# Fluoxetine Treatment of Patients With Major Depressive Disorder Who Failed Initial Treatment With Sertraline

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***Background:*** This study was conducted to determine if patients with major depressive disorder who had previously failed treatment with one serotonin selective reuptake inhibitor (SSRI) would respond to a different SSRI.

***Method:*** Adult outpatients (N = 106) with DSM-III-R major depressive disorder and a history of either intolerance (N = 34) or nonresponse (N = 72) to treatment with sertraline were treated with fluoxetine (mean dose = 37.2 mg/day) in a standardized, open-label, 6-week clinical trial. Outcome was assessed at each visit using the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI-Improvement and CGI-Severity) scales, and the Patient's Global Improvement (PGI) scale.

***Results:*** Ninety-one patients (86%) completed the study. Sixty-seven patients (63%) responded to fluoxetine (i.e., experienced ≥ 50% reduction in $HAM\text{-}D_{28}$ total score at endpoint versus baseline). In addition, clinically and statistically significant improvements were noted on all measures of depressive symptoms and global functioning. There was a nonsignificant trend for patients with a history of less vigorous sertraline trials to respond more favorably to fluoxetine. Fluoxetine therapy was generally well tolerated, and there were only slight differences in adverse events reported by patients who had been intolerant to sertraline versus those who were nonresponders.

***Conclusion:*** These findings indicate that fluoxetine and sertraline, two widely used SSRIs, are not interchangeable. Patients who either have had trouble tolerating or have not responded to sertraline may do well on fluoxetine treatment.

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The serotonin selective reuptake inhibitors (SSRIs) have rapidly become the most widely prescribed class of antidepressants in the United States. The SSRIs currently account for at least 70% of all antidepressant sales (Decision Resources, Inc., Waltham, Mass. 1995. Unpublished data). The popularity of the SSRIs is largely attributable to their convenience, their generally more favorable side effect profile, and their safety in overdose.[1] Nevertheless, the SSRIs are far from universally effective; typically 33% to 50% of patients who begin a trial with one of these agents either are unable to tolerate a therapeutic dosage or are not responsive to an adequate trial.[2,3] Thus, alternate treatment strategies are needed for the significant number of patients who do not benefit from an initial SSRI trial.

Depressed outpatients who fail to respond to an initial trial of antidepressant medication are typically treated in one of three ways: they are given an augmenting agent, switched to a dissimilar antidepressant, or prescribed a second trial of a similar medication within the same general class.[3,4] Although the third strategy was favored a decade ago when physicians' choices consisted principally of the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), the recent availability of a number of additional classes of antidepressants has lessened enthusiasm for this strategy. Moreover, the results of a recent meta-analytic review suggest that treatment with a second agent within the same class may be less effective than either lithium augmentation or treatment with an alternative class of medication (e.g., an MAOI).[3] However, it is not clear if the experiences gained with the older antidepressants generalize to treatment with

the SSRIs. For example, several reports have suggested that lithium augmentation may not be as useful in SSRI-resistant depressions as in TCA-resistant cases.[5,6] Further, it is not known if difficulties tolerating one SSRI herald potential problems with other members of the same class.

Three recent reports suggest that intolerance[7] or nonresponse[8,9] to one SSRI may not predict a poor response to a second "classmate." Brown and Harrison[7] studied 91 depressed outpatients who were treated openly with sertraline after first failing to tolerate a trial of fluoxetine. Despite the apparent similarity of these compounds, fully 90% of fluoxetine-intolerant patients were able to complete a 4-week trial of sertraline and, of those, 71% responded. Joffe et al.[8] reported a 51% marked or complete response rate in an open clinical study of 55 depressed outpatients. These patients were treated with a second SSRI after failing to respond to at least a 5-week trial of a different SSRI at minimum therapeutic doses or higher. In the third study, Zarate et al.[9] retrospectively identified a heterogeneous series of inpatients who had not responded to fluoxetine and subsequently were treated with sertraline. The case series included 25 patients with major depressive disorder, as well as 6 patients with bipolar depression. At hospital discharge, 13 (42%) of the 31 depressed patients were judged to be responders, although almost 40% of the responders (5/13) had relapsed at follow-up. Thus, a second SSRI may be a more worthwhile option for outpatients who fail to respond to an initial trial.

We report here the results of a standardized, prospective trial of fluoxetine treatment of 106 patients with major depressive disorder who presented with a history of intolerance (N = 34) or nonresponse (N = 72) to sertraline treatment in their current depressive episode. In addition to documenting the response rate to, and tolerability of, fluoxetine therapy in this group, we report the relative efficacy of fluoxetine in relation to the tolerability and intensity of the previous trial of sertraline.

## METHOD

### Patients

All patients, 76 women (71.7%) and 30 men (28.3%), provided explicit written consent for research participation. Patients were enrolled at 12 sites in the United States. The study group was at mid-life (mean ± SD age = 42.9 ± 12.1 years), and 90.6% were white. The current depressive episode for 33 patients (31.1%) was at least 1 year in duration. Ninety patients (84.9%) had a history of prior episodes of depression, with an average of 3.7 prior episodes per patient. Forty-six patients (43.4%) had experienced their first depressive episode prior to age 20.

Potentially eligible patients met the DSM-III-R criteria for a current major depressive episode (nonbipolar, nonpsychotic). The criteria were applied after a clinical interview via a standardized checklist, and eligibility was reviewed by each site's principal investigator. Exclusion criteria included any psychotic mental disorder, bipolarity (including past hypomania), obsessive-compulsive disorder, active alcohol or substance abuse disorders, antisocial personality disorder, severe borderline personality disorder, and a past history of unstable or poorly controlled medical illness. Current medical stability was confirmed by a detailed history and physical examination, laboratory studies (CBC with differential, electrolytes, BUN, creatinine, liver function studies, thyroid function studies, and urinalysis), and, when clinically indicated, a 12-lead electrocardiogram.

### Prior Sertraline Treatment History

The study group was selected specifically on the basis of a history of failure to benefit from sertraline treatment during the current episode of depression. Patients were recruited from two main sources: new referrals and the clinical practices of the investigators. In the latter case, which represented about 40% of the sample, the unsuccessful sertraline trial was observed prospectively. In the remaining cases, the outcome of the sertraline trial was ascertained by a detailed clinical interview, which also elicited information on any other treatment trials conducted during the 6 months prior to study entry. When necessary, the investigators relied upon medical records *or* telephone contact with the previous attending physician to clarify a questionable history of nonresponse or intolerance.

Prior to intake, patients had received sertraline treatment for a mean of 121.1 days (SD = 159 days; median = 60 days; range, 3–895 days) at a mean dosage of 98.1 mg/day (SD = 61.2 mg/day; median = 75 mg; range, 50–300 mg/day). At intake, 34 patients (32.1%) reported that they had been withdrawn from sertraline because of intolerable side effects, and the remaining 72 patients were considered nonresponders. Patients intolerant to sertraline had received fewer days of prior treatment (median = 30.0 days vs. 69.0 days; mean = 77.2 days vs. 141.8 days; Wilcoxon rank-sum test, $Z = -3.71$; $p < .001$) and lower dosages (median = 50 mg/day vs. 100 mg/day; mean = 80.2 mg/day vs. 106.6 mg/day; $Z = -2.37$; $p = .018$) than nonresponders.

The patients were divided into four groups on the basis of prior sertraline treatment outcome. Group 1 (N = 34) included all patients who were intolerant to sertraline. The nonresponders were then divided on the basis of maximum reported dosage of sertraline. Group 2 (N = 30) received a sertraline dosage of 50 mg/day. Group 3 (N = 20) received a maximum daily dosage of sertraline 75 mg or 100 mg. Group 4 (N = 22) received a maximum daily sertraline dosage of at least 150 mg. Although these criteria were determined post hoc, their use permits the sample to be grouped along a clinically meaningful dimension based on the tolerability and intensity of prior sertraline treatment.

### Prior Treatment With Other Antidepressants

Seventy-two patients (68%) had received no treatment trials other than with sertraline during the 6 months prior to intake. Among the remainder, 25 (24%) had received one additional antidepressant trial, and 9 (8%) had been treated with two or more other antidepressants. Alternate antidepressants included tricyclics (N = 18), bupropion (N = 9), paroxetine (N = 8), trazodone (N = 5), venlafaxine (N = 2), and phenelzine (N = 2). In 14 cases, patients had received a trial of an investigational antidepressant compound during the previous 6 months. However, because of Food and Drug Administration (FDA) policy concerning protection of the double-blind in clinical trials, it could not be determined if these patients had been treated with an active compound or placebo. No patient had received fluvoxamine, and none had received lithium or thyroid augmentation.

### Fluoxetine Treatment Protocol

Sertraline was discontinued at least 14 days before initiation of the treatment protocol. Fluoxetine treatment was conducted according to a 7-visit, 6-week "open-label" protocol. At baseline (Week 0), patients began treatment with fluoxetine 20 mg/day (supplied as 20-mg capsules). Patients were instructed to return any unused medication at their next visit. An attending psychiatrist met with the patients weekly for the next 6 weeks. Dosage escalation, in fixed increments of 20 mg/day, was permitted during Weeks 3 through 5, up to a maximum of 60 mg/day. Dosage increases were routinely used, if tolerable, for treatment of patients who showed little response. Conversely, dosage decreases were allowed at Weeks 4 and 5 for patients who could not tolerate 40 or 60 mg/day.

During protocol treatment, patients were not permitted to receive other psychoactive medications. Moreover, patients agreed not to enter into any other form of treatment for depression, including psychotherapy.

### Assessment

All assessments were completed at each visit. The Hamilton Rating Scale for Depression (HAM-D)[10,11] was performed by an independent clinical evaluator. The evaluator was not blinded, however, to the nature of the trial. The patient completed the Beck Depression Inventory (BDI)[12] and the Patient's Global Improvement (PGI) scale.[13] The attending psychiatrist completed the Clinical Global Impressions (CGI-Improvement and CGI-Severity) scales[13] and recorded treatment-emergent adverse events (i.e., those events that first occurred or worsened during fluoxetine therapy). All events and their severity were recorded by the treating physician without regard to suspected causal relationship to the study drug.

The primary efficacy measures were on the 28-item HAM-D ($HAM\text{-}D_{28}$)[11] and the BDI. Secondary efficacy measures were improvement on the 17-item HAM-D ($HAM\text{-}D_{17}$), the CGI-Improvement scale, the PGI scale, and the HAM-D factors (anxiety/somatization, sleep disturbance, psychomotor retardation, and cognitive disturbance). The longer version of the HAM-D was used as a primary outcome measure because of its broader coverage of reversed vegetative symptoms, which are common in depressed outpatients.

Patients were considered to be fluoxetine responders if they achieved a ≥ 50% reduction in total score at endpoint compared with the baseline $HAM\text{-}D_{28}$ score. Response was also categorized by a score of 1 (much improved) or 2 (very much improved) on the CGI-Improvement and PGI scales.

### Statistical Analysis

The first goal of the study was to document the response to fluoxetine treatment and to assess the magnitude of within-subject change during the 6-week study. A second goal was to assess the tolerability of fluoxetine treatment, particularly among patients with a history of sertraline intolerance.

An intention-to-treat analysis (using the last-observation-carried-forward method) was performed on the primary and secondary measures with a series of within-subject, paired t tests. The incidence of treatment-emergent adverse events was compared between patients who were, by history, nonresponders to sertraline and those who were intolerant to sertraline using a series of two-by-two chi-square tests. All tests were two-tailed, with a significance level of .05.

Next, outcome was compared across the four groups defined by prior sertraline treatment history. In order to limit the number of largely redundant comparisons, these analyses focused on the more widely used $HAM\text{-}D_{17}$. Endpoint $HAM\text{-}D_{17}$ scores were compared across the four groups using a simple analysis of variance (ANOVA). HAM-D change scores were also compared with analysis of covariance (ANCOVA), using pretreatment HAM-D scores as the covariate. The response rates of the four groups (as categorized by prior response to sertraline) were also compared with a two-by-four chi-square test.

## RESULTS

Ninety-one (85.8%) of the 106 patients completed the 6-week trial. The mean dose of fluoxetine was 37.2 mg/day. The number of patients receiving each dose of fluoxetine was as follows: 20 mg/day (39 patients, or 36.8%), 40 mg/day (43 patients, or 40.6%), and 60 mg/day (24 patients, or 22.6%). Among the noncompleters, 1 patient withdrew because of an adverse event, 6 patients were withdrawn because of protocol violations (e.g., noncompliance, alcohol use), 2 patients were withdrawn because of lack of efficacy, and 2 patients withdrew consent for "personal reasons." The remaining 4 patients discontinued for unknown reasons.

**Figure 1. Weekly Mean HAM-$D_{28}$ Total Score During Fluoxetine Treatment**

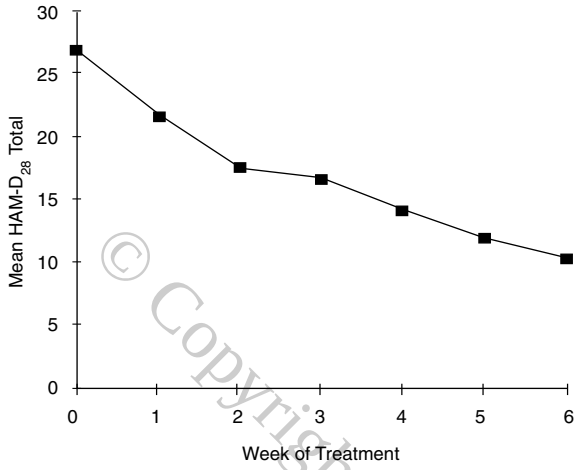


**Table 1. Beck Depression Inventory Results**

| | Fluoxetine Treatment (N = 106) | | |
|---|---|---|---|
| Factor/Variable | Mean | SD | Median |
| Baseline | 26.11 | 8.61 | 26.50 |
| Endpoint | 12.45 | 9.12 | 12.00 |
| Change[a] | –13.66[b] | 9.37 | –13.00 |

[a]Change = endpoint – baseline.
[b]p < .001.

**Table 2. Treatment Effects on Secondary Assessment Measures***

| | Fluoxetine Treatment (N = 106) | | |
|---|---|---|---|
| Factor/Variable | Mean | SD | Median |
| HAM-$D_{17}$ | | | |
| Baseline | 21.03 | 3.49 | 20.00 |
| Endpoint | 9.09 | 6.67 | 8.00 |
| Change[a] | –11.94[b] | 6.89 | –12.00 |
| HAM-D factors | | | |
| Anxiety/somatization | | | |
| Baseline | 6.62 | 1.75 | 7.00 |
| Endpoint | 3.03 | 2.29 | 3.00 |
| Change[a] | –3.59[b] | 2.59 | –4.00 |
| Sleep disturbance | | | |
| Baseline | 3.40 | 1.46 | 3.00 |
| Endpoint | 1.67 | 1.85 | 1.00 |
| Change[a] | –1.73[b] | 2.03 | –2.00 |
| Psychomotor retardation | | | |
| Baseline | 7.62 | 1.56 | 8.00 |
| Endpoint | 3.12 | 2.62 | 2.00 |
| Change[a] | –4.50[b] | 2.90 | –5.00 |
| Cognitive disturbance | | | |
| Baseline | 4.11 | 1.87 | 4.00 |
| Endpoint | 1.62 | 1.76 | 1.00 |
| Change[a] | –2.49[b] | 2.20 | –2.00 |
| Core | | | |
| Baseline | 8.84 | 1.83 | 9.00 |
| Endpoint | 3.23 | 3.14 | 2.50 |
| Change[a] | –5.61[b] | 3.52 | –6.00 |
| CGI-Severity | | | |
| Baseline | 4.29 | 0.53 | 4.00 |
| Endpoint | 2.26 | 1.08 | 2.00 |
| Change[a] | –2.03[b] | 1.17 | –2.00 |

*Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.
[a]Change = endpoint – baseline.
[b]All p values < .001.

As illustrated in Figure 1, HAM-$D_{28}$ scores decreased steadily during the 6-week trial, with a final HAM-$D_{28}$ score of 12.1 in the intention-to-treat analysis. Of note, a statistically significant ($p < .05$) reduction in HAM-$D_{28}$ scores was observed by the second week of treatment. Change in self-reported BDI scores from baseline to endpoint was comparably large and statistically significant ($p < .001$) (Table 1).

Outcomes on the secondary dependent measures are summarized in Table 2. Statistically and clinically significant reductions were observed on the HAM-$D_{17}$, all five of the HAM-D factors, and the CGI-Severity scale.

Sixty-seven patients (63.2% of those enrolled; 73.6% of completers) met the HAM-$D_{28}$ response criteria at Week 6 or endpoint. The CGI-Improvement and PGI scores were consistent with this result: 81 patients (76.4%) met the CGI response criteria and 76 patients (71.7%) met the PGI response criteria. On the HAM-$D_{28}$, response rates did not differ significantly as a function of prior treatment trials: only sertraline, 43/72 (59.7%); one other trial, 18/25 (72.0%); two or more other trials, 6/9 (66.7%) ($\chi^2 = 1.82$, df = 2, $p = .404$).

Table 3 provides a summary of the treatment-emergent adverse events that occurred with an incidence of at least 5%. The adverse events with the greatest incidence (e.g., headache, insomnia, and nausea) are typical of the SSRI class. To our surprise, none of these characteristic adverse events was more severe or more common in patients with a prior history of sertraline intolerance than in patients who were sertraline nonresponders. The incidence of three less common adverse events did show significant differences ($p < .05$) between these two groups: peripheral edema, myalgia, and pruritus were more common in the patients previously intolerant to sertraline.

Neither final HAM-$D_{17}$ scores nor change scores differed significantly across the four groups defined by the intensity of prior sertraline treatment (Table 4). However, there was a nonsignificant trend for higher response rates among the patients who had received less intensive prior sertraline trials. For example, fluoxetine response rates were 70.6%, 70.0%, 40.0%, and 59.1%, respectively, in the four treatment groups.

## DISCUSSION

In the 8 years that have followed the approval of fluoxetine hydrochloride for the treatment of depression, the SSRIs have proliferated in number and flourished in the marketplace.[1] However, no clear consensus has yet emerged with respect to the management of SSRI nonre-

**Table 3. Treatment-Emergent Adverse Events That Occurred in at Least 5% of Patients**

| | Fluoxetine Treatment (N = 106) | |
|---|---|---|
| Adverse Event | N[a] | % |
| Headache | 25 | 23.6 |
| Insomnia | 22 | 20.8 |
| Nausea | 19 | 17.9 |
| Somnolence | 18 | 17.0 |
| Asthenia | 14 | 13.2 |
| Diarrhea | 13 | 12.3 |
| Dry mouth | 12 | 11.3 |
| Rhinitis | 9 | 8.5 |
| Abnormal dreams | 8 | 7.5 |
| Anxiety | 8 | 7.5 |
| Dizziness | 8 | 7.5 |
| Dyspepsia | 8 | 7.5 |
| Nervousness | 7 | 6.6 |
| Libido decreased | 6 | 5.7 |

[a]N = number of patients reporting the treatment-emergent adverse event.

**Table 4. Response to Fluoxetine in Relation to Prior Sertraline Response**

| | Prior Sertraline Response[a] | | | |
|---|---|---|---|---|
| Variable | Group 1 (N = 34) | Group 2 (N = 30) | Group 3 (N = 20) | Group 4 (N = 22) |
| Baseline HAM-$D_{17}$ mean (SD) | 21.2 (3.4) | 20.9 (4.0) | 22.2 (3.5) | 19.9 (2.8) |
| Endpoint HAM-$D_{17}$ mean (SD)[b] | 8.6 (6.4) | 8.3 (6.7) | 12.1 (7.7) | 8.1 (5.6) |
| Change HAM-$D_{17}$ mean (SD)[c] | –12.5 (6.8) | –12.6 (7.1) | –10.1 (7.6) | –11.8 (6.2) |
| Percent responders (N)[d] | 70.6 (24) | 70.0 (21) | 40.0 (8) | 59.1 (13) |

[a]Group 1: intolerant to sertraline; Group 2: sertraline 50 mg/day; Group 3: sertraline 75 mg/day or 100 mg/day; Group 4: sertraline ≥ 150 mg/day.
[b]ANOVA, p = .59.
[c]ANCOVA, p = .28.
[d]$\chi^2 = 6.08$, df = 3, p = .11. A post hoc 2 × 2 comparison pooling Groups 1 and 2 versus Groups 3 and 4 approached statistical significance ($\chi^2 = 3.57$, df = 1, p = .06).

sponders or patients who are intolerant to these agents.[3,4] The results of the current prospective study suggest that outpatients who have failed to benefit from a trial of sertraline still have an excellent chance of responding to a trial of fluoxetine. Further, more than 70% of the patients with a history of intolerance to sertraline responded to fluoxetine. These findings, especially when coupled with the results of the prior outpatient studies of Brown and Harrison[7] and Joffe et al.[8] suggest that it is reasonable to consider at least a second SSRI trial before switching to a TCA or another newer antidepressant, such as venlafaxine, bupropion, or nefazodone.

Other options for SSRI nonresponders include adjunctive treatment with a TCA, lithium augmentation, buspirone augmentation, and withdrawal of the SSRI and, after appropriate washout, treatment with a monoamine oxidase inhibitor.[3,4] Although differences in patient characteristics and research designs limit interpretation across studies, the response rates observed in both the current study and that of Joffe et al.[8] either match or exceed those reported to date for other strategies for SSRI nonresponders.[3] For example, Thase et al.[14] reported a 43% response rate to imipramine in a prospective, double-blind "crossover" study of chronically depressed patients who had failed to respond to a 12-week trial of sertraline. Moreover, the simplicity of therapy regimen, tolerability, and safety in overdose constitute major advantages in favor of choosing a second SSRI trial instead of many other alternate strategies.

The results of the current study are more positive than those reported by Zarate et al.[9] Of note, Zarate and colleagues'[9] study group consisted of inpatients and, thus, probably included more severely depressed, treatment-resistant, and markedly comorbid patients. In this regard, Thase and Rush[3] observed that the SSRIs had much higher response rates as "second-choice" antidepressants in studies of depressed outpatients than in studies of inpatients.

Several limitations of this trial warrant discussion. Most importantly, our study did not include randomized, parallel comparison groups, and relative efficacy cannot be determined without such conditions. This shortcoming similarly applies to the studies of Brown and Harrison,[7] Joffe et al.,[8] and Zarate et al.[9] The merits of a second SSRI trial, as compared to alternate dissimilar monotherapies (e.g., TCAs, bupropion, venlafaxine, nefazodone, or mirtazapine) need to be assessed prospectively under double-blind conditions. Nevertheless, if the current study included a hypothetical comparison group of 106 patients treated with an alternate antidepressant, the treatment would have had to yield an 80% response rate in order to have been statistically more effective than the fluoxetine response rate observed in this trial.[15] When placed in the context of prior studies of antidepressant nonresponders,[3] such an occurrence would have been most improbable.

Second, this study did not include a placebo treatment condition, which precludes a strict assessment of efficacy per se. The ethics of including a placebo treatment condition in a study of patients who have not benefited from a prior antidepressant trial are controversial.[3] Moreover, the results of several prior studies suggest that a placebo treatment condition would have been unlikely to have yielded more than a 20% response rate in such patients (see Thase and Rush[3]).

Third, the majority of the prior sertraline trials were not prospectively administered by the investigators. Moreover, only about 25% of the patients in this study had received a dosage of sertraline approaching the maximum recommended for adults. Indeed, there was a nonsignificant trend suggesting that patients either who were intolerant to sertraline or who had received a low-dose trial were somewhat more responsive to fluoxetine treat-

ment. The uncertain reliability of patient reports of past treatments may have influenced these findings. However, the response rate observed in the subgroup of patients who had previously received ≥ 150 mg/day of sertraline (59.1%; 13/22) was clearly within the clinically acceptable range for a de novo antidepressant trial.

Fourth, the short-term duration of this trial does not permit us to comment on whether or not fluoxetine responses were sustained during continuation or maintenance phases of therapy. On one hand, more than 33% of the sertraline responders in the study of Zarate et al.[9] relapsed after discharge from inpatient treatment. On the other hand, studies of continuation therapy with SSRIs typically document low relapse rates in outpatient samples.[16–19]

Finally, both the length (6 weeks) and the upper dosage limitation (60 mg/day) of the current trial may have dampened the maximal fluoxetine response rate. Specifically, use of a longer course of treatment[20] and/or higher dosages[21] may have yielded a larger proportion of responders.

In summary, in this study of outpatients with major depressive disorder who had failed to benefit from a prior trial of sertraline, 86% completed a 6-week trial of fluoxetine monotherapy and 63% responded to treatment. Although interpretations are limited by the open nature of the research design, these findings provide further evidence that the SSRIs are not interchangeable and that outpatients who fail to benefit from one SSRI may have a clinically significant chance of responding to another member of this class of antidepressants.

*Drug names:* bupropion (Wellbutrin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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