Efficacy and Response Time to Sertraline Versus Fluoxetine in the Treatment of Unipolar Major Depressive Disorder

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Background: Few studies have compared the treatment efficacy of the 2 selective serotonin reuptake inhibitors sertraline and fluoxetine.

Method: A randomized, single-blind, parallel-group study of 10 weeks' duration comparing the efficacy of sertraline, 50 mg/day; sertraline, 100 mg/day; and fluoxetine, 20 mg/day, was conducted in 44 psychiatric outpatients with DSM-IV unipolar major depressive disorder. Antidepressant dosages were doubled at 6 weeks for subjects who had not achieved remission. Primary outcome measurements included the 21-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions-Improvement scale (CGI-I), with scores of ≤ 7 on the HAM-D and ≤ 2 on the CGI-I representing a positive treatment response, i.e., remission.

Results: At 4 weeks, significant differences in rate of positive treatment response were noted, with 0% for sertraline, 50 mg; 46% for sertraline, 100 mg; and 31% for fluoxetine, 20 mg ($p = .023$). At 6 weeks, positive treatment response rates were 21%, 43%, and 31% for subjects taking 50 mg of sertraline, those taking 100 mg of sertraline, and those taking 20 mg of fluoxetine, respectively, with treatment groups no longer differing significantly from each other. In subjects for whom antidepressant dose was doubled at week 6, response rates at week 10 (4 weeks on increased dose) were 40% for sertraline, 100 mg; 43% for sertraline, 200 mg; and 55% for fluoxetine, 40 mg.

Conclusion: Subjects taking sertraline, 100 mg, and fluoxetine, 20 mg, demonstrated an earlier treatment response compared with subjects taking sertraline, 50 mg. For patients without a positive response at 6 weeks, an increased antidepressant dose resulted in remission for a substantial proportion of patients when assessed 4 weeks later.

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Fluoxetine and sertraline are 2 selective serotonin reuptake inhibitors (SSRIs) that are effectively used for the treatment of depressive disorder. Although both medications have demonstrated treatment efficacy,[1,2] relatively few controlled fixed-dose studies of these 2 medications have been performed. Aguglia et al.[3] compared the efficacy of sertraline and fluoxetine in an 8-week, randomized, double-blind, prospective multicenter trial of outpatients with unipolar major depressive disorder. Subjects were treated with a starting daily dose of sertraline, 50 mg, or fluoxetine, 20 mg, for 2 weeks; the dose was increased during the following 6 weeks if clinical improvement did not occur. The final mean daily dose was 72 mg for sertraline and 28 mg for fluoxetine, with no significant differences between treatment groups. In a randomized, double-blind, prospective study, Bennie et al.[1] demonstrated that 76% of patients treated with fluoxetine, 20 mg, and 76% of patients treated with sertraline, 50 mg, had a 50% or greater decrease in Hamilton Rating Scale for Depression (HAM-D) scores from baseline to 6 weeks of treatment. However, 2 retrospective studies[4,5] found that patients treated with sertraline for depression required an upward dose titration from the initial 50-mg dose compared with patients treated with 20 mg of fluoxetine for comparable clinical improvement.

Our site recently performed a retrospective chart review study[6] to determine medication dosages prescribed to obtain euthymia in outpatients with a diagnosis of uni-

polar major depressive disorder treated with fluoxetine or sertraline. Positive response was operationalized as a greater than 50% improvement in depression sustained for at least 1 month. Among 59 outpatients, 81% of fluoxetine responders and 32% of sertraline responders were at the manufacturer's recommended starting dose of 20 mg and 50 mg, respectively, at the time of positive clinical response.[6] Results of that study suggest that either 50 mg of sertraline was an inadequate dose for a significant number of patients for the resolution of their depression or that clinicians did not prescribe the manufacturer's recommended starting dose for a long enough period to demonstrate a positive response before raising the dose. Quitkin et al.[7] suggest that antidepressant treatment should be changed at the end of 4 weeks for patients whose depression has not improved at least minimally, changed at the end of 5 weeks for patients whose conditions are unimproved after 5 weeks but minimally improved in a prior week, and continued for at least 6 weeks for patients whose conditions are minimally improved at the end of 5 weeks. In the Cantrell et al. study,[6] patients were not uniformly treated with 50 mg of sertraline for a full 4 weeks prior to dosage increase. To examine the efficacy of fixed doses of sertraline and fluoxetine, we performed a 10-week, randomized, single-blind study of sertraline, 50 mg/day; sertraline, 100 mg/day; and fluoxetine, 20 mg/day, for the treatment of outpatients with unipolar major depressive disorder.

METHOD

This study was a 10-week parallel comparison (with a blinded rater) of sertraline, 50 mg/day; sertraline, 100 mg/day; and fluoxetine, 20 mg/day, for the treatment of patients with DSM-IV unipolar major depressive disorder. This study was conducted at the University of California at Los Angeles Neuropsychiatric Institute and the West Los Angeles Veterans Affairs (VA) Medical Center and was reviewed and approved by the institutional review board at both sites. Written informed consent was obtained in a manner approved by the institutional review board at each site. Primary inclusion criteria consisted of outpatients between the ages of 18 and 62 years with an Axis I diagnosis of unipolar major depressive disorder (single, recurrent, or chronic), confirmed with the Structured Clinical Interview for DSM-IV,[8] and a score of 14 or higher on the 21-item HAM-D.[9] Subjects with a diagnosis of a mood disorder secondary to a general medical condition, bipolar disorder, or active substance abuse and subjects with history of prior treatment failure with sertraline or fluoxetine were excluded from the study. For subjects with a history of substance abuse, a 30-day period of sobriety was required prior to entry into the study.

Subjects were randomly assigned in an open manner to treatment with sertraline, 50 mg/day; sertraline, 100 mg/day; or fluoxetine, 20 mg/day. Assessments to evaluate mood improvement were performed every 2 weeks by a rater blinded to medication status. Scales included the HAM-D and Clinical Global Impressions-Improvement scale (CGI-I).[10] The primary outcome variable was remission, operationalized as a HAM-D score ≤ 7 and a CGI-I score ≤ 2. For subjects who did not achieve remission by week 6, antidepressant dosages were doubled to 100 mg of sertraline, 200 mg of sertraline, or 40 mg of fluoxetine. Subjects were assessed every 2 weeks for the remaining 4 weeks for treatment response.

The intent-to-treat population consisted of 53 patients, 17 randomly assigned to 50 mg of sertraline, 18 randomly assigned to 100 mg of sertraline, and 18 randomly assigned to 20 mg of fluoxetine. Benzodiazepines were allowed for sedative use as well as maintenance treatment for preexisting anxiety at the dose taken prior to study entry. For patients requiring an anxiolytic after entry into the study, lorazepam (0.5 mg) was prescribed.

Statistical Methods

Preliminary analyses were performed on demographic characteristics to ensure random assignment to medication group. Analyses of variance (ANOVAs) were conducted to examine continuous variables, and chi-square tests were used to examine categorical variables. The Fisher and Yates exact confidence method was used to calculate 95% confidence intervals.[11]

RESULTS

Analyzable data were available for 44 of the 53 patients originally randomized to treatment. Five patients discontinued secondary to side effects, including nausea, diarrhea, headaches, and anxiety (2 patients taking 50 mg of sertraline, 2 patients taking 100 mg of sertraline, and 1 patient taking 20 mg of fluoxetine); an additional 4 patients were lost to follow-up (1 patient taking 50 mg of sertraline, 2 patients taking 100 mg of sertraline, and 1 patient taking 20 mg of fluoxetine). Data analysis for the first 6 weeks was performed on 44 subjects. Table 1 describes baseline demographic characteristics, psychiatric and medical history, psychotherapy treatment, and concurrent sedative/anxiolytic use for the 44 subjects. Baseline HAM-D and CGI-I scores for the 3 treatment groups were similar, with no significant differences between groups (see Table 1).

One patient became hypomanic after an increase in sertraline from 50 mg to 100 mg and was withdrawn from the study at week 7. A second patient whose dose was increased from 100 mg to 200 mg of sertraline was unable to tolerate the higher dose. Thus, data analysis for the remainder of the study was performed on 42 subjects. Discontinuation rates at 6 weeks and 10 weeks were similar in all 3 groups.

Table 1. Baseline Demographics[a]

Patient Profile	Sertraline, 50 mg/d (N = 14)	Sertraline, 100 mg/d (N = 14)	Fluoxetine, 20 mg/d (N = 16)	p Value
Female, N (%)	9 (64)	6 (43)	8 (50)	.51
Age, mean (SD), y	42.43 (13.50)	37.64 (5.56)	41.13 (12.13)	.50
Education, mean (SD), y	14.85 (2.34)	15.86 (2.54)	14.75 (3.64)	.54
Ethnicity, N (%)				
White	9 (64)	8 (57)	11 (69)	.54
Other	5 (36)	6 (43)	5 (31)	
Marital status, N (%)				
Single	5 (36)	11 (79)	10 (63)	.10
Other	8 (57)	3 (21)	6 (37)	
Medical history, N (%)[b]	6 (43)	4 (29)	5 (31)	.97
Comorbid psychiatric history, N (%)	5 (36)	9 (64)	10 (63)	.37
Baseline HAM-D score, mean (SD)	20.64 (2.79)	20.79 (4.69)	20.69 (4.53)	.99
Baseline CGI-Severity score, mean (SD)	4.07 (0.47)	4.00 (0.68)	4.19 (0.40)	.62
Concurrent psychotherapy, N (%)	3 (21)	3 (21)	0 (0)	.14
Concurrent sedative/ anxiolytic, N (%)	2 (14)	2 (14)	2 (13)	.99

[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.
[b]For example, hypertension/coronary artery disease, adult-onset diabetes mellitus, hypothyroidism.

Figure 1. Mean Hamilton Rating Scale for Depression (HAM-D) Score

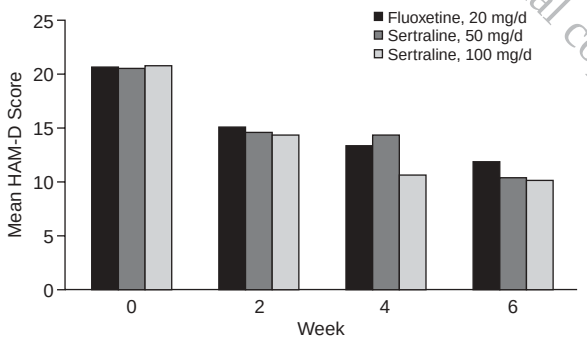


Table 2. Remission in Intent-to-Treat Population (N = 53)

Medication Group	Week 4	Week 6	Week 10
Sertraline, 50 mg/d, %	0	27	40
Sertraline, 100 mg/d, %	40	40	38
Fluoxetine, 20 mg/d, %	31	31	55
p Value	.03	.73	.71

Efficacy

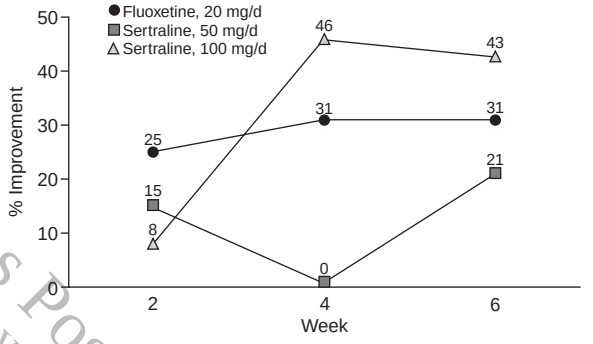
The sample size for each visit varied, ranging from 37 to 44 subjects. The mean HAM-D scale scores for each group over time are shown in Figure 1. Results are presented for the 44 subjects with analyzable data. Results for the intent-to-treat population (N = 53) were comparable and are shown in Table 2. The 95% confidence intervals are shown in Table 3.

Table 3. 95% Confidence Intervals for the Proportion in Remission

Week	Medication Group	N	%	95% Confidence Interval Lower Limit	95% Confidence Interval Upper Limit
4	Sertraline, 50 mg/d	0	0	…	25
	Sertraline, 100 mg/d	6	46	19	75
	Fluoxetine, 20 mg/d	5	31	11	59
6	Sertraline, 50 mg/d	3	21	5	51
	Sertraline, 100 mg/d	6	43	18	71
	Fluoxetine, 20 mg/d	5	31	11	59
10[a]	Sertraline, 100 mg/d	4	40	12	74
	Sertraline, 200 mg/d	3	43	10	82
	Fluoxetine, 40 mg/d	6	55	23	83
10	Sertraline, 50 mg/d + sertraline, 100 mg/d	7	54	25	81
	Sertraline, 100 mg/d + sertraline, 200 mg/d	9	69	39	91
	Fluoxetine, 20 mg/d + fluoxetine, 40 mg/d	11	69	41	89

[a]Those subjects who had their dosage doubled at 6 weeks.

Figure 2. Percentage of Patients Improved



At week 4, the percentage of patients with a positive treatment response was significantly different between the 3 groups, with no responders to sertraline, 50 mg (0/13); 46% response to sertraline, 100 mg (6/13); and 31% response to fluoxetine, 20 mg (5/16) ($\chi^2 = 7.50$, df = 2, p = .023). As shown in Figure 2, at 6 weeks 21% (3/14), 43% (6/14), and 31% (5/16) of patients had a positive response to sertraline, 50 mg; sertraline, 100 mg; and fluoxetine, 20 mg, respectively. Response rates at this time point were not significantly different for all 3 groups ($\chi^2 = 1.49$, df = 2, p = .48).

Subjects without a positive response after a minimum of 6 weeks of treatment on the starting dose had their medication dose doubled at week 6. Of the 11 subjects without a positive response to 50 mg of sertraline, 10 increased their dose to 100 mg for 4 weeks. Of these 10, 4 subjects (40%) had a positive treatment response at week 10. Seven of the 8 subjects without a positive response to 100 mg of sertraline at 6 weeks increased their dose to 200 mg for an additional 4 weeks. Of these 7, 3 subjects (43%) had a positive treatment response at week 10. All 11 subjects without a positive response to 20 mg of fluox-

etine at 6 weeks increased the dose to 40 mg for an additional 4 weeks. Of these 11, 6 (55%) had a positive treatment response at week 10. Response differences between the 3 treatment groups was not significant ($\chi^2 = 0.493$, df = 2, p = .781). The percentage of patients who discontinued treatment after an increase in dose to sertraline, 100 mg; sertraline, 200 mg; and fluoxetine, 40 mg, were 9% (1/11), 13% (1/8), and 0%, respectively.

Overall positive response rates at the end of the study for subjects who were initially randomly assigned to treatment with sertraline, 50 mg; sertraline, 100 mg; and fluoxetine, 20 mg (including responders to starting dose and responders to increased dose) were 54% (7/13), 69% (9/13), and 69% (11/16), respectively.

DISCUSSION

This study compared 50 mg/day of sertraline, 100 mg/day of sertraline, and 20 mg/day of fluoxetine in the treatment of outpatients with unipolar major depressive disorder. At 6 weeks of treatment, the percentage of positive responders (those who achieved complete remission) in each group was not significantly different. By the end of the study, overall positive response rates (including responders to starting dose and responders to increased dose) were 54%, 69%, and 69% for subjects initially randomly assigned to sertraline, 50 mg; sertraline, 100 mg; and fluoxetine, 20 mg, respectively. Although these overall "positive treatment response rates" seem low compared with reported clinical trial rates of 60% to 80%, we operationalized positive response as complete remission, defined by a HAM-D score ≤ 7 and a CGI-I score ≤ 2. These criteria are more stringent than those of many treatment studies that define positive response as a 50% or greater improvement in depression ratings.[1] A recent study by Nierenberg et al.[12] found that only 50.2% of 215 patients with major depressive disorder achieved complete remission, defined as a HAM-D score of ≤ 7, at 8 weeks of treatment with 20 mg of fluoxetine, consistent with our response rate. In our study, 64% of patients met criteria for remission (HAM-D ≤ 7 and CGI-I ≤ 2) at the end of the study. Thus, we feel that our results are comparable to those reported in the literature.

For nonresponders in all 3 treatment groups, increasing the dose of antidepressant resulted in a positive treatment response in 43% to 55% of patients. These data are consistent with those of Fava et al.,[13,14] who examined the efficacy of increased doses of fluoxetine for the treatment of unipolar major depressive disorder in patients who fail to respond to 20 mg/day. In an open-label study of 15 patients who did not respond to 8 to 12 weeks of treatment with fluoxetine at 20 mg, Fava et al.[13] found that an increase in dose to 60 to 80 mg/day for 4 weeks resulted in a statistically significant decrease in HAM-D scale scores. In a second study[14] of 41 patients who failed to respond to 8 weeks of 20 mg/day of fluoxetine and were randomly assigned to 4 weeks of treatment with fluoxetine, 40–60 mg/day; fluoxetine, 20 mg/day; desipramine, 25–50 mg/day; or fluoxetine, 20 mg/day, plus lithium, 300–600 mg/day, the high-dose fluoxetine group reported the greatest reduction in HAM-D scores. A study by Nierenberg et al.[15] suggested that nonresponse after 4 to 6 weeks of treatment with a 20-mg daily dose of fluoxetine resulted in a low probability of response by week 8. Thus, as our data support, raising the dose of an SSRI is a reasonable strategy for a substantial number of patients who do not demonstrate a positive response to "standard" SSRI dosages.

An earlier retrospective chart review by our group[6] found that significantly more fluoxetine responders compared with sertraline responders were taking the manufacturer's recommended starting dose (20 mg of fluoxetine or 50 mg of sertraline) at the time of clinical response. Our current study found that some patients who had not responded to 50 mg/day of sertraline at 4 weeks of treatment demonstrated a positive response at 6 weeks. Thus, many clinicians may raise the dose of sertraline prematurely, not allowing for an adequate length of time for a treatment response. Our response rate to 20 mg of fluoxetine was lower than that reported in the earlier chart review. Differences in results may be due to the retrospective design of the previous study and the stringent criteria for positive treatment response in the present study. Patient populations for the 2 studies also differed. The earlier retrospective review was conducted solely at a VA hospital, compared with our prospective study that included subjects from a university-based outpatient clinic as well.

Results of this study are limited by the single-blind design, which may have influenced patient response, and the lack of a placebo-control group. In addition, our small sample size may have resulted in a type II error, indicating a nonsignificant difference in response rates to 50 mg versus 100 mg of sertraline. At 6 weeks of treatment, 43% of subjects treated with sertraline, 100 mg, achieved remission, compared with 21% of subjects treated with sertraline, 50 mg. With a larger sample size, these results may be significantly different. The small sample size could also have resulted in a type I error, and therefore, our findings at week 4 await further replication. Future studies should include a larger sample size and a double-blind, placebo-controlled design.

Despite methodological limitations, our study found that response rates at 6 weeks of treatment with 50 mg of sertraline, 100 mg of sertraline, and 20 mg of fluoxetine were not significantly different. In those patients who did not show a positive response at 6 weeks, increasing the antidepressant dose resulted in a positive response for a substantial proportion of patients. Furthermore, at 4 weeks of treatment, significantly more patients had a pos-

itive response to sertraline, 100 mg, and fluoxetine, 20 mg, than to sertraline, 50 mg. These results suggest that patients may have a more robust early response to treatment with fluoxetine, 20 mg, or sertraline, 100 mg, than sertraline, 50 mg. The discontinuation rate due to side effects was not significantly greater in patients taking 100 mg of sertraline than in those taking 50 mg of sertraline. Thus, those patients who are treated with sertraline may benefit from initiating the antidepressant at a dose of 100 mg for the first few weeks of treatment, then decreasing the dose to 50 mg after significant clinical improvement has been achieved. For patients who are able to tolerate a higher initial dose of sertraline, such a treatment strategy may provide earlier relief of depressive symptoms compared with the 50-mg dose and minimize long-term adverse effects.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), lorazepam (Ativan and others), sertraline (Zoloft).

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