A Double-Blind Comparison of Fluvoxamine and Paroxetine in the Treatment of Depressed Outpatients

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Background: Fluvoxamine and paroxetine, both serotonin selective reuptake inhibitors (SSRIs), were compared at two centers in a 7-week double-blind study in outpatients with major depression, diagnosed by DSM-III-R criteria.

Method: Sixty patients were randomly assigned to receive dosage titrated upward to between 50–150 mg/day of fluvoxamine (N = 30) or 20–50 mg/day of paroxetine (N = 30). The mean ± SD daily dose administered at the last assessment was 102 ± 44 mg/day for fluvoxamine and 36 ± 13 mg/day for paroxetine. Sixteen (53%) fluvoxamine-treated patients and 10 (33%) paroxetine-treated patients were titrated to the maximum permissible dosage of either drug. Sample size was calculated to provide at least 85% power at 5% level of significance to detect at least a 1.00-point difference in mean severity of adverse events, assuming a standard deviation of 1.0.

Results: Fluvoxamine and paroxetine were similarly effective in ameliorating depression as demonstrated by mean total scores of 10.9 ± 7.3 ($p < .00$) and 11.5 ± 7.4 ($p < .00$), respectively, in the Hamilton Rating Scale for Depression (HAM-D). Adverse events were mostly mild to moderate in severity. The most common events were headache (N = 17, 57%), nausea (N = 14, 47%), sweating (N = 10, 33%), somnolence (N = 9, 30%), diarrhea (N = 9, 30%), dry mouth (N = 8, 27%), dizziness (N = 8, 27%), and, among males, impotence (N = 3, 21%) and ejaculatory abnormality (N = 3, 21%) in the paroxetine group, and headache (N = 12, 40%), somnolence (N = 12, 40%), nausea (N = 11, 37%), dry mouth (N = 11, 37%), insomnia (N = 9, 30%), asthenia (N = 7, 23%), and dyspepsia (N = 7, 23%) in the fluvoxamine group. The only statistically significant difference between treatment groups was for sweating (33% paroxetine vs. 10% fluvoxamine, $p = .028$).

Conclusion: Observed differences in some side effects, although not statistically significant, indicate that when a patient has difficulty tolerating one SSRI, the clinician may choose to change to a different agent within the same class.

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The serotonin selective reuptake inhibitors (SSRIs) are believed to ameliorate depression by blocking the clearance of serotonin from the synaptic cleft, resulting in increased synaptic serotonin availability to receptors and prolonged serotonergic activity.[1] SSRIs are better tolerated than the tricyclic antidepressants (TCAs) because they are associated with relatively fewer anticholinergic, sedative, cardiovascular, or weight-gain effects.[2] SSRIs have also been shown to be safer in overdose.[2] All currently marketed SSRIs appear to have similar efficacy in the treatment of depression, time to onset of action, and overall tolerability.[2] Despite their similar mechanisms of action, the pharmacokinetic behavior and chemical structures of the various SSRIs are quite different and are likely the basis for a divergence in their clinical profiles of action.[3]

The SSRI fluvoxamine is an effective antidepressant,[4–6] which acts by facilitating serotonergic neurotransmission.[7,8] It is approved for treatment of obsessive-compulsive disorders in the United States and for depression in over 40 other countries. After oral dosing, fluvoxamine reaches peak plasma concentrations in 2 to 8 hours,[9] and the parent drug has an elimination half-life of 15.6 hours after multiple doses,[10] making it suitable for once-daily administration.

Paroxetine, also an SSRI, which is effective and approved in the United States for use as an antidepressant, reaches peak plasma concentrations after oral administration in 3 to 8 hours.[11] Paroxetine has an elimination half-life of 24 hours, which also allows for once-daily dosing.[12,13]

The most common side effects related to the use of fluvoxamine tend to affect the gastrointestinal and the ner-

vous system and include, in descending frequency, nausea, somnolence, asthenia, headache, dry mouth, and insomnia.[14] The most common side effects of paroxetine include the identical spectrum of complaints, i.e., nausea, somnolence, headache, dry mouth, asthenia, and insomnia.[15]

Numerous placebo-controlled trials have been conducted on fluvoxamine[2,16] and paroxetine.[2,17] Active-controlled studies include comparisons with amitriptyline, imipramine, and other SSRIs.[18–22] This study is one of the first double-blind comparisons of the antidepressant efficacy and tolerability of fluvoxamine and paroxetine in outpatients with major depression.

METHOD

Patient Selection

Eligible patients aged 18 to 65 years who fulfilled the diagnostic criteria for a single or recurrent major depressive disorder, as defined by DSM-III-R,[23] were recruited at two centers. The depressive disorder could be moderate or severe, without mood incongruent psychotic features. Women of childbearing potential were required to use appropriate birth control methods, and no pregnant or nursing patients were included in the study. A minimum total score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[24] and a minimum score of 2 on the "depressed mood" item of the HAM-D were required for study entry.

Those patients who were not fluent in written or oral English, had a history of medication noncompliance or substance abuse within the previous 6 months (other than nicotine), demonstrated a placebo response during screening (i.e., ≥ 20% improvement on HAM-D total score), had been treated within 30 days with a drug with anticipated major organ toxicity, or had a severe risk of suicide or displayed autoaggressive behavior during the current depressive episode were not allowed to enter the study. Additional exclusion criteria included hypersensitivity to SSRIs, participation in previous fluvoxamine studies, other significant organic disease, clinically significant laboratory abnormalities, or other primary psychiatric diagnoses. Sufficient washout from other investigational drugs, prior psychotropic drugs, and electroconvulsive shock therapy was assured, and concomitant use of any psychotropic medications was prohibited. In addition, patients who would not be able to return for assessment due to transportation difficulties were excluded. While medications to treat gastrointestinal disturbances (antacids, laxatives), and headache (acetaminophen, aspirin, ibuprofen) and to provide nighttime sedation (chloral hydrate only) were permitted, all other medication use was prohibited unless approved by the study physician. Informed consent was obtained in writing at the time of enrollment. This study was conducted within the Institutional Review Board human subjects guidelines at the site of each participating investigator.

Study Design

All patients meeting initial participation criteria entered a placebo screening phase and returned for their final screening procedures and initial study drug administration after 1 to 2 weeks. Patients were then randomly assigned to either fluvoxamine or paroxetine treatment in a double-blind, parallel-group study design. Assessments were conducted at screening, baseline (Day 1), and at Weeks 1, 2, 3, 5, and 7 for all efficacy and safety parameters with the following exceptions: physical examination and medical and psychiatric history were conducted at screening only, and clinical laboratory evaluations were conducted at screening, baseline, and Week 7. Only the Clinical Global Impressions (CGI)[25] severity of illness rating (Item 1) was measured at screening and baseline, and subsequent CGI ratings were compared to the pretreatment status at each evaluation.

Patients received study drug in blister cards containing three capsules identical in appearance for morning and nighttime administration. Patients randomly assigned to fluvoxamine received fluvoxamine maleate in 50-mg capsules, and patients randomly assigned to paroxetine received paroxetine hydrochloride in capsules containing 20-mg or 30-mg tablets. Identical placebo units were provided to fill the blister card in accordance with the study drug dosage. Fluvoxamine capsules were given as a single dose of three capsules at bedtime, and three paroxetine capsules were given as a single morning dose, distributed according to a titration scheme that was to be adjusted based on the patient's response. Target dosage ranges of 50 mg to 150 mg daily for fluvoxamine and 20 mg to 50 mg daily for paroxetine were predetermined, and the lowest effective dose was to be maintained throughout the 7-week double-blind portion of the study. The fluvoxamine dose could be increased to 100 mg at the Week 1 visit and to 150 mg at the Week 2 visit, and the paroxetine dose could be increased to 30 mg at the Week 1 visit, to 40 mg at the Week 2 visit, and to 50 mg at the Week 3 visit. All attempts were made to maintain a constant dose during the last 3 weeks of the study.

Adverse Events and Clinical Laboratory Abnormalities

Observed or volunteered adverse events were recorded at each clinic visit, as was any intercurrent illness. A clinical laboratory battery (including hematology and serum chemistry) was conducted at screening, baseline, and Week 7. All required clinical laboratory tests were analyzed by a certified central laboratory. The number and percentage of patients experiencing each specific event for Treatment-Emergent Signs and Symptoms (TESS) (defined as experiences that appeared for the first time during the double-blind period, or experiences that appeared be-

tween screen and baseline, but increased in severity during the double-blind period) were calculated for both treatment groups. If a patient reported an adverse event during the baseline period and again, but not contiguously, it was also treated as a treatment-emergent event. The number and percentage of patients in each treatment group that experienced at least one adverse experience in each of the various COSTART[26] body systems were also calculated, and finally the number and percentage of patients reporting any adverse experience during the study were computed for both treatment groups. Criteria for marked abnormalities were defined for certain laboratory tests and vital signs, and abnormal values for these parameters were tabulated.

Patient Assessment

The HAM-D was used to assess primary antidepressant treatment efficacy. Additional efficacy measurements included the Hamilton Rating Scale for Anxiety (HAM-A),[27] the CGI for improvement and severity of illness, the depression factor from the 56-item Hopkins Symptom Checklist (SCL-56),[28] and the HAM-D cognitive disturbance and retardation factors.

Statistical Methodology

The planned number of patients per treatment group was 30, based upon calculations that would provide at least 85% power at the 5% level of significance to detect at least a 1.00-point difference in mean severity of adverse events, assuming a standard deviation of 1.0. Power calculations were based on the noncentral F distribution. Because the actual rate of adverse events was lower than that anticipated for these calculations, the sample size for most events was not large enough to detect differences between treatment groups. The rate of reporting of the most common adverse events was adequate to determine a difference of 30% with a power of 80% using a chi-square test.

Continuous and ordered categorical data were analyzed using a two-way analysis of variance with factors for treatment (fluvoxamine and paroxetine) and Center and Treatment by Center interaction as fixed factors. Discrete variable analysis was accomplished using either the Pearson chi-square statistic, or Fisher's exact test (when > 25% of the expected cell frequencies were < 5). A 5% significance level was required to demonstrate statistical significance, and all testing was two-sided. The data were analyzed with PC SAS statistical analysis software (SAS Institute, Cary, N.C.).

The efficacy and safety analyses were based on the intent-to-treat populations, defined as all randomized patients having at least one dose of double-blind medication and one post-baseline follow-up assessment either on study medication or within 3 days of study drug discontinuation. The intent-to-treat efficacy analyses were conducted at each visit and for last observation carried forward (LOCF) at Week 7 or endpoint.

Table 1. Patient Characteristics in Fluvoxamine and Paroxetine Treatment Groups (Intent-to-Treat Safety Sample)

Characteristic	Fluvoxamine N = 30		Paroxetine N = 30	
Sex				
Male	14	(47%)	14	(47%)
Female	16	(53%)	16	(53%)
Race				
White	26	(87%)	28	(93%)
Non-white	4	(13%)	2	(7%)
Age (y)				
Mean (range)	42.7	(25–60)	39.9	(25–58)
Weight (lb)				
Mean (range)	180.1	(112–264)	175.8	(111–323)
Height (in)				
Mean (range)	67.2	(62–75)	65.8	(53–72)

RESULTS

Patient Disposition

A total of 81 clinically depressed outpatients volunteered for participation in this study and began the 1- to 2-week single-blind run-in screening phase of placebo treatment. Of these, 21 patients were discontinued prior to receiving active study drug because they did not meet participation criteria (N = 6), had a placebo response (N = 6), withdrew consent (N = 3), were noncompliant (N = 3), had abnormal laboratory test results (N = 2), or had medication sensitivity (N = 1). Therefore, at the start of the double-blind period, the fluvoxamine group consisted of 30 patients, and the paroxetine group, 30 patients. All randomized patients who received study drug comprised the intent-to-treat safety population. Before efficacy assessments were conducted, 1 fluvoxamine-treated patient was terminated for protocol violation, and 1 paroxetine-treated patient was terminated for adverse events, resulting in an intent-to-treat efficacy population of 29 fluvoxamine-treated and 29 paroxetine-treated patients.

A total of 18 patients in the intent-to-treat efficacy population failed to complete the study, 10 in the fluvoxamine group and 8 in the paroxetine group. Two patients in the fluvoxamine group and 4 patients in the paroxetine group withdrew due to adverse events. One patient in the fluvoxamine group and 3 patients in the paroxetine group withdrew due to treatment ineffectiveness. One patient in the fluvoxamine group was lost to follow-up, and 2 had a protocol violation. In addition, 4 fluvoxamine-treated patients and 1 paroxetine-treated patient were discontinued from the study for "other" reasons (withdrew consent, family illness, out of town, moved).

Demographic and Baseline Characteristics

Patients in both groups were generally physically healthy. A summary of their demographic information, including sex, race, age, weight, and height, is displayed by treatment group in Table 1. There were no demographic

Table 2. Psychiatric and Depressive History (Intent-to-Treat Safety Sample)

History Item	Fluvoxamine N = 30 N	Fluvoxamine N = 30 %	Paroxetine N = 30 N	Paroxetine N = 30 %
Current syndromes				
Other Axis I disorder	2	7	1	3
Axis II disorder	1	3	0	0
Prior treatment				
Psychotherapy	3	10	5	17
Psychotropic medication	6	20	3	10
Current depressive condition				
Indistinguishable from past	3	10	1	3
Exacerbation of chronic condition	3	10	3	10
Recurrence	16	53	18	60
Different from past	1	3	1	3
First occurrence	7	23	7	23
Onset				
Sudden	7	23	5	17
Gradual	23	77	25	83
Precipitating stress	17	57	20	67
Type of depressive episode				
Single	10	33	8	27
Recurrent	20	67	22	73
Chronic episode	8	27	8	27
Melancholic	15	50	12	40
Severe episode	7	23	10	33
Seasonal pattern	0	0	0	0

differences noted between the fluvoxamine and paroxetine patient groups.

Psychiatric History

The psychiatric history for patients in the fluvoxamine and paroxetine groups was similar and indicated that most had no Axis II disorders or other Axis I disorders. Most patients had recurrent depression of gradual onset, and precipitating stress was implicated as a factor in the onset of depressive illness for the majority of patients in both treatment groups. Prior treatment with psychotropic medication was effective in 5 of 6 patients in the fluvoxamine group and in 3 of 3 patients in the paroxetine group. Details of patient baseline psychiatric and depressive history are displayed in Table 2.

Patient Treatment

The mean ± SD titrated daily dose at the last study assessment was 102 ± 44 mg for the fluvoxamine group and 36 ± 13 mg for the paroxetine group. A total of 16 (53%) patients in the fluvoxamine group were titrated to the maximum permissible dosage (150 mg/day) by the end of treatment or at their last visit; in the paroxetine group, 10 (33%) patients had received the maximum dosage (50 mg/day) by the end of treatment or at their last visit. Three fluvoxamine-treated patients and 2 paroxetine-treated patients had their dosages reduced before the end of the study.

Primary Efficacy

At baseline, the fluvoxamine and paroxetine groups were comparable in levels of depression as measured by the HAM-D total score. However, there was a statistically significantly higher (p = .012) mean baseline depression demonstrated for the patients in Center 1 compared with Center 2. The fluvoxamine- and paroxetine-treated patients at the former center had a mean baseline HAM-D total score of 26.0 and 24.9, respectively. At the latter center, the mean baseline score for fluvoxamine- and paroxetine-treated patients was 22.6 and 23.7, respectively. This difference persisted for the first 2 weeks of treatment.

Table 3. Mean Changes in Primary and Supportive Efficacy Variables After 7 Weeks of Treatment (Carry Forward Analysis: Intent-to-Treat Efficacy Sample)*

Measure	Fluvoxamine N = 29 Mean	Fluvoxamine N = 29 SD	Paroxetine N = 29 Mean	Paroxetine N = 29 SD	Between Treatment p Value
HAM-D total score	–13.45	6.75	–12.86	6.85	.763
HAM-D depressed mood item	–1.76	0.95	–1.41	1.21	.252
CGI severity of illness	–1.93	1.22	–1.52	1.18	.196
HAM-D retardation	–1.10	0.71	–0.94	0.72	.397
HAM-D cognitive disturbance	–0.52	0.40	–0.56	0.42	.649
HAM-A total score	–8.69	5.75	–8.72	7.45	.999
SCL-56 depression	–8.79	7.15	–6.00	7.11	.149

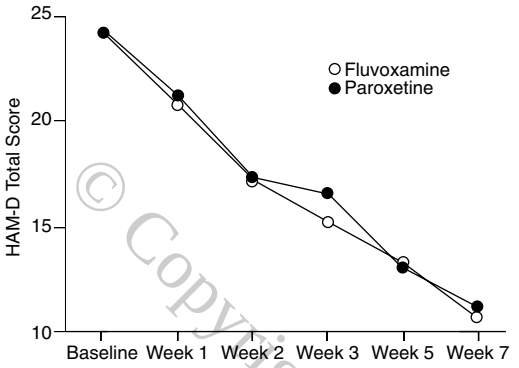
*Abbreviations: CGI = Clinical Global Impressions Scale; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; SCL-56 = 56-item Hopkins Symptom Checklist.

Analyses for all variables were based upon the last observable valid data point, at Week 7 or before, "carried forward" for individual patients. In addition, differences from baseline scores were calculated for the carry-forward data and used in the statistical analyses of efficacy. Separate visit-wise analyses were also conducted from baseline through Week 7 with similar results, and are not presented here. A summary of changes from baseline to endpoint in primary and supportive efficacy variables is found in Table 3.

Both the fluvoxamine and paroxetine treatment regimens resulted in significantly improved levels of depression compared to baseline as demonstrated by the HAM-D total score at the Week 7 carry-forward endpoint (10.9 ± 7.3, p < .00 and 11.5 ± 7.4, p < .00, respectively; two-sample t test). There were no statistically significant differences between the treatment groups in reductions of the HAM-D total score at endpoint, with a mean reduction from baseline of 13.5 ± 6.8 for the fluvoxamine group and 12.9 ± 6.9 for the paroxetine group.

In addition to the previously mentioned statistically significant Center difference between investigative sites at baseline and Weeks 1 and 2, there was a Treatment by Center interaction at Weeks 1, 2, 3, and 5. This was due to the fact that fluvoxamine demonstrated statistically superior efficacy to paroxetine at Weeks 1, 2, 3, and 5 at Center 1, where more severe depression was noted at baseline. At Center 2, paroxetine was statistically superior to fluvoxamine at Weeks 2 and 5. The fluvoxamine

Figure 1. HAM-D 21-Item Mean Total Scores (Last Observation Carried Forward) at Baseline and Across 7 Weeks of Treatment for the Fluvoxamine and Paroxetine Patient Groups



treatment effects were relatively stable at both centers. The mean HAM-D total scores for each treatment group at each assessment are displayed in Figure 1.

Supportive Efficacy Variables

There were no statistically significant differences between treatment groups for the HAM-D depressed mood item or the CGI severity of illness item at each week or at endpoint.

No statistically significant treatment differences were found for the other supportive measures of efficacy, which included the HAM-D retardation and cognitive disturbance factors, HAM-A total score, and SCL-56 (Table 3). The CGI global improvement item mean score was 1.93 ± 1.13 at endpoint for the fluvoxamine group and 2.21 ± 1.24 at endpoint for the paroxetine group ($p = .397$).

Tolerability

Almost all patients reported at least one adverse experience; treatment-emergent adverse events were reported by 100% of paroxetine-treated patients and 97% of fluvoxamine-treated patients. The most common events (> 10% in either treatment group) are summarized in Table 4. The vast majority of all events in both treatment groups were mild or moderate in severity and did not lead to discontinuation of treatment.

Paroxetine-treated patients most often reported headache (57%), nausea (47%), sweating (33%), somnolence (30%), diarrhea (30%), dry mouth (27%), dizziness (27%), impotence among males (21%), and ejaculatory abnormality among males (21%). The incidence of sweating was statistically significantly greater ($p = .028$ based on chi-square test) in the paroxetine group (33%) than in the fluvoxamine group (10%). While not statistically significant, in general, the profile of adverse events among paroxetine-treated patients suggested more serotonergic gastrointestinal effects (nausea, diarrhea, constipation). Four patients (13%) were discontinued from treatment with paroxetine due to adverse events considered to be possibly or probably related to study drug (severe anxiety; sweating, incoordination, and jitteriness; metrorrhagia, somnolence, and decreased concentration; urinary retention, headache, diarrhea, sweating, dry mouth, and dizziness).

Table 4. Most Frequently Reported Adverse Events Associated With Fluvoxamine and Paroxetine Treatment (> 10% for Either Treatment Group) (Intent-to-Treat Safety Sample)

	Number (Percentage) of Patients Reporting Event			
	Paroxetine N = 30		Fluvoxamine N = 30	
Adverse Event	N	%	N	%
Headache	17	57	12	40
Nausea	14	47	11	37
Sweating	10	33	3	10
Somnolence	9	30	12	40
Diarrhea	9	30	4	13
Dry mouth	8	27	11	37
Dizziness	8	27	6	20
Impotence[a]	3	21	2	14
Ejaculatory abnormality[a]	3	21	1	7
Insomnia	6	20	9	30
Nervousness	5	17	4	13
Libido decrease	5	17	4	13
Dream abnormality	5	17	0	0
Asthenia	4	13	7	23
Constipation	4	13	2	7
Dyspepsia	4	13	7	23
Anxiety	4	13	2	7
Tremor	4	13	3	10
Depersonalization	2	7	4	13
Palpitations	1	3	4	13
Flatulence	1	3	4	13
Dysmenorrhea[b]	0	0	3	19

[a]Percentage based on male patients only; N = 14 in both groups.
[b]Percentage based on female patients only; N = 16 in both groups.

Fluvoxamine-treated patients complained primarily of headache (40%), somnolence (40%), nausea (37%), dry mouth (37%), insomnia (30%), asthenia (23%), and dyspepsia (23%). While not statistically significant, in general, more sleep-related (somnolence, insomnia) side effects were reported in the fluvoxamine group. Two fluvoxamine-treated patients (7%) were discontinued owing to adverse events that were considered to be probably related to study drug (rash and itching; asthenia and somnolence). No clinically significant abnormal laboratory test results were reported in this study. In addition, vital signs did not show any treatment-related clinically significant effects for either group.

DISCUSSION

Although the study had insufficient power to detect more than very large differences in efficacy between

treatments, the primary and secondary treatment outcomes for this study suggest that fluvoxamine and paroxetine have similar efficacy in the treatment of clinically depressed outpatients. Both of these drugs induced clinically significant relief of depressive and anxious symptomatology following a 7-week course of treatment. There were also no clinically significant differences between the two treatment groups with respect to severity of depressive illness, amount of clinical improvement, anxiety, retardation, or cognitive disturbance, at the end of treatment. The mean titrated daily dose of fluvoxamine at the last study assessment in this trial was comparable to fluvoxamine dosing worldwide; among 35,368 patients, 99% of whom had been treated for depression, 45.9% received a modal total daily dose of 100 mg, and most other patients received either 50 mg or 150 mg daily while only 12.6% of patients received 200 mg and 2.6% received 300 mg.[14]

The differences between centers in HAM-D total score for paroxetine may have been due to slightly different dosing regimens used at both centers, resulting in different treatment effects, or to two or three marked responders in the second center among the relatively small number of patients at each center. The center differences and interactions were not maintained as a contributing factor to the overall treatment effects in the last two study weeks.

Both SSRI antidepressants were well-tolerated, and there were no serious adverse events reported. As with all SSRIs, adverse events were noted predominantly in the nervous system, body as a whole, and gastrointestinal system, and incidence rates were not statistically significantly different. Fluvoxamine was associated with a higher rate of asthenia, dry mouth, somnolence, and insomnia, while paroxetine had higher rates of headache, nausea, diarrhea, sweating, and abnormal dreams and sexual dysfunction among males (impotence and ejaculatory abnormality) and decreased libido among males and females. Although not statistically significantly different, in general more serotonergic effects (nausea, diarrhea, and constipation) occurred in paroxetine-treated patients, and more sleep-related (somnolence, insomnia) side effects occurred in the fluvoxamine group. The latter results may reflect the time of day, evening, when fluvoxamine was administered in contrast with paroxetine which was administered in the morning.

These differences in the kinds of adverse events between fluvoxamine and paroxetine may be significant to individual patient care. Depressed patients who do not tolerate a particular medication may generally do better on an alternative treatment.[29] For example, in one study, 93 patients who had been discontinued from fluoxetine treatment due to side effects were then treated with sertraline.[30] Under sertraline treatment, 69 (76%) of 91 evaluable patients experienced significant improvement in depression, while only 8 (9%) of the total of 93 patients discontinued due to side effects. In addition, the side effects that caused discontinuation of treatment from the second SSRI were different from those that caused discontinuation from the first SSRI. The apparent divergence in adverse experiences with fluvoxamine and paroxetine suggests the value of considering specific tolerability profiles when choosing the optimal and/or alternate treatment for depression.

Drug names: amitriptyline (Elavil and others), chloral hydrate (Noctec), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil), sertraline (Zoloft).

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