Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial

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Abstract

Fluvoxamine CR has been reported effective in the short-term (12-wk) treatment of generalized social anxiety disorder (social phobia). Social anxiety disorder (SAD) is, however, a chronic disorder thought to require maintenance treatment. We report on data from the extension phase of a short-term study, in order to explore the efficacy and safety profile of fluvoxamine CR (100–300 mg/d) in the longer-term treatment of this disorder. Adult outpatients with generalized social anxiety disorder (GSAD) at 35 centres in Europe, South Africa, and USA were included in an acute phase study (12 wk). Subjects who demonstrated at least minimal improvement by endpoint (n = 112), were offered participation in an extension phase, in which medication was continued for a further 12 wk under double-blind conditions. Efficacy was assessed using the Liebowitz Social Anxiety Disorder Scale (LSAS), the Clinical Global Impression Global Improvement score (CGI-I), the Clinical Global Impressions Severity of Illness score (CGI-S), and the Sheehan Disability Scale (SDS). Safety and tolerability assessments were also performed at regular intervals. Subjects treated with fluvoxamine CR had a numerically greater decrease in LSAS total scores than subjects treated with placebo at endpoint. Analysis of data from baseline (day 1) to endpoint (last observation carried forward) demonstrated that this difference tended towards significance, while severity of illness on the CGI-S and disability on the SDS were significantly lower in the fluvoxamine CR group than in the placebo group. The same trends were observed when only data from weeks 12–24 were included in the analysis; although the magnitude of changes was smaller in the extension phase than in the acute phase, fluvoxamine CR-treated subjects continued to show improvement compared to placebo-treated subjects. Most treatment-emergent signs and symptoms (TESS) were mild to moderate in severity. No unexpected abnormalities were reported on vital signs, electrocardiograms, or laboratory investigations. These data support the long-term efficacy, safety, and tolerability of fluvoxamine CR in the treatment of GSAD. Given the prevalence, persistence, and disability associated with GSAD, and the relative paucity of long-term treatment studies of SAD, the current dataset provides empirical support for the current clinical consensus that pharmacotherapy of this disorder should be continued beyond the acute phase.

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Introduction

Social anxiety disorder (SAD) (or social phobia) is a highly prevalent medical disorder, with lifetime prevalence estimates of 3.8% in the early Epidemiological Catchment Area survey (Schneier et al., 1992); 13% in the later National Comorbidity Study in the USA (Kessler et al., 1994) and 14% in Europe (Weiller et al., 1996). The disorder is disabling to the individual, as evidenced by a range of measures of social, academic, and occupational dysfunction (Mogotsi et al., 2000), and costly to society (Greenberg et al., 1999). The generalized form of the disorder, where fears are related to most social situations is particularly impairing (Kessler et al., 1998). Importantly, SAD is a chronic...
disorder, with a relatively early age of onset, and with ongoing symptoms in untreated subjects (Schneier et al., 1992).

SAD has been shown to respond to specific pharmacotherapy and psychotherapy interventions (Stein and Hollander, 2002). Early work demonstrated the value of monoamine oxidase inhibitors (e.g. phenelzine) and certain benzodiazepines (e.g. clonazepam). However, given the efficacy and tolerability of the selective serotonin reuptake inhibitors (SSRIs) (van der Linden et al., 2000), these agents have become a first-line choice in the medication treatment of SAD (Ballenger et al., 1998; Bandelow et al., 2002). Although the pathogenesis of SAD remains to be delineated fully, this recommendation is consistent with findings suggestive of serotonergic dysfunction in SAD (Stein et al., 2002c). Despite the relative paucity of long-term pharmacotherapy trials of SAD, expert consensus also recommends that maintenance treatment with these antidepressants be continued after the acute phase (Ballenger et al., 1998; Bandelow et al., 2002).

Fluvoxamine maleate (150 mg/d) was the first SSRI to be shown effective for SAD in a short-term (12-wk) randomized placebo-controlled trial (van Vliet et al., 1994), a result that was subsequently replicated in a larger multicentre study that employed a flexible-dose design (up to 300 mg/d) (Stein et al., 1999; van Vliet et al., 1994). A controlled-release formulation of fluvoxamine was subsequently developed. It has similar bioavailability, a lower maximal concentration ($C_{\text{max}}$) at a later time ($T_{\text{max}}$), as well as a slightly longer elimination half-life, compared to the original immediate release form; characteristics expected to produce a lowered incidence of adverse events, and a lower severity of adverse events should they occur, with administration of the drug as a single dose at night. Indeed, fluvoxamine CR was found to be both effective and well-tolerated in a 12-wk randomized, placebo-controlled, fixed-dose study of SAD undertaken in Europe, South Africa and USA (Westenberg et al., In Press). In this paper, we report data from the extension phase of that trial. The objective of the study was to document further changes in subjects’ condition during an additional 12 wk of treatment.

Methods

Design

This was a double-blind, 12-wk extension of a multicentre, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of flexible dosing of fluvoxamine CR (100–300 mg/d) to placebo during a 12-wk treatment period in 300 adult outpatients with generalized social anxiety disorder (GSAD). Subjects ($n=112$) who had completed the acute phase study, and had shown at least minimal improvement [defined as a Clinical Global Impression Global Improvement (CGI-I) score of 3 or less] were eligible and gave written informed consent to participate in this extension phase. Protocols were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and protocols were approved by local Institutional Review Boards at each participating site.

Subjects

Subjects were recruited from 35 centres in Europe (France, Germany, Ireland, The Netherlands, UK), South Africa and USA. Subjects gave informed written consent after risks and benefits of the trial had been fully explained. Inclusion and exclusion criteria for the acute phase have been described in detail elsewhere (Westenberg et al., In Press). Subjects were outpatients, aged 18–70 yr, had a predominant DSM-IV (APA, 1994) diagnosis of GSAD according to the modified Structured Clinical Interview (SCID), and a minimum score of 60 on the Liebowitz Social Anxiety Scale (LSAS) at screening. Women of childbearing potential or less than 1 yr post-menopausal were required to use a medically acceptable method of birth control, while pregnant and lactating women were not eligible. Subjects were excluded if they met any of the following criteria: Subjects with psychiatric disorders deemed to be predominant in the last 6 months including major depressive disorder, dysthymic disorder, or panic disorder; subjects with history or current diagnosis of schizophrenia, other psychotic disorders, bipolar affective disorder, borderline personality, or obsessive–compulsive disorder; subjects who had a score $\geq 18$ on the MADRS at screening, and subjects at serious suicidal risk; subjects with evidence of substance abuse disorder or dependence within the past 6 months, and subjects with positive results on a urine drug screen; subjects with unstable or serious medical conditions; subjects who required formal cognitive behavioural therapy (CBT) to treat social anxiety symptoms within the previous month; and subjects taking psychotropic medications.

Medication

In the acute phase, dosage was titrated weekly during the first 5 wk of the study, from 100 mg up to 300 mg at bedtime, in 50-mg increments, as tolerated. Subjects
were randomized to fluvoxamine CR or placebo according to a centrally generated random allocation sequence, with concealment of the sequence at participating sites, which were provided with numbered packs of fluvoxamine CR or placebo that were identical in appearance. Subjects in the extension phase continued the endpoint dosage of fluvoxamine CR (n = 57) or placebo (n = 55) under double-blind conditions.

**Efficacy, safety, and tolerability assessment**

Efficacy was assessed using the LSAS as a primary measure, and the CGI-I, Clinical Global Impression Severity of Illness (CGI-S), and the Sheehan Disability Scale (SDS), as secondary measures. In the extension phase, these measures were administered every 4 wk (i.e. weeks 12, 16, 20 and 24), or on early termination.

Safety assessments comprised adverse-event monitoring, concomitant medication monitoring, and vital-sign measurement (at weeks 12, 16, 20, 24 or early termination) as well as physical examination, 12-lead electrocardiogram, and clinical laboratory evaluation (haematology, serum chemistry, urinalysis, and urine drug screening, serum β-HCG in females of child-bearing potential) (at weeks 12 and endpoint).

**Statistical analysis**

Given the relatively small number of subjects projected to continue into the extension phase, and the consequent insufficient power to demonstrate statistically significant differences on the primary outcome measure, the objective of the study was to document changes in the subjects’ condition during longer term treatment. Statistical analyses were nevertheless performed on the primary and secondary efficacy parameters for the intent-to-treat (ITT) population, using both last observation carried forward (LOCF) and observed cases. For all efficacy variables, analysis of variance (ANOVA) with treatment and pooled centre as fixed factors was the main analysis. Appropriate tests for normality and homogeneity of variance were performed. All statistical tests were two-sided, and considered significant if \( p < 0.05 \). Treatment-emergent signs and symptoms (TESS) of special interest were defined a priori, included events commonly associated with treatment with SSRIs, and were summarized for each treatment group.

**Results**

**Subjects**

Of 112 subjects who enrolled in the extension phase, 56 subjects (98%) in the fluvoxamine CR-treatment group and 53 subjects (96%) in the placebo-treatment group were included in the ITT population (109 subjects). Three subjects were excluded from the ITT population because they did not have an efficacy evaluation after week 12. Of the 112 subjects who enrolled, 47 (82%) in the fluvoxamine CR-treatment group and 43 (78%) in the placebo-treatment group completed the extension phase. Mean dose of fluvoxamine CR in the extension phase was 181 mg/d, compared to a placebo equivalent dose of 164 mg/d.

At baseline (day 1 of the acute phase), most demographic (age, gender, ethnicity, marital status, years in school, occupational status) and clinical (GSAD duration, LSAS score, presence of Axis II disorders, family history of psychiatric disorder) variables did not significantly differ in subjects in the fluvoxamine CR (n = 56) and placebo (n = 53) groups. Nevertheless, subjects in the placebo group had significantly lower CGI-S scores (\( p = 0.043 \)) and more Axis I disorders (\( p = 0.05 \)) (Table 1). In the placebo group Axis I disorders included major depression (2 subjects), generalized anxiety disorder (1 subject), dysthymia (1 subject), and unspecified (4 subjects), while in the fluvoxamine CR group 2 subjects were diagnosed with dysthymia.

**Efficacy**

A decrease in LSAS total scores was seen in the fluvoxamine CR group compared to the placebo group at week 12 in participants in the acute phase (Figure 1) and at week 24 in participants in the extension phase (Figure 2). This difference in the LSAS was clearly significant at end of the acute phase, and despite the high dropout rate thereafter, analysis of data from baseline (day 1 of the acute phase) to endpoint demonstrated that the LSAS difference tended towards significance (\( p = 0.074 \)) (Table 2). Over the same time frame, severity of illness as measured by the CGI-S and disability as measured by the SDS were significantly lower in the fluvoxamine CR group than in the placebo group (\( p = 0.003 \) and \( p = 0.028 \) respectively), with CGI-I differences in the same direction but not reaching statistical significance (Table 2).

Focusing on data from weeks 12–24 in those patients that remained in the study, it is apparent that further improvement occurred in the fluvoxamine CR-treated subjects compared to placebo-treated subjects (Figure 2, Table 2). Although the magnitude of changes was smaller in the extension phase than in the acute phase, the direction of the changes was the same. Similarly, the percentage of responders (defined as a score of 1 or 2 on the CGI-I, LOCF) was slightly higher
in the fluvoxamine CR group (80%) than in the placebo group (74%), although the difference was not significant ($p = 0.322$). Again, the percentage of remitters (defined by a score of 1 on the CGI-I) was numerically higher in the fluvoxamine CR group (38%) than in the placebo group (28%), but not significantly so ($p = 0.318$).

In general, the results from the observed values analyses for all efficacy parameters were similar to those from the LOCF analyses. Adjustment of the ANOVA model to address baseline differences in CGI-S and comorbid Axis I disorder did not change the significance of the treatment group difference.

**Tolerability and safety**

Serious adverse events were reported by 2 subjects in each treatment group (psychosis and cholelithiasis...
in the fluvoxamine CR group, and unintended pregnancy and pharyngitis in the placebo group), but none was considered related to study medication. Five subjects (9%) in the fluvoxamine CR group and 2 subjects (4%) in the placebo group discontinued due to an adverse event. Most TESS were mild to moderate in severity, with no individual TESS evaluated as severe in more than 1 subject in the fluvoxamine CR group or 2 subjects in the placebo group.

The overall incidence of TESS (i.e. subjects who experienced at least one TESS) was higher in the fluvoxamine CR group (39 subjects, 68%) than in the placebo group (29 subjects, 53%). TESS reported by ≥5% of the subjects in either treatment group with a higher incidence (≥5% difference) in the fluvoxamine CR group were limited to sweating (fluvoxamine CR, 5 subjects, 9%; placebo, 2 subjects, 4%), nausea (fluvoxamine CR, 4 subjects, 7%; placebo, 1 subject, 2%), and abnormal ejaculation (fluvoxamine, 4 subjects, 7%; placebo, 0 subjects). The TESS profile was similar in the acute and extension phase in both the medication and placebo groups.

TESS of special interest were reported for a higher percentage of subjects in the fluvoxamine CR group (12 subjects, 21%) than in the placebo group (8 subjects, 15%). Notably, TESS associated with sexual dysfunction were more common in the fluvoxamine CR group (9 subjects, 16%) than in the placebo group (3 subjects, 5%). TESS reported by ≥5% of the subjects in the fluvoxamine CR group as study related included asthenia, headache, nausea, dry mouth, insomnia, sweating, and abnormal ejaculation.

No trends were observed suggesting a relationship between fluvoxamine CR and serious abnormalities on vital signs, electrocardiagrams, or laboratory investigations. In particular, there was no significant difference between fluvoxamine CR and placebo groups with respect to markedly abnormal change in body weight, defined as 7% or more weight gain or loss, during the study. Indeed, further exploration of data on weight demonstrated that subjects in the fluvoxamine CR group weighed 74.7 (1.9) kg at day 1 and 75.4 (1.9) kg at week 24, while subjects in the placebo group weighed 73.7 (2.2) kg at day 1 and 74.4 (2.2) kg at week 24 (LOCF), with no significant difference in weight change between the two groups (p = 0.715).

**Conclusion**

The current data show that during maintained treatment from weeks 12–24, subjects on fluvoxamine CR continued to improve, in contrast to subjects on placebo. Although the magnitude of such changes are smaller than those seen in the acute phase, evidence that continued improvement is seen during longer term administration of medication supports the current expert consensus that treatment of SAD should continue beyond the acute phase (Ballenger et al., 1998; Bandelow et al., 2002). It is also consistent with a number of previous placebo-controlled studies of both

<table>
<thead>
<tr>
<th>Scale</th>
<th>Treatment group</th>
<th>Mean score on day 1</th>
<th>Mean (s.t.) change from Day 1 to week 12</th>
<th>Mean (s.t.) change from Day 1 to week 24</th>
<th>Mean (s.t.) change from Week 12 to week 24 (endpoint)</th>
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<tr>
<td>LSAS</td>
<td>Fluvoxamine CR</td>
<td>98.2</td>
<td>−53.2 (4.0)</td>
<td>−59.1 (4.0)</td>
<td>−6.3 (1.6)</td>
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<td>p value 0.260</td>
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<td>0.109</td>
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<td>97.7</td>
<td>−47.9 (3.6)</td>
<td>−49.5 (3.8)</td>
<td>−1.6 (1.6)</td>
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<td>(n = 53)</td>
<td></td>
<td></td>
<td>p value</td>
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<tr>
<td>CGI-S</td>
<td>Fluvoxamine CR</td>
<td>5.0</td>
<td>−2.2 (0.2)</td>
<td>−2.6 (0.2)</td>
<td>−0.4 (0.1)</td>
</tr>
<tr>
<td>(n = 56)</td>
<td></td>
<td></td>
<td>p value 0.017*</td>
<td>0.003**</td>
<td>0.133</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4.7</td>
<td>−1.8 (0.2)</td>
<td>−1.9 (0.2)</td>
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<tr>
<td>(n = 53)</td>
<td></td>
<td></td>
<td>p value</td>
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<td></td>
</tr>
<tr>
<td>SDS</td>
<td>Fluvoxamine CR</td>
<td>19.0</td>
<td>−11.5 (1.0)</td>
<td>−12.9 (1.0)</td>
<td>−1.5 (0.3)</td>
</tr>
<tr>
<td>(n = 55)</td>
<td></td>
<td></td>
<td>p value</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Placebo</td>
<td>17.5</td>
<td>−9.4 (0.9)</td>
<td>−9.5 (1.0)</td>
<td>−0.1 (0.5)</td>
</tr>
<tr>
<td>(n = 52)</td>
<td></td>
<td></td>
<td>p value 0.150</td>
<td>0.028*</td>
<td>0.066</td>
</tr>
</tbody>
</table>

* Significant at the 0.050 level. ** Significant at the 0.010 level.
SSRIs (van Ameringen et al., 2001) and monoamine oxidase inhibitors (Fahlen et al., 1995; Liebowitz et al., 1999; Stein et al., 2002a) that have been conducted over the longer term (20 wk or more) in SAD.

Thus, in a 20-wk study of sertraline vs. placebo in GSAD, improvement on placebo reached a plateau during weeks 7–10, whereas the sertraline group gradually increased throughout the study (van Ameringen et al., 2001). Similarly, after a 12-wk moclobemide vs. placebo study, a 24-wk extension phase study showed further improvement in response rate in medication-treated subjects, but not in the placebo group (Stein et al., 2002a). It can therefore be concluded that although response to placebo is not uncommon in multicentre trials of SAD, it is ultimately less robust than the response to effective medication treatment. In the current trial, both social anxiety symptoms and associated disability continued to improve in the medication-treated group during the extension phase.

Despite the potential for showing increased efficacy of different agents over the longer term in SAD, given that many subjects choose not to enter continuation studies (Stein et al., 2002a), and that these are primarily comprised of subjects who have already shown some response to medication or placebo, the power of analyses to differentiate active compound from placebo is limited. In the current trial an ANOVA that included data from day 1 to week 24 only showed a trend towards significance for LSAS, although for CGI-S and SDS statistical significance was reached. The design of relapse prevention studies, in which medication responders are randomized to ongoing medication or to placebo, allows assessment of whether a medication has more enduring efficacy than placebo. The current data are consistent with work demonstrating that SSRIs are able to prevent relapse in the longer term treatment of SAD (Stein et al., 2002b; Walker et al., 2000).

Fluvoxamine CR continued to be safe and well tolerated by subjects during the extension phase reported here. None of the serious adverse events during this phase were judged to be treatment related. In addition, further analysis of TESS, vital signs, ECGs and laboratory evaluations demonstrated no unexpected safety concerns associated with the use of fluvoxamine CR in GSAD. That there was no significant difference in weight gain between fluvoxamine CR- and placebo-treated subjects is particularly important given the possibility that weight gain may be an adverse event associated with the long-term administration of some SSRIs. Indeed, given current expert consensus that the pharmacotherapy of SAD be continued beyond the acute phase, medication tolerability is an important issue. In this study no individual TESS was evaluated as severe in more than one subject in the fluvoxamine CR-treatment group. Furthermore, relatively few subjects withdrew from the study because of adverse events. Of note, the adverse-event profile of fluvoxamine CR was comparable to that of immediate release fluvoxamine maleate.

Several questions remain about the optimal management of SAD in the longer term. These include questions about how best to promote adherence to treatment in a chronic condition, about the optimal sequencing and combination of pharmacotherapy and psychotherapy, and about when medication should be discontinued. Although a recent controlled trial of fluvoxamine found efficacy in child and adolescents with mixed anxiety disorders, including SAD (Research Unit on Pediatric Psychopharmacology Anxiety Study Group, 2001) there is little work on long-term pharmacotherapy in this population, so raising the question of whether the adult data can be extrapolated. For the present, decisions about these kinds of questions should be individualized, and made on the basis of clinical judgement. A medication that requires once daily dosing may be helpful in promoting adherence.

In the interim, the current study is useful in suggesting that fluvoxamine CR is an effective, safe and well-tolerated treatment over the longer term in adults with GSAD. Given the prevalence, persistence and disability associated with SAD, and the relative paucity of long-term treatment studies of this disorder, the current dataset provides empirical support for the current consensus that pharmacotherapy should be continued beyond the acute phase.

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References


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