Efficacy of Fluvoxamine in the Treatment of Major Depression With Comorbid Anxiety Disorders

Shamsah B. Sonawalla, M.D.; Maya K. Spillmann, M.D.; Andrea R. Kolsky; Jonathan E. Alpert, M.D., Ph.D.; Andrew A. Nierenberg, M.D.; Jerrold F. Rosenbaum, M.D.; and Maurizio Fava, M.D.

Background: Major depression with comorbid anxiety disorder is associated with poor antidepressant outcome compared with major depression without comorbid anxiety disorder. The purpose of our study was to assess changes in depressive symptoms and anxiety levels in outpatients with major depression with comorbid anxiety disorder following 12 weeks of open treatment with fluvoxamine.

Method: We enrolled 30 outpatients (mean ± SD age = 39.4 ± 11.3 years; 16 women and 14 men) with DSM-IV major depressive disorder accompanied by one or more current comorbid DSM-IV anxiety disorders in our study. Patients were treated openly with fluvoxamine initiated at 50 mg/day, with an upward titration to a maximum of 200 mg/day (mean ± SD dose = 143 ± 45 mg/day). Efficacy assessments included the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and Clinical Global Impressions-Severity of Illness (CGI-S) and Improvement (CGI-I) scales for both depression and anxiety. Intent-to-treat analysis was used to assess outcome.

Results: The mean ± SD number of comorbid anxiety disorders per patient was 2.1 ± 1.1. Following fluvoxamine treatment, the mean ± SD HAM-D-17 score dropped from 20.2 ± 3.3 to 11.0 ± 7.0 ($p < .0001$). The mean ± SD depression CGI-S score dropped from 4.0 ± 0.6 to 2.4 ± 1.1 ($p < .0001$), and the mean ± SD anxiety CGI-S score decreased from 4.1 ± 0.8 to 2.5 ± 1.2 ($p < .0001$). Eighteen (60%) of the 30 patients had CGI-I scores ≤ 2 for both anxiety and depression at endpoint, with 53% showing a ≥ 50% reduction in HAM-D-17 scores at endpoint.

Conclusion: Although preliminary, our findings suggest that fluvoxamine is effective in treating outpatients with major depression with comorbid anxiety disorder, having a significant effect on both depression and anxiety symptoms. Further double-blind, placebo-controlled trials are needed, in a larger sample, to confirm our findings.

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Reprint requests to: Shamsah B. Sonawalla, M.D., Department of Psychiatry, WACC 812, 15 Parkman St., Massachusetts General Hospital, Boston, MA 02114.

Major depressive disorder, when accompanied by one or more comorbid anxiety disorders, is characterized by distinct pathophysiology, course and outcome, and treatment response.[1–3] In a study of 294 outpatients with major depressive disorder, we found that depressed patients with a comorbid anxiety disorder were significantly more likely to be nonresponders to fluoxetine treatment than depressed patients without a comorbid anxiety disorder.[2] Brown et al.,[3] in a study of 157 primary care patients with major depression, reported that depressed patients with a comorbid anxiety disorder presented with significantly more psychopathology and tended to prematurely terminate treatment more frequently than patients with major depression alone.

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) approved in the United States for the treatment of obsessive-compulsive disorder (OCD) since December 1994. For many years, it has been marketed for the treatment of depression in several European countries. A number of double-blind, placebo-controlled trials have shown fluvoxamine to be effective in the treatment of OCD,[4–6] panic disorder,[7,8] chronic posttraumatic stress disorder (PTSD),[9] and major depressive disorders.[10–14] Pharmacologically, fluvoxamine is a 2-aminoethyloxime aralkylketone with strong serotonin reuptake inhibiting properties, without significant affinity for postsynaptic receptors, with the exception of a moderate affinity for serotonin 5-HT_2 and α_1-adrenergic receptors.[15] It is a potent inhibitor of cytochrome P450 1A2 isoenzyme (CYP1A2) and is a moderately potent inhibitor at CYP3A4 and CYP2C as well.[16] It has an elimination half-life of about 15 to 20 hours.[17,18]

Given the efficacy of fluvoxamine in anxiety disorders such as OCD and panic disorder, we wanted to assess its efficacy in outpatients with major depression with a comorbid anxiety disorder.

METHOD

The study was carried out at the Depression Clinical and Research Program at the Massachusetts General Hospital (Boston). Study subjects were drawn from an outpatient sample of patients with major depressive disorder accompanied by one or more current comorbid anxiety disorders, diagnosed with the use of the Structured Clinical Interview for DSM-IV (SCID-I/P)[19] and with an initial 17-item Hamilton Rating Scale for Depression (HAM-D-17)[20] score ≥ 16. Over the course of 15 months (July 1996 through October 1997), 30 patients entered this open study. The study protocol was approved by the Institutional Review Board of the Massachusetts General Hospital, and the study was conducted according to the U.S. Food and Drug Administration guidelines for good clinical practice and the Declaration of Helsinki. After a complete description of the study to the patients, a written informed consent was obtained from all patients prior to participation in the study and before protocol-specified procedures were carried out. Patients were required to have a HAM-D-17 score ≥ 16 at both screen and baseline visits, and the HAM-D-17 score could not decrease by 25% or more between these 2 visits. After a 1-week washout period following the screen visit, during which no psychotropic medication was allowed, patients were started on fluvoxamine, 50 mg/day, with an upward titration to 200 mg/day, if tolerated. Patients were assessed weekly for the first 4 weeks of treatment and then every 2 weeks for the remainder of the 12-week study period. No concomitant psychotropic medications were allowed during the study.

The inclusion criteria were as follows: men and women 18 to 65 years of age with a DSM-IV diagnosis of major depressive disorder (single or recurrent, with a current episode of at least 2 weeks' duration); at least one comorbid anxiety disorder, i.e., panic disorder, OCD, social phobia, simple phobia, PTSD, or generalized anxiety disorder (GAD), according to the SCID-I/P; and normal baseline laboratory values or clinically insignificant abnormalities.

Exclusion criteria were as follows: patients with a serious suicidal or homicidal risk; a serious or unstable medical illness; a history of multiple adverse drug reactions or allergy to the study drug; mood-congruent or mood-incongruent psychotic features; current use of other psychotropic drugs; failure to respond during the course of their current major depressive episode to at least one adequate antidepressant trial, defined as 6 weeks or more of treatment with either ≥ 150 mg of imipramine (or its tricyclic equivalent), ≥ 60 mg of phenelzine (or its monoamine oxidase inhibitor equivalent), or ≥ 20 mg of fluoxetine (or its SSRI equivalent); electroconvulsive therapy (ECT) within the 6 months preceding baseline; exposure to either an investigational psychotropic drug or fluoxetine within 40 days of baseline evaluation or to any other psychotropic drug, including benzodiazepines or hypnotics, within 21 days of baseline evaluation; alcohol or substance abuse active within the last year; or comorbid psychiatric disorders such as schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, or significant antisocial personality disorder.

The HAM-D-17 and the Clinical Global Impressions Severity of Illness and Improvement scales[21] for both depression and anxiety (depression CGI-S and CGI-I, anxiety CGI-S and CGI-I) were completed at baseline and at weekly visits. The mood and anxiety disorders module of the SCID-I/P was repeated at visit 8, or endpoint for patients who discontinued the study prior to completion. The self-rated Symptom Questionnaire (SQ)[22] was completed by patients at every study visit.

The medication management sessions were conducted according to the method described by Fawcett and colleagues.[23] Adverse events were monitored and documented at every visit. Vital signs were recorded at each visit, and a physical examination was performed at screen visit and endpoint (either discontinuation or completion). The following concomitant medications were not allowed during the study: psychotropic drugs, terfenadine, astemizole, warfarin, propranolol, cisapride, and any medications containing theophylline.

Data Analysis

The (2-tailed) paired t test method was used to assess the degree of change in symptom severity, as assessed by the HAM-D-17, CGI-S for depression and anxiety, and SQ scores at baseline and endpoint, among patients treated with fluvoxamine. The statistical significance was set at $p < .05$. We used intent-to-treat analysis in examining all patients assigned to treatment and completing the baseline visit.

RESULTS

The mean ± SD age of the 30 outpatients enrolled into the study was 39.4 ± 11.3 years. The mean ± SD number of comorbid anxiety disorders per patient was 2.1 ± 1.1. There were 16 women and 14 men. Eleven of the 30 patients with major depressive disorder had current panic disorder, 17 had current social phobia, 9 had current simple phobia, 4 had current OCD, 6 had current PTSD, and 14 had current GAD. The mean ± SD final dose of fluvoxamine was 143 ± 45 mg/day. Also, eleven of the 30 study patients were previously on treatment with benzodiazepines. Of these 11 patients, 5 had stopped taking benzodiazepines 5 to 27 years prior to entering the study, 1 patient 2 to 3 years prior, 2 patients 1 to 2 years prior, 1 patient 6 months prior, and 1 patient 2 months prior to entering the study; data regarding the duration of benzodiazepine use were unavailable for 1 patient.

Table 1. HAM-D-17, Anxiety and Depression CGI-S and CGI-I, and SQ Scores Before and After Treatment With Fluvoxamine[a]

Measure	Baseline Mean ± SD (N = 30)	Endpoint Mean ± SD (N = 30)
HAM-D-17	20.2 ± 3.3	11.0 ± 7.0*
CGI-S		
Anxiety	4.1 ± 0.8	2.5 ± 1.2*
Depression	4.0 ± 0.6	2.4 ± 1.1*
CGI-I		
Anxiety	3.6 ± 1.0	2.2 ± 1.1*
Depression	3.7 ± 1.1	2.2 ± 1.2*
SQ		
Anxiety	17.7 ± 4.1	9.2 ± 6.9*
Somatic	12.6 ± 4.1	9.0 ± 6.0**
Depression	18.4 ± 6.5	11.1 ± 8.0*
Anger-hostility	12.5 ± 6.3	6.8 ± 6.7***

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SQ = Symptom Questionnaire.
*$p \leq .0001$ vs. baseline (paired t test).
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***$p \leq .001$ vs. baseline (paired t test).

Table 2. Adverse Events Reported in ≥ 2 Patients During the Study

Adverse Event	N Reporting
Gastrointestinal	
Nausea	16
Diarrhea	8
Appetite disturbances	6
Dry mouth	5
Abdominal cramps	4
Flatulence	4
Indigestion	2
Bad taste in mouth	2
Other	
Headache	17
Flu-like symptoms	16
Sedation	11
Insomnia	11
Jitteriness	10
Fatigue	7
Dizziness	7
Sexual side effects	7
"Spacey" feelings	3
Lower back pain	2
Frequent urination	2
Sweating excessively	2
Irritability	2
Vivid dreams	2
Palpitations	2
Weight loss	2

Twelve patients (40%) dropped out before completing the 12-week open study. The reasons for discontinuation were the following: lost to follow-up (N = 5), drowsiness (N = 3), dizziness (N = 2), and noncompliance (N = 2) (1 patient who discontinued for dizziness also had headache and nausea, and the other patient with dizziness also had frequent urination). Four patients discontinued the study medication at week 1, 3 patients at week 3, 1 patient at week 4, 2 patients at week 6, and 2 patients at week 10.

As shown in Table 1, there were significant decreases ($p < .0001$) in HAM-D-17, depression CGI-S, and anxiety CGI-S scores at endpoint among all subjects (N = 30). There were also statistically significant decreases in the anxiety, somatic symptom, depression, and anger-hostility SQ subscales after fluvoxamine treatment.

We defined response as depression and anxiety CGI-I scores of ≤ 2 at endpoint. Twenty (67%) of the 30 depressed patients showed a response with the depression CGI-I at endpoint. Twenty-three (77%) of the 30 patients were also responders on the anxiety CGI-I at endpoint, and 18 (60%) of the 30 patients had CGI-I ≤ 2 for both anxiety and depression at endpoint. Of all patients enrolled into the study, 16 (53%) showed a ≥ 50% reduction in HAM-D-17 scores at endpoint, and 13 (43%) had a HAM-D-17 score of ≤ 7 at endpoint. Twelve (80%) of 15 patients who completed the SCID-I/P for both mood and anxiety disorders at week 12, or earlier if discontinued, no longer met criteria for at least one of their anxiety disorders at endpoint, and 10 (67%) of 15 patients no longer met criteria for both major depressive disorder and at least one of their comorbid anxiety disorders at endpoint.

As shown in Table 2, gastrointestinal adverse events were the most commonly reported, with nausea being the most frequent. There was no significant difference between completers and dropouts in severity of illness at baseline as assessed by HAM-D-17 scores and the number of anxiety disorders as assessed by the SCID-I/P. Completers had a slightly, but not statistically significantly higher, mean ± SD number of adverse events compared with dropouts (7.3 ± 4.5 vs. 5.7 ± 3.4, respectively).

DISCUSSION

Major depression with comorbid anxiety disorder is associated with greater psychopathology [3] and less favorable treatment outcome than depression without comorbid anxiety disorder.[2] In clinical practice, therefore, major depression with comorbid anxiety disorder should be identified and appropriately treated.

In our study, fluvoxamine, at a mean final dose of 143 mg/day, was effective in the treatment of major depression with comorbid anxiety disorder, with significant improvement in both depressive and anxiety symptoms. It is of note that 43% of patients had a HAM-D-17 score of ≤ 7 at endpoint, which shows considerable improvement, given the comorbid nature of the disorder. The findings are consistent across all clinician-rated and patient-rated measures of treatment efficacy. Our findings are in agreement with those of Gonella et al.,[24] who showed, in a double-blind, placebo-controlled study of fluvoxamine and imipramine in major depressive disorder, that although both drugs significantly reduced depressive symptoms, fluvoxamine was significantly more effective than imipramine in reducing suicidal ideas and anxiety-somatic symptoms.

Forty percent of our patients dropped out before completing the 12-week study. This is similar to the dropout rates reported in clinical trials, which are typically between 20% and 40%.[25] No major safety problems were observed in our study, even though 5 patients did drop out owing to adverse events. Gastrointestinal adverse events were the most frequent in our study, and this is in agreement with the findings of previous studies with fluvoxamine.[26]

One possible explanation for the 40% dropout rate in our study is that depressed patients with comorbid anxiety disorder tend to terminate treatment prematurely more frequently than patients with major depression alone.[3] It is also possible that some of these patients dropped out because they could not tolerate the dose titration and were sensitive to side effects. In fact, although one would have expected a higher number of adverse events among dropouts, completers in our study actually showed a greater number of adverse events compared with dropouts. In a previous study,[27] we had reported that outpatients with major depressive disorder and high anxiety sensitivity, that is, higher sensitivity to somatic cues, were more likely to drop out during fluoxetine antidepressant treatment. We did not measure anxiety sensitivity in our study patients here; however, high sensitivity to somatic cues may account, in part, for the 40% dropout rate in our sample.

The findings of our study are limited by the small sample size involved and by the fact that it was an open study without a control group. Given the open nature of the trial, it is not surprising that an antidepressant, such as fluvoxamine, with documented efficacy in both anxiety and depressive disorders was effective in our study patients. However, we cannot rule out the possibility of nonspecific, placebo-like effects that might have accounted for the changes in depression and anxiety severity observed in our patients. Placebo-like effects are typically present in open trials, where response rates tend to be higher than in placebo-controlled trials.[28,29] Long-term studies are needed to study maintenance of improvement in depressive and anxiety symptoms in this population.

In summary, our preliminary results suggest that fluvoxamine is effective in the treatment of major depression with comorbid anxiety disorder. To our knowledge, this is one of the first studies examining the efficacy of SSRIs in major depression with comorbid anxiety disorder. Large, double-blind, placebo-controlled trials are needed to confirm our findings.

Drug names: astemizole (Hismanal), cisapride (Propulsid), fluoxetine (Prozac), fluvoxamine (Luvox), phenelzine (Nardil), propranolol (Inderal and others), theophylline (Theo-Dur and others), warfarin (Coumadin).

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