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ARTICLE

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Fluvoxamine treatment of generalized social anxiety disorder in Japan: a randomized double-blind, placebo-controlled study

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Abstract

The efficacy of selective serotonin reuptake inhibitors (SSRIs) for the treatment of social anxiety disorder (SAD) has been reported in the USA and Europe. However, no clinical investigation has been done with SSRIs in Japanese patients with SAD. This study was performed to determine the effectiveness and safety of fluvoxamine for generalized SAD (GSAD) in Japanese patients. In this double-blind study, patients meeting DSM-IV criteria for GSAD were randomized to receive treatment with fluvoxamine or placebo for 10 wk. Fluvoxamine treatment was initiated at 50 mg/d, and increased by 50 mg weekly to a maximum of 150 or 300 mg/d. The primary efficacy outcome was mean change from baseline on the Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) total score. The secondary outcomes were response according to the Clinical Global Impressions – Global Improvement (CGI-I) score and three domains of the Sheehan Disability Scale (SDS; used to assess psychosocial impairment). A total of 176 fluvoxamine-treated patients and 89 placebo-treated patients were eligible for the efficacy analysis. At week 10, the fluvoxamine-treated patients had a significantly greater reduction in the LSAS-J total score compared with placebo-treated patients ($p=0.0197$), with significantly more fluvoxamine recipients being at least much improved on the CGI-I scale compared with placebo-treated patients ($p=0.024$). Fluvoxamine-treated patients also had better responses on the SDS compared with placebo-treated patients ($p=0.0208$). Fluvoxamine was safe and well tolerated. These results suggest that fluvoxamine is effective for the treatment of Japanese patients with GSAD.

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Key words: Fluvoxamine maleate, generalized social anxiety disorder (GSAD), Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J), placebo-controlled double-blind study, selective serotonin reuptake inhibitor (SSRI).

Introduction

Social anxiety disorder (SAD; also known as social phobia) is characterized by fear of social situations involving performance or interaction. This disorder has been formally recognized as a distinct anxiety disorder since the third edition of DSM-III (APA, 1980) was published. SAD is one of the most common of all the anxiety disorders, with a 1-year prevalence estimated to range from ~1.7% [95% confidence interval (CI) 1.5–1.9] to 7.4% (95% CI 6.6–8.2) (Schneier et al., 1992) and a lifetime prevalence of 13.3% (Magee et al., 1996; Narrow et al., 2002) in the USA.

In Japan, a number of psychopathological and psychotherapeutic studies have been performed since the 1930s on a pathological condition similar to SAD, known as *taijin-kyofu* (in Japanese, *taijin* means 'interpersonal' and *kyofu* means 'fear') (Yamashita, 1993). *Taijin-kyofu* is a broader concept than SAD as defined in DSM-IV (APA, 1994), and includes a pathological condition called 'quasi-delusional type' or 'offensive type' of *taijin-kyofu* (which may be diagnosed as delusional disorder, somatic type or body dysmorphic disorder based on DSM-IV criteria and partly reported as olfactory reference syndrome) (Stein et al., 1998a). In DSM-IV, a pathological condition of

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'quasi-delusional type' or 'offensive type' of *taijin-kyofu* is described as a culture-bound syndrome (APA, 1994). However, not all clinical conditions of Japanese patients with *taijin-kyofu* are included in this type, and there are also many patients who are diagnosed as having SAD based on DSM-IV criteria. Therefore, *taijin-kyofu* has two subtypes; one that corresponds with SAD with diagnosis based on DSM-IV criteria (sensitive type), and the other that does not correspond with SAD (quasi-delusional type or offensive type). Unfortunately, community-based genetic, epidemiological or comorbidity studies on *taijin-kyofu*, including SAD, have not yet been performed in Japan. Some clinical samples have been reported; 7.8% of neurotic outpatients in Hokkaido University Hospital and 45.5% of patients in a special institute using Morita therapy (a useful psychotherapy developed in Japan) were diagnosed as *taijin-kyofu* (Takahashi, 1989). Yamashita (1993) reported that 100 patients who received behaviour therapy in line with the principle of Morita therapy, and who were administered mainly benzodiazepines, revealed complete or almost complete recovery (27%), considerable improvement (55%) or no apparent change (18%).

In addition to cognitive behavioural therapies (Liebowitz et al., 1999), several pharmacotherapies have been used for the treatment of SAD, including monoamine oxidase inhibitors (e.g. phenelzine, moclobemide, and brofaromine; Fahlen et al., 1995; Liebowitz et al., 1999); β-blockers (e.g. atenolol; Liebowitz et al., 1992); benzodiazepines (e.g. clonazepam; Davidson et al., 1993); and selective serotonin reuptake inhibitors (SSRIs) (e.g. fluvoxamine, paroxetine and sertraline; Ballenger et al., 1998; Davidson, 1998). SSRIs have been recommended as the first-line treatment for SAD because of their efficacy and tolerability (Ballenger et al., 1998; Davidson, 1998).

Placebo-controlled studies conducted in the USA and Europe support the efficacy of SSRIs for the treatment of generalized SAD (GSAD); however, those studies included only a small percentage of Asians. There are some differences in clinical responses (efficacy and safety) to fluvoxamine between Japanese and Western patients with depression. Concerning this, some interesting studies focusing on differences such as drug metabolic enzymes or genetic polymorphism were reported (Otsubo et al., 2005; Suzuki et al., In Press), and the results suggest that it is important to investigate the effect of SSRIs in Japanese patients with SAD.

The present multicentre, randomized, double-blind, placebo-controlled study of fluvoxamine for the treatment of GSAD is the first study conducted in Japanese patients. Furthermore, we also report the results of an open-label 52-wk treatment study in patients who completed the 10-wk double-blind treatment study.

Method

Design

This was a 10-wk, randomized, double-blind, placebo-controlled study conducted at 54 centres in Japan. The study protocol was approved by the Institutional Review Board at all study centres, and subjects gave written informed consent to participate. Data were gathered from November 2001 to August 2002.

Although the treatment duration of many double-blind studies on SSRIs using the Liebowitz Social Anxiety Scale (LSAS) is 12 wk in Western countries, LSAS scores were significantly reduced from 4–6 wk after baseline compared with placebo (Davidson et al., 2004; Liebowitz et al., 2003; Westenberg et al., 2004). Therefore, a 10-wk treatment duration was considered sufficient to detect the differences in efficacy between fluvoxamine and placebo.

Eligible patients were randomly assigned to either fluvoxamine (at an initial dose of 50 mg/d fluvoxamine in two divided doses) or placebo in a 2:1 ratio. Fluvoxamine-treated patients were randomly divided into two subgroups; a daily dose was increased by 50-mg increments per week to a maintenance dose of 150 mg/d in one subgroup and to that of 300 mg/d in the other subgroup (Figure 1). Other dosage adjustments were not permitted during the study for any reason. The concomitant use of other psychotropic medications was prohibited, with the exception of ultrashort-acting hypnotics for insomnia.

Following this study, an open-label 52-wk treatment study was conducted. Enrolled patients were started on fluvoxamine at a dose of 50 mg/d. The patient's dose was increased to at least 150 mg/d ($\leqslant$300 mg/day) within 6 wk of the start of treatment if tolerated, and then was adjusted as necessary within a dose range of 100–300 mg/d.

Subjects

Subjects were recruited using local newspaper advertisements. Eligible patients were aged 18–65 yr and were required to meet the DSM-IV criteria for GSAD, have a minimum score of $\geqslant$60 on the Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J; Asakura et al., 2002), have no serious medical history, and to have taken no psychotropic medications for at least 14 d prior to randomization. The diagnosis of GSAD was made according to DSM-IV criteria by

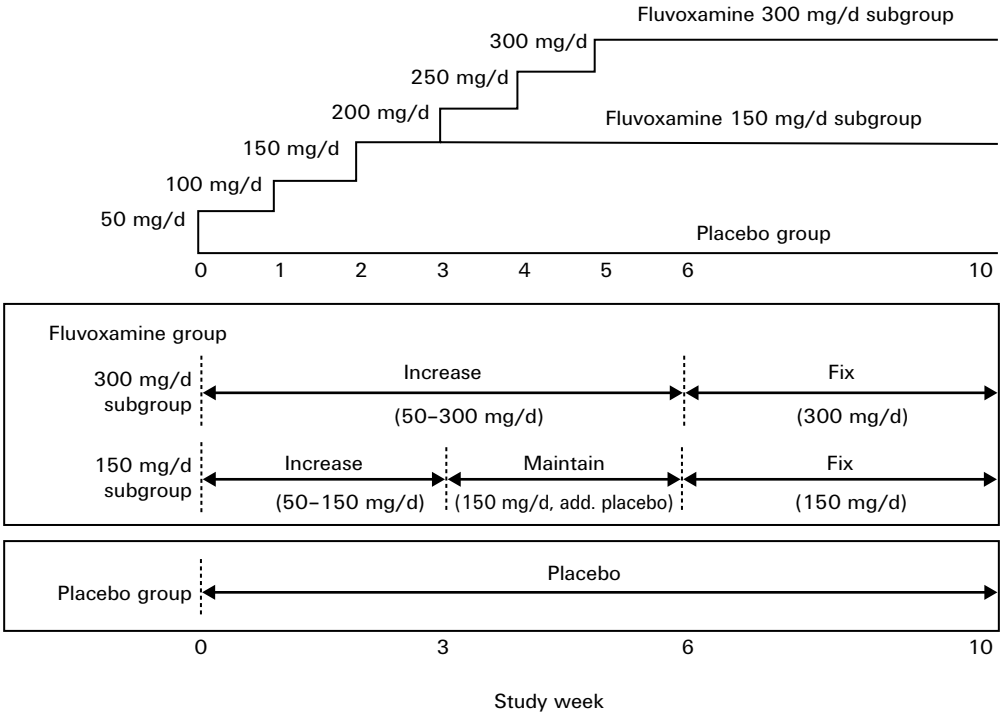

Figure 1. Study design for the double-blind section of the study (treatment groups and dosage regimen in each group).

well-trained research psychiatrists. Patients were required, in addition to meeting DSM-IV criteria for SAD, to exhibit fear and/or avoidance of at least four social situations (at least two involving interpersonal interactions). Further, patients were excluded if they had any Axis I psychiatric disorder (e.g. schizophrenia, bipolar disorder, major depressive disorder, dysthymic disorder, panic disorder, alcohol abuse/dependence), or medical or neurological disorder. Other exclusion criteria were any clinically significant abnormal laboratory or electrocardiogram (ECG) findings at the screening visit. Women who were pregnant, lactating, or not using an acceptable method of contraception were also ineligible. Additionally, no patients were judged to have suicide ideation, none had a history of prior suicide attempts, and none were considered to be at serious suicidal risk. Patients who had been judged to be at least slightly improved (score $\leqslant 3$) on the Clinical Global Impression – Global Improvement scale (CGI-I; Guy, 1976) at week 10 of the double-blind study, and who had not experienced any clinically relevant adverse events, were eligible for inclusion in the 52-wk treatment study.

Outcome measures

Patients were evaluated at nine study visits (baseline and weeks 1, 2, 3, 4, 5, 6, 8, and 10). The primary efficacy variable was mean change from baseline to end-point on the LSAS-J total score. The LSAS-J was prepared by a translation of the LSAS (Liebowitz, 1987) to Japanese, then verified by back-translation to English. Its reliability and validity were confirmed in 30 patients with SAD and 60 healthy control subjects [internal consistency (Cronbach's $\alpha = 0.95$), test–retest reliability (intra-class correlation coefficient $= 0.92$), correlation to Social Avoidance and Distress Scale (Watson and Friend, 1969) ($r = 0.64$, $p = 0.0002$)]. Secondary efficacy variables included (i) proportion of responders as determined by the CGI-I, by which a responder was defined as very much improved (score $= 1$) or much improved (score $= 2$) compared with baseline and (ii) the clinician-rated Sheehan Disability Scale (SDS; Leon et al., 1992), a Likert (0–10) scale assessing the extent of psychosocial impairment in three domains (disruption of work, social life, and home/family life). At each study visit, patients were questioned and data were recorded regarding any perceived adverse effects, which were rated according to severity and start and stop date. Vital signs were also recorded at each study visit. ECG and laboratory tests were performed prior to randomization, at week 6, and at the end of the double-blind treatment period (or earlier if the patient discontinued prematurely).

In the long-term treatment study, patients were evaluated at 19 study visits (baseline and weeks 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52). As with the double-blind study, efficacy variables were mean change from baseline to end-point on the LSAS-J total score, and the proportion of responders as determined by the CGI-I and the clinician-rated SDS (Leon et al., 1992). At each study visit, patients were questioned and data were recorded regarding any perceived adverse events, which were rated according to severity and start and stop date. Vital signs were also recorded at each study visit. ECG and laboratory tests were performed at baseline, weeks 6 (only laboratory tests), 12, 28, and 40, and at the end of treatment, or earlier if the patient discontinued prematurely.

Statistical analysis

Efficacy and safety analyses were carried out on all patients who received at least one dose of the study medication and for whom at least one valid post-baseline efficacy evaluation was obtained. Efficacy data are presented for the last observation carried forward (LOCF) dataset. The LOCF dataset used the last available on-treatment observation for each patient to estimate missing data-points. The primary time-point of interest was end-point.

This study was a double-blind, two-arm study involving two different groups of patients receiving fluvoxamine and patients receiving placebo. The fluvoxamine group consisted of two subgroups of patients receiving a maintenance dose of 150 mg/d and of 300 mg/d, in order to achieve the secondary objective of comparing therapeutic efficacy between fluvoxamine doses in Japanese SAD patients and the approved doses in Japanese depressed/obsessive–compulsive disorder (OCD) patients (50–150 mg/d) and between fluvoxamine doses in Japanese SAD patients and those (100–300 mg/d) in Western SAD patients. For this reason, the sample size calculation was based on the assumption that at least one of the two fluvoxamine subgroups would be significantly superior to the placebo group.

The number of patients calculated necessary to ensure 90% power at a two-tailed α-level of 0.05 to detect a 12-point difference in the change from baseline to end-point in the LSAS-J total score with a 20% attrition rate was $\sim$80 in each of the two fluvoxamine subgroups and the placebo group. Therefore, the total number of patients to be included in the fluvoxamine group (combining the 150 mg/d and 300 mg/d subgroups) was 160; the ratio between the number of fluvoxamine-treated patients and the number of placebo-treated patients was 2:1.

The primary efficacy analysis was performed by using an analysis of covariance (ANCOVA), which included an effect for treatment, with the pre-treatment LSAS-J total score as a covariate for the post-treatment score. The level of significance was set at 0.05. The CGI-I scores were summarized for each category to obtain the percentage of responders, which was tested with the rank sum test. For the improvement rate, Fisher's exact test was used to compare the groups. For psychosocial impairment according to the SDS, analysis of variance (ANOVA) was used to compare the groups at each time-point. These primary and secondary analyses were performed on a comparison between the fluvoxamine group (combining the 150 mg/d and 300 mg/d subgroups) and the placebo group.

Additionally, a further analysis was conducted to compare a change from baseline in the LSAS-J total score between the fluvoxamine (150 mg/d) and placebo groups and between the fluvoxamine (300 mg/d) and placebo groups, in order only to examine whether or not fluvoxamine dose range in SAD patients differs from the approved dose range in Japanese patients with depression or OCD (50–150 mg/d) or from SAD patients in Western countries (100–300 mg/d). ANOVA was used for this analysis at a two-tailed α-level of significance of 0.05.

Results

Demographics

A total of 273 patients were randomly assigned to therapy with fluvoxamine and placebo; 271 patients were eligible for efficacy and/or safety analysis, while one patient who never took any study medication and one patient who did not return after the first visit were completely excluded from the analyses (Figure 2). The efficacy analysis population was composed of 265 patients (176 receiving fluvoxamine and 89 receiving placebo), excluding six patients for whom no valid post-baseline efficacy evaluation was obtained due to premature discontinuation [four withdrew due to adverse events and two withdrew due to protocol deviations (inappropriate concomitant medications)].

The baseline demographic and clinical characteristics of the 265 patients who were included in the efficacy population are shown in Table 1. In this study, there were more male patients than female patients. The patients' mean age at their participation in the current study was in the latter half of the 30 s. Over

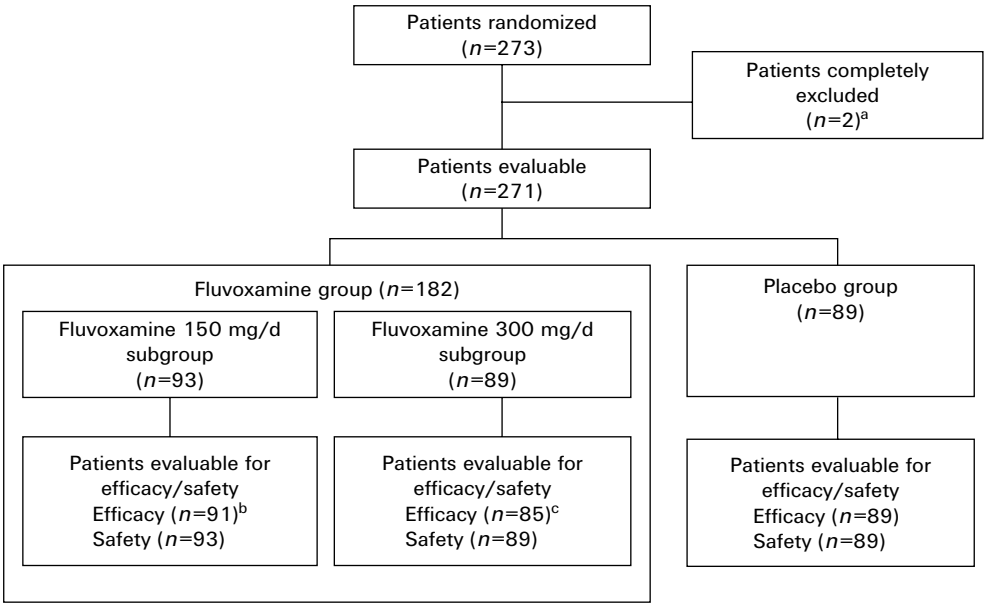

Figure 2. Disposition of patients in the double-blind study. [a] One patient received no study medication at all and one patient did not return after the first visit. [b] Two patients dropped out due to adverse events. [c] Two patients dropped out due to adverse events and two patients dropped out because of protocol deviations.

50% of patients had an onset of symptoms before they were 10 yr old and nearly 80% of patients had no prior history of psychiatric treatment.

A total of 71 patients (49 males and 22 females) were eligible for efficacy and safety analyses in the 52-wk treatment study.

Efficacy variables

Treatment with fluvoxamine resulted in a significantly greater reduction from baseline to end-point in the LSAS-J total score than treatment with placebo (LSAS-J mean total score in fluvoxamine group 58.6, in placebo group 65.8, $p=0.0197$, Figure 3). The between-treatment difference in the decrease from baseline in the LSAS-J total score was significant from week 5 to end-point (week 10) in favour of fluvoxamine (Figure 4). Fluvoxamine-treated patients experienced significant improvement compared with placebo-treated patients on the LSAS-J fear/anxiety and avoidance subscales at end-point ($p=0.0128$ and $p=0.0435$ respectively) (Figure 5).

On the basis of change in CGI-I score, fluvoxamine-treated patients had a significantly greater improvement than did placebo-treated patients ($p=0.0180$) (Table 2). When a responder was defined as a patient who had a CGI-I score of either 1 (very much improved relative to baseline) or 2 (much improved relative to baseline) at the end-point, the percentage of responders in fluvoxamine-treated patients was 45.1%, which was significantly greater compared with 30.3% in placebo-treated patients ($p=0.0240$). Fluvoxamine-treated patients also had a significantly greater reduction in the psychosocial impairment score, according to the SDS, than did placebo-treated patients ($p=0.0208$) (Table 3).

A significant difference in the decrease from baseline to end-point in the LSAS-J total score was observed between patients treated with 150 mg/d fluvoxamine and those treated with placebo ($p=0.0007$), and 300 mg/d fluvoxamine and those treated with placebo ($p=0.0355$) at end-point (Figure 6). However, aalthough the distribution of CGI scores at 4–6 wk from baseline in the fluvoxamine (150 mg/d) and placebo groups were significantly different ($p=0.0021$), scores in the fluvoxamine (300 mg/d) and placebo groups were similar ($p=0.3332$). Total SDS scores 4–6 wk from baseline in the fluvoxamine (150 mg/d) and placebo groups were also significantly different ($p=0.0165$), but those in the fluvoxamine (300 mg/d) and placebo groups were similar ($p=0.7137$).

The LSAS-J total score decreased from 54.3 ± 23.1 (mean $\pm$ S.D.) at baseline to 33.3 ± 18.8 at the end of the 52-wk treatment (Figure 7). The percentage of patients in each CGI-I category over time is shown in Figure 8. On the basis of a CGI-I score of either 1 (very much improved relative to baseline) or 2 (much improved

Table 1. Baseline demographics and patient clinical characteristics in double-blind study (efficacy population)

	Fluvoxamine ($n=176$)	Placebo ($n=89$)
Sex, *n* (%)		
Male	124 (70.5)	55 (61.8)
Female	52 (29.5)	34 (38.2)
History of consultation of psychiatry department, *n* (%)		
No	139 (79.0)	69 (77.5)
Yes	37 (21.0)	20 (22.5)
Mean age, yr (±S.D.)	39.3±11.0	37.9±11.5
Age category, *n* (%)		
10–19 yr	4 (2.3)	4 (4.5)
20–29 yr	31 (17.6)	21 (23.6)
30–39 yr	56 (31.8)	23 (25.8)
40–49 yr	49 (27.8)	21 (23.6)
50–59 yr	31 (17.6)	19 (21.3)
60–69 yr	5 (2.8)	1 (1.1)
Mean age at onset, yr (±S.D.)	20.7±11.2[a]	20.2±10.2[b]
Age at onset, *n* (%)		
0–9 yr	21 (11.9)	10 (11.2)
10–19 yr	72 (40.9)	37 (41.6)
20–29 yr	39 (22.2)	23 (25.8)
30–39 yr	25 (14.2)	9 (10.1)
40–49 yr	9 (5.1)	3 (3.4)
50–59 yr	3 (1.7)	2 (2.2)
Unknown	7 (4.0)	5 (5.6)
Mean LSAS-J		
Total score (±S.D.)	87.9±18.2	87.0±18.8
Fear subscore (±S.D.)	47.2±8.6	46.2±9.0
Avoidance subscore (±S.D.)	40.7±11.3	40.8±11.3

LSAS-J, Liebowitz Social Anxiety Scale – Japanese Version.
[a] Values were missing for seven patients.
[b] Values were missing for five patients.

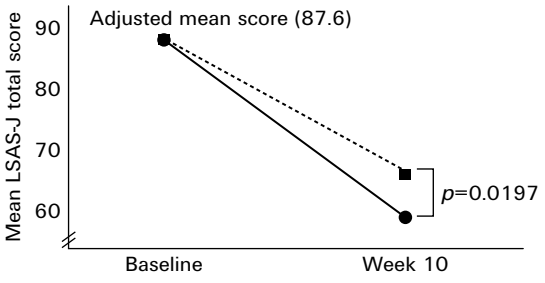

Figure 3. Change in the Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) mean total score from baseline to week 10 using ANCOVA with the baseline LSAS-J mean total score as a covariate [last observation carried forward (LOCF) analysis] (p value is by ANCOVA). –●–, Fluvoxamine ($n=176$); - -■- -, placebo ($n=89$).

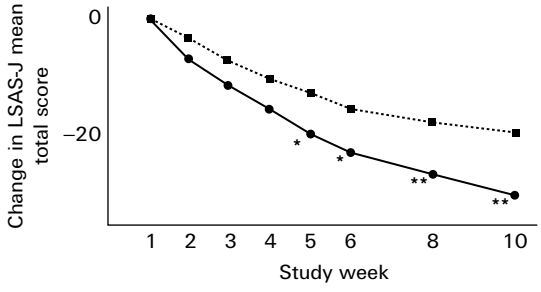

Figure 4. Change over time from baseline in Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) mean total score during double-blind study [last observation carried forward (LOCF) analysis] (* $p<0.05$ vs. placebo, ** $p<0.01$ vs. placebo; p values are by ANOVA). –●–, Fluvoxamine ($n=176$); - -■- -, placebo ($n=89$).

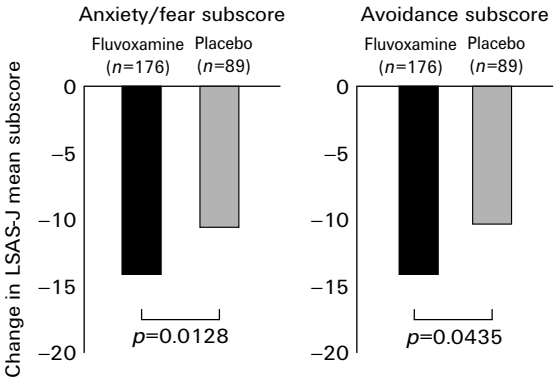

Figure 5. Change from baseline to end-point in Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) subscores during double-blind study [last observation carried forward (LOCF) analysis].

relative to baseline) at the end-point, the percentage of responders was 64.8% (46 out of 71 patients). SDS score decreased from 8.9 ± 4.8 (mean ± S.D.) at baseline to 5.8 ± 5.1 at end-point. The mean dose of fluvoxamine ranged from 176.2 to 185.5 mg/d during the flexible dose phase (weeks 7–52).

Safety results

The safety analysis population was composed of 271 patients (172 receiving fluvoxamine and 89 receiving placebo). The overall incidence of reported adverse events was 88.5% in the fluvoxamine group and 66.3% in the placebo group. The most commonly reported adverse events (⩾5% of patients) are shown in Table 4. In the fluvoxamine group, somnolence was the most frequently reported adverse event (45.1%), followed by nausea (23.1%). The incidence of adverse events was 91.4% and 85.4% in the 150 mg/d and 300 mg/d fluvoxamine groups respectively, and the likelihood of a dose-dependent increase was not observed.

Dehydration and acute renal failure were observed in one fluvoxamine recipient (at a dose of 300 mg/d at week 10) and serotonin syndrome (with complaints of mental deterioration, irritation, trembling, hidropoiesis, deep tendon hyper-reflex, and chill as symptoms) was observed in another fluvoxamine recipient (at a dose of 300 mg/d at week 6). These were classified as serious adverse drug reactions, but disappeared within 2 wk after discontinuation of study treatment. None of the patients died during the study period.

In the 52-wk open-label study, the overall incidence of reported adverse events was 95.8%. Nasopharyngitis was most frequently reported (63.4%), followed by somnolence (49.3%) and nausea (31.0%). However, the most frequent adverse events of which the causal relationship to the drug could not be ruled out was somnolence (43.7%), followed by nausea (25.4%).

Table 2. CGI-I scale categories at week 10 (LOCF analysis)

	Fluvoxamine[a]		Placebo	
	n	%	*n*	%
Very much improved	23	13.1	7	7.9
Much improved	56	32.0	20	22.5
Slightly improved	56	32.0	33	37.1
No change	38	21.7	28	31.5
Slightly worse	2	1.1	0	0.0
Worse	0	0.0	1	1.1
Much worse	0	0.0	0	0.0
p value (by rank sum test)		0.0180		

CGI-I, Clinical Global Impression – Global Improvement Scale, LOCF, last observation carried forward.
[a] One patient of the fluvoxamine group did not administer the CGI assessment.

Discussion

This study conducted in Japanese patients confirms previous observations that fluvoxamine is effective for the treatment of SAD, as demonstrated in trials conducted in the USA and Europe (Stein et al., 1999; van Vliet et al., 1994). In terms of the primary outcome measure, patients treated with fluvoxamine experienced a statistically superior improvement to placebo, based on a decrease in the mean LSAS-J total score at end-point using a LOCF analysis. Treatment with fluvoxamine also had favourable effects on overall clinical condition and social disability. Patients treated with fluvoxamine showed significant improvement on LSAS-J fear/anxiety subscale score, LSAS-J avoidance subscale score, CGI-I score, and total score of three domains of clinician-rated SDS, which was used to assess the extent of psychosocial impairment, compared with placebo-treated patients. On the basis of CGI-I scores at week 10, the proportion of responders in the fluvoxamine group in the present study was 45.1%, which was comparable to that (42.9%) of patients treated with flexible doses of fluvoxamine in a multicentre, randomized, double-blind, placebo-controlled study that was conducted for the treatment of SAD in the USA (Stein et al., 1999). In the present study, fluvoxamine treatment resulted in a consistently significant improvement of clinical symptoms as assessed with the LSAS-J total score, global improvement according to the CGI-I score, and the extent of

Table 3. SDS psychosocial impairment scores at baseline and week 10 (LOCF analysis)

Least squares (mean ± S.E.)	Fluvoxamine[a] ($n=175$)	Placebo ($n=89$)
Baseline	14.1 ± 0.4	14.1 ± 0.6
Week 10	9.8 ± 0.4	11.0 ± 0.6
p value (by ANOVA for treatment effect)	0.0208	

SDS, Sheehan Disability Scale; LOCF, Last observation carried forward; ANOVA, analysis of variance; S.E., standard error.
[a] One patient of the fluvoxamine group was not administered the psychosocial impairment test.

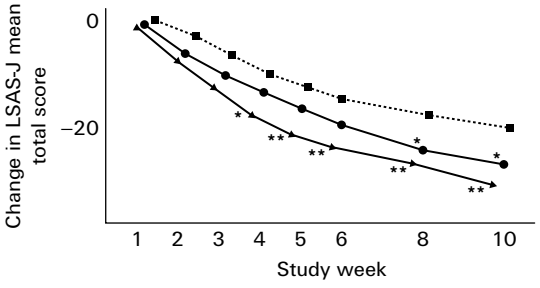

Figure 6. Change over time from baseline in Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) mean total score for each of the fluvoxamine dose subgroups and the placebo group in the double-blind study [last observation carried forward (LOCF) analysis]. (* $p<0.05$ vs. placebo, ** $p<0.01$ vs. placebo; *p* values are by ANOVA). –▲–, Fluvoxamine 150 mg ($n=91$); –●–, Fluvoxamine 300 mg ($n=85$); - -■- -, placebo ($n=89$).

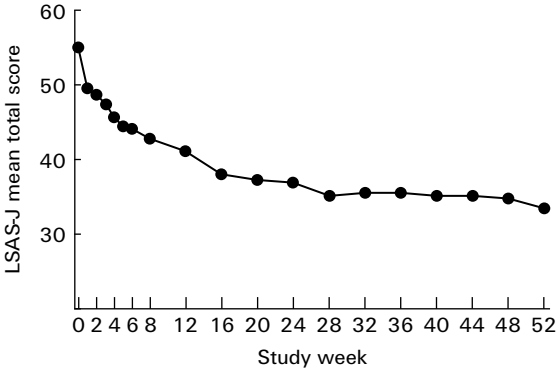

Figure 7. Change in the mean Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) total score over time in 52-wk study [last observation carried forward (LOCF) analysis].

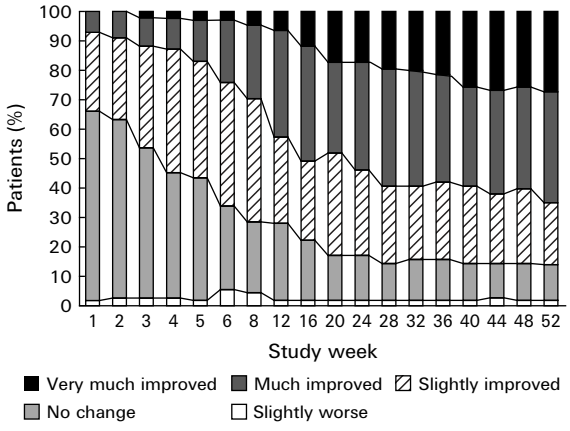

Figure 8. Percentage of patients in each Clinical Global Impression – Improvement Scale (CGI-I) category at each time-point in the 52-wk study [last observation carried forward (LOCF) analysis].

psychosocial impairment; this suggests that fluvoxamine also contributes to improvements in quality of life of patients with SAD. It has been reported that SAD interferes significantly with academic or occupational functioning, or social life (Antony et al., 1998; Greist, 1995; Schneier et al., 1992; Stein et al., 1998b). Given the disability associated with this disorder, it is notable that the fluvoxamine-treated patients in our study experienced marked improvement in functional disability. A significant difference in the decrease from baseline in the LSAS-J total score was observed between patients treated with 150 mg/d fluvoxamine and those treated with placebo ($p=0.0007$), and 300 mg/d fluvoxamine and those treated with placebo ($p=0.0355$) at end-point. Significant treatment group differences between fluvoxamine (150 mg/d) and placebo were observed at weeks 4, 6, 8, and 10, while significant treatment-group differences between fluvoxamine (300 mg/d) and placebo were observed only at weeks 8 and 10. However, as this 10-wk double-blind treatment study was not designed to compare the effects of different doses of fluvoxamine,

Table 4. Adverse events occurring in ⩾5% of patients in either treatment group during the double-blind study

Patients (%)	Fluvoxamine (n=182)	Placebo (n=89)
Somnolence	82 (45.1%)	18 (20.2%)
Nausea	42 (23.1%)	0
Malaise	30 (16.5%)	0
Nasopharyngitis	27 (14.8%)	11 (12.4%)
Constipation	23 (12.6%)	6 (6.7%)
Retching	23 (12.6%)	5 (5.6%)
Thirst	22 (12.1%)	16 (18.0%)
Headache NOS	22 (12.1%)	9 (10.1%)
Dizziness	13 (7.1%)	0
CPK increased	12 (6.6%)	0
Anorexia	11 (6.0%)	0
Stomach discomfort	11 (6.0%)	0
Diarrhoea NOS	11 (6.0%)	0
Muscle stiffness	0	5 (5.6%)
Insomnia	10 (5.5%)	0
Total	243	45

NOS, Not otherwise specified; CPK, creatine phosphokinase.

it cannot be concluded from only these results that a dose of <150 mg/d fluvoxamine has sufficient efficacy to treat SAD. SAD is a chronic anxiety disorder and the recommended treatment duration is at least 1 yr (Ballenger et al., 1998). In this regard, from the result adjusted flexibly according to individual symptoms in not only the short-term study but also the 52-wk study, the mean dose of fluvoxamine was around 180 mg/d, which should be noted. Therefore, it is important that <150 mg/d fluvoxamine should be administered at first for Japanese patients with SAD and the effects observed, then the optimal dose for each patient should be selected by evaluating effect and safety.

Furthermore, these findings suggest that long-term use of fluvoxamine can produce greater improvements in LSAS-J, CGI-I and SDS than is produced in short-term treatment. Therefore, it appears that long-term treatment with fluvoxamine is beneficial, as evidenced by greater improvement in clinical symptoms and psychosocial impairment, and greater global improvement on the CGI-I following long-term treatment.

The adverse events associated with fluvoxamine treatment in this study were similar to those reported in a clinical study for this product in the treatment of SAD in Europe (van Vliet et al., 1994). Most of the adverse events associated with fluvoxamine occurred within 1 wk after the start of treatment and the incidence of adverse events did not increase over the course of treatment despite increases in dosage. The most common adverse events were somnolence (45.1%) and nausea (23.1%). Although abnormal (delayed) ejaculation has been reported at a rate of 10% or higher in studies of other SSRIs in the treatment of SAD (Stein et al., 1998b; Van Ameringen et al., 2001), this event occurred at a rate of only 1.6% (in three patients) in the present study. This suggests that a trend in the incidence and type of adverse events may not be always the same across SSRIs. There were only two serious adverse reactions during the fluvoxamine treatment in this study, indicating this product to be safe for the treatment of SAD.

Fluvoxamine was well tolerated in the 52-wk treatment study, resulting in a low discontinuation rate due to adverse events (4.2%). The adverse reactions profile of fluvoxamine in this long-term study was similar to that in the previous short-term study.

It is presumed that sociocultural factors would be involved in the onset of mental disorders more or less in addition to biological factors. In Japan, there have been numerous investigations on the treatment of patients presenting with social anxiety. Many of these investigations have involved patients identified as sufferers from *taijin-kyofu* (Yamashita, 1993), and some of them have dealt with sociocultural differences between Japan and Western countries (Clarvit et al., 1996; Kirmayer, 1991; Yamashita, 1993). It is most significant that our study found that there are many individuals diagnosed as having SAD based on DSM-IV criteria in Japan that can respond to treatment with fluvoxamine, an SSRI, which is similar to reports in the USA and European countries.

Our findings on the gender ratio confirmed that males were predominant in this study. However, it is unknown whether the finding represents the status of gender ratio in Japanese SAD patients. There seems to be no clear sex predominance for this disorder. Epidemiological studies in the USA (Kessler et al., 1994; Schneier et al., 1992) have reported a higher lifetime prevalence of this disorder in females than in males. However, DSM-IV states that in most clinical samples, the majority are male (APA, 1994). In fact, while a clinical study of paroxetine, a SSRI, in the USA included more women (Stein et al., 1998b), a clinical study of another SSRI, sertraline, in Canada included more men (Van Ameringen et al., 2001).

The mean age in this study was 39.3 yr in fluvoxamine-treated patients and 37.9 yr in placebo-treated patients, not significantly differing from the mean age of patients in the previously mentioned paroxetine and sertraline studies (~36 yr). The mean age of onset

of this disorder in this study was 20.7 yr in fluvoxamine-treated patients and 20.2 yr in placebo-treated patients, higher than ~14 yr in the paroxetine study and ~12 yr in the sertraline study. When analysing the age of onset, however, it is apparent that many participants of this study had also developed this disorder in their teens. In Japan, like in the USA, teenagers appear to be most likely to develop the disorder.

Participants in this study had a tendency to not having undergone treatment before enrolment. This tendency in Japanese SAD patients is similar to that in Americans with SAD. In fact, while in this study, around 80% of all the participants had been untreated for this disorder, ~90% in the paroxetine study and ~80% in the sertraline study had also been untreated.

Therefore, our findings on demographic factors showed that participants in this study had a similar tendency in some factors but a different tendency in other factors compared with the findings in the other studies conducted in the USA. However, this was the first clinical report on the use of a SSRI to treat Japanese SAD patients, and only limited epidemiological discussion on Japanese SAD patients is possible based on our findings. Further epidemiological and clinical studies are required to gather more information on the status of Japanese SAD patients.

A possible limitation of the present study is that the study population was restricted to patients with a primary diagnosis of GSAD according to DSM-IV criteria, and patients were excluded from the study if they had any Axis I disorders (e.g. schizophrenia, bipolar disorder, major depressive disorder, dysthymic disorder, panic disorder, alcohol abuse/dependence). Certain problems may remain in applying the results of the present study to daily clinical practice since SAD is often associated with a high incidence of comorbidity. Additional clinical studies are needed to determine the optimal duration of therapy and the effects of concomitant psychotherapy. Furthermore, systematic studies evaluating adjunctive treatments for partial responders and alternative treatments for non-responders should be undertaken (Magee et al., 1996; Schneier et al., 1992). The effects of neuroendocrinological abnormalities and changes of biological markers in patients with SAD are neuropsychiatrically and pharmacologically very interesting and some studies are reported (Furlan et al., 2001; Takahashi et al., 2005). Although we did not investigate these issues in this study, we expect new findings for Japanese patients with SAD in the future. Recently the possibility that SSRIs induce suicide attempts and impulsion has been demonstrated (Chick et al., 2004), and many studies on patients with SAD will be necessary.

In conclusion, the results of this study confirm the efficacy of fluvoxamine in the treatment of GSAD among Japanese subjects. Treatment with fluvoxamine was well tolerated and was associated not only with improvement in symptoms, but also with improvement in functional measures. The study results are expected to improve the situation where many Japanese SAD patients have onset in childhood or early adolescence but remain untreated for a long time. In particular, some patients diagnosed as *taijin-kyofu* and treated in Japan are also diagnosed with SAD based on DSM-IV criteria. Therefore, the fact that SSRIs demonstrated similar efficacy in Japanese patients with SAD as Western patients has significant implications for therapy for *taijin-kyofu* in Japan. The results are also expected to have important implications for the promotion of SAD treatment in Japan.

Appendix

The following principal investigators (*names of site, city and prefecture of Japan*) *participated in this study*: Ken Ashizawa, M.D. (Asahiyama Hospital, Sapporo, Hokkaido); Shoichi Ebana, M.D. (Yokohama Rosai Hospital, Yokohama, Kanagawa); Motofumi Fukahori, M.D. (Imajuku Hospital, Fukuoka, Fukuoka); Kenji Fukui, M.D. (Kyoto Prefectural University of Medicine, Kyoto, Kyoto); Hiroaki Harai, M.D. (Kikuchi National Hospital, Goshi-cho, Kumamoto); Kenji Hashimoto, M.D. (Kobe University, Kobe, Hyogo); Makoto Hashimoto, M.D. (Japanese Red Cross Akita Hospital, Akita, Akita); Hisashi Higuchi, M.D. (Omagari City Hospital, Omagari, Akita); Susumu Higuchi, M.D. (National Alcoholism Center Kurihama Hospital, Yokosuka, Kanagawa); Teruhiko Higuchi, M.D. (Kohnodai Hospital, National Center of Neurology and Psychiatry, Ichikawa, Chiba); Shigeru Inamura, M.D. (Kasamatsu Hospital, Akita, Akita); Takeshi Inoue, M.D. (Hokkaido University, Sapporo, Hokkaido); Masahiro Ishikawa, M.D. (National Maizuru Hospital, Maizuru, Kyoto); Yasuhito Ishimoto, M.D. (Tokushima University, Tokushima, Tokushima); Miwako Kaiho, M.D. (National Chiba Hospital, Chiba, Chiba); Toshihiko Kasahara, M.D. (International Medical Center of Japan, Shinjuku-ku, Tokyo); Kenichi Kato, M.D. (Akasaka Kato Clinic, Fukuoka, Fukuoka); Masato Kimura, M.D. (Nippon Medical School, Bunkyo-ku, Tokyo); Takenori Kimura, M.D. (Kumamoto University, Kumamoto, Kumamoto);

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None.

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