Differential clinical effects of fluvoxamine by the effect of age in Japanese female major depressive patients

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Abstract: The effects of gender differences and age on the treatment response to fluvoxamine were investigated in major depressive Japanese patients. A total of 100 Japanese patients participated in this study. The daily dose of fluvoxamine was fixed to 100, 150 or 200 mg in the fourth week. This fixed dose was maintained until the end of the 6-week study. The patients were divided into 3 groups: younger females, older females, and males. Depressive symptoms were evaluated using the Montgomery and Åsberg Depression Rating Scale (MADRS) at pretreatment and at 1, 2, 4, and 6 weeks after the commencement of the study. Seven of the 100 patients were excluded, and the remaining 93 patients constituted the subjects (50 females, 43 males). The number of intent-to-treat responders and non-responders was 55 and 38, respectively. There was a significant difference in the changes in the time course of the MADRS score and changes in the MADRS scores at each evaluation point between the younger and older females. Younger females demonstrated a significantly better response than older females. The results suggest that fluvoxamine is more effective in younger female patients than in older female patients.

Keywords: major depressive disorder, fluvoxamine, antidepressant response, menopausal status

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs for the treatment of depression because their efficacy is similar to that of tricyclic antidepressants (TCAs); further, they have an advantage over TCAs for tolerability.[1] Despite differences in structure and activity, SSRIs, including fluvoxamine, share several common features, and there is no evidence for the superior efficacy of one agent over another. In a review of double-blind comparative studies of fluvoxamine vs imipramine for treating major depressive patients, no difference was indicated in 12 trials, while fluvoxamine was found to be the superior antidepressant in 2 trials.[2]

Depression occurs more often in women than in men, and differences are also observed between men and women in terms of the clinical features of depression and response to treatments.[3] Kornstein et al[4] suggested that women had an advantage in terms of the response rate to sertraline, while men had a higher response rate to imipramine. In this study, the responder analysis at the end point by menopausal status demonstrated that premenopausal women were significantly more likely to respond to sertraline than imipramine, whereas the response rates to sertraline and imipramine of postmenopausal women were similar. However, Hildebrandt et al[5] demonstrated similar clinical effects with antidepressant (clomipramine vs citalopram, paroxetine, and moclobemide) treatment for male and female patients with major and predominantly melancholic depression. There was also no gender difference in treatment response to sertraline in 6-month treatment of depression.[6]

In Japanese depressive patients, there was no significant difference in treatment response to fluvoxamine and paroxetine between males and females;[7] however, we

recently revealed that fluvoxamine was more effective in younger female patients than in older female and male patients in a preliminary report dealing with 66 patients. A major limitation of this study was the small number of patients, particularly the number of younger females.[8] Therefore, we recruited new patients in order to increase the total number of patients to 100. In the present study, we re-analyzed the effects of gender differences and age on the treatment response to fluvoxamine in 100 major depressive patients.

Method

Subjects

This study included a total of 100 Japanese patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for the diagnosis of a major depressive disorder and whose Montgomery and Åsberg Depression Rating Scale (MADRS)[9] scores at pretreatment were 21 or higher. Patients suffering from other axis I disorders (such as dementia, substance abuse, dysthymia, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder) and those with axis II disorders as determined by a clinical interview were excluded from the study. Patients with a past history of childhood disorders, and those with severe non-psychiatric medical disorders were also excluded. The subjects were patients aged between 20 and 69 years who had not used any psychotropic drug for at least 14 days before participating in the study. Informed consent was obtained from the subjects after providing them with a complete description of the study. Our study was performed in psychiatric units of general hospitals. Well trained psychiatrists made diagnoses and provided antidepressant treatment for the patients.

Treatment

The same dose of fluvoxamine was administered twice daily, after dinner and at bedtime, for 6 weeks. The initial daily dose was 50 mg, which was increased to 100 mg after 1 week. After another week, the dose was set to 100, 150, or 200 mg, depending on the clinical judgment of the treating psychiatrists; this fixed dose was maintained until the end of the study. Patients with insomnia were prescribed 0.25 or 0.5 mg of brotizolam, a benzodiazepine sedative hypnotic, at bedtime. No other psychotropic drugs were permitted during the study.

Data collection

The patients were divided into 3 groups: females aged <44 years, females aged ≥ 44 years, and males. For the female patients, we set the cut-off point at 44 years of age because females aged <44 years have a high potential for the intact gonadotropin-releasing hormone (GnRH) pulse pattern and functioning ovulation cycle.[10] The normal pattern of pulsatile GnRH secretion changes during the early 40s as a consequence of irregularity in hypothalamic pacemaker function; therefore, both phases of the ovarian cycle are affected during the perimenopausal period.[11,12] Several endocrine changes precede clinical menopause, such as changes in the pattern of pulsatile GnRH secretion;[11] therefore, we used 44 years as the cut-off point to distinguish the fertile period from the peri-/postmenopausal periods. The severity of the depressive symptoms was assessed using MADRS. Assessments were conducted at the baseline and at 1, 2, 4, and 6 weeks after the initiation of fluvoxamine treatment. A single person rated each patient. A decrease of 50% or higher in the baseline MADRS score was defined as a clinical response.

Statistical analysis

We used an intent-to-treat last-observation-carried-forward analysis. The clinical characteristics of the patients, responders, and non-responders were analyzed by a chi-square test or an unpaired t-test where appropriate. The distribution of responders and non-responders in the 3 groups was analyzed by a chi-square test. The changes in the time course of MADRS scores (the mean score at each evaluation point minus the mean score at the baseline) among females aged <44 years, females aged ≥ 44 years, and males were analyzed by a repeated-measures analysis of variance (ANOVA). The changes in MADRS scores at 1, 2, 4, and 6 weeks among the 3 groups were analyzed by an unpaired t test. Statistical analysis was performed using StatView version 5.0 (SAS Institute INC., Cary, NC). All the tests were two-tailed, and a p value ≤ 0.05 was regarded as significant.

Results

Among the 100 patients, 3 stopped visiting our hospitals after the first visit without providing an explanation. We excluded 4 patients from the current analysis because of poor compliance with pharmacotherapy. Therefore, the remaining 93 patients constituted the subjects, who included 50 females and 43 males (mean age $\pm$ SD = 48.8 $\pm$ 13.7 years). The final daily dose of fluvoxamine was 50 mg for 7, 100 mg for 15, 150 mg for 8, and 200 mg for 64 patients. Patient characteristics are shown in Table 1.

The number of intent-to-treat responders and non-responders was 55 and 38 patients, respectively. No significant difference was observed in average age, number

Table 1 Clinical characteristics of the total patients, responders and non-responders in this study

	Total (N = 93)	Responders (N = 55)	Non-responders (N = 38)	Analysis	
Sex (male/female)	43/50	26/29	17/21	$\chi^2 = 0.058$	p = 0.81 n.s[b]
Age (year)[a]	48.8 ± 13.7	48.0 ± 13.6	50.0 ± 13.8	t = –0.69	p = 0.49 n.s[c]
Number of previous episodes[a]	0.43 ± 0.97	0.42 ± 1.13	0.45 ± 0.69	t = –0.14	p = 0.88 n.s[c]
Melancholia (yes/no)	36/57	19/36	17/21	$\chi^2 = 0.98$	p = 0.32 n.s[b]
Pretreatment total MADRS score	29.8 ± 5.2	29.5 ± 5.09	29.9 ± 5.33	t = –0.34	p = 0.73 n.s[c]

[a]Data are expressed as mean ± SD
[b]Analysis performed with the use of a chi-square test between the responders and non-responders.
[c]Analysis performed with the use of an unpaired t-test between the responders and non-responders.

of previous depressive episodes, proportion of melancholia and non-melancholia, and severity in MADRS scores at pretreatment between the responders and non-responders (Table 1). Table 2 shows the distributions and intent-to-treat response rates to fluvoxamine between responders and non-responders. Although the response rate of the females of age group <44 years was high (75%), there was no significant difference in the distributions of the responders and non-responders between females aged <44 years and those aged ≥44 years ($\chi^2 = 2.79$, p = 0.09), females aged <44 years and males ($\chi^2 = 1.08$, p = 0.30), and females aged ≥44 years and males ($\chi^2 = 0.84$, p = 0.36).

There was a significant difference in the changes in the time course of the MADRS score between the females aged <44 years and those aged ≥44 years (F = 2.97, p = 0.02). However, there was no significant difference between females aged <44 years and males (F = 1.50, p = 0.20), and females aged ≥44 years and males at 6 weeks (F = 0.96, p = 0.43) (Figure 1). Figure 2 depicts changes in the MADRS scores in the 3 groups. There was a significant difference in the MADRS score at each evaluation point between females aged <44 years and those aged ≥44 years (1 week: t = –3.45, p = 0.001; 2 weeks: t = –2.71, p = 0.009; 4 weeks: t = –2.11, p = 0.04; and 6 weeks: t = –2.17, p = 0.04). Although a significant difference was observed between females aged ≥44 years and males for the MADRS scores in the first week (t = 2.50, p = 0.015), there was no significant difference at 2 weeks (t = 1.55, p = 0.13), 4 weeks (t = 1.12, p = 0.27), and 6 weeks (t = 1.11, P = 0.27). There was no significant difference between females aged <44 years and males for the MADRS score at each evaluation point (1 week: t = –0.70, p = 0.49; 2 weeks: t = –0.47, p = 0.64; 4 weeks: t = –0.48, p = 0.63; and 6 weeks: t = –0.68, p = 0.50).

Discussion

The results of this study reveal that the fluvoxamine treatment significantly improved the changes in the time course of MADRS score and changes in the MADRS scores at each evaluation point in younger female depressive patients (females aged <44 years) compared with older female patients (females aged ≥44 years). Our results were in agreement with those of a recent study in which the menopause status negatively affected the SSRI treatment response of Caucasian female depressive patients treated in primary care.[13] Kornstein et al[4] hypothesized a mechanism for the effect of gender differences; the female gonadal hormones, particularly estrogen, may play an important role in antidepressant activity, thereby enhancing the response to SSRIs in younger women. Halbreich et al[14] have shown that estrogen enhances monoaminergic activity and augments serotoninergic postsynaptic responsiveness. Several studies have suggested that estrogen augments the response to SSRIs in female postmenopausal major depressive patients.[15,16] Therefore, we suggested that the augmentation therapy using estrogen was useful for postmenopausal patients who did not response to SSRIs. On the other hand, sex differences in depressive response during monoamine depletions in remitted depressive patients were recently reported. In the study, women experienced greater depressive responses than men during tryptophan depletion inducing hyposerotonengic

Table 2 Distribution of the responders and non-responders among females <44 years of age, females ≥44 years of age and males

	Total (N = 93)	Female <44 (N = 16)	Female ≥44 (N = 34)	Male (N = 44)
Responder	55 (59.1%)	12 (75.0%)	17 (50.0%)	26 (60.5%)
Non-responder	38 (40.9%)	4 (25.0%)	17 (50.0%)	17 (39.5%)

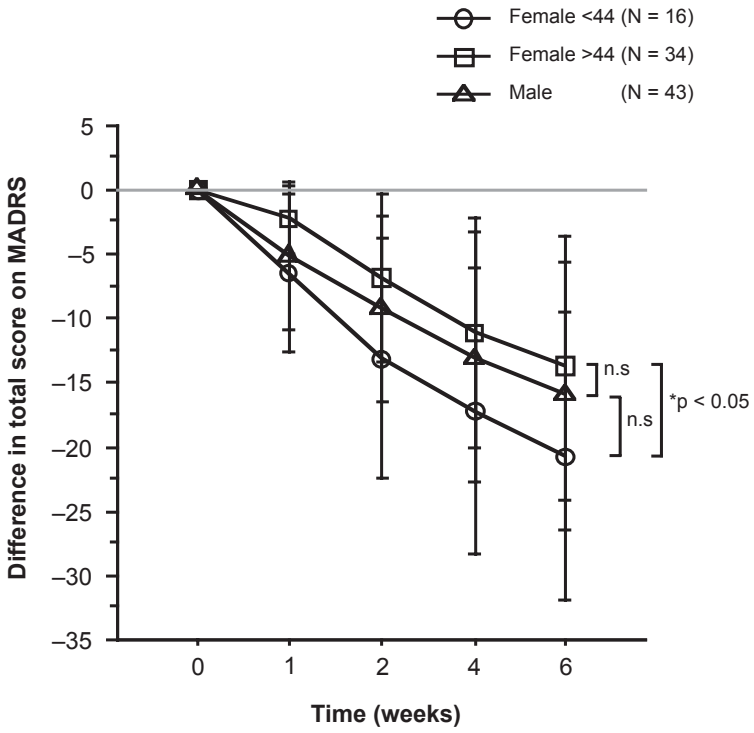

Figure 1 Changes in the time course of the MADRS scores in females aged <44 years, females aged ≥44 years, and males treated with fluvoxamine. Each point represents the mean score ± SD. Analysis was performed using a repeated-measures analysis of variance (ANOVA).
*$p < 0.05$.
Abbreviation: MADRS, Montgomery and Åsberg Depression Rating Scale.

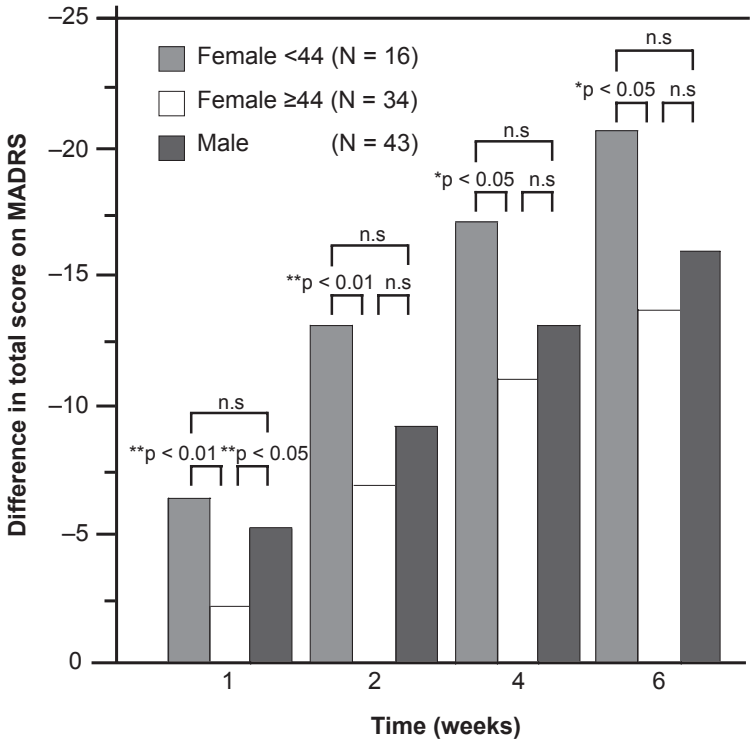

Figure 2 Changes in the MADRS scores in females aged <44 years, females aged ≥44 years, and males treated with fluvoxamine at each evaluation point. Analysis was performed using an unpaired t test.
*$p < 0.05$, **$p < 0.01$.
Abbreviation: MADRS, Montgomery and Åsberg Depression Rating Scale.

function, but not during catecholamine depletion.[17] Similar results were obtained in another recent study on healthy people.[18] These findings suggest that differential sex effects in serotonengic function may be related to gender differences in the clinical effects of SSRIs.

In conclusion, the present study suggests that fluvoxamine is more effective in younger female patients than in older female and male patients. The major limitation of this study is the lack of placebo control patients. A second limitation is the relatively small number of younger females. This limitation leads to the possibility of a false negative in the distributions of the responders and non-responders between younger females and older females.

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Disclosure

The authors report no conflicts of interest.

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