

Efficacy and Safety of Weekly Treatment With Enteric-Coated Fluoxetine in Patients With Major Depressive Disorder

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A new formulation of fluoxetine has been developed that is intended to allow for weekly dosing during the long-term treatment of depression. This 90-mg enteric-coated formulation of fluoxetine was compared with 20-mg daily fluoxetine and placebo during a 25-week continuation treatment period in a study of 501 depressed patients who had responded to acute treatment with 20-mg daily fluoxetine. Both active drug formulations were statistically superior to placebo in maintaining the acute treatment response and prolonging the time to relapse. Patients with high baseline anxiety responded similarly to the 90-mg weekly and 20-mg daily fluoxetine treatments. In addition, the 90-mg weekly fluoxetine dose had a safety profile similar to that of both daily fluoxetine dosing and placebo. The once-weekly fluoxetine formulation provides an effective and tolerable treatment option for patients requiring extended depression therapy. (*J Clin Psychiatry* 2001;62[suppl 22]:48–52)

Because of the chronic, relapsing, and recurrent nature of depression, long-term continuation treatment (4–9 months) is recommended for all patients to prevent relapse,^{1–3} and even longer-duration maintenance treatment (2 years or more) is recommended for many patients to prevent recurrence.^{2,3} Although effective and tolerable therapies are available, a large number of patients do not continue with their treatment for an adequate length of time.^{4–6} Poor compliance is not unique to the treatment of depression, but is likely exacerbated by the need for continued antidepressant therapy even though patients may have had a significant reduction in or complete amelioration of their depressive symptomatology.

Patients with other psychiatric conditions that require long-term therapy have benefited from the use of depot drug formulations that require less frequent dosing.^{7–10} Often, these therapies are used for patients who have responded well to acute treatment, have stabilized at a specific dosage, and are facing long-term or even indefinite periods of continued therapy. Graduation to a less frequent dosing strategy may provide patients with an enhanced sense of recovery, which may further improve their compliance with treatment.

The long elimination half-lives of both fluoxetine and its active metabolite, norfluoxetine, not only make this compound unique among antidepressants, but also serve as the basis for exploring the use of fluoxetine in a weekly dosing regimen. The results of initial studies of weekly fluoxetine dosing^{11–13} were largely positive, both in terms of efficacy and tolerability.

In view of those early encouraging results, an enteric-coated formulation of fluoxetine (90 mg) has been developed that is to be administered once weekly during the continuation treatment of depression. The 90-mg weekly dose was chosen based on pharmacokinetic modeling that predicted mean steady-state plasma concentrations within the range achieved by 10-mg and 20-mg daily dosing. The enteric coating is intended to reduce possible gastric discomfort as it delays dissolution until the drug has passed into an area of the gastrointestinal tract with a pH of 5.5. This also has the effect of delaying the time to peak plasma concentration.

The use of this new formulation of 90-mg weekly fluoxetine was recently studied during long-term continuation treatment.¹⁴ Relapse rates were compared for patients who responded to acute treatment with open-

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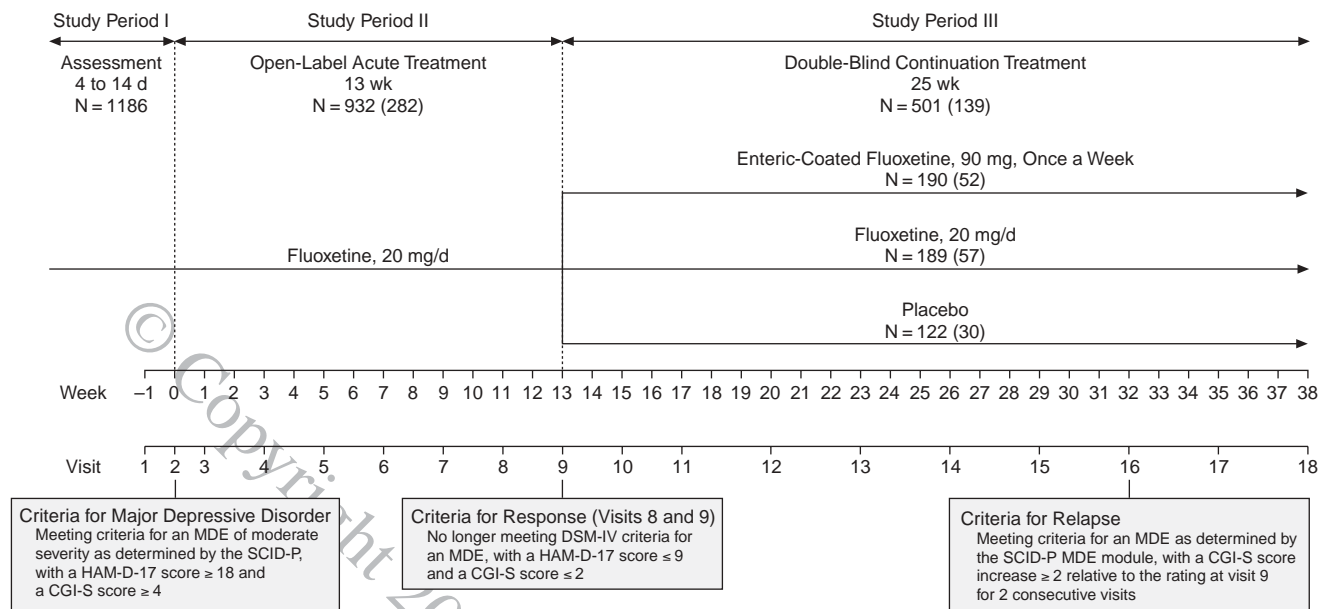
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*Adapted from Schmidt ME, Fava M, Robinson JM, et al. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. *J Clin Psychiatry* 2000;61:851–857 and from Schmidt ME, Michelson D, Judge R, et al. Long-term treatment outcomes of depression with associated anxiety: efficacy of a new weekly formulation of fluoxetine. Presented at the 153rd annual meeting of the American Psychiatric Association; May 18, 2000; Chicago, Ill.*

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Figure 1. Study Design^a

^aNumbers in parentheses represent number of patients who met criteria for high anxiety. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDE = major depressive episode, SCID-P = Structured Clinical Interview for DSM-IV, patient version.

label fluoxetine, 20 mg daily, and were then randomly assigned to the new formulation of fluoxetine, 90 mg weekly; fluoxetine, 20 mg daily; or placebo during a 25-week double-blind continuation treatment phase. In addition, because many depressed patients present with significant symptoms of anxiety,¹⁵ treatment outcome was compared in patients with and without high baseline anxiety levels.¹⁶

The study has been described fully elsewhere.^{14,16} This article reviews the study design, summarizes the main efficacy and safety findings, and discusses the efficacy results for patients with high baseline anxiety.

METHOD

Patient Population

Adult outpatients, aged 18 to 80 years and of either sex, with current nonpsychotic major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV] criteria) of at least 4 weeks' duration were included. The patient's current episode was required to be of moderate severity, as determined by a modified 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of ≥ 18 and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 4 . Among other exclusion criteria, patients who were previous fluoxetine nonresponders or who were currently treatment resistant (as determined by nonresponse to 2 or more adequate antidepressant courses) were excluded.

Study Design

This multisite study consisted of 3 study phases, as illustrated in Figure 1. After an initial assessment phase (study period I), patients entered study period II, in which they were assigned to open-label fluoxetine treatment (20 mg/day) for 13 weeks. At the end of study period II, patients who were categorized as responders (see Figure 1) were eligible for the double-blind continuation treatment phase (study period III). These patients were randomly assigned to 90 mg of fluoxetine once weekly, 20 mg of fluoxetine daily, or placebo for 25 weeks of treatment. All patients took 1 capsule of study medication every day in order to maintain the blind, with patients in the 90-mg weekly fluoxetine group taking 6 days of placebo and 1 day of active treatment per week. Over the course of continuation treatment, patients who experienced a significant reemergence of depressive symptoms (HAM-D-17 score ≥ 12 and a $\geq 50\%$ increase in HAM-D-17 score from the time of random assignment) were assessed for relapse. An optional rescue phase was offered to patients who met the criteria for relapse (see Figure 1) and is described elsewhere (reference 14 and M. E. Schmidt, M.D., manuscript in preparation).

Efficacy Assessments

Efficacy measures included diagnosis of relapse (as defined in Figure 1), as well as modified HAM-D-17,¹⁴ HAM-D-28 subscale, and CGI-S scores. The HAM-D-28 subscales included the core total (items 1, 2, 3, 7, and 8), subscale 5 (items 1, 2, 3, 7, 8, 14, 15, 16, and 17), anxiety

(items 10, 11, 12, 13, 15, and 17), depressed mood (item 1), sleep (items 4, 5, and 6), and retardation (items 1, 7, 8, and 14) scales.

Safety Assessments

Safety assessments were based on spontaneous reports of treatment-emergent adverse events, discontinuations due to adverse events, and solicited reports of adverse events as recorded in the Association for Methodology of Documentation in Psychiatry-Module 5 (AMDP-5).

Statistical Methods

Kaplan-Meier survival curves of the time-to-relapse (log-rank) analysis were compared to evaluate the efficacy of 90-mg weekly fluoxetine, 20-mg daily fluoxetine, and placebo during study period III. The modified HAM-D-17, HAM-D-28 subscales, and CGI-S scores were compared across treatment arms using an analysis of variance (ANOVA) based on last-observation-carried-forward data of baseline (visit 9, or visit 8 if visit 9 was missing) to endpoint change. Treatment, investigator, and treatment-by-investigator interactions were included as effects in the ANOVA model.

Patients were categorized as high anxiety (score > 7) or low anxiety (score ≤ 7) based on their HAM-D anxiety/somatization factor score (baseline HAM-D items 10–13, 15, and 17), and within each stratum an analysis of time to relapse was performed using the Kaplan-Meier method.

The Pearson chi-square test and the Fisher exact test were used to compare reasons for study discontinuation and treatment-emergent adverse events (during the double-blind study phase III) across treatment groups.

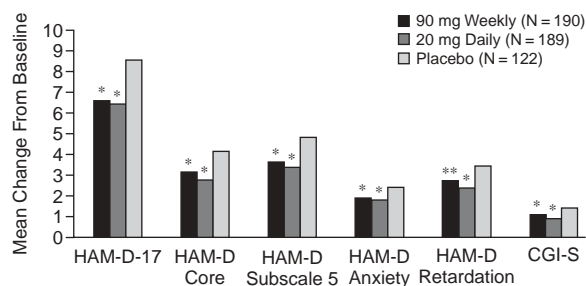
RESULTS

Demographics

All patients. The numbers of patients who entered each of the study phases and were randomly assigned to treatment are shown in Figure 1. Of the 501 patients who were randomly assigned to the double-blind treatment, 190 were assigned to 90 mg of fluoxetine weekly, 189 were assigned to 20 mg of fluoxetine daily, and 122 were assigned to placebo. No significant differences were seen across treatment groups for patient characteristics. Two patients were excluded from the primary analyses because they had no postbaseline measurements. These patients were lost to follow-up prior to visit 10.

High-anxiety patients. Patients who reported high levels of anxiety were comparable at baseline with respect to age, sex, and origin for all 3 treatment groups. A total of 139 patients (27.9%) were considered to have high baseline anxiety (HAM-D anxiety/somatization score > 7), whereas 360 patients (72.1%) were considered to have low baseline anxiety (HAM-D anxiety/somatization score

Figure 2. Efficacy Findings for All Patients^a



^aData from Schmidt et al.¹⁴ Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

*p < .05 vs. placebo.

**p < .10 vs. placebo.

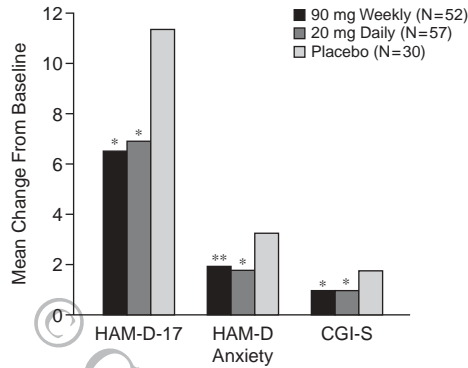
≤ 7). There was no significant difference in response to acute treatment between patients with high baseline anxiety compared with patients with low baseline anxiety.

Efficacy

All patients. Both active treatment groups were statistically superior to placebo in maintaining the acute treatment response, with increased worsening on a number of efficacy measures for patients taking placebo relative to patients taking either daily or weekly fluoxetine. The mean change from baseline on HAM-D-17, HAM-D core, HAM-D subscale 5, HAM-D anxiety, HAM-D retardation, and CGI-S scores for the 3 treatment groups is shown in Figure 2. No statistical differences were seen between the 90-mg weekly and 20-mg daily fluoxetine cohorts on any of these measures.

Log-rank time-to-relapse analysis revealed that both 90-mg weekly fluoxetine and 20-mg daily fluoxetine were statistically superior to placebo (p = .007 and p < .001, respectively) in preventing relapse. No statistical differences were found between the 90-mg weekly and 20-mg daily fluoxetine cohorts (p = .164). After 25 weeks of continuation treatment, relapse rates for each treatment group were as follows: 90-mg weekly fluoxetine, 37%; 20-mg daily fluoxetine, 26%; and placebo, 50%.

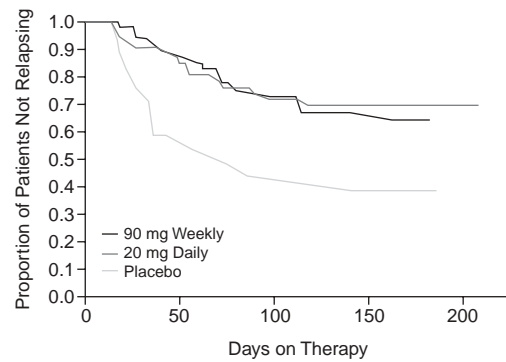
High-anxiety patients. Patients with high baseline anxiety responded well to both active treatments. The mean change from baseline on HAM-D-17, HAM-D anxiety, and CGI-S scores for patients with high baseline anxiety is shown in Figure 3. Time-to-relapse Kaplan-Meier survival curves for patients with high baseline anxiety are shown in Figure 4. Findings for the 20-mg daily fluoxetine cohort closely matched those of the 90-mg weekly fluoxetine cohort. Log-rank analysis revealed that both the 90-mg weekly fluoxetine and the 20-mg daily fluoxetine treatment groups were statistically superior to placebo (p = .006 and p = .004, respectively) and were not statistically different from one another (p = .847).

Figure 3. Efficacy Findings for High-Anxiety Patients^a

^aAbbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

* $p < .05$ vs. placebo.

** $p < .10$ vs. placebo.

Figure 4. Time to Relapse for High-Anxiety Patients (N = 139)^a

^aAdapted from Schmidt et al.¹⁶ Overall treatment effect, log-rank $p = .004$; 90 mg weekly vs. 20 mg daily, log-rank $p = .847$; 90 mg weekly vs. placebo, log-rank $p = .006$; 20 mg daily vs. placebo, log-rank $p = .004$.

Safety

The profile of treatment-emergent adverse events reported by patients was largely similar across treatment arms. Of the events reported by at least 5% of patients, only 1 event (diarrhea) was seen significantly more often with 90-mg weekly fluoxetine than with placebo ($p < .05$), and only 2 events (nervousness and thinking abnormally) were seen significantly more often in the 90-mg weekly than in the 20-mg daily fluoxetine groups ($p < .05$). Among solicited adverse events, as captured by the AMDP-5, gastric discomfort was seen significantly more often by patients taking 20-mg daily fluoxetine ($p = .005$) compared with patients taking 90-mg weekly fluoxetine. Diarrhea was reported at a similar rate for all treatment groups.

In general, patients appeared to tolerate the switch from open-label to double-blind treatment well. During the first 2 weeks after random assignment, patients assigned to the 90-mg weekly fluoxetine group did experience more back pain and diarrhea than patients in either the 20-mg daily fluoxetine or placebo groups ($p = .044$ and $p = .047$, respectively, overall). Patients taking placebo, however, reported more vomiting than did patients in either the 90-mg weekly or 20-mg daily fluoxetine groups ($p = .014$ overall).

Seven patients reported serious adverse events during the double-blind continuation phase. Four of these patients (2 in the 90-mg weekly fluoxetine and 2 in the 20-mg daily fluoxetine groups) were hospitalized for events not thought to be related to treatment. One patient (90-mg weekly fluoxetine) developed mania, and 2 patients (1 in the 90-mg weekly fluoxetine group and 1 in the placebo group) developed suicidal ideation.

There were no significant differences across treatment groups regarding reasons for discontinuation, with the exception of relapse and study completion. Relapse rates were highest in the placebo group (46.7%) and lowest in

the 20-mg daily fluoxetine group (30.2%). Similarly, study completion rates were highest in the 20-mg daily fluoxetine group (44.4%) and lowest in the placebo group (28.7%). Fourteen of the randomly assigned patients discontinued due to an adverse event or events.

DISCUSSION

The results of this study confirm the benefit for patients with major depressive disorder of continued active drug therapy following an acute treatment response to fluoxetine. Fluoxetine, given in either a daily or weekly dosing regimen, was effective in long-term relapse prevention.

The efficacy of the weekly fluoxetine dose was comparable to that achieved by the daily dose. Analyses of time to relapse, as well as HAM-D-17, HAM-D anxiety, CGI-S scores, and HAM-D-28 subfactor scores, demonstrated the superiority of active fluoxetine relative to placebo and showed that there were no significant differences between the active treatment regimens.

In a previous study¹⁷ of the long-term antidepressant efficacy of fluoxetine, 20 mg/day, patients with high baseline anxiety appeared to derive greater benefit in relapse prevention compared with patients with low baseline anxiety.¹⁸ Because of the possibility that patients with high baseline anxiety might differ in their response to different doses and dosing schedules during long-term treatment, this study also examined the efficacy of daily and weekly fluoxetine dosing in comparison to placebo in this important subpopulation of depressed patients. High baseline anxiety did not appear to impact the effectiveness of either treatment. The proportion of patients with high baseline anxiety who relapsed was significantly reduced compared with placebo for both the 90-mg weekly and the 20-mg daily fluoxetine treatments.

In general, the side effects experienced during the study were consistent with those found in previous long-term studies of fluoxetine and were comparable across treatment groups, with only a few statistical differences. The enteric coating of the 90-mg weekly fluoxetine dose delays dissolution until the pellets of drug move into the alkaline medium of the duodenum. This is intended to reduce possible gastric discomfort that might be associated with such a dose or dosing interval. An increase in lower gastrointestinal complaints (such as diarrhea) might then be expected with this new formulation. Although a statistical increase in reports of diarrhea was found with 90-mg weekly fluoxetine compared with placebo for spontaneously reported adverse events, no differences between treatment groups in rates of diarrhea reporting were seen for solicited adverse events. Two additional events, nervousness and thinking abnormally, were seen at a statistically increased frequency with 90-mg weekly fluoxetine compared with 20-mg daily fluoxetine. Differences relative to placebo were not significant for either of these events. The clinical significance of these findings is unclear.

Based on the data discussed above, 90-mg weekly fluoxetine is effective in preventing relapse during the long-term treatment of depression and in maintaining remission in patients, including those with high levels of anxiety. The new formulation is also well tolerated and has a safety profile very similar to that of 20-mg daily fluoxetine. These data suggest that for patients with depression, weekly fluoxetine dosing provides an effective, safe alternative therapy for continuation treatment. The potential for added convenience with less frequent dosing may significantly benefit both patients and providers in the effective management of long-term depression therapy.

Drug name: fluoxetine (Prozac).

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