A Double-Blind Study of Long-Term Treatment With Sertraline or Fluvoxamine for Prevention of Highly Recurrent Unipolar Depression

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Background: We evaluated and compared the efficacy and safety of sertraline and fluvoxamine in a randomized, double-blind, parallel-group study during a follow-up of 24 months.

Method: Sixty-four patients with recurrent, unipolar depression (DSM-IV criteria) who had at least one depressive episode during the 18 months preceding the index episode were accepted into the trial. Patients were randomly assigned to one of the two long-term treatment groups and evaluated monthly by trained psychiatrists, blinded to treatment option, on the basis of the Hamilton Rating Scale for Depression.

Results: All patients completed the 24-month follow-up period. Sertraline and fluvoxamine showed an equal efficacy in preventing new recurrences. In fact, there was no significant difference in survival rates between the two medication groups: 7 sertraline-treated patients (21.9%) and 6 fluvoxamine-treated patients (18.7%) had a single new recurrence ($z = 0.14$; $p = .88$). Moreover, recurrence observed during maintenance therapies was less severe and/or of shorter duration than index episodes.

Conclusion: Long-term treatment with sertraline or fluvoxamine has been shown to be effective for prevention of highly recurrent unipolar depression. The high tolerability of these compounds, together with their prophylactic effectiveness, has an important role in improving the quality of life of these patients.

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Substantial evidence indicates that tricyclic antidepressants as well as lithium are effective in the long-term treatment of recurrent depression.[1–5] Recent studies have reported that serotonin selective reuptake inhibitors (SSRIs) can also be used in preventing relapses and recurrent episodes of depression. In this regard, fluoxetine was found to be more efficacious than placebo in the long-term treatment of recurrent depression.[6] Additionally, paroxetine, sertraline, and citalopram performed better than placebo in continuation and prophylactic therapies.[7–9]

It is well established that the population included in prophylactic studies should have sufficient expected morbidity within the period of the trial, where the best predictor of subsequent recurrence is the frequency of prior episodes and a minimum prior recurrence rate is often used as a selection criterion.[10] On this basis, we have recently found that subjects with a high recurrence of unipolar depression treated with fluvoxamine for 36 months had a lower frequency of new recurrences when compared to those undergoing lithium prophylactic treatment.[11]

Nevertheless, the efficacy of SSRIs other than fluvoxamine as prophylactic treatment in a population with a high probability of recurrence has not yet been tested. Moreover, no study has been conducted to investigate comparative long-term treatments between the different SSRIs.

Here, we report a randomized, double-blind, parallel-group study of the efficacy and safety of sertraline and fluvoxamine during a 24-month follow-up in a population of unipolar patients who had a high probability of recurring depressive episodes.

METHOD

Sample

Patients consecutively admitted to the Research Center for Mood Disorders of the S. Raffaele Hospital in Milan for a recurrent, major depressive episode (DSM-IV criteria)[12] ($N = 273$) were screened for the absence of other Axis I diagnoses, important physical illness, a history of low compliance to past treatments, mania or hypomania in first- and second-degree relatives, and prior long-term maintenance treatments and the presence of at least one

depressive episode during the 18 months preceding the index episode. Patients with longer recurrence cycles were excluded to allow a meaningful comparison of the preventive efficacy of the maintenance treatments within our 24-month follow-up time limit. Seventy-seven patients met the selection criteria.

At the time of recovery (4 months of remission confirmed by the absence of depressive symptoms according to DSM-IV criteria, absence of functional impairment, and Hamilton Rating Scale for Depression [HAM-D][13] score < 8), 64 of the patients (15 men and 49 women) gave their informed consent before entering the 2-year trial.

During the acute index episode, these patients were treated with tricyclics (77%), SSRIs (6%), reversible inhibitor of monoamine oxidase-A (3%), or combined drug treatments (14%). At the end of the continuation phase (4 months), these treatments were gradually discontinued within 3 weeks. Thereafter, patients were randomly assigned to one of the two long-term treatment groups.

Study Design

Sertraline 100 mg/day was administered to 32 subjects, while 32 other patients received fluvoxamine 200 mg/day for a follow-up period of 24 months. During this period, patients were evaluated monthly by trained psychiatrists who were blinded to the treatment option. If a patient presented signs of clinical worsening and functional impairment and had a HAM-D score > 15, additional treatment was prescribed by raising sertraline dosage up to 200 mg/day or fluvoxamine up to 300 mg/day. The patient was examined once a week until symptoms abated.

Side effects were recorded by using the Dosage Record and Treatment Emergent Symptom Scale (DOTES).[14]

Several clinical and demographic variables of interest were also recorded: sex, current age, age at onset, and duration of illness. In addition, we evaluated the overall rate of depressive episodes between the onset of the disorder and the beginning of maintenance therapy (pretreatment index = number of episodes/months of duration of illness × 100) as the measure of the episode frequency before long-term therapy.[15] This information was collected directly from the patient and from a relative, as co-informant, using the affective disorder section of the Diagnostic Interview Schedule.[16]

Statistical Analyses

The Savage-Cox test was used to compare survival curves, and the Cox proportional hazards model[17] was employed to calculate the hazard of recurrence, taking into account the variables of interest.

Chi-square and t tests were used to compare the demographic and clinical characteristics of the patients.

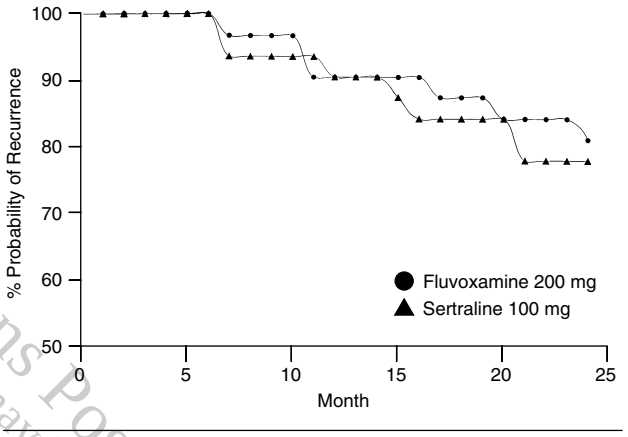
Analyses to test the power of our sample in detecting differences of recurrence rates were performed considering a two-tailed alpha level of .05; rates of differences between groups ranged from 15.6% to 46.9% (odds ratio [OR] = 2.45–9), with a base rate of 15.6% (5 subjects) in the reference group. Power was considered satisfactory when higher than .80; for the calculations, we used the GPOWER package.[18]

Table 1. Baseline Clinical and Demographic Characteristics of the Two Therapy Groups*

	Sertraline (N = 32)		Fluvoxamine (N = 32)	
Characteristic	Mean	SD	Mean	SD
Current age (y)	47.3	11.0	49.0	13.7
Age at onset (y)	35.4	10.6	37.6	13.8
Duration of illness (mo)	142.8	4.8	136.8	0.1
Number of episodes	6.8	2.1	7.2	2.5
Pretreatment recurrence index	4.8	2.7	5.2	5.0
Hamilton Rating Scale for Depression index episode	26.9	1.6	27.3	2.1

*Gender male/female ratios: sertraline = 7/25, fluvoxamine = 8/24. No statistical difference was found between groups (chi-square test for sex; Student's t test for other variables).

Figure 1. Survival Curve of Time to Recurrence



RESULTS

All subjects completed the 24-month follow-up period. No patient had a return of the acute symptoms either in the continuation or in the transition phases. No polarity switch was observed during the study. As can be seen in Table 1, none of the baseline clinical and demographic characteristics were significantly different in the two groups of therapy.

Figure 1 shows the survival curves of subjects treated with sertraline or fluvoxamine. At the end of the study, there was no significant difference in survival rates between the two medication groups. In fact, 7 sertraline-treated patients (21.9%) and 6 fluvoxamine-treated patients (18.7%) had only a single new recurrence (z = 0.14; p = .88).

Table 2. Proportional Hazards Analysis

Variable	z Value	p Value
With all variables in the analysis		
Therapy	0.14	.88
Sex	0.04	.97
Current age	0.10	.92
Age at onset	1.50	.13
Duration of illness	2.32	.2
Number of episodes	3.12	.002
Stratifying by therapy and recurrence index		
Therapy	1.29	.2
Pretreatment recurrence index	3.56	.0004

Table 3. Comparison of Clinical Characteristics Between Patients With and Without Recurring Episodes of Depression

	Patients With Recurring Episodes (N = 13)		Patients With No Recurring Episodes (N = 51)		
Characteristic	Mean	SD	Mean	SD	p Value[a]
Current age	48.5	12	48.0	14.3	.9
Age at onset	35.6	12	40.0	12	.2
Duration of illness (mo)	154.8	0.1	96.0	27.6	.0001
Number of episodes	14.5	0.2	4.03	0.1	.0001
Pretreatment recurrence index	9.4	5.0	4.2	3.0	.0001

[a]Student's t test.

Among sertraline-treated patients, the cumulative probability of having no new recurrence was 93.7% at Month 7, 90.6% at Month 12, 87.5% at Month 15, 84.3% at Month 16, and 78.1% at Month 21. Among fluvoxamine-treated patients, the cumulative probability was 96.8% at Month 7, 90.6% at Month 11, 87.5% at Month 17, 84.3% at Month 20, and 81.3% at Month 24.

As can be seen in Table 2, the Cox survival analysis revealed no difference in sex, current age, or age at onset between subjects with recurrences and those with no recurrences. On the other hand, the number of episodes ($p = .002$) and the duration of illness ($p = .02$) significantly affected the risk of recurrence. When the proportional hazards model was run with therapy and recurrence index scores, the therapy z value was 1.29 and the p value was .2; the pretreatment recurrence index z value was 3.56 and the p value was .0004.

The comparison of clinical characteristics between patients with and without recurrences is shown in Table 3. Patients with recurrences displayed a higher mean pretreatment recurrence index than those with no recurrences.

Moreover, recurrences observed during maintenance therapies were less severe and/or of shorter duration than index episodes. In fact, the intensity of episodes (determined by mean ± SD HAM-D scores) during sertraline or fluvoxamine treatment decreased from 28.2 ± 1.4 to 22.8 ± 0.9 ($t = 8.5$, $df = 12$, $p = .0001$) and from 28.1 ± 3.4 to 22.6 ± 2.3 ($t = 3.2$, $df = 10$, $p = .008$), respectively. The duration of episodes decreased from 10.7 ± 2.4 to 5.2 ± 1.1 weeks for sertraline ($t = 5.5$, $df = 12$, $p = .0001$) and from 10.5 ± 2.8 to 5.8 ± 1.4 weeks for fluvoxamine ($t = 3.6$, $df = 10$, $p = .004$).

During the first month of therapy, among patients treated with sertraline, 2 reported mild nausea (6.2%) and 4 abnormal ejaculation (12.5%); among patients treated with fluvoxamine, 3 reported mild nausea (9.4%), 3 anorexia (9.4%), 1 headache (3.1%), and 1 somnolence (3.1%). These side effects disappeared spontaneously during the maintenance study, and a dosage reduction of the medications was never required.

DISCUSSION

It is well established that the main goal for a successful prophylactic treatment is the reduction of the number and severity of subsequent recurrences.[19] In line with this notion, our results show a recurrence-preventing activity for sertraline and fluvoxamine.

In our sample, we found that the higher frequency of episodes prior to the beginning of the preventive treatment predicted a worse outcome. This finding was independent of the prophylactic agent administered and is in agreement with our previous findings, showing that response to long-term treatment appeared to be strictly related to recurrence rate.[11,20] From a clinical point of view, it is difficult to envisage an effective maintenance therapy for "highest risk" patients. Even if the use of lithium instead of, or in combination with, antidepressants in the maintenance therapy is controversial,[5,11,21] it could be interesting to investigate whether the addition of lithium to an SSRI may be useful in preventing depressive recurrence.

Interestingly, considering as a prophylactic effect not only the decreased risk of recurrence but also the reduction of symptomatologic intensity and/or the duration of new episodes, we found that in patients with recurring episodes of depression both of these parameters were significantly reduced in the two groups of therapy. Regarding this latter point, it could be important to consider that the monthly evaluation of patients allowed rapid pharmacologic treatment in case of recurrence.[1]

All recruited subjects completed our follow-up period, indicating the high tolerability (safety and few side effects) of sertraline and fluvoxamine. This seems to be an advantage, since poor compliance represents one of the main practical problems during long-term treatment.[22]

One limitation of our study is the lack of a placebo group. Considering that patients with recurrent major depression have at least a 70% risk of subsequent recurrences,[21] and after recovery from a major depressive episode there is a 50% probability that subjects will experience a new episode within 2 years,[23] it is likely that no difference in recurrence rates between drug versus placebo would have occurred in our sample.

A crucial issue is also the size of the clinical difference we could detect in our study. Power analyses revealed an adequate power to detect moderate to large differences in recurrence rates between the two groups. In detail, by hypothesizing a small difference of recurrence (5 vs. 10 patients, 15.6% difference, OR = 2.45), we find the power in our sample is only .31; if we consider larger differences, we observed moderate (5 vs. 15 patients, 31% difference, OR = 4.76, power = .73) to good (5 vs. 20 patients, 46.9% difference, OR = 9, power = .96) powers. Considering these calculations, we can argue that in our sample, the observed difference (1 patient, 3%) is absolutely not significant, and also in a much larger sample, it would not reach the significance level.

Since in clinical practice the medication that induces remission of the acute episode is generally used for maintenance therapy, another critical point of our study could be the change of drug in the maintenance phase. On the other hand, our data provide evidence that sertraline and fluvoxamine prevent the recurrence of further episodes in patients with a high recurrence rate, and the efficacy of these drugs is accompanied by satisfactory safety and toleration, thus improving the quality of life of the patients who use them.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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