ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Necessity of normative data on the Japanese version of the Wechsler Memory Scale-Revised Logical Memory subtest for old-old people

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Aim: Episodic memory is vulnerable to deterioration in people suffering from Alzheimer's disease. Currently, the Logical Memory (LM) subtest of the Wechsler Memory Scale-Revised (WMS-R) is used internationally as an operational definition to identify people with mild cognitive impairment (MCI). However, the Japanese version of the LM has not been adequately normalized for old-old people. Therefore, norms of the LM for people aged 75 years and over are required, and the effects of sex, age and education on performance were evaluated.

Methods: A total of 50 (27 female and 23 male) participants without a history of dementia and symptomatic stroke events recruited from the community and hospital populations were investigated using the Mini-Mental State Examination, the LM and some interference tasks.

Results: The mean scores (standard deviations) of the sample were 15.5 (5.4) on LM-I and 9.9 (6.6) on LM-II. The distributions of the LM-I and -II scores satisfied the normality assumption. The LM-I and LM-II scores correlated with age and the LM-I score correlated with educational background.

Conclusions: For the Japanese version of the LM, the means, standard deviations and distribution features of the old-old sample are presented. Although the normal sample was chosen to closely match the demographic profile of the Japanese population, the present sample might have had a higher educational background than the age-matched population, especially the males. Further study is required to standardize the Japanese version of the LM subtest for each 5-year interval for latter-stage elderly people. **Geriatr Gerontol Int 2013; 13: 726–730.**

Keywords: episodic memory, Logical Memory, mild cognitive impairment, normative data, old-old people.

Introduction

A mild cognitive impairment (MCI) as a result of Alzheimer's disease (AD) is seen as memory impairment, and this symptom is the key early marker in the prodromal stages of AD.[1] Although the memory deficits in individuals with MCI are clinically discernible, in order to make a diagnosis of MCI, amnesia that does not interfere notably with activities of daily life (ADL) must be identified. It is operationally defined as performance 1.0–1.5 standard deviations (SD) below age- and education-adjusted norms on an episodic memory measure of delayed verbal recall.[2]

The Logical Memory (LM) subtest of the Wechsler Memory Scale (WMS), which includes immediate (LM-I) and 30-min delayed (LM-II) trials of prose recall, is a large contributor to discriminating between healthy older adults and individuals with very mild AD. Guillozet *et al.* reported that AD pathology is more numerous in medial temporal lobe regions associated with the LM scores of the revised version of WMS (WMS-R),[3] and shows a relationship with LM performance on the WMS-R in individuals in the non-demented stage.[4] Although the relative ability of memory tests to discriminate between the AD convertor type of MCI and normal aging has not been well characterized, a previous study reported that the LM-II was one of the best predictors for detecting progression from MCI to AD over a 4-year period.[1] The LM of the WMS-R is one of the standard memory criteria for MCI clinical and research; for example, in the Alzheimer's Disease Neuroimaging Initiative study.[5]

Various factors have been associated with LM test score differences. Abikoff *et al.* have already reported that age and education norms are generated for immediate, 30-min delayed and 24-h delayed recall in the LM of the WMS, and performance is more closely related to educational background.[6] Their sample ranged in age from 18 to 81 years, with a mean educational level of 13.96 years (range 6–18 years). The LM performance increase is somewhat more common with higher levels of education.[6,7] However, Abikoff *et al.* noted that "Although education was more highly related to scores than was age, small but significant relationships between age and verbal recall remained over and above the influence of education.[6]" The impact of age is most obvious in 24-h delayed recall, and drop-off in performance occurs over the age of 60 years. Therefore, the latest version of the WMS has paid attention to elderly participants in the form of advancing an elderly battery.

However, the WMS-R version is the only LM task that has been standardized for Japanese people, and the normative sample has been limited to the ages of between 16 and 74 years. The incidences of AD, combined dementia and other types of dementia rise with increasing age, particularly after the age of 85 years.[8] Although not only for young-old people, but also for old-old or oldest-old people, an amnestic state examination of high accuracy is required, because the Japanese versions of the WMS-R, LM-I and LM-II have not been adequately normalized for latter-stage elderly people. In the current study, normative data for the LM in Japanese elderly people aged 75 years and older were gathered.

Methods

Participants

A total of 50 (27 female and 23 male) participants without a history of dementia and symptomatic stroke events were recruited from the community and hospital populations living in two urban areas. All participants could attend the trial sites alone. The sample size determination was based on the original version of the WMS-R and the general recommendation on statistics in psychology and education, taking a sample of 50 and over per age group interval.[9] A total of 30 participants (60%) had no history of psychiatric problem as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revised (SCID),[10] and they did not report clinical evidence of amnesia and ADL impairment. There is nothing to suggest that participants did not hear something at the time of auditory stimulus presentation in the study. They ranged in age between 75 and 87 years (mean ± SD: 79.3 ± 3.6 years), and in educational background between 6 and 18 years (mean ± SD: 11.7 ± 3.1 years).

The ethics committee of the Tokyo Metropolitan Institute of Gerontology and the Nagoya University School of Medicine approved the present study, and each participant signed a consent form after being sufficiently informed about the outline of the study by the principal investigator.

Tasks

Logical Memory (LM)-I and -II from the Japanese version of the WMS-R[11] were carried out. In the LM-I, participants were asked to immediately recall from the number of prose units twice: the first trial presented story A verbally, and the second trial presented story B verbally. In the LM-II, participants were asked to recall words from the two stories 30 min later. During the time delay, participants were asked to carry out the Mini-Mental State Examination (MMSE)[12] and some interference tasks.

In the present study, not all of the participants carried out every task item, other than LM-I, II and MMSE. As the purpose of the present study was to provide normative data for LM-I and -II, the sample size was kept the same; hence, missing data were not substituted. The results are based on the eight task scales.

Statistical analysis

All statistical analyses were carried out using SPSS 17.0 J. for Windows (SPSS, Chicago. IL, USA). Normative data are provided in the form of means and standard deviations (SD) broken down by sex, age and educational background. Correlation analyses between LM scores and various factors were carried out using the Pearson product-moment correlation coefficient. A *P*-value of less than 0.05 was considered significant. The percentile rank of each LM-I or -II score was calculated, after the Shapiro–Wilk test was carried out to check the normality of the sampling distribution.

Results

Sample characteristics

In the present sample, the mean ± SD score of MMSE (27.3 ± 2.2) reflected the expected distribution of general cognitive status for aged groups. The normative sample was confirmed to match closely the demographic profile of this population as reported in a recent census. Table 1 shows the percentiles of the normalization sample by age, sex and educational background compared with these population averages in Japan (Statistics Bureau 2010: Ministry of Internal Affairs and Communications). The results showed that the sample might have had a higher educational background than Japan's age-matched population.

Table 1 Percentiles of the normalization sample by age, sex and educational background

Age (years)	Sex	Education					
		0–11 (years)		12 (years)		>13 (years)	
		Sample	Population (Japan)	Sample	Population (Japan)	Sample	Population (Japan)
>75	Male	25.9	45.6	18.5	37.6	40.7	16.8
	Female	63.0	53.3	18.5	41.3	18.5	5.4
	Total	48.0	50.3	20.0	39.9	32.0	9.8

The estimated population was calculated excluding active students and unknown individuals of education backgrounds from total number.

Table 2 Performance of the sample aged 75 years and older

		Mean SD (min–max)
LM-I		15.5 ± 5.4 (5–8)
	Story A	8.3 ± 3.2 (3–16)
	Story B	7.4 ± 2.8 (2–14)
LM-II		9.9 ± 6.6 (0–25)
	Story A	5.0 ± 3.8 (0–13)
	Story B	4.9 ± 3.2 (0–12)

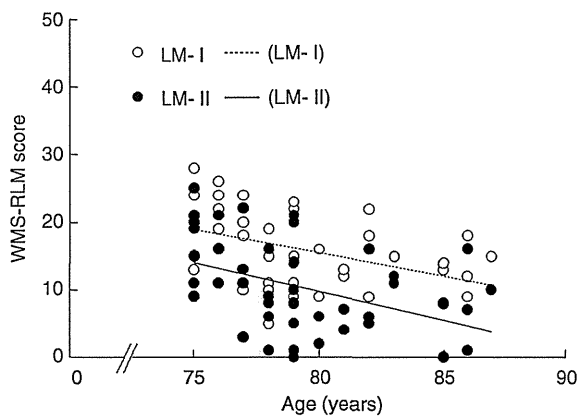I, immediate recall; II, delayed recall; LM, Wechsler Memory Scale-Revised Logical Memory subtest.

Reference data of the normal group

Mean scores (SD) of the sample were 15.5 (5.4) on LM-I and 9.9 (6.6) on LM-II. Table 2 summarizes the performance of the sample. To check the normality of the sampling distribution, coefficients of skewness and kurtosis were calculated for each trial. In the LM-I, the skewness value was 0.19 and the kurtosis value was −0.89; in the LM-II, the skewness value was 0.32 and the kurtosis value was −0.82. The distributions of the LM-I and -II scores satisfied the normality assumption using the Shapiro–Wilk test ($P > 0.05$).

Characteristics and performances

To examine the effect of sex on performance, unpaired t-tests comparing the LM-I and -II scores in male and female participants were carried out. In both the LM-I and -II, no significant difference was found. The mean scores (SD) of the male group were 15.6 (5.5) on the LM-I and 10.8 (6.4) on the LM-II, compared with 16.3 (5.5) on the LM-I and 10.0 (6.8) on the LM-II in the female group.

To examine associations between age (years) or educational background (years) and LM scores, correlation analyses were carried out. The LM-I and LM-II scores were moderately correlated with age ($r = -0.44$, $P < 0.01$; $r = -0.45$, $P < 0.01$), and the LM-I score was moderately
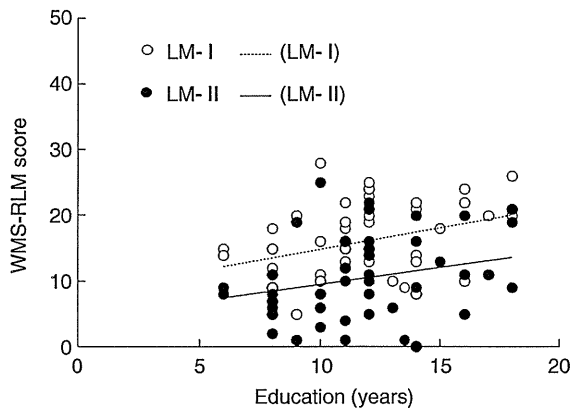

Figure 1 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) subtest scores (*y*-axis) and age in years (*x*-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

correlated with educational background ($r = 0.36$, $P < 0.05$). There was no significant correlation between the LM-II score and educational background ($r = 0.23$, not significant.). The figures show scatter plots of the WMS-R LM scores and age in years (Fig. 1), or years of education (Fig. 2). Considering that the sample had a moderate to high education, partial correlation analyses between age (years) and LM scores were carried out. The LM-I and LM-II scores were moderately correlated with age ($r = -0.36$, $P < 0.05$; $r = -0.40$, $P < 0.01$).

Discussion

In the current study, LM normal performances of healthy Japanese people aged 75 years and older were surveyed, and the effects of sex, age and education on performance were identified. The means, SD and distribution features of the LM-I and -II of the WMS-R are presented for Japanese old-old people.

The sample had mean (SD) scores of 15.5 (3.2) on the LM-I and 9.9 (6.6) on the LM-II. According to

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Figure 2 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) scores (y-axis) and years of education (x-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

Sugishita,[11] people in each age group (16–17 years ($n = 50$), 20–24 years ($n = 54$), 35–44 years ($n = 56$), 55–64 years ($n = 50$), 65–69 years ($n = 52$) and 70–74 years ($n = 54$)) had the following scores: on the LM-I, 27.7 (7.2), 26.6 (6.4), 25.1 (7.5), 22.0 (7.1), 19.5 (6.8) and 18.5 (7.5), respectively; and on the LM-II, 24.9 (7.7), 22.8 (6.7), 20.7 (7.6), 16.8 (7.0), 15.3 (7.0) and 13.2 (6.8), respectively. These results are consistent with previous data, and indicate an age-related decrease in LM task performance.[6,13] Considering the Flynn effect, the present data should not be compared directly with the previous data by Sugishita.[11] It is recommended that a larger study for the normalization of LM in older people be carried out.

Furthermore, the study showed that the LM-I and -II scores were moderately negatively correlated with age in a healthy sample aged 75 years and older. In particular, the LM-II score reflected the individual difference associated with age, independent of educational background. The result also confirms the age-related changes in memory functions. This finding, that the LM-II was *not* correlated with education leaves room for interpretation. Although the present sample from among community-dwelling older adults had generally better health and education, high-risk MCI persons might have been present in definite proportions, or the normal population might have individuals who, despite educational levels, may have been less able in cognitive abilities throughout their life.[14,15] According to the Mayo clinic's team, the LM-II data were *not* correlated with education in a community-based healthy sample.[15] They noted that the education-WMS performance association in the restricted age range of their older sample did not reflect true underlying relationships between the intelligence quotient (IQ) and task performance, and they recommended that WMS norms be

stratified by IQ. The education-LM performance association might reflect these confounding factors.

Although the present sample was chosen to closely match the demographic profile of the Japanese population, the sample might have had a higher educational background than the age-matched population, especially among males. Community-based surveys in rural areas should also be carried out at the same time as surveys in urban areas. Thus, the sample bias is inappropriate for determining the "range of normal" memory functioning in an older population.[15] Norms stratified to be representative of the general population have great diagnostic value. However, the present result showed that the aging-related memory decline was observed in highly educated people, who had a greater likelihood of preserving cognitive function than people with low educational achievement. The result suggests that normalization of LM must be carried out for latter-stage elderly Japanese people. To establish the norms for the Japanese version of the LM, a further community-based study using the Intelligence Scale in parallel will be necessary. In addition, it will be necessary to compare between the LM norms based on the separately-carried out condition and that based on the completely-carried out WMS-R condition, and to normalize the latest version of WMS in Japanese people, because the latest version has a short battery for ages 65–90 years (the Older Adult Battery), including the new LM composed of the 14-paragraph-story (story A) and the 25-paragraph-story (story B).

The present estimated values based on LM scores of people aged 75 years and older, which are currently based on the population aged less than 75 years, show that current percentile ranks underestimate the memory ability of people aged 75 years and older. Furthermore, the present study obviously showed that the LM-I and LM-II scores were correlated with age. These results suggest the necessity of normative data on the Japanese version of the WMS-R LM subtest for each 5-year interval for the population aged 75 years and older, like the original version. In the future, for old-old people, it will be necessary to carry out a survey to establish norms of the WMS-R LM for each 5-year interval.

Acknowledgments

Disclosure statement

No potential conflicts of interest were disclosed.

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SHORT COMMUNICATION

Effects of low-dose mirtazapine on driving performance in healthy volunteers

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Objective This study aimed to assess whether a lower initial dose of mirtazapine can lessen the harmful effect on driving performance or not in a double-blinded, placebo-controlled crossover trial.
Methods Thirteen healthy men received 8 days of continuous nocturnal doses of mirtazapine at 7.5 mg or 15 mg, or placebo. At baseline and on days 2 and 9, subjects performed three driving tasks (road-tracking, car-following, and harsh-braking tasks) using a driving simulator and a Continuous Performance Test. Stanford Sleepiness Scale (SSS) scores were also assessed. In the mirtazapine 7.5 mg series, 15 mg of mirtazapine was additionally administered on day 9, followed by all the same assessments on day 10.
Results Mirtazapine 7.5 mg had no significant effects on any tasks except for SSS compared with placebo. Mirtazapine 15 mg impaired road-tracking task and SSS. The increase in mirtazapine dose also had no significant effects on any tasks compared with those before dose increase.
Conclusions Mirtazapine 7.5 mg did not cause driving impairment compared with mirtazapine 15 mg, while both doses of mirtazapine produced subjective somnolence. The increase in mirtazapine had no detrimental effects on psychomotor performance. Initial low-dose mirtazapine may be safer for automobile driving than the normal starting dose. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—mirtazapine; sedation; driving performance; cognitive function; starting dose

INTRODUCTION

Mirtazapine is a noradrenergic and specific serotonergic antidepressant with a unique pharmacologic profile that differs from currently available antidepressants. The therapeutic effects are derived by blockade of the alpha$_2$-adrenoreceptors and by indirect stimulation of serotonin (5-HT)$_1$ receptors, via blockade of 5-HT$_2$ and 5-HT$_3$ receptors (de Boer, 1995). Efficacy of mirtazapine has been established in a systematic review and meta-analysis of randomized controlled trials (Cipriani *et al.*, 2009; Watanabe *et al.*, 2008). Mirtazapine is also one of the most commonly used drugs for chronic insomnia in the US because of safety and lower dependence.

Despite the efficacy of mirtazapine, a key clinical problem is tolerability, and the most commonly reported adverse event is somnolence (Watanabe *et al.*, 2010). Sedation and somnolence are considered as the most important causes of driving impairment in patients being treated with antidepressants (Ramaekers, 2003). In fact, previous studies have suggested that acute administration of mirtazapine could impair road-tracking performance (Ramaekers *et al.*, 1998; Ridout *et al.*, 2003; Wingen *et al.*, 2005). Therefore, administration methods that can reduce driving impairment of mirtazapine are needed for patients' social lives and public safety.

It is considered that a lower initial dose of mirtazapine provides potent histaminergic blockade inducing prominent somnolence, whereas a higher initial dose of mirtazapine is associated with reduced

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sedating antihistaminergic activity through increased noradrenergic transmission (Stahl *et al.*, 1997; Stimmel *et al.*, 1997). Generally, dose reduction may be used to relieve antidepressants' detrimental effects, but little is known regarding the effects of mirtazapine, especially at lower doses, on driving performance. The aim of the present study was thus to evaluate the effects of a lower initial dose of mirtazapine on driving performance and cognitive function. By measuring the effects of different low doses of mirtazapine on driving performance, we evaluated the driving safety of an initial low dose of mirtazapine.

MATERIAL AND METHODS

Thirteen healthy male volunteers (32–49 years old, mean ± SD, 39.2 ± 6.2 years) were included through health interviews and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. All applicants had had a driving license for ≥10 years and had been driving a car daily (minimum 5000 km/year). The study was approved by the ethics review committees of the Nagoya University Graduate School of Medicine and Nagoya University Hospital, and written informed consent was obtained from each subject before participation.

The present study used a double-blind, placebo-controlled, three-way crossover design. Each subject received 8 days of continuous bedtime dosing with either 7.5 or 15 mg of mirtazapine, or matched placebo in identical capsules across three different treatment series. Under the mirtazapine 7.5 mg series, 15 mg of mirtazapine was additionally administered on day 9. Dosing started at bedtime on day 1, preceding the first test day (day 2). A washout period of ≥7 days was provided between each treatment series. All subjects received substantial training in both driving and cognitive tests 1–2 weeks before the first testing until reaching a plateau level. After baseline assessments without treatment, subsequent assessments were performed on days 2 and 9 at 0930 for each treatment series. In addition, the same assessments were performed on day 10 (dose increase from 7.5 to 15 mg) only for the mirtazapine 7.5 mg series. The study schedule is shown in Figure 1.

A driving simulator (DS) (Toyota Central R&D Labs, Nagakute, Japan) was used to examine three driving skills that have been associated with traffic accidents. The details of DS configuration and tasks have been described previously (Iwamoto *et al.*, 2008).
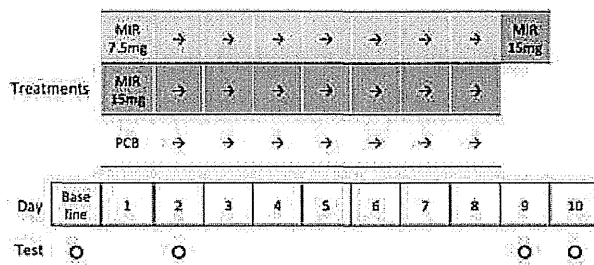

Figure 1. Summary of treatments and schedules in this study. Each subject received nocturnal dosing with mirtazapine (MIR) 7.5 mg, MIR 15 mg, or matched placebo (PCB) for 8 days in a double-blind, crossover design. In the MIR 7.5 mg series, MIR 15 mg was also administered on day 9. A washout period of ≥7 days was provided between each treatment session. Assessments were performed at baseline (once before treatment) and on days 2, 9, and 10 (only in the MIR 7.5 mg series) of each treatment series

The road-tracking test measures standard deviation of lateral position (SDLP) on a gently winding road at a constant speed of 100 km/h. The car-following test measures coefficient of variation of the distance between preceding car and subject's own (Uchiyama *et al.*, 2003). Subject was 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. As for the cognitive test, the Continuous Performance Test—Identical Pairs version (Cornblatt *et al.*, 1988) was used to measure sustained attention. A series of four-digit stimuli was used, and performance was measured by the signal detection index d-prime, a measure of discriminability computed from "hits" and "false alarms". The Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) is also used to examine the level of alertness at the beginning of each test day.

To compare the conditions following the administration of the three drugs, the differences between the baseline values and each evaluation point values were analyzed. Two-way repeated-measures analysis of variance with time and drug as factors was used to analyze the outcome variables over 8 days. Post-hoc tests were examined with one-way repeated-measures analysis of variance followed by the Bonferroni test at each evaluation point. Outcome variables on day 10 in the mirtazapine 7.5 mg series were compared with those on day 9 in the same series using paired *t*-tests. All tests were two-tailed, with the alpha level set at 0.05.

RESULTS

In the road-tracking test, 1 subject failed to complete the test on day 2 for both the mirtazapine 7.5 and 15 mg series, as he was sliding off the track. No other subjects were stopped prematurely and crashed during driving test. Because of technical malfunctions, road-tracking test, harsh-braking test, and Continuous Performance Test data were incomplete for 1 subject. Only complete data sets were included in analyses.

A summary of the results is shown in Table 1. There is a significant *main drug effect* in the road-tracking test $(F = 10.2, df = 1, 13, p = 0.004)$. SDLP in the mirtazapine 15 mg series was significantly greater than that observed in the mirtazapine 7.5 mg or placebo series on day 2 $(p = 0.004,$ both). There is no significant drug × time interaction or *main drug effect* in other driving and cognitive tests. There is a significant drug × time interaction in sleepiness $(F = 6.46, df = 2, 24, p = 0.006)$. SSS scores in the mirtazapine 7.5 and 15 mg series were significantly greater than that observed in the placebo series on day 2 $(p = 0.028$ and $p = 0.027,$ respectively). The results for SDLP and SSS on days 2 and 9 are presented in Figure 2. With regard to increased mirtazapine on day 9, any variables on day 10 did not significantly changed compared with those on day 9.

DISCUSSION

The present results indicate that mirtazapine 7.5 mg did not significantly affect driving performances and sustained attention, although mirtazapine 15 mg had a significantly deleterious effect on road-tracking performance. However, mirtazapine 7.5 mg, like 15 mg, significantly increased subjective sleepiness compared with placebo in acute dosing. Mirtazapine-induced sleepiness decreased over time and was no longer clinically relevant after repeated dosing. Furthermore, the increase in mirtazapine from 7.5 to 15 mg did not impair any performance. This study examines the effects of an initial lower dose of mirtazapine on both driving performance and cognitive function.

Mirtazapine-induced sedation is considered attributable in large part to potent blockade of histamine$_1$ receptors. Antihistamine activity is thought to be offset by increased noradrenergic transmission at higher doses (Stahl et al., 1997; Stimmel et al., 1997). Radhakishun et al. (2000) showed that initial mirtazapine doses of 15 and 30 mg had similar impacts on subjective alertness, but few data have been accumulated to confirm this theory, particularly at lower doses. In the case of antihistamines, dose-dependent effects on psychomotor performance including driving performance (Theunissen et al., 2004) and brain

Table 1. Summary of the results of driving tests, cognitive test, and subjective measurement in healthy subjects enrolled in a crossover trial of mirtazapine 7.5 mg, mirtazapine 15 mg and placebo $(N = 13)$

Measure	Test time	Mean (SD)		
		Placebo	Mirtazapine 7.5 mg	Mirtazapine 15 mg
Driving test	Baseline		42.9 (12.6)	
SDLP* (cm)	Day 2	40.7 (10.6)	41.3 (9.8)	48.3 (11.2)
	Day 9	42.5 (11.5)	40.3 (10.6)	44.8 (12.3)
	Day 10	...	40.8 (10.5)	...
DCV	Baseline		37.4 (25.0)	
	Day 2	39.3 (40.4)	57.3 (85.7)	67.0 (86.2)
	Day 9	27.9 (18.5)	24.5 (21.1)	27.1 (24.8)
	Day 10	...	26.3 (21.8)	...
BRT** (ms)	Baseline		542.3 (43.9)	
	Day 2	533.3 (70.8)	521.2 (41.1)	538.6 (44.7)
	Day 9	525.2 (43.5)	526.8 (41.0)	538.9 (52.9)
	Day 10	...	527.0 (38.8)	...
Cognitive test	Baseline		3.0 (0.8)	
CPT (d')**	Day 2	3.4 (0.7)	3.4 (0.5)	3.1 (0.8)
	Day 9	3.4 (0.7)	3.6 (0.5)	3.4 (0.7)
	Day 10	...	3.6 (0.6)	...
Subjective measurement	Baseline		2.4 (0.5)	
SSS	Day 2	2.5 (0.7)	3.3 (0.9)	3.8 (1.3)
	Day 9	2.5 (0.6)	2.3 (0.5)	2.6 (0.6)
	Day 10	...	2.5 (0.6)	...

SDLP, standard deviation of lateral position; DCV, distance coefficient of variation; BRT, brake reaction time; CPT, Continuous Performance Test; SSS, Stanford Sleepiness Scale.
Baseline data were assessed once before treatment.
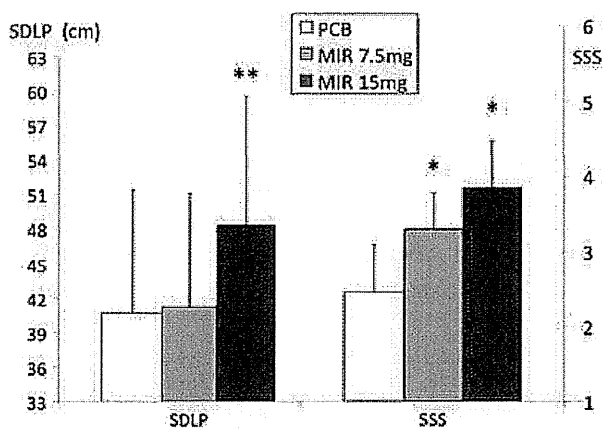*$N = 11$, **$N = 12$,

Figure 2. Mean standard deviation of lateral position (SDLP) (left) and Stanford Sleepiness Scale (SSS) (right) on days 2 of the crossover treatment with mirtazapine (MIR) 7.5 mg, MIR 15 mg, or placebo (PCB). **Post-hoc Bonferroni test demonstrated that SDLP under the MIR 15 mg series was significantly greater than that observed under the MIR 7.5 mg series or PCB series ($p < 0.01$, both). *Post-hoc Bonferroni test demonstrated that SSS in the MIR 7.5 and 15 mg series were significantly greater than that observed in the PCB series ($p < 0.05$, both). All statistics were corrected for baseline values

histamine$_1$ receptor occupancy have been confirmed using positron emission tomography (Tashiro *et al.*, 2009). The same effect may also be applicable to mirtazapine only at single low dose. In fact, the present study showed that SDLP after single dose of mirtazapine 7.5 mg was significantly lower than that of 15 mg and SSS after single dose of mirtazapine 7.5 mg was nonsignificantly lower than that of 15 mg. In addition, this impairing effect of mirtazapine disappeared after repeated dosing because of tolerance (Ramaekers, 2003) as with antihistamines. Moreover, the sensitivity of road-tracking test for histamine$_1$ antagonism may be related to the difference in driving impairment between mirtazapine 7.5 and 15 mg doses. Further studies should investigate the dose-dependene of mirtazapine effects using subjective and objective measures of sedation, including neuroimaging.

Mirtazapine 7.5 mg did not impair road-tracking performance in acute dosing, but significantly increased subjective sleepiness. This discrepancy between objective performance and subjective sedation may be attributable to different level and mechanisms of sedation (Hindmarch, 1998). Wezenberg *et al.* (2007) showed that objective sedation tests helped uncover differences in sedative effects, whereas subjective testing or use of a visual analogue scale could not discriminate between drugs and dosages. In the present study, mirtazapine 7.5 mg may result in less sedation as measured by driving performance than

mirtazapine 15 mg, whereas SSS did not discriminate between sedation with different dosage regimens. Furthermore, evening dose of mirtazapine produced somnolence, but its effect on driving performance was mild in the next day (Ramaekers, 2003). On the contrary, the predictive validity of the alertness for driving performance was low (Verster and Roth, 2012). Thus, the examinations of both objective and subjective measures are important when considering psychotrophics' effects on driving performance.

Previous study examined low-dose effects of esmirtazapine on actual driving (Ramaekers *et al.*, 2011). Esmirtazapine 4.5 mg, unlike 1.5 mg, impaired actual road-tracking performance, and its' acute effect on driving impairment is suggested to be dose-dependent. It is difficult to clearly explain that esmirtazapine 4.5 mg caused significant driving impairment and mirtazapine 7.5 mg did not. Esmirtazapine has approximately the same affinity to histamine$_1$ receptors as mirtazapine and is believed to be responsible for alpha$_2$ heteroreceptor blockade and the 5-HT$_3$ receptor antagonism (de Boer *et al.*, 1988; Kooyman *et al.*, 1994; Haddjeri *et al.*, 1996). This discrepancy in driving impairment cannot be accounted for by the difference in receptor binding profiles. Instead, sample size, sex of subjects (Timmer *et al.*, 2000; Borobia *et al.*, 2009), CYP2D6 genotype (Timmer *et al.*, 2000; Brockmoller *et al.*, 2007; Borobia *et al.*, 2009; Ramaekers *et al.*, 2011), and the sensitivity of driving test may explain the different results. Future study needs to draw a comparison between mirtazapine and esmirtazapine in the same low dose. Meanwhile, dose-dependent influence of mirtazapine may be consistent with that of esmirtazapine at low dosage.

The present study has several limitations. First, participation was restricted to a small number of healthy adult male volunteers. Female, elderly, and depressed patients were not included. Mirtazapine could both impair driving performance (Wingen *et al.*, 2005) and improve driving ability in depressed patients (Brunnauer *et al.*, 2008; Shen *et al.*, 2009). Meanwhile, depressed patients' psychomotor impairments related to driving abilities were influenced by different classes of antidepressants (Brunnauer *et al.*, 2006). Because of many confounding factors such as antidepressant treatment and the depression itself, it is important to examine the effect of antidepressant on driving performance in healthy subject to find the inherent influences of antidepressants for driving impairment. Future study needs to elucidate the impact of same antidepressants in depressed patients in same experimental line and make a comparison with depressed patients. Second, the validity and sensitivity of DS need to be considered. This

DS has not been validated against real car driving; however, our past results using same DS are roughly consistent with preceding results using actual driving test (Iwamoto et al., 2008; Takahashi et al., 2010). In future studies, we are aiming to verify the validity of DS for real car driving in cooperation with Toyota Central R&D Labs to return the results of research to society. Third, we need to evaluate dose–response relationships within the range of up to 30 mg, to clarify the impact of a lower initial dose of mirtazapine on driving performance.

Finally, mirtazapine 7.5 mg did not impair road-tracking performance compared with mirtazapine 15 mg. An initial lower dose of mirtazapine may have less harmful effect on driving performance and be more suitable for some patients as a starting dosage.

CONFLICT OF INTEREST

There is no conflict of interest that is directly relevant to the content of this study.

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