Switching Patients From Daily Citalopram, Paroxetine, or Sertraline to Once-Weekly Fluoxetine in the Maintenance of Response for Depression

Cherri M. Miner, M.D.; Eileen B. Brown, Ph.D.;
Jill S. Gonzales, B.S.; and Reema Munir, B.S.

Background: Major depressive disorder is frequently a chronic, recurrent condition necessitating maintenance treatment. For some patients, compliance with daily pharmacotherapy is difficult over time. As an alternative approach, a once-weekly administered formulation of fluoxetine has recently been made available. This raises the important question of whether once-weekly enteric-coated fluoxetine, 90 mg, is effective for maintenance of response in patients whose depressive symptoms have responded to daily dosing with selective serotonin reuptake inhibitors (SSRIs) such as citalopram, paroxetine, or sertraline.

***Method*:** Patients had met DSM-IV criteria for major depressive disorder prior to beginning treatment for their current episode, had received 6 to 52 weeks of treatment with citalopram (20–40 mg/day [N = 83]), paroxetine (20 mg/day [N = 77]), or sertraline (50–100 mg/day [N = 86]), and had responded to that treatment (Clinical Global Impressions-Severity of Illness [CGI-S] score ≤ 2, modified 17-item Hamilton Rating Scale for Depression [HAM-D-17] score ≤ 10). Patients meeting these criteria (N = 246) continued treatment with their current SSRI for 1 week, then were switched to open-label enteric-coated fluoxetine, 90 mg, taken once weekly for 12 weeks. Safety measures were comparisons of spontaneously reported and solicited treatment-emergent adverse events. Efficacy measures were percentages of patients who discontinued the study for relapse and lack of efficacy and comparison of change from baseline to endpoint in scores on the modified HAM-D-17, subscales of the HAM-D-28, and the CGI-S. Quality of life measures were assessed with the MOS 36-Item Short-Form Health Survey (SF-36). We hypothesized that the once-weekly administration of fluoxetine could be safely and effectively initiated among subjects who had been stabilized on daily SSRI treatment.

Results: Seventy-nine percent of patients successfully completed a switch to enteric-coated fluoxetine, 90 mg, with 9.3% discontinuing due to relapse or lack of efficacy. Enteric-coated fluoxetine at a once-weekly dose of 90 mg was well tolerated in all groups. No significant increases were found in the HAM-D-17 total, HAM-D-28 subscores, or CGI-S score. Patients showed improvement from baseline to endpoint in most of the SF-36 health concepts.

Conclusion: Enteric-coated fluoxetine taken once weekly appears to be well tolerated and efficacious in patients who responded to acute therapy with other SSRIs and were subsequently switched to fluoxetine once weekly for continuation/maintenance therapy.

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Corresponding author and reprints: Cherri M. Miner, M.D., Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 2423, Indianapolis, IN 46285.

Depression is a serious illness that requires long-term treatment.[1] In spite of the public health burden presented by depression and the availability of a number of medications with well-demonstrated antidepressant efficacy, the most recent consensus statement on medical care of depression in the United States reported that many subjects are seriously undertreated.[2] One factor contributing to this undertreatment is problems with adherence to treatment; for example, not complying with a recommended medical regimen. The introduction of the selective serotonin reuptake inhibitors (SSRIs), medications with more benign side effect profiles than tricyclic antidepressants, has significantly enhanced compliance.[3] Nonetheless, some patients may be reluctant to continue taking daily doses of antidepressant medication for an extended period, especially when they are feeling better and the day-to-day benefits of treatment are not readily apparent. Reluctance to stay on treatment may also be associated with patients' lack of education regarding the importance of continuation treatment, fear of stigmatization, the inherent difficulty of remembering to take a prescription on a daily basis, persistent side effects, and/or the lack of choice in selecting treatment frequencies. Simple, once-weekly dosing may be a more convenient option for these patients. Weekly dosing may provide a strategy for enhancing psychological well-being and overall tolerability, leading to improved compliance with long-term treatment of depression due to patients' increased willingness to take their medication.

To fulfill this need for alternative dosing regimens, a new 90-mg enteric-coated formulation of fluoxetine was developed specifically for weekly dosing during continuation treatment of depression. Schmidt et al.[4] reported that

90-mg enteric-coated fluoxetine given weekly and 20-mg fluoxetine given daily reduced the risk of relapse versus daily placebo in patients who had remitted after acute phase treatment with fluoxetine, 20 mg daily. The data corroborated the findings of previous longer-term fluoxetine and other SSRI studies[5–10] in which relapse rates ranged from 8% to 26% and generally confirmed the value to patients of preventing relapse by continuing antidepressant treatment after the initial response. Schmidt and colleagues[4] also reported that the tolerability and safety of fluoxetine, 90 mg dosed weekly, were not significantly different from the existing safety profile of fluoxetine, 20 mg dosed daily. During the optional rescue treatment phase of the study, in which patients who relapsed were offered an increased drug dose, fluoxetine, 90 mg dosed twice weekly (90 mg every 4 days), was also well tolerated and had a safety profile consistent with the known profile of fluoxetine (M. E. Schmidt, M.D.; M. Fava, M.D.; J. S. Gonzales, B.A.; et al., unpublished data, 2001). Compliance to once-weekly fluoxetine during long-term treatment of depression was also evaluated in a separate study and was reported to be higher than compliance to once-daily fluoxetine (85.9% vs. 79.4%, respectively).[11] The study suggested that patients will not be more likely to forget doses prescribed to be taken weekly. Additionally, the study suggested that a once-weekly regimen could be a valued alternative for many patients in that weekly dosing may be more convenient and less of an intrusion in daily activities.

Based on this information, it is predicted that weekly dosing of enteric-coated fluoxetine, 90 mg, will be well tolerated and will maintain efficacy in patients who have responded to acute treatment with antidepressant compounds other than fluoxetine, specifically those that have a mechanism of action and adverse event profile similar to fluoxetine. However, the risk of relapse for switching subjects from other such SSRIs to weekly fluoxetine is unknown. This article reports the safety and efficacy of switching subjects who have responded to 6 to 52 weeks of citalopram (20–40 mg/day), paroxetine (20 mg/day), or sertraline (50–100 mg/day) to 90-mg enteric-coated fluoxetine given once weekly for the maintenance of response in depression. Guidance to physicians in the use of this novel dosage formulation and regimen is given.

METHOD

Patient Population

Patients were male or female outpatients, aged 18 to 78 years, who met DSM-IV criteria for nonpsychotic major depressive disorder prior to beginning treatment for their current episode of depression. Patients had received at least 6 weeks but no more than 52 weeks of treatment with citalopram (20–40 mg/day), paroxetine (20 mg/day), or sertraline (50–100 mg/day) for a current episode of depression and had demonstrated response to treatment (Clinical Global Impressions-Severity of Illness scale [CGI-S][12] scores ≤ 2 and modified 17-item Hamilton Rating Scale for Depression [HAM-D-17][13] scores ≤ 10).

Patients with a lifetime history of any psychotic disorder or bipolar mood disorder, as well as a substance abuse disorder in the preceding 6 months, 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. Pregnant or lactating patients and patients with unstable medical conditions were also excluded from the study. Patients did not receive any form of psychotherapy directed toward treating their depression during the study, other than good clinical care.

Written informed consent was obtained from all the patients in accordance with the Helsinki conventions. The study protocol was approved by the Institutional Review Board of each of the 18 study centers.

Study Design

This was a multicenter, open-label study of patients currently undergoing treatment for major depressive disorder with an SSRI other than fluoxetine. It was conducted at 18 study centers in the United States by psychiatrists and primary care physicians. The study consisted of 2 periods, the first of which was a 1-week assessment phase (study period 1) during which all patients continued taking their prescribed medication—citalopram (20–40 mg/day), paroxetine (20 mg/day), or sertraline (50–100 mg/day). This phase was followed by a 12-week, open-label treatment phase (study period 2) during which all patients received enteric-coated fluoxetine, 90 mg, once weekly and were seen at approximately 4-week intervals. Patients took their last dose of the previous SSRI on the first day of study period 2 and then took their first dose of fluoxetine, 90 mg, the next day. Patients took fluoxetine, 90 mg, once per week on the same day of every week. If the patient forgot to take his or her medication, the patient took that dose the following day, or the next day on which the patient remembered to take it. Patients then returned to taking their fluoxetine, 90 mg, on the day of the week originally assigned. Patients recorded the date they took each dose on the designated area of the study drug blister card. Compliance was assessed by direct questioning and verification of dose dates at each visit.

Patients who took each weekly dose ± 2 days from the originally assigned day of the week were considered to be compliant. If patients had a significant reemergence of depressive symptoms during the open-label treatment phase (50% or more increase in the modified HAM-D-17 total relative to their score at baseline and a modified HAM-D-17 score > 12), they were seen at up to weekly intervals to monitor for recovery of response (modified

HAM-D-17 ≤ 12 and CGI-S ≤ 2) or relapse. Relapse was defined as (1) a modified HAM-D-17 score ≥ 18 and an increase in CGI-S score of 2 or more relative to the rating at baseline, for 2 consecutive visits or (2) a worsening of symptoms that in the investigator's clinical judgment did not meet protocol relapse criteria but that prompted a discussion between the patient and physician in which, due to increased depressive symptomatology, the patient expressed a wish to discontinue the trial. Patients in the second relapse category were classified as discontinuing from the study for lack of efficacy, while patients in the first category were classified as discontinuing for relapse. Patients in both categories were removed from the study and received follow-up care.

Assessments

Efficacy. One focus of the study was the evaluation of continued maintenance of antidepressant response. Efficacy measures included the percentage of patients who discontinued the study for relapse or lack of efficacy. Additional efficacy measures included ratings on the modified HAM-D-17, HAM-D-28 subscales (core factor total, anxiety, 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 to 3, 7 to 11, 13 to 15, and 17 were combined with either items 4, 5, 6, 12, and 16 (for typical neurovegetative symptoms) or 22, 23, 24, 25, and 26 (for atypical or reversed neurovegetative symptoms). The higher of the 2 combinations was used for determining protocol eligibility, response, and relapse. This modification weights atypical symptoms equally with typical symptoms and was used in previous studies of the long-term efficacy of fluoxetine.[4,5] The HAM-D-28 subscales were defined as follows: core factor total (sum of items 1, 2, 3, 7, and 8), anxiety (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).

Quality of life. The MOS 36-Item Short-Form Health Survey (SF-36)[14–17] is a patient-rated health status measure designed to evaluate functioning and well-being in chronic disease, mental health specialty, and general primary care populations. The SF-36 consists of 36 questions that assess 8 health concepts: (1) physical functioning, (2) role limitations due to physical problems, (3) social functioning, (4) bodily pain, (5) general mental health, (6) role limitations due to emotional problems, (7) vitality, and (8) general health perceptions. The transformed raw scores were analyzed for this publication and range from 0 to 100 with higher scores representing better health status and functioning.

In addition, patients answered a patient satisfaction questionnaire prior to receiving once-weekly fluoxetine and again at the end of the study. Questions included how satisfied they were with their medication, whether they would choose a daily or a weekly formulation if given the choice, which dosing regimen was more convenient, and which best fit their lifestyle.

Safety. Evaluation of the safety of switching to enteric-coated fluoxetine, 90 mg, was the primary objective of this study. Safety was assessed by the evaluation of treatment-emergent adverse events, discontinuations due to adverse events, and change in clinical laboratory data and vital signs. Safety data were also 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.[18] The AMDP-5 scale ranges from 0 (absent) to 3 (severe). Adverse events were also collected by spontaneous report and were recorded without regard to causality.

Statistical Methods

The baseline measurement for the efficacy and safety analyses was collected at visit 2 (the visit just prior to patients' receiving treatment with enteric-coated fluoxetine**)**. If this measurement was missing, the baseline was considered visit 1 (the patient's initial assessment visit). Patients' endpoint measure is defined as their last measurement available in study period 2.

Patient characteristics, including demographics and severity of illness at the time of entry into the study, were summarized for each previous SSRI therapy group at baseline. Differences among prior SSRI treatment groups were assessed using a chi-square test for categorical variables and an analysis of variance (ANOVA) with previous SSRI therapy in the model. For the analysis of number of previous episodes of major depressive disorder, the ANOVA was based on ranks due to a nonnormal distribution of the data.

The change from baseline to endpoint (intent to treat, last observation carried forward) within each previous therapy was assessed with a Wilcoxon signed rank procedure for the modified HAM-D-17 total score, HAM-D subscale factors, and CGI-S. The change from baseline to endpoint was compared among the previous therapy groups with an ANOVA with prior SSRI therapy and investigator as effects in the model for the same parameters. The 8 health components of the SF-36 were analyzed in the same fashion.

Reasons for discontinuation from the study and adverse events (either reported spontaneously or solicited using the AMDP-5) that first occurred or worsened during fluoxetine therapy were compared between previous therapy groups using a Fisher exact test. The percentages of patients who experienced improvement from baseline on the AMDP-5 measures were also compared using a Fisher exact test. The percentage of patients reporting satisfaction with their antidepressant prior to switching and after switching was compared using the McNemar test.

RESULTS

Demographics

Of the 291 patients who enrolled in this study, 45 patients discontinued before receiving study drug. Of these, 6 discontinued due to patient decision, 1 patient was lost to follow-up, and 38 patients did not meet entry criteria for the study. The remaining 246 patients met the required criteria for study entry and proceeded to open-label treatment with fluoxetine, 90 mg once weekly (study period 2). Of these 246 patients, 83 had been treated with citalopram; 86, with sertraline; and 77, with paroxetine. Analyses revealed no statistically significant differences between the treatment groups in age, gender, ethnic origin, mean duration of time on treatment with their previous SSRI, or disease state characteristics, such as severity of depression (Table 1).

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

Demographic	Citalopram (N = 83)	Paroxetine (N = 77)	Sertraline (N = 86)	Between-Group p Value
Female, N (%)	65 (78.3)	51 (66.2)	63 (73.3)	.228
Age, mean (SD), y	43.6 (11.8)	43.0 (12.8)	41.1 (11.8)	.385
White, N (%)	76 (91.6)	69 (89.6)	77 (89.5)	.600
Modified HAM-D-17 total, mean (SD)	4.3 (3.3)	3.5 (3.1)	3.8 (2.2)	.215
CGI-S, mean (SD)	1.4 (0.6)	1.2 (0.5)	1.4 (0.5)	.084
Dose of previous therapy, mean (SD), mg	26.9 (9.5)	20.0 (0)	77.0 (24.9)	NA
Duration of current MDD episode, mean (SD), mo	15.3 (23.0)	13.4 (14.3)	19.3 (19.8)	.140
Duration of previous daily SSRI therapy, mean (SD), mo	3.8 (2.6)	3.8 (2.9)	4.6 (3.3)	.140
Age at first episode, mean (SD), y	33.7 (12.2)	32.6 (12.7)	30.0 (12.7)	.150
Patients with previous MDD, N (%)	55 (66.3)	51 (66.2)	62 (72.1)	.643
No. of previous MDD episodes, mean (SD)	2.1 (3.0)	3.7 (15.0)	2.3 (2.6)	.502

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

Efficacy Analyses

Seventy-nine percent of patients successfully completed treatment. Among those who discontinued, 1.6% met criteria for relapse and an additional 7.7% discontinued for lack of efficacy, based on the perception of the physician and/or patient. Last-observation-carried-forward (LOCF) analysis of baseline-to-endpoint differences of the modified HAM-D-17 total, HAM-D-28 subscale factors, and CGI-S revealed that patients in the 3 previous therapy groups had similar, very slight increases on nearly all of the measures (Table 2). There were no statistically significant increases within these groups, and there were no statistically significant differences between the groups on these efficacy measures.

Prior to being switched to fluoxetine once weekly, 48.9% of the patients had received their previous SSRI treatment for less than 13 weeks compared with 51.2% of the patients who were on their previous therapy 13 weeks or longer. Similar rates of relapse and discontinuation for lack of efficacy were observed for both groups: 1.7% met criteria for relapse and 7.5% discontinued for lack of efficacy in those patients with a shorter duration of previous treatment compared with 1.6% who met criteria for relapse and 7.9% who discontinued for lack of efficacy in patients with a longer duration of previous treatment.

Table 2. Summary of Efficacy Endpoints After Once-Weekly Fluoxetine Treatment[a]

Analysis	Citalopram (N = 83)	Paroxetine (N = 73)[b]	Sertraline (N = 86)
Relapse/lack of efficacy, N (%)	10 (12.0)	5 (6.5)	8 (9.3)
Between-group p value	.494		
CGI-S			
Change to endpoint, mean (SD)	0.1 (0.9)	0.2 (0.9)	0.2 (1.2)
Within-group p value	.308	.158	.422
Between-group p value	.995		
Modified HAM-D-17			
Change to endpoint, mean (SD)	0.6 (5.2)	0.4 (4.7)	1.1 (5.5)
Within-group p value	.996	.911	.485
Between-group p value	.609		
HAM-D-28 subscale factors			
Core factor total			
Change to endpoint, mean (SD)	0.3 (2.2)	0.0 (1.9)	0.5 (2.4)
Within-group p value	.533	.661	.218
Between-group p value	.379		
Retardation scale			
Change to endpoint, mean (SD)	0.3 (1.8)	0.1 (1.6)	0.4 (2.1)
Within-group p value	.355	.592	.252
Between-group p value	.651		
Anxiety total			
Change to endpoint, mean (SD)	0.1 (1.8)	0.2 (2.0)	0.5 (2.2)
Within-group p value	.740	.306	.127
Between-group p value	.545		
Sleep total			
Change to endpoint, mean (SD)	–0.1 (1.2)	0.2 (1.2)	–0.1 (1.3)
Within-group p value	.583	.343	.656
Between-group p value	.624		

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression.
[b]Group N = 77 for relapse/lack of efficacy (all patients receiving continuation treatment are included); N = 73 for other efficacy measures (data missing for 4 patients).

Quality of Life

Overall, results of the change in SF-36 scores from baseline to endpoint indicate a typically positive experience for patients treated with fluoxetine once weekly (Table 3), with some noting improvement relative to their daily treatment experience. Statistically significant improvements were seen for general mental health, role limitations due to emotional problems, and vitality, regardless

Table 3. Summary of SF-36 Endpoints After Once-Weekly Fluoxetine Treatment[a]

Health Concept	Citalopram (N = 81)	Paroxetine (N = 72)	Sertraline (N = 82)
General health perceptions			
Change to endpoint, mean (SD)	5.8 (17.2)	0.5 (15.0)	1.5 (13.4)
Within-group p value	.007	.699	.321
Between-group p value	.044		
General mental health			
Change to endpoint, mean (SD)	4.9 (24.3)	4.5 (20.7)	7.7 (20.8)
Within-group p value	.019	.042	< .001
Between-group p value	.701		
Role limitations due to emotional problems			
Change to endpoint, mean (SD)	18.1 (48.0)	16.2 (44.1)	17.5 (43.9)
Within-group p value	< .001	.002	< .001
Between-group p value	.738		
Role limitations due to physical problems			
Change to endpoint, mean (SD)	1.9 (34.9)	–1.0 (34.5)	–0.9 (34.6)
Within-group p value	.475	.830	.925
Between-group p value	.534		
Social functioning			
Change to endpoint, mean (SD)	2.9 (29.9)	4.5 (29.8)	7.0 (27.8)
Within-group p value	.196	.130	.042
Between-group p value	.865		
Vitality			
Change to endpoint, mean (SD)	7.4 (21.8)	9.3 (26.0)	8.5 (23.4)
Within-group p value	.012	< .001	.002
Between-group p value	.850		
Bodily pain			
Change to endpoint, mean (SD)	6.0 (23.1)	–3.1 (21.7)	–0.7 (22.3)
Within-group p value	.027	.369	.841
Between-group p value	.024		
Physical functioning			
Change to endpoint, mean (SD)	1.9 (10.3)	1.4 (8.9)	0.2 (13.6)
Within-group p value	.015	.137	.646
Between-group p value	.333		

[a]Scores range from 0 to 100 with higher scores representing better health status and functioning. Group Ns are smaller than baseline group Ns because data are missing for some patients. Some patients never returned, so data were not available. Abbreviation: SF-36 = MOS 36-Item Short-Form Health Survey.

of prior SSRI therapy. In addition, there were statistically significant improvements seen for those patients who were on treatment with citalopram for general health perceptions, bodily pain, and physical functioning. A statistically significant improvement was seen for social functioning for those patients previously treated with sertraline. Patients on treatment with paroxetine and sertraline reported a nonsignificant mean negative change for the role limitations due to physical problems and the bodily pain concepts.

Prior to receiving once-weekly fluoxetine, most patients said they were very or somewhat satisfied with their once-daily antidepressant (76.4%) and that they would recommend it to a friend (80.6%). After taking once-weekly fluoxetine, 83.4% said they were very or somewhat satisfied with it (p = .063 compared with 76.4%) and 84.7% of the patients stated that they would choose the once-weekly fluoxetine over the daily antidepressant, if given a choice. They also said that once-weekly fluoxetine better fit their lifestyle (82.2%) compared with their once-daily antidepressant and that they found that once-weekly fluoxetine was very or somewhat more convenient compared with a once-daily formulation (94.5%).

Table 4. Treatment-Emergent Adverse Events Reported Spontaneously for All Patients Receiving Weekly Fluoxetine[a]

	Citalopram (N = 83)		Paroxetine (N = 77)		Sertraline (N = 86)		Between-Group
Event	N	%	N	%	N	%	p Value
Rhinitis	15	18.1	9	11.7	18	20.9	.266
Headache	11	13.3	11	14.3	19	22.1	.259
Nervousness	15	18.1	8	10.4	14	16.3	.353
Insomnia	9	10.8	12	15.6	9	10.5	.557
Diarrhea	5	6.0	13	16.9	5	5.8	.036
Sinusitis	4	4.8	9	11.7	8	9.3	.302
Cough increased	5	6.0	5	6.5	7	8.1	.860
Weight gain	5	6.0	4	5.2	6	7.0	.945
Nausea	2	2.4	4	5.2	7	8.1	.232
Pain	4	4.8	4	5.2	5	5.8	1.00
Vomiting	3	3.6	5	6.5	5	5.8	.772

[a]Events occurring in ≥ 5% of all patients. Patients are counted once if they experienced the event at any visit after being assigned the 90-mg fluoxetine dose.

Safety Analyses

Spontaneously reported treatment-emergent adverse events. There were no serious, causally related treatment-emergent adverse events among subjects switched from daily SSRIs to once-weekly fluoxetine. The most frequently occurring spontaneously reported treatment-emergent adverse events were rhinitis (17.1%), headache (16.7%), nervousness (15.0%), and insomnia (12.2%) (Table 4). These most commonly reported adverse events that first occurred or worsened upon switching to once-weekly fluoxetine were comparable across treatment groups. Table 4 presents those events with an incidence of ≥ 5% that were reported during continuation treatment. After the switch to once-weekly fluoxetine, diarrhea was the only treatment-emergent adverse event reported at a clinically and statistically significantly different rate among the 3 prior SSRI therapy groups. Five patients each in the citalopram (6.0%) and sertraline (5.8%) treatment groups and 13 patients (16.9%) in the paroxetine group reported diarrhea as an adverse event.

Table 5 displays the treatment-emergent adverse events of headache, nervousness, insomnia, and diarrhea at each visit. The frequency of the events across visits does not sum up to the numbers reported in Table 4. This is because Table 4 counts patients only once if they experienced the event at any visit after being assigned the 90-mg dose, while in Table 5, patients may be included in more than 1 visit if the event they were experiencing continued over time. The rate of headache remained fairly constant over time, while the rates for nervousness declined over time. The rates for insomnia decreased over time for citalopram and sertraline, but increased slightly for paroxetine. The rate for diarrhea decreased over time for paroxetine but remained somewhat stable (and relatively low) for the other 2 SSRIs.

Table 5. Spontaneous Reports of Headache, Nervousness, Insomnia, and Diarrhea, by Visit, for All Patients Receiving Weekly Fluoxetine[a]

	Citalopram			Paroxetine			Sertraline		
Event	Total N	N	%	Total N	N	%	Total N	N	%
Headache									
Week									
4	83	7	8.4	77	6	7.8	86	12	14.0
8	76	6	7.9	68	5	7.4	79	9	11.4
12	70	5	7.1	63	5	7.9	70	9	12.9
Nervousness									
Week									
4	83	13	15.7	77	6	7.8	86	10	11.6
8	76	8	10.5	68	3	4.4	79	7	8.9
12	70	4	5.7	63	3	4.8	70	2	2.9
Insomnia									
Week									
4	83	7	8.4	77	6	7.8	86	7	8.1
8	76	3	3.9	68	5	7.4	79	4	5.1
12	70	2	2.9	63	7	11.1	70	2	2.9
Diarrhea									
Week									
4	83	3	3.6	77	9	11.7	86	2	2.3
8	76	1	1.3	68	7	10.3	79	2	2.5
12	70	3	4.3	63	5	7.9	70	1	1.4

[a]Patients could be included in more than 1 visit if the event they were experiencing continued over time.

AMDP-5 solicited events. Solicited adverse events were captured using the AMDP-5. Table 6 presents AMDP-5 events with an incidence of ≥ 5% that were solicited from all patients during once-weekly fluoxetine treatment. There were no statistically significant differences between prior therapy groups in the incidence of worsening for these events. There was a statistically significant difference detected between prior SSRI therapies for the rates of improvement for excessive appetite and decreased libido. Excessive appetite was improved in 3.7% of the sertraline patients versus 12.7% of the paroxetine patients and 17.1% of the citalopram patients (overall $p = .013$; sertraline vs. paroxetine, $p = .067$; sertraline vs. citalopram, $p = .009$; paroxetine vs. citalopram, $p = .502$). Decreased libido was improved in 9.8% of the sertraline patients and only 1.4% of the paroxetine patients, but in 19.5% of the citalopram patients (overall $p < .001$; sertraline vs. paroxetine, $p = .038$; sertraline vs. citalopram, $p = .121$; paroxetine vs. citalopram, $p < .001$). It should be noted that lack of power may have contributed to lack of detection of other significant differences. While some patients reported worsening of some symptoms measured by the AMDP-5, a similar proportion of patients reported improvement of those same symptoms.

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 groups. Within-group comparisons showed a statistically significant baseline-to-endpoint increase in patient weight in all 3 treatment groups: citalopram mean change = 0.4 kg (0.9 lb), $p = .017$; paroxetine mean change = 0.9 kg (2.0 lb), $p = .003$; and sertraline mean change = 1.0 kg (2.2 lb), $p < .001$. When only those individuals with clinically meaningful weight gain or loss were considered, 3.0% of all patients gained more than 7% of their body weight from baseline to endpoint while 2.6% of the patients lost more than 7% of their body weight. Minor treatment effects were noted on the baseline-to-endpoint change for a few of the laboratory analytes, none of which were associated with clinically significant differences between the groups.

Reasons for discontinuation. Of all the patients assigned to continuation treatment, 12 (4.9%) discontinued due to an adverse event. Nineteen patients (7.7%) discontinued due to lack of efficacy, and 4 (1.6%) discontinued due to relapse, yielding a combined relapse/lack of efficacy discontinuation rate of 9.3%. Lost to follow-up was the only reason for study discontinuation with a statistically significant difference between the treatment populations (Table 7).

Compliance

Compliance rates were exceptionally high. There was no evidence of decreased compliance over time, with 99.6%, 97.2%, and 99.5% of patients being compliant at 4, 8, and 12 weeks of treatment, respectively, with enteric-coated fluoxetine, 90 mg, given once weekly.

DISCUSSION

In this study, patients with major depressive disorder whose depression had responded to treatment with citalopram (20–40 mg/day), paroxetine (20 mg/day), or sertraline (50–100 mg/day) were switched to 90-mg enteric-coated fluoxetine given once weekly for the maintenance of response in depression. Efficacy was evaluated after 12 weeks of continuation treatment. Efficacy results of this study were consistent with the once-weekly fluoxetine findings of Schmidt et al.,[4] as well as previous longer-term studies of once-daily fluoxetine,[5,9,19] with 79% of patients successfully completing the protocol, indicating maintenance of antidepressant response, as well as satisfactory tolerability. The combined relapse/lack of efficacy rate of 9.3% for this study corroborated the findings of previous longer-term fluoxetine and other SSRI studies,[7–10] in which relapse rates ranged from 8% to 26%. Consistent with relapse rates of other studies, the rate found in this study generally confirmed the value of fluoxetine, 90 mg, given once weekly for the continuation treatment of depression.

Patients across all 3 treatment groups reported a generally positive experience with fluoxetine given once weekly as assessed by the SF-36 quality of life survey. Statistically significant improvements were seen for general mental health, role limitations due to emotional problems, and vitality, regardless of prior SSRI therapy. The general mental health component assesses general

Table 6. Comparison of AMDP-5 Events After Once-Weekly Fluoxetine Treatment: Worsened Versus Improved Events[a]

	Sertraline (N = 82)				Paroxetine (N = 71)				Citalopram (N = 82)				Overall (N = 235)			
	Worsened		Improved		Worsened		Improved		Worsened		Improved		Worsened[b]		Improved	
AMDP-5 Event	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sleep/vigilance																
Difficulty falling asleep	8	9.8	11	13.4	13	18.3	7	9.9	12	14.6	8	9.8	33	14.0	26	11.1
Interrupted sleep	15	18.3	15	18.3	13	18.3	16	22.5	14	17.1	19	23.2	42	17.9	50	21.3
Shortened sleep	10	12.2	9	11.0	11	15.5	6	8.5	9	11.0	7	8.5	30	12.8	22	9.4
Early waking	12	14.6	12	14.6	7	9.9	6	8.5	9	11.0	12	14.6	28	11.9	30	12.8
Drowsiness	9	11.0	13	15.9	11	15.5	9	12.7	18	22.0	17	20.7	38	16.2	39	16.6
Appetite disturbances																
Decreased appetite	7	8.5	3	3.7	3	4.2	4	5.6	6	7.3	6	7.3	16	6.8	13	5.5
Excessive appetite	8	9.8	3	3.7	4	5.6	9	12.7	12	14.6	14	17.1	24	10.2	26	11.1[c]
Decreased libido	10	12.2	8	9.8	11	15.5	1	1.4	6	7.3	16	19.5	27	11.5	25	10.6[d]
Gastrointestinal disturbances																
Dry mouth	4	4.9	12	14.6	5	7.0	7	9.9	10	12.2	13	15.9	19	8.1	32	13.6
Nausea	3	3.7	2	2.4	3	4.2	2	2.8	7	8.5	3	3.7	13	5.5	7	3.0
Gastric discomfort	4	4.9	4	4.9	5	7.0	6	8.5	9	11.0	4	4.9	18	7.7	14	6.0
Diarrhea	6	7.3	7	8.5	9	12.7	4	5.6	7	8.5	8	9.8	22	9.4	19	8.1
Cardiac/respiratory disturbances																
Dizziness	5	6.1	3	3.7	3	4.2	2	2.8	8	9.8	6	7.3	16	6.8	11	4.7
Palpitations	5	6.1	3	3.7	4	5.6	2	2.8	3	3.7	2	2.4	12	5.1	7	3.0
Other somatic disturbances																
Headache	10	12.2	14	17.1	4	5.6	6	8.5	11	13.4	15	18.3	25	10.6	35	14.9
Backache	10	12.2	7	8.5	3	4.2	6	8.5	8	9.8	11	13.4	21	8.9	24	10.2
Heaviness in legs	5	6.1	4	4.9	3	4.2	2	2.8	4	4.9	4	4.9	12	5.1	10	4.3
Other symptoms																
Increased dreams	9	11.0	5	6.1	5	7.0	3	4.2	11	13.4	3	3.7	25	10.6	11	4.7

[a]Events occurring in ≥ 5% of all patients. Group Ns are smaller than baseline group Ns because data are missing for some patients. Some patients never returned, so data are not available. Abbreviation: AMDP-5 = Association for Methodology of Documentation in Psychiatry-Module 5.
[b]No statistically significant differences were found between the prior therapy groups in the incidence of worsening.
[c]Statistically significant differences were found between the prior therapy groups (p = .013) in the incidence of improvement.
[d]Statistically significant differences were found between the prior therapy groups (p < .001) in the incidence of improvement.

Table 7. Treatment Discontinuations During Once-Weekly Fluoxetine Treatment

Reason for Discontinuation	Citalopram (N = 83)		Paroxetine (N = 77)		Sertraline (N = 86)		Between-Group p Value
	N	%	N	%	N	%	
Completion	65	78.3	62	80.5	67	77.9	.923
Adverse event	4	4.8	3	3.9	5	5.8	.932
Lack of efficacy	9	10.8	3	3.9	7	8.1	.246
Lost to follow-up	0	0.0	4	5.2	1	1.2	.043
Patient decision	3	3.6	2	2.6	4	4.7	.912
Relapse	1	1.2	2	2.6	1	1.2	.692
Protocol requirement	1	1.2	1	1.3	1	1.2	1.0

mental health, including depression, anxiety, behavioral-emotional growth, and general positive affect. Role limitations due to emotional problems is the extent to which emotional problems interfere with work or other daily activities, including decreased time spent in work activities, accomplishing less than wanted, and not working as carefully as usual. The vitality component is a measure of feeling energetic and full of "pep" versus tired and worn-out. Additional quality of life measures that showed statistically significant improvements were general health perceptions, bodily pain, and physical functioning for those patients who were on treatment with citalopram and social functioning for those patients who were on treatment with sertraline. The quality of life measures are of particular interest in that patients who were considered antidepressant responders when they entered the study, with a mean baseline HAM-D-17 score of 3.9, experienced significant improvements in these quality of life measures after switching to once-weekly enteric-coated fluoxetine, 90 mg. The meaning of this finding warrants further investigation with regard to how psychiatry currently defines not only response and remission, but also treatment goals. Based on the current standard definition of remission (HAM-D score ≤ 7),[20] most of the patients in this study would have been considered remitters at baseline. However, the finding that these very important variables regarding quality of life showed significant improvement after the medication regimen was switched while a comparable antidepressant response was maintained suggests that there are variables beyond general depressive symptom assessment that should be considered when evaluating treatment response and ultimately setting treatment goals.

The patient satisfaction questionnaire at endpoint indicated that most patients would choose once-weekly fluoxetine over their once-daily antidepressant, despite the fact that most patients expressed satisfaction with their once-daily antidepressant at the beginning of the study. The questionnaire also revealed that once-weekly fluoxetine was more convenient for most patients and better fit their lifestyles than the once-daily antidepressants.

In general, patients switching from citalopram, paroxetine, or sertraline to once-weekly enteric-coated fluoxetine experienced no clinically significant changes in vital signs, laboratory analytes, the likelihood of experiencing an adverse event, or the type and severity of adverse events experienced. As shown by the analysis of the AMDP-5 findings, some patients experiencing adverse events on treatment with their baseline SSRI noted symptom improvement or resolution when switched to enteric-coated fluoxetine, 90 mg. However, for each adverse event captured, a similar number of patients noted development or worsening in the severity of the event upon switching. It should be noted that the study population consisted of patients who had tolerated their previous once-daily antidepressant treatment and that the change to a new drug is typically associated with some treatment-emergent adverse events. When the most frequent treatment-emergent adverse events by week that developed upon switching to once-weekly fluoxetine were examined, the rates of some of these events declined while others stayed the same.

The safety profile for the once-weekly fluoxetine patients in this study was similar to that observed with the once-weekly fluoxetine patients of Schmidt et al.,[4] as well as those in a previous longer-term study of once-daily fluoxetine.[21] The risk for serious adverse events was low for patients switched to the once-weekly fluoxetine formulation and similar to the rate reported by Schmidt et al.[4] for switching patients from daily to weekly fluoxetine dosing. Rates of discontinuation related to adverse events were also low for patients switched from the other SSRIs to once-weekly fluoxetine.

Given the long half-life of fluoxetine and its active metabolite, norfluoxetine, the consideration of a less frequent dosing regimen has long been proposed.[19,22] With the current state of knowledge in the treatment of depression advocating the use of continuation treatment after the initial resolution of depressive symptoms, a less frequent dosing regimen may be an alternative that promotes improved compliance. This study demonstrated that patients are able to achieve high compliance with the weekly dosing regimen with a compliance rate of no less than 97%. This high level of compliance may be facilitated through the improved convenience of a weekly medication. Alternatively, this dosing regimen may reframe the meaning of the medication for the patient, moving from a daily treatment directed at improving specific symptoms to one in which the medication is taken for the preservation of health, with the use of a less frequent dosing regimen highlighting that change.

Limitations to this study include the lack of a blinded control arm in which patients were continued on their current SSRI therapy. Lack of the control arm prevented the comparison of the relapse rate for patients switched to once-weekly fluoxetine with that of patients continued on treatment with their current SSRI. An additional limitation of this study is the variability in duration of treatment with the baseline SSRI of 6 to 52 weeks. Some patients were in the early continuation phase following the acute treatment of their depression and would be at a higher probability of experiencing a relapse. Others, however, were in the long-term maintenance phase of their treatment and would have a lower likelihood of experiencing a relapse. Our data, however, showed similar rates of relapse and discontinuation for lack of efficacy when subjects who received their previous SSRI treatment for less than 13 weeks were compared with those who received it 13 weeks or longer. The variability in treatment length in this study makes it difficult to directly compare relapse rates among studies and is the most likely reason that the relapse rate in the Schmidt et al.[4] study was higher than the rate reported in this study.

Overall, the study results strongly suggest that switching patients who have responded to acute treatment with citalopram, paroxetine, and sertraline to once-weekly enteric-coated fluoxetine, 90 mg, for the continuation treatment of depression is safe and efficacious. While the antidepressant response remained constant, patients experienced improvement in multiple measures of quality of life after switching to fluoxetine once weekly.

Some of the patients switched to fluoxetine once weekly did relapse, as has also been reported among patients undergoing long-term treatment for depression while taking therapeutic daily doses of antidepressants.[5–10] As such, the clinical supervision and monitoring recommended for all patients requiring long-term treatment of depression is also recommended for patients switched from other SSRIs to once-weekly fluoxetine for the continuation treatment of depression.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft).

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