in a recent meta-analysis.[39] The authors report nightly doses equivalent to ≤5 mg of diazepam significantly increase SDLP the following morning but not in the following afternoon. Doses equivalent to diazepam 10 mg or more caused a larger increase in SDLP. However, the strength of the experimental studies is the ability to assess the different doses of specific drugs on driving performance at different time intervals after dosing, whereas calculating pooled estimates across clinically heterogeneous studies may lead to loss of valuable information. In this respect, the patterns of impairment of SDLP observed with different benzodiazepine and non-benzodiazepine hypnotics[15,71,72] and antidepressants[16] have been reviewed recently by the original research group, comparing the impairment observed with drugs with what is observed with different blood alcohol levels (0.05, 0.08 and 0.1 g/dL). However, these reviews do not comprehensively review the effects of drugs on more complex driving skills, which are tested in other actual and simulated driving studies. Thus, the present review on experimental studies evaluates the effects of individual drugs on both actual and simulated driving tests.

**Benzodiazepines and 'Z drugs'**

All 49 studies that we retrieved administered benzodiazepines orally in therapeutic doses. The doses were generally equivalent to diazepam 10–20 mg in most studies.
Lower doses have been used in a few studies: diazepam 5–7 mg in two studies,\cite{44,73} nitrazepam 5 mg in one study\cite{60} and lorazepam 0.5 mg in one study.\cite{53} Two different dosing regimens that correspond to their therapeutic use have been applied by researchers in testing anxiolytics and hypnotics. The common design for anxiolytics was to test driving performance from half an hour to about 5 hours after dosing. Hypnotics were always administered at night (replicating their therapeutic use) and driving was tested in the following morning (9–10 hours after dosing) or afternoon (16–17 hours after dosing).

**Benzodiazepine anxiolytics**

The results obtained in our search include five anxiolytics, viz. diazepam, lorazepam, alprazolam, clobazam and medazepam. The latter two drugs are not widely used at present.

**Diazepam:** Diazepam was tested in 11 studies. Driving performance was assessed at different times post-dose, ranging from 30 minutes\cite{9} to 5 hours.\cite{68} Acute increase in SDLP\cite{73} and brake reaction time\cite{63} has been observed after a 10 mg dose in on-road driving tests. A single 5 mg dose did not cause a significant increase in SDLP in healthy volunteers,\cite{73} but did increase with three-times-daily dosing.\cite{53} The impairing effect of the latter dosing regimen was observed up to 7 days in healthy volunteers\cite{53} and up to 3 weeks in patients with anxiety.\cite{52} These observations suggest that even administered in low doses, repeated administration of long-acting benzodiazepine, like diazepam, may cause significant impairment. In driving simulator tests, 10–15 mg doses caused increased collisions,\cite{9} increased tracking errors and reaction times,\cite{68,70} and impairments in composite measures of overall
driving performance.[55,74] In the last study, driving impairment persisted even after 1 week of treatment. One driving simulator study did not show a significant effect after diazepam 0.11 mg/kg bodyweight (approximately 7 mg) or 0.22 mg/kg bodyweight (approximately 15 mg).[44] This is the only non-blind study (healthy volunteers knew what drug they had taken) included in this review. The authors argue that those who take sedative drugs in real-life know that the drugs may affect their driving performance and thus might take extra effort to compensate. However, there was a wide inter-subject variability in driving performance in this study probably attributable to the complex driving task and relatively short practice session; these factors may also account for the lack of significant effects of diazepam. In summary, the experimental studies indicate that diazepam can impair a wide range of task processes in driving, and the impairment appears to be significant even after 3 weeks of continuing treatment. These findings are consistent with the epidemiological evidence that showed increased accident risk in diazepam users.[19,33,37]

Lorazepam: Lorazepam was tested in five studies. SDLP was the outcome measure in three experiments and all showed a significant increase with lorazepam even after 1 week of treatment.[53,75] Of these, one study was on a group of patients with anxiety; the experimenters continued treatment for 2 weeks and found a significant impairment even at the end of this period.[53] Two closed-course studies show that the drug can cause increased brake reaction time and impairment of more complex driving manoeuvres, including parking, turning and avoiding obstacles.[7,59]

Alprazolam: The two studies involving alprazolam showed a 1 mg dose can severely impair highway driving performance as indexed by SDLP.[76,77] Sustained-release preparation of the drug caused less impairment but was still significant.[77]
Clobazam: No significant short-term impairment was detected in different driving manoeuvres after 3 days of treatment with 10 mg three times daily\cite{63} or after 20 mg in the morning.\cite{59} One other study detected impairment after 6 days of treatment.\cite{6}

Medazepam: The long-acting anxiolytic medazepam caused driving impairment in patients even after 3 weeks of treatment.\cite{51}

Benzodiazepine and newer hypnotics

The effect of nocturnal doses of hypnotics on driving in the following morning generally depends on the half-life; however, there are some exceptions. The long half-life (>24 hours) hypnotics include flurazepam, flunitrazepam and nitrazepam.

Flurazepam (half-life of active metabolite 40–250 hours): Flurazepam was tested in six driving performance studies and all report impairment with the drug. 1–2 days of treatment caused a significant increase in SDLP and SDS that lasts up to 10–11 hours after 30 mg dosing in healthy volunteers, and up to 16–17 hours in patients with insomnia after 15–30 mg.\cite{5,47} One study on patients showed the following morning’s impairment was persistent even after 1 week of continuing treatment.\cite{47} Another actual driving experiment found impaired manoeuvring skills in a slalom task 12 hours after a 15 mg dose.\cite{62} Driving simulator tests showed increased tracking error and brake reaction time and reduced speed of driving.\cite{10,78} These findings are consistent with the Neutel\cite{33} 1995 study where flurazepam was associated with a 5-fold increase in the risk of injurious traffic accidents.
**Flunitrazepam (half-life 18–26 hours, active metabolite 36–200 hours):** A single 2 mg dose of flunitrazepam did not affect the SDLP after 10 hours in a group of young patients with sleep disturbances in one study, but did cause a significant increase that lasted 16–17 hours after two doses in another study. This may be due to accumulation of this long half-life benzodiazepine. In line with these findings, another on-road driving study showed impaired steering control that persisted for more than 7 days after initiation of treatment in a group of patients with insomnia. Of the three driving simulator studies, one also reported increased lateral deviation and speed variation 10 hours after a 1 mg dose. These experimental findings corroborate a 3- to 4-fold increase in injurious traffic accident risk observed in a recent large-scale epidemiological study.

**Nitrazepam (half-life 15–38 hours):** Nitrazepam was tested in two studies. A 10 mg dose increased SDLP, which was observed 16–17 hours after a nocturnal dose in a group of young women with insomnia. This impairment persisted even after 8 days of continuing treatment. This evidence supports the epidemiological findings where nitrazepam was associated with 170% increase in traffic accidents in the first week of use. A lower dose (5 mg) caused increased brake reaction time in a driving simulator 9 hours after intake, but did not cause a significant increase in the number of errors in avoidance manoeuvres in a closed-course driving test.

Three other hypnotics (temazepam, loprazolam, lormetazepam) extracted in this review have intermediate plasma half-lives (8–24 hours).

**Temazepam (8–22 hours):** All five studies that tested the effects of temazepam used 20 mg nightly doses. SDLP was not significantly affected either in healthy elderly volunteers after a single dose or in young women with insomnia.
who received three consecutive doses\textsuperscript{[45]} the following morning (i.e. 10 hours after dosing). Two other driving studies reported that the drug did not impair manoeuvrability in healthy volunteers\textsuperscript{[62]} or steering control in young insomniacs\textsuperscript{[46]} 10–12 hours after a single dose or multiple doses. Interestingly, temazepam also did not affect lateral position, speed deviation or reaction time in a group of elderly volunteers, even when tested only 5.5 hours after a 2:00am dose.\textsuperscript{[49]} However, one cohort study shows that temazepam is associated with increased traffic accident risk during the first 4 weeks of use and, to a lesser extent, during an extended period of use.\textsuperscript{[37]}

\textit{Loprazolam (half life 6–12 hours):} The only study on loprazolam (1 and 2 mg) shows impairment in highway driving (as measured by SDLP) even 16–17 hours after two nightly doses in young patients with sleep disturbances.\textsuperscript{[5]} This study also showed strong correlation between driving impairment and plasma drug concentration. This long-lasting impairment more-closely resembles the pattern observed with long half-life hypnotics (e.g. flurazepam and flunitrazepam) rather than that observed with other intermediate half-life hypnotics (e.g. temazepam).

\textit{Lormetazepam (half-life 10–12 hours):} Effects of lormetazepam on driving was tested in five experimental studies. Lormetazepam 1 or 2 mg administered at night did not have significant acute or subchronic effects in the morning on SDLP in patients with insomnia.\textsuperscript{[47]} Healthy volunteers showed a significant impairment 10 hours after the first 2 days of administration but not 16 hours after the second dose.\textsuperscript{[69]} In driving simulation experiments, lorazepam 2 mg increased tracking errors and reaction time when tested at 1–5 hours,\textsuperscript{[68]} but did not have significant
acute\textsuperscript{10,69,81} or subchronic\textsuperscript{10} effects when tested the morning following a nightly dose.

Short-acting hypnotics that have been tested for the effects on driving include triazolam, midazolam, zopiclone, zolpidem, zaleplon and eszopiclone.

\textit{Trazolam (half-life 2–3 hours)}: One driving simulator study showed increased tracking errors up to 4.5 hours and delayed brake reaction time up to 1.5 hours after triazolam 0.25 mg\textsuperscript{70}, but no significant effects were observed on simulated driving when tested the morning following a 0.25 mg or 0.5 mg nightly doses\textsuperscript{60,78}. However, given that there is some evidence that triazolam may be associated with increased accident risk,\textsuperscript{33} it is worth investigating drug effects also with on-road driving tests.

\textit{Midazolam (half-life approximately 2 hours)}: The only study on midazolam did not show a significant impairment in brake reaction time 10 hours after midazolam 15 mg\textsuperscript{64}.

\textit{Zopiclone (half-life 5–6 hours)}: Effects of zopiclone have been tested in four standardized on-road driving studies and five driving simulator experiments. All studies used the standard treatment dose of 7.5 mg. Despite the short half-life of the drug, there is consistent evidence that SDLP increases 5 hours\textsuperscript{82} and 10 hours after a bedtime dose in healthy young volunteers,\textsuperscript{80,82,83} and 10 hours post-dose in elderly individuals\textsuperscript{57}. One driving simulator study also reported increased lateral position deviation 10 hours after dosing but not after 12 hours\textsuperscript{79}. Other driving simulator studies reported increased collisions after 9–11 hours\textsuperscript{50}, increased tracking errors after 1.5 hours\textsuperscript{70,84} and delayed brake reaction time after 1.5 and 4.5 hours\textsuperscript{70}. These findings parallel the markedly high traffic accident risk associated with zopiclone in
epidemiological studies.\textsuperscript{[18,26]} This is an unexpected trend given the short plasma half-life of zopiclone.

\textit{Zolpidem (half-life approximately 2 hours):} Two actual driving studies and one simulator study examined the effects of zolpidem 10 mg around 4–5.5 hours after middle of the night dosing. This dose increased SDLP and SDS in healthy volunteers in both actual driving studies\textsuperscript{[80,85]} and increased the variance of lateral position in patients with insomnia in the simulator study.\textsuperscript{[49]} Similarly, increased poor lateral position and speed control were reported at 2 hours but not 13 hours after a 10 mg dose in another driving simulator study.\textsuperscript{[86]} One actual driving study and two simulator studies showed that zolpidem 10 mg does not impair SDLP in young insomniacs,\textsuperscript{[48]} or mean lateral position variance in healthy elderly\textsuperscript{[79]} or young insomnia patients,\textsuperscript{[50]} when tested the following morning (i.e. 9–10 hours post-dose). The experimental evidence indicates that a 10 mg bedtime dose of zolpidem does not affect the basic control processes of driving the following morning but does impair if taken in the middle of the night. The largest cohort study conducted so far reports a 2-fold increase in traffic accident risk in young zolpidem users during the first 4 weeks of use,\textsuperscript{[18]} while another did not find a significant increase in the risk.\textsuperscript{[37]} However, the exposure was based on prescription records, so that neither of the two studies is able to provide information on actual time of administration of the hypnotic. There is also a theoretical possibility that even if the basic control processes of driving are intact the morning following a bedtime dose (as has been observed in the experimental studies), more complex driving skills required for accident avoidance may still be impaired.
Zaleplon (half-life 1 hour): Effects of zaleplon have been examined in only three on-road driving studies. They showed that SDLP or SDS in healthy young individuals are not affected by a 10 or 20 mg dose when tested 10 hours (i.e. the morning after a bedtime dose)\[83,85\] or 4–5 hours after dose administration\[82,85\] (i.e. the middle of the night dose).

Eszopiclone (half-life 6 hours): According to the two driving experiments conducted so far, eszopiclone 3 mg did not affect the brake reaction time in either healthy young or elderly individuals, when tested 9–19.5 hours post-dose.\[67\]

Antidepressants

Antidepressants have been used in therapeutic doses in almost all studies. Driving performance has been tested 1–5 hours after dosing, except in five studies\[^{43,87-90}\] where drugs were administered at night and driving was tested the following morning.

The effect of antidepressants on automobile driving seems to be determined mainly by the sedative effect profile, and probably also by the anticholinergic effects of the drugs.

Sedating antidepressants

Amitriptyline: Effects of amitriptyline have been examined in four actual driving experiments and four simulated driving tests. Three showed acute increase in SDLP after 25 mg\[^{5,89}\] and 75 mg.\[^{91}\] A comparable driving simulator experiment found increased SDLP and headway variability 4 hours after amitriptyline 25 mg,\[^{92}\] with a moderate positive correlation between plasma amitriptyline concentration and
Only one study tested driving the morning following a nocturnal dose. The investigators found increased SDLP even 13 hours after a 25 mg nocturnal dose in patients with neuropathic pain. The other four studies reported impaired tracking/steering control and brake reaction time 2–5 hours after a 50 mg dose.

**Other tricyclic and related antidepressants:** All studies where healthy adult volunteers were administered sedative antidepressants in multiple daily doses reported increased SDLP. Acute (1–4 hours post-dose) impairment of SDLP has been reported with imipramine 50 mg twice daily, doxepin 25 mg three times daily, and mianserin 10 mg three times daily. Three studies on the effects of nocturnal doses showed that SDLP was increased the following day (13–17 hours post-dose) with mirtazepine 15 mg and 30 mg, but not after dothiepin 75 mg or mianserin 30 mg. The only experimental study on elderly participants showed no acute effects (2 hours post-dose) of imipramine 50 mg on SDLP, although a significant increase was observed in their younger counterparts.

**Effects of continuing treatment:** Post-dose impairment in SDLP remained significant even after 1–2 weeks of treatment with mianserin, but not with imipramine, doxepin, mirtazepine or amitriptyline. Only three studies examined the subchronic effects of sedative antidepressants on driving in patient groups. One study of chronic pain patients showed that the impairing effects (as indexed by increased SDLP) of amitriptyline disappear after 15 days of continuing treatment. The other two driving simulator studies on depressed patients showed improvement of performance after 2–4 weeks of treatment with mirtazepine.
latter study also found that performance did not improve in an untreated control group.[43]

Non-sedating antidepressants

In contrast to tricyclic and other sedating antidepressants, newer non-sedating antidepressants do not appear to have acute or subacute effects on driving when tested with standardized highway driving tests or driving simulation tests. Absence of any significant acute or subchronic effects on SDLP or speed variability in healthy volunteers has been demonstrated with the SSRIs paroxetine (10 mg),[92] fluoxetine (20 mg)[87] and escitalopram (10–20 mg),[88] the serotonin-noradrenaline reuptake inhibitor venlafaxine (37.5–75 mg twice daily)[97] and the monoamine oxidase inhibitor moclobemide (200 mg twice daily).[96] The only study on depressed patients reports that driving performance (as tested on a simulator) improves after 2-weeks of treatment with the non-sedating antidepressant reboxetine, as well as with the sedative antidepressant mianserin.[40]

Opioids

Only three experimental studies examined the effects of opioids on driving (supplementary table 3, Supplemental Digital Content). One study on healthy volunteers showed increased collisions in a driving simulator task after a single 50 mg dose of codeine,[9] while the other showed no significant acute effects of an oxycodone-paracetamol combined preparation (5 mg/325 mg and 10 mg/650 mg) on SDLP or SDS.[98] However, in the latter study, a dose-response relationship was observed and subjective reporting indicated that the participants had to apply more
effort in driving compared with control conditions. The only study on patients with chronic pain was a pre-test, post-test design where driving performance was tested before and 2 months after initiation of a transdermal fentanyl treatment.\textsuperscript{[42]} There was no significant change in performance as assessed with a driving simulator test.

**Drug-alcohol interactions and drug-drug interactions**

A limited number of experimental studies compared the effects of drugs alone with drug-alcohol combinations on driving skills. The addition of alcohol was found to worsen the acute impairment caused by lormetazepam,\textsuperscript{[68]} flurazepam,\textsuperscript{[78]} triazolam\textsuperscript{[70]} and amitriptyline.\textsuperscript{[94]}

One study reports the interactive effects of diazepam with amitriptyline and with mirtazepine. Severity of tracking error was greater with diazepam-antidepressant combinations than with any of the drugs alone.\textsuperscript{[70]}

**DISCUSSION**

The present paper reviews the research evidence on the effects of three different classes of sedative drugs (benzodiazepines, antidepressants and opioids) on driving performance, and their association with traffic accidents, taking into account different drug and patient factors that modify these effects in a practical context.

Our meta-analyses of case-control and cohort studies indicate that benzodiazepines, as a group, are associated with a 60–80% increase in the risk of traffic accidents. Meta-analysis of case-control studies on accident culpability shows that drivers responsible for traffic accidents are 40% more likely to be positive for
benzodiazepines than those who are not responsible, suggesting that benzodiazepines actually may play a causative role in traffic accidents.

Deleterious effects of benzodiazepines are potentiated by co-ingestion of other sedative substances. The present review shows that the presence of alcohol and benzodiazepines was associated with 7.7-fold increase in the risk of traffic accident. Evidence from experimental studies supports this assertion. Benzodiazepines also interact with sedative antidepressants to impair driving skills and increase the risk of accidents. Although drug warning labels and consumer sites generally warn about the increased sedative effects of drug-alcohol combinations, they do not specify the effects on driving. We believe that drug information sheets/warning labels should specify this interactive effect on driving, and prescribers should warn patients that the benzodiazepine-alcohol combination may markedly increase the risk of accidents even if the blood alcohol levels are below the legal limit (generally 0.5–0.8 g/dL in most countries).

Epidemiological studies also suggest that benzodiazepine-associated traffic accident risk is less in elderly drivers than in younger adults. Low benzodiazepine-associated accident risk in elderly drivers may occur for a variety reasons. Elderly individuals tend to be prescribed with lower doses of benzodiazepines compared with their younger counterparts. Perhaps elderly drivers taking benzodiazepines may appreciate the potential deleterious effects of drugs more and resort to safer driving patterns or limit driving while they are taking drugs. Epidemiological studies, however, do not provide information of drug doses or driving patterns and thus fail to support or refute any of the above speculations. Only a few driving experiments have been carried out in the elderly; they do not make a clear distinction between
drug effects on the young and the elderly. Although driving experiments in elderly drivers who have been given sedative drugs may have safety and ethical concerns, further research in this group is necessary because increased life-expectancy and independence has increased the proportion of elderly drivers in the community, and many elderly patients take benzodiazepine hypnotics.

General patterns emerging from epidemiological and experimental studies also indicate that anxiolytics, taken in single or multiple doses during the daytime, tend to impair driving somewhat independently of their half-lives. As for hypnotics, the accident risk and the possibility of daytime driving impairment tend to be related to their plasma half-lives, but with exceptions.

Results of the experimental studies suggest that diazepam, flurazepam, flunitrazepam, nitrazepam and the short-half-life non-benzodiazepine hypnotic zopiclone may cause significant driving impairment, and the findings of epidemiological studies show that use of these same drugs are associated with a significant increase in traffic accident risk. The accident risk remains elevated, at least during the first 2–4 weeks after commencement of treatment, and nocturnal doses cause impaired driving performance, at least leading up until the following afternoon in the case of benzodiazepine hypnotics and the following morning in the case of zopiclone. Diazepam is the most extensively studied benzodiazepine. Even though widely prescribed, there is strong evidence that diazepam worsens driving performance and is associated with increased accident risk, at least for the first 3–4 weeks after commencement of anxiolytic treatment. Impairing effects of the above sedative drugs raise important, but controversial legal implications. The 2- to 3-fold increase in accident risk associated with these long-acting benzodiazepines and
zopiclone is equivalent to what has been observed with a blood alcohol concentration of 0.05–0.08 g/dL,\[99,100]\ which is above the legal limits for driving in most countries. A series of on-road driving studies also illustrate that SDLP observed with therapeutic doses of the hypnotics is above these legal limits for alcohol.\[14]\ For hypnotic medication, an option for prescribers is to avoid these hypnotics (flurazepam, flunitrazepam, nitrazepam and zopiclone) if patients are engaged in driving. Relatively safer alternatives would be shorter acting hypnotics, such as triazolam, temazepam, zolpidem and zaleplon, which were not found to cause driving impairment, at least in experimental studies (although there is evidence that some of the drugs are associated with increased accident risk). Still, patients should be cautioned against the possible effects on driving and the course of hypnotic treatment should be continued only for the minimum required period. We believe, in the present clinical context, patients with anxiety who are prescribed diazepam should be strongly encouraged not to drive, at least during the first 4 weeks of treatment. However, unlike hypnotics, the research evidence does not readily offer safer alternatives for prescribers; all other anxiolytics, with daytime dosing, were found to impair driving, at least in healthy volunteers. Large-scale epidemiological studies and experimental studies on patient groups are imperative to examine the safety of other anxiolytics.

There is no clear distinction between sedative and non-sedative antidepressants in their association with traffic accidents in epidemiological studies, particularly in young patients using antidepressants.\[26,36,37]\ Presumably, one major source of confounding in patient studies is the condition to which the drugs are prescribed (i.e. depression). Antidepressants interact differently with depression at
different stages of treatment to influence driving ability. To begin with, cognitive and psychomotor deficits of depression itself may limit driving capacity of an individual. Because the antidepressants do not bring therapeutic effects immediately after commencement of treatment, depressed patients may show driving impairment during the first 1–2 weeks of treatment, even if their antidepressants are non-sedative. Patients taking sedative antidepressants may be affected more than those on non-sedating antidepressants during this initial stage because of the acute sedative effects of the drugs, as has been observed in healthy volunteers in experimental studies. Continuing treatment beyond 3–4 weeks tends to improve depression, and patients tend to become tolerant to sedative effects, depression begins to be alleviated and patients may develop tolerance to sedative effects of sedating antidepressants. This is supported by limited experimental evidence that showed that young patient groups treated with sedative or non-sedative antidepressants improved their driving skills after a few weeks\(^\text{[40,43,89]}\) while untreated patients did not.\(^\text{[43]}\) In general, epidemiological studies have failed to eliminate residual confounding effects of depression because they have basically compared those who use antidepressants (i.e. depressed patients) with those who did not (most likely non-depressed individuals). Case-crossover\(^\text{[26]}\) and self-controlled case-series\(^\text{[37]}\) studies have attempted to overcome this methodological constraint by employing within subject designs, thus controlling for depression, at least to some extent.

Limited evidence suggests that TCAs may be associated with an increased traffic accident risk in the elderly. Experimental evidence is very scarce on this group and hence it is impossible to confirm whether this is due to differential effects of antidepressants, depression or a complex interaction between the two.
Few epidemiological studies conducted so far suggest that opioid users (at least in young drivers) may be at greater risk of traffic accidents in the first few weeks of treatment; however, scarce experimental data do not provide conclusive evidence on whether opioids impair driving in patients receiving treatment. As with antidepressants, the interactive effect of opioids, and underlying conditions such as chronic pain, on driving performance is also not clear.

Apart from the biases and limitations of the individual studies, there are certain limitations of the present review. We could not include certain epidemiological studies\(^\text{[26,30,37]}\) in the meta-analyses as they did not contain the necessary information required to calculate risk estimates that are compatible with the majority of the studies. Although the magnitudes of the risk estimates of these studies were different from the pooled estimates, the direction of the association was the same. It has to be acknowledged that even the best efforts of combining epidemiological and experimental evidence failed to establish a complete causative pathway between psychoactive drugs and traffic accidents. In other words, epidemiological studies showed that some of these drugs are associated with (but not necessarily cause) an increased risk of traffic accidents. Driving performance studies showed that those drugs caused an impairment of driving, but this does not necessarily mean that the impairment is practically significant enough to increase the risk of accidents. As a compromise, some researchers have calibrated driving performance measures (e.g. degree of weaving of vehicle as indexed by SDLP) against different levels of exposure to substances already known to increase accident risk (e.g. different blood levels of alcohol).\(^\text{[5]}\) Future research can further narrow this gap in the path of causation by correlating the performance measures (e.g. SDLP) directly with the risk
of accidents of the same subjects (e.g. number of traffic accidents the test subjects encounter during a certain fixed time period before and after SDLP measurement). In fact, a similar approach had been used recently to validate trail-making test B performance (which is a neuropsychological measure of visual scanning, visuomotor coordination, divided attention and executive functions) as a predictor of motor vehicle crash risk.[101]

CONCLUSIONS

Although there are inherent limitations in pharmacoepidemiological and experimental study designs in detecting the effects of sedative drugs on driving and traffic safety, a clearer picture emerges in combining the findings of the two different types of studies. The results show that benzodiazepine use is associated with a significant increase in the risk of traffic accidents and accident responsibility of drivers. The accident risk is markedly increased by co-ingestion of alcohol. Driving impairment was generally related to plasma half-lives of hypnotics, but with notable exceptions. Anxiolytics, with daytime dosing, impaired driving independent of their half-lives. We believe that these findings will help in formulating more specific clinical guidelines and precautions in the use of benzodiazepines.

Limited epidemiological evidence suggests that TCAs may be associated with increased accident risk, at least in the elderly. Experimental studies also indicate that sedative, but not non-sedative antidepressants impair driving performance at the initiation of treatment. However, long-term experimental studies with regular follow-up are necessary to elucidate how antidepressants and their complex interaction with depression affect driving performance over the course of treatment in depressed
patients. Opioid users may be at a higher risk of traffic accidents; however, experimental evidence on their effects on driving is scarce.

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performance in young, healthy volunteers. Hum Psychopharmacol 1998; 13 Suppl. 2: S87-97


Supplementary data
Available through http://adisonline.com/drugsafety/toc/2011/34020

**Supplementary table 1:** Benzodiazepines and driving performance: experimental studies (All treatments are single oral doses unless specified otherwise. **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>
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<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>
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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)</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>Hindmarch 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>
<td>No. of errors and time taken for gap estimation, reverse parking, garage parking, manoeuvring ability</td>
<td>Reverse parking delayed with clobazam. No other changes.</td>
<td>Acute effect not examined. Negative effects on day 7 may be due to absence of drug effect or to tolerance.</td>
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<td>Author(s)</td>
<td>Design</td>
<td>Sample Description</td>
<td>Intervention Levels</td>
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<td>Biehl, 1979</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>24 male students (18-24y) with high neuroticism score</td>
<td>Clobazam 20mg</td>
<td>Driving in traffic</td>
<td>29 variables of driving performance: Observer-rated items and objective measurements</td>
<td>Break reaction time delayed with diazepam compared to clobazam. No other differences.</td>
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<td>Diazepam 10mg</td>
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<td>Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.</td>
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<td>Placebo morning for 3 days</td>
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<td>Hindmarch and Gudgeon, 1980</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>12 female volunteers (26-40y)</td>
<td>Clobazam 10mg</td>
<td>Multiple car driving manoeuvres</td>
<td>Reverse parking, three point turn, slalom about fixed bollards, width estimation, BRT</td>
<td>Poor performance in parking, three-point turn, slalom and braking after lorazepam compared to clobazam and placebo. No difference in any measures between clobazam and placebo.</td>
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<td>Placebo t.i.d. x 3 days + 1 dose in morning of 4th day</td>
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<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>Driving performance measured according to a checklist by a trained observer</td>
<td>Poor performance in patients taking diazepam</td>
<td>Temporal relationship between diazepam dosing and testing not specified. Medical conditions of the control group not mentioned.</td>
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<td>Bets and Birtle, 1982</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>12 healthy volunteers, all women</td>
<td>Flurazepam 15mg</td>
<td>Actual driving test</td>
<td>manoeuvring ability, gap-acceptance</td>
<td>Poor manoeuvring skills with flurazepam. More hits on sides in passable gaps after both drugs.</td>
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<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</td>
<td>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</td>
<td>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>
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<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</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP</td>
<td>Increased SDLP after 10mg diazepam than in other conditions.</td>
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<td>Hindmarch and Subhan, 1983</td>
<td>Double-blind, placebo-controlled, 4-way crossover</td>
<td>7 healthy female volunteers (25-40y)</td>
<td>Placebo: Midazolam 15mg Alcohol 0.5g/kg Midazolam 15mg + alcohol</td>
<td>10h (i.e. following morning)</td>
<td>Actual driving test</td>
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<td>BRT</td>
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<td>No impairment with midazolam, alcohol or midazolam alcohol combination.</td>
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<tr>
<td>O'Hanlon, 1984</td>
<td>Double-blind, placebo-controlled, 4-way crossover</td>
<td>24 former hypnotic drug users, females aged 25-40y</td>
<td>Flurazepam 30mg Flurazepam 15mg Secobarbitalone 200mg Placebo 2 nights at 10pm</td>
<td>10-11h &amp; 16-17h after 2nd dose</td>
<td>Standardised highway driving test (~100km)</td>
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<td>SDLP</td>
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<td>Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h).</td>
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<tr>
<td>O'Hanlon, 1984</td>
<td>Double-blind, placebo-controlled, 4-way crossover</td>
<td>16 former hypnotic drug users, females aged 25-40y</td>
<td>Loprazolam 2mg Loprazolam 1mg Flunitrazepam 2mg Placebo On 2 nights at 10pm</td>
<td>10-11h &amp; 16-17h following 2nd dose</td>
<td>Standardised highway driving test (~100km)</td>
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<td>Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h).</td>
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<td>Degree of impairment increases with plasma loprazolam concentration</td>
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<tr>
<td>Willumeit et al., 1984a</td>
<td>Double-blind, placebo-controlled, 3-way crossover</td>
<td>12 healthy volunteers (11 men, 1 woman. 21-30y)</td>
<td>Lormetazepam 2mg Flurazepam 30mg Placebo At 10pm daily for 7 days.</td>
<td>Morning after last dose</td>
<td>Driving simulator test (30 min) Correct tracking executions with steering, Reaction time</td>
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<td></td>
<td>Flurazepam: less correct tracking executions and prolonged reaction time compared to placebo</td>
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<td>Lormetazepam: no difference from placebo</td>
</tr>
<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 or without alcohol 0.6g/kg.</td>
<td>1h, 3h, 5h</td>
<td>Driving simulator test (30 min) Correct tracking executions with steering, Reaction time</td>
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<td></td>
<td>Lormetazepam: impaired correct tracking executions and delayed reaction time, both with and without alcohol. Drug effects potentiated by alcohol Diazepam: impaired correct tracking executions only at 1h postdose. Delayed reaction time throughout. No potentiation of alcohol effects</td>
</tr>
<tr>
<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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<td>Driving simulator: BRT Actual driving: Number of mistakes in an avoidance manoeuvre</td>
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<td>No significant differences except delayed BRT with nitrazepam on day-2 morning.</td>
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<tr>
<td>O'Hanlon and Volkerts, 1986</td>
<td>Double-blind, placebo-controlled 2-way crossover study</td>
<td>11 insomniacs, women, 26-38y</td>
<td>Placebo 2 days &gt; Temazepam 20mg or Nitrazepam 10mg x 8 days &gt; placebo 3 days (dosing at 10pm)</td>
<td>10h &amp; 16h after day 2, 4, 6, 9, 11, 13 dose</td>
<td>Standardised highway driving test (~100km)</td>
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<td>SDLP</td>
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<td>Temazepam: Minimum or no impairment at 10h (morning). No impairment in afternoon (16h). Nitrazepam: Significant impairment with repeated doses. Worse in the afternoon.</td>
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<tr>
<td>Author(s) 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>
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<tr>
<td>Brookhuis et al., 1990</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>16 patients with insomnia (6 males, 10 females, 26-41y)</td>
<td>Placebo x 2 nights &gt; Lormetazepam 1mg or lormetazepam 2mg or flurazepam 30mg x 8 nights &gt; Placebo x 3 nights</td>
<td>10h &amp; 16h after 2 placebo doses (baseline), 2, 4 &amp; 7 active drug doses and 1 &amp; 3 resumed-placebo doses</td>
<td>Standardised highway driving test (72km)</td>
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<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 No drug</td>
<td>Not specified</td>
<td>Standardised driving tasks in a driving simulator</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>
</tr>
<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>
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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>
<td>Standardised highway driving test (100km) &amp; Model TS2 driving simulator test</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Treatments</td>
<td>Before, and after</td>
<td>Type</td>
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<tr>
<td>Kuitunen, 1994</td>
<td>Double-blind placebo-controlled</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>
</tr>
<tr>
<td>Kuitunen, 1994</td>
<td>Double-blind placebo-controlled</td>
<td>12 healthy volunteers</td>
<td>Zopiclone 7.5 mg, Triazolam 0.25mg, Placebo, Alcohol 0.5 g/kg, Zopiclone / triazolam + alcohol</td>
<td>Before, and after 1.5h &amp; 4.5h</td>
<td>Driving simulator test</td>
</tr>
<tr>
<td>Mattila et al., 1994</td>
<td>Double-blind placebo-controlled</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>
</tr>
<tr>
<td>O'Hanlon et al., 1995</td>
<td>Double-blind placebo-controlled</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</td>
<td>Standardised highway driving test (~100km)</td>
</tr>
<tr>
<td>O'Hanlon et al., 1995</td>
<td>Double-blind placebo-controlled</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</td>
<td>Standardised highway driving test (~100km)</td>
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<tr>
<td>O'Hanlon et al., 1995</td>
<td>Randomised double-blind placebo controlled</td>
<td>24 men and 36 women with anxiety (24-64y) in 3 groups</td>
<td>Lorazepam 2mg (n=18), Alpidem 5mg (n=19), Placebo (n=19), b.i.d. run-in, treatment and washout periods, 7, 8 &amp; 6 days respectively</td>
<td>Day 1 before run-in, Day 8 &amp; 15, 3-4h after morning dose</td>
<td>Standardised highway driving test (~100km)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Interventions</td>
<td>Test</td>
<td>Metrics</td>
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<tr>
<td><strong>Vermeeren et al., 1995</strong></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)</td>
<td>SDLP</td>
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<tr>
<td><strong>Vermeeren et al., 1998b</strong></td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>23 healthy women (24-45y)</td>
<td>Chlorpheniramine 8mg / 12mg noce &gt; terfenadine 60 mg mane Flurazepam 30mg night &gt; placebo morning Placebo mighte &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><strong>Vermeeren et al., 1998a</strong></td>
<td>Double-blind placebo controlled 7-way crossover</td>
<td>28 healthy volunteers (14 men, 14 women. 23-40y)</td>
<td>Zaleplon 10/20mg &gt;placebo Placebo &gt; zaleplon 10/20mg Zopiclone 7.5mg &gt; placebo Placebo &gt; zopiclone 7.5mg Placebo &gt; placebo Bedtime &gt; 5h later</td>
<td>5h after 2nd dose</td>
<td>Standardised highway driving test (~100km)</td>
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<tr>
<td><strong>(Bocca et al., 1999)</strong></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>
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<td><strong>Mercier-Guyon et al., 1999</strong></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</td>
<td>~15-min drive in 900m circuit with different driving manoeuvres</td>
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<td><strong>Vanakoski et al., 2000</strong></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>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Measures</td>
<td>Results</td>
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<td>Van Laar et al., 2001</td>
<td>Double-blind placebo</td>
<td>18 healthy male volunteers (25-36y)</td>
<td>Lorazepam 1.5mg; Ritalserine 5mg; Placebo b.d. X 7 days</td>
<td>3h after last dose; Standardised highway driving test (~100km)</td>
<td>Significant increase in SDLP with lorazepam. No effect on SDS by any of the drugs.</td>
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<tr>
<td>Verster et al., 2002a</td>
<td>Double-blind placebo</td>
<td>30 healthy volunteers (15 men, 15 women). Age (SD): 24.0±2.4y</td>
<td>Zaleplon 10mg or 20mg; Zolpidem 10mg or 20mg; Placebo Middle of the night</td>
<td>4h; Standardised highway driving test (~100km)</td>
<td>Zolpidem: SDLP and SDS significantly increased with both doses. Significant dose-response relationship. Zaleplon: No significant difference from placebo.</td>
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<td>Vermeiren et al., 2002</td>
<td>Double-blind placebo</td>
<td>30 healthy volunteers (15 men, 15 women, 21-45y)</td>
<td>Zopiclone 7.5mg; Zaleplon 10mg; Placebo</td>
<td>10h; Standardised highway driving test (~100km)</td>
<td>Zopiclone: Significantly increased compared to zolpidol and placebo Zaleplon: No difference from placebo</td>
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<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>Lorometazepam 1mg Placebo X 3 nights</td>
<td>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>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; Standardised highway driving test (~100km)</td>
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<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</td>
<td>Baseline and 5.5h after each dose; Driving simulator test (110km)</td>
<td>Lateral position deviation Speed deviation Reaction time Time to collision</td>
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<tr>
<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>Zopiclone (10 mg); Lorometazipam (1 mg); Placebo x 7 nights at 10:30pm</td>
<td>9-11h (7:30am - 9:30am), on day 2 &amp; day 8; Simulated driving in light traffic (~ 60 min)</td>
<td>Lateral position deviation Speed deviation Reaction time Number of collisions</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Design</td>
<td>Participants</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>Control 1</td>
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<tr>
<td>Leufkens et al., 2007</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>18 healthy volunteers (9 men, 9 women. 20-45y)</td>
<td>Alprazolam slow release (XR) 1mg Alprazolam immediate release (IR) 1mg Placebo</td>
<td>4h Standardised highway driving test (~100km)</td>
<td>SDLP SDS</td>
</tr>
<tr>
<td>Boyle et al., 2008</td>
<td>Randomised double-blind placebo-controlled 2-way crossover</td>
<td>32 healthy volunteers (17 men and women. 19-47y)</td>
<td>Eszopiclone 3mg Placebo</td>
<td>Before and 9.00-10.25h after dosing Closed-circuit driving</td>
<td>BRT</td>
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<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</td>
<td>Before and 9.00-10.25h after dosing Closed-circuit driving</td>
<td>BRT</td>
</tr>
<tr>
<td>Otmani et al., 2008</td>
<td>Randomised double-blind placebo-controlled 4-way crossover</td>
<td>16 healthy volunteers (12 men and 4 females. 45-55y)</td>
<td>Prolonged-release melatonin 2mg Zolpidem 10mg Both drugs Placebo</td>
<td>2h &amp; 13h Driving simulator test (60min, light traffic)</td>
<td>Number of collisions, standard deviation from the speed limit, standard deviation of absolute speed, standard deviation from ideal route</td>
</tr>
<tr>
<td>Leufkens et al., 2009</td>
<td>Double-blind placebo-controlled 5-way crossover</td>
<td>25 healthy volunteers (13 men, 12 women. Age (SD): 31.4±7.5y)</td>
<td>Gaboxadol 15mg &gt; placebo Zopiclone 7.5mg &gt; placebo Placebo &gt; gaboxadol 15mg Placebo &gt; zolpidem 10mg Placebo &gt; placebo 11pm &gt; 4am</td>
<td>9am (10h after night dose, 5h after early morning dose) Standardised highway driving test (~100km)</td>
<td>SDLP SDS</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 Standardised highway driving test (~100km)</td>
<td>SDLP SDS</td>
</tr>
<tr>
<td>Meskali et al., 2009</td>
<td>Double-blind placebo-controlled 3-way crossover</td>
<td>16 healthy elderly volunteers (8 women, 8 men. 55-65y)</td>
<td>Flunitrazepam 1mg Zopiclone 10mg Zopiclone 7.5mg Placebo 11pm</td>
<td>10h Driving simulator test (urban route with accident scenarios)</td>
<td>Number of collisions (of 5 accident scenarios per treatment)</td>
</tr>
</tbody>
</table>
**Supplementary table 2:** Antidepressants and driving performance: experimental studies (All treatments are single oral doses unless specified otherwise. **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 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</th>
</tr>
</thead>
<tbody>
<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): 22.1(1.2)y</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</td>
<td>Driving simulator test</td>
<td>Steering control (Proportion of steering errors to total correct responses)</td>
<td>Before alcohol: No group differences. After alcohol: no change in double placebo group, but increased in amitriptyline groups. Worst in double amitriptyline group.</td>
<td>Placebo only group did not show any impairment after alcohol despite having a BAC of 0.08% which can impair driving.</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>
<td>Weaving task: Imipramine increased the number of errors, when results collapsed across all testing days. No acute effect after a single dose. Gap estimation: No group difference</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></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>
<td>Increased SDLP following amitriptyline, doxepin and mianserin. 1/3 of subjects on amitriptyline could not complete the test.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Doses</td>
<td>Procedure</td>
<td>Outcome Measures</td>
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<tr>
<td>Hindmarch 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</td>
<td>Same day, time not specified</td>
<td>Tracking task in a driving simulator</td>
<td>Increased deviation (poor performance) after amitriptyline. No impairment after other drugs.</td>
<td></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>15 mg of diazepam, 50 mg of amitriptyline, 15 mg of mirtazapine</td>
<td>Before, and after 1.5h &amp; 4.5h</td>
<td>Driving simulator test</td>
<td>Tracking errors RT</td>
<td></td>
<td></td>
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<tr>
<td>Ramaekers et al., 1994</td>
<td>Double-blind placebo controlled 3-way crossover</td>
<td>18 healthy volunteers (9 men, 9 women. 26-54y)</td>
<td>Moclobemide 200 mg b.i.d., Mianserin 10 mg t.i.d., Placebo</td>
<td>2.5h after 3rd daily dose on day 1 and day 8</td>
<td>Standardised highway driving test (~100km)</td>
<td>Increased SDLP after mianserin on both days. No change with moclobemide.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramaekers et al., 1994</td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>16 healthy volunteers (8 men, 8 women. 23-40y)</td>
<td>Brofaromine 50mg b.i.d., Brofaromine 75mg b.i.d., Doxepin 25 mg t.i.d., Placebo</td>
<td>3h after 3rd daily dose on day 1 and day 8</td>
<td>Standardised highway driving test (~100km)</td>
<td>Increased SDLP after doxepin on day 1 but not on day 8. No change with brofaromine.</td>
<td></td>
<td></td>
</tr>
<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 8 days + 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>
<td>No significant effects of either drug on SDLP or headway variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robbe and O’Hanlon, 1995</td>
<td>Double-blind placebo-controlled 4-way crossover</td>
<td>16 healthy male volunteers (21-28y)</td>
<td>Paroxetine 20mg morning, Paroxetine 40mg morning, Amitriptyline 50mg &amp; 25mg morning Placebo</td>
<td>1.5h &amp; 5h after morning dose on day 1 &amp; 8</td>
<td>Standardised highway driving test (~100km)</td>
<td>Day 1: Impaired with amitriptyline both 1.5h &amp; 5h postdose. No impairment with paroxetine. Day 8: Not impaired by any of the treatments.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Laar et al., 1995</td>
<td>Double-blind placebo controlled 4-way crossover</td>
<td>12 healthy adults (24-38y) &amp; 12 elderly (60-72y). 6 men, 6 women each.</td>
<td>Nefazodone 100mg, Nefazodone 200 mg, Imipramine 50 mg Placebo</td>
<td>2.25h after morning dose on day 1 &amp; day 7</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP: No significant effect by drugs. Effect of TCA imipramine is in contrast to those observed in epidemiological studies.</td>
<td></td>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Treatments</th>
<th>Testing Events</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<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 8 days Mianserin 30mg x 7 days &gt; 60mg x 8 days 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>
<td>SDLP Significant, but minor increase in day 2 &amp;16 with mirtazapine. Marginally increased in day 8 with mianserin.</td>
</tr>
<tr>
<td>O’Hanlon et al., 1998</td>
<td>Randomized, double-blind, placebo-controlled, 4-way crossover</td>
<td>37 healthy volunteers (22-40y) enrolled, 22 completed</td>
<td>Venlafaxine 37.5 mg b.i.d. x 14 days Venlafaxine 37.5 mg b.i.d. x 7 days &gt; 75 mg b.i.d. x 7 days Mianserin 10 mg t.i.d. x 7 days &gt; 20 mg t.i.d. x 7 days Placebo t.i.d. x 14 days</td>
<td>2h postdose on day 1, 7, 8 &amp; 15</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP SDS 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.</td>
</tr>
<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 Mianserin delayed BRT significantly longer than other three conditions. Tianeptine 37.5mg causes a marginal delay. No effect by tianeptine 12.5mg.</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 1 day</td>
<td>2h</td>
<td>Driving test with reactions to visual and auditory stimuli</td>
<td>BRT Driving performance evaluated by instructors Impaired with alcohol. Milnacipran has no effect compared to placebo and does not modify the effect of alcohol.</td>
</tr>
<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>
<td>SDLP SDS Mirtazapine: Increased SDLP day 2. No effect on day 9 or 16. No effect on SDS. Escitalopram: No effect on either SDLP or SDS. 1 subject could not complete driving test after 30mg single dose mirtazapine</td>
</tr>
<tr>
<td>Veldhuijzen et al., 2006</td>
<td>Randomised double-blind placebo-controlled 2-way crossover</td>
<td>7 chronic neuropathic pain patients (4 men, 3 women. 42-58y)</td>
<td>Amitriptyline 25mg Placebo at night x 15 days</td>
<td>13h, on day 2 and day 16</td>
<td>Standardised highway driving test (~100km)</td>
<td>SDLP Subjective self-assessment of driving quality. 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>Brunnauer 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 &amp; 14 days after initiation of treatment</td>
<td>Driving simulator test</td>
<td>Number of collisions 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. Timing of dosing before testing is not specified.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>intervene</td>
<td>Measures</td>
<td>Outcomes</td>
<td>Notes</td>
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<tr>
<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>
</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>Morning and afternoon: baseline, day 2, 9, 16 and 30 (untreated group tested baseline, day 2 &amp; 9)</td>
<td>Computerised driving simulator test</td>
<td>Number of crashes, deviation of lateral position</td>
</tr>
</tbody>
</table>

Moderate positive correlation between SDLP and plasma amitriptyline concentration. Incomplete follow up of the untreated group.
### Supplementary table 3: Opioids and driving performance: experimental studies

(All treatments are single oral doses unless specified otherwise. 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 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</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, 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>Menefee et al., 2004</td>
<td>Prospective one group pre-test, post-test design</td>
<td>23 patients (17 men, 6 women, 18-67y) on &lt;15mg equivalent of oxycodone</td>
<td>Transdermal fentanyl 1 month titration period and 1 month stabilization period (median 50micrograms/h) period</td>
<td>Not applicable</td>
<td>Driving simulator task</td>
<td>Reaction time and errors in braking, steering, speed and signalling</td>
<td>No differences in outcome measures before and during treatment.</td>
<td></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>
</tbody>
</table>
References for Supplementary Tables:


Vermeeren A, O'Hanlon JF, Declerck AC, Kho L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. Acta Ther 1995;21(1):47-64.

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with escitalopram, mirtazapine, and placebo: a crossover trial. J Clin Psychiatry
CHAPTER 4

Research Hypothesis and Objectives

The literature reviewed in the two previous chapters indicates that therapeutic doses of CNS-Ds can increase the risk of traffic accidents and cause acute impairment in driving and multiple cognitive functions underpinning driving and other everyday activities. Some research demonstrates a dose dependency in impairment, and this is supported by the common clinical observation that patients show more sedation after an overdose than expected with therapeutic doses. Therefore one can expect cognitive deficits to be exaggerated and last longer in CNS-D overdose compared with therapeutic doses of those drugs.

Deficits of cognitive functions underlying daily activities are not of major concern in a hospitalised patient, first because prevention of complications takes the priority during the acute phase of intoxication and second because inpatients are mostly bed-ridden and are assisted by the hospital staff in carrying out most of their activities including getting on and off the bed, toileting, taking meals etc. In contrast however, even a subclinical cognitive impairment could be consequential if the effects persist at the time of discharge, when the individual is otherwise deemed fit to return to the community and expected within the community to be ‘back to normal’.

The research presented in this thesis focuses on possible impairment that is present at the time of discharge from hospital and may persist beyond that time. We hypothesised that the patients admitted with CNS-D overdose have residual cognitive
impairment at the time of discharge and are more prone to traffic accidents during the immediate post-discharge period. We conducted two studies to test these hypotheses.

**Study 1: Cognitive functions in patients clinically recovered from central nervous system depressant drug overdose**

The aim of this study was to determine whether patients with CNS-D overdose are cognitively impaired at the time they are clinically deemed fit to be discharged from hospital. We focused our assessment on three neurocognitive domains underpinning daily activities of social and professional life:

a) visual attention and visuomotor skills,

b) executive functions and working memory and

c) impulsivity and decision-making.

Using a battery of neuropsychological tests tapping into the above domains, we compared the performance of a group of patients following CNS-D overdose with that of a Control Group with non-CNS-depressant drug (CNS-ND) overdose at the point of discharge from the hospital-treated overdose episode. Given the broad range of acute cognitive deficits caused by therapeutic doses of CNS-D, we hypothesised the CNS-D Group would be impaired in all domains when compared to the Control Group.

The findings of the study are reported in two journal papers.


**Study 2: Risk of road traffic accidents in patients discharged following treatment for psychotropic drug overdose**

In this study, we examined whether patients treated in hospitals in the New South Wales (NSW), Australia for self-poisoning with CNS-Ds are more prone to traffic accidents during the period following discharge from hospitals. Using a data-linkage approach and self-controlled case series analysis we compared the traffic accident risk of a group of patients overdosed with CNS-Ds in the period following the overdose with the risk during a control period where they were not affected by the overdose. Given the wide variation of the half-lives (and the doses) of drugs taken by patients, we assumed the drug effects to last for up to 3 days to 1 week following overdose. As the majority of the patients with CNS-D overdose tend to be discharged with in 2 days, we hypothesised that these patients are at an increased risk of a traffic accident during the post-discharge period compared to the control period.

This study is reported in a journal paper (Paper 4, Chapter 7):

Cognitive Impairment in Patients Clinically Recovered from Central Nervous System Depressant Drug Overdose

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This is a non-final version of an article published in final form in Dassanayake TL, Michie PT, Jones AL, Carter GL, Mallard T, Whyte IM. Cognitive impairment in patients clinically recovered from central nervous system depressant drug overdose. *Journal Clinical Psychopharmacology*. In press

Journal website: http://journals.lww.com/psychopharmacology/pages/default.aspx
ABSTRACT

CNS-depressant drugs (CNS-Ds) are known to impair cognitive functions. Overdose of these drugs is common and the majority of the hospital-treated patients are discharged within 24–48 hours. No previous studies have examined whether they have residual impairment at the time of discharge. Our aim was to evaluate whether patients with CNS-D overdose are impaired in cognitive domains important in daily activities at that time. We compared visuomotor skills (Trail-Making A and choice reaction time), executive functions (viz. attentional set-shifting: Trail-Making B, and planning: Stockings of Cambridge task [SOC] from the Cambridge Neuropsychological Test Automated Battery [CANTAB]), working memory (Letter-Number Sequencing) and impulsivity and decision-making (CANTAB Information Sampling) in 107 patients with CNS-D overdose (benzodiazepines, opioids or antipsychotics) with a Control Group of 68 with non-CNS-D overdose (acetaminophen, SSRI and SNRIs) on discharge from hospital. Outcome measures were adjusted for demographic and clinical covariates in multivariate regression models. Compared to the Controls, the CNS-D Group was significantly impaired in all domains: they had prolonged Trail-Making completion times and reaction times, poorer working memory and planning and were more impulsive in decision-making. Their SOC performance was comparable to the Control Group for simple problems but worsened with increasing task complexity. The results show that patients with CNS-D overdose could be impaired in multiple cognitive domains underlying everyday functioning even at the time they are deemed medically fit to be discharged. Such impairments could adversely affect social and professional lives of this relatively young population during the immediate post-discharge period.
INTRODUCTION

Many individuals in the community are prescribed drugs with central nervous system (CNS) depressant effects. A single dose of central nervous system depressant drugs (CNS-Ds) including benzodiazepines, opioids and tricyclic antidepressants can cause acute impairment in activities such as driving, and an array of cognitive and psychomotor functions underlying everyday activities. These cognitive and psychomotor effects include impaired visual attention and reaction time, attentional set-shifting, planning, and working memory, and increased impulsivity. Similarly, acute cognitive effects have also been reported with atypical antipsychotics. These acute effects have been demonstrated in experimental studies conducted mostly on healthy volunteers and to a lesser extent, on patient groups.

In contrast, research is lacking on the extent of impairment in patients who take CNS-Ds in overdose even though CNS-D overdose is one of the most common modes of poisoning in developed countries, accounting for around 71,000 hospital-treated drug overdoses in the US (2006), 39,000 in the UK (mid 2009 – mid 2010) and 12,000 in Australia (mid 2007 – mid 2008). An extensive literature search retrieved only two studies that examined cognitive functioning following CNS-D overdose. Both reported anterograde amnesia following benzodiazepine overdose in ward patients, which improved from day 1 to day 2 after overdose. Given the evidence of acute effects of single doses of a variety of CNS-Ds, the sedative effects of overdose would obviously lead to profound impairments in number of cognitive and psychomotor domains in the acute stage. While such deficits are unlikely to be pertinent to the functionality of an inpatient who is under scrutiny of medical staff, in
contrast, even a subclinical cognitive impairment could be consequential if the effects persist at the time of discharge, when the individual is otherwise deemed fit enough to return to the community. Length-of-hospital-stay statistics, particularly those in the UK\textsuperscript{19} and Australia\textsuperscript{20} indicate that majority of these patients are discharged from hospitals within 24–48 hours of admission. Given that acute effects of even therapeutic doses can last overnight,\textsuperscript{1} the length of hospital stay following overdose could be too short for the adverse cognitive effects of the drugs to wear off – yet these effects may not be detected on the basis of routine history and clinical examination by staff making the decision to discharge the patient.

The aim of the present study was to determine whether patients with CNS-D overdose are cognitively impaired at the time they are clinically deemed fit to be discharged from hospital. We focused our assessment on three neurocognitive domains underpinning daily activities of social and professional life:

- a) visual attention and visuomotor skills,
- b) executive functions and working memory and
- c) impulsivity and decision-making.

Using a battery of neuropsychological tests tapping into the above domains, we compared the performance of a group of patients following CNS-D overdose with that of a Control Group with non-CNS-depressant drug (CNS-ND) overdose at the point of discharge from the hospital-treated overdose episode. Given the broad range of acute cognitive deficits caused by therapeutic doses of CNS-D, we hypothesized the CNS-D Group would be impaired in all domains when compared to the Control Group.


**METHOD**

**Recruitment of participants**

The study was carried out in the Department of Clinical Toxicology and Pharmacology of the Calvary Mater Newcastle (CMN) Hospital, which is the tertiary referral centre for poisonings in the Hunter and New England Region of New South Wales, Australia. All deliberate self-poisoning patients at CMN are admitted by the Department of Clinical Toxicology and Pharmacology. These patients are also seen by the Consultation-Liaison Psychiatry Team who determines the psychiatric diagnosis according to DSM-IV criteria. This model of management has been previously described.\(^2\) All admissions to the Department of Clinical Toxicology and Pharmacology are recorded in the Hunter Area Toxicology Services (HATS) Database, which is used as a digital repository for clinical and research purposes. The structure of this database has been described elsewhere.\(^3\) Ethics approval for the study was granted by the Hunter New England Human Research Ethics Committee.

Patients aged between 18 and 70 years admitted to the hospital following deliberate self-poisoning were prospectively screened for eligibility during daily ward-rounds. Those who overdosed with benzodiazepines, atypical antipsychotics or opioids were considered for inclusion into the CNS-D Group, whereas those who overdosed with acetaminophen, selective serotonin-reuptake inhibitors (SSRIs) or serotonin-noradrenaline-reuptake inhibitors (SNRIs) were considered for inclusion into the Control Group. Drug overdose was ascertained based on history, clinical picture and circumstantial evidence (e.g. availability of empty blister packs). A drug overdose was defined as acute administration of 2 or more times the defined daily dose (DDD: the assumed average maintenance dose per day for a drug used for its...
main indication in adults) as specified by WHO Collaborating Centre for Drug Statistics Methodology. Overdoses with multiple drugs, or subsequent admissions of already tested participants were not considered for inclusion in the study. Patients were excluded if they had any neurological illness that may affect cognitive functions, a history of head injury causing neurological damage, vision or hearing impairment, or acute psychosis or aggression at the time of clinical encounter, or if their first language was not English. Eligible participants were introduced to the study once they were deemed medically fit to be discharged from the Toxicology Service. Informed written consent was obtained from those who were willing to participate. Neuropsychological assessment was carried out just before they were due to leave the hospital.

**Neuropsychological assessment**

Three neurocognitive domains and general intelligence were assessed using a battery of validated neuropsychological tests.

a) *Visual attention and visuomotor skills*: Trail-Making Test A (TMT-A)\(^{26}\) and Cambridge Neuropsychological Test Automated Battery (CANTAB) choice reaction time (CRT)\(^{27}\)

b) *Executive functions and working memory*: Trail-Making Test B (TMT-B),\(^{26}\) CANTAB Stocking of Cambridge (SOC)\(^{27}\) and Letter-Number Sequencing Test (LNS)\(^{28}\)

c) *Impulsivity and decision-making*: CANTAB information sampling task (IST)\(^{27}\)

d) *Premorbid intelligence* (IQ): National Adult Reading Test (NART)\(^{29}\)
A medically qualified graduate trained to perform individual tests (author TLD) administered all tests for each study participant. Test instructions were followed verbatim based on the detailed criteria provided with each component test administration guide, in order to maintain uniformity of administration. Those patients who had their own room in the ward were tested there, whereas those who did not were tested in a separate interview room. The tests were administered in the order TMT-A, TMT-B, LNS, NART, CRT, IST and SOC.

1. **Trail-Making Test (TMT)**\(^{26}\) (*duration: 5 – 10 minutes*).

TMT-A consists of encircled numbers from 1 to 25 positioned irregularly on a sheet of paper. Subjects must connect these numbers in ascending order using a pencil as quickly as possible. TMT-B has numbers 1–13 and letters A–L. Subjects have to connect the numbers in ascending order and letters in alphabetical order, alternating between the two. Any errors are pointed out by the examiner as soon as they are made and thus errors are taxed with an increase in the test completion time, which is the main outcome measure in each part. TMT-A measures attention and visual scanning. TMT-B in addition taps into cognitive flexibility or the ability to switch attention between two conceptual sets.\(^{30-32}\) The difference between the completion times of TMT-B and TMT-A (TMT B-A) reflects the executive component of the task as it is generally agreed that subtraction controls for visual scanning and movement time.

2. **Letter-Number Sequencing (LNS)**\(^{28}\) (*duration: ~ 5 minutes*).

This is a test of working memory capacity. The examiner reads aloud a group of numbers and letters (e.g. V–1– J–5) and the subjects have to answer by recalling the numbers first 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 is increased until the subject fails all three sequences at a given length. The number of correct sequences is the test score.

3. National Adult Reading Test (NART)\textsuperscript{29} (duration: \textasciitilde 5 minutes).

The NART was administered to estimate pre-overdose IQ, as a potential covariate of the neuropsychological measures of the present study. Verbal responses were recorded, and scored by one of the authors (PTM) who was blind to the type of overdose of participants. Wechsler Adult Intelligence Scale (WAIS) full scale IQ was estimated using the regression equation derived by Crawford et al., 1989: $\text{IQ} = 128.50 - 0.84 \times (\text{NART errors})$.\textsuperscript{33}

4. Cambridge Neuropsychological Test Automated Battery (CANTAB)\textsuperscript{27} (duration: 35 – 40 minutes).

The component tests of CANTAB have been modified from well documented animal testing paradigms, so that behavioral data can be also related to neural systems underlying distinct cognitive domains analyzed by component tests.\textsuperscript{31} Test administration and scoring is computerized so that minimizing any biases that can be introduced during test administration. A selected set of CANTAB tests were administered on a Paceblade Slimbook\textsuperscript{TM} 110 Series 12.1” tablet PC. Two obligatory training tests, viz. Motor-Screening (MOT, duration 3 minutes) and Big/Little Circles (BLC, duration 3 minutes) were administered initially to introduce the subjects to the test system. Upon completion of the two screening tests, 3 further tests were administered:
Choice Reaction Time (CRT, duration ~ 7 minutes). This is a test of attention and psychomotor speed. An arrow-shape stimulus is displayed on either the right or the left hand side of the screen and the subject presses the right or left hand button of a press-pad depending on the side of the screen where the stimulus appears. The subject has to respond as quickly as possible without making mistakes. Average CRT calculation was based on 100 trials. Also calculated were the number of correct trials, incorrect trials (where the wrong button was pressed) and omissions.

Information Sampling Task (IST, duration 10 – 15 minutes). IST tests the rationality and impulsivity in decision-making. Twenty-five gray boxes and two colored panels are presented on the screen. Boxes open when touched to assume one of the two colors from the panels, and remain open. The subjects are instructed that they are playing a game for points. They have to open one box at a time, and decide which color is inside the majority of the 25 boxes based on the sample of boxes opened. Once their decision is made, the subject registers their choice by touching the correspondingly colored panel. The test has two conditions. In the Fixed-Win Condition, correct decisions are rewarded with 100 points regardless of the number of boxes opened at the time of decision-making. In the Decreasing-Win Condition, the maximum points that could be won starts with 250 and drops by 10 with each box opened. In both conditions, incorrect decisions cost 100 points. The test has 10 assessed trials each in the Fixed-Win Condition and the Decreasing-Win Condition. The order of the two conditions was counterbalanced among subjects in each group. The main outcome measure of interest is designated P, which is the probability that the color chosen by the subject at the point of decision is correct (with a maximum possible value of 1), based on the evidence available at that time, and assuming each
box has a 0.5 probability of assuming one of the two colors. Thus, P is an index of the rationality of the decision made by the subject: lower the P value, the more impulsive the decision is. P was calculated separately for the Fixed-Win (IST-FWP) and Decreasing-Win Conditions (IST-DWP).

Stockings of Cambridge (SOC, duration ~ 10 minutes). SOC is a computerized version of the Tower of London task and 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, subjects 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 outcome measures that we focused on were the number of problems solved in minimum moves and the mean number of the moves spent in solving an n-move problem (Mean-n-Moves), n being 2, 3, 4 or 5.

Demographic and clinical data

Demographic information (gender, age, and years of education) was collected at the time of testing. The following clinical data related to the present study were extracted from the Hunter Area Toxicology Services (HATS) database:

The data fields retrieved from the HATS database include those related to long-term clinical conditions (viz. major psychiatric illnesses, regular medication) and the episode of drug-overdose (viz. type and dose of drug taken in overdose, time of overdose, length of hospital stay, co-ingestion of alcohol, lowest GCS score recorded, any mechanical ventilation and in-ward treatment with potentially sedative drugs).
Data analysis

Sample characteristics were compared between the two groups with independent sample t-tests (for continuous variables) and Chi-squared tests (for categorical variables) (Table 1).

The main outcome measures analyzed in the present study were: TMT-A completion time, TMT-B completion time, TMT B-A, LNS number of correctly recalled sequences, CRT latency, IST-FWP, IST-DWP and SOC problems solved in minimum moves and SOC Mean-n-Moves. Because all outcome measures were continuous variables, the values beyond four standard deviations away from the mean were considered extreme outliers and were removed before analysis.

Planned intergroup comparisons

Each outcome measure except SOC Mean-n-Moves was modeled in multiple linear regression (MLR) models entering Group, gender, age, number of years of education, IQ, presence of a potentially cognitively impairing psychiatric illness, co-ingestion of alcohol, and in-ward treatment with potentially sedative drugs as explanatory variables. Stepwise MLR models were used so that only the statistically significant variables were retained in the final MLR model. Since NART testing to estimate premorbid IQ could be conducted only in 133 participants, MLR models were created in two steps for each main outcome measure. The first model was created for the subsample with IQ scores, entering IQ and the other independent variables. If IQ remained as a significant predictor, that model was retained as the appropriate. If IQ was dropped in the process of this first stepwise regression, another stepwise regression model was fitted to the full sample entering only the other
independent variables. MLR assumptions were checked for each model by creating histograms for regression standardized residuals and scatter plots for standardized residuals vs. standardized predicted values.

SOC Mean-n-Moves was analyzed in a mixed analysis-of-variance (ANOVA) model with Group as a between-subject factor, Task difficulty (i.e. minimum possible moves for a problem: 2, 3, 4 or 5) as the within-subject factor and other independent variables as covariates. Greenhouse-Geisser epsilon was used to correct for violations of sphericity.

The level of significance for the planned comparisons was set at a cut-off p value of 0.05.

**Unplanned within-Group comparisons**

After observing of the results of intergroup comparisons, we conducted two types of analyses within Groups: 1) *Subgroup comparisons* based on the drug class and half-life, 2) *Intra-Group MLR analysis for CNS-D overdose* to explore the factors associated with cognitive impairment in the CNS-D Group. Since these unplanned comparisons were made for nine outcome measures, the cut-off level of significance for subgroup comparisons and MLR models was set at a p value of 0.005.

All statistical analyses were conducted using SPSS Statistics™ version 17 for Windows™.
RESULTS

Sample characteristics

We considered 236 patients for eligibility, excluded 27 and approached 209 (128 CNS-D and 81 CNS-ND) to participate in the study (Figure 1). One-hundred and seventy five patients completed the TMT: 107 with CNS-D overdose (response rate: 83.6%) and 68 with CNS-ND overdose (response rate: 84.0%) (Figure 1). The CNS-D Group comprised 57 patients who overdosed with benzodiazepines (25 diazepam, 18 temazepam, 10 alprazolam, 3 clonazepam, and 1 lorazepam), 25 with atypical antipsychotics (20 quetiapine, 4 olanzapine and 1 risperidone), and 25 with opioids (11 codeine, 7 oxycodone, 3 morphine, 2 methadone, 1 dextropropoxyphene and 1 tramadol). The control group consisted of 34 patients who overdosed with SSRIs or SNRIs (11 desvenlafaxine, 5 escitalopram, 5 sertraline, 4 citalopram, 2 paroxetine, 1 duloxetine and 1 fluoxetine) and 34 with acetaminophen.

Figure 1: Participant recruitment
The sample characteristics are displayed in Table 1. The CNS-D Group was significantly older than the Control Group. Gender distribution, level of education, IQ, time from overdose to testing and the magnitude of overdose were similar between the two groups. Nearly half of the participants in each group had a major psychiatric illness (those diagnosed in the present sample were major depression, bipolar disorder and schizoaffective disorder). Around one third of each group had co-ingested alcohol. Nine patients in the CNS-D group had a lowest recorded GCS score less than nine after overdose. Of these, eight received mechanical ventilation. The mean time from exposure to testing in the CNS-D Group was 32 hours, and 85% of this group were tested within 48 hours after exposure.

**Table 1:** Demographic and clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>CNS-D Group (n = 107)</th>
<th>Control Group (n = 68)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of females</td>
<td>74 (69.2)</td>
<td>51 (75.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>37.5 (12.5)</td>
<td>30.1 (12.9)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean (SD) years of education</td>
<td>11.4 (1.9)</td>
<td>11.8 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean IQ (SD)</td>
<td>106.4 (6.2)</td>
<td>107.4 (6.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Number (%) with major psychiatric illness</td>
<td>53 (49.5)</td>
<td>33 (48.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) time from exposure to testing (hours)</td>
<td>31.9 (21.8)</td>
<td>26.4 (18.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) length of hospital stay (hours)</td>
<td>29.2 (20.3)</td>
<td>25.5 (16.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) amount taken ( x DDD)</td>
<td>14.4 (22.6)</td>
<td>16.5 (16.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Number (%) co-ingested alcohol</td>
<td>39 (36.4)</td>
<td>22 (32.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*CNS-D = central nervous system depressant, DDD = defined daily dose*
Group comparisons of neurocognitive measures

One extreme outlier for TMT-A and one for CRT latency were removed from the dataset prior to analysis. Summary measures based on the rest of the data are displayed in Table 2. All outcome measures were significantly impaired in the CNS-D Group compared with the Control Group. Other significant determinants of performance were age and IQ. Education, gender, psychiatric illnesses, co-ingestion of alcohol, in-ward sedative treatment and time from exposure to testing were not significantly associated with any of the outcome measures in the MLR analysis. Having observed a significant Group and Age effect on many outcome measures, a new variable Group x age interaction was entered into the MLR models to explore any difference in the effect of age on outcome measures in two Groups. However, that did not significantly improve any of the models, so the final MLR models contained only the main effects (Table 2).

Visual attention and visuomotor skills

Both TMT-A and CRT were significantly prolonged in the CNS-D Group. Test performance was also impaired with increasing age but was not influenced by IQ. The regression models with Group and age explained 20.8% of the variation in TMT-A [adjusted $R^2=0.208$, $F(2,171)=23.75$, $p<0.0001$] and 20.7% of the variation in CRT [adjusted $R^2=0.207$, $F(2,139)=19.37$, $p<0.0001$]. TMT-A completion time and CRT were moderately correlated ($r=0.393$, $p<0.0001$). Based on the fitted regression equation, a participant in the CNS-D group had a predicted TMT-A completion time equal to that of Control Group participant 22 years older, and a predicted CRT latency equal to that of a Control participant 15 years older.
Table 2: Summary results of neuropsychological measures

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>CNS-D Group</th>
<th>Control Group</th>
<th>Multiple linear regression modelling</th>
<th>Being in the CNS-D Group is equivalent to,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>CNS-D vs. Control</strong></td>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Visual attention and visuomotor skills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-A (s)</td>
<td>107</td>
<td>36.2 (13.6)</td>
<td>68</td>
<td>27.4 (7.7)</td>
</tr>
<tr>
<td>CRT latency (ms)</td>
<td>85</td>
<td>390.3 (110.9)</td>
<td>57</td>
<td>329.4 (56.5)</td>
</tr>
<tr>
<td><strong>Executive functions and working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-B (s)</td>
<td>107</td>
<td>103.9 (62.9)</td>
<td>67</td>
<td>68.5 (39.5)</td>
</tr>
<tr>
<td>TMT B-A (s)</td>
<td>107</td>
<td>66.8 (55.1)</td>
<td>67</td>
<td>41.3 (37.9)</td>
</tr>
<tr>
<td>LNS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>86</td>
<td>8.80 (2.19)</td>
<td>58</td>
<td>10.02 (2.15)</td>
</tr>
<tr>
<td>SOC-Correct&lt;sup&gt;b&lt;/sup&gt;</td>
<td>79</td>
<td>7.72 (1.87)</td>
<td>54</td>
<td>9.07 (1.75)</td>
</tr>
<tr>
<td>SOC Slope</td>
<td>79</td>
<td>1.822 (0.518)</td>
<td>54</td>
<td>1.514 (0.391)</td>
</tr>
<tr>
<td><strong>Impulsivity and decision-making</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISTFWP</td>
<td>84</td>
<td>0.780 (0.096)</td>
<td>57</td>
<td>0.837 (0.109)</td>
</tr>
<tr>
<td>ISTDWP</td>
<td>84</td>
<td>0.721 (0.075)</td>
<td>56</td>
<td>0.755 (0.089)</td>
</tr>
</tbody>
</table>

<sup>a</sup>LNS: Number of sequences recalled correctly, <sup>b</sup>SOC Correct: SOC problems solved in minimum moves.

<sup>c</sup>IST-FWP and IST-DWP increased (i.e. impulsivity decreased) with age and thus negative values signify greater impulsivity in CNS-D Group.

CNS-D = central nervous system-depressant, TMT = Trail Making Test, CRT = Choice Reaction Time, LNS = Letter Number Sequencing,

SOC = Stockings of Cambridge, ISTFWP = rationality in the fixed-win condition of Information Sample Task, ISTDWP = rationality in the decreasing-win condition of Information Sample Task.
Executive functions and working memory

TMT-B. TMT-B completion time was significantly delayed in CNS-D overdose (p=0.005), with increasing age (p<0.0001) and lower IQ (p=0.004). In combination, these factors accounted for 34% of the variation of TMT-B [R²=0.342, F(1,129)=23.88, p<0.0001]. The results of regression analysis of TMT B-A were very similar (Table 2).

LNS. CNS-D Group performed worse than the Control Group in the LNS task (p=0.0003). The test performance also correlated positively with IQ (p=0.003), but there was no significant association with age. Based on the regression equation, the predicted performance of a CNS-D participant was equal to that of a Control participant with an IQ of 16 points less.

SOC. On average, the CNS-D Group solved less SOC problems in minimum moves than the Control group (p=0.001). The number solved in minimum moves also declined with increasing age (p<0.0001). The predicted number of problems solved by a CNS-D Group participant was equal to the number solved by a Control participant 20 years older.

In the mixed ANOVA models for the SOC Mean-n-Moves based on Group (between-subject factor), task difficulty (i.e. minimum possible moves for a problem: 2, 3, 4 or 5: within-subject factor) and other covariates, only age turned out to be a significant covariate so that the final analysis for Group x Task Difficulty model was adjusted only for age (Figure 2). Both Group [F(1,129)=10.39, p=0.002] and age [F(1,129)=7.466, p=0.007] were significant predictors of Mean-n-Moves signifying that the Mean-n-Moves was greater in the CNS-D Group and increased with age. Group x Task difficulty interaction was significant [F(1.78, 229.61)=4.78, p=0.012],
indicating the CNS-D Group took more moves to solve the problems than Control Group as task difficulty increased. The interaction exhibited a significant linear contrast \([F(1,129)=9.901, p=0.002]\), indicating that the Group performance diverged linearly with increasing task difficulty. Consequently, we modeled the increase in Mean-n-Moves against task difficulty as a linear function, (viz. SOC slope) such that if one completes all problems in minimum moves (i.e. if Mean-n-moves=minimum moves) the slope would be 1. Similar to other outcome measures, SOC Slope was fitted in a MLR model (Table 2). The SOC Slope of the CNS-D Group (Mean=1.822, SD=0.518) was significantly steeper than that of the Control Group (Mean=1.514, SD=0.391), indicating that the performance of the CNS-D Group deteriorates linearly with increasing number of moves in SOC task \([F(1,130)=13.58, p=0.0003]\). However, Group identity accounted for only 8.8% of the variation in SOC Slope \((R^2=0.088, F(1,130)=13.58, p=0.0003)\). None of the other independent variables had a significant association with SOC Slope.

**Impulsivity and decision-making (IST)**

Both IST-FWP \((p=0.003)\) and IST-DWP \((p=0.002)\) were significantly lower in CNS-D Group than those of the Control Group. In contrast to results on other domains of cognition, older persons performed better on the IST with increasing age correlating with better IST-FWP \((p=0.034)\) and IST-DWP \((p=0.002)\). Higher IQ was associated with higher IST-FWP \((p=0.028)\) but not IST-DWP.
Figure 2: Group x Task Difficulty interaction in the Stockings of Cambridge Task: Mean number of moves taken to solve 2, 3, 4 and 5-move problems by the CNS-D and the Control Groups, adjusted for age (covariates appearing in the model are evaluated at age = 34.1 years).

Unplanned comparisons

Subgroup comparisons

Three subgroup analyses were conducted on each main outcome measure with series of one-way ANOVA tests and subsequent pairwise comparisons. These subgroup analyses were:

a) CNS-D subgroup analysis based on drug class- Benzodiazepines (n=57) vs. Atypical Antipsychotics (n=25) vs. Opioids (n=25),

b) CNS-D subgroup analysis based on half life - Short (<6h, n=49) vs. Medium (6-24h, n=29) vs. Long (>24h, n=34), and
c) non-CNS-D subgroup analysis based on drug class - Acetaminophen (n=34) vs. SSRIs/SNRIs (n=34).

One-way ANOVA tests and subsequent Bonferroni-corrected pairwise comparisons did not show any significant differences. No multivariate analyses were performed for these subgroups.

**Intra-Group analysis for CNS-D overdose**

Stepwise MLR models were fitted including the variables used in the main analysis and a new variable, lowest recorded GCS score following overdose (as a measure of degree of maximum CNS-depression caused by overdose) which was modelled as a dichotomous variable (<9 vs. ≥9). Increasing age was associated with impaired TMT-A, TMT-B, TMT B-A, CRT, LNS and SOC number of problems solved in minimum moves, lower IQ with impaired TMT-B, TMT B-A and LNS, and low GCS with impaired LNS. Older age was associated with higher IST-DWP.

**DISCUSSION**

To our knowledge, this is the first study that has examined subclinical impairment in a range of cognitive domains following clinical ‘recovery’ from CNS-D overdose. We focused on three domains of cognitive functions viz. visual attention and visuomotor skills, executive functions and working memory, and decision-making. The CNS-D Group was impaired in all test outcome measures in all three domains. In addition to the main effects, a Group x task difficulty interaction was observed in SOC task indicating that the patients may perform normally in simple
tasks but performance could fall behind as the executive demands become more complex.

Other factors associated with test performance were age and IQ. In line with previous findings in healthy populations, visuomotor skills viz. TMT-A\textsuperscript{35} and CRT\textsuperscript{36} were increasingly impaired with increasing age whereas these relatively low-level tasks were not dependent on IQ. As has been observed in healthy populations\textsuperscript{35,37} measures of executive functions and working memory were generally dependent on both age and IQ, except SOC which did not significantly correlate with IQ and LNS which did not correlate with age. In contrast to the other two domains, older age was associated with lower impulsivity and more rational decision-making.

Although we could not find comparable previous studies on cognitive effects of drug overdose, and the present CNS-D Group is too heterogeneous to compare with well-controlled samples in experimental studies on specific drugs, the cognitive deficits in the CNS-D Group are generally similar to the acute effects reported in previous experimental studies. Such adverse effects of benzodiazepines and opioids include impaired visual attention and psychomotor skills,\textsuperscript{3,7-10} attentional set-shifting,\textsuperscript{11} planning\textsuperscript{12} and working memory,\textsuperscript{13} and increased impulsivity.\textsuperscript{14}

Being a cross-sectional study, this study falls short of proving such causative association despite the biological plausibility of a causal relationship. However, we do not have any reason to believe that the results reflect a pre-overdose difference in intellectual functioning between CNS-D group and the Control Group because the estimated pre-morbid IQ in the CNS-D Group was normal and comparable with that of the Control Group. The only systematic intergroup difference was the higher age of
the CNS-D group, but cognitive impairment remained significant after adjusting for
the effect of age and other confounding factors.

Residual cognitive impairments in patients discharged following CNS-D
overdose could affect their daily activities during the immediate post discharge
period. They represent a relatively young cross-section of the population and, unlike
the elderly, they tend to return to social and working environments with high
cognitive demands. In this respect, driving is one activity of concern in modern
society. According to cognitive models of driving, visual attention, visuomotor
skills, and ability to switch attentional-set are among major determinants of driving
behavior. The regression models for tests that tap into these domains (CRT, TMT-A
and TMT-B) suggest that drug effects could be equivalent to a cognitive aging by 10–
20 years. This could be detrimental particularly because the impairment is acute and
the patients do not have time to develop coping mechanisms as they do with normal
ageing. The impairment associated with CNS-D overdose cannot be solely attributed
to impaired processing speed however. Time-independent tasks (SOC, LNS and IST)
show that CNS-D overdose is associated with impaired planning and working
memory and higher impulsivity in decision making. Worsening SOC task
performance observed with increasing executive demands is similar to the pattern that
has been reported in patients with frontal lobe lesions.

The findings of the present study have research and clinical implications.
Follow up studies are required to delineate the time course of cognitive recovery in
CNSD overdose. Epidemiological studies on real-life outcomes in the future should
investigate how such impairment could affect someone who takes up driving or
operating machinery in the immediate post-discharge period. However, findings of
the present study should make clinicians more aware of the possible subclinical
effects of CNS-D overdose. While reassuring the discharged patients that they are not
likely to experience long term complications of drug toxicity, clinicians should also
warn them that their cognitive functions may not have fully recovered and they may
not be fit enough to carry out certain daily activities immediately after discharge.
Which activities a patient should refrain from depends on a patient’s regular social
and professional commitments. Driving would be one of these, owing to its complex
and time-constrained cognitive and psychomotor demands and safety implications of
errors. In the light of the observation that they tend to make more errors in executive
tasks and more impulsive in decision-making, these patients should also be advised to
be more cautious in making major decisions in their social and professional life on
their own. For how long a patient should refrain from such activities is open to
clinical judgment until evidence from follow up studies and real-life outcome studies
is available.

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Cognitive Skills Underlying Driving in Patients Discharged Following Self-Poisoning with Central Nervous System Depressant Drugs

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ABSTRACT

**Background:** Central nervous system depressant drugs (CNS-Ds) can impair cognitive functions and driving. They are also the most common drugs taken in overdose in hospital-treated episodes of self-poisoning. In Australia most of these patients are discharged within 48 hours, while they still have possible subclinical drug-effects. We aimed to determine whether patients treated for self-poisoning with CNS-Ds are impaired in the Trail-Making Test (TMT, part A and B), a neuropsychological test that is known to correlate with driving performance.

**Methods:** This study was conducted from November 2008 to April 2011 in a referral center for poisonings in New South Wales, Australia. 107 patients discharged from the clinical toxicology unit following treatment for self-poisoning of CNS-Ds (benzodiazepines, atypical antipsychotics or opioids) and a Control Group of 68 discharged following self-poisoning of non-CNS-depressant drugs (acetaminophen or non-sedating antidepressants) were tested with the Trail-Making Test (TMT, part A and B). Owing to the known association of impaired TMT with driving impairment and increased risk of traffic accidents, performance ≤ the 10\textsuperscript{th} percentile for age was defined as significant impairment in each part of the TMT. The odds ratio (OR) for impairment in each part was calculated in multivariate logistic regression (MLR) models adjusted for gender, education, IQ and presence of a major psychiatric illness. A secondary MLR analysis was conducted only for those patients (78 CNS-D and 54 Control Group participants) who were directly discharged home, after excluding those who were transferred for further psychiatric care.

**Results:** The odds of impairment in the CNS-D Group was 2.8 times that of the Control Group on TMT-A [38(35.5%) vs. 11(16.2%): adjusted OR=2.76,
95% CI: 1.28–5.97], and 4.6 times on TMT-B [67 (62.6%) vs. 22 (32.4%): adjusted OR = 4.63, 95% CI: 2.06–10.42]. The results were similar in the subgroup of patients discharged home, with the odds of impairment in the CNS-D Group was 3.3 times that of the Control Group on TMT-A [25 (32.1%) vs. 7 (13.0%): adjusted OR = 3.30, 95% CI: 1.28–8.52], and 3.6 times on TMT-B [46 (59.0%) vs. 17 (31.5%): adjusted OR = 3.64, 95% CI: 1.44–9.20]. TMT-B impairment in the CNS-D Group remained significant even after adjusting for TMT-A performance.

Conclusions: Patients with CNS-D overdose may have significant impairment in cognitive skills underlying driving at the time of discharge from hospitals. Clinicians should warn these patients that their driving skills might still be impaired, even if they are considered ‘clinically’ recovered, and advise them not to drive during the first 1-2 days following discharge.

INTRODUCTION

A large body of literature shows that CNS-depressant drugs (CNS-Ds), even in therapeutic doses, are associated with increased risk of traffic accidents (Dassanayake et al. 2011, Rapoport et al. 2009, Vermeeren 2004) and can cause acute impairment in driving (Dassanayake et al. 2011, Vermeeren 2004) and cognitive skills underlying driving (Stewart 2005, Zaen 1995). In contrast, research is lacking on the extent of impairment in patients who take CNS-Ds in overdose even though it is the most common mode self-poisoning among adults in developed countries, accounting for around 71,000 hospital-treated drug overdoses in the US (Coben et al. 2010), 39,000 in the UK (National Institute of Health 2011) and 12,000 in Australia (Australian Institute of Health and Welfare 2011). Drug effects tend to last longer in
overdose and thus it is possible that many patients with CNS-D overdose could have significant impairment in driving skills at the time of discharge from hospitals, which is less than 48 hours from the time of admission for the majority of these patients in the UK (National Institute of Health 2011) and Australia (Australian Institute of Health and Welfare 2011). In Australia the discharge decision is based on clinical examination, and no specific psychometric tests are administered to evaluate recovery of cognitive skills.

The primary aim of the present study was to examine whether patients treated for self-poisoning of CNS-Ds are impaired in cognitive skills underlying driving at the time of discharge, when they are deemed clinically fit-enough to return to the community. In the absence of pre-overdose baseline measurements, we compared their performance with that of a Control Group of patients discharged after self-poisoning of a non-CNS-depressant (CNS-ND).

We tested driving-related cognitive skills in our participants using the Trail-Making Test (TMT, part A and B) (Bowie and Harvey 2006, Reitan 1986) a neuropsychological test that has been widely applied in off-road evaluation of fitness-to-drive (Korner-Bitensky et al. 2006). Previous research, albeit based on elderly participants, shows that individuals with TMT-B completion time ≤ the 10th percentile for age have 2.5-fold increase in risk of failing a standardized driving test (Classen et al. 2008) and 1.5-fold increase in risk of a traffic accident (Stutts et al. 1998). The TMT-B was found to be a feasible bedside test that can be administered in a busy emergency department setting (Betz and Fisher 2009).
METHODS

Setting and study design

This was a cross-sectional study carried out in the Department of Clinical Toxicology and Pharmacology of the Calvary Mater Newcastle (CMN) hospital from November 2008 to April 2011. CMN is the tertiary referral centre for poisonings in the Hunter New England Region of New South Wales, Australia. All patients with self-poisoning at CMN are admitted by the Department of Clinical Toxicology and Pharmacology and these patients are also seen by the Consultation-Liaison Psychiatry Team who determines the psychiatric diagnosis according to DSM-IV criteria. This model of management has been previously described (Whyte et al. 1997). Once cleared by the Clinical Toxicology Team and seen by the Consultation-Liaison Psychiatry Team, patients are either discharged home or – in case of high-suicidal-risk patients – transferred to the Psychiatric Emergency Care Centre (PECC). Some patients assessed at PECC are discharged home on the same day while others are kept longer as inpatients. All admissions to The Department of Clinical Toxicology and Pharmacology are recorded in the Hunter Area Toxicology Services (HATS) Database, which is used as a digital repository for clinical and research purposes. The structure of this database has been described elsewhere (Whyte et al. 2002). Ethics approval for this study was granted by the Hunter New England Human Research Ethics Committee.

Participants

The study sample was prospectively recruited from the patients admitted under the care of the Department of Clinical Toxicology and Pharmacology at the
We considered patients aged 18–70 years admitted following self-poisoning with any drug belonging to one of 3 classes of CNS-D drugs (viz. benzodiazepines, atypical antipsychotics, opioids) or 2 classes of CNS-ND drugs (viz. non-sedating antidepressants consisting of selective serotonin reuptake inhibitors and serotonin noradrenalin reuptake inhibitors, and acetaminophen), for eligibility for the CNS-D Group or the Control Group, respectively.

We ascertained self-poisoning based on history, clinical picture and circumstantial evidence, and only included those who took two or more times the defined daily dose [DDD: the assumed average maintenance dose per day for a drug used for its main indication in adults (Centre for Drug Statistics Methodology 2010)] of a drug of interest. Patients with multiple drug ingestions were not eligible.

Patients were excluded 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, or if their first language was not English.

The patients who fulfilled the eligibility criteria were identified during daily clinical toxicology ward rounds. We introduced the study to eligible patients after they were deemed medically fit to be discharged from the unit by the clinical toxicologist and obtained informed written consent from those who were willing to participate. Irrespective of the intended destination of discharge (i.e. home or PECC), all consented patients were tested just before they were due to leave the Department of Clinical Toxicology (i.e. once they were cleared by the Clinical Toxicology Team and seen by the Consultation-Liaison Psychiatry Team).
Test instruments

**Trail-Making Test (TMT):** The TMT (Reitan 1986) is a timed paper and pencil test consisting of two parts: A and B. TMT-A has circled numbers from 1 to 25 positioned irregularly on a sheet of paper, and the participant is instructed to connect the numbers in ascending order as quickly as possible. TMT-B has numbers 1-13 and letters A-L, and the numbers must be connected in ascending order and the letters in alphabetical order, alternating between the two sets (1–A–2–B.. etc). In each part, if the subject makes an error the examiner points that out promptly and the subject has to go back to the last correctly linked circle and resume the task. Time to complete each part – which depends on both speed and accuracy – is measured in seconds. The test administration takes only 5-10 minutes. Performance in both parts depends on visuomotor skills and processing speed, however part B in addition demands the ability to switch attention between two conceptual sets (Bowie and Harvey 2006, Strauss et al. 2006).

We dichotomized TMT results, so that performance ≤ the 10th percentile for their age was defined as impaired in the respective part of the test (i.e. in part A and part B). Test instructions, administration criteria and the age-stratified percentiles were adopted from Strauss et al. (2006).

**National Adult Reading Test (NART):** NART (Nelson and Willison 1991), a validated premorbid estimate of intelligence quotient (IQ) was administered to assess general intelligence which is a potential covariate affecting TMT performance. The test-sheet comprises 50 phonetically irregular words that the participants read aloud at their own pace. Verbal responses were recorded, and scored by a different researcher.
blind to the type of overdose of participants. Wechsler Adult Intelligence Scale (WAIS) full scale IQ was estimated from the number of errors, using the regression equation derived by Crawford et al. (1989): IQ = 128.50 – 0.84 (NART errors).

Testing for driving-fitness was conducted as part of a more extensive study that was aimed at determining the spectrum of neurocognitive impairment in CNS-D overdose. The participants subsequently took part in several other neuropsychological tests that are not reported in this paper.

**Clinical data**

The clinical data on long-term clinical conditions (e.g. major psychiatric illnesses, regular medication) and the episode of drug-overdose (viz. type and dose of drug taken in overdose, time of overdose, length of hospital stay, co-ingestion of alcohol, lowest GCS score recorded, any intensive care and mechanical ventilation) were extracted from the HATS database. It was not feasible to obtain data on time of discharge from PECC, in those who were transferred to that unit.

**Data analysis**

The initial data analysis included all patients recruited irrespective of the destination of discharge or transfer. As the patients transferred to the PECC may have been kept longer, they were excluded and a secondary analysis was conducted only on those who were discharged home directly after the testing session.

Sample characteristics were compared between the CNS-D and Control Groups with independent sample t-tests (for continuous variables) and Chi-squared tests (for categorical variables) (Table 1). A series of preliminary univariate logistic regressions were also carried out to explore associations between each demographic /
clinical variable (except age for which TMT results were already stratified) and TMT outcome.

The association of the type of overdose (CNS-D vs. Control Group) with impairment in each part of the TMT was examined initially with univariate logistic regression and then in multivariate logistic regression (MLR) models. MLR models were adjusted for demographic (viz. gender, IQ and years of education) covariates. Presence of a major psychiatric illness was also incorporated into the MLR model as a covariate since those illnesses are known to impair TMT performance (Bora et al. 2009, Bowie and Harvey 2006). We did not include co-ingestion of alcohol as a covariate in the MLR model because we expected any effects of alcohol (if co-ingested with drugs) to have worn-off at the time of testing, and hence co-ingestion of alcohol was not a significant predictor of test impairment in univariate analysis.

Since NART testing to estimate premorbid IQ could not be conducted in all participants, two MLR models were created for each part of the TMT: the first, for the full sample entering Group, gender, years of education, major psychiatric illness as independent variables, and the second, for the subsample with IQ estimates entering IQ and the other independent variables (Table 4).

Sedation associated with drug overdose can impair psychomotor speed and coordination thus increasing both TMT-A and TMT-B completion times. We aimed to eliminate the influence of psychomotor slowing by fitting another MLR model comparing TMT-B performance in two Groups adjusting for TMT-A performance and other covariates (Table 5). This analysis was also conducted for the full sample and the subsample with IQ estimates.
Level of significance was set at a p value of 0.05 for all analyses. Statistical analysis was conducted using STATA® version 11.1 (Statacorp, College Station, Texas).

RESULTS

We considered 236 patients for eligibility, excluded 27 and approached 209 (128 CNS-D and 81 CNS-ND) to participate in the study (Figure 1). One-hundred and seventy five patients completed the TMT: 107 with CNS-D overdose (response rate: 83.6%) and 68 with CNS-ND overdose (response rate: 84.0%). Of these, 78 (72.9%) patients with CNS-D overdose and 54 (79.45%) with CNS-ND overdose were directly discharged home from the Department of Clinical Toxicology.

Sample characteristics

The gender distribution, education, co-ingestion of alcohol with overdose, prevalence of major psychiatric illnesses, and the time from exposure to testing were similar between the CNS-D and Control Groups (Table 1). The CNS-D Group was on average 7 years older than the Control Group. The NART was administered to 97 participants (57 CNS-D and 40 Control Group), so only their IQs could be estimated. The characteristics of this subsample with IQ scores were very similar to that of the full sample (Table 1). The mean IQs of both groups were similar and were slightly above the mean expected in the general population.
Figure 1: Participant recruitment
The numbers of patients who took different drugs are shown in Table 2. Forty two (73.7%) out of 57 patients overdosed with benzodiazepines, 19 (76.0%) out of 25 overdosed with atypical antipsychotics, 10 (40.0%) out of 25 overdosed with opioids, 32 (94.1%) out of 34 overdosed with non-sedating antidepressants and 2 (5.9%) out of 34 with acetaminophen overdose had been taking the same drug in therapeutic doses before the episode of overdose. In the subsample of patients who were directly discharged home, 31 patients overdosed with benzodiazepines, 14 overdosed with antipsychotics, 9 overdosed with opioids, 25 overdosed with non-sedating antidepressants and one patient overdosed with acetaminophen had been taking the same drug in therapeutic doses.

Among all patients tested, around half of the patients in each group had an underlying major psychiatric illness (Table 1). This was around 40% among patients who were discharged home. By far the most prevalent psychiatric illness was depressive disorder (Table 3). In addition, 4 patients in the CNS-D Group had bipolar disorder and 2 had schizoaffective disorder. Nine patients in the CNS-D Group had a lowest GCS score of less than nine after the overdose. Of these, eight received mechanical ventilation. The lowest recorded GCS score in the Control Group participant was 13.

Of the patients discharged home, 70 (89.7%) in the CNS-D Group and 46 (85.1%) in the Control Group reported that they regularly drive a motor vehicle. In this sample of patients, 69 (88.4%) participants of the CNS-D Group and 49 (90.7%) of the Control Group were discharged within 48 hours after admission.
Table 1: Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>All tested patients</th>
<th></th>
<th>Patients discharged home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total sample (n = 175)</td>
<td>Subsample with IQ scores (n = 133)</td>
<td>Total sample (n = 132) Subsample with IQ scores (n = 97)</td>
</tr>
<tr>
<td></td>
<td>CNS-D (n = 107)</td>
<td>Control (n = 68)</td>
<td>p value</td>
</tr>
<tr>
<td>Continuous variables: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.5 (12.5)</td>
<td>30.1 (12.9)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.4 (1.9)</td>
<td>11.8 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>IQ score</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time from exposure to testing (hours)</td>
<td>31.9 (21.8)</td>
<td>26.4 (18.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of hospital stay (hours)</td>
<td>29.2 (20.3)</td>
<td>25.5 (16.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of defined daily doses taken</td>
<td>14.4 (22.6)</td>
<td>16.5 (16.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Categorical variables: number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>74 (69.2)</td>
<td>51 (75.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Psychiatric Illness</td>
<td>53 (49.5)</td>
<td>33 (48.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Co-ingestion of alcohol</td>
<td>39 (36.4)</td>
<td>22 (32.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 2: Numbers of patients overdoses with different drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Among all tested patients</th>
<th>Among patients discharged home</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Temazepam</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Atypical antipsychotics:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Opioids:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Morphine</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Methadone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Non-sedating antidepressants:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Citalopram</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Acetaminophen</strong></td>
<td>34</td>
<td>28</td>
</tr>
</tbody>
</table>
### Table 3: Numbers of patients with major psychiatric illnesses

<table>
<thead>
<tr>
<th>Psychiatric illness</th>
<th>Among all tested patients</th>
<th>Among patients discharged home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNS-D Group (n = 107)</td>
<td>Control Group (n = 68)</td>
</tr>
<tr>
<td></td>
<td>CNS-D Group (n = 78)</td>
<td>Control Group (n = 54)</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>46</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

### Trail-Making Test

**All tested patients:**

Based on the age-stratified 10th percentile cut-off, 38 (35.5%) of the CNS-D Group and 11 (16.2%) of the Control Group had impaired TMT-A performance (unadjusted OR=2.85, 95%CI: 1.34–6.09), whereas 67 (62.6%) of the CNS-D Group and 22 (32.4%) of Control Group were impaired in TMT-B (unadjusted OR=3.5, 95%CI: 1.84–6.65).

The MLR models created for TMT-A and TMT-B, in the full sample and the subsample with IQ scores (Table 4). For TMT-A, only the MLR model that used the full dataset was significant. In this model the odds of impairment in TMT-A in the CNS-D Group was 2.8 times that of the Control Group (adjusted OR=2.76, 95%CI: 1.28–5.97). In addition, psychiatric illness was a significant predictor of TMT-A impairment, with the odds of impairment in those who had a pre-existing major psychiatric illness was twice that of those who did not (adjusted OR=2.13, 95%CI: 1.06–4.30).
Both MLR models for TMT-B were statistically significant. The model without IQ explained only 9.5% of the variation in the outcome, whereas that with IQ scores explained 17.5% of the variation in the impairment in TMT-B. In the second model (that adjusted for gender, years of education, IQ and psychiatric illness) the odds of TMT-B impairment in the CNSD Group was 4.6 times the odds of impairment in the Control Group (adjusted OR=4.63, 95%CI: 2.06–10.42). TMT-B performance also improved with better education: each additional year of education was associated with 25% reduction in the odds of impairment (adjusted OR=0.75, 95%CI: 0.60–0.93).

Impairment of TMT-B in the CNS-D Group remained significant even after making additional adjustments for TMT-A performance (adjusted OR = 4.37, 95%CI: 1.92–9.97, Table 5).

Patients discharged home:

The results were similar in the analysis that was restricted to the patients who were discharged home after testing: 25 (32.1%) of the CNS-D Group and 7 (13.0%) of the Control Group had impaired TMT-A performance (unadjusted OR=3.17, 95%CI: 1.26–7.99), whereas 46 (59.0%) of the CNS-D Group and 17 (31.5%) of Control Group were impaired in TMT-B (unadjusted OR=3.13, 95%CI: 1.51–6.49).

On MLR analysis (Table 4), odds of impairment in the CNS-D Group was 3.3 times that of the Control Group on TMT-A (adjusted OR=3.30, 95%CI: 1.28–8.52), and 3.6 times on TMT-B (adjusted OR=3.64, 95%CI: 1.44–9.20). Impairment of TMT-B in the CNS-D Group remained significant even after adjusting for TMT-A performance (adjusted OR=3.59, 95%CI: 1.40–9.20, Table 5).
Table 4: Multiple logistic regression models for TMT-A and TMT-B in the CNS-D vs. Control Groups adjusted for demographic and clinical covariates.

<table>
<thead>
<tr>
<th></th>
<th>All tested patients</th>
<th>Patients discharged home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMT-A</td>
<td>TMT-B</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>CNS-D vs. Control</td>
<td>2.76 (1.28 – 5.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Females vs. Males</td>
<td>0.88 (0.41 – 1.88)</td>
<td>0.74</td>
</tr>
<tr>
<td>Education (per additional year)</td>
<td>0.91 (0.76 – 1.08)</td>
<td>0.284</td>
</tr>
<tr>
<td>Psychiatric Illness</td>
<td>2.13 (1.06 – 4.30)</td>
<td>0.034</td>
</tr>
<tr>
<td>Overall model</td>
<td>( \chi^2 = 13.51, \text{df} = 4, p = 0.009 )</td>
<td>R² = 0.0651</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Subsample with IQ scores (n = 133)</th>
<th></th>
<th>Subsample with IQ scores (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>CNS-D vs. Control</td>
<td>2.09 (0.87 – 5.02)</td>
<td>0.098</td>
<td>4.63 (2.06 – 10.42)</td>
</tr>
<tr>
<td>Females vs. Males</td>
<td>0.75 (0.32 – 1.75)</td>
<td>0.502</td>
<td>1.59 (0.68 – 3.75)</td>
</tr>
<tr>
<td>Education (per additional year)</td>
<td>0.83 (0.68 – 1.03)</td>
<td>0.085</td>
<td>0.75 (0.60 – 0.93)</td>
</tr>
<tr>
<td>IQ (per additional 1 point)</td>
<td>0.99 (0.93 – 1.06)</td>
<td>0.774</td>
<td>0.95 (0.89 – 1.02)</td>
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<tr>
<td>Psychiatric Illness</td>
<td>1.67 (0.74 – 3.78)</td>
<td>0.221</td>
<td>1.70 (0.76 – 3.78)</td>
</tr>
<tr>
<td>Overall model</td>
<td>( \chi^2 = 9.66, \text{df} = 5, p = 0.085 )</td>
<td>R² = 0.0622</td>
<td>( \chi^2 = 32.28, \text{df} = 5, p &lt; 0.0001 )</td>
</tr>
</tbody>
</table>
Table 5: Multiple logistic regression models for TMT-B in CNS-D vs. Control Groups adjusted for TMT-A, demographic and clinical covariates.

<table>
<thead>
<tr>
<th></th>
<th>All tested patients</th>
<th></th>
<th></th>
<th>Patients discharged home</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total sample (n = 175)</td>
<td>Subsample with IQ (n = 133)</td>
<td>Total sample (n = 132)</td>
<td>Subsample with IQ (n = 97)</td>
<td></td>
</tr>
<tr>
<td>CNS-D vs. Control</td>
<td>2.90 (1.46 – 5.74)</td>
<td>0.002</td>
<td>4.37 (1.92 – 9.97)</td>
<td>&lt;0.001</td>
<td>2.62 (1.20 – 5.69)</td>
</tr>
<tr>
<td>TMT-A</td>
<td>4.29 (1.91 – 9.62)</td>
<td>&lt;0.001</td>
<td>2.65 (1.05 – 6.71)</td>
<td>0.04</td>
<td>4.70 (1.77 – 12.50)</td>
</tr>
<tr>
<td>Females vs. Males</td>
<td>1.21 (0.57 – 2.53)</td>
<td>0.619</td>
<td>1.73 (0.72 – 4.15)</td>
<td>0.222</td>
<td>0.80 (0.34 – 1.88)</td>
</tr>
<tr>
<td>Education (per additional year)</td>
<td>0.80 (0.67 – 0.96)</td>
<td>0.018</td>
<td>0.76 (0.61 – 0.95)</td>
<td>0.016</td>
<td>0.84 (0.69 – 1.03)</td>
</tr>
<tr>
<td>IQ (per additional 1 point)</td>
<td>-</td>
<td>-</td>
<td>0.95 (0.89 – 1.02)</td>
<td>0.139</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric Illness</td>
<td>1.14 (0.58 – 2.24)</td>
<td>0.704</td>
<td>1.58 (0.70 – 3.56)</td>
<td>0.274</td>
<td>1.11 (0.50 – 2.46)</td>
</tr>
<tr>
<td>Overall model</td>
<td>$\chi^2 = 36.99$, df = 5, p &lt; 0.0001, $R^2 = 0.1525$</td>
<td>$\chi^2 = 36.70$, df = 5, p &lt; 0.0001, $R^2 = 0.1991$</td>
<td>$\chi^2 = 25.12$, df = 5, p = 0.0001, $R^2 = 0.1375$</td>
<td>$\chi^2 = 22.34$, df = 6, p &lt; 0.001, $R^2 = 0.1672$</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

Our findings show that patients deemed clinically recovered from CNS-D overdose tend to show subclinical deficits when challenged with a task that taps into the cognitive skills underlying driving. The patients with CNS-D overdose who were discharged home were 3.3 times more likely to be impaired in TMT-A and 3.6 times in TMT-B compared with a comparable Control Group of patients discharged following overdose of CNS-NDs. The impairment was more evident in TMT-B with around 60% of the patients with CNS-D overdose performing ≤ the 10th percentile for their age. Impaired TMT-B performance in the CNS-D Group was evident even after adjusting for TMT-A impairment, indicating that the observed cognitive impairment was not simply a reflection of psychomotor impairment.

Strengths and limitations

To our knowledge, this is the first study demonstrating subclinical cognitive impairment following CNS-D overdose. Given this study involved prospective recruitment of patients with self-poisoning, with both groups having high and similar response rates, we believe the chances of any systematic bias in consenting to participate was low. The research question and the target clinical population led us to select an observational cross-sectional design and hence the study falls short of proving that CNS-depressant overdose caused the cognitive impairment. However, we attempted to minimize the influence of confounding factors by selecting an appropriate control group and by adjusting the outcome-measure estimates for potential demographic and clinical covariates. Apart from these, other non-specific factors such as psychological disturbances and lower motivation that could follow the attempt of self-harm may have reduced the test performance. However, there is no
reason to believe that these factors are systematically different between the CNS-D and the Control Groups of participants. It is also unlikely that the CNS-D sample represent a group of individuals with low overall cognitive capabilities, because we excluded those who had pre-existing cognitive impairment and the recruited CNS-D group had an average IQ estimate that is similar to that of the Control Group. Around 75% of the patients with CNS-D overdose were discharged home directly following clinical recovery from the overdose. Of those nearly 90% were discharged within 48 hours after admission. This is similar to the length-of-hospital stay data for CNS-depressant overdoses across Australia (Australian Institute of Health and Welfare 2011) and the UK (National Institute of Health 2011).

A limitation of this study is that patients were not asked to make a subjective assessment of their ability to drive during the immediate post-discharge period. Correlating the findings of such assessment with TMT results would have helped to elucidate whether patients can make an accurate assessment of their impairment and thus capable of self limiting their driving during the post-discharge period. Other possible limitation is that the intoxicant is based on self-report, not on laboratory analysis however we do not believe that this could have introduced a systematic bias.

**Implications for fitness to drive**

Both TMT-A and TMT-B require the individual to scan the visual environment and make appropriate moves (albeit with a pencil) as quickly as possible. Cognitive models of driving signify these visuomotor skills as a basic component in driving behavior (Michon 1985, Ranney 1994). In addition to visuomotor skills, TMT-B requires switching attention between the numbers and letters while keeping the relevant numerical and alphabetical order rules in working
memory. This taps into more demanding cognitive skills where one has to switch attention voluntarily between two sets of information (Bowie and Harvey 2006, Strauss et al. 2006), such as in more complex traffic situations where a driver needs to switch attention between the vehicle in front and the oncoming traffic while keeping relevant road rules in mind. In line with this, Richardson and Marottoli (2003) found TMT-B performance to have a moderate correlation with simple driving maneuvers (e.g. turning the vehicle: \( r = 0.38 \)) and a strong correlation with more complex maneuvers (e.g. lane change: \( r = 0.73 \)). We chose the 10th percentile cut-off limit based on studies in healthy older drivers that showed that a TMT-B performance within 10th percentile limit for age is associated with 2.5-fold increased risk of failing a standardized driving test (Classen et al. 2008) and a 1.5-fold increase in the risk of a traffic accident (Stutts et al. 1998). According to pioneering studies on alcohol and traffic accidents (Allsop 1966), such increase in accident risk in turn is equivalent to that associated with a blood alcohol level of 0.07% which is above the legal limit for driving in most countries. Same risk-estimates may not be valid for a younger population discharged from hospitals after self-poisoning with CNS-Ds, our finding that nearly 60% of the patients return to the community with a cognitive impairment of a similar extent warrants clinical attention and further research.

**Research and clinical implications**

Future research should aim to estimate the impact of CNS-D overdose on the risk of major driving-related adverse outcomes such as traffic accidents and infringements during the post-discharge period. Such adverse events are rare so that the most feasible and statistically powerful design would be large-scale
epidemiological studies that link hospital admission databases with traffic event
databases so that the researchers can create retrospective cohorts and investigate
whether the patients are more prone to traffic accidents or infringements during the
period following discharge. We could not perform follow up cognitive assessments in
the patients with CNS-D overdose. Such serial assessments in the post-discharge
period would help to delineate the temporal nature of cognitive recovery in CNS-D
overdose.

Until such evidence is available, we believe that the association between
CNS-D overdose and impairment in cognitive skills underlying driving on discharge
is compelling enough to influence clinical care of these patients. With increasing
demand on hospital beds, it may be impossible to keep these patients longer in
hospital wards, however, clinicians should explain to patients who are ‘clinically’
cleared and are considered fit enough to go home, that their driving skills might still
be impaired after a CNS-D overdose, and advise them not to drive during the first day
or two following discharge. As our results also indicate that this impairment becomes
more evident in situations that require higher levels of cognitive skills, the patients
themselves may not realize that they cannot cope, until they are actually in a complex
driving situation.

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CHAPTER 7

(PAPER 4)

Risk of Road Traffic Accidents in Patients Discharged Following Treatment for Psychotropic Drug Overdose: A Self-Controlled Case Series Study in Australia

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Can be accessed from
ABSTRACT

Background: Use of psychotropic drugs is known to impair driving and increase the risk of road traffic accidents. They are also the most common drugs taken in overdose in hospital-treated episodes of self-poisoning. Most patients who take psychotropic drug overdoses are discharged within 48 hours, while they still have possible subclinical drug-effects.

Objective: Using a self-controlled case series design, we aimed to determine whether patients with psychotropic drug overdose are at a higher risk of a traffic accident in the period following discharge compared to a control period not associated with hospital-treated drug overdose.

Methodology: Using the New South Wales (NSW) Admitted Patient Data Collection (APDC) as the primary source, we retrieved 40845 hospital separation records dated between 1 July 2000 and 30 June 2008 (8-years) in patients aged 18–80 years admitted to a hospital in NSW following an intentional self-poisoning with a psychotropic drug (coded X61 or X62 as the ICD-10 external cause of injury). Of these, 33459 hospital separations (of 24284 patients) were considered eligible as the patients were discharged directly into the community where they could have driven a motor vehicle. We selected three separate post-admission periods (3 days, 1 week and 4 weeks), subtracted the number of inpatient days from each and calculated three separate post-discharge periods (immediate, intermediate and extended, respectively) for each episode of poisoning. The control period was the duration of the study period where the individual was 18 years or older, excluding the total person days in the post-discharge period/s and the index inpatient period/s. The APDC dataset was linked to the NSW Roads and Traffic Authority CrashLink dataset to identify any
accidents in which each patient was involved as a motor-vehicle driver during the follow-up period. Incidence rate ratio (IRR) for matched post-discharge and control periods was found using random effects Poisson regression.

**Results:** 72% of the subjects were discharged within 2 days following their admission with self-poisoning. Compared to the corresponding control periods the risk of a traffic accident was 3.5-times (IRR=3.49; 95%CI 1.66, 7.33; p=0.001) during the immediate, 1.9 (IRR=1.88; 95%CI 1.09, 3.25; p=0.023) during the intermediate, and 1.6 (IRR=1.65; 95%CI 1.27, 2.15; p=0.0002) during the extended post-discharge period.

**Conclusions:** Self-poisoning with psychotropic drugs is associated with a markedly increased risk of a traffic accident during the first few days following discharge. These findings raise clinical and medico-legal implications concerning fitness-to-drive during this period. The risk reduces with time but remains significantly elevated after 4 weeks post-overdose. Further research is necessary to find out the factors contributing to this ongoing risk.
**BACKGROUND**

Psychotropic drugs\(^a\) could impair driving and be associated with increased risk of road traffic accidents.\(^{[1-3]}\) Pharmacoepidemiological studies in particular have focused on accident risk associated with therapeutic use of medications including benzodiazepines,\(^{[4-9]}\) antidepressants\(^{[5, 8-11]}\) and opioids \(^{[5, 8, 11, 12]}\). However, psychotropic drugs are also among the most common substances taken in overdose, accounting for around 100000 hospital-treated overdoses per-year in the US (2006),\(^{[13]}\) 46000 in the UK (mid 2009–mid 2010)\(^{[14]}\) and 20000 in Australia (mid 2007–mid 2008).\(^{[15]}\) Most of these patients are discharged from hospitals relatively early with an average length of hospital stay of 1 day in the UK\(^{[14]}\) and 1-2 days in Australia.\(^{[15]}\) Therefore, many patients who are deemed ‘clinically’ recovered might be returning to the community while still having residual effects of the drugs on which they overdosed.

However, no study so far has examined whether patients with psychotropic drug overdose are more prone to major adverse outcomes such as traffic accidents during the period following their discharge from hospital. In the present study, we aimed to assess whether patients treated in hospitals in NSW for self-poisoning with psychotropic drugs are more prone to traffic accidents during the period following discharge from hospitals. Using a self-controlled case series approach,\(^{[16, 17]}\) we compared the traffic accident rates of a group of patients overdosed with psychotropic drugs in the period following the overdose with the rate in a control period where they were not affected by the overdose.

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\(^a\) Although opioids may not be classified under psychotropic drugs in a strict sense, they are included under the term ‘psychotropic drugs’ in the present paper to avoid verbosity. However, the distinction is made when necessary.
METHODS

Data sources

We used a record-linkage approach based on two population databases in New South Wales (NSW), Australia.

1. NSW Admitted Patient Data Collection (APDC):

   APDC includes records for all separations (i.e. discharges, transfers and deaths) in all NSW public and private hospitals and day procedure centres. The database records include a range of demographic data items (e.g. sex, date of birth, residential address), administrative items (e.g. admission and separation dates and times, mode of separation) and coded health information (e.g. principal diagnosis (ICD-10 version 4), external cause of injury (ICD-10 version 4) and any complications that occurred and procedures performed during the admission). ICD-10 coding is assigned routinely for all hospital admissions in the NSW by Clinical Coders employed by the NSW Ministry of Health. The APDC does not record individual drugs taken in self-poisoning.

2. NSW Roads and Traffic Authority Traffic Accident (CrashLink) Database:

   The CrashLink database held by the NSW Roads and Traffic Authority maintains the records of traffic accidents that occur in NSW. An accident is entered in the database if it a) is reported to the police, b) occurred on a road open to the public, c) involved at least one moving road vehicle and d) involved at least one person being killed or injured or at least one motor vehicle being towed away. Therefore, minor non-injurious accidents are generally not entered into the database.
The CrashLink database records a range of data items pertaining to each vehicle controller (i.e. drivers of motor vehicles including motor cycles) involved in an accident, including demographic data items (e.g. sex, date of birth, postcode of residence) and items related to the accident (e.g. date and time of accident, road conditions, casualties). The CrashLink Dataset for the 8-year period from 1 July 2000 to 30 June 2008 consisted of 664225 motor vehicle controller records.

**Data extraction and linkage**

Using the APDC as the primary data source, we retrieved all hospital separations following an intentional self-poisoning with a psychotropic drug [coded X61 (antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified) or X62 (narcotics and hallucinogens, not elsewhere classified) as the ICD-10 version 4 external cause of injury] from a NSW hospital during an 8-year period from 1 July 2000 to 30 June 2008 (i.e. the study period), where the patient was aged 18–80 years on the day of separation. This dataset consisted of 40845 hospital separations involved 27087 patients. Of these, 7386 separations were either transfers to other inpatient institutions or in-hospital deaths and thus were excluded. The remaining 33459 separations involved 24284 individuals who were treated for intentional self-poisoning with psychotropic drugs and discharged to the community within the study period (Figure 1). Using demographic data items, the APDC data for these eligible individuals was linked to the CrashLink database to retrieve the accident records (if any) for each individual within the study period.
Ethical considerations

The primary APDC and CrashLink dataset linkage was conducted by NSW Centre for Health Record Linkage (CHeReL), independently of the researchers. Personally identifiable data items were removed from APDC and CrashLink records in the process and researchers were provided with de-identified data where each subject was assigned with a project person number. Ethics clearance for the study was granted by the NSW Population and Health Services Research Ethics Committee.

Data analysis

Because this was the first study of its kind, we did not have previous estimates for the period where individuals could be at risk of driving impairment following a psychotrophic drug overdose. Therefore, we defined three post-admission periods (3 days, 1 week and 4 weeks), subtracted the number of inpatient days (because the patients did not drive during this period) from each post-admission period and
calculated three post-discharge risk periods (viz. immediate, intermediate and extended, respectively) of different lengths for each episode of overdose. Given the wide variation of the half-lives (and the doses) of drugs taken by the patients in the study, we assumed it is biologically plausible that any effect of drug overdose could last for up to 3 days to 1 week, but not up to 4 weeks. When the same patient was hospitalised for psychotropic drug overdose more than once within the study period, the total person-days were calculated for each post-discharge period by adding the separate post-discharge periods (illustrated in Figure 2). The control period for each subject was the total duration where the individual was 18 years or older during the follow-up period, excluding the total person-days included in the post-discharge period/s and the preceding inpatient days. The traffic accidents within each post-discharge period and corresponding control period were counted for each participant after combining the APDC and CrashLink datasets.

The data were analysed with random-effects Poisson regression models to calculate the Incidence rate ratio (IRR) between each post-discharge period (viz. immediate, intermediate and extended) and corresponding control period. For each analysis, the records where length of hospital stay was longer than the defined post-admission period (i.e. 3 days, 1 week or 4 weeks) were excluded owing to the underlying assumption that a patient is no longer affected by drug exposure after the end of that period.

Because we defined 3 post-discharge periods and performed three IRR comparisons for the same cohort, we used a modified Bonferroni correction procedure – the step-wise Hochberg approach\cite{18} – to test statistical significance. The procedure ranks the p-values (three p-values in this study) and tests the first (lowest
p-value) at 0.05/3. If it is significant the procedure then tests the next one at 0.05/2, if it is significant the next one at 0.05/1. If one of the p-values is not significant, all those below it on the ranking are non-significant.

Data were analysed using STATA version 11 (StataCorp, College Station, Texas).

Figure 2: Total post-discharge period and control period based on 1-week post-admission period in a hypothetical subject admitted twice during the study period, the first occurring on 1 July 2002 at the age of 19 years. When calculations are repeated for the same subject, a) based on 3-day post-admission period: post-discharge period = 3 days and control period = 2550 days; b) based on 4-week post-admission period: post-discharge period = 53 days, control period = 2500 days.

RESULTS

Sixty percent of the subjects were females. The mean (SD) of age was 37.5 (13.3) years, and 75% of the subjects were 45 years or younger. Of the 33459 hospital admissions 9175 were repeat admissions. Twenty percent of the patients were discharged on the same day, and 72% were discharged within 2 days following admission. There were 2825 traffic accidents where an individual in the group was involved as a driver during the study period.
The number of accidents and the computed incident rate ratios (IRRs) for each post-discharge period vs. control period are shown in Table I. Numbers of subjects included in the analyses were different depending on the selected post-discharge period (Table I, column 2), because those who were still inpatients at the end of the selected post-admission period (3, 1 week or 4 weeks) were excluded from the cohort eligible for that analysis. According to the Hochberg step-wise approach for multiple comparisons, 4-week period that gave rise to the lowest p-value was tested first at 0.017, followed by the 3-day period at 0.025 and the 7 day period at 0.05 cut-off.. All three IRRs were significant in these comparisons.18381 patients were discharged within 3 days following admission. In this group the accident rate in the post-discharge period within first 3 days following admission was 3.5 times (IRR 3.49; 95% CI 1.66, 7.33; p = 0.001) that in the corresponding control period. 21751 patients were discharged in the first week following admission. The IRR of accidents between post-discharge and control periods in this group was 1.9 (IRR 1.88; 95% CI 1.09, 3.25; p = 0.023). 23940 patients were discharged within the first 4 weeks following admission and the accident risk remained significantly elevated\(^b\) during the post-discharge period within this 4-week period (IRR 1.65; 95% CI: 1.27, 2.15, p = 0.0002).

\(^b\) In order to eliminate the effect of accidents occurred during first 3 days on the risk calculated for the 4-week post overdose period we also defined a post-discharge period between 3 to 28 days (i.e. a period mutually exclusive from 3-day post-overdose period) and recalculated the IRR. Fifty-one accidents occurred during this period and the IRR remained significantly elevated (IRR 1.53, 95% CI: 1.16, 2.02, p = 0.003) indicating that this is a genuine increase in accident risk, independent of the excess accidents occurred during the immediate post-discharge period.
Table I: Incidence rate ratios (IRR) for traffic accidents between post-discharge periods and control periods.

<table>
<thead>
<tr>
<th>Defined post-discharge period (duration post-admission)</th>
<th>Number of subjects included</th>
<th>Post-discharge period</th>
<th>Control period</th>
<th>IRR</th>
<th>95% Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crashes</td>
<td>Total person-days</td>
<td>Accidents / 100,000 person days</td>
<td>Crashes</td>
<td>Total person-days</td>
</tr>
<tr>
<td>Immediate (3 days)</td>
<td>18381</td>
<td>7</td>
<td>44176</td>
<td>15.8</td>
<td>2271</td>
<td>51 169 460</td>
</tr>
<tr>
<td>Intermediate (1 wk)</td>
<td>21751</td>
<td>13</td>
<td>155490</td>
<td>8.4</td>
<td>2617</td>
<td>60 565 832</td>
</tr>
<tr>
<td>Extended (4 wks)</td>
<td>23940</td>
<td>58</td>
<td>824606</td>
<td>7.0</td>
<td>2733</td>
<td>66 096 087</td>
</tr>
</tbody>
</table>
DISCUSSION

To our knowledge, this is the first study that examined whether patients treated in hospital for intentional self-poisoning with psychotropic drugs are more prone to traffic accidents as motor vehicle drivers in the period following discharge from hospital. The results show that 72% of those patients are discharged with in 2 days following admission. Their traffic accident risk during the first 1-3 days following discharge is 3.5 times their baseline accident risk. The risk reduces with time but remains significantly elevated after 4 weeks post-overdose.

Although our data are from mid-2000 to mid-2008, they are still clinically relevant, if not more so now than in 2008, because the length of hospital stay after an overdose has not changed and hospital admissions following psychotropic drug overdose has increased in Australia\textsuperscript{15} and other high-income countries.\textsuperscript{13, 19} We obtained data from NSW population-wide databases and thus case selection was not affected by sampling biases. The records have been entered prospectively into each source database using standard disease classification criteria and traffic accident definition criteria so that entries were not influenced by recall bias or other response bias. We eliminated confounding by unmeasured between-subject factors by using a self-controlled case-series design where each subject acted as their own control. Further, selection of a long control period increased the power of the study and eliminated the influence of random fluctuations of accident risk within the study period. We assumed that the risk of accidents did not change with time over the 8-year study period, which may not be the case in the presence of certain time-dependent intra-individual risk factors such as age and severity of any underlying psychiatric illnesses. However, the control period included both pre- and post-
overdose periods within the study duration, thus minimising the influence of any
time-variant risk factors. The linked dataset in the present study – particularly the
accident counts – was too small to perform stratified subgroup analyses based on
different demographic factors such as age and sex.

We did not have data on the percentage of drivers in the group or the driving
habits of individual subjects. However, the accident rate in the study group during the
control period (4.1-4.4 per 100000 person-days, Table I) was very similar to the rate
in general population in NSW: 664,225 reported accidents in NSW during the 8-year
study period from an average population of 5 million\(^20\) people between 18-80 years
of age is equivalent to an accident rate of 4.5 per 100000 person-days. Eighty-three
percent of the population older than 17 years held a driver’s licence in NSW in
2005.\(^{21}\) The above accident rates are an underrepresentation of all traffic accidents
that occurred in NSW during the study period because an accident is reported to the
New South Wales (NSW) Roads and Traffic Authority and entered into the
CrashLink database only if it fulfils all of the criteria listed above under Methods. For
example, non-injurious accidents with minor property damage are not reported to the
Roads and Traffic Authority.

As this is the first study that examined driving impairment following acute
psychotropic drug overdose, and included overdoses with different drugs, we did not
have an empirical basis to define a single ‘at risk’ period for the individuals
discharged from hospitals. Therefore, employing a more inclusive approach we
defined three ‘at-risk’ periods post-overdose (3 days, 1 week and 4 weeks), and
adjusted the level of statistical significance for multiple comparisons. Among the
patients discharged within 3 days following admission, the accident risk within 1-3
days following discharge was 3.5 times that of their baseline risk. Given that the accident rate in the control period in the group is similar to that of the general population in NSW, the results signify a genuine increase in risk. A 3.5-fold rise in accident risk is equivalent to that associated with a blood alcohol level of 0.09 g/dl, nearly double the legal limit (0.05g/dl) in NSW. The risk diminished with time as expected, but remained significantly elevated even after 4 weeks. The IRR of 1.65 observed after 4 weeks is equivalent to that observed with a blood alcohol level of 0.06 to 0.07 g/dl which is still above the legal limit in NSW and other states in Australia and other countries.

A high accident risk observed in first 3 days post-overdose seems compatible with drug-effects. Although the APDC dataset does not specify the psychotropic drugs taken in overdose, the majority of the ingested drugs are expected to be CNS-depressants (viz. benzodiazepines, barbiturates, antipsychotics, opioids and sedating antidepressants) as they accounted for around 80% of the psychotropic drug overdoses in patients hospitalised from 1 July 2000 to 30 June 2008 in Australia. Increased accident risk at 4 weeks cannot be explained simply by acute effects of drugs taken in the overdose episode. Aggravation of underlying psychiatric illnesses, increased stress around the period following deliberate self-harm, and/or change in psychiatric medications during post-overdose psychiatric consultations are some possible causes that could make these individuals more prone to traffic accidents, but we do not have data to test these speculations.

Some patient characteristics (e.g. tolerance due to chronic use/abuse of the drug taken in overdose), drug factors (e.g. drug class, dose, half-life of the drug) and their complex interactions can modify the severity and the duration of intoxication.
Information on these factors was not available in the source databases of this study. Even when such meticulous documentation is available in a database, epidemiological modelling of an infrequent outcome like traffic accidents based on all these factors would require extensively large datasets to have reasonable statistical power.

**Conclusions**

Our findings suggest important clinical and medico-legal implications in relation to post-discharge management of patients with intentional-self poisoning of psychotropic drugs. We believe that clinicians should warn those patients who are discharged within 1–2 days after overdose (which constitute 72% of these patients) that they are 3-4 times more likely to encounter a traffic accident if they drive during the first couple of days following discharge, and should advise them not to drive during that period. Our results also suggest that the accident risk remains elevated at medico-legally significant levels even at 4 weeks after the day of admission. However, applying driving restrictions for this extended period for each patient with psychotropic drug overdose would be a rather contentious issue until more robust evidence identifies the specific factors that increase the 4-week accident risk in patients following psychotropic drug overdose. Future research should aim at larger population-based studies that enable such fine-grained analysis. At the same time it is worth exploring the feasibility of administering clinical tests of fitness-to-drive to patients at the time of discharge and perhaps before resuming driving, with the aim of assessing the risk on an individual basis.
Acknowledgements:

This study was funded by the University of Newcastle Centre for Health Record Linkage (CHeReL) Committee with CheReL Data Linkage Credits. All stages of the study and manuscript preparation were independent of the funding body. We acknowledge NSW Department of Health for providing hospital separation data, NSW Roads and Traffic Authority (RTA) for providing traffic accident data and CHeReL for conducting primary APDC and CrashLink data linkage. We thank Jane Roberson and Catherine D’Este from the School of Medicine and Public Health of the University of Newcastle for their contribution in designing this study. The authors have no conflicts of interest to declare.

(Note: A detailed description of the data linkage process and explanatory notes on self-controlled case series analysis are included in Appendix 1. This text and the Appendix 1 are not parts of the original publication.)

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CHAPTER 8

Conclusions

Patients with central nervous system depressant drug (CNS-D) overdose are currently discharged after treatment in hospitals based on clinical signs of recovery. Patients are usually deemed medically fit to be discharged once they recover from acute intoxication and can engage in basic activities necessary for self-care such as feeding, getting off the bed, walking and toileting. These Basic Activities of Daily Living ((BADL) (Katz et al., 1970) are largely dependent on orientation and motor functions which are routinely assessed in a clinical setting with tests for orientation (time, place and person), hand-eye co-ordination, gait, nystagmus etc. Such assessment ensures that the patient no longer needs medical supervision and is safe to be at home.

Routine clinical assessment of these patients however, does not tap into higher cognitive functions that underpin more complex activities that a relatively young population is likely to undertake during the post-discharge period in their households, community and workplace. The broad question addressed in this thesis is whether the patients ‘clinically recovered’ from CNS-D overdose are fit enough to carry out these more complex daily activities during the post-discharge period.

In this thesis we addressed this question at two levels. First, using a battery of validated neuropsychological tests, we examined whether CNS-D overdose leads to impairment of cognitive functions underlying daily activities that the discharged patients are expected and likely to carry out during the post-discharge period. The
second, an epidemiological study examined whether CNS-D overdose increases the risk of traffic accidents – which is a major adverse outcome in real life – in the period following discharge.

The epidemiological study utilised population-based datasets and included all admissions to hospitals in NSW from mid 2000 to mid 2008 for psychotropic drug overdose while the clinical study recruited patients admitted from November 2008 to April 2011 in tertiary referral centre in NSW. The sample of patients with CNS-D overdose in the clinical study was very similar to the population-based cohort of the epidemiological study in terms of age and gender distribution and the duration of hospital stay (Table 1), verifying that the clinical study sample is representative of the patients hospitalised with CNS-D overdose in NSW.

**Table 1:** Comparison of the sample characteristics of the clinical study and the epidemiological study

<table>
<thead>
<tr>
<th></th>
<th>CNS-D Group in the clinical study</th>
<th>Cohort in the epidemiological study</th>
</tr>
</thead>
<tbody>
<tr>
<td>% females</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>37.5 (12.5)</td>
<td>37.5 (13.3)</td>
</tr>
<tr>
<td>% discharged within 2 days</td>
<td>85%</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Cognitive impairment and its impact on daily activities**

Our findings demonstrate that patients ‘clinically recovered’ from CNS-D overdose have significant impairments in multiple cognitive functions including visual attention and visuomotor skills, executive functions and working memory, and
decision-making. When compared with the controls, patients with CNS-D overdose also showed worsening of performance with increasing executive task demands.

The patients who take CNS-D overdoses represent a relatively young subsection of the population. Compared with the elderly, they are likely to return to social and working environments with higher cognitive demands. Deficits in attention (particularly switching of attention between tasks), working memory and planning could impact on a broad range of activities from simple household chores such as cooking, to more complex duties at the workplace and the community. Increased impulsivity could also contribute to poor decision-making in their social, financial and health affairs. In spite of extensive cognitive impairment, those faculties are imperative for patients discharged after self-harm – more so than for the general population – because those patients are more likely to encounter strained social relationships, workplace backlogs and complex psychological and medical management plans during the period following discharge.

With regression modelling we estimated that the impairments observed in discharged patients is equivalent to a ‘cognitive ageing’ by 10-20 years depending on the cognitive domain tested. However, unlike normal ageing, drug overdose effects are acute and do not allow time for these individuals to develop alternate coping strategies. On hindsight, we believe that estimating their subjective awareness of the impairment and correlating it with the objective impairment would have been useful in understanding whether patients have an accurate estimate of their impairment, even if they may not possess coping strategies.
CNS-D overdose and driving

Converging evidence from the neuropsychological assessment and epidemiological approach indicates that CNS-D overdose have deleterious effects on driving. The traffic accident risk of these individuals increases by 3-4 times in the immediate post discharge period, a risk equivalent to a blood alcohol level of 0.09g/dl (Compton et al.; McLean et al., 1980), nearly double the legal limit (0.05g/dl) for driving in Australia. The risk remained significantly elevated during the first week following overdose. Direct testing of discharged patients revealed widespread deficits in cognitive and psychomotor skills underpinning driving. These ranged from visual attention and visuomotor deficits that could adversely affect operational processes of driving (e.g. maintaining lane position and headway) to impairments of executive functions (attentional set-shifting, planning, working memory) that are crucial in more complex interactions in the driving environment. Patients also had higher levels of impulsivity in decision-making which could also compromise their driving safety. TMT-B results, dichotomised based on its relationship with driving performance (Classen et al., 2008; Richardson and Marottoli, 2003) and traffic accident risk (Stutts et al., 1998), suggests that as much as 60% of the patients with CNS-D overdose may be grossly impaired (≤10th percentile) at the time of discharge from hospital.

Self-harm – irrespective of the agent used – is accompanied with psychological stress which in turn could impair driving. A previous study conducted in NSW shows that young drivers who reported self harm within the previous year have a relative risk of 1.37 (95% CI 1.09–1.72) of being involved in a traffic accident relative to those who reported no self-harm (Martiniuk et al., 2009). Although our epidemiological study – by design – is unable to tease apart the contribution of drugs
and the act of self-harm on the accident-risk during the post-discharge period, the risk that we observed in the immediate post-discharge period is markedly higher. The 53% increase in accident risk that we observed at 4 weeks post-overdose is more consistent with the effect size observed by Martiniuk et al. above.

**Implications for management of patients during the post-discharge period**

We believe – given the increasing demand for beds in hospital emergency departments – it may not be feasible for the clinicians to keep these patients until complete cognitive recovery. Therefore, whilst providing reassurance to patients with CNS-D overdose about to be discharged from hospital that the drug effects are self-limiting and the patients are not likely to experience long term complications of drug toxicity, clinicians should warn patients that their cognitive functions may not have fully recovered. Demands for making major decisions, multitasking, operating machinery, driving a vehicle etc. often depends on one’s social and professional commitments so that health professionals should specify which activities to be avoided / limited based on the situation of individual patients. Medical practitioners should also take this into account when determining the time that the patient should

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*Effects of self-harm per se could be assessed by applying the same epidemiological study design to a cohort of patients hospitalised with self-poisoning with drugs that do not have psychoactive effects. The APDC dataset (2000-2008) had only around 10,000 records for self-poisonings with non-psychoactive drugs. This sample size was underpowered for a meaningful statistical analysis.*
be away from their work, for instance, when issuing medical certificates for employed individuals.

Impaired driving in particular has clinical and medicolegal implications. CNS-D overdose is not as common as many other risk factors for traffic accidents, such as alcohol and sleep deprivation. However, unlike in the case of those risk factors, all patients with CNS-D overdose go through the health care system before they take up driving after discharge and hence constitute a well-defined population of ‘at-risk drivers’ whose additional risk might be prevented.

Under present Australian Driving Licensing Authorities guidelines, medical conditions that cause short term impairment of driving requires the health professionals to advise patients not to drive for the period where the condition might affect the patient (Austroads Inc., 2003). In compliance with confidentiality and privacy regulations, medical practitioners are not required to report those conditions directly to the driving licensing authorities unless the patient continues to drive despite appropriate counselling and is likely to endanger the public. Clinicians should therefore explain to the discharged patients that they are 3-4 times more likely to involve in a traffic accident if they drive during the immediate post-discharge period, and strongly advise the patients not to drive at least for 2-3 days following discharge, preferably during the first week. Driving fitness criteria are more stringent for commercial vehicle drivers owing to public health concerns (Austroads Inc., 2003). As the increased traffic accident risk remains significantly elevated even 1-4 weeks after exposure, commercial vehicle drivers in particular may have to avoid work for 1 week or longer.
Driving impairment and increased accident risk caused by CNS-Ds could be potentiated by co-ingestion of alcohol or other sedative medications (Dassanayake et al., 2011). It is possible that the same interaction could occur if patients with CNS-D overdose take alcohol or a sedative drug before the effects of the CNS-D overdose wear off. Therefore patients should be advised that their impairment could worsen if they take alcohol or another sedative during the first few days following discharge.

Given the cognitive deficits demonstrated, some patients may not be able to remember the advice given verbally. This may be a particular problem in patients overdosed with benzodiazepines who are prone to anterograde amnesia (Verwey et al., 2000; Verwey et al., 2005). Therefore it is preferable to give these instructions verbally and in writing.

**Future directions**

*Role of bedside tests.* Standard driving fitness tests used by driving regulatory authorities consist of an extensive battery of laboratory and on-the-road driving tests (NSW Transport, Roads and Maritime Services, 2011). Such comprehensive screening of patients with CNS-D overdose is not feasible, cost-effective or safe. However, as elaborated in Chapter 6, TMT-B is a feasible and time-efficient method of assessing cognitive impairment, and shows the potential in predicting driving impairment with reasonable ecological validity in a clinical setting. The relationship between TMT-B and driving performance (Classen et al., 2008; Richardson and Marottoli, 2003) and traffic accident risk (Stutts et al., 1998) has primarily been demonstrated in healthy elderly individuals. Therefore further research is necessary to
validate TMT-B as a bedside driving-fitness test in a younger population that constitute the majority of patients hospitalised with CNS-D overdose.

Assessment of time course of cognitive recovery. Although the epidemiological study examines the traffic accident risk at different intervals following discharge, we could not perform follow up cognitive assessments in the patients recruited for the clinical study, owing to practical difficulties in getting the patients back to the hospital to perform comprehensive neuropsychological assessments. Such follow up assessment would help to delineate the temporal nature of cognitive recovery after CNS-D overdose. Follow up cognitive testing at 7 and 28 days post-overdose would enable examination of whether cognitive test performance correlated with the observed pattern in traffic accident risk. TMT-B is likely to be the most appropriate for follow up testing because 1) the majority of the patients were impaired in TMT-B in the first assessment and 2) impaired TMT-B is known to be associated with increased traffic accident risk and 3) the test is quick and feasible to administer. However, like most other neuropsychological tests (Bartels et al., 2010; Hausknecht et al., 2007), TMT-B is prone to marked practice effects when re-administered at intervals of 2-3 weeks (Bartels et al., 2010). This however, diminishes significantly when alternate test forms are used for retesting (Beglinger et al., 2005). Given this evidence, the best practice in follow up assessment would be to test with alternate forms of TMT-B and interpret the results taking into account the practice-related improvement. Together with objective testing, further studies should also rate patients’ subjective assessment of their impairment, as an accurate self-assessment helps patients to self-limit their activity until they recover from the effects of overdose.
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Appendix
Appendix 1: Detailed description of data linkage process and explanatory notes on self-controlled case series analysis

Data linkage

The primary data linkage was carried out by the NSW Centre for Health Record Linkage (CHeReL). The variables used for this linkage were the first name, surname, date of birth and address. The primary dataset that defined the study group was derived from NSW Admitted Patient Data Collection (APDC) and comprised all hospital separations following an intentional self-poisoning with a psychotropic drug [coded X61 (antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified) or X62 (narcotics and hallucinogens, not elsewhere classified) as the ICD-10 version 4 external cause of injury] from a NSW hospital during an 8-year period from 1 July 2000 to 30 June 2008 (i.e. the study period), where the patient was aged 18–80 years on the day of separation. CHeReL also acquired the linkage variables for all vehicle controller records entered in the NSW Roads and Traffic Authority (RTA) CrashLink database for the study period (n = 664,225).

Probabilistic record linkage methods and ChoiceMaker software (ChoiceMaker Technologies, Inc. New York, NY 10010) was used to link the datasets. ChoiceMaker uses ‘blocking’ and ‘scoring’ to identify definite and possible matches. During blocking, ChoiceMaker searches the target datasets for records which are possible matches to each other. There are two types of blocking. The exact blocking algorithm requires records to have the same set of valid fields and the same
values for these fields. The automated blocking algorithm builds a set of conditions that are used to find as many as possible records that potentially match each other. Scoring employs a combination of a probabilistic decision, which is computed using a machine learning technique, and absolute rules, which include upper and lower probability cut-offs, to determine the final decision as to whether each potential match denotes or possibly denotes the same person. The record pairs between upper and lower cut-offs undergo clerical review by Record Linkage Officers (RLOs). Upper and lower probability cut-offs initially start at 0.75 and 0.25 for a linkage. After the first run through ChoiceMaker, a random sample of 1,000 groups of matched records with probabilities that lie above the upper cut-off are reviewed by hand. If the false positive rate is above 5/1,000 the upper cut-off is raised to force these matches into the clerical review area. If there are no false positives, the upper cut-off is lowered to reduce the burden of clerical review. Similarly, a random sample of groups of matched records with probabilities that lie below lower cut-off is reviewed by hand. If the false negative rate is above 5/1,000 the lower cut-off is lowered to force these matches into the clerical review area. If there are no false negatives, the lower cut-off is raised to reduce the burden of clerical review. The process is then rerun with successive adjustments until the false positive rates and false negative rates are in the range of 0-5/1000 matches. The uncertain matches (i.e. with a probability in between final lower and upper cut-offs) undergo clerical review by RLOs, which in turn undergo quality assurance checks by database managers or senior RLOs. Present APDC- CrashLink data linkage recorded a false positive rate of 0.2% and a false negative rate <0.5%. The linkage process is described in detail in CHeReL website http://www.cherel.org.au/downloads.html
Once the linkage process is complete CHeReL assigns a project person number (PPN) to each matched and unmatched individual in the primary dataset and each matched individual in the secondary dataset. Accordingly, each individual in the APDC dataset and each CrashLink record that matched an APDC record were assigned with PPNs. CHeReL also links the PPN to a unique identifier for each record within each database (Record ID in APDC and Crash ID in CrashLink). CHeReL sent the PPNs and matching unique identifiers to the data custodians at NSW Department of Health (for APDC data) and NSW RTA (for CrashLink data). Upon receiving the PPNs, data custodians used the PPN – unique identifier link to extract relevant records from their databases. Accordingly APDC and CrashLink data custodians extracted the relevant records for each PPN, and sent the research variables tagged with PPN to the researchers. We linked the de-identified APDC and CrashLink records using PPNs and created the final common data-tables for analysis.

**Self-controlled case series (SCCS) analysis**

The SCCS approach defines a retrospective cohort, defines exposed and control periods assuming that effects of drug overdose are self-limiting and compares the incidence of outcome events (i.e. traffic accident) in the exposed and control periods. It is a modified cohort study design where the periods of exposure and non-exposure are defined in a within-subject design.

**Assumptions of independence**

The SCCS approach and Poisson regression modelling that we used in the study makes the following assumptions:
1. One accident in a given individual is independent of any previous accidents.

2. Drug overdoses (i.e. exposures) are independent of traffic accidents: It is possible that an individual meets with a traffic accident and as a result of the psychological stress etc. self-poison with a psychotropic-drug. This reverses the direction of causality that is assumed in this study. We believe traffic accident is a rare cause for CNS-D overdose among drivers. Even if that happens, it will increase the accident count in the pre-admission or the control period pushing the calculated incidence rate ratio (IRR) towards the null.

3. Observation periods are independent of traffic accidents: The total observation period of the retrospective cohort was from 1 July 2000 to 30 June 2008. This period was defined based on the availability of APDC (i.e. exposure) data rather than traffic accident data. Therefore the observation period is independent of the outcome variable.

**Preventing double counting of overdose events**

Some subjects were admitted a second (and perhaps a third) time to a hospital within the exposed period of the first admission. This could be a separate exposure or a repeat encounter with the health care system that is related to the exposure that led to first admission. In the analysis, this makes it possible for an accident to fall within the 'exposed periods' following both admissions, which in turn could result in the accident being counted twice as two separate accidents. To prevent this happening, we isolated such multiple admissions for each exposed period (immediate,
intermediate and extended) and counted the accidents only in relation to the first admission within the defined exposed period. The number of in-hospital days of these subsequent admissions with in the defined post-discharge period was subtracted in counting the number of exposed days following the first admission.

**Possible trends in accident rates within the study duration due to external factors**

In addition to driver factors, environmental and vehicle-related factors (changes in policing, roads and vehicles) might have also modified/reduced the risk of a crash during the 8-year study period. Our analysis does not explicitly take this into account. However, the control (non-exposed) period included both pre- and post-overdose periods within the study duration (albeit of different lengths in different patients), and hence negated any effects of such secular trends.

We also did not consider possible seasonal variations of accident rates in the analysis. It is possible that accidents are increased during the festive seasons, long weekends etc. There is no reason to believe that such periods are distributed unequally in the exposed periods and non-exposed periods, unless patients take more drug overdoses just before /during those periods. We examined the dates of each accident that occurred during the Immediate Post-Discharge Period. None of those accidents occurred in a long weekend.
Appendix 2: Evidence of acceptance of publications in press

Paper 2:

From: Journal of Clinical Psychopharmacology Thursday - 12 January, 2012 5:16 AM
<barbara.kern@tufts.edu>
To: Tharaka Dassanayake <tharaka.dassanayake@uon.edu.au>
Subject: Your Revised Submission
Attachments: Mime.822 (6036 bytes) [View] [Save As]

CC: barbara.kern@tufts.edu
Ref.: Ms. No. JCP-D-11-00319R1
Cognitive impairment in patients clinically recovered from central nervous system depressant drug overdose.
The Journal of Clinical Psychopharmacology

Dear Dr. Dassanayake:

I am pleased to tell you that your Revised manuscript has now been Accepted for publication in the Journal of Clinical Psychopharmacology. Thank you for making the requested revisions and for your thorough cover letter.

Prior to publication, we need a few missing details for references #28 (city of publisher); 29 (company name); 30, 31; and 32 (city for these 3). You can email me this information at your convenience, and I will add it (barbara.kern@tufts.edu). Copyright/Disclosure Form: You already submitted your signed Copyright Forms for each author with your revision, so this is fine. You will receive page proofs to check and a reprint order form by email about two months prior to the actual publication date, which we do not know as yet. We will Publish articles Ahead of Print on our Journal website (www.psychopharmacology.com), AFTER initial author and Editor corrections have been made on the page proofs.

All sources of funding/support and relevant disclosures and conflicts of interest for ALL authors must be stated, or indicate "The authors declare no conflicts of interest". [NOTE: You provided this information, so this is complete.]

Thank you for your patience and for your contribution to the Journal.

Sincerely,
Barbara Kern, Managing Editor
Journal of Clinical Psychopharmacology
Tufts University School of Medicine
Department of Pharmacology
136 Harrison Avenue
Boston, MA  02111
Email: barbara.kern@tufts.edu
Dear Dr Dassanayake:

Ref: Cognitive skills underlying driving in patients discharged following self-poisoning with central nervous system depressant drugs

Your paper is accepted for publication in Traffic Injury Prevention with final revisions.

Please do the following:

1) finalize the paper according to the review comments
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3) check that the figures match the Journal style. Figure guidelines are available online and attached.
4) email the following items to:

gcpi_production@taylorandfrancis.com

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• Figures in .eps, .tiff, .png or .jpg format and at least 300 dpi in resolution.
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Sincerely,
David C Viano, Editor-in-Chief
Traffic Injury Prevention
dviano@comcast.net

Reviewer(s)' Comments to Author:

Reviewer: 1
Comments to the Author
The authors addressed my concerns in their revision.

Reviewer: 2
Comments to the Author
One of the possible limitations that could be addressed in the discussion is that the intoxicant is based on self-report, not on laboratory analysis. One cannot exclude that other drugs were taken in addition to the ones named by the patients.
P 5, line 32: is the term 'all consented patients' correct?