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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

Naoko Kawano,[1,2] Shuichi Awata,[1] Mutsuo Ijuin,[1] Kunihiro Iwamoto[2] and Norio Ozaki[2]

[1]*Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, and* [2]*Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan*

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]

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Correspondence: Ms Naoko Kawano PhD, Department of Psychiatry, Graduate School of Medicine, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
Email: n-kawano@med.nagoya-u.ac.jp

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 converter 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 Disoriders, 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) Sample	Population (Japan)	12 (years) Sample	Population (Japan)	>13 (years) 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.

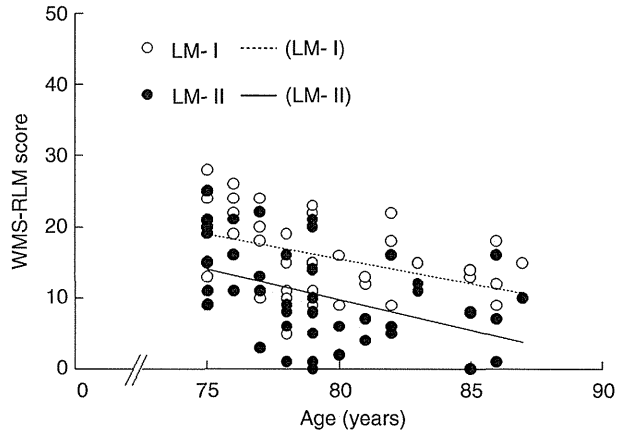

Figure 1 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) subtest scores (y-axis) and age in years (x-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

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 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

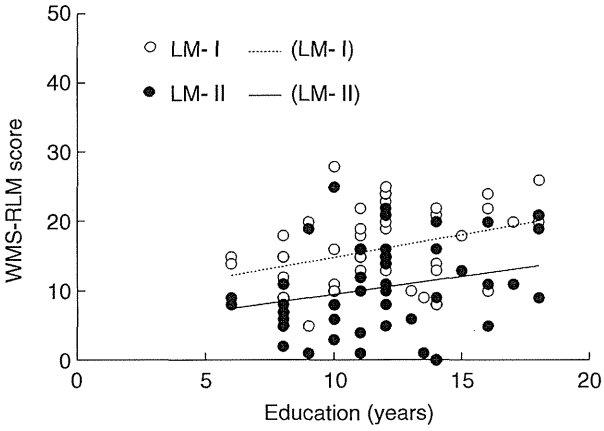

Figure 2 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) scores (*y*-axis) and years of education (*x*-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

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.

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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

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

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

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

*Correspondence to: K. Iwamoto, MD, PhD, Department of Psychiatry, Nagoya University, Graduate School of Medicine, 65 Tsurumai, 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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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.

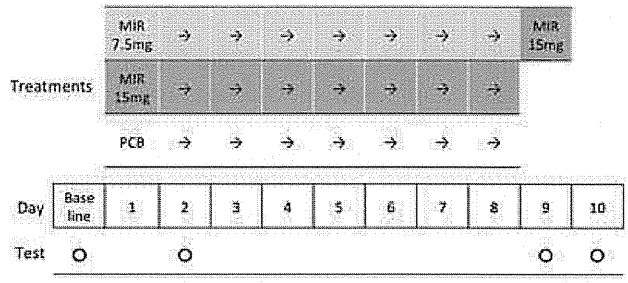

Figure 1. Summary of treatments and schedules in this study. Each subject received nocturnal dosing with mirtazapine (MIR) 7.5 mg, MIR 15 mg, or matched placebo (PCB) for 8 days in a double-blind, crossover design. In the MIR 7.5 mg series, MIR 15 mg was also administered on day 9. A washout period of ≥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

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). 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.
*$N=11$, **$N=12$,

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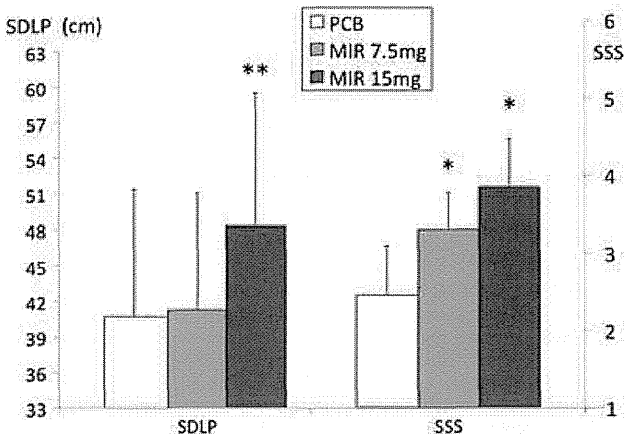

Figure 2. Mean standard deviation of lateral position (SDLP) (left) and Stanford Sleepiness Scale (SSS) (right) on days 2 of the crossover treatment with mirtazapine (MIR) 7.5 mg, MIR 15 mg, or placebo (PCB). **Post-hoc Bonferroni test demonstrated that SDLP under the MIR 15 mg series was significantly 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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SHORT COMMUNICATION

Differential effects of diazepam, tandospirone, and paroxetine on plasma brain-derived neurotrophic factor level under mental stress

Ai Tamaji[1,2], Kunihiro Iwamoto[1]*, Yukiko Kawamura[2], Masahiro Takahashi[3], Kazutoshi Ebe[4], Naoko Kawano[1], Shohko Kunimoto[1], Branko Aleksic[1], Yukihiro Noda[2] and Norio Ozaki[1]

[1]*Department of Psychiatry, Graduate School of Medicine, Nagoya University, Nagoya, Aichi, Japan*
[2]*Division of Clinical Science and Neuropsychopharmacology, Graduate School of Pharmacy, Meijyo University, Nagoya, Aichi, Japan*
[3]*Department of Psychiatry, Graduate School of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan*
[4]*Toyota Central R&D Labs., Inc., Nagakute, Aichi, Japan*

Objectives Serum brain-derived neurotrophic factor (BDNF) levels are reduced in depressed patients, and successful antidepressant treatment leads to increases in BDNF levels. However, little is known about how psychotropic drugs affect the mechanism of the human response to mental stress. We investigated the influence of psychotropic drugs on plasma BDNF levels under mental stress using a driving simulator (DS) task.
Methods Fourteen healthy male volunteers received one of four drugs, diazepam (5 mg), tandospirone (20 mg), paroxetine (10 mg), and matched placebo, in a double-blind, crossover manner. Subjects were asked to perform the DS task 4 h post-dosing. Plasma BDNF levels were measured before and after the DS task.
Results Plasma BDNF levels under the placebo, diazepam, and tandospirone conditions significantly decreased after the DS task compared with before the task. Conversely, no significant differences in plasma BDNF levels were detected under the paroxetine condition.
Conclusion As these three psychotropic drugs have differential effects on plasma BDNF levels under mental stress after 4 h post-dosing, antidepressants, unlike anxiolytics, might have a prompt positive effect on the mental stress response. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—antidepressant; anxiolytic drug; brain-derived neurotrophic factor; mental stress

INTRODUCTION

Stress is common in everyday life and is believed to affect happiness, health, and cognition (Caspi *et al.*, 2003). A role for brain-derived neurotrophic factor (BDNF) in the effects of stress and the response to antidepressant treatment is supported by studies demonstrating opposing regulation of this neurotrophic factor (Charmey, 2004). BDNF, the most abundant neurotrophin in the brain, enhances the growth and maintenance of several neuronal systems and serves as a neurotransmitter modulator (Shimizu *et al.*, 2003). BDNF is present in blood and can pass through the blood–brain barrier carried by a high-capacity, saturable transport system (Pan *et al.*, 1998). Although the source and function of blood BDNF remains unknown, recent reports have shown that more than 99% of blood BDNF proteins are stored in platelets and can be released in serum (Radka *et al.*, 1996) and that blood levels of BDNF might in part reflect BDNF levels in the brain (Karege *et al.*, 2002, Mitoma *et al.*, 2008).

The "neurotrophin hypothesis of depression" is based largely on two observations: a decrease in hippocampal BDNF levels is correlated with stress-induced depressive behavior, and antidepressant treatment enhances the expression of BDNF (Martinowich *et al.*, 2007). Recent studies suggested that serum BDNF levels are reduced in depression (Sen *et al.*, 2008, aan het Rot *et al.*, 2009). Antidepressants are thought to upregulate the expression of BDNF and its receptor and to promote adult neurogenesis, which might be the core pharmacological effect of antidepressants (Martinowich and Lu, 2008); successful antidepressant treatment leads to an increase in plasma BDNF levels (Lee and Kim, 2008).

*Correspondence to: K. Iwamoto, Department of Psychiatry, Nagoya University, Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, 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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Stress can decrease the expression of BDNF in the hippocampus (Duman and Monteggia, 2006). However, little is known about how psychotropic drugs affect the human response to mental stress. In our previous study, we examined the effects of antidepressants and anxiolytic drugs using driving simulator (DS) tasks (Iwamoto *et al.*, 2008, Takahashi *et al.*, 2010). Here, we adapted the DS task as the psychological stressor in order to examine how mental stress influences plasma BDNF levels and to investigate the effect of psychotropic drugs on plasma BDNF levels under mental stress conditions.

MATERIAL AND METHODS

Fourteen healthy male volunteers (32–44 years old, mean ± SD, 37.2 ± 3.6 years) were included. All subjects had had a driving license for at least 10 years and regularly drove a car for a minimum of 5000 km per year. Health interviews and the Structured Clinical Interview for DSM-IV conducted at the time of the study indicated that none of the participants had any physical or psychiatric disorders. The study was approved by the Nagoya University Graduate School of Medicine and Nagoya University Hospital ethics review committee, and written informed consent was obtained from each subject prior to participation.

The schedule of this study is shown in Figure 1. The study was a double-blind, placebo-controlled, crossover study with four periods of treatment, each separated by a washout period of at least 7 days. Each subject was assigned to receive four treatments in a randomized, counterbalanced order set by laboratory personnel, who did not test subjects and analyze results. The random allocation sequence of each subject was concealed until the study termination. During each treatment period, the subjects received a single dose of each of the study drugs: diazepam (5 mg), tandospirone (20 mg), paroxetine (10 mg), and matched placebo. The doses selected were based on general clinical recommendation for starting dose. All treatments were supplied in identical capsules for the double-blind design.

Each subject took one of the four drugs at 11:00 AM. The DS task was conducted 4 h after drug administration when the plasma concentration of paroxetine reaches its maximum (Doyle *et al.*, 1989, Ghose, 1989). Blood samples (10 mL) were collected in anticoagulant tubes before and after the DS task. Blood sample was immediately centrifuged at 1700 g for 10 min, and plasma sample was stored at −30 °C until used. Plasma BDNF levels were determined by enzyme-linked immunosorbent assay (Promega Co., Madison, WI, USA).

The car-following task in the DS task was used as the mental stressor. The details about this simulator (Toyota Central R&D Labs, Inc., Japan) are available elsewhere (Uchiyama *et al.*, 2003, Iwamoto *et al.*, 2008). The weighted average scores [adaptive weighted workload (AWWL)] (Miyake and Kumashiro, 1993) in the abridged Japanese version of the National Aeronautics and Space Administration Task Load Index (NASA-TLX) (Haga and Mizukami, 1996) was used to evaluate the mental stress of the car-following task. Seventeen healthy male volunteers completed the following two mental stress tasks using the DS in random order. One was a standard driving task, which required the subjects to drive the car freely on the road, and another was the car-following task that required the subjects to maintain a constant distance between the cars without the discretion of subjects. The time needed for the completion of both tasks is 5 min. The subjects were asked to rate the NASA-TLX after finishing each task, and the AWWL scores for each condition were calculated for subsequent analysis.

Statistical differences were determined with the paired *t*-test. Significance levels were set to 5% for all tests.

RESULTS

The AWWL scores for the car-following task condition were significantly higher than the normal driving task condition (mean ± SD: 55.2 ± 16.9 vs. 38.2 ± 20.8; $p < 0.01$).

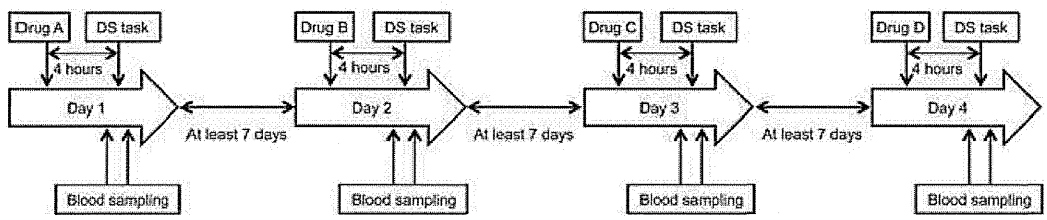

Figure 1. The figure shows the schedule of the study. Days 1, 2, 3, and 4 are treatment periods; each is separated by a washout period of at least 7 days. During each treatment period, the subjects received a single dose of one of the study drugs (drugs A, B, C, and D): diazepam (5 mg), tandospirone (20 mg), paroxetine (10 mg), and matched placebo. Each subject took one of the four drugs at 11:00. The DS task was conducted 4 h after drug administration. Blood samples were collected before and after the DS task

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The effects of psychotropic drugs on plasma BDNF levels before and after the car-following task are shown in Figure 2. Under the placebo condition, plasma BDNF levels after the car-following task were significantly decreased compared with the plasma BDNF levels before the task (mean ± SD: 0.64 ± 0.31 vs. 0.34 ± 0.21, $p < 0.01$). We also found that under the diazepam and tandospirone conditions, plasma BDNF levels after the car-following task were significantly decreased compared with plasma BDNF levels observed before the task (mean ± SD: 0.49 ± 0.23 vs. 0.34 ± 0.21, $p < 0.05$ and mean ± SD: 0.59 ± 0.36 vs. 0.31 ± 0.14, $p < 0.01$, respectively). Conversely, these changes were not observed under the paroxetine condition (mean ± SD: 0.57 ± 0.27 vs. 0.79 ± 0.63, $p = 0.19$).

DISCUSSION

From the AWWL scores, we considered the car-following task as a mental stress condition. In the present study, we investigated the effect of psychotropic drugs on plasma BDNF levels under mental stress using a DS task as the stressor. Although the task associated with increased mental stress significantly decreased plasma BDNF levels under the diazepam, tandospirone, and placebo condition, the same effect was not observed under the paroxetine condition.

Regarding psychological stress, a previous study of healthy subjects demonstrated that levels of perceived mental stress in the workplace were inversely correlated with serum BDNF levels (Mitoma *et al.*, 2008). Both acute and chronic mental stress may reduce serum BDNF levels. According to these findings, mental stress might negatively affect stress-vulnerable depressed patients in whom serum BDNF levels are already decreased.

A previous report indicated that antidepressants could enhance BDNF gene expression by activating cyclic adenosine monophosphate response element binding protein (Martinowich and Lu, 2008). Furthermore, a recent study showed that antidepressants directly promote BDNF release from platelets in rats (Watanabe *et al.*, 2010). Considering that plasma BDNF levels did not significantly decrease under mental stress following acute administration of paroxetine in our result, paroxetine might promote short-term (several minutes) BDNF release from platelets in human models, although further examination would be needed.

Although anxiolytic drugs such as diazepam and tandospirone can relieve stress-related symptoms, there are no reports indicating that anxiolytic drugs influence plasma BDNF levels. One study showed that stimulation of the gamma-aminobutyric acid system (i.e., diazepam) in adult Wistar rats results in an immediate decrease in hippocampal BDNF mRNA levels (Zafra *et al.*, 1991). To our knowledge, the effects of diazepam on plasma BDNF levels have not been examined in humans. The present results suggest that benzodiazepine had no influence on plasma BDNF

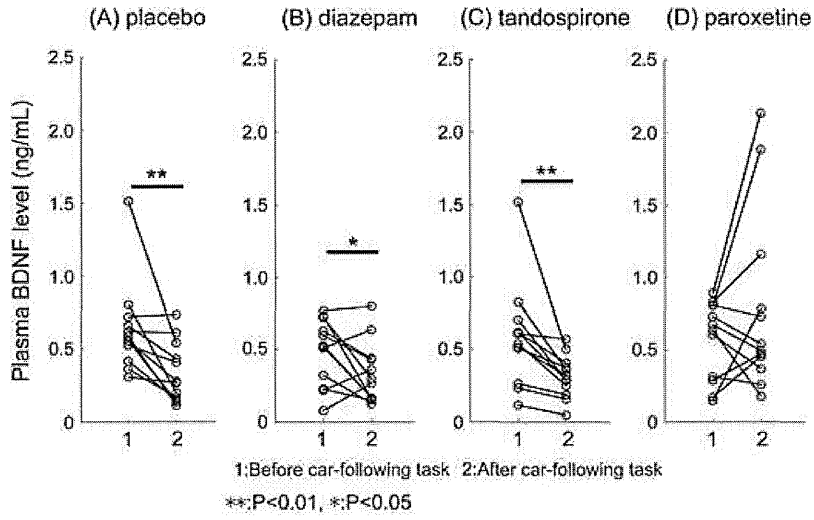

Figure 2. The effects of psychotropic drugs on plasma BDNF levels before and after the car-following task. Panel (A) shows the change in plasma BDNF levels during the placebo condition. Plasma BDNF levels after the car-following task are significantly decreased compared with levels before the task (p 0.01). Panels (B) and (C) show plasma BDNF levels following diazepam and tandospirone conditions. Plasma BDNF levels are significantly decreased after the car-following task compared with levels before ($p < 0.05$ and $p < 0.01$, respectively). Panel (D) shows plasma BDNF levels under the paroxetine condition. There is no significant difference in plasma BDNF levels before and after the car-following task ($p = 0.19$)

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levels immediately following stress. In terms of the "neurotrophin hypothesis of depression," antidepressants, but not anxiolytic drugs, can ameliorate the symptoms of depression and prevent stress-related recurrence of depression.

The present study has several limitations. First, the sample was restricted to a small number of healthy adult male volunteers. It is possible that the responses to mental stress in female, depressed, or elderly patients could differ widely from those of healthy, younger men. Second, the present study evaluated only the immediate effects of low-dose administration of the drugs on plasma BDNF levels. Third, a 5-min simulator task may be inadequate for assessing mental stress. Although AWWL scores showed that this task induced mental stress, there is a possibility of a type 1 error because of the small sample size. Therefore, future studies using a larger number of subjects with repeated drug administration over a range of doses need to be conducted for conclusions to be drawn regarding the effects on plasma BDNF level. From the AWWL score, we regarded the car-following task as a mental stress condition, although there is no significant difference in plasma cortisol levels before and after the car-following task (data not shown). Then it is necessary to examine how the duration of the DS task influences plasma BDNF levels in more detail. Fourth, the degree of stress associated with the DS task needs to be examined by measuring changes in other stress-related variables (e.g., heartbeat and skin electrical resistance). Fifth, we did not examine plasma BDNF level change at 4 h post-dosing without DS task to elucidate whether drug treatments without DS task could affect plasma BDNF levels. Finally, we evaluated only 4-h time point for DS task when plasma concentration of paroxetine reaches its maximum. Because three drugs have different pharmacokinetic and pharmacodynamic profiles, we need to examine plasma BDNF level change at a time when plasma concentrations of diazepam and tandospirone reach their maximum in future study.

Our findings should be interpreted with following caveat. The treatments for depression, such as antidepressants (Shimizu *et al.*, 2003), electroconvulsive therapy (Okamoto *et al.*, 2008), and sleep deprivation (Gorgulu and Caliyurt, 2009) increase expression of BDNF. Although this is suggesting that there is an etiological link between the development of depression and BDNF, scientific studies have found that numerous brain areas show altered activity in depressed patients (Krishnan and Nestler, 2008), and it has not been possible to determine a single cause of depression.

In conclusion, diazepam, tandospirone, and paroxetine could have different effects on plasma BDNF levels under mental stress after 4 h post-dosing. Furthermore, antidepressants, unlike anxiolytics, might have immediate positive effects on the mental stress response.

CONFLICT OF INTEREST

None declared.

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Sexual dysfunction and hyperprolactinemia in Japanese schizophrenic patients taking antipsychotics

Tsutomu Kikuchi [a,b], Kunihiro Iwamoto [a,*], Kazumi Sasada [a], Branko Aleksic [a], Keizo Yoshida [a,c], Norio Ozaki [a]

[a] Department of Psychiatry, Nagoya University, Graduate School of Medicine, Japan
[b] Department of Psychiatry, Matsuzaki Hospital, Japan
[c] Health Care Promotion Department, DENSO Corporation, Japan

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ABSTRACT

This study aimed to estimate the prevalence of sexual dysfunction, evaluated by the Nagoya Sexual Function Questionnaire (NSFQ), and hyperprolactinemia in patients with schizophrenia and examine a relationship between sexual dysfunction and serum prolactin levels. This cross-sectional, comparative study was performed using a sample comprising 195 Japanese schizophrenic in- and outpatients treated with antipsychotics (117 males and 78 females). Data were collected from October 2009 to January 2010 using single, cross-sectional ratings of sexual function assessed by the NSFQ and concurrent measurement of serum prolactin levels. The prevalence of sexual dysfunction in patients with schizophrenia was high (males 66.7%; females 79.5%). Hyperprolactinemia (>25 ng/ml) was highly prevalent among schizophrenia patients, affecting 53.8% of females and 51.3% of males. Among female patients, 16.7% had prolactin levels>100 ng/ml. There was no relationship between sexual dysfunction and serum prolactin levels. The present study demonstrated a higher prevalence of sexual dysfunction and hyperprolactinemia in Japanese schizophrenia patients. Clinicians should keep these problems in mind and discuss potential solutions with patients to improve patients' quality of life and adherence to therapy.

1. Introduction

Despite evidence showing that sexual dysfunction is common in patients with schizophrenia (Cutler, 2003; Ghadirian et al., 1982; Kotin et al., 1976; Smith et al., 2002), physicians tend to overlook or disregard sexual dysfunction during the psychiatric evaluation of schizophrenic patients. For example, approximately 50–70% of male schizophrenic patients and 30–50% of female schizophrenic patients have sexual dysfunction (Fakhoury et al., 2001; Ghadirian et al., 1982). Sexual disturbances in such patients may be due to various factors, including the symptoms of schizophrenia (Aizenberg et al., 1995), secondary effects of living with a severe, chronic mental health condition, or adverse effects of antipsychotics or other medications (Smith et al., 2002). In particular, drugs that raise prolactin levels, such as risperidone, are associated with significantly higher rates of sexual problems (40–60%) compared with prolactin-sparing drugs (e.g., quetiapine, ziprasidone, and aripiprazol) (<30%) (Knegtering et al., 2004; Knegtering et al., 2006; Montejo Gonzalez et al., 2005; Montejo and Rico-Villademoros, 2008a; Montejo et al., 2010a, 2010b; Serretti and Chiesa, 2011).

The studies mentioned above present data about sexual dysfunction among patients with schizophrenia in Western countries. Conversely, there are few studies in Asian populations, including Japanese patients (Fujii et al., 2010). The prevalence of sexual concerns differs in healthy individuals according to their ethnicity. However, the accurate estimation of prevalence is complicated by the reluctance of psychiatric staff (i.e., psychiatrists and nurses) to discuss sexual concerns with patients (Withersty, 1976; Wolfe and Menninger, 1973). These problems are more pronounced in Far Eastern countries, perhaps due to socio-cultural reasons (Moreira et al., 2005, 2006). From a clinical point of view, it is important to be aware of sexual dysfunction in patients with schizophrenia and apply the knowledge of sexual dysfunction to the treatment of schizophrenia, because this symptomatology is relatively common among patients and may contribute to poor quality of life (QOL) and poor adherence with therapy (Gopalakrishnan et al., 2006; Olfson et al., 2005).

In Western countries, several instruments are used to assess sexual dysfunction, including the Arizona Sexual Experience Scale (ASEX)

Abbreviations: ASEX, Arizona Sexual Experience Scale; CLIA, chemiluminescence immunoassay; CP, chlorpromazine; CSFQ, Changes in Sexual Functioning Questionnaire; NSFQ, Nagoya Sexual Function Questionnaire; PRSexDQ-SALSEX, Psychometric Properties of the Psychotropic-Related Sexual Dysfunction Questionnaire; QOL, Quality Of Life; UKU, Udvalg for Kliniske Undersogekser Side Effect Rating Scale.

* Corresponding author at: Department of Psychiatry, Nagoya University, Graduate School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8550, Japan. Tel.: +81 52 744 2282; fax: +81 52 744 2293.
E-mail address: iwamoto@med.nagoya-u.ac.jp (K. Iwamoto).

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(McGahuey et al., 2000), the sexual part of Udvalg for Kliniske Undersogekser Side Effect Rating Scale (UKU) (Lingjaerde et al., 1987), Psychometric Properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) (Montejo and Rico-Villademoros, 2008b; Montejo et al., 2000), and the Changes in Sexual Functioning questionnaire (CSFQ) (Clayton et al., 1997). Although most instruments are useful (in particular, SALSEX is very brief, user-friendly, and reliable), some of them are rather long (CSFQ has 36 items for men and 35 items for women). In addition, the contents of ASEX, UKU, and PRSexDQ-SALSEX include vaginal dryness, vaginal lubrication, and orgasmic dysfunction, which may be intrusive for *patients and clinicians who feel embarrassed to talk about sexual concerns directly (Asian people in particular)*, and difficult to use (UKU involves a semi-structured interview). Therefore, it may not be easy to use these instruments among schizophrenic patients who are reluctant to discuss their sexual concerns, a topic that is sometimes considered taboo not only in Asian but also in Western countries. To address this problem, we recently developed and validated a short, minimally intrusive, and self-administered instrument called the Nagoya Sexual Function Questionnaire (NSFQ) (Kikuchi, et al., 2011).

From a pharmacological point of view, side effects of antipsychotics characterized by sexual dysfunction are related to hyperprolactinemia (Haddad and Wieck, 2004). More than 50% of schizophrenic patients treated with a prolactin-raising antipsychotic drugs experience hyperprolactinemia (Haddad and Wieck, 2004). Psychiatric staff tend to disregard symptoms of hyperprolactinemia that involve sexual dysfunction (loss of/decreased libido, erectile dysfunction [men], gynecomastia [men], amenorrhoea/oligomenorrhoea [women]), because clinical signs are subtle or even if the symptoms of hyperprolactinemia become obvious, patients and professionals are embarrassed to discuss them (Haddad and Wieck, 2004). Moreover, it is unclear to what extent sexual dysfunction is due to a direct effect of increased prolactin levels (Haddad and Wieck, 2004). Additionally, sexual dysfunction in Asian schizophrenic patients is a topic that has not been fully investigated due to the socio-cultural reasons stated above.

Considering the lack of the studies conducted in a Japanese population, and the implication for therapeutic intervention, our study aimed to estimate the prevalence of sexual dysfunction obtained from the measurement of NSFQ and hyperprolactinemia in Japanese schizophrenic patients and examine the relationship between sexual dysfunction and serum prolactin levels.

2. Methods

The present study was a cross-sectional, comparative trial. Data were collected from October 2009 to January 2010 using a single, cross-sectional rating of sexual function assessed by the NSFQ. Concurrently, measurement of serum prolactin levels was performed. Subjects were returning outpatients and inpatients with a diagnosis of schizophrenic disorder according to DSM-IV criteria. All patients had been stabilized on antipsychotic medication for more than 8 weeks. Patients were excluded if they had a general medical condition or a history of a surgical procedure known to cause sexual dysfunction. Psychotropic medications such as benzodiazepines, anticholinergics, antidepressants, and mood stabilizers were allowed if the patients were already receiving these medications prior to study enrollment. However, in this research, no patient was receiving antidepressants.

After obtaining demographic and medication/treatment information, an introductory presentation was made, during which the nature of the study was explained to the patients, and written informed consent was obtained from patients willing to participate. The study was approved by the Ethics Committee of the Nagoya University School of Medicine.

The NSFQ is a self-administered sexual function scale (Kikuchi, et al., 2011). The NSFQ was developed through the collaborative effort of specialists in psychiatry and urology. The NSFQ consists of seven items. Each item is evaluated on a six-point scale: (1) not at all; (2) almost never; (3) sometimes; (4) often; (5) always; and (6) unsure. The answers of (1) through (5) are assigned scores of 1 to 5 points, respectively, and (6) is assigned 1 point; total scores range from 5 to 35. The items for men are: 1) pulsating sensation in the breast/mammary area; 2) galactorrhea; 3) interest in women; 4) sexual interest; 5) sexual self-confidence; 6) erectile dysfunction; and 7) ejaculatory dysfunction. The items for women are: 1) menstrual irregularity; 2) pulsating sensation in the breast/mammary area; 3) galactorrhea; 4) interest in men; 5) sexual interest; 6) sexual self-confidence; and 7) sexual arousal. Subjects were asked to answer questions 6 and 7 if they gave scores of (2)–(5) for questions 1–5. To estimate the potential prevalence of sexual dysfunction, subjects with a score of 3 or higher on any relevant items in the NSFQ were considered to have sexual side effects. Subjects with a score of 3, 4, or 5 on each of the relevant items were considered to have mild, moderate, or severe sexual side effects, respectively. The prevalence of total sexual dysfunction was calculated by the following equation: the number of patients with a score of 3 or higher on any of the NSFQ items was divided by the total number of patients regardless of sexual dysfunction. Data for menstrual irregularity were recorded only for female subjects younger than 45 years. Prolactin levels were determined by chemiluminescence immunoassay (CLIA) (Siemens, Munich, Bayern, Germany). Blood was drawn for prolactin levels from 9:30 a.m. to 10:30 a.m. In this study, normal prolactin levels for female and male patients were $\leq$25 ng/ml and $\leq$20 ng/ml, respectively. All analyses were performed using JMP version 5.1.2 (SAS Institute, Inc., Cary, NC). The student *t*-test was used to compare: (1) mean prolactin levels between patients with and without sexual dysfunction, and (2) mean total score of the NSFQ and prolactin levels between men and women. We performed one-way factorial analysis of variance and multiple comparison tests (Tukey's Honestly Significant Difference test) to compare mean total NSFQ scores of among stratified prolactin levels (male: 0–20 ng/ml, 20–50 ng/ml, 50–100 ng/ml, female: 0–25 ng/ml, 25–50 ng/ml, 50–100 ng/ml, 100–150 ng/ml, 150–200 ng/ml), and mean total NSFQ scores and prolactin levels among groups receiving aripiprazole, olanzapine, risperidone, and polytherapy. The chi square test was used to test for differences between the frequency of total sexual dysfunction between men and women, and among groups receiving aripiprazole, olanzapine, risperidone, and polytherapy in men and women. We performed multiple regression analysis with the total NSFQ score as the dependent variable and prolactin level, age, sex, duration of illness, duration of treatment, number of antipsychotics, and dose of antipsychotics (chlorpromazine [CP] equivalent) as independent variables. A p value$<$0.05 was considered statistically significant.

3. Results

3.1. Characteristic of patients

Clinically relevant patient characteristics are presented in Table 1. Patients were divided into monotherapy groups receiving a single antipsychotic of risperidone, olanzapine, aripiprazole, or others, and the polytherapy group. The mean CP equivalent doses of antipsychotics and concomitant drugs (benzodiazepines and anticholinergics) in each group are shown in Table 1.

3.2. Prevalence of sexual dysfunction

Prevalence of sexual dysfunction is shown in Table 2. We observed gender-specific differences in the prevalence of sexual dysfunction. Specifically, the prevalence of moderate and severe sexual dysfunction in female patients was significantly higher than in male patients (chi square 6.633 p = 0.01).

Table 1
Characteristic of patients.

	Males	Females
N	117	78
Age (years)	43.9 ± 12.7	45.9 ± 12.1
Duration of illness (months)	247.2 ± 194.0	231.5 ± 162.9
Treatment of illness (months)	226.5 ± 187.2	199.9 ± 164.2
Dose of antipsychotics (mg/day)[a]	629.7 ± 406.7	595.4 ± 379.5
Dose of concomitant benzodiazepines (mg/day)[b]	7.0 ± 11.8	1.0 ± 1.9
Dose of concomitant anticholinergics (mg/day)[c]	1.2 ± 1.7	0.6 ± 1.8
Drug group		
Risperidone only		
N	42	27
Dose of risperidone (mg/day)[a]	539.5 ± 288.4	570 ± 349.5
Dose of concomitant benzodiazepines (mg/day)[b]	1.6 ± 3.1	1.6 ± 2.2
Dose of concomitant anticholinergics (mg/day)[c]	1.6 ± 1.8	0.7 ± 2.1
Olanzapine only		
N	15	9
Dose of olanzapine (mg/day)[a]	507.1 ± 233.5	722.2 ± 120.1
Dose of concomitant benzodiazepines (mg/day)[b]	3.3 ± 4.7	0.8 ± 2.1
Dose of concomitant anticholinergics (mg/day)[c]	0.2 ± 0.8	0
Aripiprazole only		
N	14	17
Dose of aripiprazole (mg/day)[a]	344.6 ± 297.8	411.8 ± 228.1
Dose of concomitant benzodiazepines (mg/day)[b]	8.6 ± 17.8	0.5 ± 1.0
Dose of concomitant anticholinergics (mg/day)[c]	0	0.4 ± 1.2
Other drugs (as monotherapy)		
N	3	7
Dose of antipsychotics (mg/day)[a]	165.5 ± 92.6	218.5 ± 107.6
Dose of concomitant benzodiazepines (mg/day)[b]	3.4 ± 4.7	0
Dose of concomitant anticholinergics (mg/day)[c]	0	3.1 ± 4.4
Polytherapy		
N	45	18
Numbers of antipsychotics	2.5 ± 0.7	2.44 ± 0.8
Dose of antipsychotics (mg/day)[a]	878.1 ± 464.9	889.4 ± 461.0
Dose of concomitant benzodiazepines (mg/day)[b]	9.1 ± 11.1	1.0 ± 1.0
Dose of concomitant anticholinergics (mg/day)[c]	0.21 ± 0.8	0

Values are mean ± SD unless otherwise noted.
[a] Chlorpromazine-equivalent dose.
[b] Diazepam-equivalent dose.
[c] Biperiden-equivalent dose.

The most prevalent symptom of male sexual dysfunction was lack of sexual self-confidence in both the moderate and severe groups, whereas the most prevalent symptom of female sexual dysfunction was menstrual irregularity in the moderate group and lack of sexual interest in the severe group.

3.3. Total NSFQ score and serum concentrations of prolactin

The total NSFQ score and serum concentrations of prolactin are shown in Table 3. Results showed that hyperprolactinemia was highly prevalent among schizophrenia patients (males, 51.3%; females, 53.8%). Moreover, 16.7% of female patients showed extremely high concentrations of prolactin (>100 ng/ml). The mean prolactin level in female patients (45.3 ± 46.7 ng/ml) was significantly higher than in male patients (21.5 ± 16.7 ng/ml) ($t=5.0357$, $p<0.001$), but there was no significant difference between male patients (12.7 ± 5.5) and female patients (14.0 ± 5.1) in mean total NSFQ score ($t=1.6743$, $p=0.0957$). There were no significant differences in total NSFQ score among stratified prolactin levels in male patients ($F=1.219$ $df=116$, $p=0.299$) and female patients ($F=0.486$, $df=77$, $p=0.746$). Similar values of total NSFQ scores were observed in all stratified levels of prolactin.

3.4. Antipsychotic effect

Total NSFQ score, the frequency of total sexual dysfunction, and prolactin level of each antipsychotic treatment group are summarized by gender in Table 4. There were significant differences in the prolactin levels among the antipsychotic groups receiving aripiprazole, olanzapine, polytherapy, and risperidone in males ($F=13.251$, $df=114$, $p<0.001$; aripiprazole<polytherapy, $p<0.001$; aripiprazole<risperidone, $p<0.001$; olanzapine<polytherapy, $p=0.026$; olanzapine<risperidone, $p<0.001$) and females ($F=14.107$, $df=70$, $p<0.001$; aripiprazole<polytherapy, $p<0.01$; aripiprazole<risperidone, $p<0.001$; olanzapine<risperidone, $p<0.01$). As a whole, prolactin levels became higher in the following order: aripiprazole, olanzapine, polytherapy, and risperidone. However, the total NSFQ scores were not significantly different among the groups receiving aripiprazole, olanzapine polytherapy, and risperidone in males ($F=0.075$, $df=114$, $p=0.973$) and females ($F=1.537$, $df=70$, $p=0.213$). There was no significant difference in the frequency of total sexual dysfunction among groups receiving aripiprazole, olanzapine polytherapy, and risperidone (males, from mild to severe, chi square 1.5508 $p=0.82$; moderate and severe, chi square 4.3366 $p=0.36$; females, from mild to severe, chi square 9.0318 $p=0.06$; moderate and severe, chi square 7.6454 $p=0.11$). The frequency of total sexual dysfunction (from mild to severe) becomes higher in the following order: risperidone (64.3%), polytherapy (64.4%), olanzapine (66.7%), and aripiprazole (78.6%) in males, and olanzapine (55.6%), aripiprazole (82.4%), polytherapy (83.3%), and risperidone (92.6%) in females. Moderate and severe total sexual dysfunction becomes higher in the following order: polytherapy (33.3%), aripiprazole (35.7%), risperidone (45.2%), and olanzapine (53.3%) in males, and olanzapine (33.3%), aripiprazole (58.8%), risperidone (66.7%), and polytherapy (72.2%) in females.

3.5. Multiple regression analysis

We performed multiple regression analysis with total NSFQ score as the dependent variable and prolactin level, age, sex, duration of illness, duration of treatment, number of antipsychotics, and dose of antipsychotics (CP equivalent) as independent variables; however, no statistically significant correlations were found (R 0.2126, $p=0.2698$). No significant differences in mean prolactin levels were observed between the group with and without sexual dysfunction in males (prolactin level: 22.0 ± 17.0 in the group with sexual dysfunction, 20.6 ± 16.1 in the group without sexual dysfunction, $t=0.4245$, $p=0.6720$) and females (prolactin level: 50.0 ± 48.0 in the group with sexual dysfunction, 27.1 ± 37.1 in the group without sexual dysfunction, $t=1.7694$, $p=0.0808$).

4. Discussion

This study surveyed sexual dysfunction using a self-administered sexual functional scale, the NSFQ, and showed that sexual dysfunction is highly prevalent among Japanese patients suffering from schizophrenia. Our study revealed that patients' sexual dysfunction extended over multiple domains that were evaluated by different items of the NSFQ.

According to previous studies (Cutler, 2003; Ghadirian et al., 1982), the rate of sexual dysfunction was reported to be lower in female patients with schizophrenia than males with schizophrenia. However, Fujii et al. (2010) reported that sexual dysfunction in males is similar to that in females, and their results were consistent with our findings. As Fujii et al. noted, this tendency could be influenced by menstrual irregularities that are classified as sexual dysfunction. However, if menstrual irregularities (48.6%) were excluded from our dataset, the prevalence of sexual dysfunction in females did not change significantly (from 79.5% to 70.5%). The reason for the difference between the current study and prior research is that NSFQ reveals not only symptoms of sexual dysfunction that are obvious, such as menstrual irregularities, but also symptoms of sexual dysfunction that women are reluctant to discuss and therefore can be easily overlooked by medical professionals.

Table 2
Prevalence of sexual dysfunction in males and females.

Gender	Category	≥3 (from mild to severe) n (%)	≤3 n (%)	≥4 (moderate and severe) n (%)	≥4 n (%)
Males	Total sexual dysfunction	78 (66.7)	39 (33.3)	47 (40.2)	70 (59.8)
	Pulsating sensation in the breast/mammary area	12 (10.3)	–	6 (5.1)	–
	Galactorrhea	2 (1.7)	–	0 (0)	–
	Interest in women	46 (39.3)	–	19 (16.2)	–
	Sexual interest	48 (41)	–	18 (15.4)	–
	Sexual self-confidence	53 (45.3)	–	25 (21.4)	–
	Erectile dysfunction	33 (28.2)	–	14 (12.0)	–
	Ejaculatory dysfunction	33 (28.2)	–	17 (14.5)	–
Females	Total sexual dysfunction	62 (79.5)	16 (20.5)	46 (59.0)	32 (41.0)
	Menstrual irregularity	17/35 (48.6)	–	7/35 (20)	–
	Pulsating sensation in the breast/mammary area	21 (26.9)	–	6 (7.7)	–
	Galactorrhea	6 (7.7)	–	3 (3.8)	–
	Interest in men	33 (42.3)	–	13 (16.7)	–
	Sexual interest	36 (46.2)	–	19 (24.4)	–
	Sexual self-confidence	26 (33.3)	–	13 (16.7)	–
	Sexual arousal	18 (23.1)	–	12 (15.4)	–

The prevalence of slight to severe and moderate to severe sexual dysfunction in females was significantly higher than that in males (mild and severe sexual dysfunction, chi square 3.900 $p = 0.0483$; moderate and severe sexual dysfunction, chi square 6.662 $p = 0.0098$).

Our results also showed that hyperprolactinemia was highly prevalent among schizophrenia patients, and mean prolactin levels were significantly higher in female patients than in male patients. In particular, 16.7% of female patients showed extremely high concentrations of prolactin (>100 ng/ml). Prior cross-sectional studies estimating the prevalence of hyperprolactinemia in schizophrenia patients treated with conventional antipsychotics or risperidone reported that approximately 60% of women and 40% of men had hyperprolactinemia (Haddad and Wieck, 2004; Halbreich, et al., 2003; Smith et al., 2002), with mean prolactin levels in women of 62.7 ng/ml and those in men of 32.4 ng/ml (Halbreich et al., 2003). Moreover, prior cross-sectional studies estimating the prevalence of hyperprolactinemia in schizophrenia patients treated with atypical antipsychotics (olanzapine, 29 patients; clozapine, 28 patients; risperidone, 19 patients) showed that 42% of women and 21% of men had hyperprolactinemia (Melkersson, 2005). In our study, many patients were treated with conventional antipsychotics or risperidone (men, 74.4%; women; 57.7%), so the results of this study were similar to previous studies in patients treated with conventional antipsychotics or risperidone.

Hyperprolactinemia can lead to various adverse hormonal effects, including sexual dysfunction, gynecomastia, amenorrhea, and galactorrhea (Cutler, 2003; Smith et al., 2002), and evidence from both medical and psychiatric populations supports an association between hyperprolactinemia and sexual dysfunction. However, it is still not clear to what extent sexual dysfunction is influenced directly by hyperprolactinemia (Haddad and Wieck, 2004). Several studies reported a relation between sexual dysfunction and prolactin levels (Arató et al., 1979; Bruke et al., 1994; Ghadirian et al., 1982; Smith et al., 2002). However, other studies, including the current findings, have failed to support an association between hyperprolactinemia and sexual dysfunction (Hamner, 2002; Kleinberg et al., 1999; Spollen et al., 2004). Several issues may explain these conflicting results. First, libido and orgasm are related to dopaminergic neuronal circuits, so dopamine blockade by antipsychotics may have an impact on libido and orgasm (Giuliano and Allard, 2001). Second, the secondary effects of prolactin elevation, that is, reduction of plasma levels of testosterone, estrogen, luteinizing hormone, or follicle-stimulating hormone, could lead to sexual side effects (Rinieris et al., 1989;

Table 3
Total NSFQ score and prolactin levels (ng/ml) in males and females.

Gender	Mean prolactin level (ng/ml)		Mean total NSFQ score		Stratified prolactin level (ng/ml)	n (%)	Mean total NSFQ score
		a		b			c
Males	21.5 ± 16.7		12.7 ± 5.5		0 - 20	57 (48.7)	11.9 ± 4.9
							13.4 ± 6.1
					20 - 50	55 (47.0)	
					50 - 100	5 (4.3)	14.4 ± 4.5
							d
					0 - 25	36 (46.2)	13.5 ± 6.2
					25 - 50	15 (19.2)	15.3 ± 3.1
Females	45.3 ± 46.7				50 - 100	14 (17.9)	14.1 ± 3.5
			14.0 ± 5.1				
					100 - 150	11 (14.1)	13.5 ± 5.3
					150 - 200	2 (2.6)	16.5 ± 0.7

In addition to the mean total score of NSFQ and prolactin levels (ng/ml) in males and females, the mean total NSFQ scores corresponding to stratified prolactin levels are presented. The mean prolactin level in females was significantly higher than in males ($^{a}t = 5.0357$, $p < 0.001$), but there was no significant difference in mean total NSFQ score between males and females ($^{b}t = 1.6743$, $p = 0.0957$). There were no significant differences in total NSFQ scores among stratified prolactin levels in males ($^{c}F = 1.219$ $df = 116$, $p = 0.299$) and females ($^{d}F = 0.486$, $df = 77$, $p = 0.746$).