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SHORT COMMUNICATION

Effects of repeated dosing with mirtazapine, trazodone, or placebo on driving performance and cognitive function in healthy volunteers

Kazumi Sasada[1], Kunihiro Iwamoto[1]*, Naoko Kawano[1], Kunihiro Kohmura[1], Maeri Yamamoto[1], Branko Aleksic[1], Kazutoshi Ebe[2], Yukihiro Noda[3,4] and Norio Ozaki[1]

[1]*Department of Psychiatry, Graduate School of Medicine, Nagoya University, Nagoya, Aichi, Japan*
[2]*Toyota Central R&D Labs., Inc., Nagakute, Aichi, Japan*
[3]*Division of Clinical Science and Neuropsychopharmacology, Graduate School of Pharmacy, Meijo University, Nagoya, Aichi, Japan*
[4]*The Academic Frontier Project for Private Universities, Comparative Cognitive Science Institutes, Meijo University, Nagoya, Aichi, Japan*

Objective This study aimed to evaluate the effects of repeated treatments with the sedative antidepressants mirtazapine and trazodone on driving performance and cognitive function.
Methods Nineteen healthy men received continuous nocturnal doses of 15-mg mirtazapine , 25-mg trazodone, or placebo for 8 days in a double-blinded, three-way crossover trial. Subjects were asked to perform three driving tasks (road tracking, car following, and harsh braking) using a driving simulator and cognitive tasks (the Wisconsin Card Sorting Test, Continuous Performance Test, and N-back Test) at baseline and on Days 2 and 9. Stanford Sleepiness Scale scores were also assessed.
Results Mirtazapine significantly increased the standard deviation of lateral position in the road-tracking task as compared with trazodone on Day 2. Mirtazapine significantly increased Stanford Sleepiness Scale scores as compared with trazodone and placebo. For the remaining tasks, no significant effects of treatment were observed.
Conclusions Acute treatment of mirtazapine impaired road-tracking performance and increased sleepiness, but sedative effects disappeared under repeated administrations. Trazodone did not affect driving performance or cognitive function under acute or repeated administrations. Both initial sedative effects and pharmacological profiles should be taken into consideration when using sedative antidepressants. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—sedative antidepressant; mirtazapine; trazodone; driving performance; cognitive function

INTRODUCTION

Many antidepressants are available for psychiatric treatment, but pharmacological profiles of these drugs differ widely. The choice of antidepressant is determined by safety, tolerability, efficacy, payment, and simplicity, which are summarized by the mnemonic STEPS (Preskorn, 1996). Although sedation is one of the unpleasant side effects (Bourin and Briley, 2004), sedative antidepressants can represent a useful treatment option for some patients with agitation or insomnia (Mann, 2005; Linden and Westram, 2010).

Among the sedative antidepressants, tricyclic antidepressants (TCAs) show anticholinergic properties as well as sedative properties. Because of these properties, TCAs have been repeatedly shown to impair cognitive and psychomotor performance (Serretti *et al*., 2010), including car driving (Ramaekers, 2003; Iwamoto *et al*., 2008). Thus, non-sedating antidepressants may represent a better option (Bourin and Briley, 2004; Versiani *et al*., 2005). However, the sedative antidepressants trazodone and mirtazapine are among the most commonly used drugs for chronic insomnia in the USA because of safety and lower dependence potential. Therefore, these two drugs need to be examined with respect to psychomotor performance in daily life, including car-driving skills.

Previous studies have suggested that mirtazapine could impair road-tracking performance (Wingen *et al*., 2005). However, the effects of mirtazapine on driving skills associated with traffic accidents have not been fully investigated. Moreover, the effects of trazodone on

*Correspondence to: K. Iwamoto, MD, PhD, Department of Psychiatry, Graduate School of Medicine, Nagoya University, 65, Tsuruma-cho, Showa, Nagoya, Aichi 466-8550, Japan. Tel: +81 52 744 2282; Fax: +81 52 744 2293. E-mail: iwamoto@med.nagoya-u.ac.jp

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driving skills have rarely been studied (Roth *et al*., 2011). The aim of the study was to evaluate the effects of repeated treatment with mirtazapine or trazodone on driving performance using methods designed to test the risk of rear-end collisions, the most common type of traffic accidents.

MATERIAL AND METHODS

Nineteen healthy male volunteers (26–49 years old, mean ± standard deviation, 38.8 ± 6.8 years) were included through health interviews and the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. All participants had a driving license for ≥5 years and regularly drove a car (minimum, 5000 km/year). The study was approved by the ethics committee of the Nagoya University Graduate School of Medicine and Nagoya University Hospital, and written informed consent was obtained from each individual before participation.

This study used a double-blind, placebo-controlled, three-way crossover design. Each subject received 8 days of continuous bedtime dosing with either 15-mg mirtazapine, 25-mg trazodone, or matched placebo in identical capsules across three different treatment series. The doses selected were clinical recommended starting doses (Sadock *et al*., 2005). Dosing started at bedtime on Day 1, preceding the first test day (Day 2). A washout period of ≥7 days was provided between treatment series.

Baseline assessments were conducted only once before the treatment session. After baseline assessments without treatment, subsequent assessments were performed on Days 2 and 9 at 09:30 AM for each treatment series. We used a driving simulator (DS) (Toyota Central R&D Labs, Nagakute, Japan) to examine three driving skills that appeared to be associated with traffic accidents, including frequent rear-end collisions. The details of DS configuration and tasks have been described previously (Iwamoto *et al*., 2008). The road-tracking test measures the standard deviation of lateral position (SDLP) on a gently winding road at a constant speed of 100 km/h. The car-following test measures the coefficient of variation of the distance between a preceding car and subject's own (Uchiyama *et al*., 2003). Subjects were required to maintain a constant distance between cars. The harsh-braking test measures mean brake reaction time in seven braking trials to avoid crashing into the humanoid models that randomly ran into the road. Each test was recorded every 20 ms and lasted for 5 min. The three cognitive tests, described in detail previously (Iwamoto *et al*., 2008), were examined using a computer. The modified version of the Wisconsin Card Sorting Test (Heaton, 1981) was used to measure executive function. This performance was measured by category achievement, perseverative errors of Nelson, and difficulty of maintaining set. The Continuous Performance Test, Identical Pairs version (Cornblatt *et al*., 1988), was used to measure sustained attention. A series of four-digit stimuli were used, and performance was measured by the signal detection index *d*-prime, a measure of discriminability computed from "hits" and "false alarms." The *N*-back test (Callicott *et al*., 2000, 2003) was used to assess working memory. A two-back condition was used, and performance was measured as the percentage of correct responses. All subjects were trained in both driving and cognitive tests 1–2 weeks before first testing until the plateau level. The Stanford Sleepiness Scale (SSS) (Hoddes *et al*., 1973) is used to examine the level of alertness.

A two-way repeated-measures analysis of variance with time and drug as factors was used to analyze percentage changes in outcome variables over 8 days. If a significant interaction between factors was observed, these variables at each evaluation point were examined with one-way repeated-measures analysis of variance, followed by the Bonferroni *post hoc* test. All tests were two tailed, and the alpha value was set at 0.05.

RESULTS

In the road-tracking test, one subject administered mirtazapine failed to complete the test on Day 2. Because of technical malfunctions, car-following test, road-tracking test, and Continuous Performance Test data were incomplete for one subject, and harsh-braking test data were incomplete for two subjects. Only complete data sets were included in the analyses.

A summary of the results is shown in Table 1. There is a significant Drug × Time interaction in the road-tracking test ($F = 3.520$, $df = 2, 46$, $p = 0.023$). The SDLP of the mirtazapine condition was significantly greater than that observed in the trazodone condition on Day 2 ($p = 0.001$). The results of SDLP are presented in Figure 1. There is no significant Drug × Time interaction in other driving tests and cognitive tests.

There is a significant Drug × Time interaction in sleepiness ($F = 10.630$, $df = 1,\ 34$, $p < 0.001$). SSS scores under mirtazapine conditions were significantly greater than those observed under trazodone and placebo conditions on Day 2 ($p < 0.001$ each). Results of the SSS are presented in Figure 2.

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Table 1. Summary of the results of driving tests, cognitive tests, and subjective measurements in healthy subjects enrolled in a crossover trial of 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 19$)

Measure	Test time	Mean (*SD*)		
		Placebo	Mirtazapine (15 mg)	Trazodone (25 mg)
Driving test				
SDLP (cm)[a]	Baseline	42.4 (11.02)		
	Day 2	42.2 (12.32)	48.5 (11.61)	41.1 (11.65)
	Day 9	42.2 (11.26)	43.1 (10.69)	39.9 (9.59)
DCV[b]	Baseline	37.4(24.50)		
	Day 2	55.6 (87.45)	64.8 (75.46)	37.7 (30.79)
	Day 9	31.1 (19.45)	32.2 (26.33)	44.5 (42.44)
BRT (ms)[a]	Baseline	536.5 (46.57)		
	Day 2	528.4 (70.81)	539.6 (44.20)	526.5 (43.31)
	Day 9	524.1 (49.04)	543.6 (52.24)	529.8 (41.22)
Cognitive test				
CPT (d')[b]	Baseline	2.9 (0.75)		
	Day 2	3.3 (0.71)	3.0 (0.80)	3.3 (0.75)
	Day 9	3.2 (0.81)	3.2 (0.85)	3.4 (0.61)
WCST (CA)[c]	Baseline	5.6 (0.67)		
	Day 2	5.7 (0.71)	5.7 (0.64)	5.8 (0.52)
	Day 9	5.7 (0.57)	5.7 (0.57)	5.8 (0.67)
WCST (PEN)[c]	Baseline	0.7 (1.07)		
	Day 2	0.7 (1.07)	1.0 (2.27)	0.4 (0.67)
	Day 9	1.1 (1.48)	0.7 (1.16)	0.5 (0.94)
WCST (DMS)[c]	Baseline	0.3 (0.73)		
	Day 2	0.2 (0.52)	0.2 (0.49)	0.3 (0.73)
	Day 9	0.1 (0.31)	0.3 (0.57)	0.3 (0.44)
Two-back (accuracy, %)[c]	Baseline	93.6 (15.35)		
	Day 2	94.4 (10.76)	90.6 (12.05)	87.2 (23.12)
	Day 9	97.0 (6.27)	92.1 (12.67)	94.0 (11.65)
Subjective measurement (SSS)[c]	Baseline	2.3 (0.46)		
	Day 2	2.4 (0.74)	3.8 (1.15)	2.3 (0.46)
	Day 9	2.4 (0.49)	2.7 (0.65)	2.4 (0.58)

Baseline data were assessed once before treatment.
SDLP, standard deviation of lateral position; DCV, distance coefficient of variation; BRT, brake reaction time; CPT, Continuous Performance Test; WCST, The Wisconsin Card Sorting Test; CA, category achievement; PEN, perseverative errors of Nelson; DMS, difficulty of maintaining set; SSS, Stanford Sleepiness Scale.
[a] $n = 17$
[b] $n = 18$
[c] $n = 19$

DISCUSSION

The present results demonstrated that mirtazapine significantly impaired road-tracking performance and increased subjective sleepiness in acute dosing. No other performances were significantly affected by any treatment condition during the 8 days. The effects of mirtazapine on diving performances in this study are roughly consistent with data shown in previous studies (Ramaekers *et al*., 1998; Ridout *et al*., 2003; Wingen *et al*., 2005).

Mirtazapine also did not impair car-following performance in this study. To the best of our knowledge, this represents the first study to demonstrate the effects of mirtazapine on car-following performance. Whereas the road-tracking test requires subjects to handle a wheel rather than manipulate the pedals, the car-following test requires subjects to constantly switch between accelerator and brake pedal rather than handle a wheel. This means that the road-tracking test is a comparatively monotonous visuomotor task, whereas the car-following test is a more complex executive function task. Wezenberg *et al*. (2007) suggested that mirtazapine was likely to impair simpler cognitive tasks requiring less cognitive effort. Mirtazapine may tend to affect monotonous driving tasks such as the road-tracking test. Meanwhile, amitriptyline, a TCA, impaired both road-tracking and car-following performances in our DS (Iwamoto *et al*., 2008). Its anticholinergic activity may harm car-following performance, as more cognitive effort is required (Sakulsripong *et al*., 1991, Curran *et al*., 1998). The difference of the effects of these sedative antidepressants on driving performance may be explained by the pharmacological properties. On the other hand, for braking performance, mirtazapine and amitriptyline did not impair brake reaction time (Iwamoto *et al*., 2008), but diazepam, a benzodiazepine,

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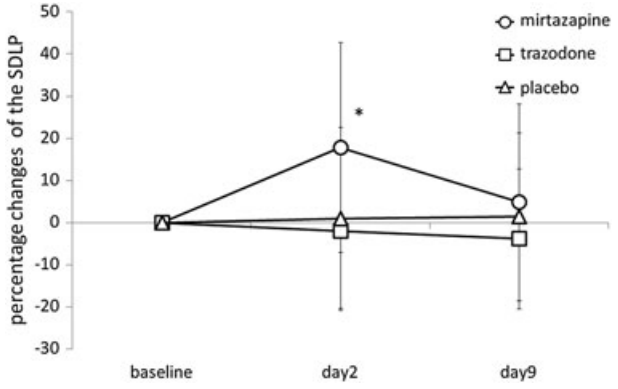

Figure 1. Mean (standard deviation) standard deviation of lateral position (SDLP) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 17$). Differences in SDLP were examined by a two-way repeated-measures analysis of variance. Differences in SDLP at each evaluation point were examined with a one-way repeated-measures analysis of variance followed by a Bonferroni test (*post hoc* test). A significant Drug × Time interaction was noted among the three conditions ($F = 3.520$, $df = 2,46$, $p = 0.023$). **Post hoc* testing demonstrated that SDLP of the 15-mg mirtazapine condition was significantly greater than that of the 25-mg trazodone condition on Day 2 ($p = 0.001$).

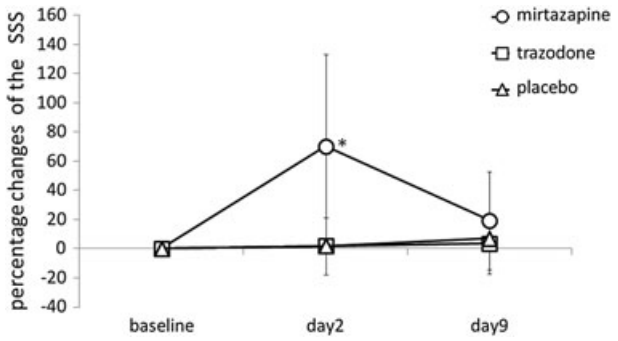

Figure 2. Mean (standard deviation) Stanford Sleepiness Scale (SSS) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 19$). Differences in SSS were examined by a two-way repeated-measures analysis of variance. Differences in SSS at each evaluation point were examined by a one-way repeated-measures analysis of variance followed by a Bonferroni test (*post hoc* test). Significant Drug Time interactions were seen among the three conditions ($F = 10.630$, $df = 1$, 34, $p < 0.001$). **Post hoc* testing demonstrated that SSS of the 15-mg mirtazapine condition was significantly greater than that observed in the placebo and 25-mg trazodone conditions on Day 2 ($p < 0.001$ each).

did result in impairments (Takahashi *et al*., 2010). The harsh-braking task is likely to be affected by a peripheral muscle relaxant effect rather than a cognitive detrimental effect. Because subjective assessments and psychometric tests did not fully predict drug effects on driving performance (Verster and Roth, 2012a, 2012b), further researches are needed to elucidate the impact of psychotropics on car-driving performance.

The present study showed that 25-mg trazodone did not impair both driving and cognitive performances, although the previous study showed that 50-mg trazodone did not impair driving performance but affected memory and learning (Roth *et al*., 2011) and that more than 100 mg of trazodone affected memory and attention (Curran *et al*., 1998; Sakulsripong *et al*., 1991). Although these differences may be attributable to the dosage of trazodone and cognitive tasks, pharmacological profiles of trazodone may be also in part responsible for these results. The sedative effect of trazodone is associated with its high affinity to the histamine H1 receptor; however, trazodone has features of a weak anticholinergic activity and short half-life (Bryant and Ereshefsky, 1982). Therefore, a low dose of trazodone may produce no detrimental effects on psychomotor performance as antihistamines have dose-dependent effects on psychomotor performance including driving performance (Theunissen *et al*., 2004).

In the present study, the sedative effects of mirtazapine were no longer apparent on Day 9. According to pharmacological profiles, mirtazapine is a strong histamine H1 receptor antagonist without anticholinergic activity, and its activity contributed to detrimental effects. In assessing sedative properties with medications, an important issue is the degree to which tolerance to the sedative effect develops. Tolerance to sedative effects of mirtazapine may develop rapidly, as with histamine H1 antihistamines (Richardson *et al*., 2002). Development of tolerance may apply equally to repeated doses of trazodone. Meanwhile, TCAs often exert an anticholinergic activity that can cause different detrimental effects on cognitive performance. In the case of amitriptyline, tolerance to sedative effects, based on subjective and behavioral measures, develops within 1–2 weeks (Deptula and Pomara, 1990; Veldhuijzen *et al*., 2006), although several studies have indicated intolerance of amitriptyline based on several cognitive measures (Sakulsripong *et al*., 1991; van Laar *et al*., 2002). Anticholinergic properties should thus be considered in cases of tolerance to sedative antidepressants.

The effects of antidepressant on driving performance are different in healthy subjects and psychiatric patients and are also influenced by age and gender of the subjects. In addition, both the psychopharmacological treatment and the pathology itself may impair driving ability. Recent epidemiological studies showed that exposure to antidepressants including selective serotonin reuptake inhibitors was associated with an increased risk of motor vehicle accidents, unlike with past studies (Meuleners *et al*., 2011; Chang *et al*., 2013). As for the experimental studies, newer antidepressants, unlike TCAs, have no detrimental effects on driving performance (Ramaekers, 2003), and mirtazapine could also improve driving ability in depressed patients (Brunnauer *et al*., 2008; Shen *et al*., 2009). These discrepancies may

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be explained in part by age, dosage, dosing period, active depressive symptom, comorbid psychotropic drugs, and methodological variances (Sansone and Sansone, 2009). Especially, benzodiazepines often prescribed in clinical settings may increase the risk of motor vehicle accidents (Dassanayake *et al*., 2011). Meanwhile, many depressed patients before hospital discharge showed impairments in psychomotor functions related to driving abilities, and those were influenced by different classes of antidepressants (Brunnauer *et al*., 2006). The effects of antidepressants on driving ability in depressed patients under treatment have not yet been fully defined because of many confounding factors such as psychopharmacological treatment and the depression itself. Thus, it is important to examine the effects of antidepressants on driving performance in healthy subjects to find the inherent influences of antidepressants for driving impairments. However, future studies need to elucidate the impact of similar antidepressants in depressed patients in a similar experimental line and make a comparison with depressed patients.

The present study has several limitations. First, participation was restricted to healthy adult volunteers, and the sample size is relatively small. Neither elderly nor patient populations were included in the study. The elderly are more vulnerable to the side effects of pharmacological treatments. In addition, depression and insomnia can affect driving performance (Brunnauer *et al*., 2008; Shen *et al*., 2009) and cognitive function. Both properties of antidepressant and disorder should be considered in clinical settings. Second, the validity and sensitivity of the DS need to be considered; however, our past results using same DS are roughly consistent with preceding results (Iwamoto *et al*., 2008; Takahashi *et al*., 2010). Although cognitive tasks used in this study were employed in many psychiatric researches and our past studies, the sensitivity of these tasks regarding the assessment for drug effects should be considered, too. Third, dosage selection may be lower than that of past studies, because we used the initial starting dose for clinical practice. Considering an affinity for histamine H1 receptor in particular, the dose of trazodone may be low in comparison with that of mirtazapine.

Finally, acute treatments of mirtazapine did not impair car-following or harsh-braking performances but did impair road-tracking performance, although this impairment disappeared under repeated administrations. The lower dose of trazodone did not affect driving or cognitive performances under acute or repeated administrations. Both initial sedative effects and pharmacological profiles should be taken into consideration in prescribing sedative antidepressants.

CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this study.

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REFERENCES

Bourin M, Briley, M. 2004. Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many psychotropic drugs. *Hum Psychopharmacol* **19**: 135–139.

Brunnauer A, Laux G, Geiger E, Soyka M, Moller HJ. 2006. Antidepressants and driving ability: results from a clinical study. *J Clin Psychiatry* **67**: 1776–1781.

Brunnauer A, Laux G, David I, Fric M, Hermisson I, Moller HJ. 2008. The impact of reboxetine and mirtazapine on driving simulator performance and psychomotor function in depressed patients. *J Clin Psychiatry* **69**: 1880–1886.

Bryant SG, Ereshefsky L. 1982. Antidepressant properties of trazodone. *Clin Pharm* **1**: 406–417.

Callicott JH, Bertolino A, Mattay VS, *et al*. 2000. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* **10**: 1078–1092.

Callicott JH, Egan MF, Mattay VS, *et al*. 2003. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* **160**: 709–719.

Chang CM, Wu EC, Chen CY, *et al*. 2013. Psychotropic drugs and risk of motor vehicle accidents: a population-based case–control study. *Br J Clin Pharmacol* **75**: 1125–1133.

Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. 1988. The Continuous Performance Test, Identical Pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Res* **26**: 223–238.

Curran HV, Sakulsriprong M, Lader M. 1998 Antidepressants and human memory: an investigation of four drugs with different sedative and anticholinergic profiles. *Psychopharmacology (Berl)* **95**: 520–527.

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 Saf* **34**: 125–156.

Deptula D, Pomara N. 1990. Effects of antidepressants on human performance: a review. *J Clin Psychopharmacol* **10**: 105–111.

Heaton RK. 1981. *The Wisconsin Card Sorting Test (Manual)*. Psychological Assessment Resources: Odessa, FL.

Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. 1973. Quantification of sleepiness: a new approach. *Psychophysiology* **10**: 431–436.

Iwamoto K, Takahashi M, Nakamura Y, *et al*. 2008. The effects of acute treatment with paroxetine, amitriptyline, and placebo on driving performance and cognitive function in healthy Japanese subjects: a double-blind crossover trial. *Hum Psychopharmacol* **23**: 399–407.

Linden M, Westram A. 2010. Prescribing a sedative antidepressant for patients at work or on sick leave under conditions of routine care. *Pharmacopsychiatry* **43**: 1–6.

Mann JJ. 2005. The medical management of depression. *N Engl J Med* **353**: 1819–1834.

Meuleners LB, Duke J, Lee AH, Palamara P, Hildebrand J, Ng JQ. 2011. Psychoactive medications and crash involvement requiring hospitalization for older drivers: a population-based study. *J Am Geriatr Soc* **59**: 1575–1580.

Preskorn SH. 1996. *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors*. Professional Communications: Caddo, OK.

Ramaekers JG. 2003. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiatry* **64**: 20–29.

Ramaekers JG, Muntjewerff ND, Veggel LMAV, Uiterwijk MMC, O'Hanlon JF. 1998. Effects of nocturnal doses of mirtazapine and mianserin on sleep and on daytime psychomotor and driving performance in young, healthy volunteers. *Hum Psychopharmacol* **13**: 87–97.

Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. 2002. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol* **22**: 511–515.

Ridout F, Meadows R, Johnsen S, Hindmarch I. 2003. A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance. *Hum Psychopharmacol* **18**: 261–269.

Roth AJ, McCall WV, Liguori A. 2011. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. *J Sleep Res* **20**: 552–558.

Sadock BJ, Sadock VA, Sussman N, Cancro R. 2005. *Kaplan and Sadock's Pocket Handbook of Psychiatric Drug Treatment*. Lippincott, Williams & Wilkins: Philadelphia, PA.

Sakulsripong M, Curran HV, Lader M. 1991. Does tolerance develop to the sedative and amnesic effects of antidepressants? A comparison of amitriptyline, trazodone and placebo. *Eur J Clin Pharmacol* **40**: 43–48.

Sansone RA, Sansone LA. 2009. Driving on antidepressants: cruising for a crash? *Psychiatry (Edgmont)* **6**: 13–16.

Serretti A, Calati R, Goracci A, Di Simplicio M, Castrogiovanni P, De Ronchi D. 2010. Antidepressants in healthy subjects: what are the psychotropic/psychological effects? *Eur Neuropsychopharmacol* **20**: 433–453.

Shen J, Moller HJ, Wang X, Chung SA, Shapiro GK, Li X, Shapiro CM. 2009. Mirtazapine, a sedating antidepressant, and improved driving safety in patients with major depressive disorder: a prospective, randomized trial of 28 patients. *J Clin Psychiatry*, **70**, 370–377.

Takahashi M, Iwamoto K, Kawamura Y, *et al*. 2010. The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers. *Hum Psychopharmacol* **25**: 260–267.

Theunissen EL, Vermeeren A, van Oers AC, van Maris I, Ramaekers JG. 2004. A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo. *Clin Exp Allergy* **34**: 250–258.

Uchiyama Y, Ebe K, Kozato A, Okada T, Sadato N. 2003. The neural substrates of driving at a safe distance: a functional MRI study. *Neurosci Lett* **352**: 199–202.

van Laar MW, Volkerts ER, Verbaten MN, Trooster S, van Megen HJ, Kenemans JL. 2002. Differential effects of amitriptyline, nefazodone and paroxetine on performance and brain indices of visual selective attention and working memory. *Psychopharmacology (Berl)* **162**: 351–363.

Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. 2006. Acute and subchronic effects of amitriptyline on processing capacity in neuropathic pain patients using visual event-related potentials: preliminary findings. *Psychopharmacology (Berl)* **183**: 462–470.

Versiani M, Moreno R, Ramakers-van Moorsel CJ, Schutte AJ. 2005. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs* **19**: 137–146.

Verster JC, Roth T. 2012a. Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. *Psychopharmacology (Berl)* **219**: 775–181.

Verster JC, Roth T. 2012b. Predicting psychopharmacological drug effects on actual driving performance (SDLP) from psychometric tests measuring driving-related skills. *Psychopharmacology (Berl)* **220**: 293–301.

Wezenberg E, Sabbe BG, Hulstijn W, Ruigt GS, Verkes RJ. 2007. The role of sedation tests in identifying sedative drug effects in healthy volunteers and their power to dissociate sedative-related impairments from memory dysfunctions. *J Psychopharmacol* **21**: 579–587.

Wingen M, Bothmer J, Langer S, Ramaekers JG. 2005. Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: a crossover trial. *J Clin Psychiatry* **66**: 436–443.