A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Controlled-Release Fluvoxamine in Patients With Obsessive-Compulsive Disorder

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Objective: The aim of this 12-week, double-blind, flexible-dose, placebo-controlled, parallel-arm, multicenter trial was to determine the safety and efficacy of fluvoxamine in a controlled-release (CR) formulation in adult outpatients with obsessive-compulsive disorder (OCD).

Method: 253 adult outpatients with DSM-IV OCD were randomly assigned to receive 100 to 300 mg of fluvoxamine CR (N = 127) or placebo (N = 126) once daily for 12 weeks. Intent-to-treat analyses of efficacy assessments with the Yale-Brown Obsessive Compulsive Scale (YBOCS), Clinical Global Impressions-Severity of Illness scale (CGI-S), and Clinical Global Impressions-Improvement scale (CGI-I) were conducted.

Results: Fluvoxamine CR was significantly ($p < .05$) superior to placebo in decreasing YBOCS total score beginning at week 2. This early response was sustained at all subsequent visits. At endpoint, there was a mean decrease of 8.5 ± 0.7 (31.7%) in the YBOCS total score compared with baseline in the fluvoxamine CR treatment group versus a mean decrease of 5.6 ± 0.7 (21.2%) in the placebo group ($p = .001$). Fluvoxamine CR was also significantly superior to placebo in lowering the severity of illness (CGI-S, $p = .002$) and in producing clinical improvement (CGI-I, $p < .01$). At endpoint, significantly greater percentages of the fluvoxamine CR treatment group were responders ($p = .002$) and remitters ($p = .019$) compared with the placebo group.

Conclusion: Over 12 weeks, fluvoxamine CR treatment was associated with a statistically significant and clinically relevant reduction in OCD severity and was found to be safe and well tolerated. The early onset of therapeutic effect, starting from week 2, was of particular interest.

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Obsessive-compulsive disorder (OCD) is a chronic, sometimes disabling illness characterized by anxiety-provoking, intrusive obsessions and a need to perform time-consuming compulsive rituals that cause marked distress or significant functional impairment.[1,2] The treatment of OCD advanced significantly with the introduction of the potent serotonin reuptake inhibitor (SRI) clomipramine and selective serotonin reuptake inhibitors (SSRIs).[3–5]

Currently, several SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) have U.S. Food and Drug Administration approval with an indication for the treatment of OCD and have proven efficacy and safety profiles.[6–13] With efficacy similar to that of clomipramine, SSRIs may improve treatment compliance because patients experience fewer severe side effects.[7,12,14,15] In 3 studies comparing the safety and efficacy of clomipramine and fluvoxamine in 10-week parallel-design trials, no significant differences in efficacy measurements were reported.[14,16,17] Subjects taking fluvoxamine reported fewer anticholinergic side effects and less sexual dysfunction but more headache and insomnia than those taking clomipramine. OCD has a chronic course, and few patients will achieve complete symptom remission.[3] Long-term treatment is likely for most patients with OCD; thus, substantial symptom relief, better drug tolerability, and a more convenient dosing regimen are all important for treatment

compliance. Discontinuation of treatment results in a resurgence of symptoms in up to 80% of patients, even after treatment has been administered for more than 2 years.[18] In one study, the risk of relapse was 2.7 times greater in patients who discontinued therapy compared with patients who remained on medication.[19]

The lag time before response to SSRI treatment in OCD is substantial, generally 5 to 8 weeks and up to 12 weeks.[20] However, pulse loading with intravenous clomipramine[21] and a high-dose initiation of oral SSRI[22] may be associated with a more rapid onset of action.

Fluvoxamine maleate has been shown to be effective in a number of double-blind, controlled treatment studies in OCD,[9,10,14,16] social anxiety disorder,[23] panic disorder,[24,25] chronic posttraumatic stress disorder,[26] and major depressive disorders.[27–31] Fluvoxamine maleate should be administered twice daily. A new, controlled-release (CR) formulation of fluvoxamine maleate, fluvoxamine CR, with different pharmacokinetic properties, has been developed. The ability to administer fluvoxamine CR once daily may increase patient compliance with long-term therapy, and reduced fluctuations in plasma concentration may be associated with fewer side effects and greater symptom improvement. The present study was conducted to investigate the safety and efficacy of once-daily dosing of fluvoxamine CR in patients with OCD.

METHOD

Study Design

This multicenter, randomized, double-blind, placebo-controlled study compared the efficacy and safety of flexible dosing of fluvoxamine CR (100–300 mg/day) with placebo during a 12-week treatment period in subjects with OCD. The protocol was approved by the institutional review boards at each clinical site. Following a 1-week placebo washout, subjects were randomly assigned to receive either fluvoxamine CR or placebo. Subjects randomly assigned to receive fluvoxamine CR began at a bedtime dose of 100 mg and were titrated weekly as tolerated in 50-mg increments to a bedtime dose between 100 and 300 mg/day over the first 6 weeks of treatment; thereafter, the dose was to remain constant for the duration of the double-blind period. Subjects unable to tolerate the dose of 100 mg during the first week of treatment were discontinued from the study. After week 1 and through the end of week 6, the dose could be decreased, in the event of an intolerable adverse event, to 1 capsule from the usual prescription of 2 capsules at bedtime. If an intolerable adverse event required a dose decrease after week 6, the subject was discontinued from the study. No increase in dose was permitted after a decrease. Adherence to study regimen was assessed by pill counts, and patients who took less than 80% or more than 120% of a prescribed dosage during the interval between visits on 2 or more occasions were considered nonadherent and discontinued from the study. During the double-blind treatment phase, efficacy was assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS)[32] and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.[33] YBOCS and CGI-S assessments were performed at screening, at day 1 (baseline), and at the end of weeks 2, 4, 6, 8, 10, and 12; the CGI-I was administered at all visits after baseline. Safety measures obtained at every visit included vital signs, weight, adverse events, and concomitant medications. An electrocardiogram (ECG) and physical examination were performed at the screening and week 12 visits; laboratory testing (serum chemistry, hematology, and urinalysis) was performed at screening, baseline, and weeks 6 and 12. All week 12 assessments were performed upon early discontinuation.

Subject Selection

Male and female outpatients aged 18 years or older were eligible if they met the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria for OCD and the diagnosis was confirmed through the Structured Clinical Interview for DSM-IV.[34] Subjects were required to have scores of 21 or higher on the YBOCS and 16 or lower on the 17-item Hamilton Rating Scale for Depression.[35]

Subjects with any other current primary DSM-IV diagnosis were excluded from participation in the study. Also excluded were subjects considered to be at significant risk of suicide; subjects with unstable or serious medical conditions, clinically significant ECG abnormalities, or clinically significant laboratory abnormalities; and subjects with a positive urine drug test at screening. Women who were pregnant, lactating, or of childbearing potential and not using a medically acceptable method of contraception were excluded. Subjects who received electroconvulsive therapy within 90 days prior to or during the study were excluded. Subjects with a documented history of nonresponse to an adequate trial of an SRI for treatment of OCD, defined as no clinically meaningful improvement after at least 6 weeks of therapy with a therapeutically relevant dose, were excluded. The following concomitant medications were not allowed during the study: psychotropic or psychotherapeutic drugs, astemizole, cisapride, terfenadine, theophylline, warfarin, digoxin, diltiazem, propranolol, and any over-the-counter herbal remedies or weight loss agents with suspected psychotropic properties. After a complete description of the study was provided to the subjects, written informed consent was obtained.

Statistical Methodology

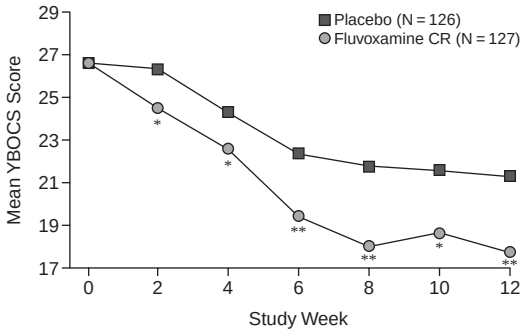
All analyses of the efficacy parameters were performed on the intent-to-treat population, which included

Table 1. Characteristics of OCD Patients at Baseline by Treatment

Characteristic	Fluvoxamine CR (N = 127)	Placebo (N = 126)	p Value
Age, y			
Mean ± SE	38.1 ± 1.1	36.7 ± 1.0	.335
Range	19–70	18–69	
Gender, N (%)[a]			.232
Male	51 (40)	41 (33)	
Female	76 (60)	85 (67)	
Duration of current episode of OCD, y			
Mean ± SE	16.2 ± 1.2	16.5 ± 1.2	.959
Range	0–55	0–55	
Baseline YBOCS total score			
Mean ± SE	26.6 ± 0.3	26.3 ± 0.3	.460
Range	21–38	21–36	
Baseline CGI-S score			
Mean ± SE	4.7 ± 0.1	4.6 ± 0.1	.157
Range	4–7	3–7	
HAM-D score, mean ± SE	6.8 ± 3.6	7.3 ± 3.7	.190

[a]Percentages are based on the number of subjects randomly assigned to treatment.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 1. Mean YBOCS Total Scores (LOCF) During Treatment With Fluvoxamine CR or Placebo in the Intent-to-Treat Population With OCD



*p < .050.
**p < .010.
Abbreviations: CR = controlled release, LOCF = last observation carried forward, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

all subjects who were randomly assigned to double-blind therapy, had at least 1 dose of study medication, had a baseline efficacy evaluation, and had at least 1 evaluable postbaseline efficacy measurement on any efficacy parameter. Statistical analyses were performed using data from visitwise and the last-observation-carried-forward (LOCF) algorithms. All statistical tests were 2-sided and were considered statistically significant if $p < .05$. The changes from baseline to endpoint in YBOCS and CGI-S scores using LOCF, as well as CGI-I scores using LOCF, were analyzed using an analysis of variance model with terms for treatment and pooled center. Responder and remitter analyses were implemented by Fisher exact test and were considered as significant if $p < .05$.

RESULTS

A total of 253 subjects were randomly assigned to treatment in this study: 127 subjects in the fluvoxamine CR treatment group and 126 subjects in the placebo group. There were no statistically significant differences between the 2 groups in demographics or disorder characteristics at baseline (Table 1). Of the subjects randomly assigned to treatment, 117 (92%) in the fluvoxamine CR group and 120 (95%) in the placebo group were included in the efficacy analyses. Sixteen subjects were excluded from the efficacy analyses because no study medication was taken or no postbaseline efficacy assessment was measured. The mean daily dose of fluvoxamine CR over the duration of the study was 210 mg and at the endpoint was 271 mg, compared with placebo equivalent doses of 231 mg and 293 mg, respectively.

Subjects treated with fluvoxamine CR experienced a statistically significant improvement from week 2 compared with those treated with placebo in the primary efficacy variable of YBOCS total score. This improvement was sustained at all subsequent visits (Figure 1). The mean ± standard error decrease from baseline to endpoint in YBOCS total score was 8.5 ± 0.7 (31.7% change) in the fluvoxamine CR treatment group compared with 5.6 ± 0.7 (21.2% change) in the placebo treatment group ($F = 10.48$, $df = 1,218$; $p = .001$) (Table 2).

Analysis of both the obsession and compulsion subtotals of the YBOCS also revealed a significant treatment difference in favor of fluvoxamine at endpoint, with mean ± SE reductions on both obsession subtotal (5.2 ± 0.4 [39.6% change] vs. 3.1 ± 0.4 [24.4% change]; $F = 12.6$, $df = 1,218$; $p < .001$) and compulsion subtotal (4.7 ± 0.5 [34.3% change] vs. 3.4 ± 0.4 [24.8% change]; $F = 3.96$, $df = 1,218$; $p = .048$). Of note, the significant treatment effect first appeared at week 2 for the obsession subtotal and at week 6 for the compulsion subtotal (Figure 2).

This strong positive response observed for the primary efficacy variable was supported by the results for the secondary efficacy variables (Table 2). Fluvoxamine CR was statistically superior in producing clinical improvement, as measured by the CGI-I, when compared with placebo. The difference was significant from week 2 onward (Figure 3). The center effect was tested for both primary and secondary efficacy measurements, and the variability among the centers was not statistically significant.

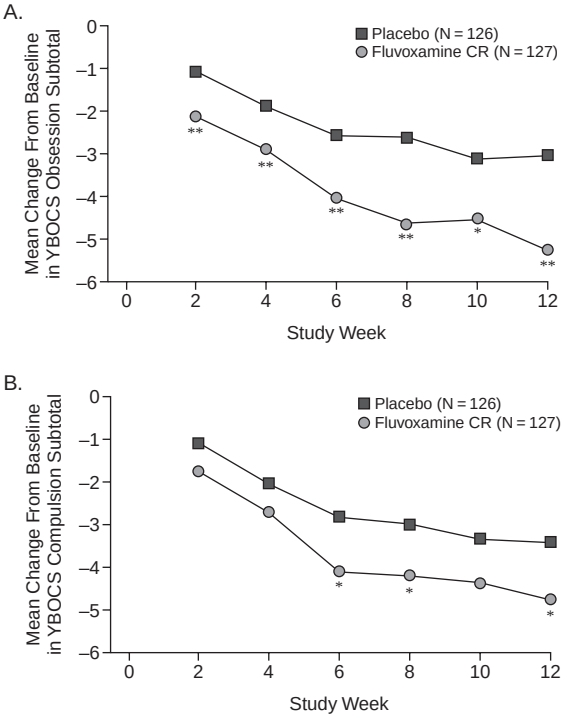
A responder was defined as any subject whose CGI-I rating was "very much improved" or "much improved." The significant difference in response rates between the treatment groups was observed from visit 2 onward (Figure 4).

Table 2. Efficacy Parameters in OCD Subjects[a]

Efficacy Parameter	Fluvoxamine CR (N = 117)	Placebo (N = 120)	p Value
YBOCS total score			
Baseline	26.8 ± 0.3	26.4 ± 0.3	
Endpoint[b]	17.6 ± 1.1	21.0 ± 1.0	
Change from baseline	–8.5 ± 0.7	–5.6 ± 0.7	.001[c]
CGI-S score			
Baseline	4.7 ± 0.1	4.6 ± 0.1	
Endpoint[b]	3.8 ± 0.3	4.1 ± 0.3	
Change from baseline	–1.0 ± 0.1	–0.6 ± 0.1	.002[c]
CGI-I score			
Endpoint[b]	2.7 ± 0.1	3.2 ± 0.1	
Range	1–5	1–6	< .001[d]
Responder, N (%)[e]	51 (44)	28 (23)	.002[f]

[a]Values are expressed as least squares mean ± standard error unless otherwise noted.
[b]Endpoint is defined as the last postbaseline value while on study medication.
[c]p Value for fluvoxamine CR versus placebo treatment group is based on an analysis of variance (ANOVA) model fit to the rank of the change from baseline YBOCS (or CGI-S) score with terms for treatment and pooled center.
[d]p Value for fluvoxamine CR versus placebo treatment group is based on an ANOVA model fit to the value of CGI-I score with terms for treatment and pooled center.
[e]The percentages (44% and 23%) are ratios of responders to total intent-to-treat population.
[f]p Value for fluvoxamine CR versus placebo treatment group is based on Fisher exact test.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 2. Mean Change From Baseline in YBOCS (A) Obsession and (B) Compulsion Subtotal Scores (LOCF) During Treatment With Fluvoxamine CR or Placebo in the Intent-to-Treat Population With OCD



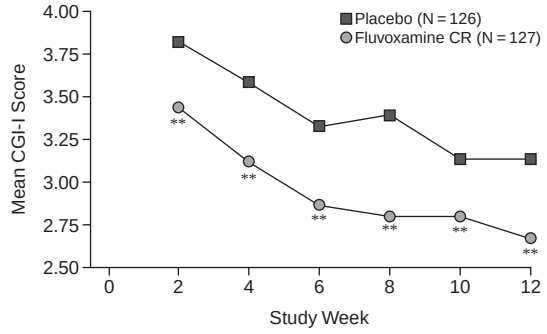
*p < .050.
**p < .010.
Abbreviations: CR = controlled release, LOCF = last observation carried forward, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

To provide a benchmark for future OCD clinical trials, we also performed a post hoc analysis on responder rate according to criteria often utilized by others, including YBOCS decrease of 25% or greater and 35% or greater. Using YBOCS decrease of 25% or greater as the definition of response, 74 subjects (63%) responded in the fluvoxamine CR treatment group, while 55 subjects (46%) responded in the placebo group at the endpoint (p = .009, Fisher exact test). Using YBOCS decrease of 35% or greater as the definition of response, 53 subjects (45%) responded in the fluvoxamine CR treatment group, while 36 subjects (30%) responded in the placebo group at the endpoint (p = .016, Fisher exact test).

In another post hoc analysis, we decided to compare the remission rate in the fluvoxamine CR– and placebo-treated groups. Although there is no universally accepted definition of remission for OCD, we analyzed our data using 2 different YBOCS scores as the definition of remission. When we used a YBOCS total score of ≤ 8 at endpoint, which generally corresponds to mild symptom severity with minimal functional interference, as the definition of remission, 21 subjects (18%) in the fluvoxamine CR treatment group experienced a remission at the end of the study compared with 9 subjects (8%) in the placebo group (p = .019, Fisher exact test). A YBOCS total score of ≤ 16 at endpoint generally corresponds to subclinical symptom severity, and patients with this severity level have been excluded from entry into all previous SSRI clinical trials for OCD. When we used this definition of remission, 51 subjects (44%) in the fluvoxamine CR treatment group experienced a remission at the end of the study compared with 37 subjects (31%) in the placebo group (p = .045, Fisher exact test). Of note, all of the above post hoc analyses showed significant separation of fluvoxamine CR from placebo.

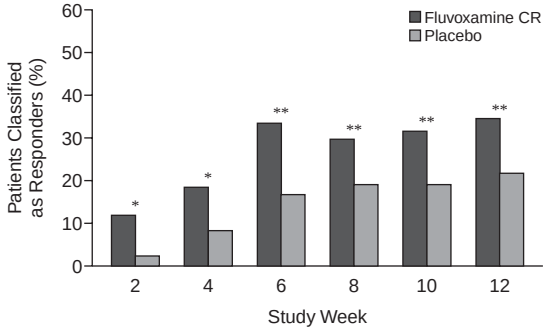
The analysis of safety data showed that, of the 253 subjects who were randomly assigned to treatment, 84 subjects (66%) in the fluvoxamine CR treatment group and 95 subjects (75%) in the placebo treatment group completed the study. Of 253 subjects, 124 subjects in each group were included in the safety analysis because 3 subjects in the fluvoxamine CR treatment group and 2 subjects in the placebo treatment group took no medication. The reasons for withdrawal were similar across the treatment groups except for withdrawal due to adverse experiences. A higher percentage of subjects in the fluvoxamine CR treatment group (23 subjects, 19%) discontinued due to adverse experiences than in the placebo treatment group (8 subjects, 6%). The majority of those adverse experiences were reported to be in the nervous system in both

Figure 3. Mean CGI-I Scores (LOCF) During Treatment With Fluvoxamine CR or Placebo in the Intent-to-Treat Population With OCD



**p < .010.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CR = controlled release, LOCF = last observation carried forward, OCD = obsessive-compulsive disorder.

Figure 4. Percentage of Subjects Classified as "Responders"[a] on the CGI-I Among Completed Subjects (observed data analysis) During OCD Treatment With Fluvoxamine CR or Placebo



[a]Defined as "much improved" or "very much improved" on the CGI-I.
*p < .050.
**p < .010.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CR = controlled release, OCD = obsessive-compulsive disorder.

treatment groups. For fluvoxamine CR, the 5 most common adverse events associated with discontinuation and reported by more than 2 subjects were nausea (7 subjects, 6%), insomnia (6 subjects, 5%), somnolence (5 subjects, 4%), dizziness (4 subjects, 3%), and diarrhea (3 subjects, 2%). For placebo, the only adverse event associated with discontinuation reported by more than 2 subjects was insomnia (3 subjects, 2%). No deaths were reported during this study. A total of 5 serious adverse events were reported for 5 subjects in the fluvoxamine CR treatment group, and 2 serious adverse events were reported for 2 subjects in the placebo treatment group during this study. All serious adverse events were judged by the investigator to be either unlikely to be related or unrelated to study medication. Most subjects reported at least 1 treatment-emergent sign or symptom during the study (fluvoxamine CR, 120 subjects [97%]; placebo, 106 subjects [85%]). Treatment-emergent signs and symptoms reported by ≥ 10% of the subjects in either treatment group and with a higher incidence (≥ 5% difference) in the fluvoxamine CR treatment group are displayed in Table 3. These signs and symptoms fell predominately into the gastrointestinal (nausea, diarrhea, anorexia) and central nervous (insomnia, somnolence, asthenia) body systems.

Table 3. Treatment-Emergent Signs and Symptoms Reported by ≥ 10% of Subjects and With a Difference in Incidence (≥ 5%) Between Treatment Groups: Safety Population, N (%)

COSTART Preferred Term	Fluvoxamine CR (N = 124)	Placebo (N = 124)
Insomnia	43 (35)	25 (20)
Nausea	42 (34)	16 (13)
Somnolence	34 (27)	14 (11)
Asthenia	31 (25)	10 (8)
Infection	23 (19)	34 (27)
Diarrhea	22 (18)	10 (8)
Anorexia	16 (13)	6 (5)

Abbreviation: CR = controlled release.

Treatment-emergent signs and symptoms related to sexual dysfunction (abnormal ejaculation, anorgasmia, impotence, and decreased libido) were specially evaluated. Abnormal ejaculation and anorgasmia were only reported for subjects in the fluvoxamine CR treatment group (4 subjects [8%] and 6 subjects [5%], respectively). Impotence was reported for 3 subjects (2%) in the fluvoxamine CR treatment group and for 2 subjects (2%) in the placebo treatment group. Decreased libido was reported for 9 subjects (7%) in the fluvoxamine CR treatment group and 4 subjects (3%) in the placebo treatment group.

Throughout the course of the study, the mean change from baseline in body weight was between –0.8 kg (–1.8 lb) and 0.1 kg (0.2 lb) in the fluvoxamine CR treatment group compared with 0.0 kg (0.0 lb) to 0.5 kg (1.1 lb) in the placebo group.

Assessment of medication compliance data showed that 86% of subjects in the fluvoxamine CR treatment group were medication adherent (taking between 80%–120% of the prescribed dose) compared with 92% of subjects in the placebo treatment group (p = .258, Fisher exact test).

DISCUSSION

This study demonstrated that fluvoxamine CR was significantly superior to placebo in all efficacy measures, including the change from baseline to endpoint in YBOCS and CGI-S scores, as well as CGI-I score and responder rate at endpoint. The magnitude of the decrease from baseline in YBOCS total score (fluvoxamine CR 8.5 ± 0.7 [31.7% change] vs. placebo 5.6 ± 0.7 [21.2% change])

and CGI-I score (fluvoxamine CR 2.7 ± 0.1 vs. placebo 3.2 ± 0.1) at endpoint for subjects treated with fluvoxamine CR in this study was similar to those observed in previous studies of fluvoxamine,[9,10] fluoxetine,[11] paroxetine,[12] and sertraline.[13] While differences of 2.9 points in YBOCS total score and 0.5 points in CGI-I score between the fluvoxamine CR and placebo groups are numerically small, a substantial number of fluvoxamine CR–treated subjects showed robust improvement in OCD symptoms.

Of interest, the differences between fluvoxamine CR and placebo achieved statistical significance at week 2 in the primary efficacy variable, YBOCS total score, and in the secondary efficacy variables, CGI-I score and responder rate. Fluvoxamine CR showed consistent earlier onset of therapeutic effects across different efficacy parameters compared with results of previous studies involving other SSRIs. In those large placebo-controlled studies, fluoxetine and paroxetine achieved statistically significant improvement over placebo in YBOCS total score from week 5 and week 6, respectively.[11,12] Sertraline achieved statistically significant improvement in YBOCS total score from week 2, but this early onset was not observed in other efficacy measurements.[13] A recent sertraline study with a rapid titration regimen (150 mg/day reached at day 5 from the beginning of therapy) did show an early separation at weeks 4 and 6 from the slow titration regimen (150 mg/day reached at day 15).[22] The original formulation of fluvoxamine achieved statistically significant improvement in YBOCS score from week 6, in CGI-I score from week 4, and in responder rate from week 4 or week 6.[9,10] In contrast, the SSRI clomipramine showed statistically significant separation from placebo starting at week 1 or week 2.[36]

When the obsession and compulsion subtotals of the YBOCS were analyzed separately, the significant treatment differences between fluvoxamine CR and placebo were observed from week 2 in obsessions and from week 6 in compulsions. Those results are in the same direction as the previous fluvoxamine study; in that study, however, fluvoxamine did not achieve statistically significant improvement over placebo until week 4 in obsessions and week 10 in compulsions.[9] These findings imply an earlier effect on the emotional and cognitive aspects that comprise obsessions in OCD; compulsive rituals, which can be overt or covert, appear to respond later. This is consistent with the learning theory perspective, which posits that obsessions engender anxiety, whereas compulsions are attempts to reduce anxiety. In some patients with OCD, treatment response may follow a sequential process that is the reverse of symptom development such that patients "give up" their compulsions only after the anxiety or discomfort associated with obsessions is first reduced. Another implication is that fluvoxamine CR has potentially early antianxiety effects, a testable hypothesis.

The marked response to SSRIs in OCD normally takes 5 to 8 weeks and may take up to 12 weeks to achieve.[20] The finding that fluvoxamine CR has significant early onset of therapeutic effects may have important implications. The current study had a 50% larger sample size compared with previous fluvoxamine studies,[9,10] but this did not seem to account for the earlier separation of treatment response in this study. There are several possible explanations for the early onset. First, because fluvoxamine CR is a controlled-release formulation with less daily fluctuation in drug concentration (peak to trough concentration), subjects may spend more time every day above the minimal therapeutic effective concentration. Second, because fluvoxamine CR has a lower maximal concentration compared with fluvoxamine after the same dosing, subjects were started at a higher dosage of fluvoxamine CR but still enjoyed a similar safety profile, akin to a pulse-dosing strategy with clomipramine.[21] With this consideration, a more aggressive dosing strategy was adopted at the beginning of the titration phase of the present study. Subjects began to take fluvoxamine CR at a dose of 100 mg/day (the minimal effective dose level of conventional fluvoxamine) and were titrated in increments of 50 mg per week. In previous fluvoxamine studies, subjects started at a dose of 50 mg/day, then increased to 100 mg/day after 4 days and to 150 mg/day after 8 days.[9,10] Thus, subjects in the present study received a total of 850 mg of fluvoxamine CR over the first 8 days, compared with 600 mg of fluvoxamine maleate in the earlier fluvoxamine trials, and this increase was most evident over the first 4 days. The mean daily dose at the endpoint of this study was 271 mg for fluvoxamine CR, compared with 215 mg to 251 mg over the maintenance phase in the previous fluvoxamine studies.[9,10] The results from this aggressive dosing are in accord with a recent study suggesting early response with a high initial dose of SSRI.[22] Third, conceivably, the more rapid dose escalation of fluvoxamine CR compared with conventional fluvoxamine may allow for early effects on gene expression, as has been suggested in pulse-loading intravenous treatment studies in OCD.[21]

The proportion of subjects classified as "responders" to fluvoxamine CR, based on their CGI-I score, increased steadily throughout the study. At endpoint (LOCF), 44% of fluvoxamine CR–treated subjects were considered "much improved" or "very much improved" compared with 23% of subjects in the placebo group. The response level was similar to that observed in a previous study of fluvoxamine versus placebo (38% and 15%, respectively).[10] This response level was also similar to those observed in other SSRI studies using the same definition of responders: sertraline 39% versus placebo 30%,[13] and fluoxetine 38% without placebo data.[5] With other definitions of response (YBOCS decrease of ≥ 25% or YBOCS decrease of ≥ 35%), the levels of response were within the range of response levels reported for other SSRIs in OCD

clinical studies.[11,12] As a measure of the magnitude of the clinical effect, significantly more patients in the fluvoxamine CR treatment group experienced a "remission" (as defined by both endpoint YBOCS score ≤ 8 and YBOCS score ≤ 16) compared with the placebo group.

The analysis of safety data showed that fluvoxamine CR was safe and well tolerated in the dosage range of 100 to 300 mg/day over the 12-week treatment period. The good tolerability of fluvoxamine CR is also reflected in the high medication compliance rate (86%) in this treatment group. Although a higher percentage of subjects in the fluvoxamine CR treatment group (19%) discontinued due to adverse events when compared with the placebo treatment group (6%), discontinuation was comparable to that observed in previous fluvoxamine studies (fluvoxamine 19% vs. placebo 7.7% in one study[9] and fluvoxamine 11.3% vs. placebo 1.3% in another[10]), even though the starting dose in the current study was higher (100 mg/day) and taken once daily instead of the divided doses used in prior studies. The percentage of discontinuation due to adverse experiences for fluvoxamine CR is within the range of percentage reported for other SSRIs in OCD clinical studies.[11–13] Of note, there was no weight gain with fluvoxamine CR.

In conclusion, a 12-week study of fluvoxamine CR treatment, given once daily, was associated with a statistically significant and clinically relevant reduction in OCD severity, resulting in onset of therapeutic effects starting from week 2. Results also indicated that it was a safe and generally well-tolerated medication.

Drug names: clomipramine (Anafranil and others), digoxin (Lanoxin, Lanoxicaps, and others), diltiazem (Cardizem CD, Cartia XT, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil), propranolol (Inderal and others), sertraline (Zoloft), theophylline (Slo-Bid, Aerolate, and others), warfarin (Coumadin and others).

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