UNIVERSITY
OF TASMANIA

The effect of 5 mg of diazepam on driving-related skills:

Equating impairment to a blood-alcohol concentration level,

and investigating subjective perception of impairment

By Madelyn Derrick

B.Psych (Hons)

School of Psychology

Submitted in partial fulfilment of the requirements for the
Doctorate of Psychology in Clinical Psychology
at the University of Tasmania, June 2013

Acknowledgments

This project was assisted by the provision of funds and facilities from Dr Raimondo Bruno and the Psychopharmacology and Clinical Psychopathology (PCP) group at the University of Tasmania. I would like to acknowledge the supervision of Dr Bruno, whose support and guidance throughout this project is immensely appreciated. I would also like to acknowledge the supervision of Dr Frances Martin, particularly during the formative stages of the project, and the advice and assistance offered by Dr Saxby Pridmore. Finally, I would like to express my gratitude to my husband and children who have offered unwavering support throughout this project.

Statement of Ethical Conduct: The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University (ethics approval no. H10309)

Declaration of Originality: This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

Authority of Access: This thesis may be made available for loan and limited copying and communication in accordance with the Copyright Act 1968.

Signed by Madelyn Derrick **Date**

Table of Contents

Introduction 2
Driving under the influence of benzodiazepines 4
Diazepam-induced driving impacts 6
Method of review of driving impacts 7
Review results - driving-related skills studies 9
Review results - driving simulator studies 21
Review results - on-road driving studies 24
Habituation to psychomotor effects 26
Epidemiological studies 29
Summary of diazepam-induced driving impacts 32
Subjective perception of psychomotor impairment 33
Subjective perception of sedation 38
Equating diazepam-induced impairment to a blood-alcohol concentration 41
Equivalency of effect method 41
Regression equation method 48
Conclusions of review 49
Aims of the current study 51
Method 52
Participants 52
Materials 53
Alcohol Use Disorders Identification Test (AUDIT) 53
Kessler Psychological Distress Scale (K10) 53
Weschler Test of Adult Reading (WTAR) 54
Digit-symbol substitution task (DSST) 54
Cognitive Drug Research (CDR) attention battery 54
Dual Task 56
Occupational Safety Performance Assessment Test (OSPAT) 57
Visual Analogue Scales 58
Procedure 58
Design and analyses 60
Control variables 61
Test battery variables 61
Composite performance variables 62

Results 66
Control measures 66
Baseline measures 67
Table 8. Group means, ANOVA results and effect sizes for objective performance variables at baseline 67
Objective performance measures 68
Psychomotor processing speed measure 68
Sensory motor reaction time measures 69
Vigilance measures 71
Divided Attention measures 72
Tracking measure 75
Subjective experience measures 79
Subjective alertness measures 79
Subjective competence measures 80
Comparisons of effects 83
Comparisons of psychomotor function effects 84
Comparisons of speed and accuracy effects 85
Comparisons of tracking performance and overall objective performance 85
Comparisons of pre-test and post-test subjective ratings 86
Comparisons of objective performance and subjective experience of performance 87
Table 12. Tests of significance of differences between effect sizes for selected variables 92
Summary of results 93
Discussion 94
Effects of 5mg of diazepam on driving-related skills 94
Psychomotor processing speed 94
Sensory motor reaction time 95
Vigilance 98
Divided attention 99
Speed and Accuracy effects 100
Patterns for task complexity 101
Summary of driving-related skills findings 105
BAC equivalency of psychomotor effects 105
Summary of BAC equivalency findings 109
Subjective perceptions of psychomotor effects 109

Perceptions of fatigue 110
Perceptions of competence 113
Summary of subjective perceptions of psychomotor effects 116
Limitations of findings 117
Limitations due to singular dose 117
Limitations due to age of participants 119
Practical implications of findings 122
Conclusions 123
References 126
Appendices 132

Abstract

A mixed-measures research design was employed to investigate the effects of a single acute 5mg dose of diazepam on psychomotor performance and subjective experience. Following a double-blind protocol, 34 benzodiazepine-naive participants were administered 5mg of diazepam or placebo. Tasks measuring the driving-related skills of psychomotor processing speed, sensory motor reaction time, vigilance, divided attention and tracking, as well as subjective alertness and subjective competence, were completed for 150 minutes post-ingestion. Deleterious effects of diazepam tended to peak at 60 minutes post-ingestion, with the largest effects being of a moderate magnitude. Psychomotor processing speed and vigilance were more deleteriously affected than sensory motor reaction time and divided attention. Dissociations between the alertness and competence ratings given before and after test battery completion suggest that self-monitoring accuracy may not be fully intact under the influence of the 5mg dose. A method for equating impairment to a blood-alcohol concentration (BAC) equivalency was trialled. This method involved the application of a regression equation to performance decrement measurements from the tracking task. The BAC equivalency of impairment found in the current study utilising this method was .041%, however it is recognised that this is likely to be an underestimation for older diazepam users and for people taking regular, repeated 5mg doses for the first several weeks. Consequently, many diazepam users may be impaired by diazepam to an extent considered risky for driving (more than .05% BAC). It is reasonable to suggest that Medical Practitioners should educate patients when prescribing diazepam, so that patients are aware of the steps they can take to reduce their crash risk when under the influence of diazepam.

Introduction

Benzodiazepines, often referred to as sedatives or minor tranquilisers, are a class of drug used primarily in the treatment of anxiety and insomnia. Other medical applications include use as anticonvulsants, particularly during alcohol withdrawal where seizures are a risk; and as muscle relaxants, amnestics and anaesthetics during surgical procedures (Stewart & Westra, 2002). Drugs within the benzodiazepine class differ in terms of their profile of clinical effects, speed of absorption and duration of action. Those with a longer duration of action are prescribed more commonly to treat anxiety and tend to be referred to as anxiolytic benzodiazepines, whereas those with a shorter duration of action are prescribed more commonly to treat insomnia and are often referred to as hypnotic benzodiazepines (Karch, 2007).

Benzodiazepines act by modulating the activity of gamma-amino butyric acid (GABA) (Rivas-Vazquez, 2003). GABA is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). Benzodiazepines act as agonists at certain $GABA_A$ receptor sites, resulting in an increase in the inhibitory effects of GABA. The $GABA_A$ receptor subtypes that are currently known to be sensitive to benzodiazepines are those including the subunits α_1, α_2,α_3, and α_5, and relatively recent research has identified the locality and function of some of these subunits (Möhler, Fritschy, & Rudolph, 2002). $Alpha_1$subunits have been shown to mediate the sedative, hypnotic, anticonvulsant and amnestic effects of benzodiazepines. These subunits are found in abundance throughout the thalamus and cortical areas of the brain, which are involved in a wide variety of CNS functions. $Alpha_2$subunits have been shown to mediate anxiety processes, and are found throughout the amygdala, hippocampus and cerebral cortex, which are all brain structures known to play a role in mediating anxiety. $Alpha_2$subunits are also found in abundance in the spinal cord from where they have been shown to mediate muscle relaxation effects. It is thought that different types of benzodiazepines may have preferential binding at the different $GABA_A$ receptor subunits, and that

this contributes to the variance in clinical effects seen amongst the benzodiazepines (Rivas-Vazquez, 2003).

Research investigating the roles of the various subtypes of $GABA_A$ receptor sites is paving the way for the development of anxiolytic drugs that target $GABA_A$ receptor subtypes more selectively. It is expected that such drugs would be capable of mediating anxiety processes by modulating activity at the α_2 subunit whilst not impacting on activity at other subunits, and thereby reducing the incidence of unwanted side effects (Möhler, et al., 2002). Meanwhile, the low selectivity of action at $GABA_A$ receptor sites by currently marketed benzodiazepines means that these drugs have a wide array of unwanted effects. Sedation, daytime drowsiness, ataxia, slurred speech, inattention, memory impairment and psychomotor slowing and dis-coordination are the most frequently reported side effects (Rivas-Vazquez, 2003). These are particularly problematic for those taking benzodiazepines to reduce anxiety during the day. Other adverse effects include accumulative effects with repeated dosing, tolerance, dependence and a withdrawal syndrome following extended use (Bateson, 2002).

There is a large body of research, much of it conducted in the 1970s, that has examined the psychomotor effects of various types of benzodiazepines. In an early review of this research, Hindmarch (1980) concluded that sensory processing, central integration, motor responses, and sensory motor co-ordination are aspects involved in psychomotor performance that are shown to be consistently impaired by benzodiazepines. In another review of the literature specifically examining the effects of benzodiazepines in benzodiazepine-naive volunteers, Wittenborn (1979) concluded that benzodiazepines detract from psychomotor performance in a dose-related fashion, with a slowing of the speed at which repetitive tasks are performed being the primary effect. Furthermore, following a review of the psychomotor effects of benzodiazepines the day after an evening dose, Johnson and Chernik (1982) concluded that impairment does continue into the following day. The longer-acting anxiolytic benzodiazepines (such as diazepam) were thought to generally result in greater impairment in this respect.

Driving under the influence of benzodiazepines

The well-established finding of benzodiazepine-induced psychomotor impairment naturally creates concern over the ability to drive a motor vehicle safely whilst under the influence of benzodiazepines, and experimental studies do provide evidence for impairing effects of benzodiazepines on driving skills. Rapoport and Banina (2007) reviewed the results of studies investigating benzodiazepine effects on driving simulator performance and on the ability to maintain lane position during on-road highway driving. It was concluded that benzodiazepines are for the most part found to increase reaction time and impair maintenance of lane position during driving simulation, and are consistently found to impair maintenance of lane position in on-road driving.

Results from epidemiological studies suggest that the psychomotor side effects detected in experimental studies do lead to increased crash risk when driving. Two known meta-analyses of epidemiological studies have been conducted in recent years. Both examined benzodiazepines in isolation (i.e. not just in combination with alcohol and other drugs) and included studies using both case-control and cohort sampling methods. Rapoport and colleagues (2009) conducted a meta-analysis on 6 case-control and 3 cohort studies, and found a 60% increase in likelihood of being involved in a motor vehicle crash amongst benzodiazepine users. Dassanayake and colleagues (2011) conducted meta-analyses on twelve case-control and six cohort studies separately. A 59% increase in the likelihood of being involved in a crash was found amongst the case-control studies, and an 81% increase in the likelihood of being involved in a crash was found amongst the cohort studies.

The risks faced during the first week of benzodiazepine use have been shown to be particularly high. A very large scale cohort study (which included 98 000 control participants) monitored 148 000 anxiolytic benzodiazepine (oxazepam, lorazepam and diazepam) users and 78 000 hypnotic benzodiazepine (triazolam and flurazepam) users for two months after filling a prescription, and incidences of drivers' hospitalisations following crashes were recorded (Neutel, 1995). The crash risk

faced by anxiolytic benzodiazepine users during the first week following the filling of a prescription was found to be very high, with users found to be 13.8 times more likely to be involved in a crash than non-users. The increased risks attenuated over subsequent weeks with users being 5.6 times more likely to be involved in a crash within two weeks, and 2.6 times more likely within four weeks. Hypnotic benzodiazepine users were found to be 9.1 times more likely to be involved in a crash during the first week following a prescription fill. These increased risks also attenuated over subsequent weeks, although to a somewhat slower extent than for the anxiolytics, with hypnotics users being 6.5 times more likely to be involved in a crash within two weeks, and 4.0 times more likely within four weeks. The development of tolerance to benzodiazepines (Bateson, 2002) may explain the attenuation of risk found in this study.

With the recognition of benzodiazepines increasing the odds of being involved in a crash, studies have been conducted to determine whether the use of benzodiazepines increases the likelihood of causing a crash. A case-control study found drivers who tested positive for benzodiazepines alone (i.e. not in combination with alcohol or other drugs) were significantly more frequently culpable than those who were drug free, and culpability was shown to significantly increase with benzodiazepine-blood concentration levels (Longo, Lokan, & White, 2001). To exclude the influence of recreational benzodiazepine use on these findings, a further study separated out the drivers with only therapeutic levels of benzodiazepines from those with intoxicating levels (Longo, Hunter, Lokan, White, & White, 2000). Significantly higher culpability was still evident amongst drivers with therapeutic levels of benzodiazepines, who were 3.3 times more likely to be culpable in a multiple vehicle crash than drug-free drivers were.

These culpability effects are not limited to minor crashes and remain notable when crashes involving fatalities are investigated. A case-control study found that the presence of anxiolytic benzodiazepines (those with a half-life of longer than 24 hours) resulted in significantly increased odds (33% to 68% more likely) of having committed unsafe driving actions immediately prior to a

fatal crash, and hence more likely to have been culpable for the crash than drug-free drivers (Dubois, Bedard, & Weaver, 2008). The presence of hypnotic benzodiazepines (those with a half-life of less than 24 hours) also resulted in significantly increased odds of culpability in fatal crashes (50% to 59% more likely than drug-free drivers).

The impairing psychomotor effects of benzodiazepines as a class of drug have been well established, with experimental and epidemiological evidence suggesting that driving capabilities are detrimentally affected. The recent advances in our knowledge of the pharmacological actions of benzodiazepines mean that the specific effects of one type of benzodiazepine may be different from another (Bourin & Briley, 2004). Hence, to establish the effects of diazepam on driving capabilities it is now important to consider this drug in isolation.

Diazepam-induced driving impacts

Diazepam is currently the most commonly dispensed anxiolytic benzodiazepine in Australia. Over 2.2 million diazepam prescriptions were filled in Australia in 2009, with around 1.95 million of these being for the 5mg tablets (Department of Health and Ageing, 2011). Common brand names available in Australia include Valium, Valpam, Ducene and Antenex. Selective serotonin reuptake inhibitors (*SSRIs*) or serotonin–norepinephrine reuptake inhibitors (*SNRIs*) remain the preferred ongoing pharmacological treatment for anxiety disorders, and diazepam is recommended only as a short-term intervention for a period of up to four weeks (Rang & Dale, 2007). Indicated uses for diazepam include: for alleviation of severe stress and anxiety symptoms for a short period following a particularly stressful or traumatic event; for intermittent alleviation of anxiety symptoms in someone prone to sudden and short bouts of anxiety; and for assistance with anxiety management whilst waiting for SSRIs or SNRIs to take effect, which can take up to three to four weeks (Sadock & Sadock, 2007). The National Health and Medical Research Council of Australia recommend that benzodiazepines should be prescribed at the lowest possible dose for effect, and for the shortest period of time necessary (National Health & Medical Research Council, 1999). The recommended

dose range for diazepam is 5mg to 40mg a day (MIMS Australia, 2006), with most being prescribed a starting dose of 5mg.

Compared to other benzodiazepines, diazepam is rapidly absorbed, rapid in onset of effects, and long-acting (Kaplan & Sadock, 1996). Peak plasma levels occur within 30 to 90 minutes following ingestion, and the elimination half-life is around 40 hours (Sansom, 2009). The overall duration of action tends to be between 24 and 48 hours(Rang & Dale, 2007). Peak effects do not necessarily occur at the same time as peak plasma concentration (e.g. Cutson, Gray, Hughes, Carson, & Hanlon, 1997; Hart, Hill, Bye, Wilkinson, & Peck, 1976; Ingum, et al., 1992; Jalava, Mattila, Tarssanen, & Vanakoski, 1995) and may vary depending on the specific effect. It is the relatively long duration of action of diazepam and the fact that it is frequently taken during the day (as opposed to the hypnotic benzodiazepines prescribed for use immediately before going to bed at night) that creates much concern over the impact of its side effect profile – particularly the psychomotor effects and their impact on driving capabilities. A review of the literature that provides evidence for the impact of diazepam on driving capabilities follows.

Method of review of driving impacts

For the purposes of reviewing the literature on diazepam-induced driving capabilities, a literature search was aimed at finding all studies conducted to date that had investigated the effects of diazepam on either on-road driving, simulator driving, or driving-related skills. Driving-related skills were conceptualised as the psychomotor functions of psychomotor processing speed, sensory-motor reaction time, vigilance, and divided attention, and tracking. This particular set of functions was chosen for a number of reasons. Firstly, the Guidelines for Research in Drugged Driving (Walsh, Verstraete, Huestis, & Morland, 2008) recommend assessing three core levels of behaviour when investigating crash risk – automative behaviour, control behaviour, and executive planning behaviour – and collectively the selected functions represent all three of these levels of behaviour. Secondly, these functions are the most commonly assessed in studies investigating drug effects on

psychomotor capabilities. Finally, the tasks typically used to examine these functions are all well established and have been validated as being sensitive to drug effects. In addition to studies investigating psychomotor effects of diazepam, epidemiological studies investigating the impacts of diazepam use on rates of involvement in crashes were searched for, so as to determine the extent to which diazepam-induced psychomotor impairment does result in on-road crashes.

Searches were conducted using the databases Medline, Web of Science, Science Direct, ProQuest, Scopus and PsychInfo, and were limited to English language articles only. Search terms included benzodiazepines, diazepam, driving, simulator, on-road, accident, crash, psychomotor, tracking, processing speed, divided attention, vigilance, sustained attention, focussed attention, sensory-motor, and reaction time. Appropriate variations of these terms were also searched (e.g. drive, driver, drives). The range for year of publication was not limited for the search. Only studies including a control group are included in the review. As diazepam is recommended only for short-term or intermittent use (National Health & Medical Research Council, 1999), the impact of diazepam on individuals unhabituated to its effects is of primary concern. For this reason, unless otherwise stated, only studies investigating the effects of a single, acute oral dose of diazepam in healthy benzodiazepine-naïve participants are included in this review. Exceptions to these criteria occur when reviewing the habituation studies that examine the effects of a repeated dose of diazepam over a short time frame, and when reviewing the epidemiological studies. Additionally, in a small number of included studies that utilised a cross-over design, participants in the diazepam group may have been exposed to a different type of benzodiazepine on a singular, earlier occasion.Given the vast range of sample sizes used in the research, a discussion of effect sizes is considered more appropriate than a review of the statistical significance of results alone. Unfortunately, the majority of studies reviewed were published before systematic reporting of effect sizes became an expectation. Where possible effect sizes are calculated (Hedges *g*) based on means and standard deviations/standard errors reported in text or table format. If change from baseline scores are not reported, the absence of the standard deviation for the change from baseline means

prevents direct calculation of effect sizes. In this case, effect sizes are calculated for baseline test results, and for post-ingestion test results, and the difference between these is referred to as the "effect size change from baseline". Effect sizes of 0.2 to 0.5 are considered to be small; effect sizes of 0.5 to 0.8 are considered to be moderate; and effect sizes of more than 0.8 are considered to be large (Cohen, 1988).

For each review section, a table summarises the findings in the literature. The tables summarise findings of differences between placebo and diazepam-treated participant groups that are statistically significant, and where possible, differences between placebo and diazepam-treated participant groups in effect size changes from baseline. A difference in effect size change from baseline of 0.5 or more is considered to be meaningful and noteworthy for this purpose. At the end of each section of the review the literature is synthesised with a view to approximate the magnitude and duration of effect of diazepam on driving capabilities. Acute doses of less than 10mg are referred to as low doses; acute doses of between 10 and 20mg are referred to as moderate doses; and acute doses of greater than 20mg are referred to as high doses. Particular attention is paid to results from studies utilising a low dose (usually 5mg) for the following reasons: firstly, 5mg is the dose most prevalently prescribed in Australia (Department of Health and Ageing, 2011); and secondly, individuals who have not been taking the drug regularly, and hence have not developed a tolerance to its effects, are most likely to be prescribed a low dose, in line with prescribing guidelines (National Health & Medical Research Council, 1999).

Review results - driving-related skills studies

The effects of diazepam on psychomotor processing speed, sensory-motor reaction time, vigilance and divided attention are reviewed below (note that tracking skills are typically investigated in on-road and simulator studies, and will be reviewed in those corresponding sections). Table 1, 2, 3, and 4 summarise the research relevant to each psychomotor skill category.

Psychomotor processing speed

Digit-symbol substitution tests, or their variant symbol-digit substitution tests, are well-established measures of psychomotor processing speed and have been commonly used in diazepam studies. Table 1 summarises the following review of psychomotor processing speed studies. Jalava and colleagues (1995) investigated diazepam effects utilising a digit-symbol substitution task (DSST) along with a digit copying task to represent the manual component of the DSST. Volunteers were administered either a 15mg or 30mg dose of diazepam or a placebo, and tests were administered 1, 3 and 6 hours post-ingestion. The 15mg dose did not result in significant differences from placebo on either task, however a moderate deleterious effect of diazepam on DSST performance for up to 6 hours post-ingestion is evident. Effect size changes from baseline (*g*) were 0.69 at 1 hour post-ingestion, 0.69 at 3 hours post-ingestion and 0.47 at 6 hours post-ingestion. The 30 mg dose resulted in significantly impaired digit copying performance at 1 and 3 hours post-ingestion, and significantly impaired DSST performance at all three testing points. Large deleterious effects of diazepam on DSST performance were evident with effect size changes from baseline (*g*) of 1.14, 1.48 and 0.95 at 1, 3 and 6 hours post-ingestion respectively. These results confirm the effects of diazepam on sensory-motor reaction time as having a cognitive component as well as the manual component (the simple copying task).

Mattila (1988) also investigated the effects of a 15mg dose of diazepam on DSST performance and found the dose to significantly impair performance relative to placebo effects at a test-point 1.5 hours post-ingestion. A moderate effect was evident with an effect size change from baseline (*g*) of 0.66. Group differences were no longer significant at 3 hours post-ingestion and the effect was small (effect size change from baseline (*g*) of 0.22). In a later study Mattila and colleagues (1998) again found the 15mg dose to result in significantly impair DSST performance this time at testing points 1.5 and 3.5 hours post-ingestion. A large deleterious effect was evident at 1.5 hours post-ingestion with an effect size change from baseline (*g*) of 0.84. A small effect was evident at 3.5 hours post-ingestion with an effect size change from baseline (*g*) of 0.48. This small effect was still evident at a

further test point 5 hours post-ingestion where the effect size change from baseline (*g*) was 0.42. Vanakoski and colleagues (2000) also found a 15mg dose to result in poorer DSST performance than placebo at a testing point 1.5 hours post-ingestion, however at the 4 hours post-ingestion performance had returned to levels similar to placebo.

Whilst most studies tend to utilise younger participants, two studies specifically looked at diazepam effects on DSST performance in older participants. Vanakoski and colleagues (2000) found a 10mg dose to have no significant effects on performance amongst participants aged 55 to 57 years at 1.5 and 4 hours post-ingestion. Conversely, in a group of participants aged 66 to 76 years, Cutson and colleagues (1997) found a similar dose (9.8mg per 70kg of bodyweight) to result in significantly poorer performance than placebo at test points 30 and 60 minutes post-ingestion. Performance returned to levels similar to placebo by 1.5 hours post-ingestion.

Lower doses of diazepam have also been shown to impair DSST performance. Hart and colleagues (1976) found that whilst a 2.5mg dose resulted in performance similar to placebo levels at 2 hours 45 minutes post-ingestion, a 5mg dose resulted in significant impairment at this test point. Neither dose showed significant effects at the next testing point of 6 hours post-ingestion.

The reviewed studies consistently show deleterious effects of diazepam on psychomotor processing speed. Doses as low as 5mg have been shown to significantly impair performance in this regard. The lowest dose investigated so far , 2.5mg, was not shown to have an effect on performance, however, effects were not tested until 2 hours 45 minutes post-ingestion. Studies with more frequent test points find performance effects to peak earlier than this (Cutson, et al., 1997; Echizenya, et al., 2007; Echizenya, et al., 2003; Ingum, et al., 1992; Jalava, et al., 1995), hence the possibility of this low dose having an impairing effect at an earlier stage cannot be ruled out. The duration of effects on psychomotor processing speed in these studies appears variable, ranging from 1 hour through to 6 hours, with no clear dose-related patterns. The study that reported effects still being evident at 6 hours post-ingestion utilised a very high dose of 30mg. The studies that utilised

Table 1. Effects of diazepam doses on psychomotor-processing speed over time

Task type	Diazepam dose	Individual test points post-ingestion	Researchers
Digit-symbol substitution	2.5mg	2hrs 45 mins$^{\sim}$, 6hrs$^{\sim}$	Hart et al., 1976
Digit-symbol substitution	5mg	2hrs 45 mins*$^{\sim}$, 6hrs$^{\sim}$	Hart et al., 1976
Digit-symbol substitution	9.8mg/70kg (participants aged 66-76)	0.5hrs*$^{\sim}$, 1hr*$^{\sim}$, 1.5hrs$^{\sim}$, 2hrs$^{\sim}$, 4hrs$^{\sim}$, 6hrs$^{\sim}$, 8 hrs$^{\sim}$	Cutson et al., 1997
Digit-symbol substitution	10mg (participants aged 55-57)	1.5hrs$^{\sim}$, 4 hrs$^{\sim}$	Vanakoski et al., 2000
Digit-symbol substitution	15mg (participants aged 55-57)	1.5hrs*$^{\sim}$, 4 hrs$^{\sim}$	Vanakoski et al., 2000
Digit-symbol substitution	15mg	1.5hrs*†, 3 hrs	Mattila, 1988
Symbol-digit substitution	15mg	1hr*†, 3.5hrs*, 5 hrs	Mattila et al., 1998
Symbol-digit substitution	15mg	1hr†, 3hrs†, 6 hrs	Jalava et al., 1995
Symbol-digit substitution	30mg	1hr*†, 3hrs*†, 6hrs*†	Jalava et al., 1995
Digit copying	15mg	1hr$^{\sim}$, 3hrs$^{\sim}$, 6 hrs$^{\sim}$	Jalava et al., 1995
Digit copying	30mg	1hr*$^{\sim}$, 3hrs*$^{\sim}$, 6 hrs$^{\sim}$	Jalava et al., 1995

Notes.† denotes a deleterious effect size change from baseline of greater than 0.5 (Hedges *g*); $^{\sim}$denotes where effect sizes could not be calculated due to insufficient information; * denotes significantly poorer task performance ($p<.05$) following diazepam relative to placebo; all studies investigated the acute effects of a singular dose of diazepam in benzodiazepine-naive participants.

more moderate doses report effects diminishing between 1.5 and 5 hours post-ingestion, with a small deleterious effect still evident at 5 hours post-ingestion in one study. The only study to utilise a 5mg dose shows effects to diminish somewhere between 2 hours 45 minutes and 6 hours.

Sensory-motor reaction time

Tasks used to measure sensory-motor reaction time include simple reaction time tasks, involving a single response to a stimulus; choice reaction time tasks involving a choice between one of two possible responses to a stimulus; and complex choice reaction time tasks which involve making decisions about responses to stimuli based on more complex rules. All three levels of sensory-motor reaction time tasks have been employed in diazepam studies. Table 2 summarises the following review of sensory-motor reaction time studies. Following 10 and 20mg doses of diazepam, Ingum and colleagues (1992) tested simple reaction time at each individual's peak diazepam plasma

concentration (median of 1.5 hours post-ingestion), with both doses being found to result in significantly longer reaction times than placebo. Ogle and colleagues (1976) found a lower dose of 5mg to result in significantly poorer performance relative to placebo at testing points 1 and 3 hours post-ingestion. Hart and colleagues (1976) also found a 5mg dose to result insignificantly poorer performance. Impairment for this dose was detected at a testing point 2 hours post-ingestion, but not at 5 hours 15 minutes post-ingestion. In the same study a 2.5mg dose was found to result in performance similar to that following placebo at both test points.

In two studies using a similar methodology, Echizenya and colleagues (2007; 2003) investigated the effects of 5mg and 10mg doses on an auditory choice reaction time task completed by participants aged 18 to 23 years. Both studies found the 5mg dose to have no significant effects on performance averaged over 20 to 240 minutes post-ingestion, relative to placebo, however, a moderate deleterious effect of diazepam was evident in the 2007 study with an effect size change from baseline (*g)* of 0.70. The 10mg dose resulted in significantly prolonged reaction times over the course of 240 minutes in both studies. Very large deleterious effects were evident in the 2007 study with an effect size change from baseline (*g*) of 1.37. Whilst both studies involved relatively young participants, the second study included an additional, older participant group(aged 53 to 71 years). In this older group 5mg was found to result in significantly prolonged reaction times over the course of 240 minutes, with an effect size change (*g*) of 1.00, indicating a large deleterious effect. In both of these studies testing was conducted every twenty minutes, however, analyses for each test point were not reported. As only the average effect of test points conducted between 20 and 240 minutes post-ingestion were reported, the magnitude of peak effects are not known. It is likely that the effect sizes provided here are underestimations of peak effects, and that the non-significant effects reported for the 5mg dose may well have reached statistical significance at their peak.

Coull and colleagues (1995) found a 10mg dose to significantly prolong reaction times at 40 minutes post-ingestion in a choice reaction time task involving additional distracting stimuli. When the

complexity of the task was increased the impairing effect of this dose continued to be evident. In a highly complex choice reaction time task Ingum and colleagues (1992) also found a 10mg dose to result in significantly poorer performance than placebo. The mean maximal increase in reaction time occurred at 1.5 hours post-ingestion, and both the 10mg dose and a 20mg dose were found to result in significantly slower responses around this time. The reviewed studies are consistent in showing diazepam-induced prolonged sensory-motor reaction time. There are several studies supporting the deleterious effects of diazepam in doses as low as 5mg, with moderate effects

Table 2. Effects of diazepam doses on sensory-motor reaction time over time

Task type	Diazepam dose	Individual test points post-ingestion	Researchers
Simple reaction time	2.5mg	2 hrs~, 5 hrs 15 mins~	Hart et al., 1976
Simple reaction time	5mg	2 hrs*~, 5 hrs 15 mins~	Hart et al., 1976
Simple reaction time	5mg	1hr*, 3 hrs*~	Ogle et al., 1976
Simple reaction time	10mg	90 mins*~	Ingum et al., 1992
Simple reaction time	20mg	90 mins*~	Ingum et al., 1992
Choice reaction time	5mg	20-240 mins~	Echizenya et al., 2003
Choice reaction time	10mg	20-240 mins*~	Echizenya et al., 2003
Choice reaction time	5mg (participants aged 53-71)	20-240 mins*†	Echizenya et al., 2007
Choice reaction time	5mg (participants aged 18-23)	20-240 mins†	Echizenya et al., 2007
Choice reaction time	10mg (participants aged 18-23)	20-240 mins*†	Echizenya et al., 2007
Choice reaction time	10mg	40 mins*~	Coull et al., 1995b
Complex choice reaction time	10mg	40 mins*~	Coull et al., 1995b
Complex choice reaction time	10mg	90 mins*~	Ingum et al., 1992
Complex choice reaction time	20mg	90 mins*~	Ingum et al., 1992

Notes.† denotes a deleterious effect size change from baseline of greater than 0.5 (Hedges *g*); ~denotes where effect sizes could not be calculated due to insufficient information; * denotes significantly poorer task performance ($p<.05$) following diazepam relative to placebo; all studies investigated the acute effects of a singular dose of diazepam in benzodiazepine-naive participants.

apparent in younger participants and large effects apparent in older participants. These effects were averaged over the testing schedule and it is likely that they would have been of a greater magnitude at the time of peak effect. Whilst a lower dose of 2.5mg was not shown to result in impairment at 2 hours post-ingestion, it remains possible that this dose would have had an effect at an earlier time point when performance effects were at a peak. Only two studies reported performance across multiple testing points allowing for an assessment of duration of effects, and these suggest that the effects of a 5mg dose diminish some time between 3 hours and 5 hours 15 minutes post-ingestion.

Vigilance

Vigilance is tested via tasks that require the continuous direction of attention to a discrete set of stimuli. Vigilance over a relatively short duration of time (i.e. five minutes or less) is often referred to as 'focussed attention', whilst vigilance over a longer period of time is often referred to as 'sustained attention'. Cancellation tasks are commonly employed as a measure of focussed attention, and involve identifying target numbers, letters or symbols amongst sets of non-target numbers, letters or symbols. Rapid visual information processing tasks (RVIP tasks) are commonly employed as a measure of sustained attention, and involve the detection of target sequences of numbers, letters or symbols amongst a series of randomly presented numbers, letters or symbols. Table 3 summarises the following review of reaction time results from vigilance studies utilising Cancellation tasks, RVIP tasks, and related tasks.

Utilising a two-tiered dosage regimen, Rich and colleagues (2006) administered participants weighing less than 60kg a 10mg dose of diazepam, whilst those weighing more than 60kg were administered a 15mg dose, resulting in an average of 13.3mg per 70kg of bodyweight. A 90 second cancellation task was administered five times in the first 45 minute block post-ingestion, and a further five times in the second 45 minute block post-ingestion. Mean performance during each of the two blocks was shown to be significantly impaired by diazepam. The placebo group was shown to perform increasingly well over consecutive trials of the task, whilst the diazepam group were

unable to benefit from practice effects and actually decreased in performance level from the baseline trial. Utilising the same methodology and dosage pattern (resulting in an average dose of 12.6 mg per 70kg of bodyweight) Brown and colleagues (1996) also found performance on this task to be impaired relative to placebo over the first 1.5 hours post-ingestion.

Mattila and colleagues (1988) found performance on a cancellation task (of unknown duration) to be significantly poorer following a 15mg dose of diazepam relative to placebo. Significant effects were apparent at a testing point 1.5 hours post-ingestion, but not at 3 hours post-ingestion. Loke and colleagues (1985) found performance impairment on a 60 second cancellation task at a slightly lower dose. A dose of 10.5mg per 70kg of bodyweight (along with the higher dose of 21mg per 70kg of bodyweight) was shown to result in impaired performance at testing points 50 and 130 minutes post-ingestion. Kelland and Lewis (1996) also found cancellation performance (in a task of variable duration) to be impaired following a 10mg dose, at 30 minutes post-ingestion. This result was confirmed on a 50 second computerised version of the cancellation task – a digit vigilance test.

Takahashi and colleagues (2010) measured the effects of a lower dose on vigilance utilising a 2.5 minute Continuous Performance Test (similar to a RVIP task). The significance of differences between groups receiving 5mg of diazepam and a placebo were not reported, however, the reporting of means at baseline, 1 hour and 4 hours post-ingestion allow for calculation of effect sizes. Effect size changes from baseline indicate a small effect of diazepam on task performance at 1 hour post-ingestion (g = 0.23). The effect size change from baseline at 4 hours post-ingestion was negligible (g = 0.01).

The results reviewed so far have involved vigilance tasks taking only several minutes to complete. A number of studies have investigated the effects of diazepam on tasks requiring extended sustaining of attention. Deakin and colleagues (2004) utilised a 7 minute RVIP task, and found that whilst performance on this task did not appear to be affected by 5mg or 10mg doses of diazepam 40 minutes post-ingestion, when compared to placebo, a 20mg dose resulted in slower reaction times

and increased numbers of errors. Coull and colleagues (1995) also utilised this task and found conflicting results. Both 5mg and 10mg doses were shown to result in poorer performance than placebo. Whilst the timing of the task administration is not known for this study, it is feasible that impairment was detected in this study due to a closer coinciding of peak performance effects and test administration than in the prior study.

Utilising even longer vigilance tasks, Hart and colleagues (1976) investigated the effects of the low doses of 2.5mg and 5mg of diazepam. Neither dose was found to affect performance on a 15 minute cancellation task, with performance remaining similar to placebo levels. However, this task was not administered until 2 hours 15 minutes post-ingestion, and it is plausible that performance effects had peaked and diminished prior to this. A one hour long auditory vigilance task was administered between 45 minutes and 1 hour 45 minutes post-ingestion and would have been likely to coincide with peak performance effects. On this task, where participants were required to detect tones of 0.4 seconds in duration amongst a series of tones of 0.5 seconds in duration, both the 2.5mg and 5mg doses resulted in significantly poorer performance than placebo. These effects were no longer apparent at the second administration of this task between 4 and 5 hours post-ingestion.

From these studies it is apparent that vigilance is consistently affected by diazepam, and by doses as low as 2.5mg. Whilst one study found statistically significant effects for 2.5mg and 5mg doses during the period of peak effect, another suggested that this may only be a small magnitude deleterious effect (g = 0.23). Tests that both coincide with peak performance effects and are sufficiently sensitive are likely to be necessary to be able to detect diazepam-induced impairment at doses as low as 5mg or less. The reviewed studies involving moderate doses suggest that vigilance impairment can be detected as early as 30 minutes post-ingestion, and diminishes some time between 2 hours 10 minutes and 3 hours post-ingestion. The reviewed studies involving lower doses suggest that vigilance effects diminish anywhere between 1 hour 45 minutes and 4 hours, however, are likely to diminish at the earlier end of this range.

Table 3. Effects of diazepam doses on vigilance over time

Task type	Diazepam dose	Individual test points post-ingestion	Researchers
Cancellation	2.5mg	2 hrs 15 mins˜, 5 hrs 30 mins˜	Hart et al., 1976
Cancellation	5mg	2 hrs 15 mins˜, 5 hrs 30 mins˜	Hart et al., 1976
Cancellation	10mg	30 mins*˜	Kelland& Lewis, 1996
Cancellation	10.5mg/70kg	50 mins*˜, 130 mins*˜	Loke et al., 1985
Cancellation	12.6mg/70kg	0 - 1.5 hrs*˜	Brown et al., 1996
Cancellation	13.3mg/70kg	0 – 45 mins*˜, 45 – 90 mins*˜	Rich et al., 2006
Cancellation	15mg	1.5 hrs*˜, 3 hrs˜	Mattilla et al., 1988
Cancellation	21mg/70kg	50 mins*˜, 130 mins*˜	Loke et al., 1985
Auditory vigilance	2.5mg	45 mins - 1hr 45 mins*˜, 4 - 5 hrs˜	Hart et al., 1976
Auditory vigilance	5mg	45 mins - 1hr 45 mins*˜, 4 - 5 hrs˜	Hart et al., 1976
Digit vigilance	10mg	30 mins*˜	Kelland& Lewis, 1996
Rapid visual information processing	5mg	Not reported*˜	Coull et al., 1995a
Rapid visual information processing	10mg	Not reported*˜	Coull et al., 1995a
Rapid visual information processing	5mg	40 mins˜	Deakin et al., 2004
Rapid visual information processing	10mg	40 mins˜	Deakin et al., 2004
Rapid visual information processing	20mg	40 mins*˜	Deakin et al., 2004
Continuous performance test	5mg	1 hr-, 4 hrs-	Takahashi et al., 2010

Notes.† denotes a deleterious effect size change from baseline of greater than 0.5 (Hedges *g*); ˜denotes where effect sizes could not be calculated due to insufficient information; * denotes significantly poorer task performance ($p<.05$) following diazepam relative to placebo; - denotes where tests of significance of poorer task performancefollowing diazepam relative to placebo are not reported; all studies investigated the acute effects of a singular dose of diazepam in benzodiazepine-naive participants.

Divided attention

Divided attention refers to the ability to attend to multiple tasks simultaneously. Divided attention tasks often combine reaction time or vigilance tasks for this purpose. Table 4 summarises the following review of divided attention studies. Jalava and colleagues (1995) investigated

performance on a visual divided attention task at 1, 3 and 6 hours post-ingestion of diazepam. A moderate deleterious effect of 15mg of diazepam was evident at 1 hour and 3 hours post-ingestion, with effect size changes from baseline (*g*) of 0.50 and 0.61 respectively. Group differences did not reach significance at any time point for this dose. Large deleterious effects were indicated for a 30mg dose, with effect size changes from baseline (*g*) of 1.06 at 1 hour post-ingestion, 1.50 at 3 hours post-ingestion, and 0.97 at 6 hours post-ingestion. The impairment relative to placebo reached significance at the 3 hour post-ingestion test point. When the difficulty level of the task was increased through the addition of a third component (an auditory component), an interesting pattern emerged. Deleterious effects were for the most part *smaller* in magnitude compared to when the task was less complex, particularly so for the 3 hour post-ingestion test-point where both doses resulted in a reduced deleterious impact relative to other time-points. The 15mg group dose resulted in an effect size change from baseline (*g*) of 0.88 at 1 hour post-ingestion. A small beneficial effect was evident at 3 hours post-ingestion (effect size change from baseline (*g*) = 0.26) and the effect was negligible at 6 hours post-ingestion. Effect size changes from baseline (*g*) following the 30mg dose were 0.80 at 1 hour post-ingestion, 0.59 at 3 hours post-ingestion and 0.95 at 6 hours post-ingestion. The researchers do not comment on this unexpected pattern of results, however it is possible that the more challenging tasks resulted in increased effort being exerted, as has been noted in other literature (e.g. Anshel, Weinberg, & Jackson, 1992; Gardner, 1990; Ma & Trombly, 2004; Molloy & Parasuraman, 1996).

Boucart and colleagues (2007) tested divided attention capabilities via a visual divided attention task administered at the point of each individual's peak diazepam plasma concentration (mean of 30 minutes post-ingestion). Task performance was shown to be detrimentally affected by doses of both 7mg and 21mg per 70kg of bodyweight. Slower reaction times and an increased number of omission errors relative to a placebo group were evident.

Moskowitz and Smiley (1982) administered diazepam twice daily to participants over the course of 9 days. On the first day of testing, after participants ingested their initial dose of 10mg, performance impairment was detected on a 12 minute visual divided attention task. Diazepam resulted in significantly poorer performance than a placebo at 1 hour post-ingestion. Group differences ameliorated at testing points beyond 1 hour, with the diazepam and placebo groups performing to a similar level at 3 and 5 hours post-ingestion.

The results of this small number of studies suggest that divided attention capabilities are impaired by diazepam, with significant effects found for doses as low as 7mg, and effects shown to be of a moderate to large magnitude for moderate doses (15mg). Of note is the pattern found in one study where deleterious effects reduced in magnitude with increased task complexity. The duration of effect of a low dose is not known, as the only study to utilise a low dose had only one test point that was 30 minutes post-ingestion. Effects of moderate to high doses appear to be detectable from as early as 30 minutes post ingestion through to upwards of 6 hours for higher doses.

Table 4. Effects of diazepam doses on divided attention over time

Task type	Diazepam dose	Individual test points post-ingestion	Researchers
Visual divided attention	7mg/70kg	30 mins*˜	Boucart et al., 2007
Visual divided attention	10mg	1 hr*˜, 3 hrs˜, 5 hrs˜	Moskowitz and Smiley, 1982
Visual divided attention	21mg/70kg	30 mins*˜	Boucart et al., 2007
Visual divided attention	15mg	1 hr†, 3 hrs†, 6 hrs	Jalava et al., 1995
Visual divided attention	30mg	1 hr†, 3 hrs*†, 6 hrs†	Jalava et al., 1995
Visual and auditory divided attention	15mg	1 hr†, 3 hrs, 6 hrs	Jalava et al., 1995
Visual and auditory divided attention	30mg	1 hr*†, 3 hrs†, 6 hrs†	Jalava et al., 1995

Notes.† denotes a deleterious effect size change from baseline of greater than 0.5 (Hedges *g*); ˜denotes where effect sizes could not be calculated due to insufficient information; * denotes significantly poorer task performance ($p<.05$) following diazepam relative to placebo; all studies investigated the acute effects of a singular dose of diazepam in benzodiazepine-naive participants.

Review results - driving simulator studies

Computerised driving simulators allow for a controlled and safe method of approximating and assessing driving performance. The driving simulators employed in benzodiazepine studies vary greatly in terms of complexity and extent of ecological validity, although most include tracking (ability to maintain lane position suggestive of hand-eye coordination) and reaction time components as a minimum. Diazepam-induced impairments have been shown on relatively simple driving simulators, such as that requiring the 'driver' to complete a tracking task using a steering wheel as the input device for the program as well as in more complex driving simulators, requiring the division of attention across multiple tasks.

Mattila and colleagues (1988) tested the effects of 15mg of diazepam on tracking ability using a driving simulator that required the maintenance of lane position via a steering wheel. The simulator ran for 5 minutes and was completed at test points 1.5 and 3 hours post-ingestion. The difficulty level was increased for the second half of the test. Diazepam resulted in significantly more tracking errors than placebo at the 1.5 hour test point, however, only for the first (easier) half of the test. The effect size change from baseline (*g*) was 0.77 for the first half. This deleterious effect decreased for the more difficult second half of the test, with a small effect size change from baseline (*g*) of 0.41. Effect size changes from baseline (*g*) at 3 hours post-ingestion were negligible. In another study Mattila (1988) tested the effects of 15mg of diazepam on this simulator, this time with the addition of a simultaneous choice reaction time task. Diazepam was again found to result in significantly greater tracking errors at 1.5 hours post-ingestion, with an effect size change from baseline (*g*) of 0.38. Reaction times were also significantly prolonged at this test point, and a large effect was evident with an effect size change from baseline (*g*) of 0.84. At the second test point 3 hours post-ingestion group reaction time remained affected (effect size change from baseline (*g*) of 0.35). Tracking error effects were small and group differences did not reach significance on either measure at this test-point. In a later study Mattila and colleagues (1998) found 15mg of diazepam to

significantly impair both tracking and reaction time performance on this simulator at 1 hour post-ingestion, with very large effects being evident. The effect size changes from baseline (*g*) were 1.15 for the tracking measure and 1.41 for reaction time. The effects may have been larger in this study as the first post-ingestion test point occurred 30 minutes earlier than in the previous two studies and may have more closely coincided with actual peak performance effects. Effects on reaction time remained deleterious and moderate at 3.5 hours and 5 hours post-ingestion, with effect size changes from baseline (*g*) of 0.62 and 0.50 respectively. Group differences did not reach statistical significance at either of these test points. Group differences were also non-significant for the tracking measure at these test points, and effects remained negligible.

Kuitenen (1994) investigated the effects of 15mg of diazepam on a 5 minute simulated driving task similar to that used in the above studies. Maintenance of lane position via a steering wheel was required simultaneously as responding to both visual and auditory stimuli in a choice reaction time component of the task. At a test point 1.5 hours post-ingestion, a placebo group's tracking performance improved from baseline levels whilst the diazepam group's performance declined, however, this difference did not reach statistical significance. Reaction time was however significantly prolonged by diazepam relative to placebo. No significant differences between the groups were evident at the next test point 4.5 hours post-ingestion.

Vanakoski and colleagues (2000) investigated driving simulator performance in younger (22 to 24 years) and older (55 to 57 years) participants under both 'light' and 'dark' driving conditions. The simulator consisted of simple tracking for the first five minutes of the test, and complex tracking (involving the addition of a simultaneous choice reaction time task) for the second five minutes of the test. The 'dark' condition simulated combinations of minimal lighting, an unclean windscreen, and confronting flashes of light. Testing was conducted at 1.5 hours and 4 hours post-ingestion, however, the results for each of these test points were not reported separately. Both the younger and older participants showed impaired performance relative to placebo following 15mg and 10mg

of diazepam respectively, with significantly increased tracking errors and prolonged reaction times. Additionally, the older participants made a greater number of reaction errors compared to when given placebo. Interestingly, simple tracking appeared to be more affected by diazepam than complex tracking, and overall performance measures did not differ between the light and dark conditions in the diazepam groups, despite the increased difficulty of the dark condition evident in baseline measures.

Willumeit and colleagues (1984) tested the effects of a 10mg dose of diazepam on an extended driving simulator task at 1, 2 and 3 hours post-ingestion. The simulator ran for 30 minutes and included a choice reaction time component, requiring responding to visual stimuli by pressing a foot pedal, and a tracking component, requiring using a steering wheel to guide a light towards a target and maintain its position. Relative to placebo, diazepam appeared to result in poorer tracking performance at 1 hour post-ingestion, and prolonged reaction times throughout all three test-points, however, group differences did not reach statistical significance.

Moskowitz and Smiley (1982) utilised an elaborate driving simulator composed of a car-cab with a large projector screen, where steering, accelerating and braking resulted in changes on the screen. The simulator ran for 30 minutes. Tasks included accurate steering, maintaining lane position whilst compensating for simulated wind gusts, maintaining a constant distance behind a car moving at variable speeds, following direction signs, emergency decision making (braking or swerving to avoid an object dependent on whether there was a vehicle following or not), and manoeuvring through an obstacle-ridden slalom course. Participants were administered diazepam twice a day (totalling 15mg/day) for 9 days. On the first day of treatment, 1 hour following a 10mg dose of diazepam, overall performance was shown to be significantly impaired relative to placebo. The diazepam group were shown to be less adept at speed control, tracking control and target detection following this initial acute dose.

A recent study tested the effects of a 5mg dose of diazepam on simulated driving (Takahashi, et al., 2010). The simulator was designed to examine three driving skills associated with crashes – lane position maintenance (tracking), speed control and emergency breaking. Although the reporting of analyses do not allow for a determination of significance of differences between the diazepam and placebo groups in this study, effect sizes can be calculated. The effect of 5mg of diazepam on each of the measures post-ingestion was deleterious. Tracking effects appear to have been moderate at 1 hour post-ingestion with an effect size change from baseline (*g*) of 0.51, and small at 4 hours post-ingestion with an effect size change from baseline (*g*) of 0.38. Speed effects appear to have been small at 1 hour post-ingestion with an effect size change from baseline (*g*) of 0.32, and negligible at 4 hours post-ingestion with an effect size change from baseline (*g*) of 0.11. Breaking reaction time effects appear to have been negligible at 1 hour post-ingestion with an effect size change from baseline (*g*) of 0.19, and small at four hours-post ingestion with an effect size change from baseline (*g*) of 0.36.

As with the driving-related skills studies, the driving simulator studies reviewed consistently find diazepam to impair performance, however, the differences between diazepam and placebo groups do not always reach statistical significance in these studies. Doses as low as 10mg have shown significant effects, and moderate effects have been evident following a 5mg dose. The small number of studies means that it is difficult to draw conclusions as to the duration of deleterious effects, however there is evidence to suggest effects of a 5mg dose lasting for up to four hours. As with the divided attention studies, the results from several of the driving simulator studies suggest that the deleterious effects of diazepam may reduce in magnitude with increasing task complexity.

Review results - on-road driving studies

On-road studies allow for maximum ecological validity, however, ethical and legislative concerns have limited the number of studies using this methodology. Only two placebo-controlled studies are known to have investigated the acute effects of a single dose of diazepam using on-road driving

testing. O'Hanlon and colleagues (1982) tested the effects of 5mg and 10mg doses of diazepam on lane position maintenance (i.e. tracking) during on-road driving. Participants were required to drive on a four-lane highway at night, for 100kms, beginning 1 hour post-ingestion. The 5mg dose appeared to have no effect with participants performing almost identically to those in the placebo group. The 10mg dose however resulted in significantly poorer lane position maintenance. Three out of 9 participants in this group 'weaved' to an extent considered to be risky (more than 35 cm variation) and crossed over into an adjacent lane or road shoulder, whilst no participants in the 5mg or placebo groups crossed over the boundaries of their lane.

In a later study, administering the same on-road driving test to a larger sample, O'Hanlon and colleagues (1995) found a 5mg diazepam dose to result in impairment. The diazepam group showed significantly poorer lane position maintenance than a placebo group over the course of the driving test (one to two hours post-ingestion). Four of the 16 participants in the diazepam group 'weaved' to the extent considered risky whilst, as in the earlier study, none of the placebo group left the boundaries of their lane throughout the test.

From these two on-road studies it appears that tracking ability whilst on-road is affected by diazepam, and significant effects induced by doses as low as 5mg become apparent with a sufficient sample size. Effects were evident between one and two hours post-ingestion in both studies, however, any further conclusions as to duration of effects cannot be drawn due to both studies having only a single testing point. It should also be noted that testing in these on-road studies was limited to highway driving. This is a relatively simple and monotonous task compared to other driving scenarios. For example, driving through urban streets in heavier traffic is likely to be a more complex task requiring a greater division of attention, more varied information processing and more numerous reactions to stimuli. Therefore, the effect of diazepam on driving in other 'on-road' scenarios may differ to that found in the above two reviewed studies.

Habituation to psychomotor effects

The studies reviewed so far have focussed on the acute effects of a single dose of diazepam in benzodiazepine-naive volunteers, and there is substantial evidence to suggest that diazepam does result in deleterious psychomotor effects. The extent to which habituation to diazepam attenuates these effects, and the rate at which this occurs, has not yet been discussed. Tolerance is known to occur with all benzodiazepines, with individuals requiring an increasing dose over time to produce an equivalent effect(Rang & Dale, 2007). However, tolerance to diazepam effects is thought to develop slowly (Verster, Veldhuijzen, & Volkerts, 2005), leaving a window where diazepam users may continue to experience psychomotor effects at a similar level to that following the initial acute dose. Given the accumulation of diazepam and its active metabolites that is known to occur with repeated dosing (Lader, 1987), it may even be possible that psychomotor effects become even more pronounced before attenuating as tolerance develops. A small number of studies have investigated the psychomotor effects of regular diazepam doses during this window of time, and are reviewed below.

Moskowitz and Smiley (1982) utilised an elaborate driving simulator and a visual divided attention task (both described in previous sections) to test diazepam effects after 8 days of continued dosing. Volunteers were administered 10mg in the morning and 5mg at night, and tested on the morning of days one and eight. The driving simulator task was administered pre-dose and 1 hour post-ingestion, and the divided attention task was administered pre-dose and 1, 3 and 5 hours post-ingestion. On the first day of treatment (as previously reviewed), overall driving simulator performance was shown to be significantly impaired relative to placebo, with speed control, tracking control and target detection measures all suggesting impairment. Divided attention was also impaired one-hour post-ingestion, as evidenced by prolonged reaction times. A rapid recovery from the dose effects between 1 and 3 hours was evident - reaction times remained prolonged at 3 hours post-ingestion, however, not to an extent that was statistically significant. On the eighth day of testing, pre-dose results found only a tracking impairment, with no group differences evident in

other measures. These pre-dose results suggest that non-acute, accumulative diazepam effects were minimal. Post-ingestion results again showed overall driving simulator performance to be significantly impaired relative to placebo. Speed control, tracking control and target detection (reaction time) measures all showed impairment, and these acute effects were stronger on day eight than on day one. Recovery time from the dose was noticeably slower than on day one, as evidenced by significantly prolonged reaction times on the divided attention task at both 1 and 3 hours post-ingestion. Reaction times remained prolonged at 5 hours post-ingestion, however not significantly. This study found overall diazepam-induced impairment to be greater in extent and duration on the eighth day of treatment than on the first. This finding suggests that tolerance to this particular diazepam dosing regimen does not fully compensate for the accumulating levels of diazepam and its active metabolites within eight days.

Mattila (1988) investigated driving simulator performance and psychomotor processing speed after a 15mg dose of diazepam, on both days one and eight of a 10mg a day dosing regimen. Psychomotor processing speed was tested with a digit-symbol substitution test (DSST), and the driving simulator consisted of tracking (lane position maintenance) and choice reaction time components. Testing was conducted pre-dose and 1.5 hours and 3 hours post-ingestion on both test days. Small to large effects were apparent following the acute dose on day one (as previously reviewed) with diazepam being found to result in increased tracking errors (effect size change from baseline (*g*) of 0.38), prolonged reaction times (effect size change from baseline (*g*) of 0.84), and poorer DSST performance (effect size change from baseline (*g*) of 0.66), relative to placebo at 1.5 hours post-ingestion. There were few accumulative effects of diazepam and its active metabolites apparent at pre-dose testing on day eight, with no group differences on the measures being evident. Post-ingestion testing on day eight revealed significantly poorer DSST performance at 1.5 hours following diazepam, with a small effect evident (effect size change from baseline (*g*) of 0.37). Reaction time at this test point was also moderately impaired with an effect size change from baseline (*g*) of 0.61. Effects on tracking errors were negligible. These findings suggest that tolerance

to this dosing regimen of diazepam partially occurs within eight days, with psychomotor processing speed and reaction time impairment appearing to be more resistant to habituation than tracking.

O'Hanlon and colleagues (1995) investigated the impacts of 5mg of diazepam three times a day on highway driving. Participants were tested on days one and eight of the dosing regimen, commencing one hour post-ingestion. The driving test, taking just over one hour, involved completing a 100km circuit on a four lane highway at night with the instruction to maintain speed (at 95km/hr) and a steady lane position. On day one, following the initial dose of diazepam, participants' ability to maintain lane position was found to be significantly impaired relative to a placebo group. Post-ingestion testing on day eight again revealed significant diazepam-induced impairment with the difference between diazepam and placebo group performance being even greater than on day one. The lack of pre-dose testing on day eight makes it difficult to assess the contribution of accumulative effects of diazepam and its active metabolites to this finding, however, these results can be interpreted to suggest that habituation to diazepam effects on highway driving ability does not develop within eight days on this dosing regimen.

Van Laar and colleagues (1992) investigated the acute effects of a 5mg dose of diazepam following a regular dosing regimen of 5mg three times a day. Participants were diagnosed with generalised anxiety disorder (mild to moderate severity), and had not taken benzodiazepines for a period of at least 30 days before the study, however, most were not benzodiazepine-naive. A placebo was administered for one week and baseline testing completed before commencing the diazepam treatment. Participants were then tested on days 7, 14, 21 and 28 of the treatment. The test was an on-road driving test and involved completing a 100km circuit on a highway at night, commencing 1.5 hours post-ingestion, with the instruction to maintain a constant speed and a steady lane position. The ability to control vehicle speed was significantly impaired relative to placebo-baseline levels on day 7. Speed variability was similar on days 14, 21 and 28, and did not significantly differ from placebo-baseline levels. Lane position maintenance (i.e. tracking) was found to be significantly

impaired relative to placebo-baseline measures on days 7, 14 and 21 of treatment. Performance had not returned to placebo-baseline levels by day 28, however, this performance difference did not reach statistical significance. Effects were greatest on day 7 and steadily declined from there. Four participants crossed over into adjacent lanes on day 7, and testing was terminated for two of these participants due to it being considered too risky to continue driving. Despite the methodological shortcomings of this study for the purpose of this review (i.e. lack of controls for practice effects; variable history of benzodiazepine use amongst participants), it is reasonable to interpret these results as supporting the slow development of tolerance to this dosing regimen. Habituation to effects on highway driving ability did not occur until three to four weeks after commencing treatment.

The usefulness of the results of three of the four studies reviewed above is limited by the short testing schedules. All three found impairment on some or if not all psychomotor measures to be greater after eight days of continued treatment than it was on the first day, suggesting that habituation to psychomotor effects does not occur within the first eight days, and accumulative effects from continual dosing may lead to increasing impairment for a period of time. This was true for 5mg, 10mg and 15mg doses. As there were no testing points beyond eight days in these studies it cannot be known when habituation would have occurred. The results from the only study to continue longer suggest that habituation does not completely occur for three to four weeks. The results from this study only apply to a 5mg dose, and to its effects on highway driving, which of course may differ to other driving scenarios. What can be concluded from these studies is that habituation to the psychomotor effects of even low therapeutic doses of diazepam (i.e. 5mg) is likely to develop over several weeks or longer.

Epidemiological studies

Epidemiological research investigating crash risk that has separated diazepam users from other benzodiazepine users is scarce. Only two studies are known to have done this. The first study,

conducted by Bramness and colleagues (2007), coupled records from a national prescription database, a road accident registry, and a population database in Norway to investigate the incidences of crashes in drivers taking diazepam. Standardised incidence ratios (SIRs) were calculated to compare the incidence of crashes for the first fourteen days after filling a diazepam prescription, with the incidence of crashes for individuals not prescribed diazepam. A SIR of 2.5 was found, meaning that individuals prescribed diazepam were 150% more likely to be involved in a crash than those not prescribed diazepam. This study also calculated the SIR for drivers unhabituated to diazepam effects. Only drivers who had not been prescribed diazepam for at least 180 days prior to filling a prescription were included in the analysis. A SIR of 3.3 was found, meaning that individuals new to diazepam use were 230% more likely to be involved in a crash in the first 14 days after filling a prescription.

The second epidemiological study, conducted by Gibson and colleagues (2009), utilised data collected from primary care records in the United Kingdom to investigate the incidences of involvement in crashes of people prescribed a wide range of medications including beta-blockers, opioids, analgesics, anti-depressants, antihistamines, benzodiazepines and non-benzodiazepine hypnotics. This study utilised a case-series design where the incidences of crashes for an individual when taking the relevant prescribed medication are compared to when not taking the medication. For the four week period following the first prescription of diazepam, patients were found to have an incidence rate ratio (IRR) of 1.93, meaning that they were 93% more likely to be involved in a crash when taking diazepam compared to when not. For the period of diazepam usage beyond four weeks the IRR increased to 2.77, meaning that they were 177% more likely to be involved in a crash when taking diazepam. Of all the medications investigated, diazepam was found to have the highest association with crash involvement.

Both of these studies provide clear evidence for increased crash risk amongst diazepam users. Whilst diazepam users were not separated according to dose in these studies, both studies included

analyses of diazepam users who were either new to diazepam use, or had not used it for an extended period of time. It could be expected that most of these diazepam users would have been prescribed low doses (i.e. 5mg or less) in line with prescribing guidelines (National Health & Medical Research Council, 1999)Hence, it is reasonable to infer that the increased crash risk brought about by a 5mg dose of diazepam would be close to the ratios reported in these studies.

It is interesting to note the differing patterns of risk over continued use suggested by these two studies. The higher crash risk in new diazepam users compared to all diazepam users found in the study by Bramness and colleagues (2007) suggests an attenuation of crash risk with continued diazepam use. This finding is in keeping with that of a study considering several common anxiolytic benzodiazepines (oxazepam, lorazepam and diazepam) together. As reviewed earlier, Neutel and colleagues (1995) found the crash risk of anxiolytic benzodiazepine users to decrease quite sharply during the first four weeks of use (13.8 times more likely to be involved in a crash in the first week, 5.6 times more likely in the first two weeks, and 2.6 times more likely in the first four weeks). This attenuation of risk over time is consistent with the attenuation of psychomotor side effects found to occur in the experimental studies, suggesting that habituation to psychomotor effects is responsible for decreasing risk. In contrast to these studies, Gibson and colleagues (2009) found crash risk for new diazepam users to be lower during the first 28 days of use than after the first 28 days of use. Whilst the authors of this study do not comment on this result, it seems possible that the participant group still using diazepam after 28 days may have had more significant mental health issues and as a result their dose was increased or they were prescribed a higher initial dose. The increased risk after 28 days of use may therefore reflect a positive association between dose and crash risk, mediated by the known positive association between dose and deleterious psychomotor effects (e.g. Deakin, et al., 2004; Hart, et al., 1976; Jalava, et al., 1995). New users were not separated from non-new users in this way in the study by Bramness and colleagues (2007), which may explain why these studies differed in their findings. Experimental studies investigating the process of habituation to diazepam (reviewed earlier) do not provide any clarity as to the relationship between duration of use and

crash risk due to not having collected data for a sufficient length of time. Whilst there is evidence to suggest that new diazepam users do face increased crash risk, more systematic research would need to be conducted to establish when and to what extent habituation and attenuation of risk occur with a 5mg dose.

Summary of diazepam-induced driving impacts

It can be concluded from this review so far that diazepam has clear effects on driving related skills, driving simulator performance, and on-road driving. There is sufficient evidence to suggest that even low therapeutic doses (i.e. less than 10mg) do deleteriously impact on driving and driving-related performance. The lack of effect size reporting, and the reliance on tests of significance to indicate impairment in studies with small sample sizes, has meant that the full extent of impairment resulting from a low dose is likely to have been underestimated in this review. Only two studies enabled the calculation of effect sizes for a low dose. One found small to moderate effects of a 5mg dose (effect size changes from baseline ranging from $g = 0.32$ to $g = 0.51$) at a time likely to be close to peak impact (Takahashi, et al., 2010). The other found moderate and large effects of a 5mg dose (effect size changes from baseline of $g = 0.70$ and 1.00) (Echizenya, et al., 2007), however, this was based on an averaged performance over time, and hence would be an underestimation of the magnitude of effect at peak impact. Drawing conclusions as to the duration of the effect of low doses is problematic due to the small number of studies utilising low doses, the lack of regular testing points within these studies, and the inconsistencies in the analyses reported across these studies. From the ranges of duration of effect discussed for each psychomotor function above it seems likely that the effects of low doses are detectable for several hours. This is supported by the results from the small number of studies using driving simulators, where diazepam was shown to impact on driving simulator performance for up to four hours, even at a low 5mg dose. It is interesting to note that increased task difficulty does not necessarily result in increased diazepam-induced impairment. In a number of studies diazepam has shown greater effects when the task was simple than when it was more complex. It is plausible that increases in task complexity break the

monotony of more simple tasks and result in greater motivation (Molloy & Parasuraman, 1996) . The likely increase in effort and concentration may to some extent counteract the deleterious psychomotor effects of diazepam.

It appears that habituation to the deleterious effects of low doses of diazepam is not likely to occur for several weeks or longer, and epidemiological evidence suggests that the deleterious impacts found in experimental studies do lead to actual on-road crashes. Given that long term use of benzodiazepines is not recommended (National Health & Medical Research Council, 1999) the proportion of prescribed diazepam users overall who are unhabituated to the psychomotor effects is likely to be substantial (i.e. those in the first few weeks or longer of short-term regular use, or those who use diazepam intermittently). In addition to these individuals are those that misuse diazepam who may also not be habituated to the psychomotor effects (dependent on extent and duration of use). This may be a considerable number of people – 1.4% of Australian respondents to the 2010 National Drug Strategy Household study admitted using a tranquiliser or sleeping pill for non-medical purposes in the preceding year (Australian Institute of Health and Welfare, 2010). The overall implication is that a substantial proportion of diazepam users at any one time face increased risks of being involved in crashes if driving whilst affected.

Subjective perception of psychomotor impairment

Self-monitoring is of critical importance if driving under the influence of medications that may impair driving – if an impaired driver is not able to accurately assess their driving ability they may unknowingly put themselves and others at risk by either continuing to drive or by not taking precautionary measures, such as exerting greater concentration. There is an indication in the literature to date that benzodiazepines may have deleterious effects on the ability to self-monitor. A number of studies have provided consistent evidence for a benzodiazepine-induced impairment in the ability to monitor psychomotor performance, by comparing the accuracy of task performance estimates of benzodiazepine and placebo groups. Lorazepam has been shown to significantly impair

the ability to estimate DSST performance immediately prior to task completion (i.e. pre-task performance estimates) (Mintzer & Griffiths, 2003; Preston, Guarino, Kirk, & Griffiths, 1989), as has triazolam (Evans, Funderburk, & Griffiths, 1990). Triazolam has also been shown to significantly impair the ability to evaluate DSST performance immediately after task completion (Roache & Griffiths, 1985) and the ability to evaluate performance on a circular lights task immediately after task completion (i.e. post-task performance estimates) (Roache, Cherek, Bennett, Schenkler, & Cowan, 1993). In all cases, the benzodiazepine dose resulted in an overestimation of performance.

Interestingly, in the only known benzodiazepine study to report both pre-task performance estimates and post-task performance evaluations in a way that enables comparison, the pre-task estimates were more affected by triazolam than the post-task estimates (Preston, et al., 1989). Both the pre and post-task estimates were noticeably less accurate following triazolam than placebo, however, only the pre-task estimates were impaired to an extent that was statistically significant. It is plausible that this result is an indication of differential sensitivities of aspects of self-monitoring to benzodiazepines.

The self-monitoring effects found in the above studies do not appear to be solely due to an indirect result of sedation. This is due to the fact that self-monitoring effects have been shown to be more pronounced for benzodiazepines than other types of sedatives, such as pentobarbital (Preston, et al., 1989) and scopolamine (Mintzer & Griffiths, 2003). Furthermore, these self-monitoring effects may not be solely attributed to the known amnestic properties of benzodiazepines. Deleterious effects on accuracy of psychomotor performance estimates have been shown to be dissociated from effects on memory tasks (Mintzer & Griffiths, 2003). It seems likely that the effect of benzodiazepines on self-monitoring results from a more direct impact on the cognitive processes involved in self-monitoring.

Benzodiazepine research designed to investigate self-monitoring accuracy has only involved triazolam and lorazepam so far. Whilst consistent results have been found with these two

benzodiazepines, it is not known whether self-monitoring is compromised by all benzodiazepines. The differing pharmacological actions of various types of benzodiazepines (Bourin & Briley, 2004) mean that effects on self-monitoring are likely to differ amongst them. This has been shown to be the case with a range of other cognitive functions (e.g. Curran, Schiwy, & Lader, 1987; Fleishaker, Garzone, Chambers, Sirocco, & Weingartner, 1995; Jalava, et al., 1995; Craig Rush, Higgins, Hughes, & Bickel, 1993).

There are no known studies that have been specifically designed to investigate diazepam effects on self-monitoring of psychomotor performance, however, a number of studies report both objective and subjective performance measures at equivalent time points for both drug and placebo-treated groups which enables a comparison of objective and subjective effects. The subjective performance measures in these studies are ratings of competence indicated on visual analogue scales with anchor points of '*very good/very poor performance'* or *'proficient/incompetent'*. A method for approximating self-monitoring accuracy within these studies is to examine the patterns of results and look for dissociations between the objective and subjective performance measures. It could be expected that if self-monitoring capabilities were compromised, subjective comptence measures would not increase and decrease alongside objective performance measures (i.e. there would be a dissociation between the subjective and objective measures of performance).

There are two known studies including subjective competence measures that allow for the calculation of effect sizes. In both of these studies there is a notable time-related pattern that is suggestive of a dissociation between subjective and actual performance following a 15mg dose of diazepam. Mattila and colleagues (1988) report statistics suggestive of small differences between the magnitudes of deleterious effects for objective and subjective measures at 1.5 hours post-ingestion (with effect size changes from baseline (*g*) of 0.70 for tracking, and 0.88 for subjective competence). Yet at 3 hours post-ingestion the differences between these objective and subjective measures are much larger, with effect size changes from baseline (*g*) of 0.17 for tracking, and 0.93

for subjective competence. The fact that actual performance improved between 1.5 hours and 3 hours whilst subjective competence ratings remained relatively similar suggests that a dissociation between the measures is present. The same pattern is noted in a later study by Mattila and colleagues (1998). At 1 hour post-ingestion effect size changes from baseline (*g*) are 1.11 for subjective competence, and range from 0.84 to 1.41 for the objective measures (all deleterious effects). At 3.5 hours post-ingestion effect size changes from baseline (*g*) are 0.97 for subjective competence, and range from 0.00 to 0.62 for the objective measures (all deleterious effects). Again, subjective competence ratings did not reflect the improvement in actual performance that occurred between 1 and 3.5 hours. The dissociation between the subjective and objective measures in these studies suggests that self-monitoring was affected by diazepam. However, it cannot be said with certainty whether there was an overestimation of performance at the first test points or an underestimation of performance at the second test points. Given that there does not appear to be any evidence for benzodiazepines resulting in an underestimation of performance, it seems to be more plausible that diazepam resulted in an overestimation of performance at the first test points in these studies. The fact that actual performance effects were larger in magnitude at the first test points adds more weight to the likelihood of self-monitoring effects being more prominent at this point as well.

There are further studies that allow for a comparison between subjective competence ratings and actual performance, however, these studies do not report the means and standard deviations necessary to be able to calculate effect sizes. The vast majority of these studies found significant differences between the competence ratings given by diazepam and placebo groups alongside significant differences in actual performance (Ghoneim, Mewaldt, & Hinrichs, 1984 ; Hart, et al., 1976; Kelland & Lewis, 1996; Mattila, et al., 1988; Mattila, et al., 1998; Vanakoski, et al., 2000). These studies suggest that participants had some awareness of reduced performance following diazepam, however, they do not provide any evidence for the accuracy of this awareness.The potential for a dissociation between subjective and actual performance in these studies becomes

more apparent when patterns across multiple doses within studies are considered. Ghoneim and colleagues (1984) investigated the effects of 7, 14 and 21mg of diazepam, along with placebo. Whilst dose-related decreases in performance on a vigilance task were evident, participants rated their competence nearly identically during the period of peak psychomotor effects across the three doses. Similarly, Hart and colleagues (1976) found that 5mg of diazepam resulted in significantly slower processing speed than 2.5mg of diazepam whilst subjective ratings of competence did not differ significantly for the two doses. A similar pattern of results is found in the small number of studies investigating multiple doses of other benzodiazepines that have reported inter-dose analyses – with higher doses resulting in significantly poorer performance than lower doses, whilst differences in subjective ratings of competence do not reach statistical significance (Begg, Drummond, & Tiplady, 2001; Farre, Teran, & Cami, 1996; Preston, et al., 1989). Again, given that there does not appear to be any evidence for benzodiazepines resulting in an underestimation of performance, it seems to be more plausible that the lack of ability for subjective measures to discriminate between the varying doses in these studies was due to the higher doses resulting in an overestimation of performance, rather than the lower doses resulting in an underestimation of performance.

There is sufficient evidence to suggest that diazepam may deleteriously impact on the ability to accurately monitor psychomotor performance, as has been shown for other benzodiazepines. This potential is evident for diazepam doses as high as 15mg and as low as 5mg. When dissociations between subjective competence ratings and actual performance are evident, it seems likely that the dissociation results from over-confidence in performance, meaning that individuals under the influence of diazepam may not be fully aware of the extent to which their psychomotor capabilities are affected. This is concerning in the context of driving a motor vehicle, and raises the question as to what extent self-monitoring deficits may play a role in the increased crash risks that diazepam users face.

Subjective perception of sedation

The Therapeutic Goods Act 1989 requires diazepam to be labelled with the caution "This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery" (Department of Health and Ageing 2009). The usefulness of the information conveyed on this label in reducing crash risk is reliant on an individual's ability to perceive the sedative effects. Furthermore, it is reliant on the assumption that psychomotor impairment occurs only in the presence of subjective sedation or drowsiness. There are no known studies to date that have been conducted with the aim of providing evidence for or against this notion. A method for approximating the reliability of psychomotor impairment only occuring in the presence of subjective sedation would be to examine patterns of results in the literature and look for dissociations between the objective performance and subjective sedation measures. It could be expected that if psychomotor impairment did only occur in the presence of subjective sedation when under the influence of diazepam, subjective sedation measures would increase and decrease alongside objective performance measures (i.e. there would not be a dissociation between these measures).

Benzodiazepine studies that allow for a comparison between subjective sedation ratings and actual performance at similar time-points have yielded inconsistent results. The results of some studies suggest a dissociation between subjective sedation and actual performance, with psychomotor performance being significantly affected whilst subjective sedation effects remain non-significant (e.g. Roache & Griffiths, 1985; C. Rush, Frey, & Griffiths, 1999; Tiplady, Bowness, Stien, & Drummond, 2005). Other studies do not provide evidence for a dissociation with subjective sedation being significantly affected alongside actual performance (Allen, Curran, & Lader, 1993; Begg, et al., 2001; Farre, et al., 1996; Mintzer & Griffiths, 2003; Roache, et al., 1993; Verster, Volkerts, & Verbaten, 2002).

There are two known diazepam studies including subjective sedation measures that allow for the calculation of effect sizes, enabling a more precise examination of potential dissociations. In one of these studies there is a notable time-related pattern that is suggestive of a dissociation between subjective sedation and objective performance. Takahashi and colleagues (2010) found a 5mg dose to result in small to moderate deleterious effects on a series of objective measures (derived from a vigilance task and a driving simulator task) at 1 hour post-ingestion (with effect size changes from baseline (*g*) ranging from 0.19 to 0.51). These effects were slightly reduced in magnitude at 4 hours post-ingestion (with effect size changes from baseline (*g*) ranging from 0.10 to 0.35). Meanwhile effects on subjective sedation (as measured by the *Subjective Sleepiness Scale*) increased in magnitude across these time points, with effect size changes from baseline (*g*) of 0.85 at 1 hour post-ingestion, and 1.03 at 4 hours post-ingestion. It may well be that diurnal variations are involved in this dissociation between subjective sedation and objective performance effects. This however, does not change the implication of these results, in that there appears to be a dissociation between subjective sedation measures and actual performance measures in this study.

Patterns of effect sizes across two age groups in a study by Echizenya and colleagues (2007) are also indicative of a dissociation between subjective sedation and actual performance. In this study an older group of participants (53 to 71 years) and a younger group of participants (18 to 23 years) were administered a 5mg dose or placebo. In the older participants a deleterious effect on choice reaction time (CRT) performance was of a greater magnitude than that on subjective sedation (as measured by the *Subjective Sleepiness Scale)* with effect size changes from baseline (*g*) of 1.00 and 0.32 respectively. The opposite pattern was evident for the younger participants, with CRT effects being of a lower magnitude than subjective sedation effects (effect size changes from baseline (*g*) of 0.70 and 0.90 respectively). Age did not impact on subjective sedation in the same manner that it did on actual performance in this study, which is suggestive of a dissociation between these measures.

Further studies allow for a comparison of subjective sedation and actual performance under the influence of diazepam, however, effect sizes can not be calculated for these studies. A large number of these studies found subjective sedation measures to be significantly affected by diazepam along side objective performance measures (Brown, et al., 1996; Echizenya, et al., 2003; Kelland & Lewis, 1996; Mattila & Mattila, 1988; Rich, et al., 2006; Vanakoski, et al., 2000). Some studies, however, provide evidence for a dissociation between subjective sedation and actual performance. In two separate studies Mattila and colleagues (1988; 1998) found 15mg of diazepam to result in significantly poorer tracking performance and significantly slower psychomotor processing speed, whilst subjective ratings of sedation remained non-significantly affected. Similarly, Hart and colleagues (1976) found that 5mg of diazepam resulted in significantly slower processing speed than 2.5mg of diazepam whilst differences between the subjective ratings of sedation for the two doses were non-significant. Deakin and colleagues (2004) also found significant dose-related (5mg, 10mg and 20mg) decrements in actual performance whilst dose-related effects on subjective sedation ratings were non-significant.

The dissociations between subjective sedation measures and actual performance measures highlighted in the above studies are all indicative of diazepam affecting drowsiness and psychomotor performance in discrete ways. Subjective sedation effects do not necessarily increase and decrease alongside actual performance measures across time post-ingestion, across diazepam dose increases, or across age. Doses as low as 5mg and as high as 20mg have been shown to result in dissociated sedative and performance effects. These findings suggest that subjective sedation may not be a reliable predictor of actual psychomotor performance, and the potential for experiencing psychomotor performance detriment in the absence of feeling drowsy remains a possibility. This raises questions about the usefulness of the information conveyed on current benzodiazepine labelling in reducing crash risk.

Equating diazepam-induced impairment to a blood-alcohol concentration

The 2006 Guidelines for Research on Drugged Driving (Walsh, et al., 2008) recommend quantifying the effects of drugs on driving by equating them to a blood-alcohol concentration (BAC). Doing this not only provides for a common comparison point for the driving impacts of various drugs, but also allows for greater public understanding of how a drug may affect the ability to drive safely. A recent survey of 7000 Australians found that whilst respondents were well informed about the impacts of alcohol on driving respondents were generally uninformed about the impact of prescription drugs on driving, and had little idea about how long they should wait before driving following pharmaceutical drug use (Mallick, Johnston, Goren, & Kennedy, 2007). It was found that 30% of respondents who had used benzodiazepines reported driving within three hours of use, compared to just 14% of alcohol drinkers admitting to driving at over .05% BAC (the legal limit in Australia). Being able to equate benzodiazepine-induced performance decrement with a BAC level may provide a readily understandable measurement of impairment that can enable people to understand the risks they face whilst driving under the influence of benzodiazepines.

One method of equating impairment would be to compare impairment on a particular task for varying doses of a benzodiazepine and varying BACs, and look for equivalent levels of effect. An alternative method would be to establish a regression equation for specifying the relationship between BAC and impairment on a particular task, and then apply this regression equation to benzodiazepine-induced impairment on the same task. Literature that would enable the use of either of these methods to equate diazepam-induced impairment is reviewed below.

Equivalency of effect method

As there are a great number of studies that have investigated either diazepam-induced or ethanol-induced psychomotor effects, it would be idyllic to pool the results of these studies so as to determine an equivalency of effect, however this is simply not plausible. Amongst these studies differing time courses for drug ingestion and testing, and differing task details such as duration,

extent of training, and measurements reported, would make it very difficult to do this accurately. Hence, only studies that have investigated both diazepam and ethanol simultaneously are useful in this regard.

Surprisingly, there is a very small number of studies investigating diazepam and ethanol effects that have employed a methodology that allows for equating effects - the majority have been interested in the interactive effects of diazepam and ethanol. With this aim in mind researchers have either not included placebo conditions for both drugs, or have introduced the second drug condition after the first time point, meaning that practice or fatigue effects between the two drug groups would not be equivalent. Of the small number of known studies that do allow for a comparison of effects, none have had the specific aim of determining the equivalency of effects. The usefulness of their results in this regard is limited by the small number of doses of both drugs, and the statistical analyses reported. These studies do however give some approximate indications of the BAC equivalent impairment that diazepam could be expected to produce, and will now be reviewed. Table 5 shows a summary of the findings of these studies. It should be noted that the preferred choice of units for expressing BAC differs between various countries and can result in slight variations, and hence the BAC equivalencies reported below are not exact, but represent a close approximation.

Ingum and colleagues (1992) investigated the effects of 10mg and 20mg of diazepam and 0.9g/kg of ethanol on a choice reaction time task and a simple reaction time task. The ethanol dose was found to result in a mean peak BAC of .071%. All three drug conditions showed significant impairment compared to a placebo group. At the point of peak task impairment the 20mg diazepam dose resulted in significantly longer reaction time (as indicated by both tasks) than the ethanol dose. The 10mg diazepam dose also resulted in a more prolonged reaction time than the ethanol dose, however, this difference did not reach statistical significance ($p>.05$). These results suggest that acute doses of 20mg of diazepam results in sensory-motor reaction time impairment greater than

.071% BAC, and that 10mg of diazepam results in impairment at least equal to but possibly greater than .071% BAC.

Mattila and colleagues (1998) investigated the effects of diazepam (15mg) and ethanol (0.65 + 0.35g.kg^{-1}) on a DSST and a simulated driving task that included choice reaction time and tracking components. The reporting of statistics for this study allows for the calculation of effect sizes. Peak effects of diazepam on task performance (at one hour post-ingestion) occurred at a time point closest to when the ethanol group had a mean BAC of .082% (1.5 hours post-ingestion). The detrimental effects of 15mg of diazepam at this time point were of a greater magnitude than those induced by a BAC of .082% on all three measures. For the DSST there was an effect size change from baseline (*g*) of 0.84 for the diazepam group and 0.48 for the ethanol group, and for the tracking component on the driving simulator there was an effect size change from baseline (*g*) of 1.15 for the diazepam group and 0.88 for the ethanol group. The largest disparity between the groups was seen on the choice reaction time component of the driving simulator where there was an effect size change from baseline (*g*) of 1.41 for the diazepam group and 0.37 for the ethanol group. The examination of effect sizes for this study suggests that a 15mg dose of diazepam results in psychomotor processing speed, tracking, and sensory motor reaction time impairments of greater than .082% BAC.

Jalava and colleagues (1995) investigated the effects of 15mg of diazepam and 0.65 + 0.35g.kg^{-1}of ethanol on a DSST and a divided attention task. At one hour post-ingestion the ethanol group had a mean BAC of .072%. The reporting of statistics for this study allows for the calculation of effect sizes. For the DSST there was a deleterious effect size change from baseline (*g*) of 0.69 for the diazepam group and 1.07 for the ethanol group, indicating the psychomotor processing speed impairment induced by the 15mg diazepam dose in this study was equivalent to less than a BAC of .072%. There were two versions of the divided attention task – one containing only visual stimuli, and a more complex version containing both visual and auditory stimuli. When the task contained

only visual stimuli the ethanol group outperformed the diazepam group. Diazepam had a deleterious effect on performance with an effect size change from baseline (*g*) of 0.50 whilst ethanol had a negligible (beneficial) effect on performance with an effect size change from baseline (*g*) of 0.14. A different result emerged when both visual and auditory stimuli were included, with the diazepam group outperforming the ethanol group. The diazepam group had a deleterious effect size change from baseline (*g*) of 0.88 whilst the ethanol group had a deleterious effect size change from baseline (*g*) of 1.23. This examination of effect sizes suggests that a 15mg dose of diazepam results in divided attention impairment of greater than .072% BAC when the task is visual only, and of less than .072% BAC when the task is both visual and auditory. This pattern of results for the sensory modalities of the divided attention task held at a test point 3 hours post-ingestion, and when the diazepam dose was increased to 30mg. This suggests that diazepam and ethanol may differ in their effects on the processing of auditory and visual sensory inputs. Alternatively they may differ in their effects in the context of changing task complexity with ethanol effects being more sensitive to increases in complexity than diazepam effects.

Vanakoski and colleagues (2000) investigated the effects of diazepam and ethanol on a DSST and a simulated driving task which included reaction time and tracking error measures as well as a global measure of overall driving performance. Only analyses testing the differences in performance of the drug groups relative to placebo groups were reported, hence comparisons between the diazepam and ethanol groups can only be judged by examining the means. A group of young participants (22-24 years) were administered 15mg of diazepam or $0.8g.kg^{-1}$ of ethanol, which resulted in a mean BAC of .098% two hours after ingestion. Ethanol and diazepam resulted in roughly equivalent DSST performance, which was significantly impaired relative to placebo. Again, both drugs resulted in roughly equivalent overall performance on the simulated driving task, which was significantly poorer than placebo. However, slight differences between the drugs in the nature of this effect were apparent, with diazepam appearing to result in slower reaction times than ethanol, and ethanol appearing to result in more tracking errors than diazepam. Overall the results indicate that in

younger people acute doses of 15mg of diazepam result in psychomotor impairment roughly equivalent to .098% BAC, however, this may be a slight underestimation of sensory-motor reaction time impairment and a slight overestimation of tracking impairment.

In a second arm of this study Vanakoski and colleagues (2000) administered older participants (55-77 years) 10mg of diazepam or 0.7g.kg^{-1} of ethanol, and followed the same methodology as with the younger participants. The ethanol dose resulted in a mean BAC of .091% two hours after ingestion. In these participants only ethanol resulted in significantly poorer DSST performance than placebo. Whilst the diazepam-induced performance detriment relative to placebo was not significant, inspection of the means suggests that the diazepam group performed more similarly to the ethanol group than the placebo group. Overall performance on the simulated driving task was significantly poorer than placebo for both drugs, however, more so for ethanol than diazepam. Whereas as reaction time was nearly identical for the two drugs, ethanol tended to result in more tracking errors than diazepam. Overall the results indicate that in older people 10mg of diazepam results in sensory-motor reaction time impairment roughly equivalent to .091% BAC, and psychomotor processing speed and tracking being not quite as impaired as this.

Kuitenen (1994) investigated the effects of 15mg of diazepam and 0.8g/kg of ethanol (resulting in a BAC of .079%) on a DSST and a simulated driving task including tracking and choice reaction time components. Only analyses testing the differences in performance of the drug groups relative to placebo groups or baselines measures were reported, and so again comparisons between the diazepam and ethanol groups can only be judged by examining the means. On all measures performance following placebo remained stable, whilst performance following diazepam or ethanol tended to decline. On the DSST and on the tracking component of the driving simulator task ethanol appeared to result in more impairment than diazepam, however, diazepam appeared to result in more prolonged reaction time than ethanol on the choice reaction time component of the driving simulator task. These results indicate that 15mg of diazepam results in roughly equivalent

psychomotor impairment to .079% BAC, however, the true equivalence may be higher for sensory-motor reaction time, and slightly lower for tracking and psychomotor processing speed.

Using similar tasks Mattila and Mattila (1988) investigated the effects of 15mg of diazepam and .08g/kg of ethanol. At 1.5 hours post-drug ingestion the BAC of the ethanol group was .097%. At this time point both drugs significantly and equivalently impaired performance on the DSST. Whilst neither drug significantly affected errors on the tracking component of the driving simulator, choice reaction time was prolonged by both drugs. Statistical tests comparing the two drug groups were not reported, however, inspection of the means suggests that diazepam resulted in greater reaction time impairment than ethanol. These results indicate the psychomotor processing speed impairment induced by 15mg of diazepam to be equivalent to that induced by .097% BAC, with sensory-motor reaction time impairment being even greater than this.

Considering the above research, it is clear that diazepam doses of 10mg or more are capable of resulting in psychomotor impairment equivalent to a BAC considered risky for driving (i.e. more than .05%). Based on this small number of studies sensory-motor reaction time effects of a 10mg dose appear approximately equivalent to as high as .091% BAC, whilst a 15mg dose may approximate an effect equivalent to .098% BAC or more. A 15mg dose may affect divided attention more greatly than .072% BAC, however, this may depend on task complexity and the sensory modalities involved. Psychomotor processing speed and tracking abilities appear to be less affected by a 10mg dose than .091% BAC, and equivalently affected by a 15mg dose and a BAC as high as .098%. The BAC equivalency of a 5mg dose is not known as no known studies allowing for a comparison of ethanol and diazepam effects have utilised this dose.

In several of the studies reviewed BAC equivalencies differed for various psychomotor functions. This is particular noteworthy in Vanakoski and colleagues (2000) where it was evident that ethanol impacted more on the errors made in a particular task whereas diazepam impacted more on reaction time for that task. This highlights an important issue when attempting to equate

Table 5. Approximate blood-alcohol concentration (BAC) equivalency of diazepam effect

Psychomotor function	Diazepam dose	Approximate BAC equivalency	Researchers
Sensory-motor reaction time	10mg	≈ .071%	Ingum et al., 1992
	10mg	≈ .091%	Vanakoski et al., 2000
	15mg	≈ .079%	Kuitenen, 1994
	15mg	> .082%	Mattila et al., 1998
	15mg	>.097%	Mattila & Mattila, 1988
	15mg	≈ .098%	Vanakoski et al., 2000
	20mg	>.071%	Ingum et al., 1992
Psychomotor processing speed	10mg	< .091%	Vanakoski et al., 2000
	15mg	≈ .079%	Kuitenen, 1994
	15mg	> .082%	Mattila et al., 1998
	15mg	≈ .097%	Mattila & Mattila, 1988
	15mg	≈ .098%	Vanakoski et al., 2000
	15mg	< .072%	Jalava et al., 1995
Tracking	10mg	< .091%	Vanakoski et al., 2000
	15mg	≈ .079%	Kuitenen, 1994
	15mg	> .082%	Mattila et al., 1998
	15mg	≈ .098%	Vanakoski et al., 2000
Divided attention (visual)	15mg	> .072%	Jalava et al., 1995
Divided attention (visual and auditory)	15mg	< .072%	Jalava et al., 1995

Notes. The method utilised to determine the equivalency of effects varies between studies, and is noted in text; ≈ denotes an approximate equivalence of effect between specified diazepam dose and relevant BAC; < denotes the effect of the specified diazepam dose as being less deleterious than the relevant BAC; > denotes the effect of the specified diazepam dose as being more deleterious than the relevant BAC.

benzodiazepine-induced impairment to a BAC. Differences between benzodiazepines and ethanol in the exact profile of psychomotor effects are likely to exist, meaning that an accurate BAC equivalence on one aspect of psychomotor function (e.g. psychomotor processing speed) may be less accurate on another (e.g. vigilance). Given that driving requires the use of multiple psychomotor functions, when using laboratory-based tests to measure 'driving-related skills' it may be more appropriate to equate benzodiazepine-induced impairment to a BAC range, or to ensure that tests used are fairly representative of the psychomotor functions used when driving.

Regression equation method

A promising methodology for equating benzodiazepine-induced performance with a BAC involves the use of a regression equation specifying the relationship between BAC and impairment on a given psychomotor task. No known studies have attempted this to date, however, a regression equation specifying the relationship between BAC and psychomotor performance has been established by Dawson and Reid (1997). A commercially available manual tracking task, called the Occupational Safety Performance Assessment Test, or OSPAT (OSPAT Pty Ltd, 2005), was used as the measure of psychomotor performance in the research resulting in this regression equation. The OSPAT provides a measure of tracking, which reflects a composite of reaction time, focused attention and hand-eye coordination. It is not currently known to have been validated as sensitive to benzodiazepine effects, however, it has been validated as being sensitive to fatigue effects (Petrilli, Jay, Dawson, & Lamond, 2005). The OSPAT is commonly used as a fitness-for-duty test in a variety of industries that require employees to operate vehicles and machinery. Dawson and Reid (1997) used performance decrement on this task to equate fatigue-induced impairment with a BAC level, so as to demonstrate the involvement of fatigue in workplace accidents. The regression equation has since been used to equate methadone-induced impairment with a BAC level as well (Newcombe & White, 2007).

The regression equation method for determining BAC equivalency has several benefits. The first

being that it allows for a more exact method of determining the BAC equivalency of various drugs than the equivalency of effect method reviewed above. A specific equivalency can be given rather than a range. A particularly important benefit is the efficiency that the regression equation methodology allows for. Studies can be conducted without the need to administer ethanol to an additional participant group, nor the need to collect data on BAC levels, thereby reducing the time spent collecting and analysing data. The regression equation offered by Dawson and Reid (1997) further increases the efficiency of this method due to the OSPAT being a relatively brief task at just 90 seconds long. Establishing a valid regression equation for equating BAC equivalencies is an important pursuit as it will enable researchers to equate BAC equivalencies with greater ease, and hence be more able to adhere to the recommendations put forward in the Guidelines for Research on Drugged Driving (Walsh, et al., 2008). This will in turn enable prescribers to make more-informed decisions when prescribing drugs that impact on driving, and will enable greater public understanding of the risks they may face by driving under the influence of prescription medicines.

Conclusions of review

Diazepam is the most commonly prescribed anxiolytic benzodiazepine in Australia, with a 5mg dose being the mostly commonly prescribed dosage (Department of Health and Ageing, 2011). As with other benzodiazepines, the psychomotor effects of diazepam are well established. Psychomotor processing speed, sensory-motor reaction time, vigilance, divided attention, and tracking are all aspects of psychomotor function involved in driving, and have all been shown to be deleteriously impacted upon by diazepam. This has been shown in studies investigating on-road driving performance, driving simulator performance, and performance on driving-related skills tests. There is sufficient evidence to suggest that even a low dose of 5mg of diazepam does impair driving capabilities, with effects shown to range from small through to large in magnitude. The maximal extent of impairment resulting from this common dose is not currently clear in the literature. The

lack of frequency of test points in the reviewed studies mean that that the impact of a 5mg dose at peak effects is not well established, and reported effects are hence likely to be an underestimate of the true maximal effects. The lack of frequency of testing in these studies also makes it difficult to determine the duration of effect of this dose.

It appears that habituation to the deleterious effects of low doses of diazepam is not likely to occur for several weeks or longer, and epidemiological evidence suggests that the deleterious impacts found in experimental studies do lead to actual on-road crashes. Given that long term use of benzodiazepines is not recommended (National Health & Medical Research Council, 1999) the proportion of prescribed diazepam users overall who are unhabituated to the psychomotor effects is likely be substantial (i.e. those in the first few weeks or longer of short-term regular use, or those who use diazepam intermittently). The overall implication is that a substantial proportion of diazepam users at any one time face increased risks of being involved in crashes if driving whilst affected.

The increased risks faced by diazepam users are of particular concern given that it cannot be said with any certainty that diazepam users are aware of the impairing effects. Dissociations between subjective competence ratings and actual performance effects in the literature suggest that diazepam may impact on the cognitive processes necessary for accurate self-monitoring of psychomotor performance. Additionally, feelings of sedation may not be a good predictor of psychomotor impairment, given that research has shown that impairment can be present in the absence of feeling fatigued. The implication of this is that current labelling on diazepam, which cautions not to drive if feeling fatigued, may be ineffective in reducing the likelihood of someone driving whilst impaired by diazepam.

Equating diazepam-induced psychomotor impairment to a BAC would provide a readily understandable measure of the risks people face driving under the influence of diazepam. There are no known studies that have attempted to do this to date. The results from research that has

included diazepam and ethanol groups does suggest that moderate and high doses of diazepam affect psychomotor performance to an extent considered risky for driving (i.e. more than .05% BAC). It cannot currently be said whether it is safe to drive under the influence of a 5mg dose.

Aims of the current study

The primary aim of the current study is to investigate the impact of a 5mg dose of diazepam on driving capabilities. This will be done by establishing the maximal magnitude and duration of effect on the driving-related skills of psychomotor processing speed, sensory-motor reaction time, vigilance, divided attention, and tracking. A secondary aim will be to trial a methodology for equating any impairment from the 5mg dose to a BAC. This methodology will involve applying the regression equation offered by Dawson and Reid (1997) to OSPAT performance results. A further secondary aim of the current study will be to conduct a preliminary examination of the subjective experience of the 5mg dose. Subjective competence ratings will be examined to ascertain whether any impairment brought about by the 5mg dose is subjectively detectable. Subjective sedation ratings will be examined to ascertain whether impairment is always accompanied by feeling fatigued following this dose. It is expected that this preliminary examination will generate further research questions around diazepam effects on self-monitoring accuracy, and the reliability of subjective sedation as a predictor of actual performance, and hence the usefulness of the information conveyed on current cautionary labelling for diazepam.

Method

Participants

Thirty-four benzodiazepine-naïve females were recruited to participate in the study, allowing for a power of 80% for detecting a moderate effect size (Hedges *g* = 0.5). Participants were aged between 18 and 51 years old, with a mean age of 24.2 (SD = 8.1). Participants were recruited from introductory psychology units at the University of Tasmania, and via recruitment materials displayed around the university campus. Reimbursement for participation was offered by way of course credit (for those enrolled in certain Psychology units) or a payment of forty Australian dollars. Only females were eligible to participate in the study. This is due to gender being a known factor impacting on benzodiazepine effects (Verster & Mets, 2009), and there being a need to minimise extraneous variability in the data due to the relatively small sample size. Males were excluded rather than females due to benzodiazepine use being higher amongst females than males (e.g. Magrini, et al., 1996). Only those holding a current driver's licence were eligible to participate. Nicotine smokers, regular illicit drug users, people dependant on substances that depress the central nervous system (e.g. methadone, oxycodone), and people who consume alcohol at harmful levels, as indicated by a score of greater than 8 on the Alcohol Use and Disorders Identification Test (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), were excluded from the study to prevent possible confounding effects of nicotine, alcohol and other drugs. People with high levels of psychological distress, as indicated by a score of greater than 25 on the Kessler Psychological Distress Scale (K10) (Andrews & Slade, 2001), were excluded due to the possible confounding effects of psychological distress on task performance. Participants at risk of any contraindications for diazepam use (MIMS Australia, 2006) were excluded for their own protection. Contraindications included pregnancy or breast feeding, chronic obstructive airways disease, respiratory or cardiorespiratory impairment, liver or kidney impairment, sleep apnoea, myasthenia gravis, galactose intolerance, glucose or galactose malabsorption, narrow angle glaucoma, and epilepsy. Additionally the use of the following

medications was contraindicated due to the potential for interactions: disulfiram, cimetidine, omeprazole, ketoconazole, fluvoxamine, fluoxetine, cisapride, and any anticonvulsant or anticholinergic medications.

Materials

A battery of tasks was used to investigate objective performance and subjective experience, and was administered in a uniform order, in line with neuropsychological research practices.

Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT (Babor, et al., 2001) is a questionnaire developed by the World Health Organisation to identify the consumption of alcohol at levels harmful to health. It has been shown to have excellent psychometric characteristics and external validity in identifying individuals with harmful as well as clinically problematic patterns of drinking (Dawe, Loxton, Hides, Kavanagh, & Mattick, 2002). Drinking large quantities of alcohol in a single sitting has been shown to result in changes in brain functioning (e.g. Nichols & Martin, 1996), hence the necessity to measure and control for harmful alcohol use effects on task performance. The AUDIT was administered to enable the exclusion of participants who consume alcohol at harmful levels and to enable the control of group differences in alcohol use. Scores range from 0 to 40, with higher scores indicating more problematic alcohol use. Scores above 19 are considered to be indicative of possible alcohol dependence whilst scores above 8 are considered to be indicative of alcohol use at harmful levels. The inclusion cut-off score for this study was 8.

Kessler Psychological Distress Scale (K10)

The K10 is a scale of psychological distress, and contains ten questions pertaining to negative emotional states experienced over the four previous weeks (Andrews & Slade, 2001). The K10 is a good indicator of mental health, and is used extensively by mental health services throughout Australia (ABS, 2001). A strong association between K10 scores and psychiatric diagnoses of anxiety and depression has been found (ABS, 2001). Due to the known negative impact of anxiety and

depression on cognition (Sadock & Sadock, 2003), it was considered necessary to control for these impacts on task performance. The K10 was administered to enable the exclusion of participants with clinical levels of psychological distress and to enable the control of group differences in levels of psychological distress. Scores range from 10 to 50, with higher scores indicating greater levels of psychological distress. A score of greater than 25 is considered to be indicative of a high level of psychological distress and a likely presence of a mental disorder of at least moderate severity (Andrews & Slade, 2001). The inclusion cut-off score for this study was 25.

Weschler Test of Adult Reading (WTAR)

The WTAR (Weschler, 2001) is a test of reading recognition, requiring participants to read aloud a list of 50 words that have irregular grapheme-to-phoneme translation. The age-standardised WTAR score (the number of words correctly pronounced) has been shown to be a significant predictor of both verbal intelligence and general intelligence (Weschler, 2001). The WTAR was administered to enable the control of group differences in intellectual functioning.

Digit-symbol substitution task (DSST)

The DSST, based on the Weschler Adult Intelligent Scale Third Edition DSST (Weschler, 1997), was used to measure psychomotor processing speed. For this task participants were required to draw the appropriate symbol (from a code table matching each of the digits one to nine to a distinct symbol) under each digit, in order, in a list of 80 randomly sequenced digits (ranging from one to nine). The dependent variable for this task was DSST score, being the number of symbols correctly assigned in 90 seconds. Six parallel forms of this task were used, with each form containing a newly-ordered set of symbols (Hinton-Bayre & Geffen, 2005).

Cognitive Drug Research (CDR) attention battery

The CDR attention battery forms part of the CDR computerised cognitive assessment system. This cognitive testing system was developed at the University of Reading in the United Kingdom and has since been acquired by United BioSource Corporation who continue to offer it for use in clinical

research. The system has been used to measure cognitive function under a wide range of conditions, such as dementia (e.g. Wesnes, et al., 2002), sleep deprivation (e.g. Macher, 2004), and hypnotic medication (e.g. Mayleben, et al., 2004). The CDR attention battery was used in the current study to measure sensory-motor reaction time and vigilance. The tasks used from this battery included Simple Reaction Time, Choice Reaction Time, and Digit Vigilance. All three tasks were computer based and required a response via a two-button response pad (with buttons labelled 'yes' and 'no'). Note that some details relating to the timing of tasks (stimulus presentation time, inter-stimulus interval, response windows) were not available due to these details being subject to commercial confidence.

Simple reaction time

This task required the participant to press the 'yes' button on the response pad as quickly as possible when the word 'yes' appeared on the screen. This occurred at varying inter-stimulus intervals. The dependent variable was Simple reaction time (milliseconds).

Choice reaction time

In this task the word 'yes' or the word 'no' appeared on the screen. This occurred at varying inter-stimulus intervals in a randomised order with equal probabilities of 'yes' and 'no' target stimuli. The participant was required to respond with the corresponding button on the response pad as quickly as possible. The dependent variables were Choice reaction time (milliseconds; only for correct responses) and Choice response accuracy (as a percentage).

Digit vigilance

A randomly selected digit (ranging from 1 to 9) was displayed on the right hand side of the screen throughout the task. A series of 150 digits (ranging from 1 to 9) was displayed in a randomised order in the centre of the screen at a rate of 80 per minute (resulting in a task duration of 112 seconds). The task required the participant to press the 'yes' button on the response pad as quickly as possible when the digit in the centre of the screen matched that displayed on the right. The dependent

variables were Vigilance reaction time (milliseconds, only for correct responses), and Vigilance response accuracy (as a percentage).

Dual Task

A Dual Task was used to measure divided attention. The task was designed locally for the purpose of the current study. Whilst the usability of this task has been informally examined during pilot-testing, no formal assessments of reliability and validity have been undertaken as yet. Task A required responding to photos of traffic scenes by pressing a key on a key pad when the application of the brakes of a vehicle was required to prevent a crash. A new stimulus was presented on a screen every 1500ms, and remained on screen for 1500ms. With each stimulus there was a 25% probability that a response would be required. Figure 1 displays examples of target (image on left) and non-target (image on right) stimuli in task A. Simultaneously the participant was required to respond to a changing shape presented in the top left corner of the screen (task B). A blue-coloured circle or square (20mm in diameter or length) appeared every 1500ms, remained on screen for 1500ms , and changed simultaneously with the traffic scenes. The probability of a square appearing was 15%, and participants were required to respond to a square by a key press. No response was required for a circle. Figure 2 displays the target (image on left) and non-target (image on right) stimuli for task B. Participants were instructed that the two tasks are of equal importance and that they should try and respond as quickly and as accurately as they can to both. The Dual Task ran for 120 seconds in total. The sequence of traffic scenes and shapes was randomised, and newly randomised for each attempt at the task. The sequence of stimuli was constrained so that two responses were never required at the same time. The dependent variables were Task A reaction time (milliseconds, for correct responses only) and Task A hit rate (as a percentage), and Task B reaction time (milliseconds, for correct responses only) and Task B hit rate (as a percentage).

Figure 1.Examples of target (left) and non-target (right) stimuli for task A of the Dual Task

Figure 2. Target (left) and non-target (right) stimuli for task B of the Dual Task

Occupational Safety Performance Assessment Test (OSPAT)

The OSPAT (OSPAT Pty Ltd., 2005) is an unpredictable tracking task that measures reaction time, focused attention and hand-eye coordination. It required participants to continually return an unpredictably moving cursor to the centre of a circular target presented on a screen, for a period of 90 seconds. The movement of the target is varied in relation to performance using a stair-casing procedure, allowing the task to increase in difficulty as performance improves. A track ball was used to manoeuvre the cursor. The dependent variable was the OSPAT score. This was a performance score produced from an algorithm (subject to commercial confidence) that takes into consideration both accuracy and time taken to adapt to change. Higher scores indicated greater performance. Measures of performance decrement on this test enabled the application of the regression equation

(Dawson & Reid, 1997) to equate psychomotor impairment with a BAC level. The regression equation specifies 1.16% performance decrement per .01% BAC.

Visual Analogue Scales

Visual Analogue Scales (VASs) were used for the subjective measures. These scales were designed locally for the purpose of the current study. The usability of these scales has been informally examined during pilot-testing, however no formal assessments of reliability and validity have been undertaken as yet. Participants were asked to mark on a 100mm long line the point that corresponds with their agreement with the associated statement. The pre-test VASs anchors were 'I feel alert'/ 'I do not feel alert' (to measure subjective alertness) and 'I feel that I will be able to perform the tasks to the best of my ability'/'I do not feel that I will be able to perform the tasks to the best of my ability' (to measure subjective competence). The post-test VASs were 'I feel alert'/ 'I do not feel alert', and 'I feel that I was able to perform the tasks to the best of my ability'/'I do not feel that I was able to perform the tasks to the best of my ability'. The corresponding dependent variables were Pre-test subjective alertness, Post-test subjective alertness, Pre-test subjective competence, and Post-test subjective competence.

Procedure

Blinding processes followed the specifications of the Consolidated Standards of Reporting Trials statement (Schulz, Altman, & Moher, 2010). Participants were randomly assigned to one of two treatment groups following simple randomisation procedures. The randomisation sequence was generated using the Random Number Generator: Version 2.0 (Devilly, 2007), and prepared by an investigator with no involvement in the study. Members of one treatment group were to ingest a capsule containing 5mg of diazepam, whilst member of the other treatment group were to ingest a capsule containing placebo. Participants were informed that they would be ingesting either a low dose of diazepam or a placebo. The two capsule types were identical in appearance. Each capsule was concealed in an envelope marked with a unique number, and the treatment group to which

each of these numbers belonged remained concealed from the researcher. The researcher and all participants remained blind to the treatment assignment until data analysis was complete.

Table 6 outlines the process for testing sessions. Each testing session took 220 minutes. Participants were informed of the process for participating in the study and an informed consent form was then signed (see Appendix A). A screening questionnaire (including the AUDIT and the K10) was administered to allow for the assessment of exclusion criteria (see Appendix B). Next the participant's blood pressure was taken to get a baseline measure. In some people benzodiazepines can produce a drop in blood pressure that could result in fainting (Rosenfeld & Loose, 2007). For this reason, blood pressure was monitored throughout the testing session following each completion of the test battery. Participants then completed the WTAR, followed by training on the OSPAT task, CDR tasks, and Dual Task, for the purpose of minimising practice effects after drug ingestion. Participants then completed the test battery in the following order: the pre-test VAS, the DSST, the OSPAT, the Simple reaction time task, the Digit vigilance task, the Choice reaction time task, the Dual Task, and the post-test VAS. This test battery took approximately 15 minutes to complete. Participants were then handed an envelope and asked to ingest the capsule inside. After an initial 30 minute rest period, the test battery was repeated every 30 minutes, for a total of six times including baseline testing. The test schedule was designed so as to increase the likelihood of capturing maximal performance effects, whilst still allowing for a rest period between test points, and so as to capture the latest point post-ingestion where meaningful performance effects were likely to be present. This decision took into consideration the duration of significant effects noted in the reviewed studies and the fact that peak plasma levels tend to occur within 30 to 90 minutes post-ingestion (Sansom, 2009). In between testing, participants watched a DVD or read material of their choice. Participants did not consume food or beverages throughout the testing session, with the exception of water. Participants were previously asked to refrain from consuming caffeinated products on the day of testing, until the testing session was complete.

Table 6. Testing session procedure

Prior to drug/placebo ingestion	Informed consent completed
	Screening questionnaire administered
	Blood pressure recorded
	WTAR administered
	Training on OSPAT, Simple Reaction Time, Choice Reaction Time, Digit Vigilance and Dual Task
	Test battery completed (baseline/test point 1)
0 mins post-ingestion	Ingestion of 5mg diazepam or placebo
	Rest
30 mins post-ingestion	Test battery completed (test point 2)
	Blood pressure recorded
45 mins post-ingestion	Rest
60 mins post-ingestion	Test battery completed (test point 3)
	Blood pressure recorded
75 mins post-ingestion	Rest
90 mins post-ingestion	Test battery completed (test point 4)
	Blood pressure recorded
105 mins post-ingestion	Rest
120 mins post-ingestion	Test battery completed (test point 5)
	Blood pressure recorded
135 mins post-ingestion	Rest
150 mins post-ingestion	Test battery completed (test point 6)
	Blood pressure recorded
165 mins post-ingestion	End of testing session

Notes. WTAR is Weschler Test of Adult Reading; OSPAT is Occupational Safety Performance Assessment Test.

Design and analyses

The design was a double-blind, placebo-controlled, mixed measures design. The between subjects factor was Group (Diazepam, Placebo) and the within subjects factor was Time (0, 30, 60, 90, 120,

and 150 minutes). All dependent variables are listed in Table 7. Analyses were conducted for each of these variables as outlined below. SPSS version 18 for Windows and Comprehensive Meta Analysis version 2.2.057 were used for statistical evaluation. Hedges *g,* with a correction applied to adjust for the bias in this estimation of the population effect size, was used as the measure of effect throughout this study due to the relatively small sample size used. Effect sizes of a negative value indicate a detrimental effect of diazepam on performance. Effect sizes of |0.2| to |0.5| are considered to be small; effect sizes of |0.5|to |0.8|are considered to be moderate; and effect sizes of more than |0.8|are considered to be large (Cohen, 1988). Effect sizes of less than |0.2| are considered to be negligible and not to have any practical significance for on-road driving performance.

Control variables

The control variables included Age, AUDIT score, K10 score and WTAR score. These variables were analysed using one-way Analysis of Variance (ANOVA) (with a significance value of $p<.05$), and effect sizes were calculated.

Test battery variables

The objective performance variables included the following: DSST score, Simple reaction time, Choice reaction time, Choice response accuracy, Vigilance reaction time, Vigilance response accuracy, Task A reaction time, Task A hit rate, Task B reaction time, Task B hit rate, and OSPAT score. The subjective experience variables were Pre-test subjective alertness, Post-test subjective alertness, Pre-test task subjective competence, and Post-test subjective competence. Baseline results were analysed to determine if the Diazepam and Placebo groups were similar prior to drug ingestion. Effect sizes were calculated for the differences between the groups on each of the test battery variables at baseline. Additionally one-way ANOVA were conducted to determine if group differences reached significance ($p<.05$).

For test-points post-drug ingestion scores were calculated as the change from baseline. A mixed ANOVA (Greenhouse-Geisser adjusted), with Time (30, 60, 90, 120, 150 minutes post-ingestion) as the within subjects factor and Group as the between groups factor, was conducted for each of the test battery variables. To enable the determination of duration and maximal effects of the diazepam dose, effect sizes were calculated for group differences at each test point post-ingestion, along with one-way ANOVA to determine the significance of group differences. An increased likelihood of type one errors due to the number of one-way ANOVAs conducted was recognised and the determination of effect sizes was expected to protect against interpretation of statistically significant but meaningless group differences. Whilst ANOVA results were to be reported, the interpretation of the test battery results in this study would focus on effect sizes. Effects of diazepam on the objective task variables were to be described as 'deleterious' in both the case of a reduction in performance from baseline levels by the Diazepam group,which was greater than the reduction by the Placebo group, or the case of a reduced benefit from practice effects by the Diazepam group (i.e. the Diazepam group did not improve from baseline levels to the same extent that the Placebo group did).

A BAC equivalency of maximal deleterious effect was calculated through the application of a regression equation derived by Dawson and Reid (1997) to OSPAT scores. The regression equation was 1.16% performance decrement per .01% BAC. Performance decrement from baseline was calculated for each individual participant, for each test-point. The equation was then applied to the mean decrement for each group for each of these test-points.

Composite performance variables

Selected test battery variables were combined into composite measures using meta-analytic techniques (see Table 7). Change from baseline scores for the test battery variables were used for this. *Psychomotor processing speed composite* was derived from DSST score alone; *Sensory motor reaction time composite* was derived from Simple reaction time, Choice reaction time and Choice

response accuracy; *Vigilance composite* was derived from Vigilance reaction time and Vigilance response accuracy; *Divided attention composite* was derived from Task A reaction time, Task B reaction time, Task A hit rate and Task B hit rate; *Speed composite* was derived from Simple reaction time, Choice reaction time, Vigilance reaction time, Task A reaction time and Task B reaction time; *Accuracy composite* was derived from Choice response accuracy, Vigilance response accuracy, Task A hit rate and Task B hit rate; *Psychomotor performance composite* was derived from all of the objective performance variables in the test battery. Effect sizes were calculated for each of the composite measures to allow for comparisons amongst the psychomotor functions, for comparisons between the subjective experience variables and average psychomotor performance, and for comparisons between OSPAT score and average psychomotor performance. The Comprehensive Meta Analysis software used to analyse this data provided Hedges *g* as the measure of effect, along with *z* scores and *p* values for group comparisons. *Z* scores and *p* values were also calculated for comparisons between some effect sizes.

Table 7. Dependent variables

	Variable descriptions
Control variables	
Age	Age in years
AUDIT score	Level of consumption of alcohol at harmful levels, as measured by the Alcohol Use and Disorders Identification Test (AUDIT). Higher scores indicate more harmful use.
K10 score	Level of psychological distress as measured by the Kessler Psychological Distress Scale (K10). Lower scores indicate greater levels of distress.
WTAR score	Number of words correctly pronounced in the Weschler Test of Adult Reading (WTAR) (age-standardised). Higher scores indicate a greater estimated verbal intelligence.

Table 7. Continued…

Test battery variables – objective performance	
DSST score	Number of symbols correctly assigned in the Digit-symbol substitution task (DSST). Higher scores indicate greater performance.
Simple reaction time (ms)	Change from baseline in the average time taken to make a response in the Simple reaction time task. Lower scores indicate greater performance.
Choice reaction time (ms)	Change from baseline in the average time taken to make a correct response in the Choice reaction time task. Lower scores indicate greater performance.
Choice response accuracy (%)	Change from baseline in the percentage of trials in which a correct response was made in the Choice reaction time task. Higher scores indicate greater performance.
Vigilance reaction time (ms)	Change from baseline in the average time taken to make a correct response in the Digit vigilance task. Lower scores indicate greater performance.
Vigilance response accuracy (%)	Change from baseline in the percentage of trials requiring a response in which a correct response was made in the Digit vigilance task. Higher scores indicate greater performance.
Task A reaction time (ms)	Change from baseline in the average time taken to make a correct response for Task A (driving scenarios) in the Dual Task. Lower scores indicate greater performance.
Task A hit rate (%)	Change from baseline in the percentage of trials in the Dual Task requiring a response for Task A (driving scenarios) in which a correct response was made. Higher scores indicate greater performance.
Task B reaction time (ms)	Change from baseline in the average time taken to make a correct response for Task B (shape recognition) in the Dual Task. Lower scores indicate greater performance.
Task B hit rate (%)	Change from baseline in the percentage of trials in the Dual Task requiring a response for Task B (shape recognition) in which a correct response was made. Higher scores indicate greater performance.
OSPAT score	Change from baseline in the quality of performance on the Occupational safety performance assessment test (OSPAT). Scores are based on accuracy and time taken to adapt to change, with higher scores indicating greater performance.

Table 7. Continued…

Test battery variables – subjective experience	
Pre-test subjective alertness	Change from baseline in Visual analogue scale (VAS) response to: 'I feel alert', measured at the start of test battery completion. Higher scores indicate a greater increase/lower decrease in agreement with the statement.
Post-test subjective alertness	Change from baseline in VAS response to: 'I feel alert', measured at the end of test battery completion. Higher scores indicate a greater increase/lower decrease in agreement with the statement.
Pre-test subjective competence	Change from baseline in VASresponse to: 'I feel that I will be able to perform the tasks to the best of my ability', measured at the start of test battery completion. Higher scores indicate a greater increase/lower decrease in agreement with the statement.
Post-test subjective competence	Change from baseline in VASresponse to: 'I feel that I was able to perform the tasks to the best of my ability', measured at the end of test battery completion. Higher scores indicate a greater increase/lower decrease in agreement with the statement.
Composite performance variables	
Psychomotor processing speed composite	A measure representing the mean performance on DSST score alone.
Sensory motor reaction time composite	A composite measure representing the mean performance on Simple reaction time, Choice reaction and Choice response accuracy.
Vigilance composite	A composite measure representing the mean performance on Vigilance reaction time and Vigilance response accuracy.
Divided attention composite	A composite measure representing the mean performance on Task A reaction time, Task B reaction time, Task A hit rate and Task B hit rate.
Speed composite	A composite measure representing the mean performance on Simple reaction time, Choice reaction time, Vigilance reaction time, Task A reaction time and Task B reaction time.
Accuracy composite	A composite measure representing the mean performance on Choice response accuracy, Vigilance response accuracy, Task A hit rate and Task B hit rate.
Psychomotor performance composite	A composite measure representing the mean performance on all objective performance variables (i.e. DSST score Simple reaction time, Choice reaction, Choice response accuracy, Vigilance reaction time, Vigilance response accuracy, Task A reaction time, Task B reaction time, Task A hit rate, Task B hit rate, and OSPAT score).

Results

Control measures

The groups did not significantly differ in Age, $F(1,32) = 1.78$, $p = .192$, $g = 0.04$, with the Diazepam group having a mean age of 22.35 years (*SD* = 4.17) and the Placebo group having a mean age of 26.00 (*SD* = 10.48). There were also no significant group differences in WTAR score, $F(1,29) = .185$, $p = .670$, $g = 0.15$, with the Diazepam group having a mean WTAR score of 108.9 (*SD* = 9.98) and the Placebo group having a mean WTAR score of 107.31 (*SD*= 10.12).

There was a weak trend towards significant group differences in AUDIT score, $F(1,32)= 2.99$, $p = .094$, $g = 0.58$, with the Diazepam group having a mean AUDIT score of 3.88 (*SD* = 3.26) and the Placebo group having a mean AUDIT score of 5.65 (*SD* = 1.67). This indicates a slightly higher level of problematic alcohol use in the Placebo group, however there were no participants in either group who scored within the range indicative of a harmful level of alcohol use (i.e. scores higher than 8).

There was a trend towards significant group differences in K10 score, $F(1,32) = 3.22$, $p = .082$, $g = 0.60$, with the Diazepam group having a mean K10 score of 14.88 (*SD* = 2.85) and the Placebo group having a mean K10 score of 16.71 (*SD* = 3.08). This indicates that the Placebo group had a slightly higher level of psychological distress, however, there were no participants in either group who scored within the range indicative of high levels of distress (i.e. scores higher than 25).

Overall these results indicate that the Diazepam and Placebo groups are relatively similar in terms of age, level of alcohol use, level of psychological distress and general intelligence. Although trends towards significant group differences in problematic alcohol use and psychological distress are evident, these are not considered likely to impact on task performance due to participants in both groups all scoring within a non-harmful AUDIT range and a low psychological distress K10 range.

Baseline measures

The groups differed in baseline scores for Task A hit rate with the Diazepam group having a significantly lower hit rate relative to the Placebo group, $F(1,33)= 5.09$, $p=.031$, $g = -0.76$. Trends towards significant group differences were evident for Choice reaction time, with prolonged reaction time in the Diazepam group, $F(1,33) = 3.84$, $p= .059$, $g = -0.66$, and for Vigilance reaction time, again

Table 8. Group means, ANOVA results and effect sizes for objective performance variables at baseline

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size *g*
Objective performance variables				
Digit-symbol substitution task (DSST) score (*n* =34)	64.88 (10.48)	66.94 (9.16)	*F*(1,32)=.365, *p*=.550	-0.21
Simple reaction time (ms) (*n*=34)	261.98 (39.77)	252.83 (33.23)	*F*(1,33)=.530, *p*=.472	-0.24
Choice reaction time (ms) (*n*=34)	444.44 (55.44)	412.67 (37.40)	*F*(1,33)=3.84, *p*=.059	-0.66
Choice response accuracy (%) (*n*=34)	95.88 (2.78)	96.82 (3.00)	*F*(1,33)=0.90, *p*=.350	-0.32
Vigilance reaction time(ms) (*n* =33)	412.30 (32.03)	394.16 (27.84)	*F*(1,33)=3.03, *p*=.092	-0.59
Vigilance response accuracy (%) (*n* =33)	98.47 (2.40)	98.04 (2.71)	*F*(1,33)=0.10, *p*=.631	0.17
Task A reaction time (ms) (*n*=34)	575.42 (47.03)	582.63 (77.29)	*F*(1,33) = 0.11, *p* = .745	0.11
Task B reaction time(ms) (*n*=34)	676.63 (93.08)	644.27 (123.69)	*F*(1,33)=0.74, *p*=.395	-0.29
Task A hit rate (%) (*n*=34)	92.06 (5.88)	96.47 (5.52)	*F*(1,33)=5.09, *p*=.031	-0.76
Task B hit rate (%) (*n*=34)	84.31 (10.43)	88.24 (12.09)	*F*(1,33)=1.03, *p*=.319	-0.34
Occupational Safety Performance Assessment Test (OSPAT) score(*n*=34)	14.41 (1.70)	14.97 (1.38)	*F*(1,33)=1.14, *p*=.293	-0.36
Subjective experience variables				
Pre-test subjective alertness (mm) (*n* = 34)	67.62 (18.76)	65.49 (19.06)	*F*(1,33) = 0.11, *p* = .746	0.11
Post-test subjective alertness (mm) (*n* = 34)	76.65 (21.33)	71.92 (21.29)	*F*(1,33) = 0.42, *p* = .522	0.22
Pre-test task subjective competence (mm)(*n* = 34)	78.96 (16.34)	73.50 (22.39)	*F*(1,33) = 0.66, *p* = .423	0.27
Post-test subjective competence (mm) (*n* = 34)	79.93 (19.33)	74.29 (28.44)	*F*(1,33) = 0.46, *p* = .504	0.23

Notes. n=17 for each treatment group except for Vigilance reaction time and Vigilance response accuracy, where a technical error during task completion meant that n= 16 for the Diazepam group and n = 17 for the Placebo group; greater performance is indicated by higher DSST scores, lower Simple reaction times, lower Choice reaction times, higher Choice response accuracy, lower Vigilance reaction times, higher Vigilance response accuracy, lower Task A reaction times, lower Task B reaction times, higher Task A hit rates, higher Task B hit rates, and higher OSPAT scores; scores for subjective experience variables indicate the level of agreement with visual analogue scale statements (measured in millimetres) with higher scores indicating a greater level of agreement; negative values for effect sizes indicate the Placebo group having greater performance than the Diazepam group or having greater agreement with the relevant visual analogue scale statement than the Diazepam group.

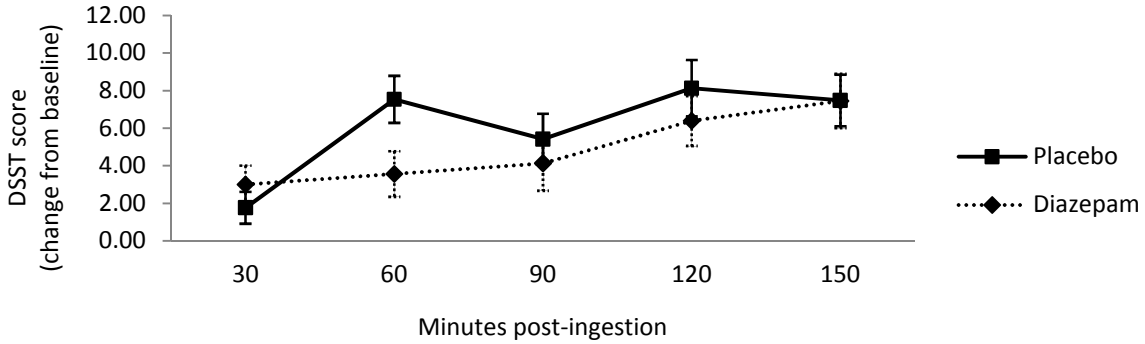
with prolonged reaction time in the Diazepam group, $F(1,33) = 3.03$, $p = .092$, $g = -0.59$. The groups did not differ significantly on any other task battery variables (see Table 8). Change from baseline scores were used for all analyses of post-ingestion effects so that the impact of differences in baseline scores on the between-groups comparisons was minimised. ANCOVA was considered as an option to adjust post-ingestion scores, however, there were many variables where the data did not meet the assumptions of the technique and hence ANCOVA-adjusted scores were unreliable. As such, the use of change from baseline scores was considered to be a reasonable alternative, and the more valid approach of the two (Vickers & Altman, 2001).

Objective performance measures

Psychomotor processing speed measure

The mean changes from baseline in DSST score at each time point are displayed in Figure 3. Effect sizes and the significance of group differences at each time point are displayed in Table 9. Greenhouse-Geisser adjusted ANOVA revealed a significant main effect for Time, $F(3,104) = 12.77$, $p < .001$, a non-significant main effect for Group, $F(1,31) = 0.57$, $p = .458$, and a significant interaction between Group and Time, $F(3,104) = 2.84$, $p = .036$. Maximal effects occurred at 60 minutes post-ingestion where diazepam moderately and deleteriously impacted on performance, $F(1,32)=5.01$, $p=.032$, $g = -0.76$. Effects at all other time points were small or negligible ($g<0.5$), and deleterious effects ($g>0.2$) were no longer evident beyond 120 minutes post-ingestion. Error rates for this task were not analysed due to the low incidence of errors occurring (3 in total throughout testing). The mean number of errors committed was 0 for both groups at all time points with the exception of a mean of 0.08 ($SD = 0.28$) for the Diazepam group at 60 minutes post-ingestion, and means of 0.08 ($SD = 0.28$) for both the Diazepam and Placebo groups at 90 minutes post-ingestion.

Figure 3. Mean Digit-symbol substitution test (DSST)score



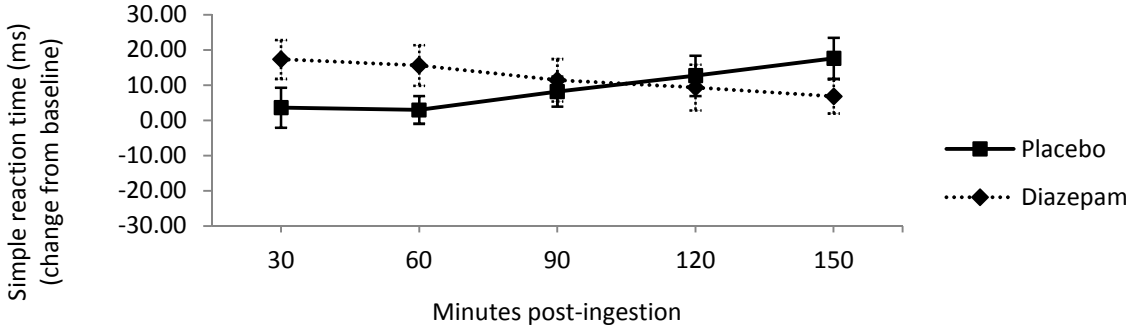
Notes. Higher DSST scores indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Sensory motor reaction time measures

The mean changes from baseline in Simple reaction time, Choice reaction time and Choice response accuracy at each time point are displayed in Figures 4 through to 6. Effect sizes and the significance of group differences at each time point are displayed in Table 9. Greenhouse-Geisser adjusted ANOVA of Simple reaction time revealed a non-significant main effect for Time, $F(3,105) = 0.16$, $p = .937$, a non-significant main effect for Group, $F(1,32) = 0.28$, $p = .598$, and a significant interaction between Group and Time, $F(3,105) = 3.31$, $p = .020$. Maximal effects occurred at 60 minutes post-ingestion where diazepam had a moderate deleterious effect on performance, $F(1,33) = 3.24$, $p = .081$, $g = -0.60$. A moderate effect was also present at 30 minutes post-ingestion, again with diazepam deleteriously impacting on performance, $F(1,33)=2.99$, $p=.093$, $g = -0.58$. Effects at all other time points were non-significant ($p>.05$) and small or negligible ($g<0.5$), and deleterious effects ($g>0.2$) were no longer evident beyond 60 minutes post-ingestion.

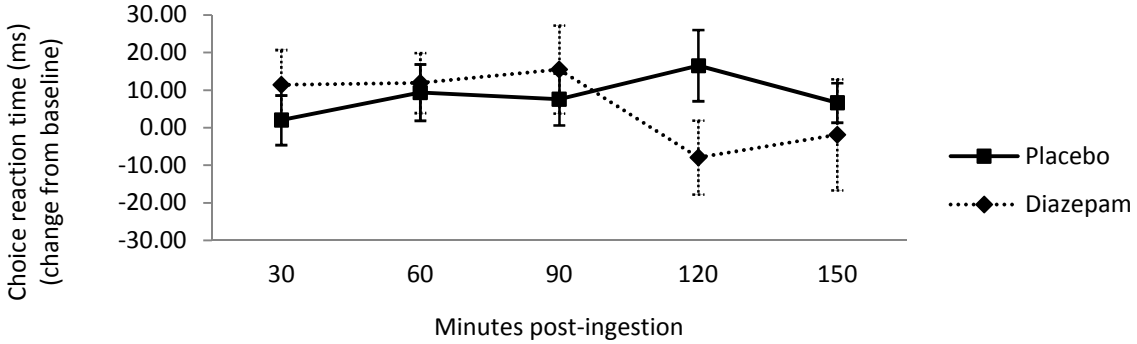
Greenhouse-Geisser adjusted ANOVA of Choice reaction time revealed a non-significant main effect for Time, $F(3,107) = 0.88$, $p = .478$, a non-significant main effect for Group, $F(1,32) = 0.06$, $p = .811$, and a significant interaction between Group and Time, $F(3,107) = 2.81$, $p = .037$. Maximal effects occurred at 120 minutes post-ingestion where diazepam had a moderate and beneficial effect on performance, $F(1,33)=3.21$, $p=.083$, $g = 0.60$. Effects at all other time points were either negligible or

Figure 4. Mean Simple reaction time



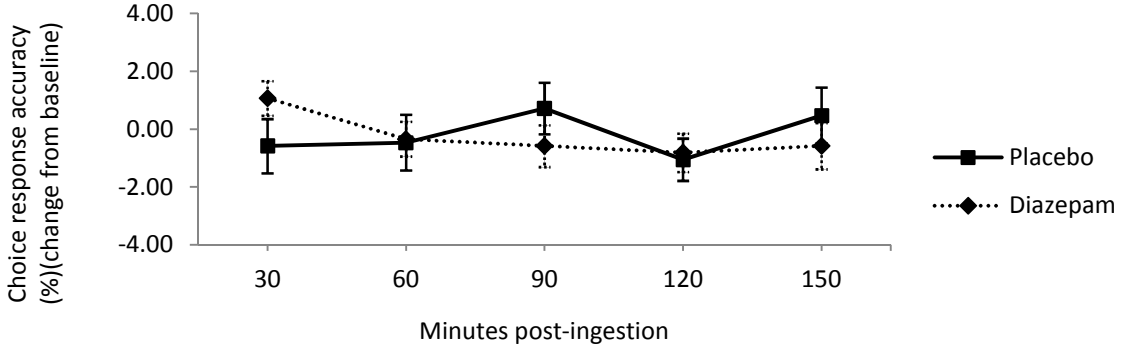
Notes. Lower Simple reaction times indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Figure 5. Mean Choice reaction time



Notes. Lower Choice reaction times indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Figure 6. Mean Choice response accuracy



Notes. Higher Choice response accuracy indicates greater increase/lower reduction in performance from baseline levels; error bars represent standard errors; mean Choice response accuracy at baseline was 95.88% (*SD* = 2.78) for the Diazepam group and 96.82% (*SD* = 3.00) for the Placebo group.

deleterious and small (g< 0.5). Deleterious effects (g> 0.2) were no longer evident beyond 90 minutes post-ingestion.

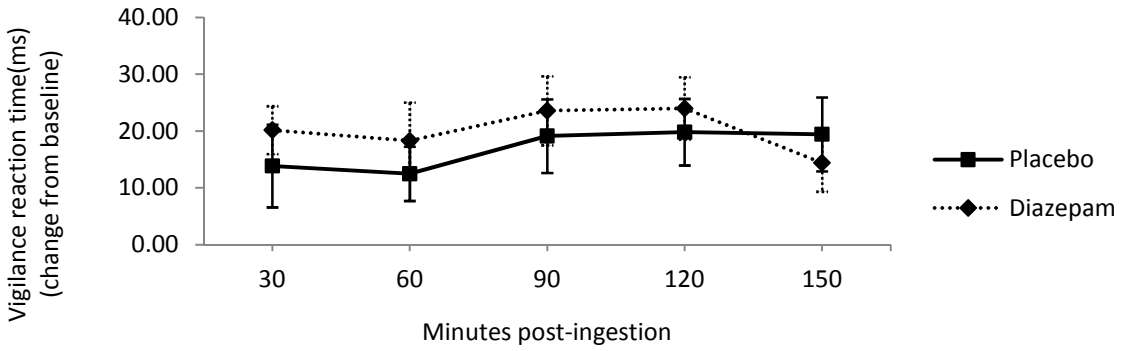
Greenhouse-Geisser adjusted ANOVA of Choice response accuracy revealed a non-significant main effect for Time, $F(3,110) = 1.37$, $p = .252$, a non-significant main effect for Group, $F(1,32) = 0.01$, $p = .936$, and a trend towards an interaction between Group and Time, $F(3,110) = 2.20$, $p = .084$. Maximal effects occurred at 30 minutes post-ingestion where diazepam had a moderate and beneficial effect on performance, $F(1,33)=2.20$, $p=.148$, $g = 0.50$. Effects at all other time points were either negligible or deleterious but small (g< 0.5). Very small deleterious effects were evident at the final test-point 150 minutes post-ingestion (g= -0.28).

Vigilance measures

The mean changes from baseline in Vigilance reaction time and Vigilance response accuracy at each time point are displayed in Figures 7 and 8. Effect sizes and the significance of group differences at each time point are displayed in Table 9. Greenhouse-Geisser adjusted ANOVA of Vigilance reaction time revealed a non-significant main effect for Time, $F(4, 109) = 0.97$, $p = .418$, a non-significant main effect for Group, $F(1,31) = 0.23$, $p = .634$, and a non-significant interaction between Group and Time, $F(4,109) = 0.62$, $p = .630$. Maximal effects occurred at 30 minutes post-ingestion where diazepam had only a small deleterious effect on performance, $F(1,32)=0.55$, $p=.465$, $g = -0.25$. Effects at all other time points were also small or negligible (g<0.5), and deleterious effects (g>0.2) were no longer evident beyond 60 minutes post-ingestion.

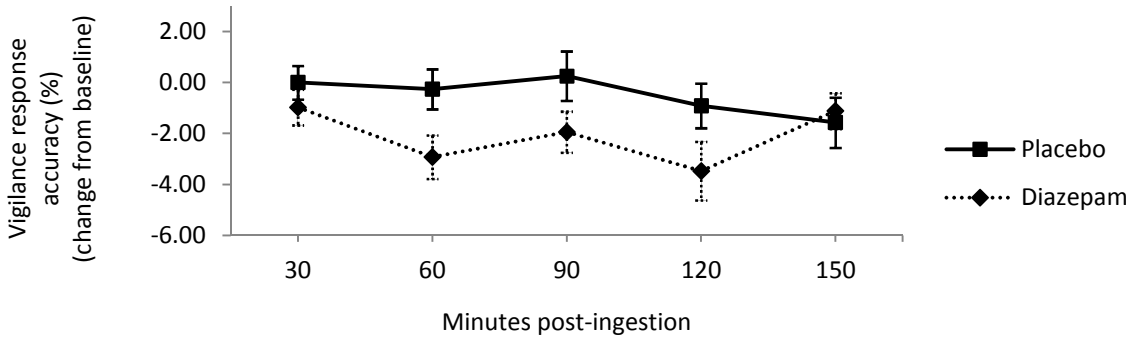
Greenhouse-Geisser adjusted ANOVA of Vigilance response accuracy revealed a non-significant main effect for Time, $F(4, 110) = 2.01$, $p = .106$, a trend towards a significant main effect for Group, $F(1,31) = 3.20$, $p = .083$, and a non-significant interaction between Group and Time, $F(4,110) = 2.01$, $p = .106$. Maximal effects occurred at 60 minutes post-ingestion where diazepam had a moderate and deleterious effect on performance, $F(1,32)=5.27$, $p=.029$, $g = -0.78$. Moderate effects were also

Figure 7. Mean Vigilance reaction time



Notes. Lower Vigilance reaction times indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Figure 8. Mean Vigilance response accuracy



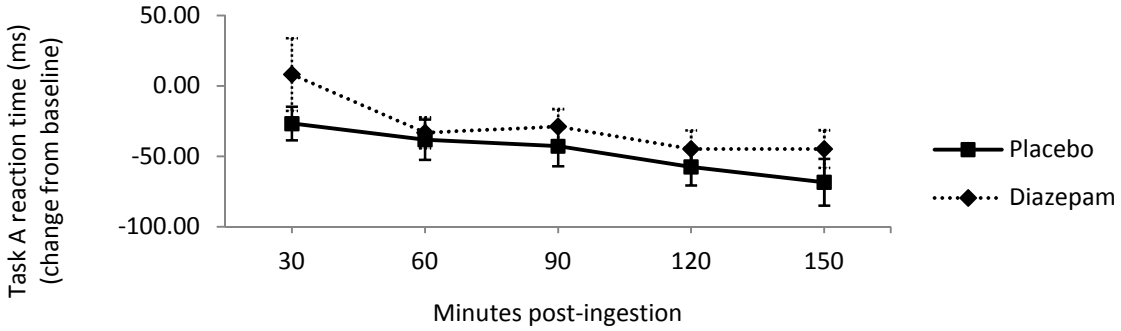
Notes. Higher Vigilance response accuracy indicates greater increase/lower reduction in performance from baseline levels; error bars represent standard errors; mean Vigilance response accuracy at baseline was 98.47% (*SD* = 2.40) for the Diazepam group and 98.04% (*SD* = 2.71) for the Placebo group.

evident at 90 minutes, $F(1,32)=3.01$, $p=.093$, g = -0.59, and 120 minutes, $F(1,32)=3.19$, $p=.084$, g = -0.61, with diazepam deleteriously impacting on performance at both points. Effects at all other time points were small or negligible ($g< 0.5$). Deleterious effects ($g> 0.2$) were no longer evident beyond 120 minutes post-ingestion.

Divided Attention measures

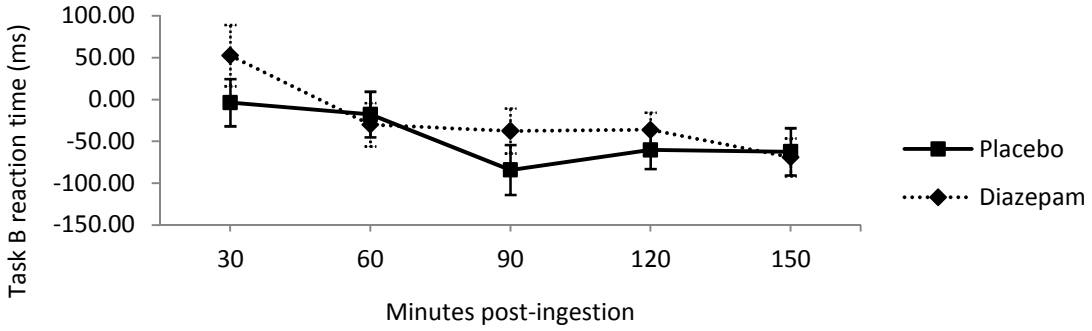
The mean changes from baseline in Task A reaction time, Task B reaction time, Task A hit rate and Task B hit rate at each time point are displayed in Figures 9 through to 12. Effect sizes and the significance of group differences at each time point are displayed in Table 9. Greenhouse-Geisser

Figure 9. Mean Task A reaction time



Notes. Lower Task A reaction times indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Figure 10. Mean Task B reaction time

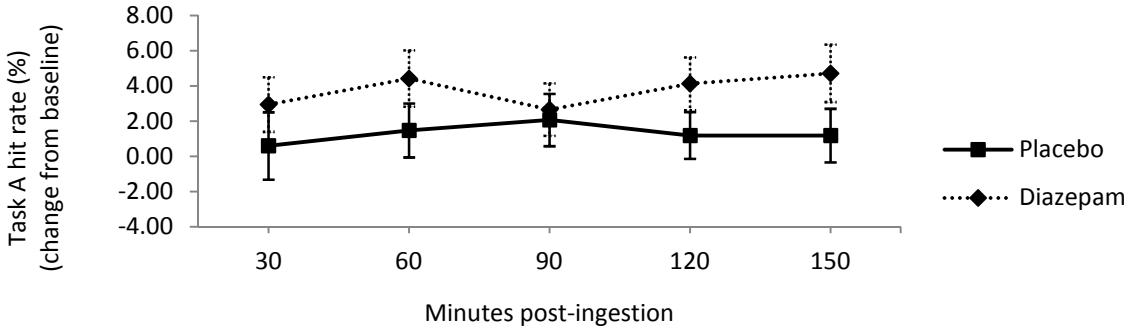


Notes. Lower Task B reaction times indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

adjusted ANOVA of Task A reaction time (driving scenario reaction time) revealed a significant main effect for Time, $F(2,58) = 6.94$, $p = .003$, a non-significant main effect for Group, $F(1,32) = 1.07$, $p = .310$, and a non-significant interaction between Group and Time, $F(2,58) = 0.68$, $p = .497$. Maximal effects occurred at 30 minutes post-ingestion where diazepam had only a small deleterious effect on performance, $F(1,33)=1.50$, $p=.230$, $g = -0.41$. Effects at all other time points were also small or negligible ($g< 0.5$). A small deleterious effect was evident at the final test-point 150 minutes post-ingestion ($g= -0.37$).

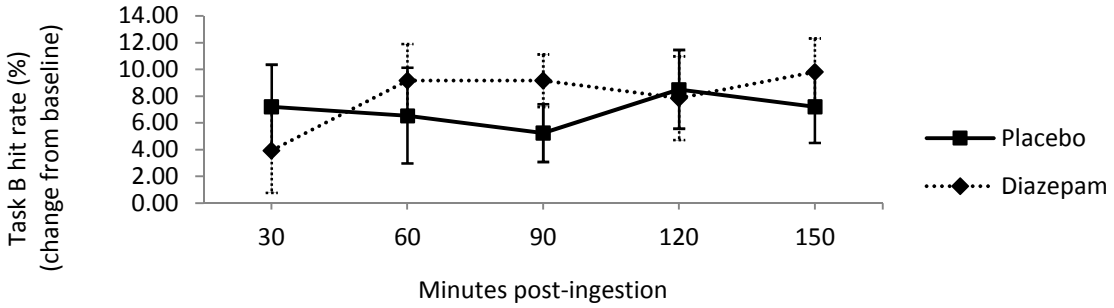
Greenhouse-Geisser adjusted ANOVA of Task B reaction time (shape recognition reaction time)

Figure 11. Mean Task A hit rate



Notes. Higher Task A hit rates indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors; mean Task A hit rate at baseline was 92.06% (*SD* = 5.88) for the Diazepam group and 96.47% (*SD* = 5.52) for the Placebo group.

Figure 12. Mean Task B hit rate



Notes. Higher Task B hit rates indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors; mean Task B hit rate at baseline was 84.31% (*SD* = 10.43) for the Diazepam group and 88.24% (*SD* = 12.09) for the Placebo group.

revealed a significant main effect for Time, $F(2,73) = 7.33$, $p = .001$, a non-significant main effect for Group, $F(1,32) = 0.52$, $p = .476$, and a non-significant interaction between Group and Time, $F(3,98) = 1.27$, $p = .288$. Maximal effects occurred at 30 minutes post-ingestion where diazepam had only a small deleterious effect on performance, $F(1,33)=1.48$, $p=.233$, $g = -0.41$. Effects at all other time points were also small or negligible ($g< 0.5$), and deleterious effects ($g> 0.2$) were no longer evident beyond 120 minutes post-ingestion.

Greenhouse-Geisser adjusted ANOVA of Task A hit rate (driving scenario hit rate) revealed a non-significant main effect for Time, $F(3,100) = 0.62$, $p = .612$, a non-significant main effect for Group,

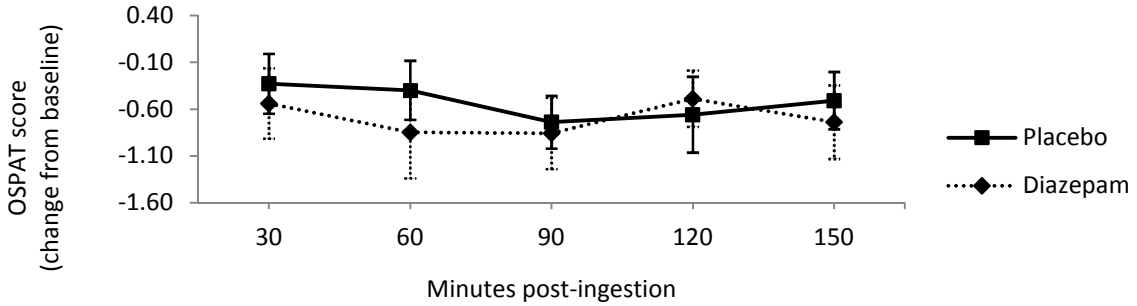
$F(1,32) = 1.69$, $p = .203$, and a non-significant interaction between Group and Time, $F(3,100) = 0.82$, $p = .492$. Maximal effects occurred at 150 minutes post-ingestion where diazepam had a non-significant but moderate beneficial effect on performance, $F(1,33)= 2.51$, $p= .123$, $g = 0.53$. Effects at all other time points were negligible or small and also beneficial ($g< 0.5$).

Greenhouse-Geisser adjusted ANOVA of Task B hit rate (shape recognition hit rate) revealed a non-significant main effect for Time, $F(4, 112) = 0.90$, $p = .454$, a non-significant main effect for Group, $F(1,32) = 0.10$, $p = .758$, and a non-significant interaction between Group and Time, $F(4,112) = 1.44$, $p = .229$. Maximal effects occurred at 90 minutes post-ingestion where diazepam had a non-significant but small beneficial effect on performance, $F(1,33)=1.81$, $p=.188$, $g = 0.45$. Effects at all other time points were negligible or deleterious and small ($g< 0.5$). The only time point where a deleterious effect ($g> 0.2$) was evident was at 30 minutes post-ingestion.

Tracking measure

The mean changes from baseline in OSPAT score at each time point are displayed in Figure 13. Effect sizes and the significance of group differences at each time point are displayed in Table 9. Greenhouse-Geisser adjusted ANOVA of OSPAT score revealed a non-significant main effect for Time, $F(3,109) = 0.56$, $p = .664$, a non-significant main effect for Group, $F(1,32) = 0.18$, $p = .675$, and a effect on performance, $F(1,33)=0.59$, $p=.449$, $g = -0.26$. Effects at all other time points were negligible ($g< 0.2$). The estimated blood-alcohol equivalency of performance decrement from baseline was calculated (using the regression equation of 1.16% performance decrement per .01% BAC) for 60 minutes post-ingestion, where group differences were the largest. The Placebo group's performance had declined by 2.4% from baseline. The blood-alcohol concentration equivalence of this decrement is estimated to be .020%, likely reflective of fatigue. The Diazepam group's performance at this time point had declined by 4.8%, with the estimated blood-alcohol concentration of this decrement being .041% - an additional .021%.

Figure 13. Mean Occupational Safety Performance Assessment Test (OSPAT) score



Notes. Higher OSPAT scores indicate greater increase/lower reduction in performance from baseline levels; error bars represent standard errors.

Table 9. Group means, ANOVA results and effect sizes for changes from baseline in individual objective performance variables post-ingestion

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size Hedges *g* (and 95% confidence interval)
Digit-symbol substitution task (DSST) score (*n* =34)				
30 minutes	3.00 (4.13)	1.76 (3.49)	*F*(1,32)=0.86, *p*=.360	0.32 (±0.67)
60 minutes	3.56 (5.01)	7.53 (5.16)	*F*(1,32)=5.01, *p*=.032*	**-0.76 (±0.69)**
90 minutes	4.13 (6.03)	5.41 (5.60)	*F*(1,32)=0.40, *p*=.530	-0.22 (±0.67)
120 minutes	6.38 (5.48)	8.12 (6.19)	*F*(1,32)=0.73, *p*=.400	-0.29 (±0.67)
150 minutes	7.44 (5.96)	7.47 (5.64)	*F*(1,32)<0.01, *p*=.987	-0.01 (±0.67)
Simple reaction time (ms) (*n* = 34)				
30 minutes	17.30 (22.83)	3.60 (23.35)	*F*(1,33)=2.99, *p*=.093^	**-0.58 (±0.67)**
60 minutes	15.57 (23.80)	3.00 (16.22)	*F*(1,33)=3.24, *p*=.081^	**-0.60 (±0.67)**
90 minutes	11.39 (24.84)	8.17 (17.44)	*F*(1,33)=0.19, *p*=.664	-0.15 (±0.66)
120 minutes	9.32 (26.85)	12.66 (23.60)	*F*(1,33)=0.15, *p*=.703	0.13 (±0.66)
150 minutes	6.82 (20.06)	17.60 (24.01)	*F*(1,33)=2.02, *p*=.165	0.47 (±0.67)

Table 9. Continued…

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size Hedges *g* (and 95% confidence interval)
Choice reaction time (ms) (*n* = 34)				
30 minutes	11.42 (38.21)	1.98 (27.25)	*F*(1,33)=0.69, *p*=.413	-0.28 (±0.66)
60 minutes	11.90 (32.98)	9.36 (30.93)	*F*(1,33)=0.05, *p*=.818	-0.08 (±0.66)
90 minutes	15.49 (48.38)	7.53 (28.40)	*F*(1,33)=0.34, *p*=.563	-0.20 (±0.66)
120 minutes	-7.95 (40.56)	16.54 (39.10)	*F*(1,33)=3.21, *p*=.083	0.60 (±0.67)
150 minutes	-1.89 (60.99)	6.62 (21.70)	*F*(1,33)=0.29, *p*=.592	0.18 (±0.66)
Choice response accuracy (%)(*n* = 34)				
30 minutes	1.06 (2.46)	-0.59 (3.86)	*F*(1,33)=2.20, *p*=.148	0.50 (±0.67)
60 minutes	-0.35 (2.47)	-0.47 (3.97)	*F*(1,33)=0.01, *p*=.918	0.04 (±0.66)
90 minutes	-0.59 (2.98)	0.71 (3.67)	*F*(1,33)=1.27, *p*=.267	-0.38 (±0.66)
120 minutes	-0.82 (2.74)	-1.06 (3.01)	*F*(1,33)=0.06, *p*=.813	0.08 (±0.66)
150 minutes	-0.59 (3.30)	0.47 (3.97)	*F*(1,33)=0.72, *p*=.404	-0.28 (±0.66)
Vigilance reaction time (ms)(*n* = 33)				
30 minutes	20.20 (16.80)	13.89 (29.97)	*F*(1,32)=0.55, *p*=.465	-0.25 (±0.67)
60 minutes	18.30 (27.02)	12.51 (19.63)	*F*(1,32)=0.50, *p*=.485	-0.24 (±0.67)
90 minutes	23.61 (24.29)	19.14 (26.63)	*F*(1,32)=0.25, *p*=.619	-0.17 (±0.67)
120 minutes	24.01 (22.02)	19.84 (24.12)	*F*(1,32)=0.27, *p*=.608	-0.18 (±0.67)
150 minutes	14.42 (20.22)	19.46 (26.84)	*F*(1,32)=0.37, *p*=.549	0.21 (±0.67)
Vigilance response accuracy (%)(*n* =33)				
30 minutes	-0.97 (2.81)	0.00 (2.72)	*F*(1,32)=1.02, *p*=.320	-0.34 (±0.67)
60 minutes	-2.92 (3.42)	-0.26 (3.23)	*F*(1,32)=5.27, *p*=.029*	**-0.78 (±0.69)**
90 minutes	-1.94 (3.23)	0.26 (4.00)	*F*(1,32)=3.01, *p*=.093^	**-0.59 (±0.68)**
120 minutes	-3.47 (4.59)	-0.91 (3.61)	*F*(1,32)=3.19, *p*=.084^	**-0.61 (±0.68)**
150 minutes	-1.11 (2.81)	-1.57 (4.06)	*F*(1,32)=0.14, *p*=.711	0.13 (±0.67)

Table 9. Continued…

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size Hedges *g* (and 95% confidence interval)
Task A reaction time(ms)(*n*=34)				
30 minutes	8.03 (106.43)	-26.72 (48.89)	*F*(1,33)=1.50, *p*=.230	-0.41 (±0.66)
60 minutes	-33.33 (44.95)	-38.22 (59.04)	*F*(1,33)=0.07, *p*=.787	-0.09 (±0.66)
90 minutes	-28.93 (51.16)	-42.80 (58.76)	*F*(1,33)=0.54, *p*=.468	-0.25 (±0.66)
120 minutes	-44.80 (54.73)	-57.50 (54.18)	*F*(1,33)=0.46, *p*=.502	-0.23 (±0.66)
150 minutes	-44.86 (55.06)	-68.43 (68.44)	*F*(1,33)=1.22, *p*=.277	-0.37 (±0.66)
Task B reaction time(ms)(*n*=34)				
30 minutes	52.34 (150.80)	-3.80 (116.47)	*F*(1,33)=1.48, *p*=.233	-0.41 (±0.66)
60 minutes	-30.26 (106.56)	-17.95 (112.17)	*F*(1,33)=0.11, *p*=.745	0.11 (±0.66)
90 minutes	-37.67 (110.57)	-84.17 (123.03)	*F*(1,33)=1.34, *p*=.255	-0.39 (±0.66)
120 minutes	-36.44 (85.12)	-60.31 (93.40)	*F*(1,33)=0.61, *p*=.442	-0.26 (±0.66)
150 minutes	-69.14 (93.32)	-62.40 (116.04)	*F*(1,33)=0.04, *p*=.853	0.06 (±0.66)
Task A hit rate (%)(*n*=34)				
30 minutes	2.94 (6.39)	0.59 (7.88)	*F*(1,33)=0.91, *p*=.346	0.32 (±0.67)
60 minutes	4.41 (6.59)	1.47 (6.32)	*F*(1,33)=1.77, *p*=.193	0.45 (±0.66)
90 minutes	2.65 (6.15)	2.06 (6.14)	*F*(1,33)=0.08, *p*=.782	0.09 (±0.67)
120 minutes	4.12 (6.18)	1.18 (5.46)	*F*(1,33)=2.16, *p*=.151	0.49 (±0.66)
150 minutes	4.71 (6.72)	1.18 (6.26)	*F*(1,33)=2.51, *p*=.123	0.53 (±0.67)
Task B hit rate (%)(*n*=34)				
30 minutes	3.92 (12.99)	7.19 (12.99)	*F*(1,33)=0.54, *p*=.469	-0.25 (±0.66)
60 minutes	9.15 (11.27)	6.54 (14.73)	*F*(1,33)=0.34, *p*=.565	0.19 (±0.66)
90 minutes	9.15 (8..08)	5.23 (8.89)	*F*(1,33)=1.81, *p*=.188	0.45 (±0.66)
120 minutes	7.84 (12.89)	8.50 (12.13)	*F*(1,33)=0.02, *p*=.880	-0.05 (±0.66)
150 minutes	9.80 (10.31)	7.19 (11.07)	*F*(1,33)=0.51, *p*=.481	0.24 (±0.66)

Table 9. Continued…

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size Hedges *g* (and 95% confidence interval)
Occupational Safety Performance Assessment Test (OSPAT) score(*n*=34)				
30 minutes	-0.54 (1.55)	-0.33 (1.32)	*F*(1,33)=0.19, *p*=.669	-0.14 (±0.66)
60 minutes	-0.85 (2.02)	-0.40 (1.30)	*F*(1,33)=0.59, *p*=.449	-0.26 (±0.66)
90 minutes	-0.86 (1.57)	-0.74 (1.16)	*F*(1,33)=0.07, *p*=.797	-0.09 (±0.66)
120 minutes	-0.49 (1.24)	-0.66 (1.67)	*F*(1,33)=0.11, *p*=.743	0.11 (±0.66)
150 minutes	-0.74 (1.62)	-0.51 (1.26)	*F*(1,33)=0.22, *p*=.641	-0.16 (±0.66)

Notes: n=17 for each treatment group except for Vigilance reaction time and Vigilance response accuracy, where a technical error during task completion meant that n= 16 for the Diazepam group and n = 17 for the Placebo group; greater increase in performance from baseline is indicated by higher DSST scores, lower Simple reaction times, lower Choice reaction times, higher Choice response accuracy, lower Vigilance reaction times, higher Vigilance response accuracy, lower Task A reaction times, lower Task B reaction times, higher Task A hit rates, higher Task B hit rates, and higher OSPAT scores; negative values for effect sizes indicate the Diazepam group having a greater decrease/smaller increase in performance from baseline than the Placebo group; effect sizes in bold indicate a deleterious diazepam effect of a moderate or larger magnitude ($g > 0.5$); * denotes significantly poorer task performance following diazepam relative to placebo ($p<.05$); ^ denotes a trend towards significantly poorer task performance following diazepam relative to placebo ($p<.10$).

Subjective experience measures

Subjective alertness measures

The mean changes from baseline for each time point for Pre-test subjective alertness and Post-test subjective alertness are displayed in Figures 14 and 15. Effect sizes and the significance of group differences at each time point are displayed in Table 10. Greenhouse-Geisser adjusted ANOVA of Pre-test subjective alertness revealed a non-significant main effect for Time, $F(3,87) = 0.93$, $p = .421$, a non-significant main effect for Group, $F(1,32) = 1.16$, $p = .290$, and a significant interaction between Group and Time, $F(3,87) = 3.70$, $p = .018$. Maximal effects occurred at 90 minutes post-ingestion where diazepam had a moderate effect, with the Diazepam group reporting a smaller increase in alertness from baseline than the Placebo group, $F(1,33)=3.80$, $p=.060$, $g = -0.65$. A moderate effect of the same direction was also present at 60 minutes post-ingestion, $F(1,33)=2.97$, $p=.095$, $g = -0.58$,

whilst effects at all other time points were small or negligible (g<0.5). Deleterious effects (g>0.2) were no longer evident beyond 120 minutes post-ingestion.

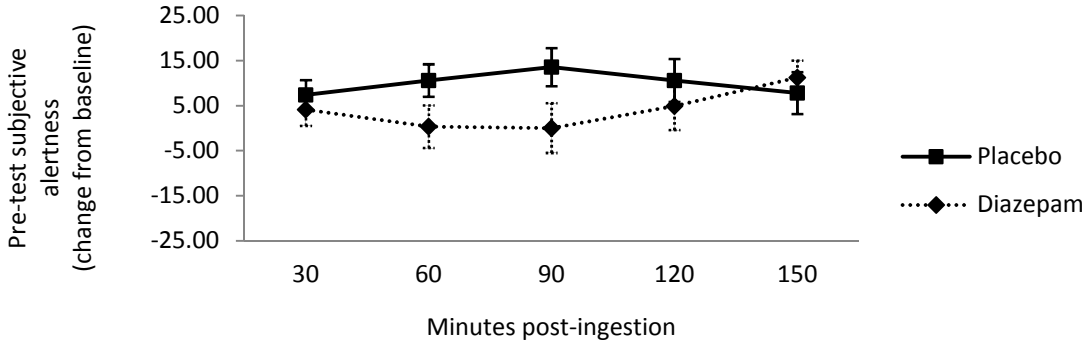
Greenhouse-Geisser adjusted ANOVA of Post-test subjective alertness revealed a significant main effect for Time, $F(3,87) = 3.35$, p =.026, a significant main effect for Group, $F(1,32)= 7.33$, p =.011, and a significant interaction between Group and Time, $F(3,87) = 5.50$, p = .002. Maximal effects occurred at 60 minutes post-ingestion where diazepam had a large effect, with the Diazepam group reporting a greater reduction in alertness from baseline than the Placebo group, $F(1,33)=12.04$, p=.002, g = -1.16. Large effects of the same direction were also present at 30 minutes post-ingestion, $F(1,33)=10.86$, p=.002, g = -1.10, and 90 minutes post-ingestion, $F(1,33)=8.09$, p=.008, g = -0.95. The effect decreased to a moderate level at 120 minutes, $F(1,33)=2.54$, p=.121, g = -0.53. A very small deleterious effect was still evident at 150 minutes post-ingestion (g=-0.2).

Subjective competence measures

The mean changes from baseline for each time point for Pre-test subjective competence and Post-test subjective competence are displayed in Figures 16 and 17. Effect sizes and the significance of group differences at each time point are displayed in Table 10. Greenhouse-Geisser adjusted ANOVA of Pre-test subjective competence revealed a non-significant main effect for Time, $F(3,80) = 0.51$, p=.643, a non-significant main effect for Group, $F(1,32)= 1.84$, p =.185, and a non-significant interaction between Group and Time, $F(3,80) = 1.75$, p = .173. Maximal effects occurred at 90 minutes post-ingestion where diazepam had a moderate effect, with the Diazepam group predicting a greater reduction in task performance than the Placebo group, $F(1,33)=4.66$, p=.038, g = -0.72. A moderate effect of the same direction was also present at 60 minutes post-ingestion, $F(1,33)=2.47$, p=.126, g = -0.53. Effects at other time points were small or negligible (g<0.5). Deleterious effects (g>0.2) were no longer evident beyond 120 minutes post-ingestion.

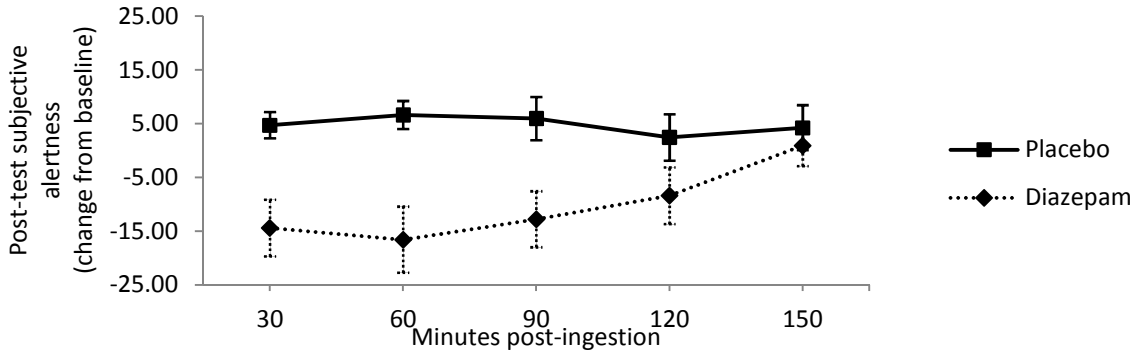
Greenhouse-Geisser adjusted ANOVA of Post-test subjective competence revealed a non-significant main effect for Time, $F(3,98) = 2.10$, p =.104, a trend towards a significant effect for Group, $F(1,32)=$

Figure 14. Mean Pre-test subjective alertness



Notes. Scores indicate change from baseline in level of agreement with the visual analogue scale statement "I feel alert", with higher scores indicating greater agreement; error bars represent standard errors.

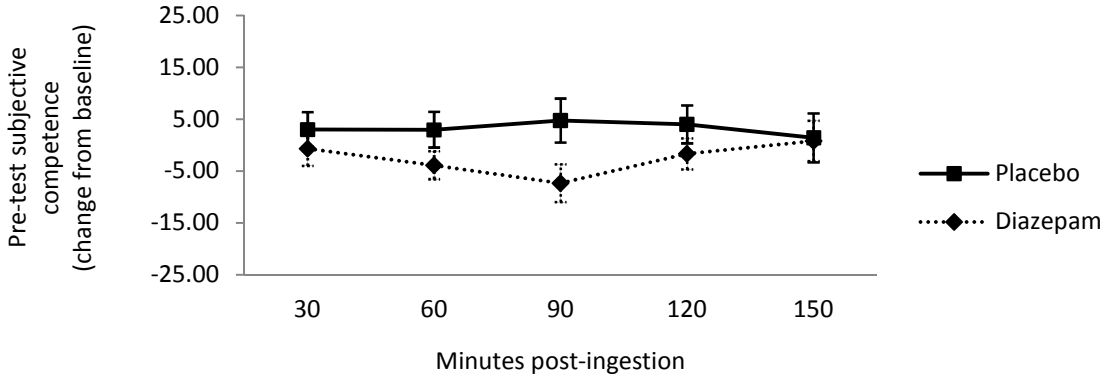
Figure 15. Mean Post-test subjective alertness



Notes. Scores indicate change from baseline in level of agreement with the visual analogue scale statement "I feel alert", with higher scores indicating greater agreement; error bars represent standard errors.

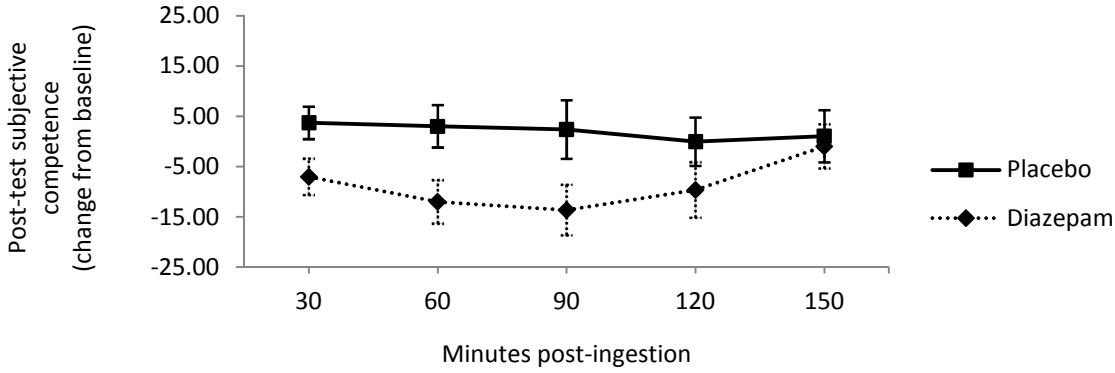
3.25, p =.081, and a significant interaction between Group and Time, $F(3,98) = 2.83$, p = .042. Maximal effects occurred at 60 minutes post-ingestion where diazepam had a large effect, with the Diazepam group estimating a greater reduction in performance than the Placebo group, $F(1,33)$= 6.19, p=.018, g = -0.83. Moderate effects of the same direction were present at 30 minutes post-ingestion, $F(1,33)$=4.89, p=.034, g = -0.74, and 90 minutes post-ingestion, $F(1,33)$=4.35, p=.045, g = -0.70. Effects at other time points were small or negligible (g< 0.5). Deleterious effects (g> 0.2) were no longer evident beyond 120 minutes post-ingestion.

Figure 16. Mean Pre-test subjective competence



Notes. Scores indicate change from baseline in level of agreement with the visual analogue scale statement "I feel that I will be able to perform the tasks to the best of my ability", with higher scores indicating greater agreement; error bars represent standard errors.

Figure 17. Mean Post-test subjective competence



Notes. Scores indicate change from baseline in level of agreement with the visual analogue scale statement "I feel that I was able to perform the tasks to the best of my ability", with higher scores indicating greater agreement; error bars represent standard errors.

Comparisons of effects

Meta-analytic techniques were used to pool the effects of selected variables so that various aspects of psychomotor performance were each represented by a single index, and the impact of diazepam on these aspects of performance could be considered. The Sensory motor reaction time composite variable represents the pooled effects of Simple reaction time, Choice reaction time and Choice response accuracy; the Vigilance composite variable represents the pooled effects of Vigilance

Table 10. Group means, ANOVA results and effect sizes for changes from baseline in individual subjective performance variables post-ingestion

Variable	Diazepam group mean (and *SD*)	Placebo group mean (and *SD*)	ANOVA result	Effect size Hedges *g* (and 95% confidence interval)
Pre-test subjective alertness (mm) (*n* = 34)				
30 minutes	4.12 (14.99)	7.34 (13.51)	*F*(1,33)=0.43, *p*=.516	-0.22 (±0.66)
60 minutes	0.30 (19.53)	10.55 (14.85)	*F*(1,33)=2.97, *p*=.095^	**-0.58 (±0.67)**
90 minutes	0.00 (22.72)	13.52 (17.38)	*F*(1,33)=3.80, *p*=.060^	**-0.65 (±0.67)**
120 minutes	4.85 (21.77)	10.55 (19.61)	*F*(1,33)=0.64, *p*=.428	-0.27 (±0.66)
150 minutes	11.22 (15.51)	7.76 (19.26)	*F*(1,33)=0.33, *p*=.568	0.19 (±0.66)
Post-test subjective alertness (mm) (*n* = 34)				
30 minutes	-14.43 (21.76)	4.73 (10.07)	*F*(1,33)=10.86, *p*=.002*	**-1.10 (±0.71)**
60 minutes	-16.61 (25.40)	6.61 (10.78)	*F*(1,33)=12.04, *p*=.002*	**-1.16 (±0.71)**
90 minutes	-12.80 (21.49)	5.94 (16.63)	*F*(1,33)=8.09, *p*=.008*	**-0.95 (±0.69)**
120 minutes	-8.43 (21.72)	2.43 (17.84)	*F*(1,33)=2.54, *p*=.121	**-0.53 (±0.67)**
150 minutes	0.91 (15.75)	4.25 (17.26)	*F*(1,33)=0.35, *p*=.560	-0.20 (±0.66)
Pre-test subjective competence (mm)(*n* = 34)				
30 minutes	-0.67 (13.79)	3.03 (13.63)	*F*(1,33)=0.62, *p*=.437	-0.26 (±0.66)
60 minutes	-3.88 (11.09)	2.97 (14.14)	*F*(1,33)=2.47, *p*=.126	**-0.53 (±0.67)**
90 minutes	-7.34 (15.04)	4.73 (17.47)	*F*(1,33)=4.66, *p*=.038*	**-0.72 (±0.68)**
120 minutes	-1.70 (12.33)	4.00 (15.09)	*F*(1,33)=1.45, *p*=.237	-0.40 (±0.66)
150 minutes	0.79 (16.01)	1.39 (19.49)	*F*(1,33)=0.01, *p*=.922	-0.03 (±0.66)
Post-test subjective competence (mm) (*n* = 34)				
30 minutes	-7.03 (14.91)	3.70 (13.33)	*F*(1,33)=4.89, *p*=.034*	**-0.74 (±0.68)**
60 minutes	-12.01 (17.82)	3.03 (17.44)	*F*(1,33)=6.19, *p*=.018*	**-0.83 (±0.69)**
90 minutes	-13.64 (20.67)	2.37 (23.97)	*F*(1,33)=4.35, *p*=.045*	**-0.70 (±0.68)**
120 minutes	-9.64 (22.75)	-0.06 (19.82)	*F*(1,33)=1.72, *p*=.200	-0.44 (±0.66)
150 minutes	-0.97 (18.16)	1.03 (21.43)	*F*(1,33)=0.09, *p*=.771	-0.10 (±0.66)

Notes. Scores indicate the change from baseline in level of agreement with visual analogue scale statements (measured in millimetres); higher scores indicate a greater increase from baseline in agreement; negative values for effect sizes indicate the Diazepam group having a greater decrease/smaller increase in agreement with the relevant visual analogue scale statement from baseline than the Placebo group; effect sizes in bold indicate a deleterious diazepam effect of a moderate or larger magnitude ($g > 0.5$);* denotes significantly reduced agreement with the relevant visual analogue scale in the Diazepam group relative to the Placebo group ($p<.05$); ^ denotes a trend towards significantly reduced agreement with the relevant visual analogue scale in the Diazepam group relative to the Placebo group ($p<.10$).

reaction time and Vigilance response accuracy; the Divided attention composite represents the pooled effects of Task A reaction time, Task B reaction time, Task A hit rate and Task B hit rate; the Psychomotor processing speed composite variable represents the effect of DSST score alone; the Speed composite variable represents the pooled effects of Simple reaction time, Choice reaction time, Vigilance reaction time, Task A reaction time and Task B reaction time; and the Accuracy

composite variable represents the pooled effects of Choice response accuracy, Vigilance response accuracy, Task A hit rate and Task B hit rate. Additionally, the Psychomotor performance composite variable represents the pooled effects of all objective performance variables in the study. The effect sizes at each time point for each of these composite variables are graphed in Figures 18 through to 22, along with OSPAT score (from the tracking task used to equate BAC equivalency), Pre-test subjective alertness, Post-test subjective alertness, Pre-test task subjective competence, and Post-test subjective competence. Visual examination and of these graphs allows for an approximate comparison of the effects of diazepam on the various aspects of objective psychomotor performance and subjective psychomotor experience. Table 11displays the effect sizes (with 95% confidence intervals) and results of tests for significance of group differences for each of the composite variables.

Comparisons of psychomotor function effects

The psychomotor functions of psychomotor processing speed, sensory motor reaction time, vigilance and divided attention are represented by their respective composite variables. Comparisons amongst these functions may indicate whether certain psychomotor functions are more sensitive to diazepam than others. At 30 minutes post-ingestion vigilance was the only function to be deleteriously affected by diazepam however the magnitude of this effect was small (g=-0.30). Effects on sensory motor reaction time and divided attention were negligible at this point and there was a small beneficial effect on psychomotor processing speed (g=0.32). At 60 minutes post-ingestion both psychomotor processing speed and vigilance were moderately and deleteriously affected (g=-0.76 and -0.50 respectively), whilst the effect was very small for sensory motor reaction time (g=-0.21) and negligible for divided attention (g<0.2). At both 90 and 120 minutes post-ingestion deleterious effects were again negligible for divided attention, and only small for the other three functions (g<0.5). Effects were negligible for all four functions at 150 minutes post-ingestion. Overall, it appears that psychomotor processing speed and vigilance were the psychomotor

functions most sensitive to the diazepam dose in this study, with maximal effects occurring at 60 minutes post-ingestion.

Comparisons of speed and accuracy effects

Comparisons of the effect of diazepam on the speed and accuracy components of task performance may indicate whether one of these components is more sensitive to diazepam. These components are represented by the Speed composite variable and the Accuracy composite variable. Small deleterious effects of diazepam on speed were evident at 30 minutes post-ingestion (g=-0.38) and 90 minutes post-ingestion (g=-0.23), and effects were negligible at other time points (g<0.2). Effects of diazepam on accuracy remained negligible across all time points. Hence, it appears that speed components of performance were more sensitive to the diazepam dose than accuracy components of performance in this study, with maximal effects occurring at 30 minutes post-ingestion. Tests of significance for the differences between Speed composite and Accuracy composite at each time point were conducted. A trend towards a significantly larger effect of diazepam on Speed composite compared to Accuracy composite was evident at 30 minutes post-ingestion ($z = 1.72$, $p = .085$). Differences did not reach significance at other time points (p>.05) (see Table 12 for all results).

Comparisons of tracking performance and overall objective performance

Comparisons of the effect of diazepam on performance on the tracking task (as represented by the variable OSPAT score) with objective performance from all tasks in the test battery (as represented by the Psychomotor performance composite variable) may provide some indication as to the extent to which the tracking task validly represents overall performance throughout the study. This is important due to the tracking task being used to equate psychomotor performance with a blood-alcohol concentration in this study. Small deleterious effects of diazepam were evident for both OSPAT score (g=-0.26) and the Psychomotor performance composite variable (g=-0.25) at 60 minutes post-ingestion. Effects were negligible for both at all other time points (g<0.20). Tests of significance for the differences between OSPAT score and Psychomotor performance composite

were conducted, and differences did not reach significance at any time point (p>.05) (see Table 12 for all results). Based on these comparisons it appears that the OSPAT score does validly represent average performance on the tasks from this test battery. The BAC equivalency of performance derived from the tracking task can therefore be considered representative of average psychomotor performance throughout testing in this study.

Comparisons of pre-test and post-test subjective ratings

Comparisons of the effect of diazepam on subjective ratings given prior to test battery completion (Pre-test subjective alertness and Pre-test subjective competence) with the effects on subjective ratings given after test battery completion (Post-test subjective alertness and Post-test subjective competence) may provide some indication as to whether the Diazepam and Placebo groups followed similar patterns of subjective experience throughout the testing schedule. Pre-test subjective alertness remained noticeably less deleteriously affected by diazepam than Post-test subjective alertness throughout testing. These differences were largest at 30 minutes post-ingestion (g=-0.22, g = -1.10, respectively), followed by at 60 minutes post-ingestion (g = -0.58, g = -1.16, respectively). The differences remained stable across 90, 120 and 150 minutes post-ingestion. Tests of significance for the differences between Pre-test subjective alertness and Post-test subjective alertness at each time point were conducted. A trend towards a significantly larger effect of diazepam on Post-test subjective alertness compared to Pre-test subjective alertness was evident at 30 minutes post-ingestion (z = 1.79, p = .073). Differences at 60 minutes post-ingestion did not reach significance (z = 1.17, p = .241), nor at any other time points (p>.05) (see Table 12 for all results). From these comparisons it appears that the Diazepam group tended to experience a slightly greater reduction in subjective alertness than the Placebo group, following completion of the test battery throughout the testing schedule.

Post-test subjective competence was more greatly affected by diazepam than Pre-test subjective competence at both 30 minutes (g = -0.74, g = -0.26, respectively) and 60 minutes post-ingestion (g

= -0.83, *g* = -0.53, respectively). The difference was greatest at 30 minutes post-ingestion. At 90, 120 and 150 minutes post-ingestion the differences in effect were negligible. Tests of significance for differences between the compared effect sizes were conducted and no significant results were found ($p>.05$) (see Table 12 for results). From these comparisons it appears that the Diazepam group experienced a slightly greater reduction in subjective competence than the Placebo group, following completion of the test battery for the first 60 minutes post-ingestion.

Comparisons of objective performance and subjective experience of performance

Comparisons of the effects of diazepam on average objective performance and subjective ratings of alertness may indicate whether performance can be deleteriously impacted upon in the absence of subjective sedation. Diazepam effects on both Pre-test subjective alertness and Post-test subjective alertness were more deleterious than the effect on the Psychomotor performance composite throughout testing in this study. This indicates that deleterious performance effects were always accompanied by a subjective sense of fatigue in this study.

Comparisons of the effects of diazepam on average objective performance and subjective ratings of competence may indicate whether deleterious performance effects are subjectively detectable under the influence of diazepam. Diazepam effects on both Pre-test subjective competence and Post-test subjective competence were more deleterious than the effect on Psychomotor performance composite throughout testing. This indicates that deleterious performance effects were always detectable to some extent by participants in this study.

Figure 18. Effects of diazepam on objective performance variables and subjective experience variables at 30 minutes post-ingestion

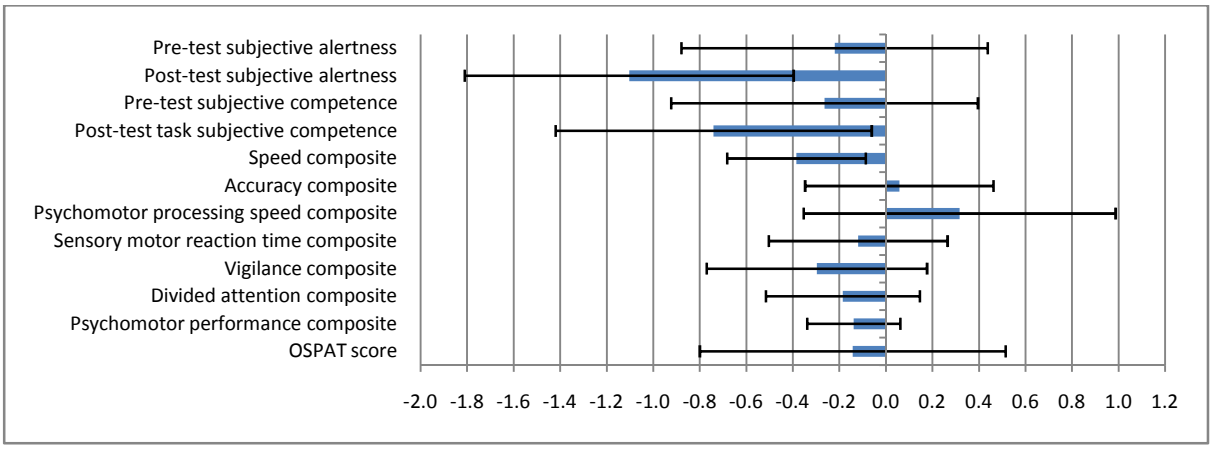


Figure 19.Effects of diazepam on objective performance variables and subjective experience variables at 60 minutes post-ingestion

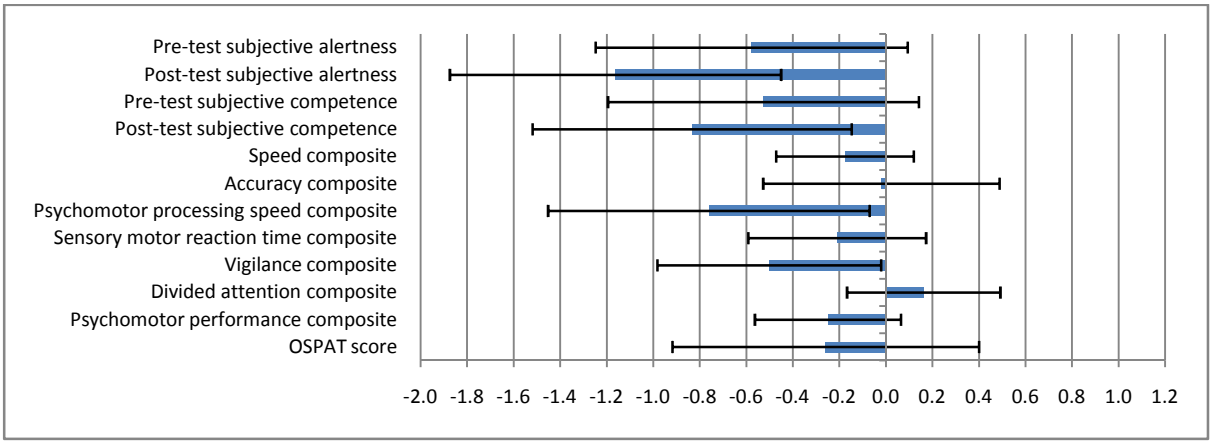


Figure 20.Effects of diazepam on objective performance variables and subjective experience variables at 90 minutes post-ingestion

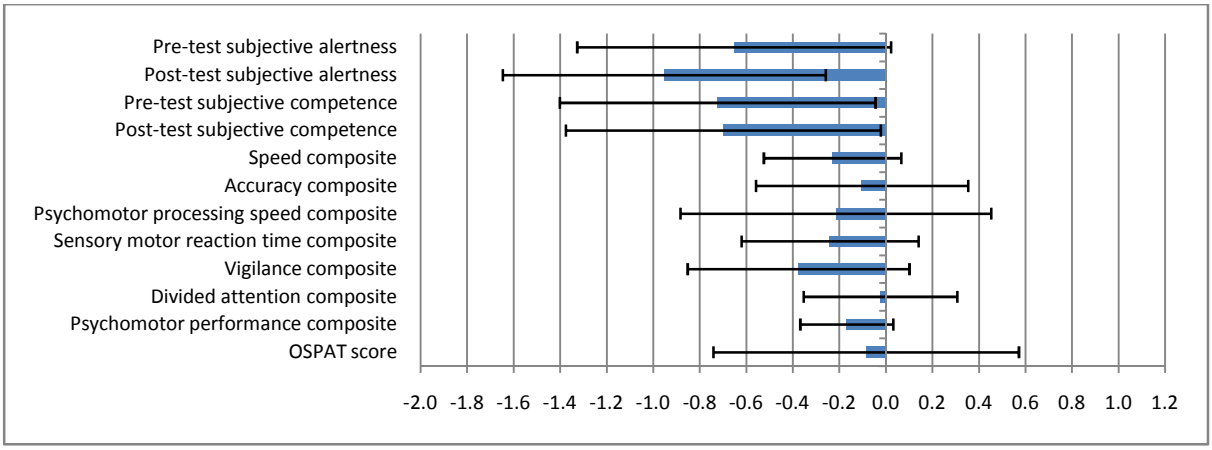


Figure 21.Effects of diazepam on objective performance variables and subjective experience variables at 120 minutes post-ingestion

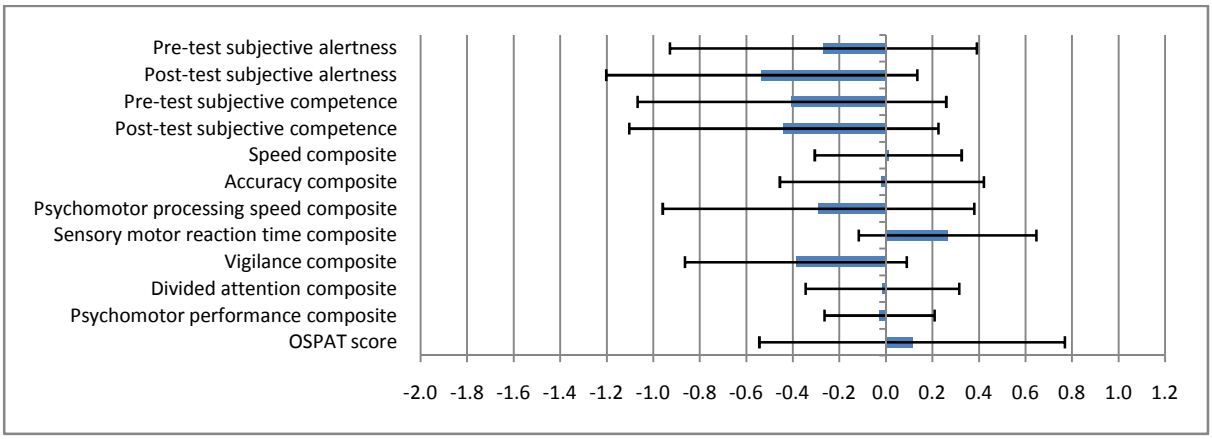
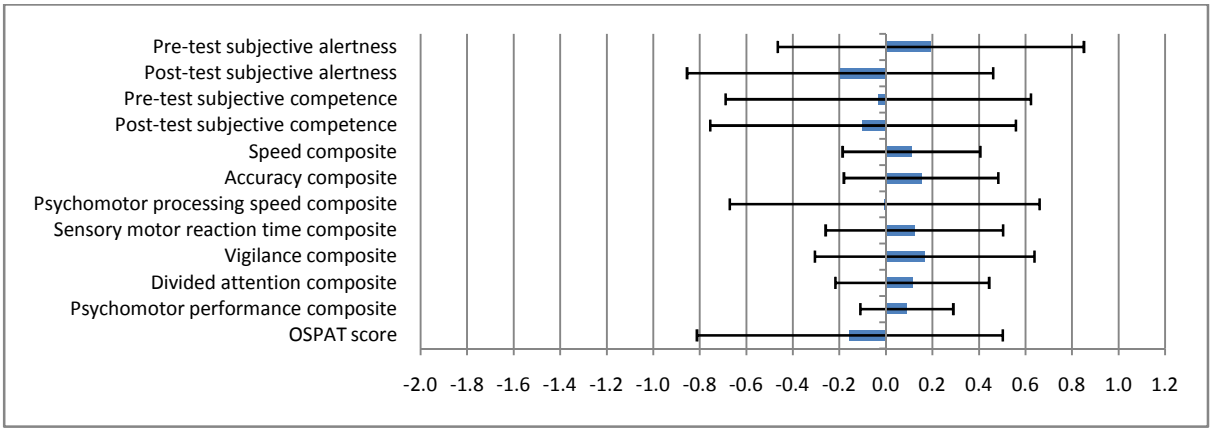


Figure 22.Effects of diazepam on objective performance variables and subjective experience variables at 150 minutes post-ingestion



Notes for Figures 18 to 22. 95% confidence intervals for each effect size are represented by error bars; negative effect sizes for composite objective performance variables indicate diazepam having a detrimental effect on performance; negative effect sizes for subjective experience variables indicate diazepam having the effect of reducing agreement with the relevant visual analogue scale statements.

Table 11. Group differences and effect sizes for composite variables

Variable		Group differences (*z* and *p* values)	Effect size Hedges *g* (and 95% confidence interval)
Psychomotor processing speed composite			
	30 minutes	*z*=0.92, *p*=.354	0.32 (±0.67)
	60 minutes	*z*=-2.16, *p*=.031*	**-0.76 (±0.69)**
	90 minutes	*z*=-0.63, *p*=.528	-0.22 (±0.67)
	120 minutes	*z*=-0.85, *p*=.396	-0.29 (±0.67)
	150 minutes	*z*=-0.01, *p*=.988	-0.01 (±0.67)
Sensory motor reaction time composite			
	30 minutes	*z*=-0.61, *p*=.543	-0.12 (±0.38)
	60 minutes	*z*=-1.07, *p*=.283	-0.21 (±0.38)
	90 minutes	*z*=-1.24, *p*=.217	-0.24 (±0.38)
	120 minutes	*z*=1.36, *p*=.173	0.27 (±0.38)
	150 minutes	*z*=0.63, *p*=.529	0.12 (±0.38)
Vigilance composite			
	30 minutes	*z*=-1.23, *p*=.220	-0.30 (±0.47)
	60 minutes	*z*=-2.04, *p*=.041*	**-0.50 (±0.48)**
	90 minutes	*z*=-1.54, *p*=.123	-0.38 (±0.48)
	120 minutes	*z*=-1.59, *p*=.112	-0.39 (±0.48)
	150 minutes	*z*=0.69, *p*=.488	0.17 (±0.49)
Divided attention composite			
	30 minutes	*z*=-1.09, *p*=.274	-0.19 (±0.33)
	60 minutes	*z*=0.97, *p*=.333	0.16 (±0.33)
	90 minutes	*z*=-0.14, *p*=.890	-0.02 (±0.33)
	120 minutes	*z*=-0.09, *p*=.929	-0.02 (±0.33)
	150 minutes	*z*=0.67, *p*=.501	0.11 (±0.33)

Table 11 continued…

Variable		Group differences (*z* and *p* values)	Effect size Hedges *g* (and 95% confidence interval)
Speed composite			
	30 minutes	*z*=-2.53, *p*=.011*	-0.38 (±0.30)
	60 minutes	*z*=-1.17, *p*=.244	-0.18 (±0.30)
	90 minutes	*z*=-1.52, *p*=.128	-0.23 (±0.30)
	120 minutes	*z*=0.06, *p*=.951	0.01 (±0.32)
	150 minutes	*z*=0.73, *p*=.467	0.11 (±0.30)
Accuracy composite			
	30 minutes	*z*=0.28, *p*=.780	0.06 (±0.41)
	60 minutes	*z*=-0.07, *p*=.940	-0.02 (±0.51)
	90 minutes	*z*=-0.44, *p*=.660	-0.10 (±0.46)
	120 minutes	*z*=-0.08, *p*=.939	-0.02 (±0.44)
	150 minutes	*z*=0.89, *p*=.372	0.15 (±0.33)
Psychomotor performance composite			
	30 minutes	*z*=-1.35, *p*=.177	-0.14 (±0.20)
	60 minutes	*z*=-1.55, *p*=.120	-0.25 (±0.31)
	90 minutes	*z*=-1.65, *p*=.100	-0.17 (±0.20)
	120 minutes	*z*=-0.23, *p*=.821	-0.03 (±0.24)
	150 minutes	*z*=0.88, *p*=.377	0.09 (±0.20)

Notes: Negative values for effect sizes indicate the Diazepam group having a greater decrease/smaller increase in performance from baseline than the Placebo group; effect sizes in bold indicate a deleterious diazepam effect of a moderate or larger magnitude ($g > 0.5$); * denotes significantly poorer task performance following diazepam relative to placebo ($p<.05$).

Table 12. Tests of significance of differences between effect sizes for selected variables

Variable	Time point	Effect size *g*	Comparison variable	Time point	Effect size *g*	Significance of difference	
						z	*p*
Speed composite			Accuracy composite				
	30 mins	-0.38		30 mins	0.06	1.72	.085
	60 mins	-0.18		60 mins	-0.02	0.52	.602
	90 mins	-0.23		90 mins	-0.10	0.46	.648
	120 mins	0.01		120 mins	-0.02	0.10	.922
	150 mins	0.11		150 mins	0.15	0.18	.856
Psychomotor performance composite	30 mins	-0.14	OSPAT score	30 mins	-0.14	0.01	.990
	60 mins	-0.25		60 mins	-0.25	0.03	.979
	90 mins	-0.17		90 mins	-0.09	-0.24	.813
	120 mins	-0.03		120 mins	0.11	-0.39	.694
	150 mins	0.09		150 mins	-0.16	0.70	.485
Pre-test subjective competence	30 mins	-0.26	Post-test subjective competence	30 mins	-0.74	0.99	.323
	60 mins	-0.53		60 mins	-0.83	0.63	.530
	90 mins	-0.72		90 mins	-0.70	0.05	.960
	120 mins	-0.40		120 mins	-0.44	0.07	.943
	150 mins	-0.03		150 mins	-0.10	0.14	.890
Pre-test subjective alertness	30 mins	-0.22	Post-test subjective alertness	30 mins	-1.10	1.79	.073
	60 mins	-0.58		60 mins	-1.16	1.17	.241
	90 mins	-0.65		90 mins	-0.95	0.61	.544
	120 mins	-0.27		120 mins	-0.53	0.55	.580
	150 mins	0.19		150 mins	-0.20	0.82	.411

Notes. Negative values for effect sizes for Speed composite, Accuracy composite, Psychomotor performance composite or OSPAT score indicate a deleterious effect of diazepam; Negative values for effect sizes for Pre-test subjective alertness, Post-test subjective alertness, Pre-test subjective competence or Post-test subjective competence indicate an effect of reduced agreement with the corresponding visual analogue scale statement.

Summary of results

In the current study, maximal deleterious effects of diazepam, relative to placebo, on both objective performance and subjective experience measures tended to occur at 60 minutes post-ingestion, and had for the most part ameliorated by the final test point at 150 minutes post-ingestion. Psychomotor processing speed and vigilance were the psychomotor functions most affected, with moderate deleterious effects evident for the Psychomotor processing speed composite (*g*=-0.76) and the Vigilance composite (*g*=-0.50) at 60 minutes post-ingestion.The Sensory motor reaction time composite showed only small deleterious effects (maximum of *g*=-0.24 at 90 minutes post-ingestion), however, within this composite moderate deleterious effects on the simple reaction time measure (maximum of *g*=-0.60 at 60 minutes post-ingestion) were masked by occasional beneficial effects on the choice reaction time measures. Effects on the divided attention measures remained small throughout testing (*g*<0.5). Measures of speed in performance were more greatly affected than measures of accuracy, with small deleterious effects of diazepam on the Speed composite evident (maximum of *g*=-0.38 at 30 minutes post-ingestion), whilst effects on the Accuracy composite were negligible (all *g*<0.2). Maximal effects on the tracking task were only small (*g*=-0.26 at 60 minutes post-ingestion for OSPAT score) and this effect was similar in magnitude to the average objective performance effect (*g*=-0.25 at 60 minutes post-ingestion for the Psychomotor performance composite). The BAC equivalency of the Diazepam group's maximal performance decrement on the tracking task was .041% - twice that of the Placebo group. Deleterious objective performance effects were accompanied by a subjective sense of fatigue throughout testing. Post-test alertness ratings were more deleteriously affected than pre-test alertness ratings at all test points (maximum of *g*=-1.16 at 60 minutes post-ingestion, and maximum of *g*=-0.65 at 90 minutes post-ingestion, respectively). Moderate deleterious effects were evident for both Pre-test subjective competence (maximum of *g*=-0.72 at 90 minutes post-ingestion) and Post-test subjective competence (maximum of *g*=-0.83 at 60 minutes post-ingestion), indicating that diazepam-induced performance detriment was subjectively detectable to some extent throughout testing.

Discussion

Effects of 5mg of diazepam on driving-related skills

The primary aim of the current study was to establish the duration and maximal magnitude of effect of a 5mg dose of diazepam on driving-related skills. These skills were conceptualised as the psychomotor functions of psychomotor processing speed, sensory motor reaction time, vigilance, and divided attention. Diazepam affected each of these functions to varying degrees, with maximal deleterious effects tending to occur at 60 minutes post-ingestion, and deleterious effects having ameliorated by the final test point 150 minutes post-ingestion. Some of these deleterious effects consisted of a reduction in performance from baseline levels by the Diazepam group, which was greater than the reduction by the Placebo group. Other deleterious effects consisted of reduced benefit from practice effects by the Diazepam group (i.e. the Diazepam group did not improve from baseline levels to the same extent that the Placebo group did). The duration of effect found in the current study is in keeping with both the window of likely peak plasma effects (Sansom, 2009), and the window of peak psychomotor effects found in many diazepam studies (e.g. Cutson, et al., 1997; Echizenya, et al., 2007; Echizenya, et al., 2003; Ingum, et al., 1992; Jalava, et al., 1995).

Psychomotor processing speed

Psychomotor processing speed, measured by the DSST, was the psychomotor function most deleteriously affected by diazepam at maximal effects. Deleterious effects peaked with a moderate magnitude at 60 minutes post-ingestion (g=-0.76). Small deleterious effects remained evident through to at least 120 minutes post-ingestion. Whereas the Placebo group greatly improved their DSST performance between 30 and 60 minutes, the Diazepam group do not appear to have been able to benefit from practice across these test-points. The magnitude of DSST effect of diazepam at 60 minutes post-ingestion is similar to that found in two studies utilising a 15mg dose (Jalava, et al., 1995; Mattila, et al., 1988), however, the duration of effect was longer for this higher dose than in the current study. The duration of DSST effect found in another study utilising a 5mg dose was

found to be much longer than in the current study, with significant effects still evident 185 minutes post-ingestion (Hart, et al., 1976). The extent to which differences in experimental power between this study and the current study may have contributed to this finding of longer duration of effect cannot be said. This particular study had a smaller sample (12 participants) than the current study, however, unlike the current study, a within subjects crossover design was employed, and hence comparisons of experimental power are difficult to conduct.

Interestingly, diazepam had a small beneficial effect on DSST performance at the first test point 30 minutes post-ingestion in the current study. As the DSST was the first task in the test battery, it is plausible that the Diazepam group exerted more effort into this first task in an attempt to overcome any initial drowsiness experienced. As performance on other tasks was deleteriously affected at this test point the extra effort put into the DSST may not have been able to be maintained throughout the remainder of the battery. If a similar level of extra effort was put into the DSST at the 60 minute test-point, it may not have been enough to overcome the peak psychomotor effects at this point. This pattern of greater exertion of effort earlier in performance is often seen during extended-duration tasks (Verster & Roth, in press), and it is reasonable to presume that this pattern would also occur to some extent across the duration of a task battery.

Sensory motor reaction time

Sensory motor reaction time was measured by the Simple reaction time and Choice reaction time tasks in this study. The diazepam dose resulted in deleterious sensory motor reaction time effects that peaked at 90 minutes post-ingestion with only a small magnitude of effect (g=-0.24). Deleterious effects were no longer evident at 120 minutes post-ingestion. These small composite sensory motor reaction time effects results from Simple reaction time task effects being ameliorated by the less deleterious Choice reaction time task effects. Deleterious Simple reaction time effects lasted for at least 60 minutes, peaking across the 30 and 60 minute test points, with similarly moderate effects evident (g=-0.58 and -0.60). Effects of sufficient magnitude to reach statistical

significance have been found at 60 minutes post-ingestion in a further study examining the effects of a 5mg dose (Ogle, et al., 1976). Peak effects have also been shown to occur at 60 minutes post-ingestion for higher doses (10mg and 20mg) in a study conducting testing at the same time-points as the current study (Ingum, et al., 1992).

The duration of Simple reaction time effect following a 5mg dose was found to be longer by two studies, with significant effects still being evident at 2 hours post-ingestion in a study by Hart and colleagues (1976), and at 3 hours post-ingestion in the study by Ogle and colleagues (1976). The duration of the Simple reaction time task is not known for the study by Ogle and colleagues (1976), however, the Simple reaction time task used by Hart and colleagues (1976) ran for 15 minutes – substantially longer than the two-minute Simple reaction time task employed in the current study. The extra length may have increased the sensitivity of the task in this earlier study, hence the longer duration of effect. It is also possible that the extra length meant that the task draws heavily on sustained attention capabilities, which may be differentially affected by diazepam than sensory-motor reaction time. Sustained attention has been shown to be particularly sensitive to diazepam effects (Coull, Middleton, et al., 1995). As mentioned previously, differences in experimental power between the study by Hart and colleagues (1976) and the current study cannot be determined and hence it is possible that increased experimental power has also contributed to finding a longer duration of effect on this task.

The pattern of Choice reaction time effects over the test points is somewhat counterintuitive, with small deleterious effects evident at 30 minutes, negligible effects at 60 minutes, small effects again at 90 minutes, and a beneficial effect of moderate magnitude at 120 minutes (g=0.60). The magnitude of deleterious effects are much lower than those found for this dose in a study by Echizenya and colleagues (2007), where a moderate deleterious effect was found for performance averaged over 20 to 240 minutes post-ingestion (g=-0.70). In the Echizenya et al. study however, the Choice reaction time task ran for five minutes and contained auditory stimuli, whereas in the current

study the Choice reaction time task ran for two minutes and contained visual stimuli. It is possible that the lengthened version of the task was more sensitive to effects, but also possible that there are differences in the effect of diazepam on the processing of visual and auditory stimuli. An event-related potential study has shown two other benzodiazepines (lorazepam and flunitrazepam) to differ in their profile of impacts on visual and auditory processing (Pompéia, Manzano, Galduróz, Tufik, & Bueno, 2003), hence it seems plausible that diazepam could differentially impact visual and auditory processing as well.

The slight improvement in Choice reaction time performance between the 30 and 60 minute test points in the current study is unlikely to be due to an early peak of actual sensory motor reaction time effects at 30 minutes, as performance declined again between the 60 and 90 minute test points. Also, no known studies have found peak Choice reaction time effects to occur earlier - Echizenya and colleagues (2007) found peak Choice reaction time effects following a 5mg dose to occur between 60 and 80 minutes post-ingestion; and Ingum and colleagues (1992), who utilised an identical testing schedule to the current study, found peak Choice reaction time effects of 10mg and 20mg doses to occur 90 minutes post-ingestion. A plausible explanation for the Choice reaction time results in the current study is that participants were able to increase their efforts in response to feeling fatigued at the 60 minute test-point. At the 90 minute test-point the increase in effort may not have been sufficient to counteract a reduced performance capacity, and as capacity increased at 120 minutes the increased effort resulted in the beneficial outcome.

Where as the Placebo group were able to improve the accuracy of their Choice reaction time performance over the first three test points, the Diazepam group's accuracy declined, indicating that they were unable to benefit from practice effects to the extent that the Placebo group did. There were some similarities between the pattern of effects for the reaction time and accuracy measures for the Choice reaction time task - accuracy effects were negligible at 60 minutes, small and deleterious at 90 minutes, and negligible again at 120 minutes. A stark contrast is the moderately

beneficial accuracy effect at 30 minutes. The suggested explanation for the reaction time result could still hold in light of the accuracy findings, with the possibility that additional effort was exerted on the accuracy component of the Choice reaction time task, in response to feeling fatigued at the 30 minute mark. Unfortunately there are no known studies utilising a 5mg dose that report Choice reaction time task accuracy measures to be able to compare these results with.

Vigilance

Vigilance, measured by a computerised Digit Vigilance task, was the psychomotor function with the most enduring deleterious effects resulting from the diazepam dose in this study. Deleterious effects were evident for at least the first 120 minutes post-ingestion. Effects reached their maximum at 60 minutes post-ingestion, with a moderately deleterious effect being evident (*g*=-0.50), and were of a small magnitude at 30, 90 and 120 minutes post-ingestion.

Accuracy during the vigilance task was more deleteriously affected than reaction time. Accuracy effects peaked at 60 minutes post-ingestion, and remained deleteriously moderate at the 90 and 120 minute test points (*g*=-0.78, -0.59 and -0.61). Unfortunately, there are no known studies utilising a 5mg dose that report accuracy measures from a vigilance task to be able to compare these results with.

Vigilance reaction time effects were small and deleterious across the 30 and 60 minutes post-ingestion test points. These peak effects were of a similar magnitude to that found for a 5mg dose 60 minutes post-ingestion in a previous study (Takahashi, et al., 2010). Two further studies found a 5mg dose to result in effects large enough to reach statistical significance (the effect sizes were not reported for these studies) (Coull, Middleton, et al., 1995; Hart, et al., 1976). These two studies did however utilise vigilance tasks that ran for substantially longer that used in the current study, with Hart and colleagues (1976) using a 1 hour long auditory vigilance task, and Coull and colleagues (1995) using a 7 minute long vigilance task with a working memory component. Vigilance decrement over time is a typical characteristic of simple, long-duration tasks. For example, on-road

studies of highway driving tend to find differences in lane-position maintenance between impairing drug and placebo groups to reduce with each 10km segment (Verster & Roth, in press). Hence, the ability of a task to detect impairing drug effects tends to increase with task duration, and it is likely that the vigilance effects found in the current study are smaller than those in other studies due to reduced task duration and sensitivity.

Divided attention

In this study divided attention was measured by a Dual Task, requiring responses to driving scenarios (task A) and changing shapes (task B) presented on a screen. Divided attention was the psychomotor function least deleteriously affected by the diazepam dose, with effects remaining negligible throughout testing. Performance on both task A and task B remained relatively similar throughout testing except for at 30 minutes post-ingestion, suggesting that participants were able to successfully follow the instruction to divide their attention equally between the two tasks, except for at this test point.

Effects on the reaction time measures were similar for both tasks. Effects were small and deleterious for the first 120 minutes of testing, except for negligible effects at 60 minutes, with peak effects occurring at 30 minutes post-ingestion for both tasks. Whilst the Placebo group were able to improve on their reaction time at each test-point post-ingestion, the Diazepam group had prolonged reaction times at 30 minutes post-ingestion, relative to their baseline performance. Significantly prolonged reaction times were also found by Boucart and colleagues (2007) 30 minutes after a low dose. In the current study the Diazepam group were able to 'catch up' to the Placebo group at 60 minutes post-ingestion, however, were not able to sustain the same rate of improvement as the Placebo group did beyond this point.

Effects of diazepam on the accuracy measures were either beneficial or negligible for both tasks, except for a very small deleterious effect for Task B at 30 minutes post-ingestion. This is the same test point at which deleterious reaction time effects on this task peaked. As there does not appear

to be evidence for diazepam enhancing accuracy of performance in previous studies, it can only be assumed that the beneficial accuracy effects found in the current study are due to increased effort by the Diazepam group once fatigue or performance impairment was recognised. This may also explain the improved reaction time performance found at 60 minutes post-ingestion. It may be the case that increased effort was not able to overcome the performance impairment evident in reaction time for Task A and Task B, and for Task B accuracy, at 30 minutes post-ingestion when deleterious performance effects were at their peak. Given the pattern of reaction time and accuracy effects, it seems likely that any extra effort exerted was focussed more on accuracy. This explains both the beneficial effects for accuracy found throughout testing, as well as the finding of a beneficial effect for Task A accuracy at 30 minutes post-ingestion despite deleterious effects on Task B accuracy and on reaction time for both tasks. It is not surprising that a preference for retaining focus on task A appears to have occurred, given this was the more salient task – it required responses more frequently than task B, and the stimuli were substantially larger on screen than those for task B.

Speed and Accuracy effects

Composite variables for speed and accuracy were created so that these two aspects of psychomotor performance could be considered and compared. Whilst overall accuracy effects remained negligible throughout testing, small deleterious speed effects were found at 30 and 90 minutes post-ingestion. These results suggest a pattern of speed of performance being somewhat relinquished for the sake of maintaining accuracy during diazepam-induced psychomotor performance. This pattern is illustrated in both the CRT task and Dual Task results where reaction time was more deleteriously affected than accuracy throughout the window of peak effects (30 to 90 minutes post-ingestion). This speed-accuracy trade off pattern has been found previously for diazepam (e.g. Ingum, et al., 1992; Kuitunen, 1994; Vanakoski, et al., 2000) as well as for other benzodiazepines (e.g. Roache, et al., 1993; Tiplady, et al., 1998; Tiplady, Hiroz, Holmes, & Drummond, 2003).

One inconsistency in the current study comes from the digit vigilance results. The results from the digit vigilance task show accuracy to be more deleteriously affected than speed, most noticeably at 60, 90 and 120 minutes post-ingestion. It is not known whether other studies have found a similar pattern of results for vigilance tasks – most studies examining vigilance have either not reported accuracy measures, or have utilised 'pencil and paper' cancellation tasks that do not allow for an assessment of accuracy. It is therefore difficult to consider the likelihood of this result being merely an anomaly, or being due to a specific diazepam-induced effect on the vigilance psychomotor function. Another possibility is that this reversal of the typical diazepam-induced speed-accuracy trade-off is dependent on a particular characteristic of the vigilance task employed in this study. Considering the various characteristics of the CRT, Dual Task and Digit Vigilance task, there is one characteristic in which the Digit Vigilance task differs to the other two tasks – the rate of presentation of stimuli. Stimuli are presented much faster in the Digit Vigilance task, meaning that decisions must be made at a faster rate. The accuracy measure for this task reflects only omission errors, meaning that the accuracy effect reflects how often the Diazepam group ran out of time to make a response or become aware that a response was required. It is possible that the time needed for accurate decision making under the influence of diazepam is longer than that offered in this task. Reaction time effects for the Digit Vigilance task remained in the same range of magnitude as for the Choice reaction time task and Dual Task results, suggesting that it is not the case that the Diazepam group focussed on speed at the expense of accuracy for this task (having done the opposite in the Choice reaction time task and Dual Task), but rather that the task did not allow the time needed by the Diazepam group to make accurate responses.

Patterns for task complexity

Intuitively, it would be expected that deleterious effects of diazepam would be more apparent in tasks that are more challenging. However, it is noticeable amongst the results of the current study that deleterious effects tended to reduce as task complexity increased. This is evident in the finding that the most demanding task in the test battery, the Dual Task, was one of the least deleteriously

affected, and in the finding of greater deleterious effects on Simple reaction time than Choice reaction time.

The Simple reaction time task employed in the current study is clearly less complex than the Choice reaction time task, however, Simple reaction time effects were more deleterious than Choice reaction time effects at 30, 60 and 120 minutes. The only other study known to have examined diazepam effects on both Simple reaction time and Choice reaction time also found that the Choice reaction time task did not have more deleterious effects than the Simple reaction time task (Ingum, et al., 1992). Using a highly complex Choice reaction time task, Ingum and colleagues (1992) found peak Simple reaction time and peak Choice reaction time effects to be roughly equivalent (reaching similar levels of statistical significance). Several other studies have found increases in task complexity to result in less deleterious performance. Mattilla and colleagues (1988) found the effects of a 15mg dose to be less deleterious for a driving simulator tracking task when the difficulty level was increased; Jalava and colleagues (1995) found the effects of a 15mg dose to be less deleterious for a divided attention task when a third component was added to the task; and Vanakoski and colleagues (2000) found the effects of 10mg and 15mg doses to be less deleterious when a Choice reaction time task was added to a simple tracking task on a driving simulator.

One possible explanation for the pattern of results noted above may be that be that diazepam could have more deleterious impacts on the motoric aspects of psychomotor performance than on the cognitive aspects - the less cognitively-demanding a task is, and the more that performance measures reflect motor performance, the more deleterious the effects may be. This explanation is however problematic given the tracking results found in the current study. Tracking, as measured by the OSPAT, was one of the least affected tasks, yet is arguably one of the least cognitive tasks. Also, a study that examined the effect of diazepam on both a DSST and a digit-copy test (representing the motoric component of the DSST) found the DSST to be more deleteriously affected than the digit-copy test (Jalava, et al., 1995).

An alternative explanation for the tendency of deleterious effects to reduce as task complexity increased in the current study may be due to the reduction of arousal levels that diazepam induces. Arousal levels are an important determinant of psychomotor capability, with the relationship between arousal and capability traditionally described as an inverted U curve - both low and high levels of arousal are associated with lower capability whilst moderate levels of arousal are associated with higher capability (Fuller, 2005). Factors that influence arousal may be internal, such as sleepiness or sedative drug effects, or external, such as stimulation from a challenging task. It is quite plausible that in the current study the diazepam dose lowered arousal levels, and thereby reduced performance of the Diazepam group overall, however during more complex tasks the stimulation provided by the challenge of the task increased arousal levels, allowing the Diazepam group a level of arousal that enabled more adequate performance.

In the area of vigilance research in particular, the concept of under-stimulation resulting in performance decline is referred to as *mindlessness.* It is suggested that monotony leads to a withdrawal of attentional effort during sustained task performance, and an increasingly disengaged (and therefore *mindless*) manner of responding (Manly, Robertson, Galloway, & Hawkins, 1999; Robertson, Manly, Andrade, Braddeley, & Yiend, 1997). In applying the concept of mindlessness to the results of the current study, it could be assumed that the less complex the task was, the more it would be subject to detrimental mindlessness effects. It is plausible that the sedative effects of diazepam meant that participants in the Diazepam group were more susceptible to a level of mindlessness that impacted on performance.

Another potential contributor to the task complexity effects found in the current study is a deliberate increase in effort by the Diazepam group in recognition of the task challenge. Increased effort with increased task complexity is a well-established phenomenon in the area of human performance (e.g. Anshel, et al., 1992; Gardner, 1990; Ma & Trombly, 2004; Molloy & Parasuraman, 1996). In the current study the Placebo group may not have found the more complex tasks

particularly challenging, and therefore approached these tasks in a manner similar to the more simple tasks (i.e. in a relaxed manner). Meanwhile, the Diazepam group may have experienced more difficulty with these tasks (due to the psychomotor effects of the diazepam dose) and increased their concentration and effort levels as a response.

The implication of these arousal, mindlessness and increased effort effects amongst the Diazepam group is that compensatory measures could be taken to overcome diazepam-induced impairment to some extent during actual driving. Moderating external factors (such as adjusting the air-conditioning, or playing music to increase arousal or alertness levels) or internal factors (such as exerting extra concentration on the task of driving) may improve driving performance whilst impaired by diazepam. There would of course be limits to the extent of impairment that could be overcome. These limits may be evident in the findings for the DSST, the Choice reaction time task and the Dual Task in the current study, where effects became more deleterious at a test-point following one where the effects were counter-intuitively low, or even beneficial, as discussed previously. At this later test point, the deleterious impacts of the dose may have been too high to be able to overcome with an increase in effort or arousal.

Further research aimed at determining the limits of task complexity that may be overcome under this diazepam dose is warranted. A well-validated driving simulator may be the most useful way of determining whether diazepam-induced impairment can be overcome by increasing arousal levels or applying extra effort. Driving simulators used in previous research have simulated a range of realistic driving scenarios including windy conditions, traffic moving at variable speeds, emergency decision-making (brake or swerve), and the following of direction signs (Moskowitz & Smiley, 1982), as well as simulating both day and night-time driving conditions (Mattila, 1988). To validly represent the differing complexity levels encountered whilst driving these types of scenarios should be built in to simulators along with a range of traffic conditions, from city-driving in heavy traffic through to more monotonous highway driving.

Summary of driving-related skills findings

The current study found a 5mg dose of diazepam to result in deleterious psychomotor effects for at least 120 minutes, with effects tending to peak at 60 minutes post-ingestion. Psychomotor processing speed and vigilance were the psychomotor functions most affected, with maximal effects reaching a moderate magnitude. Sensory motor reaction time was less affected, whilst divided attention remained unaffected throughout testing. Diazepam affected speed measures more than accuracy measures, and this speed-accuracy trade off is found to occur in other benzodiazepine studies. Deleterious effects tended to reduce in magnitude as task complexity increased, as has been found in other studies, and this may be due to the more complex tasks resulting in increased arousal or effort. Hence, compensatory measures may be taken to overcome the deleterious psychomotor effects of a 5mg dose of diazepam.

The number of studies that have examined effects of a 5mg dose of diazepam are limited, as are the studies that have utilised a testing schedule with as high frequency as the current study, and as such it is difficult to compare the results of the current study to previous findings. Where comparisons have been possible, the current study tended to find effects of a smaller magnitude or of a shorter duration than in previous studies. The relatively short duration of the tasks employed in the current study may have reduced their sensitivity to diazepam effects, resulting in an underestimation of actual effects. It is also possible that the shorter task duration meant that task performance relied less heavily on sustained attention capabilities – a function shown to be particularly sensitive to diazepam effects.

BAC equivalency of psychomotor effects

A secondary aim of the current study was to trial a methodology for equating the effects of a 5mg dose of diazepam on driving-related skills to a BAC equivalency. This methodology involves applying a regression equation (Dawson & Reid, 1997) to performance scores on the OSPAT, a computerised tracking task.

The effect of the diazepam dose on tracking in the current study, as measured by the OSPAT, was negligible at all time points except 60 minutes post-ingestion, where a small deleterious effect was evident (*g*=-0.26). The regression equation (Dawson & Reid, 1997) was applied to OSPAT scores at this time point. At 60 minutes post-ingestion the Diazepam group's performance had declined from baseline levels to a point equivalent to .041% BAC, whilst the Placebo group's performance had declined from baseline levels to a point equivalent to .020% BAC. The Placebo group's BAC equivalency was reflective of task fatigue, and potential placebo effects, and remained low and non-risky for driving. The performance detriment experienced by the Diazepam group however was approaching a level considered risky for driving (i.e. more than .05% BAC). The additional performance detriment that the Diazepam group experienced (equivalent to .021% BAC) can be assumed to reflect a level of psychomotor impairment on top of task fatigue effects.

There are no known studies comparing the singular effects of 5mg of diazepam and ethanol to enable comparison with these results. A recent change in Norway's drugged driving laws does however indicate the potential of the BAC equivalence found in the current study being an underestimation of actual impairment. Norway have set legal limits on the plasma concentrations of a variety of illicit and prescription drugs for driving. These limits have been developed based on drugged driving research evidence, however, the exact methodology for this has not yet been published. Based on their review of the literature .05% BAC has been deemed to be equivalent in driving impairment to a diazepam-plasma concentration of 143 ng/ml (Vindenes, et al., 2012). Two studies investigating effects of 5mg of diazepam are known to have measured plasma concentrations (Echizenya, et al., 2007; Echizenya, et al., 2003). These studies found 5mg of diazepam to result in an average peak plasma concentration of 234.6 +/- 23.1 ng/ml in 8 healthy young males (aged 18 to 23 years), and 235.2 +/-31.8 ng/ml in 7 healthy older males (aged 53 to 71 years). These peak concentrations occurred at around 50 minutes post-ingestion for both groups. These concentrations are well above that suggested to be equivalent to .05% BAC by the researchers

in Norway. In light of this the likely accuracy of the .041% BAC equivalency found in the current study must be considered critically.

There is potential for the relatively short duration of the tracking task employed in the current study to have contributed to an underestimation BAC equivalency. As discussed previously, tasks tend to become more sensitive to benzodiazepine effects when they are of a long duration (Verster & Roth, in press). The OSPAT used to measure tracking in the current study was relatively short at just 90 seconds. The tracking effects found to result from the diazepam dose appear to be smaller than effects found in other studies employing tracking tasks. In an on-road tracking study, O'Hanlon and colleagues (1995) found deleterious effects of a 5mg dose sufficiently large enough to reach statistical significance (effect sizes not known). The tracking task in this particular study ran for one hour and is likely to have been more sensitive to detecting impairment. A driving-simulator study utilising a 5 minute tracking task also found larger effects than the current study (Takahashi, et al., 2010). Performance following a 5mg dose in this particular study resulted in moderate deleterious effect (g=-0.51) at 60 minutes post-ingestion (Takahashi, et al., 2010) – a noticeably larger effect than that found for the OSPAT at 60 minutes post-ingestion (g=-0.26). It seems plausible that the short duration of the OSPAT does reduce its sensitivity, and hence the BAC equivalency determined from the OSPAT results may be an underestimation.

The weightings of speed and accuracy components of performance required on the OSPAT may also impact on the likelihood of the current findings being an underestimation of the BAC equivalence. The current study and previous studies have suggested that diazepam tends to detract more from speed of performance than accuracy of performance. However, alcohol has been shown the have the opposite speed-accuracy trade off pattern, with studies showing alcohol to detract more from accuracy of performance than from speed of performance (e.g. Kuitunen, 1994; Vanakoski, et al., 2000). The implication of this difference in speed-accuracy trade off is that obtaining an accurate BAC equivalence of diazepam-induced impairment is reliant on utilising performance on a task with

speed and accuracy demands equivalent to that of actual driving. Otherwise, a more accuracy-focussed task is likely to result in an underestimation of the BAC equivalence of a diazepam dose, and a more speed-focussed task is likely to result in overestimation of the BAC equivalence. The ratio of focus on speed and accuracy on the OSPAT is not known as the algorithm used to produce the performance score is subject to commercial confidence. Given that the OSPAT was one of the least sensitive tasks in the battery utilised in the current study (due to the low deleterious effect sizes detected), it seems more likely that performance scores are more heavily focussed on accuracy than speed. If this is the case, it is likely that an underestimation of BAC equivalence will have occurred, rather than an overestimation.

To determine the validity of the OSPAT in representing psychomotor performance in this study, effect sizes for the tracking task were compared to objective performance on all tasks in the test battery (as represented by the Psychomotor performance composite variable). This comparison confirmed that performance on the tracking task was representative of average performance at 60 minutes post-ingestion with very similar magnitudes of effect being evident (g=-0.26 for OSPAT score and g=-0.25 for Psychomotor performance composite). This means that the BAC equivalence of .041% can be considered representative of average psychomotor performance in this study, however, it cannot necessarily be said that 5mg of diazepam has a BAC equivalence of .041% to actual on-road driving. It has already been noted that effects found for many of the tasks in this study tend to be lower than those found in other studies, and the relatively short duration of tasks is one likely reason for this. As is the case for the OSPAT, it is not known whether the speed and accuracy demands of the task battery as a whole are reflective of the speed and accuracy demands of actual on-road driving. The test battery used in this study would need to be validated as being representative of on-road driving – a task which is beyond the scope of the current study. Meanwhile, the lack of certainty over the ecological validity of the test battery used means that an underestimation of BAC equivalency remains a possibility.

The results from this study raise some questions about the usefulness of this methodology (being the application of the regression equation to OSPAT performance data) for equating diazepam-induced driving impairment to a BAC equivalence. To rely on this methodology with confidence the OSPAT would need to be subjected to further testing to establish its ecological validity with on-road driving. Particular attention would need to be paid to ensure that the ratio of speed and accuracy demands of the OSPAT are reflective of the ratio of speed and accuracy performance required by actual driving, and that the task length was sufficient to accurately capture the full extent of drug-induced impairment. It would then be important to conduct initial studies using the OSPAT methodology for BAC equivalence with an alcohol-only treatment group as well, so that the accuracy of predicted BAC equivalencies can be confirmed.

Summary of BAC equivalency findings

The findings of the current study suggest that the BAC equivalence of performance detriment induced by a 5mg dose of diazepam is .041%. It is possible however that this is a misestimation of the true BAC equivalence for driving. The relative weightings of speed and accuracy performance components in the OSPAT performance score, along with the relatively short duration of the task may be contributing to a potential underestimation. Further research aimed at validating the OSPAT as representative of real-world driving would need to be conducted before this methodology for equating performance to a BAC could be utilised with confidence.

Subjective perceptions of psychomotor effects

A further secondary aim of the study was to conduct a preliminary examination of the subjective experience of the 5mg diazepam dose. Subjective competence was measured so that the detectability of performance impairment could be determined, and subjective sedation was measured to ascertain whether performance impairment is always accompanied by fatigue. It was expected that this preliminary examination would lead to the generation of further research questions around diazepam effects on self-monitoring accuracy, and the reliability of subjective

sedation as a predictor of actual performance, and hence the usefulness of the information conveyed on current cautionary labelling for diazepam.

Perceptions of fatigue

The alertness ratings given by participants suggest that the Diazepam group were aware of feeling fatigued during peak psychomotor effects. Effects were moderate at 60 and 90 minutes post-ingestion for the pre-test ratings of alertness. The Placebo group's pre-test ratings suggest a subtle but steady increase in alertness for the first 90 minutes post-ingestion, followed by a steady return to baseline levels by the end of testing. The Diazepam group showed the opposite pattern with pre-test ratings of alertness decreasing for the first 90 minutes post-ingestion, and then steadily returning to baseline levels by the end of testing.

Post-test ratings of alertness showed a different set of patterns. Large effects were evident for at least 90 minutes post-ingestion, and a moderate effect was evident at 120 minutes post-ingestion. The Placebo group's ratings of alertness remained similar throughout the test period, whilst the Diazepam group's ratings were greatly reduced from 30 minutes post-ingestion. From 60 minutes post-ingestion the Diazepam group's ratings remained lower than the Placebo group's, and slowly increased for the reminder of the test period.

Pre and post-test alertness rating effects were compared to determine whether the Diazepam and Placebo groups experienced similar patterns of subjective fatigue throughout testing. From these comparisons it appears that the Diazepam group experienced a slightly greater reduction in subjective alertness than the Placebo group, following completion of the test battery. The differences between pre-test alertness and post-test alertness effects are noticeably largest at 30, 60 and 90 minutes post-ingestion, where differences in effect sizes (Hedges *g*) were 0.88, 0.58, and 0.30 respectively.

Before interpreting these differences in effect the impact of the 15 minute gap (due to the test battery taking 15 minutes to complete) between each set of pre-test ratings and post-test ratings should be considered. The 15 minute gap means that at least some of the difference between the effect sizes for the pre and post-test ratings is likely to reflect the changing effect of the diazepam dose over time. The post-test ratings completed at the 30 minute post-ingestion test point are in actual fact completed 45 minutes post-ingestion, meaning that the effects of diazepam may be greater when completing the post-test rating for this test point. However, there is a clear pattern of the Diazepam group oscillating back and forth with their alertness ratings, meaning that the time-course of diazepam effects on alertness is not the sole factor responsible for differences between pre-test and post-test alertness ratings. The Diazepam group appear to have perceived a reduction in alertness by the end of each test point, and an increase in alertness by the start of the next test point. Whilst the Placebo group's ratings also oscillated in this manner it was to a very small extent, and a noticeably smaller extent than the Diazepam group's.

From these alertness ratings results it seems that in addition to feeling more fatigued throughout the period of peak diazepam effects (30 to 90 minutes post-ingestion), the Diazepam group was more fatigued by completing the test battery than the Placebo group was, and the Diazepam group was then able to revive to some extent during the 15 minute rest time between each test point. The first of these findings, that diazepam has the effect of reducing perceived alertness, is not surprising as this has been reported by a large number of studies (e.g. Brown, et al., 1996; Echizenya, et al., 2003; Hart, et al., 1976; Kelland & Lewis, 1996; Mattila & Mattila, 1988; Rich, et al., 2006; Vanakoski, et al., 2000). As far as we are aware the additional findings from the alertness ratings stand alone in the body of benzodiazepine research to date. There are no known studies that have examined both pre-test and post-test subjective sedation ratings following diazepam, nor any other benzodiazepine, and hence there are no findings from other studies that can support this result or otherwise.

Assuming the validity of the finding of the Diazepam group being more fatigued by completing the test battery than the Placebo group, it may be clinically useful to understand why this occurs. Deleterious effects of fatigue on psychomotor performance could be conceptualised as occurring when a threshold for tolerance of fatigue effects is surpassed. Using this conceptualisation, one hypothesis for the above finding is that diazepam simply reduces the amount of fatigue that can be tolerated before psychomotor effects become evident (i.e. diazepam takes an individual closer to their fatigue tolerance threshold). This hypothesis then assumes that the rate at which an individual approaches their threshold is uniform, regardless of the cause of the fatigue. For example, two individuals who are equally fatigued, one by a diazepam dose and one by sleep deprivation, will reach their threshold at the same time if simultaneously completing an identical psychomotor test battery. An alternative hypothesis is that diazepam actually increases the rate at which an individual approaches their threshold. Using the same example, the individual under the influence of diazepam would begin to show deleterious psychomotor effects in their performance earlier than the individual who was sleep deprived (ignoring any increases or reduction in diazepam effects due to the time-course of diazepam's action). There is no research to date known to provide support for either of these two hypotheses over the other. If the second hypothesis is accurate, the clinical implication is very important. The implication is that an individual will be fatigued by the act of driving a vehicle sooner than they would typically when not under the influence of diazepam, and that the duration for which they will be able to drive unaffected by fatigue will become unpredictable. It is likely that without this knowledge, an individual will underestimate the extent to which their ability to drive safely will be affected.

Assuming the validity of the finding of the Diazepam group being able to recuperate to some extent following a rest period, it would also be clinically useful to quantify the effectiveness and limitations of this. Further research could aim to answer questions such as how often and for how long should rests be taken when driving on a highway for a longer trip; and do short breaks taken during urban driving, such as when sitting at traffic lights or stationary in heavy traffic, provide enough

opportunities to recuperate sufficiently. Investigating the effects of varying doses, and different types of benzodiazepines, may mean that a 'rule of thumb' could be established to use when educating the public, such as 'take a two minute break every twenty minutes if driving on highways within the first two hours after taking a benzodiazepine', or 'avoid driving for longer than ten minutes during the first 90 minutes after taking a benzodiazepine'.

Perceptions of competence

The subjective competence ratings given by participants in the current study suggest that the Diazepam group had some awareness of their reduction in performance at test points during peak psychomotor effects. Whereas the Placebo group's competence ratings remained similar across test points, the Diazepam group's ratings showed lower expected performance from 60 to 90 minutes post-ingestion, with moderate effects evident. Ratings were then similar to those of the Placebo group beyond this point. Likewise, the Placebo group's post-test competence ratings remained similar across test-points, whilst the Diazepam group's ratings showed lower estimated performance from 30 to 90 minutes post-ingestion, with a large effect evident at 60 minutes post-ingestion and moderate effects evident at 30 and 90 minutes post-ingestion.

Pre and post-test competence rating effects were compared to determine whether the Diazepam and Placebo groups experienced similar patterns of subjective competence throughout testing. From these comparisons it appears that the Diazepam group experienced a slightly greater reduction in subjective competence than the Placebo group, following completion of the test battery for the first 60 minutes post-ingestion. This indicates that the Diazepam group were not predicting performance decrements as large as what they were indicating they detected in their post-test ratings. Effects on post-test ratings remained above 0.7 (Hedges *g*) for the first 90 minutes post-ingestion, whereas effects on pre-test ratings were smaller for the first 60 minutes post-ingestion, and only reached above 0.7 at 90 minutes post-ingestion.

As discussed for the alertness ratings above, the 15 minute gap between giving pre-test ratings and post-test ratings is likely to confound these findings to some extent, however, the pattern of effect sizes suggests that this is not solely responsible for the above findings. For example, the effect size reduced from the end of the 30 minute test-point to the start of the 60 minute test point, and then increased again at the end of the 60 minute test point, meaning that it is not the time course of diazepam effects alone that could be responsible for the above findings. It seems unlikely that the diazepam dose would result in a post-test underestimation of performance as there is no evidence of benzodiazepines resulting in such an effect in previous studies. Therefore, these findings can be taken as evidence of a diazepam-induced pre-test overestimation of psychomotor performance capabilities.

Whilst it cannot be said from these findings whether post-test competence ratings are accurate or not, it may be said that their accuracy is likely to be less detrimentally affected than that of the pre-test ratings. Further research that is able to quantify self-monitoring accuracy is warranted. The current study was limited in this respect due to the multiple test points and large task battery. A study using very specific subjective competence measures (e.g. estimated percentage reduction in reaction time, estimated number of errors etc.), at a singular post-ingestion test-point for a singular task, would be better equipped to quantify the accuracy of self-monitoring under the influence of diazepam.

The opportunities to place the subjective measure findings of the current study within the literature to date are limited. A number of other studies have found that subjective competence measures were able to discriminate between Diazepam and Placebo groups (Ghoneim, et al., 1984 ; Hart, et al., 1976; Kelland & Lewis, 1996; Mattila, et al., 1988; Mattila, et al., 1998; Vanakoski, et al., 2000), just as the current study has. However, the findings from the other studies only establish that there was some awareness of reduced performance following diazepam and do not provide any evidence for the accuracy of this awareness. There are patterns of effects across multiple doses in some of

these studies that suggest a self-monitoring impairment (Ghoneim, et al., 1984 ; Hart, et al., 1976), however, these results are not useful for comparing with the results of the single-dose current study. A number of studies have found other benzodiazepines to impair the accuracy of performance estimates completed prior to task completion (Evans, et al., 1990; Roache, et al., 1993; Roache & Griffiths, 1985) however there is only one other known benzodiazepine study that has reported both pre-test and post-test performance ratings to compare the current study's results with. This study, conducted by Preston and colleagues (1989), examined the effects of lorazepam on DDST performance and participants'estimates of their DSST scores. Estimates were collected immediately before and immediately after task completion. Participants were found to overestimate their performance both before and after task completion, with the overestimation being greater for the pre-test estimations. This finding is in keeping with that of the current study in that pre-test competence ratings appear to be less accurate than post-test competence ratings. The implication of this is that people may underestimate the extent to which their driving will be affected before they begin driving.

In the previous section a hypothesis was put forward to explain the finding that the Diazepam group appear to have been more fatigued by completing the test battery than the Placebo group. This hypothesis was that diazepam has the effect of increasing the rate at which an individual approaches their threshold for tolerating fatigue effects during psychomotor activity. This hypothesis could also contribute to explaining the tendency of the Diazepam group to overestimate performance in the pre-test competence ratings. If the rate at which an individual fatigues becomes less predictable under the influence of diazepam than when not, it could be expected that the ability to estimate performance becomes impaired. If this hypothesis is accurate, it may or may not fully account for the overestimation of performance found in the results of the current study and in previous studies. There may be a more specific diazepam-induced impairment of self-monitoring processes beyond the unpredictability created by the hypothesis put forward here, such as an impairment in 'meta-cognitive awareness' suggested to result from lorazepam by Mintzer and Griffiths (2005), or an

impairment of 'reflective cognitive functions' suggested to result from triazolam by Weingartner and colleagues (1995). The results from the current study do not allow for any further determination of the mechanisms behind the self-monitoring impairments found.

Summary of subjective perceptions of psychomotor effects

Subjective alertness ratings given by participants in this study suggest that performance impairment was always accompanied by a sense of fatigue whilst under the influence of diazepam. Comparisons of pre-test and post-test subjective alertness ratings indicate that the Diazepam group was more fatigued by completing the test battery than the Placebo group was, and the Diazepam group was then able to revive to some extent during the 15 minute rest time between each test point. These findings raise some important questions that warrant further research. The mechanism by which diazepam results in greater fatigue from activity is important to establish as it may impact on the predictability of increasing fatigue whilst driving. It would also be useful to quantify the effectiveness and limitations of being able to revive during rest periods whilst under the influence of diazepam, as this may assist with reducing crash risk for diazepam users.

Subjective competence ratings given by participants in this study suggest that there was an awareness of a reduction in performance whilst under the influence of diazepam. However, the accuracy of the Diazepam group's self-monitoring may not have been fully intact. Consistent with the findings of other benzodiazepine studies, the Diazepam group appear likely to have underestimated their impairment when estimating their competence prior to task completion. The implication of this finding is that diazepam users may not be accurate in their estimations of their driving capabilities before commencing driving. Whilst post-test competence ratings suggest that self-monitoring accuracy is less affected following task completion, it cannot be stated whether accuracy is fully intact or not. Further research is needed to determine whether diazepam users are capable of detecting impairment whilst in the act of driving.

Limitations of findings

Limitations due to singular dose

A singular acute dose of diazepam was used in this study so as to best replicate the effects of the dose in people new and therefore unhabituated to diazepam use. However, the effects found in this study would not necessarily be the effects found in people taking regular repeated 5mg doses of diazepam. It is known that habituation to the effects of diazepam takes place with chronic dosing, and this is evidenced by a reduction in clinical effects and the need to increase dosage to maintain a particular level of clinical effect (Lader, 1987). Habituation to psychomotor effects is supported by the findings from epidemiological studies of reduced crash risk over time (Bramness, et al., 2007; Neutel, 1995). Only one experimental study is known to have been conducted over a sufficient length of time to establish how long it takes for habituation to psychomotor effects to begin to take place. The findings from this study suggest that habituation to the effects of 15mg of diazepam a day on lane position maintenance during highway driving begins to take place during the fourth week of chronic dosing (Van Laar, et al., 1992). Hence it is possible that the deleterious effects found in the current study would begin to reduce within four weeks of continued use.

There is evidence to suggest however that the psychomotor effects of anxiolytic benzodiazepines increase before habituation begins to take place (Lader, 1987). Two studies have found diazepam effects to be greater on the eighth day of continued dosing than on the first day. One of these studies utlised a dosing regime of 5mg three times a day (O'Hanlon, et al., 1995) and the other a dosing regime of 5mg administered of a the morning, and 10mg administered of an evening (Moskowitz & Smiley, 1982). An accumulation of anxiolytic benzodiazepines and their active metabolites, due to their long elimination half-lives, has been generally thought to be involved in these increased effects (Lader, 1987), and diazepam-plasma concentrations have certainly been found to increase with repeated dosing over the span of eight days (Mattila, 1988; Moskowitz &

Smiley, 1982). Hence it appears likely that the effects of the 5mg dose of diazepam found in the current study would increase in magnitude for a period of time with chronic dosing.

The limitations brought about by the use of a singular dose in this study mean that the established BAC equivalency of impairment brought about by the 5mg dose (.041%) is limited in its applicability to individuals. The BAC equivalency is likely to be an underestimation for those following a regular dosing regime for a period of time (possibly up to four weeks). For individuals continuing with that dosing regime, habituation is likely to eventually take place to some extent and the BAC equivalency will likely become an overestimation of impairment. The situation is further complicated for long-term diazepam users and intermittent users. Long-term use of benzodiazepines (i.e. more than two years of continued use) has been shown to result in additional cognitive deficits that may persist for several months after discontinuation of use (for review and meta-analysis see Barker, Greenwood, Jackson, & Crowe, 2004; Barker, Jackson, Greenwood, & Crowe, 2003) and therefore the BAC equivalency of impairment found in this study would not be applicable to long-term users of diazepam. For intermittent users of diazepam, individual usage patterns would result in a wide variety of accumulative and habituation effects, and hence it would be impossible to determine the accuracy of this BAC equivalency of impairment for these diazepam users and is therefore not applicable.

The issues created by the accumulative and habituation effects brought about by chronic dosing impact on some further findings of the current study. The findings suggest that following a singular 5mg dose, it is possible to overcome deleterious effects with the application of additional effort or by increasing arousal levels for tasks of a particular level of complexity. It cannot be said to what extent this would be possible following a 5mg dose if part of a chronic dosing regime. As discussed already, accumulative effects are likely to occur for a period of time, and this may mean that it is more difficult to overcome effects by taking certain measures.

Additionally, it cannot be said to what extent the self-monitoring findings of the current study are applicable to individuals following a chronic dosing regime. In particular the questions that the findings posed, in regard to the predictability of fatigue and the consequent accuracy of subjective competence whilst in the act of driving, are complicated by repeated dosing. It was hypothesised that diazepam changes the rate at which an individual approaches their threshold for fatigue tolerance during driving, thereby making the point at which driving performance becomes affected unpredictable. Consequently, individuals are less accurate in assessing their performance impairment before task completion than after task completion. In line with this hypothesis, repeated dosing raises the question whether the point at which driving performance becomes affected actually becomes more predictable with each occasion of driving whilst under the influence of diazepam.

The current study faced practical limitations that meant that the effects of a 5mg dose could only be investigated in a singular session. It would be optimal if future research aimed at investigating the issues discussed above were to be conducted over a longer period with test sessions on day 1 of a regular dosing regime, and perhaps weekly following this for a period of four weeks or more. This methodology would allow for a full assessment of the impacts of chronic dosing alongside a singular dose. Results would then be more applicable to individuals at each stage of their course of usage.

Limitations due to age of participants

The ability to generalise the findings of the current study to the broader population is limited by the skewed age distribution of the participants. Participants were mostly students enrolled in an undergraduate university course and were typically relatively young. The mean age of participants was 24.18 years (*SD* = 8.07) however the median age was 21.5 years. Of the 34 participants, 29 were under the age of 30. One participant was 49 years, one participant was 51 years, and three participants were in their thirties.

Age is an important factor in benzodiazepine studies due to the known age-associated increases in adverse benzodiazepine effects (Greenblatt, et al., 1991). Poorer psychomotor function in the elderly (typically defined as greater than 60 years) has been shown for a range of benzodiazepines including alprazolam (Bertz, et al., 1997), triazolam (Greenblatt, et al., 1991), midazolam (Platten, Schweizer, Dilger, Mikus, & Klotz, 1998), and diazepam (Echizenya, et al., 2007; Palva, Linnoila, Routledge, & Seppala, 1982; Vanakoski, et al., 2000). One reason for these increased effects is thought to be due to higher benzodiazepine-plasma concentrations in older people following a given dose, due to age-related changes in liver functioning and resulting metabolism (Lader, 1987). However, weak associations between performance impairment and benzodiazepine-plasma concentrations in individuals (Ingum, et al., 1992; Van Laar, et al., 1992) suggest that there are further factors involved. Individual differences in sensitivity to benzodiazepine effects (in that effects differ despite equivalent benzodiazepine-plasma concentrations) have been suggested as playing a role in the individual differences seen in benzodiazepine-induce impairment (Ingum, et al., 1992; Ingum, Pettersen, Sager, & Mørland, 1994). Evidence for age-related differences in sensitivity to diazepam effects was apparent in a study by Echizenya and colleagues (2007) where older participants (53 to 71 years) were found to have similar diazepam-plasma concentrations following a 5mg dose to younger participants (18 to 23 years), yet showed significantly greater increases in psychomotor impairment. Conversely, some studies have found that elderly participants do not show greater diazepam-induced increases in psychomotor impairment relative to younger participants (Palva, et al., 1982; Vanakoski, et al., 2000). In these studies, the poorer psychomotor functioning displayed by the elderly participants was attributed to poorer initial baseline levels of performance.

Despite the discrepancies in the literature regarding the exact causes of greater benzodiazepine-induced performance impairment in older people, it is clear that that the resulting quality of psychomotor performance in older people is likely to mean that they have a lower margin of safety when driving under the influence of diazepam. To gain a clearer picture of the reasons for this,

future research needs to monitor benzodiazepine-plasma concentration levels regularly throughout testing. Whilst it may have been interesting to be able to compare diazepam-plasma concentrations in the current study with those in research including older participants, the collection of blood samples necessary to monitor these concentrations was unfortunately not possible for this study.

Given that age does appear to impact on diazepam-induced psychomotor impairment, it is quite plausible that it influences diazepam-induced self-monitoring as well. There are no known studies conducted with the aim of investigating this age effect specifically, however, Echizenya and colleagues (2007) did find a distinct dissociation between objective and subjective measures of sedation in older participants for the first two hours following 5mg of diazepam. Whilst effects on a psychomotor task and a subjective sleepiness measure were equivalent amongst younger participants, detriment on the psychomotor task was much more prominent than on the subjective sleepiness measure in the older participants. This finding suggests that the relationship between subjective experience and actual performance differs across age groups, leaving open the possibility of increased difficulties with accurately assessing subjective competence in older people.

Studies generally find benzodiazepines to be prescribed more commonly to older people than younger people (e.g. Egan, Moride, Wolfson, & Monette, 2000; Morgan, Dallosso, Ebrahim, Arie, & Fentem, 1988) with one epidemiological survey suggesting that benzodiazepine use is nearly twice as common in elderly persons (Magrini, et al., 1996). An Australian study found that amongst Australian concession card holders (i.e. those in receipt of an aged pension, disability pension, or unemployment benefits), people over 65 years account for the most use per capita of benzodiazepines (Smith & Tett, 2009). Diazepam was one of the four benzodiazepines that accounted for the majority of benzodiazepine use in this age group.

With the findings of the current study based on participants of a median age of 21.5 years, the findings may not be accurately applicable to older diazepam users. It seems likely that the effects found would be of a lower magnitude than those for older people. The implication of this is that the

BAC equivalency of diazepam effects found in this study is likely to be an underestimate of that for the typical diazepam user. Given that the BAC equivalency found in the current study was .041%, it is quite possible that the BAC equivalency of 5mg of diazepam is actually within the range considered risky for driving (i.e. above .0.5%) for most diazepam users. Research involving participants from a range of age categories is warranted to further investigate both the psychomotor and self-monitoring effects of this dose.

Practical implications of findings

The findings of the current study cast doubt over the safety of driving under the influence of a 5mg dose of diazepam. The study found the effects of this dose to be equivalent in impairment in driving-related skills to .041% BAC – a BAC that is within the range considered safe for driving (i.e. less than .05%). However, as discussed above in detail there are many circumstances under which this BAC equivalency is likely to be an underestimate of actual driving impairment. These circumstances include when driving for longer than a few minutes, driving during the first four weeks of a continuous repeated dosing regime (such as 5mg three times per day), and driving by older persons. These circumstances are likely to account for a vast number of people driving under the influence of diazepam. As such, it is not likely to be an exaggeration to assume that many people driving within the first two hours of taking a 5mg dose of diazepam could be driving at a level considered risky (i.e. impairment equivalent to more than .05%). This assumption is supported by the earlier discussion of the diazepam-plasma concentrations shown to result from a 5mg dose (Echizenya, et al., 2007; Echizenya, et al., 2003), which are well-above those deemed to be equivalent in impairment to .05% BAC in Norway (an equivalency which forms the basis of recently implemented drugged driving laws) (Vindenes, et al., 2012).

Medical practitioners should take all of the above into consideration when choosing to prescribe diazepam. Ideally, an alternative medication that has less impact on driving should be prescribed wherever possible. Otherwise, patients should be advised that it is quite possible that their driving

will be affected to an extent of greater than .05% BAC, and whilst they may feel the sedative effects of the dose, their assessment of how much this will affect their driving may not be accurate. It would be most prudent to advise patients to avoid driving for the first two hours after taking a dose. This would be particularly important for patients already feeling fatigued before taking their dose. For situations where driving is not easily avoidable, patients should be advised that their crash risk may be reduced if they minimise the duration of their trip, avoid long, monotonous stretches of road, take regular breaks, take measures to increase their arousal or alertness levels, and pay extra care and attention throughout the trip.

Conclusions

The current study found that an acute 5mg dose of diazepam in benzodiazepine naïve participants results in deleterious psychomotor effects for at least two hours, with peak effects tending to occur at around one hour post-ingestion. The largest effects were moderate in magnitude, and tended to be lower and last for a shorter period of time than those found in other studies. Some driving-related skills were more affected than others, with psychomotor processing speed and vigilance being the most deleteriously affected. Sensory motor reaction time was less affected, whilst divided attention remained unaffected by the dose. A speed-accuracy trade off was evident with accuracy being sacrificed for the sake of maintaining speed in most cases. The fact that deleterious effects seemed to reduce in magnitude as task complexity increased suggests that impairment can be overcome with compensatory measures that increase arousal levels or with the application of extra effort.

The psychomotor impairment resulting from the 5mg dose in this study was equivalent to a BAC of .041%. This BAC equivalency was determined through the application of a regression equation that specifies the relationship between performance detriment on the OSPAT, a tracking task, and BAC (Dawson & Reid, 1997). Average performance on the battery of driving-related skills tests was validly represented by OSPAT performance in this study, however, neither this test battery nor the

OSPAT has not been validated as representative of the particular ratios of skills required whilst driving. Differences in the effect of diazepam on various driving-related skills means that further research validating the OSPAT as representative of the skills required whilst driving is warranted. The efficiency that this methodology for equating drug-induced impairment to a BAC allows for would make such research a worth-while pursuit.

A preliminary investigation of the subjective experiences of alertness and competence following the 5mg dose was conducted. It was established that participants had some awareness of the performance impairment induced by the dose, and were aware of its sedative effects. Dissociations between the alertness and competence ratings given before and after test battery completion suggest that self-monitoring accuracy may not be fully intact. It seems likely that participants were less capable of estimating their diazepam-induced performance impairment before completing the test battery, compared to after completion. Also, it appears that the diazepam dose resulted in participants feeling additionally fatigued by completing the test battery. This may mean that resilience to fatigue effects during driving becomes unpredictable, and could therefore impact on the ability to make safe decisions about driving whilst under the influence of diazepam.

The current study provides sufficient evidence to cast doubt over the safety of driving during the first two hours following 5mg of diazepam. With the knowledge of increased sensitivity to diazepam-induced psychomotor effects with age, the relatively young sample used means that the psychomotor effects, and resultant BAC equivalency of .041%, are likely to be underestimated for most diazepam users, who tend to be in older age categories. The BAC equivalency is also likely to be an underestimate for those in the first few weeks of a chronic dosing regime. Until further research can be conducted, it would be reasonable for medical practitioners to apply caution when educating patients about diazepam side effects. Advising patients to avoid driving for at *least* two hours after a dose would be most prudent, however if driving is unavoidable, it would be wise to inform patients that their crash risk may be reduced if they minimise the duration of their trip, avoid

long, monotonous stretches of road, take regular breaks, take measures to increase their level of alertness, and pay extra care and attention throughout the trip. Adhering to these precautions would become more important the older a patient is, and the more fatigued the patient is feeling when entering a vehicle.

References

ABS. (2001). *Information Paper: Use of the Kessler Psychological Distress Scale in ABS Health Surveys*. Canberra: Australian Bureau of Statistics.

Allen, D., Curran, H., & Lader, M. (1993). The Effects of Single Doses of Cl284,846, Lorazepam, and Placebo on Psychomotor and Memory Function in Normal-Male Volunteers. *European Journal of Clinical Pharmacology, 45*(4), 313-320.

Andrews, G., & Slade, T. (2001). Interpreting scores on the Kessler Psychological Distress Scale (K10). *Australian and New Zealand Journal of Public Health, 25*(6), 494-497.

Anshel, M., Weinberg, R., & Jackson, A. (1992). the effect of goal difficulty and task complexity on intrinsic motivation and motor performance. *Journal of Sport Behaviour, 15*(2), 159-176.

Australian Institute of Health and Welfare. (2010). *National Drug Strategy Household Survey*. Canberra: Australian Institute of Health and Welfare.

Babor, T., Higgins-Biddle, J., Saunders, J., & Monteiro, M. (2001). The alcohol use disorder identification test: Guidelines for use in primary care. Retrieved September 16th, 2006, from http://libdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf

Barker, M., Greenwood, K., Jackson, M., & Crowe, S. (2004). Cognitive effects of long-term benzodiazepine use: A meta-analysis. *CNS Drugs, 18*(1), 37-48.

Barker, M., Jackson, M., Greenwood, K., & Crowe, S. (2003). Cognitive effects of benzodiazepine use: A review. *Australian Psychologist, 38*(3), 202-213.

Bateson, A. (2002). Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. *Current Pharmaceutical Design, 8*(1), 5-21.

Begg, A., Drummond, G., & Tiplady, B. (2001). Effects of temazepam on memory and psychomotor performance: a dose-response study. *Human Psychopharmacology-Clinical and Experimental, 16*(6), 475-480.

Bertz, R., Kroboth, P., Kroboth, F., Reynolds, I., Salek, F., Wright, C., et al. (1997). Alprazolam in Young and Elderly Men: Sensitivity and Tolerance to Psychomotor, Sedative and Memory Effects. *The Journal of Pharmacology and Experimental Therapeutics, 281*, 1317-1330.

Boucart, M., Waucquier, N., Michael, G., & Libersa, C. (2007). Diazepam impairs temporal dynamics of visual attention. *Experimental and Clinical Psychopharmacology, 15*(1), 115-122.

Bourin, M., & Briley, M. (2004). Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many psychotropic drugs. *Human Psychopharmacology, 19*, 135-139.

Bramness, J., Skurtveit, S., Mørland, J., & Engeland, A. (2007). The risk of traffic accidents after prescriptions of carisoprodol. *Accident Analysis and Prevention, 39*(5), 1050-1055.

Brown, G., Rich, J., & SimkinsBullock, J. (1996). Correlated changes in focused attention and associative encoding following diazepam ingestion. *Experimental and Clinical Psychopharmacology, 4*(1), 114-122.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). New Jersey: Lawrence Erlbaum Associates.

Coull, J., Middleton, H., Robbins, T., & Sahakian, B. (1995). Clonidine and Diazepam Have Differential-Effects on Tests of Attention and Learning. *Psychopharmacology, 120*(3), 322-332.

Coull, J., Sahakian, B., Middleton, H., Young, A., Park, S., McShane, R., et al. (1995). Differential-Effects of Clonidine, Haloperidol, Diazepam and Tryptophan Depletion on Focused Attention and Attentional Search. *Psychopharmacology, 121*(2), 222-230.

Curran, H., Schiwy, W., & Lader, M. (1987). Differential amnesic properties of benzodiazepines: A dose-response comparison of two drugs with similar elimination half-lives. *Psychopharmacology, 92*, 358-364.

Cutson, T., Gray, S., Hughes, M., Carson, S., & Hanlon, J. (1997). Effect of a single dose of diazepam on balance measures in older people. *Journal of the American Geriatrics Society, 45*(4), 435-440.

Dassanayake, T., Michie, P., Carter, G., & Jones, A. (2011). Effects of benzodiazepines, antidepressants and opioids on driving: A systematic review and meta-analysis of epidemiological and experimental evidence. *Drug Safety, 34*(2), 125-156.

Dawe, S., Loxton, N., Hides, L., Kavanagh, D., & Mattick, R. (2002). *Review of Diagnostic Screening Instruments for Alcohol and Other Drug Use and Other Psychiatric Disorders* (2nd ed.). Sydney: National Drug and Alcohol Research Centre.

Dawson, D., & Reid, K. (1997). Fatigue, alcohol and performance impairment. *Nature, 388*(6639), 235-235.

Deakin, J., Aitken, M., Dowson, J., Robbins, T., & Sahakian, B. (2004). Diazepam produces disinhibitory cognitive effects in male volunteers. *Psychopharmacology, 173*(1-2), 88-97.

Department of Health and Ageing (2009). *Poisons Standard*. Canberra: Australian Federal Government.

Department of Health and Ageing. (2011). *Australian Statistics on Medicines 2009*. Canberra: Australian Federal Government.

Devilly, G. (2007). *Random Number Generator: Version 2.0*. Melbourne: www.clintools.com.

Dubois, S., Bedard, M., & Weaver, B. (2008). The Impact of Benzodiazepines on Safe Driving. *Traffic Injury Prevention, 9*(5), 404-413.

Echizenya, M., Mishima, K., Satoh, K., Kusanagi, H., Ohkubo, T., & Shimizu, T. (2007). Dissociation between objective psychomotor impairment and subjective sleepiness after diazepam administration in the aged people. *Human Psychopharmacology-Clinical and Experimental, 22*(6), 365-372.

Echizenya, M., Mishima, K., Satoh, K., Kusanagi, H., Sekine, A., Ohkubo, T., et al. (2003). Heat loss, sleepiness, and impaired performance after diazepam administration in humans. *Neuropsychopharmacology, 28*(6), 1198-1206.

Egan, M., Moride, Y., Wolfson, C., & Monette, J. (2000). Long- term continuous use of benzodiazepines by older adults in Quebec: prevalence, incidence, and risk factors. *Journal of the American Geriatrics Society, 48*, 811 - 816.

Evans, S., Funderburk, F., & Griffiths, R. (1990). Zolpidem and Triazolam in Humans - Behavioral and Subjective Effects and Abuse Liability. *Journal of Pharmacology and Experimental Therapeutics, 255*(3), 1246-1255.

Farre, M., Teran, M., & Cami, J. (1996). A comparison of the acute behavioral effects of flunitrazepam and triazolam in healthy volunteers. [Proceedings Paper]. *Psychopharmacology, 125*(1), 1-12.

Fleishaker, J., Garzone, P., Chambers, J., Sirocco, K., & Weingartner, H. (1995). Comparison of the Spectrum of Cognitive Effects of Alprazolam and Adinazolam after Single Doses in Healthy-Subjects. *Psychopharmacology, 120*(2), 169-176.

Fuller, R. (2005). Towards a general theory of driver behaviour. *Accident Analysis and Prevention, 37*, 461-472.

Gardner, D. (1990). Task complexity effects on non-task-related movements: A test of activation theory. *Oganizational Behaviour and Human Decision Processes, 45*(2), 209-217.

Ghoneim, M., Mewaldt, S., & Hinrichs, J. (1984). Dose-response analysis of the behavioral effects of diazepam: II. Psychomotor performance, cognition and mood. *Psychopharmacology, 82*, 296-300.

Gibson, J., Hubbard, R., Smith, C., Tata, L. J., Britton, J., & Fogarty, A. (2009). Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *American Journal of Epidemiology, 169*(6), 761-768.

Greenblatt, D., Harmatz, J., Shapiro, L., Engelhardt, N., Gouthro, T., & Shader, R. (1991). Sensitivity to Triazolam in the Elderly. *The New England Journal of Medicine, 324*, 1691 - 1698.

Hart, J., Hill, H., Bye, C., Wilkinson, R., & Peck, A. (1976). Effects of Low-Doses of Amylobarbitone Sodium and Diazepam on Human-Performance. *British Journal of Clinical Pharmacology, 3*(2), 289-298.

Hindmarch, I. (1980). Psychomotor Function and Psychoactive-Drugs. *British Journal of Clinical Pharmacology, 10*(3), 189-209.

Hinton-Bayre, A., & Geffen, G. (2005). Comparability, Reliability, and Practice Effects on Alternate Forms of the Digit Symbol Substitution and Symbol Digit Modalities Tests. *Psychological Assessment, 17*(2), 237-241.

Ingum, J., Bjorklund, R., Bjorneboe, A., Christophersen, A., Dahlin, E., & Morland, J. (1992). Relationship between Drug Plasma-Concentrations and Psychomotor Performance after Single Doses of Ethanol and Benzodiazepines. *Psychopharmacology, 107*(1), 11-17.

Ingum, J., Pettersen, G., Sager, G., & Mørland, J. (1994). Relationship between unbound plasma concentrations and various psychomotor and subjective effects after intakes of diazepam and flunitrazepam. *International Clinical Psychopharmacology, 9*, 115-121.

Jalava, K., Mattila, M., Tarssanen, M., & Vanakoski, J. (1995). Lorazepam and diazepam differentially impair divided attention. *Pharmacology, Biochemistry and Behavior, 51*, 189-197.

Johnson, L., & Chernik, D. (1982). Sedative-Hypnotics and Human-Performance. *Psychopharmacology, 76*(2), 101-113.

Kaplan, H., & Sadock, B. (1996). *Pocket Handbook of Pscyhiatric Drug Treatment* (2nd ed.). Baltimore: Lippincott Williams and Wilkins.

Karch, S. (Ed.). (2007). *Drug Abuse Handbook* (2nd ed.). Boca Raton: CRC Press.

Kelland, D., & Lewis, R. (1996). The Digit Vigilance Test: Reliability, validity, and sensitivity to diazepam. *Archives of Clinical Neuropsychology, 11*(4), 339-344.

Kuitunen, T. (1994). Drug and ethanol effects on the clinical test for drunkeness: Single doses of ethanol, hypnotic drugs and antidepressant drugs. [Article]. *Pharmacology & Toxicology, 75*(2), 91-98.

Lader, M. (1987). Clinical Pharmacology of benzodiazepines. *Annual review of medicine, 38*, 19-28.

Loke, W., Hinrichs, J., & Ghoneim, M. (1985). Caffeine and Diazepam - Separate and Combined Effects on Mood, Memory, and Psychomotor Performance. *Psychopharmacology, 87*(3), 344-350.

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

Longo, M., Lokan, R., & White, J. (2001). The relationship between blood benzodiazepine concentration and vehicle crash culpability. *Journal of Traffic Medicine, 29*(1-2), 36-43.

Ma, H., & Trombly, C. (2004). Effects of task complexity on reaction time and movement kinematics in elderly people. *The American Journal of Occupational Therapy, 58*(8), 150-158.

Macher, J. (2004). Modafinil reverses the marked attentional deficits produced by acute sleep deprivation in healthy volunteers. *Journal of Psychopharmacology 18*, Suppl: A48.

Magrini, N., Vaccheri, A., Parma, E., D'Alessandro, R., Bottoni, A., Occhionero, M., et al. (1996). Use of benzodiazepines in the Italian general population: prevalence, pattern of use and risk factors for use. *European Journal of Clinical Pharmacology, 50*, 19 - 25.

Mallick, J., Johnston, J., Goren, N., & Kennedy, V. (2007). *Drugs and driving in Australia: A survey of community attitudes, experience and understanding*. Melbourne: Australian Drug Foundation.

Manly, T., Robertson, I., Galloway, M., & Hawkins, K. (1999). The absent mind: further investigations of sustained attention to response. *Neuropsychologia, 37*, 661-670.

Mattila, M. (1988). Acute and subacute effects of diazepam on human performance: Comparison of plain tablet and controlled release capusule. *Pharmacology and toxicology, 63*, 369-374.

Mattila, M., & Mattila, M. (1988). Objective and subjective effects of remoxipride, alone and in combination with ethanol or diazepam, on performance in healthy subjects. *Journal of Psychopharmacology, 2*(3), 138-149.

Mattila, M., Mattila, M., & Aranko, K. (1988). Objective and Subjective Assessments of the Effects of Flupentixol and Benzodiazepines on Human Psychomotor Performance. *Psychopharmacology, 95*(3), 323-328.

Mattila, M., Vanakoski, J., Kalska, H., & Seppala, T. (1998). Effects of alcohol, zolpidem, and some other sedatives and hypnotics on human performance and memory. *Pharmacology Biochemistry and Behavior, 59*(4), 917-923.

Mayleben, D., Roth, A., Corser, B., Nandy, P., Harris, S., & Perhach, J. (2004). Dose and time dependent discrimination of daytime sleepiness measured by multiple sleep latency tests (MSLT), Psychomotor performance tests (PPT) and Stanford Sleepiness Scale (SSS) after a single AM administration of a sedative hypnotic drug *Sleep 27*, A49.

MIMS Australia. (2006). *MIMS (issue 3)*. Sydney: Medical Publishers Association.

Mintzer, M., & Griffiths, R. (2003). Lorazepam and Scopolamine: A single-dose comparison of effects on human memory and attentional processes. *Experimental and Clinical Psychopharmacology, 11*, 56-72.

Mintzer, M., & Griffiths, R. (2005). Drugs, memory, and metamemory: A dose-effect study with lorazepam and scopolamine. *Experimental and Clinical Psychopharmacology, 13*(4), 336-347.

Möhler, H., Fritschy, J., & Rudolph, U. (2002). A new benzodiazepine pharmacology. *Journal of Pharmacology and Experimental Therapeutics, 300*(1), 2-8.

Molloy, R., & Parasuraman, R. (1996). Monitoring an automated system for a single failure: Vigilance and task complexity effects. *Human Factors, 38*(2), 311-322.

Morgan, K., Dallosso, H., Ebrahim, S., Arie, T., & Fentem, P. (1988). Prevalence, frequency, and duration of hypnotic drug use among the elderly living at home. *British Medical Journal Clinical Research 296*, 601-602.

Moskowitz, H., & Smiley, A. (1982). Effects of chronically administered busiprone and diazepam on driving-related skills performance. *Journal of Clinical Psychiatry, 43*, 45-55.

National Health & Medical Research Council. (1999). *Guidelines for the prevention and management of benzodiazepine dependence*. Canberra: Australian Government Publishing Service.

Neutel, C. (1995). Risk of traffic accident injury after a prescription for a benzodiazepine. *Annals of Epidemiology, 5*(3), 239-244.

Newcombe, D., & White, J. (2007). *Fluctuation in cognitive performance in methadone maintenance patients.* Paper presented at the Australasian Professional Society on Alcohol and other Drugs and Cutting Edge Addiction, Aukland.

Nichols, J., & Martin, F. (1996). The effect of Lorazepam on memory and event-related potentials in heavy and light social drinkers. *Psychophysiology, 33*, 446-456.

O'Hanlon, J., Vermeeren, A., Ulterwijk, M., van Veggel, L., & Swijgman, H. (1995). Anxiolytics' effects on the actual driving performanc of patients and healthy volunteers in a standardized test. *Neuropsychobiology, 31*, 81-88.

Ogle, C., Turner, P., & Markomihelakis, H. (1976). Effects of High Doses of Oxprenolol and of Propranolol on Pursuit Rotor Performance, Reaction-Time and Critical Flicker Frequency. *Psychopharmacologia, 46*(3), 295-299.

Ohanlon, J., Haak, T., Blaauw, G., & Riemersma, J. (1982). Diazepam Impairs Lateral Position Control in Highway Driving. *Science, 217*(4554), 79-81.

OSPAT Pty Ltd. (2005). *Occupational Safety Performance Assessment Test*. Western Australia: OSPAT Pty Ltd.

Palva, E., Linnoila, M., Routledge, P., & Seppala, T. (1982). Actions and interactions of diazepam and alcohol on psychomotor skills in young and middle-aged subjects. *Acta Pharmacologica et Toxicologica, 50*(5), 363-369.

Petrilli, R., Jay, S., Dawson, D., & Lamond, N. (2005). The impact of sustained wakefulness and time-of-day on OSPAT performance. *Industrial Health, 43*(1), 186-192.

Platten, H., Schweizer, E., Dilger, K., Mikus, G., & Klotz, U. (1998). Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients undergoing tooth extraction. *Clinical Pharmacology & Therapeutics 63*, 552 - 560.

Pompéia, S., Manzano, G., Galduróz, J., Tufik, S., & Bueno, O. (2003). Lorazepam induces an atypical dissociation of visual and auditory event-related potentials. *Journal of Psychopharmacology, 17*, 31-40.

Preston, K., Guarino, J., Kirk, W., & Griffiths, R. (1989). Evaluation of the Abuse Potential of Methocarbamol. *Journal of Pharmacology and Experimental Therapeutics, 248*(3), 1146-1157.

Rang, H., & Dale, M. (2007). *Pharmacology* (6th ed.). Philedelphia: Elsevier.

Rapoport, M., & Banina, M. (2007). Impact of psychotropic medications on simulated driving - A critical review. *CNS Drugs, 21*(6), 503-519.

Rapoport, M., Lanctot, K., Streiner, D., Bedard, M., Vingilis, E., Murray, B., et al. (2009). Benzodiazepine use and driving: a meta-analysis. *The Journal of clinical psychiatry, 70*, 663-673.

Rich, J., Svoboda, E., & Brown, G. (2006). Diazepam-induced prospective memory impairment and its relation to retrospective memory, attention, and arousal. *Human Psychopharmacology-Clinical and Experimental, 21*(2), 101-108.

Rivas-Vazquez, R. (2003). Benzodiazepines in contemporary clinical practice. *Professional Psychology: Research and Practice, 34*(3), 324-328.

Roache, J., Cherek, D., Bennett, R., Schenkler, J., & Cowan, K. (1993). Differential-Effects of Triazolam and Ethanol on Awareness, Memory, and Psychomotor Performance. *Journal of Clinical Psychopharmacology, 13*(1), 3-15.

Roache, J., & Griffiths, R. (1985). Comparison of Triazolam and Pentobarbital - Performance Impairment, Subjective Effects and Abuse Liability. *Journal of Pharmacology and Experimental Therapeutics, 234*(1), 120-133.

Robertson, I., Manly, T., Andrade, J., Braddeley, B., & Yiend, J. (1997). "Oops!": Performance correlates of everda7y attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35*, 747-758.

Rosenfeld, G., & Loose, D. (2007). *Pharmacology* (4th ed.). Philadelphia: Lippincott, Williams and Wilkins.

Rush, C., Frey, J., & Griffiths, R. (1999). Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. *Psychopharmacology, 145*(1), 39-51.

Rush, C., Higgins, S., Hughes, J., & Bickel, W. (1993). A comparison of the acute behavioral effects of triazolam and temazepam in normal volunteers. *Psychopharmacology, 112*(4), 407-414.

Sadock, B., & Sadock, V. (2003). *Synopsis of Psychiatry* (9th ed.). Philadelphia: Lippincott, Williams & Wilkins.

Sadock, B., & Sadock, V. (2007). *Synopsis of Psychiatry* (10 ed.). Philidelphia: Lippincott Williams and Wilkins.

Sansom, L. (Ed.). (2009). *Australian Pharmaceutical Formulary and Handbook* (21st ed.). Canberra: Pharmaceutical Society of Australia.

Schulz, K., Altman, D., & Moher, D. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *British Medical Journal, 340*, c332.

Smith, A., & Tett, S. (2009). How do different age groups use benzodiazepines and antidepressants? Analysis of an Australian administrative database, 2003-6. *Drugs & Aging, 26*, 113 - 122.

Stewart, S., & Westra, H. (2002). Introduction to the special issue on: Benzodiazepine side-effects: From the bench to the clinic. *Current Pharmaceutical Design, 8*(1), 1-3.

Takahashi, M., Iwamoto, K., Kawamura, Y., Nakamura, Y., Ishihara, R., Uchiyama, Y., et al. (2010). The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers. *Human Psychopharmacology-Clinical and Experimental, 25*(3), 260-267.

Tiplady, B., Bowness, E., Stien, L., & Drummond, G. (2005). Selective effects of clonidine and temazepam on attention and memory. *Journal of Psychopharmacology, 19*(3), 259-265.

Tiplady, B., Faineteau, H., Loganathan, A., Spiegelberg, M., Taylor, Z., & Wright, P. (1998). Effects of ethanol and temazepam on performance in memory and psychomotor tasks: a dose-response comparison. *Human Psychopharmacology: Clinical and Experimental, 13*, 285-291.

Tiplady, B., Hiroz, J., Holmes, L., & Drummond, G. (2003). Errors in performance testing: a comparison of ethanol and temazepam. *Journal of Psychopharmacology, 17*(1), 41-49.

Van Laar, M., Volkerts, E., & Van Willigenburg, A. (1992). Therapeutic effects and effects on actual driving performance of chronically administered busiprone and diazepam in anxious outpatients. *Journal of Clinical Psychopharmacology, 12*, 86-95.

Vanakoski, J., Mattila, M., & Seppala, T. (2000). Driving under light and dark conditions: effects of alcohol and diazepam in young and older subjects. *European Journal of Clinical Pharmacology, 56*(6-7), 453-458.

Verster, J., & Mets, M. (2009). Psychoactive Medication and Traffic Safety. *International Journal of Environmental Research and Public Health, 6*(3), 1041-1054.

Verster, J., & Roth, T. (in press). Vigilance decrement during the on-the-road driving tests: the importance of time-on-task in psychopharmacological research. *Accident Analysis and Prevention*.

Verster, J., Veldhuijzen, D., & Volkerts, E. (2005). Is it safe to drive a car when treated with anxiolytics? Evidence from on-the-road driving studies during normal traffic. *Current psychiatry reviews, 1*, 215-225.

Verster, J., Volkerts, E., & Verbaten, M. (2002). Effects of Alprazolam on driving ability memory functioning and psychomotor performance: A randomized, placebo-controlled study. [Article]. *Neuropsychopharmacology, 27*(2), 260-269.

Vickers, A., & Altman, D. (2001). Analysing controlled trials with baseline and follow up measurements. *British Medical Journal, 323*, 1123-1124.

Vindenes, V., Jordbru, D., Knapskog, A., Kvan, E., Mathisrud, G., Slordal, L., et al. (2012). Impairment based legilative limits for driving under the influence of non-alcohol drugs in Norway. *Forensic Science International, 219*, 1-11.

Walsh, J., Verstraete, A., Huestis, M., & Morland, J. (2008). Guidelines for research on drugged driving. *Addiction, 103*(8), 1258-1268.

Weingartner, H., Sirocco, K., Rawlings, R., Joyce, E., & Hommer, D. (1995). Dissociations in the expressions of the sedative effects of triazolam. *Psychopharmacology, 119*, 27-33.

Weschler, D. (1997). *Weschler Adult Intelligence Scale* (3rd ed.). San Antonio: The Psychological Corporation.

Weschler, D. (2001). *Wechsler Test of Adult Reading (WTAR).* (3rd ed.). San Antonio: The Psychological Corporation.

Wesnes, K., McKeith, I., Ferrara, R., Emre, M., Del Ser, T., Spano, P., et al. (2002). Effects of Rivastigmine on Cognitive Function in Dementia with Lewy Bodies: A Randomised Placebo-Controlled International Study Using the Cognitive Drug Research Computerised Assessment System. *Dementia and Geriatric Cogntive Disorders, 13*(3), 183-192.

Willumeit, H., Ott, H., Neubert, W., Hemmerling, K., Schratzer, M., & Fichte, K. (1984). Alcohol interaction of lormetazepam, mepindolol sulfate and diazepam measured by performance on the driving simulator. *Pharmacopsychiatry, 17*(2), 36-43.

Wittenborn, J. (1979). Effects of Benzodiazepines on Psychomotor Performance. *British Journal of Clinical Pharmacology, 7*, S61-S67.

Appendices

Appendix A:

Information sheet and Consent form

Date:_____

INFORMATION SHEET

Short-term diazepam intake and driving-related skills

We would like to invite you to take part in a study examining the effect of the medication diazepam on driving-related skills. Diazepam is a type of benzodiazepine commonly used as a treatment for relieving anxiety. This study is being conducted by Madelyn Dent and Aneliese Poorter, both being supervised by Dr Raimondo Bruno, Dr Frances Martin and Prof Saxby Pridmore, in partial fulfilment of the requirements of a Master of Psychology degree at the University of Tasmania.

Diazepam is the most commonly prescribed benzodiazepine in Australia to treat anxiety conditions, and millions of prescriptions for the drug are filled each year. Each bottle carries a warning label noting that people should not drive if they feel affected. However, many people do drive when taking this medication.

The aim of this study is to better understand whether these drugs do affect driving ability, and the exact types of skills that may be affected if this is the case. As such, this study will assess whether diazepam affects how quickly you can respond to things (reaction time), your concentration, or your ability to accurately do two things at the same time. You will also be asked whether you feel like the drug has affected your ability to perform on these tasks.

Who is being invited to participate?

You are invited to take part in the study if you have never previously used any form of benzodiazepine. To ensure that any results found are clearly due to diazepam use, all participants will be non-smokers, have no history of regular illicit drug use or heavy alcohol use and will not be highly distressed. We will ask you some questions to discover if you might experience an adverse reaction to diazepam. To ensure your safety, you will be excluded from the study if any concerns are raised in this regard. Participants will be randomly divided into two groups over the course of the research: those who receive a single standard 5 mg dose of diazepam, and those who receive a placebo (a tablet with no active ingredients). Neither you nor the researcher will know if you have been given diazepam or a placebo tablet until the completion of the experiment.

What would I have to do?

If you decide to take part, you will be asked some basic information about yourself (such as your age, sex, and years of schooling), what your mood has been like recently, and some questions about your alcohol and drug use. You will

also be asked to complete a task which requires you to read aloud a list of words. You will then receive training on some more tasks, and do one round of testing before being given a capsule to take. You will then complete the set of tasks every half hour, with 15 minute intervals between sets of tasks to rest and relax. You will also have your blood pressure taken at various points throughout the study, to ensure your safety. The tasks are highly unlikely to cause you any harm or discomfort, and will include computer-based tasks requiring you to: respond to one or more symbols on a computer screen as quickly as you can; and move an unpredictably jumping mouse cursor to the centre of a target on a computer screen. Paper and pen tasks will ask you to: match symbols to a list of numbers, using a code table that pairs the numbers 1 – 9 with a unique symbol; and rate various aspects of how ready and able you would be to drive at various points throughout the session.

The session will occur at the University of Tasmania, and will take approximately three and a half hours. You will be reimbursed $40 at the end of the study session for your time and out-of-pocket expenses.

Are there any risks or discomforts to me?

You may experience some effects if you are administered diazepam, such as drowsiness or dizziness. It is also possible, although very rare, that you may experience some more adverse effects from diazepam, including muscle weakness, dry mouth or upset stomach. Before taking part in the study you must organise for a reliable friend or family member to collect you from the lab at the end of the testing session, in case you are still experiencing any effects following the possible administration of diazepam. The researcher will check that this has been organised before the testing session begins. When the nominated person collects you, they will be given an information sheet with details on how to care for you, and the main points will be verbally explained. Namely, it will be explained that they should ensure you do not drive a vehicle or operate machinery for at least three hours, and do not consume alcohol for at least three hours. In the unlikely event that you do experience unpleasant side effects while completing the testing, the researchers are trained in first aid, and a registered nurse will be available on site to provide further assistance if required. Additionally, the researcher will explain that in the unlikely event of you experiencing an adverse reaction once you have left the premises, you should contact your doctor or be taken to hospital immediately.

Your participation in this study is voluntary and you may, at any time, decline to answer any question you so wish, or withdraw from the study without any consequence or explanation. You may also withdraw any data you have provided to this time if you so wish.

Will I be identifiable by being involved in this study?

You will not be personally identified in any presentation of study results, since all findings are presented anonymously in grouped results. Data from the study will be stored securely for at least five years in locked cabinets and servers in the School of Psychology, and then destroyed by shredding or deletion.

Who do I need to contact if I have any questions about the research?

If you would like more information about the research, please contact Dr Raimondo Bruno at the School of Psychology, UTAS, on 6226 2240 or Raimondo.Bruno@utas.edu.au. If you would like to find out about the results of the study, these will be available from Dr Bruno after November 2009 or at www.utas.edu.au/psychol

Has this research been approved by an ethics committee?

This project has received ethical approval from the Human Research Ethics Committee (Tasmania) Network which is constituted under the National Health & Medical Research Council. The Committees under the HREC (Tasmania) Network use the *National Statement on Ethical Conduct in Research Involving Humans* to inform their decisions. If you have any concerns of an ethical nature or complaints about the manner in which the project is conducted, you should contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on 03 6226 7479, or human.ethics@utas.edu.au. If you decide to participate in this study, you will be given copies of this information sheet to keep so that you have a record of these contact details.

Thank you for your interest in the study and for taking the time to read this information sheet. We hope you will be interested in participating in this study.

Dr Raimondo Bruno	Dr Frances Martin	Madelyn Dent	AneliesePoorter
Chief Investigator	Chief Investigator	Masters Student	MastersStudent

CONSENT FORM FOR PARTICIPATION

Title of Project: **Short-term diazepam use and driving related skills**

---

1. I have read and understood the 'Information Sheet' for this study.
2. The nature and possible effects of the study have been explained to me.
3. I understand that the study involves taking either a placebo tablet or a single standard 5mg diazepam dose, and that neither the researcher nor I will know what I am being administered.
4. I understand that I will be asked about demographic information, such as my age, sex, and years of schooling, what my mood has been like recently, and some questions about my alcohol and drug use.
5. I understand that I will be required to complete a short battery of computer-based and pen and paper tasks that will be repeated at half-hourly intervals, over the course of approximately 3 hours, with 15 minutes to rest between time points.
6. I understand that participation involves the unlikely risk(s) that I may experience an adverse reaction to a diazepam dose. However, it has been explained what these effects might be, and that I should seek medical assistance should these occur. Also, I understand that I do not have to answer any questions about which I feel uncomfortable, and I can decline to answer without the need to explain myself.
7. I understand that all research data will be securely stored on the University of Tasmania premises for at least five years, and will be destroyed when no longer required.
8. Any questions that I have asked have been answered to my satisfaction.
9. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
10. I understand that the researchers will keep my identity confidential, and that any information I supply to the researcher(s) will be used only for the purposes of the research.
11. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so wish, may request that any data I have supplied to date be withdrawn from the research.

Name of Participant:

Signature: Date:

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation

Name of Investigator

Signature of Investigator

Appendix B:

Demographic Questionnaire

(incorporating the AUDIT and K10)

Diazepam use and driving related skills

Demographic Information

1. *Age:* _____ *(in years)*

2. *What is the main language you speak at home?*

   English ☐ *1* *Oth* ☐ *2* (Please Specify_____)

3. *What grade of school did you complete?*

   Year _____

4. Have you **completed** any course after school?

   No…… *0* ☐

   Yes, trade/technical…… *1* ☐

   Yes, university/college…… *2* ☐

   *Specify qualifications*_____

5. *How are you employed at the moment?* (Mark only one)

   Not employed…… *0* ☐

   Full time…….. *1* ☐

   Part time/casual…… *2* ☐

   Full time student……... *3* ☐

   Home duties…….. *4* ☐

   Other……... *5* ☐ (Please Specify_____)

6. Please rate how alert you are feeling right now:

1	2	3	4	5	6	7	8	9	10
Extremely Alert	Very Alert	Alert	Somewhat Alert	Neither alert nor sleepy	Some signs of sleepiness	Sleepy, but it takes no effort to stay awake	Sleepy and it is taking some effort to stay awake	Very sleepy, it is taking great effort to stay awake – I am struggling against sleep	Extremely sleepy. I am falling asleep all the time

These questions are related to your use of alcohol. Remember, any information you provide is completely confidential.

Please circle the most appropriate response

Q1. How often do you have a drink containing alcohol?							
0	Never	**1**	Monthly or less	**2**	2-4 times a month	**3**	2-3 times a week	**4**	4 or more times a week
Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?							
0	1 or 2	**1**	3 or 4	**2**	5 or 6	**3**	7 to 9	**4**	10 or more
Q3. How often do you have six or more drinks on one occasion?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q4. How often during the last year have you found that you were not able to stop drinking once you had started?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q5. How often during the last year have you failed to do what was normally expected from you because of drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q6. How often during the last year have you needed a first drink in the morning to get yourself going, after a heavy drinking session?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q7. How often during the last year have you had a feeling of guilt or remorse after drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q9. Have you or someone else been injured as a result of your drinking?							
0	No	**2**	Yes, but not in last year			**4**	Yes, during the last year		
Q10. Has a relative or friend or doctor or other health worker been concerned about your drinking or suggested you cut down?							
0	No	**2**	Yes , but not in last year			**4**	Yes, during the last year		

These questions are related to your use of illicit drugs, or illicit use of prescribed drugs. Remember, any information you provide is completely confidential.

Have you taken any drugs for recreational purposes since the time we first contacted you?

If yes, please record details here:_____

_____

These questions are related to how you have been feeling over the last 4 weeks. Remember, any information you provide is completely confidential.

Please circle the most appropriate response.

In the last 4 weeks, about how often –

1. Did you feel tired out for no good reason?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

2. Did you feel nervous?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5 *Note: If response 5 chosen, go to Q4*

3. Did you feel so nervous that nothing could calm you down?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

4. Did you feel hopeless?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

5. Did you feel restless or fidgety?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5 *Note: If response 5 chosen, go to Q7*

6. Did you feel so restless that you could not sit still?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

7. Did you feel depressed?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

8. Did you feel that everything was an effort?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

9. Did you feel so sad that nothing could cheer you up?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

10. Did you feel worthless?

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5