The Efficacy and Safety of a New Enteric-Coated Formulation of Fluoxetine Given Once Weekly During the Continuation Treatment of Major Depressive Disorder

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Background: A simple, once-weekly dosing regimen could be a convenient alternative for many patients during long-term treatment of depression. Such a strategy might also be effective for improving medication compliance and the outcome of continuation treatment. The safety and effectiveness of a new formulation of enteric-coated fluoxetine (90 mg) given once weekly was tested during the continuation treatment of major depressive disorder.

Method: Patients meeting DSM-IV criteria for major depressive disorder with modified 17-item Hamilton Rating Scale for Depression (HAM-D-17) scores ≥ 18 and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores ≥ 4 were treated 13 weeks with open-label 20 mg/day of fluoxetine in a multicenter U.S. study. Responders (N = 501) were randomly assigned to receive 20 mg of fluoxetine daily, placebo, or 90 mg of enteric-coated fluoxetine weekly for 25 weeks of double-blind continuation treatment. The primary efficacy measure was the percentage of patients who relapsed. Time to relapse was tested over the 25-week continuation period using log-rank analyses of the Kaplan-Meier estimates of relapse rates. Additional analyses of efficacy included comparison of change from baseline to endpoint for the HAM-D-17, CGI-S, and HAM-D-28 subscales by last observation carried forward (LOCF). Safety measures included comparison of treatment-emergent adverse events, both spontaneous and solicited (using the Association for Methodology of Documentation in Psychiatry-Module 5), vital signs, and laboratory measures.

Results: Relapse rates for patients assigned to fluoxetine, either 20 mg daily or 90 mg weekly, were significantly lower than for placebo by log-rank analysis and LOCF analyses of secondary efficacy measures. Efficacy did not significantly differ between the 2 active drug groups by these measures. Enteric-coated fluoxetine at a once-weekly dose of 90 mg was well tolerated, and its safety profile was similar to that of daily 20 mg of fluoxetine.

Conclusion: The formulation of enteric-coated fluoxetine taken once weekly is effective, safe, and well tolerated for continuation treatment of depression in patients who responded to acute treatment with 20 mg/day of fluoxetine. Monitoring during long-term treatment for evidence of sustained remission is important regardless of dosing regimen.

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Despite the efficacy of many antidepressant medications and tolerability of the current generation of antidepressants such as selective serotonin reuptake inhibitors, it has been observed that patients commonly do not take antidepressants for an adequate length of time.[1,2] Factors contributing to such undertreatment include reluctance by the patient to stay on medication for an extended time period, especially when they are feeling well and the benefits of treatment are not immediately apparent. Reluctance to stay on treatment may also stem from objectionable side effects and fear of stigmatization. Simple, once-weekly dosing may provide a strategy for enhancing psychological well-being and overall tolerability, leading to improved compliance with long-term treatment of depression.

Fluoxetine allows for less frequent than once-daily dosing because of the long elimination half-lives of fluoxetine and the active desmethylated metabolite, norfluoxetine. No other oral agents are similarly capable of providing an antidepressant effect during continuation treatment of depression using less frequent intervals than daily dosing. Montgomery and others[3] first explored the possibility of such a regimen by giving weekly doses of fluoxetine for 6 weeks to patients that had responded to acute treatment of depression. Patients randomly assigned to receive 80 mg of fluoxetine weekly were as likely to remain well as patients assigned to 60 mg of fluoxetine daily.[3] In a randomized, double-blind trial, Burke and colleagues[4] evaluated the steady-state pharmacokinetics and efficacy of 60 mg of fluoxetine weekly for 12 weeks of continuation treatment compared with placebo or 20 mg of fluoxetine daily. The results from these 2 studies supported the hypothesis that the antidepressant effect of fluoxetine might be maintained during weekly dosing and could be comparable to that observed during continuation treat-

ment with fluoxetine taken daily. Moreover, weekly doses of 60 mg and 80 mg were reported to be well tolerated by patients in those 2 studies.

To further explore the range of doses having potential for weekly administration, pharmacokinetic modeling was used to generate estimates of the plasma concentrations during weekly dosing with different doses of fluoxetine. Ninety milligrams taken once weekly was predicted to result in mean steady-state plasma concentrations of fluoxetine and norfluoxetine that would lie between the concentrations achieved with 10 mg and 20 mg daily, although the peak-to-trough differences were expected to be greater with weekly dosing.

On the basis of this information, the 90-mg strength was selected as a once-weekly dose for the continuation treatment of depression. To reduce any gastric discomfort that might be associated with such a dose and dosing interval, a novel enteric coating was also developed that was intended to prevent the dissolution of the pellets containing fluoxetine hydrochloride until they have passed into a segment of the gastrointestinal tract where the pH exceeds 5.5. The time to peak plasma concentration is thereby delayed by approximately 2 hours compared with the immediate-release formulation (R. Bergstrom, Ph.D., data on file, Eli Lilly and Company, Indianapolis, Ind.). Adverse events associated with such a dose and dosing regimen, in particular gastrointestinal intolerance, might be lessened by the difference in the site of absorption. This article reports the efficacy and safety of this new once-weekly 90-mg enteric-coated fluoxetine formulation in the continuation treatment of depression. A study of the ability of patients to follow such a once-weekly dosing schedule was also conducted and is reported elsewhere (A. Claxton, Ph.D., manuscript submitted).

METHOD

Patient Population

Patients were male or female outpatients, aged 18 to 80 years, who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[5] criteria for nonpsychotic major depression with a current episode duration of at least 4 weeks and disease severity of at least moderate intensity, confirmed by interview with the Structured Clinical Interview for DSM-IV patient version (SCID-P)[6] (modified 17-item Hamilton Rating Scale for Depression [HAM-D-17][7,8] score of ≥ 18 and a Clinical Global Impressions-Severity of Illness scale [CGI-S][9] score ≥ 4).

Patients with a lifetime history of any psychotic disorder, bipolar mood disorder, or substance abuse disorder in the preceding year or current or recent anxiety disorder that was a primary focus of treatment were excluded. Patients were also excluded if they were previously nonresponsive to an adequate course of fluoxetine antidepressant treatment or if their current episode was unresponsive to 2 or more adequate courses of antidepressant therapy. Patients received no form of psychotherapy directed toward their depression during the study other than good clinical care. Pregnant or lactating patients and patients with unstable medical conditions were also excluded from the protocol.

Temazepam (titrated up to a maximum daily dose of 30 mg) or zolpidem (titrated up to a maximum daily dose of 10 mg) could be taken if needed for insomnia for no more than 8 nights during the acute treatment phase. No such hypnotics were permitted during the double-blind continuation phase. Written informed consent was obtained from all patients in accordance with the Helsinki conventions. The study protocol was approved by the Institutional Review Board of each of the study centers.

Study Design

This was a multicenter, placebo-controlled, double-blind, randomized study conducted at 42 study centers in the United States by psychiatrists. The study consisted of 3 periods, the first of which was an assessment phase (Study Period I). This was followed by a 13-week open-label acute treatment phase (Study Period II) during which all patients received fluoxetine, 20 mg daily. After 13 weeks, patients were evaluated and considered responders if they no longer met the diagnostic criteria for major depressive episode per DSM-IV and had a modified HAM-D-17 score ≤ 9 and CGI-S score ≤ 2 for both of the last 2 visits of Study Period II. Responders were randomly assigned to Study Period III, which consisted of 25 weeks of double-blind continuation treatment with either 90 mg of enteric-coated fluoxetine once weekly; fluoxetine, 20 mg daily; or placebo. To maintain the blind, all patients took 1 capsule of study medication every day (those randomly assigned to the enteric-coated 90-mg fluoxetine weekly dose took placebo on 6 days and active drug 1 day of the 7-day period). If patients had a significant reemergence of depressive symptoms during the continuation phase (50% or more increase in their modified HAM-D-17 total relative to their score at the time of randomization and a modified HAM-D-17 score ≥ 12), they were seen at no more than weekly intervals to monitor for relapse. Relapse was defined as (1) meeting the criteria for major depressive episode, as determined by the SCID-P major depressive episode module, except for symptom duration and (2) an increase in the CGI-S score of 2 or more relative to the rating before randomization, for 2 consecutive visits. Patients who relapsed had 2 options: (1) to discontinue the study and receive open follow-up care, or (2) to participate in a double-blind rescue treatment. Ninety-eight percent of patients who relapsed opted for the double-blind rescue treatment. The study medication dose was increased during the optional rescue therapy phase as follows: (1) patients taking placebo had treatment with fluoxetine, 20 mg/day,

reinitiated; (2) patients taking fluoxetine, 20 mg/day, had their dose increased to 40 mg/day; and (3) patients taking a 90-mg weekly dose had their dose increased to 90 mg twice a week (results in preparation).

Assessments

The primary efficacy measure was the categorical diagnosis of relapse. Additional efficacy measures included ratings on the modified HAM-D-17, HAM-D-28 subscales (core total, subscale 5, anxiety subscale, depressed mood [item 1], sleep, and retardation), and CGI-S. The modified HAM-D-17 was defined as the contribution of the combination of the following items selected from the HAM-D-28: for all patients, items 1–3, 7–11, 13–15, and 17 were combined with either items 4, 5, 6, 12, and 16 (for typical neurovegetative symptoms)[8] or items 22, 23, 24, 25, and 26 (for atypical or reversed neurovegetative symptoms). The higher score on the 2 combinations was used for determining protocol eligibility, response, and relapse. This modification weights atypical symptoms equally to typical symptoms and was used in a previous study of the long-term efficacy of fluoxetine.[10] The HAM-D-28 subscales were defined as follows: core total (sum of items 1, 2, 3, 7, and 8), subscale 5 (sum of items 1, 2, 3, 7, 8, 14, 15, 16, and 17), anxiety subscale (sum of items 10, 11, 12, 13, 15, and 17), sleep (sum of items 4, 5, and 6), and retardation (sum of items 1, 7, 8, and 14).

Safety was assessed by the evaluation of treatment-emergent adverse events, discontinuations for adverse events, and change in clinical laboratory data and vital signs. Adverse events were collected by nonprobing inquiry and were recorded without regard to causality. Supplemental safety data were solicited by the investigator using Association for Methodology of Documentation in Psychiatry-Module 5 (AMDP-5), an extensively validated tool used to review common physical signs and symptoms across 8 major symptom categories.[11] Sexual dysfunction data were collected using a patient rating scale and are reported elsewhere.[12]

Statistical Methods

Patients were included in the continuation phase efficacy, safety, and discontinuation analyses if they had continuation phase baseline and postbaseline measurements. The baseline measurement for the continuation phase efficacy analysis was visit 9 (the visit at which a patient was randomly assigned to a treatment). If this measurement was missing, the baseline was considered visit 8 (the visit immediately prior to randomization to treatment).

The efficacy of enteric-coated fluoxetine, 90 mg weekly; fluoxetine, 20 mg daily; and placebo was compared using time-to-relapse (log-rank) analysis of the Kaplan-Meier survival curves over Study Period III. The log-rank test measures the discrepancy accumulated across the entire duration of continuation treatment.

Baseline-to-endpoint changes of the last observation carried forward (LOCF) for the modified HAM-D-17 total score, HAM-D-28 subscale factors (core total, subscale 5, anxiety subscale, item 1, sleep, and retardation), and CGI-S were compared using an analysis of variance (ANOVA) with treatment, investigator, and treatment-by-investigator interaction as effects in the model.

Patient characteristics, including demographics and severity of illness at the time of entry into the study, were summarized for each treatment group at baseline. Treatment differences were assessed using a chi-square test for categorical variables and an ANOVA with treatment, investigator, and treatment-by-investigator interaction as effects in the model. Reasons for discontinuation from the study and adverse events (either reported spontaneously or solicited using the AMDP-5) that first occurred or worsened during continuation therapy for all patients randomly allocated to treatment were compared between treatment groups using a Pearson chi-square test and Fisher exact test. The treatment effect on mean change from baseline to endpoint in laboratory analyses, vital signs, and total days on therapy was assessed using ANOVA with treatment, investigator, and treatment-by-investigator interaction as effects in the model.

RESULTS

Demographics

Nine hundred thirty-two patients met the required criteria for study entry and proceeded to open-label treatment with fluoxetine, 20 mg daily (Study Period II). A total of 501 patients were randomly assigned to the double-blind continuation treatment phase, having continued to meet study criteria and demonstrate a sustained response to acute treatment. Of these 501 patients, 190 were randomly assigned to treatment with enteric-coated fluoxetine, 90 mg weekly; 189 to fluoxetine, 20 mg daily; and 122 to placebo. Analyses revealed no statistically significant differences between the treatment groups in age, gender, ethnic origin, or baseline disease characteristics such as severity of depression (Table 1).

Efficacy Analyses

Patients taking enteric-coated fluoxetine, 90 mg weekly, and fluoxetine, 20 mg daily, were significantly less likely to relapse than placebo-treated patients by time-to-relapse (log-rank) analysis of the Kaplan-Meier survival curves for the different treatments ($p = .007$ and $p < .001$, respectively). The estimated cumulative proportions of patients relapsing after 25 weeks of continuation treatment were as follows: fluoxetine, 90 mg weekly, 37%; fluoxetine, 20 mg daily, 26%; and placebo, 50%. The difference between the percentage of patients relapsing for the 90-mg weekly group compared with the 20-mg daily group was not statistically significant (Table 2).

Table 1. Patient Demographics and Baseline Scores for All Randomized Patients[a]

Demographic	Fluoxetine 90 mg Weekly (N = 190)	Fluoxetine 20 mg Daily (N = 189)	Placebo (N = 122)	Overall p Value
Female, N (%)	130 (68.4)	134 (70.9)	78 (63.9)	.435
Age, mean (SD)	40.9 (11.5)	41.7 (11.3)	42.0 (11.2)	.706
White, N (%)	174 (91.6)	164 (86.8)	111 (91.0)	.082
Modified HAM-D-17 total, mean (SD)				
Baseline	22.5 (3.4)	22.8 (3.7)	22.8 (3.3)	.678
Randomization	4.1 (2.5)	4.4 (2.7)	3.9 (2.5)	.284
SCID-P diagnosis, N (%)				
MDD	57 (30.0)	52 (27.5)	37 (30.3)	.572
MDD/atypical	33 (17.4)	29 (15.3)	13 (10.7)	
MDD/melancholic	100 (52.6)	107 (56.6)	72 (59.0)	
Previous episodes of depression, N (%)				
No	53 (27.9)	46 (24.3)	42 (34.4)	.154
Yes	137 (72.1)	143 (75.7)	80 (65.6)	

[a]Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, SCID-P = Structured Clinical Interview for DSM-III-R, patient version.

Analysis of baseline-to-endpoint differences (LOCF) of the modified HAM-D-17 total, HAM-D-28 subscale factors, and CGI-S revealed that patients in the placebo group showed significantly greater worsening compared with patients in both active treatment groups on nearly all of the measures. There were no significant differences between the 90-mg weekly and 20-mg daily patients on these efficacy measures (see Table 2).

Patients assigned to fluoxetine, either 90 mg weekly or 20 mg daily, remained in treatment significantly longer than patients assigned to placebo (105 days, 109 days, and 86 days for the 90-mg weekly, 20-mg daily, and placebo groups, respectively; see Table 2).

Safety Analyses

Treatment-emergent adverse events. Of the patients who were randomly assigned to continuation treatment, 370 (73.9%) experienced at least 1 treatment-emergent adverse event. The most frequently occurring treatment-emergent adverse events were headache (10.8%), nervousness (10.4%), rhinitis (9.8%), somnolence (9.2%), and asthenia (9.0%).

The most frequently occurring treatment-emergent adverse events in the 90-mg weekly group were nervousness (13.7%), headache (10.5%), asthenia (9.5%), and diarrhea (9.5%). In the 20-mg daily group, the most frequent events were headache (12.2%), rhinitis (12.2%), somnolence (10.6%), and asthenia (9.5%). In the placebo group, these events were nervousness (11.5%), headache (9.0%), and somnolence (8.2%). The most commonly reported treatment-emergent adverse events among patients treated with 90-mg weekly, 20-mg daily, and placebo were comparable. Table 3 presents those events with an

Table 2. Summary of Efficacy Endpoints for Continuation Treatment[a]

Analysis	Fluoxetine 90 mg Weekly	Fluoxetine 20 mg Daily	Placebo
Kaplan-Meier 25-week relapse rates (%)	37	26	50
Log-rank time-to-relapse, weeks 1–25			
Active vs placebo, p value	.007	< .001	
90 mg weekly vs 20 mg daily, p value	.164		
CGI-S			
Change to endpoint, mean (SD)	1.0 (1.4)	0.9 (1.4)	1.4 (1.5)
Active vs placebo, p value	.010	.001	
90 mg weekly vs 20 mg daily, p value	.394		
Modified HAM-D-17			
Change to endpoint, mean (SD)	6.6 (8.0)	6.4 (8.4)	8.6 (9.2)
Active vs placebo, p value	.032	.016	
90 mg weekly vs 20 mg daily, p value	.719		
Core factor total[b]			
Change to endpoint, mean (SD)	3.1 (3.7)	2.7 (3.9)	4.1 (4.3)
Active vs placebo, p value	.027	.002	
90 mg weekly vs 20 mg daily, p value	.284		
Subscale 5 total[b]			
Change to endpoint, mean (SD)	3.6 (4.5)	3.3 (4.6)	4.8 (5.1)
Active vs placebo, p value	.022	.003	
90 mg weekly vs 20 mg daily, p value	.437		
Sleep total[b]			
Change to endpoint, mean (SD)	0.8 (1.8)	0.9 (1.9)	0.9 (1.9)
Active vs placebo, p value	.487	.921	
90 mg weekly vs 20 mg daily, p value	.501		
Anxiety total[b]			
Change to endpoint, mean (SD)	1.8 (2.5)	1.7 (2.6)	2.4 (2.7)
Active vs placebo, p value	.034	.009	
90 mg weekly vs 20 mg daily, p value	.547		
Retardation total[b]			
Change to endpoint, mean (SD)	2.7 (3.3)	2.3 (3.2)	3.4 (3.8)
Active vs placebo, p value	.063	.003	
90 mg weekly vs 20 mg daily, p value	.197		
Depressed mood (item 1)			
Change to endpoint, mean (SD)	1.1 (1.3)	0.8 (1.3)	1.4 (1.5)
Active vs placebo, p value	.029	< .001	
90 mg weekly vs 20 mg daily, p value	.084		
Total days of therapy (ANOVA)			
Total days, mean (SD)	105.4 (61.9)	109.0 (66.1)	86.2 (65.0)
Active vs placebo, p value	.009	.003	
90 mg weekly vs 20 mg daily, p value	.582		

[a]Abbreviations: ANOVA = analysis of variance, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.
[b]From HAM-D-28.

Table 3. Treatment-Emergent Adverse Events[a] Reported Spontaneously During Continuation Treatment

	Fluoxetine						
	90 mg Weekly (N = 190)		20 mg Daily (N = 189)		Placebo (N = 122)		Overall
Event	N	%	N	%	N	%	p Value
Nervousness	26	13.7	12	6.3[b]	14	11.5	.054
Headache	20	10.5	23	12.2	11	9.0	.668
Asthenia	18	9.5	18	9.5	9	7.4	.815
Diarrhea	18	9.5	9	4.8	4	3.3[c]	.058
Rhinitis	17	8.9	23	12.2	9	7.4	.357
Somnolence	16	8.4	20	10.6	10	8.2	.711
Thinking abnormal	16	8.4	3	1.6[b]	6	4.9	.007
Insomnia	14	7.4	10	5.3	5	4.1	.508
Anxiety	13	6.8	10	5.3	7	5.7	.838
Nausea	12	6.3	8	4.2	9	7.4	.464
Back pain	11	5.8	11	5.8	5	4.1	.849
Abnormal dreams	11	5.8	6	3.2	3	2.5	.333
Dizziness	10	5.3	11	5.8	6	4.9	.937
Depression	10	5.3	6	3.2	6	4.9	.619
Apathy	10	5.3	5	2.6	1	0.8	.098
Pain	6	3.2	13	6.9	6	4.9	.248
Sinusitis	6	3.2	10	5.3	7	5.7	.468

[a]Occurring in ≥ 5% of patients.
[b]Pairwise p value < .05, 90 mg weekly vs 20 mg daily.
[c]Pairwise p value < .05, 90 mg weekly vs placebo.

incidence of ≥ 5% that were reported during continuation treatment.

The events "thinking abnormal" and "nervousness" occurred significantly more frequently in the 90-mg weekly group compared with the 20-mg daily group (p = .004 and p = .025, respectively). However, there were no significant differences in thinking abnormal and nervousness between the 90-mg weekly group and placebo group. Diarrhea was reported more frequently by the 90-mg weekly group compared with the placebo group (p = .042). There were no significant differences between the 20-mg daily and placebo groups. A visitwise analysis revealed that the peak reporting for both nervousness and thinking abnormal occurred across all groups during the 4 weeks following randomization. Reporting then decreased, remaining at a lower level until the end of the study. Treatment-emergent diarrhea showed no temporal pattern when the rates by visit were examined.

Adverse events during the first 2 weeks postrandomization were specifically examined to determine whether there were any unique events associated with initiating a new dosing regimen. Patients assigned to 90 mg weekly (2.1%) reported back pain more often during this period compared with patients taking 20 mg daily (0%) and placebo (0%; overall p = .044). Patients assigned to 90 mg weekly (5.3%) also reported diarrhea more often compared with patients taking 20 mg daily (1.1%) and placebo (1.6%; overall p = .047). More patients assigned to placebo (3.3%) reported vomiting during the 2 weeks postrandomization compared with patients taking 90 mg weekly (0.5%) and 20 mg daily (0%; overall p = .014).

Serious adverse events. There was no evidence of increased risk for serious adverse events among patients who received 90 mg of enteric-coated fluoxetine weekly. During Study Period III, 7 patients reported a total of 8 serious adverse events; 4 patients in the 90-mg weekly group (2 patients were hospitalized for medical illnesses not felt to be related to fluoxetine treatment, 1 patient became hypomanic during the week following randomization, and 1 patient was hospitalized for suicidal ideation that developed 7 weeks after randomization), 2 patients in the 20-mg daily group (both patients were hospitalized for medical illnesses not felt to be related to fluoxetine treatment), and 1 patient in the placebo group (hospitalization for suicidal ideation that was reported at the last visit of Study Period III).

AMDP-5 solicited events. Solicited adverse events were captured as supplemental safety measures using the AMDP-5. Of the patients randomly assigned to continuation treatment, 397 (79.2%) reported at least 1 event from the AMDP-5. Significantly fewer patients in the 90-mg weekly group (6.3%) reported gastric discomfort compared with patients in the 20-mg daily group (15.3%) (p = .005) and fewer compared with the placebo group (10.7%) (p = .201). The incidence of patients reporting diarrhea was virtually identical between the groups according to the AMDP-5 (90-mg weekly: 13.2%, 20-mg daily: 13.2%, and placebo: 10.7%). All p values were nonsignificant.

Vital signs and laboratory evaluations. The mean changes observed in vital signs were not clinically remarkable in any of the 3 treatment groups and specifically did not differ between the 90-mg weekly and 20-mg daily groups. Minor treatment effects were noted on the baseline-to-endpoint change for a few of the laboratory analytes, none of which were associated with statistically significant differences between the 90-mg weekly and placebo groups.

Reasons for discontinuation. Of all the patients randomly assigned to continuation treatment, 14 (2.8%) discontinued because of an adverse event. The only statistically significant differences between the treatment populations for any reason for study discontinuation were for relapse and study completion (Table 4). The placebo group had a higher relapse rate and lower study completion than patients in either the 90-mg weekly or 20-mg daily regimens. Investigators were not limited to the protocol definition of relapse at the time that patients were discontinued from the study. For this reason, the percentages of patients discontinued for "relapse" in Table 4 are not identical to those in Table 2, which included only those patients that met the protocol definition of relapse.

DISCUSSION

This study confirms the long-term antidepressant effect of fluoxetine during the treatment of depression.[3,10]

Table 4. Treatment Discontinuations During Continuation Treatment

Reason for Discontinuation	Fluoxetine 90 mg Weekly (N = 190) N	%	Fluoxetine 20 mg Daily (N = 189) N	%	Placebo (N = 122) N	%	Overall p Value
Completion	71	37.4	84	44.4	35	28.7	.020
Adverse event	8	4.2	4	2.1	2	1.6	.313
Lack of efficacy	3	1.6	3	1.6	4	3.3	.508
Lost to follow-up	13	6.8	14	7.4	5	4.1	.481
Patient decision	17	8.9	16	8.5	15	12.3	.497
Relapse	68	35.8	57	30.2	57	46.7	.012
Protocol requirement	8	4.2	7	3.7	1	0.8	.221
Physician decision	2	1.1	4	2.1	3	2.5	.604

It specifically demonstrates the ability of 90 mg of enteric-coated fluoxetine given weekly to reduce the risk of relapse in patients that have remitted acutely with fluoxetine, 20 mg daily. These data corroborate the findings of previous longer-term fluoxetine studies[3,10] and generally confirm the value to patients in preventing relapse by continuing antidepressant treatment following the initial response.

In this study, patients with major depressive disorder whose depression had responded to acute treatment with fluoxetine, 20 mg daily, were randomly assigned to continuation treatment with fluoxetine, either 90 mg weekly or 20 mg daily, or placebo. Efficacy was evaluated after 25 weeks of continuation treatment. Log-rank analyses showed that patients taking fluoxetine, 90 mg weekly, and fluoxetine, 20 mg daily, were significantly less likely to relapse than patients randomly assigned to placebo ($p = .007$ and $p < .001$, respectively). In additional efficacy analyses (change from baseline [LOCF] of the CGI-S, modified HAM-D-17, and multiple HAM-D-28 subscales), patients taking either fluoxetine, 90 mg weekly, or fluoxetine, 20 mg daily, experienced significantly less worsening than patients taking placebo. Although the 20-mg daily fluoxetine group was nonsignificantly less likely to be associated with a relapse than patients taking fluoxetine, 90 mg once weekly, there were no statistically significant differences on these additional efficacy analyses between the 90-mg weekly and 20-mg daily patients.

In comparing the vital signs, laboratory analytes, and treatment-emergent adverse events, the safety profile of enteric-coated fluoxetine, 90 mg weekly, was similar to that observed for fluoxetine, 20 mg daily. Additionally, the safety profile for both of these dosing groups during continuation treatment was similar to that observed in a previous longer-term fluoxetine study.[13] The risk for serious adverse events was low throughout the continuation treatment period for all groups and was not statistically different for patients who were assigned to the new formulation and dosing regimen compared with fluoxetine, 20 mg daily. Rates of discontinuation related to adverse events also were not significantly greater in those patients taking fluoxetine, 90 mg weekly, compared with fluoxetine, 20 mg daily, indicating that fluoxetine once weekly was safe and well tolerated.

Two adverse events, nervousness and thinking abnormal, were reported statistically significantly more frequently in the fluoxetine, 90-mg weekly, group compared with the 20-mg daily group. The term *thinking abnormal* corresponds to adverse event terms such as impaired concentration or thought process. The number of reports of these events in the group taking 90 mg weekly was not, however, statistically significantly greater than the frequency of occurrence in those patients taking placebo. Both events peaked during the first 4 weeks following randomization and declined thereafter. This suggests that the onset of these events may have been related to initiating double-blind treatment, were short-lived, and did not have an important impact on clinical outcomes. When they did emerge, the frequency of occurrence was no greater than for patients taking placebo.

Enteric coating was introduced as a modification that might ameliorate or reduce possible unpleasant gastric effects associated with the 90-mg weekly dose. In this study, the rate of gastric discomfort, assessed by the AMDP-5, was significantly lower for patients randomly assigned to enteric-coated fluoxetine, 90 mg weekly, compared with the patients randomly assigned to 20 mg of the "immediate release" (currently marketed form) daily. Such a difference was in a direction consistent with the proposed benefit of the enteric coating, although the comparison between these 2 formulations was confounded in this study by differences in dose and dosing interval. At the same time, one might be concerned that the new formulation might give rise to differences in lower gastrointestinal tolerability. Indeed, diarrhea was reported more often by patients assigned to the 90-mg enteric-coated fluoxetine group than patients assigned to placebo. However, on inquiry by physicians using the AMDP-5, the occurrence of diarrhea did not differ between any of the groups. These data suggest that such lower gastrointestinal symptoms experienced by patients were mild and were not clinically significant when evaluated by physicians.

The main limitation of the study is that patients with primary comorbid conditions were excluded, and therefore the results may not be generalizable to all populations with major depressive disorder. Another methodological issue concerns the relatively higher frequency of visits during the continuation phase compared with other long-term studies.[14] Given the greater likelihood of detecting a signal (i.e., any worsening in mood) when the follow-up visits are more frequent, there is also a greater chance of false positives (i.e., declaring as relapsers those patients who do have a worsening of mood without a true relapse). This issue may have been mitigated by the strict relapse criteria employed in this study.

It has been hypothesized for some time that the long half-life of fluoxetine and its active metabolite norfluoxetine could provide sustained treatment effect using infrequent dosing.[3,4] Indeed, no other antidepressant agents are currently available that could sustain significant systemic concentrations of drug using dosing intervals less than daily because of the shorter half-lives of their parent and active metabolites. The long-term antidepressant efficacy of enteric-coated fluoxetine, 90 mg once weekly, relative to placebo over 25 weeks of continuation treatment was demonstrated in this study. At the same time, the estimated cumulative proportion of patients relapsing in the 90-mg fluoxetine weekly group was higher than that of patients assigned to the 20-mg daily group, although this difference was not statistically different. For some patients, 90 mg weekly may not be equivalent to 20 mg daily over long periods of treatment. Indeed, a proportion of patients undergoing long-term treatment for depression have been observed to relapse while taking a "therapeutic" dose of antidepressant in many recent long-term studies of antidepressants.[10,15–17] Data from the present study generally support the recommendation that supervision is necessary for all patients requiring long-term treatment of depression, some of whom may require a dosage adjustment or change in treatment. Thus, continuation treatment with fluoxetine, 90 mg weekly, as in the management of any chronic medical condition, would require reasonable clinical supervision and monitoring.

Drug names: fluoxetine (Prozac), temazepam (Restoril and others), zolpidem (Ambien).

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