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A Double-Blind Clinical Trial of Fluvoxamine and Imipramine in Patients With Primary Depression

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ABSTRACT

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Fluvoxamine, a new serotonin-reuptake inhibitor, and imipramine were compared under double-blind conditions in 36 unipolar and bipolar depressed inpatients. Both drugs produced significant reductions in depressive symptomatology over a 4–6-wk course of treatment, with the greater part of the improvement occurring in the first 2 wk. No statistically significant differences were obtained between the two drugs. Adverse reactions, particularly anticholinergic ones, were much less frequently observed in the fluvoxamine group. No clinically significant laboratory abnormalities were reported for either treatment; but minor ECG irregularities were seen under both treatments. The findings generally correspond to results obtained in previous comparative clinical trials.

Key words: fluvoxamine, imipramine, depression, clinical

INTRODUCTION

Given the evidence indicating the role of a deficiency in central serotonin metabolism in the pathogenesis of depression [van Praag, 1980], there has been an intensive search for efficacious drugs with selective potentiating effect on central serotonin. Fluvoxamine is an example of a serotonin reuptake inhibitor with only negligible effect on norepinephrine reuptake [Claassen and Post, 1974; Claassen et al., 1977]. The drug possesses neither monoamine oxidase (MAO)-inhibiting effects nor amphetaminelike stimulating action. Further, in contrast to tricyclic antidepressants, fluvoxamine appears to have an almost complete lack of anticholinergic activity [Wilson et al., 1983] and a lack of adverse cardiovascular symptoms

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[Roos and Sharp, 1983]. In other clinical studies, fluvoxamine has been shown to have antidepressant activity with a minimum of adverse reactions [Saletu et al., 1976; Itil et al., 1977; Wright and Denber, 1978; Klok et al., 1981; Goodwin and Pichot, 1982]. The present trial was part of a multicenter study that was designed to compare the relative efficacy and safety of fluvoxamine and imipramine in primary depressives as well as the onset of antidepressant effects under each treatment.

METHODS

The study design was a parallel-group, double-blind trial in which 36 newly admitted depressed inpatients of both sexes were assigned by randomization list, after stratification by unipolar/bipolar type, to one of two treatment groups—fluvoxamine (17 patients) or imipramine (19 patients). Treatment was preceded by a washout period of 5–7 days, depending upon the patient's psychiatric condition and/or pretreatment drug status. Originally, the duration of treatment was set at 4 wk and then extended by protocol amendment to 6 wk. Inpatient treatment was mandatory for the first 2 wk of the trial; but, given sufficient improvement, treatment on an outpatient basis was permitted thereafter. To be eligible for the trial, patients between the ages of 18 and 60 with an established diagnosis of primary depression (unipolar or bipolar), a DSM-III diagnosis of Major Depressive Disorder, a persistent alteration of mood, had to satisfy at least four of the Research Diagnostic Criteria (RDC) symptoms for depression [Feighner et al., 1972] and have a score of at least 15 on the first 17 items of the Hamilton Depression Scale at the end of the washout period. Excluded were females not practicing contraception and patients with significant medical illneses, continuing alcohol/drug abuse, and/or a history of other psychiatric illness in which the depression was secondary. All patients signed an informed consent after the nature and purpose of the study was explained to them. Prepackaged according to the random assignment, medications were prescribed on a flexible dosage schedule and dispensed as a single dose at bedtime. The dosage range for both medications was 50–300 mg/day. A 2-wk minimum treatment period was established for inclusion into the subsequent analytic cohort.

Major psychiatric assessments were performed prior to the initiation of treatment and weekly thereafter. Included in the assessment battery [Guy, 1975] were the Hamilton Depression Scale (HAMD), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI), Nurses' Observation Rating for Inpatient Evaluation (NOSIE), and Self-Rating Depression Scale (ZUNG). Adverse reactions were assessed on the same schedule by the Dosage Record and Treatment Emergent Symptom Scale (DOTES). Laboratory examinations and ECGs were performed prior to entry into the study and every 2 wk thereafter. While vital signs were obtained on a daily basis, analyses were conducted only on weekly measurements. All psychiatric assessments for a given patient were conducted by the same rater.

RESULTS

Data were processed and analyzed by the Biometric Laboratory Information Processing System—BLIPS/TNI [Guy, 1975].

Demographic Characteristics

The major demographic characteristics of the analytic cohort (36 patients) are summarized in Table 1. Three additional patients were entered into the trial but were not included in the analytic cohort. One patient withdrew consent after 5 days and another was found not to meet entrance criteria. The third patient, in whom noncompliance was suspected, did not return after a home visit.

With only one exception, no significant differences between the fluvoxamine and imipramine groups, as measured by t-test or χ^2 were obtained. Patients assigned to the imipramine

TABLE 1. Demographic Data

Variable	Fluvoxamine (17)[a]	Imipramine (19)[a]	Total (36)[a]
Age			
MN	39.3	36.5	37.8
SD	8.1	8.5	8.3
Sex			
M	5 (29)[c]	4 (21)	9 (25)
F	12 (71)	15 (79)	27 (75)
Never married	2 (12)	3 (16)	5 (14)
Ever married	15 (88)	16 (84)	31 (86)
Education[b]			
Less HS	14 (82)	7 (37)	21 (58)
HS or More	3 (18)	12 (63)	15 (42)
No previous treatment	2 (12)	3 (16)	5 (14)
Mean No. of previous hospitalizations	2.6	1.7	2.1
DSM III diagnoses			
Major, single	-----	1 (6)	1 (3)
Major, single, melancholia	2 (12)	5 (26)	7 (19)
Major, recurrent	-----	1 (6)	1 (3)
Major, recurrent, melancholia	11 (65)	9 (46)	20 (56)
Bipolar, depressed, melancholia	4 (24)	3 (16)	7 (19)
Onset			
Rapid	5 (29)	4 (21)	9 (25)
Gradual	12 (71)	15 (79)	27 (75)
Absence of precipitating stress	11 (65)	9 (47)	20 (56)
Suicidal attempt(s)	12 (71)	15 (79)	27 (75)
Family history of psychiatric illness			
Affective disorder	2 (12)	4 (21)	6 (17)
Schizophrenia	-----	-----	-----
Alcoholism	6 (35)	7 (37)	13 (36)
Patient drug use			
Alcohol	7 (41)	6 (32)	13 (36)
Tobacco	15 (88)	13 (68)	28 (78)
Marijuana	3 (18)	4 (21)	7 (19)
"Uppers"	1 (6)	1 (5)	2 (6)
"Downers"	4 (23)	4 (21)	8 (22)

[a]No. of patients in parentheses.
[b]Chi square = 7.65, $P < .05$.
[c]No. (%) patients.

group had a significantly higher level of education than those in the fluvoxamine group. The sample can be characterized generally as a white, married, late thirties, female one in which a previous history of psychiatric treatment and hospitalization as well as previous suicidal attempts were present. Fifty-nine percent of the sample received an DSM-III diagnosis of Major Depression with recurrent episodes—most with the additional qualifier of melancholia. Twenty-two percent—mostly within the imipramine group—were diagnosed as Major Depression with a single episode; and bipolar depressives constituted 19% of the sample. Some 17% of the sample had a family history of affective illness and 36% exhibited a family history for

TABLE 2. Termination Status

Status	Fluvoxamine (17)[a]	Imipramine (19)[a]	Total (36)[a]
Protocol completion	10 (59)[b]	8 (42)	18 (50)
Withdrawal of consent	1 (6)	1 (5)	2 (6)
Adverse reaction	1 (6)	3 (16)	4 (11)
Ineffectiveness	4 (24)	5 (26)	9 (25)
Rapid improvement	----	2 (10)	2 (5)
Administrative	1 (6)	----	1 (3)
Total discharged to outpatient service	4 (25)	4 (21)	8 (23)
Total inpatients—ready for discharge	6 (38)	9 (47)	15 (43)
Total inpatients—continued treatment	6 (38)	6 (32)	12 (34)

[a]No. of patients in parentheses.
[b]No. (%) patients.

alcoholism. Interestingly, this latter incidence is matched rather closely by the alcohol usage among the patients, although in none of the patients was the use of alcohol considered to be at the abusive level.

Clinical Status

Table 2 describes the status of patients at their termination from the trial. For approximately three-fourths of the sample, protocol completion reflects the original duration of treatment; i.e., 4 wk, while, for the remainder, protocol completion reflects the amended 6 wk of treatment. With this in mind, 50% of the sample completed the protocol to which they were assigned. With the exception of adverse reactions in the imipramine group, the reasons for termination are proportionally similar to the two treatment groups. One fluvoxamine-treated patient became pregnant while in treatment (31 days) and was discontinued. She was judged to be "Very much improved" and was included in the analytic cohort. While 77% of the sample remained hospitalized on the day of termination, 43% were judged to be "ready for discharge" and were, in fact, discharged within a few days.

The level of improvement at termination as measured by the CGI is given in Table 3. Under each treatment group, statistics are presented separately for unipolar and bipolar depressives. For unipolar depressives, 92% of the fluvoxamine-treated group were judged "Improved" compared to 81% of the imipramine group. A significantly higher percent of the imipramine-treated unipolars, however, were rated as "Much" or "Very much" improved—75% compared to 54% of the fluvoxamine-treated unipolars ($\chi^2 = 13.87$, $P < .001$). These overall high rates of improvement were not sustained for the admittedly small group of bipolar depressives under either treatment. Four of the nine patients prematurely terminated for ineffectiveness were bipolar depressives. However, the two bipolar patients who were judged "Improved" were both treated with fluvoxamine.

The dose equivalence ratio for fluvoxamine and imipramine established in the protocol was 1:1. Examination of the actual prescribed mean daily dosages reveals that the ratio of fluvoxamine to imipramine was approximately 1.4:1—suggesting a somewhat higher dose requirement for fluvoxamine. Dosage manipulations necessitated by the emergence of adverse reactions, however, were significantly less in the fluvoxamine group (6%) than in the imipramine group (30%).

Remedial medications were administered on at least one occasion to approximately 80% of the patients in each treatment group. Flurazepam for sleep disturbance and acetaminophen for headache were the most frequently prescribed medications. In both instances, a higher percent of fluvoxamine-treated patients (64%) received these medications than patients in the

TABLE 3. CGI Level of Improvement at Termination

Level	Fluvoxamine			Imipramine			Total sample		
	Unipolar (13)[a]	Bipolar (4)	Total (17)	Unipolar (16)	Bipolar (3)	Total (19)	Unipolar (28)	Bipolar (7)	Total (36)
1 — Very much improved	6 (46)[b]	1 (25)	7 (41)	8 (50)	—	8 (42)	14 (57)	1 (14)	15 (41)
2 — Much improved	1 (8)	1 (25)	2 (12)	4 (25)	—	4 (21)	5 (15)	1 (14)	6 (17)
3 — Minimally improved	5 (38)	—	5 (29)	1 (5)	—	1 (5)	6 (21)	—	6 (17)
4 — Unchanged	1 (8)	2 (50)	3 (18)	2 (13)	3 (100)	5 (26)	3 (1)	5 (71)	8 (22)
5 — Minimally worse	—	—	—	—	—	—	—	—	—
6 — Much worse	—	—	—	—	—	—	—	—	—
7 — Very much worse	—	—	—	1 (5)	—	1 (5)	1 (6)	—	1 (3)
Total improved (1 + 2 + 3)	12 (92)	2 (50)	14 (82)	13 (81)	—	13 (68)	25 (89)	2 (29)	27 (75)
Total unimproved (4 + 5 + 6 + 7)	1 (8)	2 (50)	3 (18)	3 (19)	3 (100)	6 (32)	4 (11)	5 (71)	9 (25)

[a]No. of patients within parentheses.
[b]No. (%) of patients.

imipramine group (47%). Less frequently and nondifferentially prescribed were medications for constipation, diet supplementation, coughs and colds, and minor infections.

Statistical Findings

Three basic statistical analyses were performed on all efficacy measures:

1. Analysis of variance, baseline ratings—to determine equivalence of treatment groups.
2. Analysis of variance, pre/post treatment period—to include the largest cohort of patients—i.e., patients with abbreviated or missing ratings.
3. Analysis of variance, repeated measures model (last rating of any variable entered for missing data—to determine onset of action and course of treatment at each rating period.

These analyses were performed with combined unipolar and bipolar depressives and with unipolars alone.

No statistically significant group differences were obtained at baseline on the major variables of the BPRS, HAMD, CGI, or ZUNG. On one NOSIE factor, Personal Neatness, the fluvoxamine group was rated more severely ill at baseline ($P < .02$). With one exception, no statistically significant treatment differences were obtained between fluvoxamine and imipramine on any of the efficacy variables of the major psychiatric assessment scales. On one NOSIE factor, Retardation, a significant interaction ($P < .03$), reflecting improvement under fluvoxamine and increased severity under imipramine, was obtained. The predominant statistical findings were PERIOD differences reflecting improvement across time for the sample as a whole on the majority of assessment variables (at least $P < .05$, mostly $P < .001$). Figure 1 illustrates the parallel course of improvement for fluvoxamine and imipramine on three representative variables: CGI Severity of Illness, HAMD, and BPRS total scores. Viewing these three variables as a composite, it should be noted that approximately 85% of the total improvement took place within the first 14 days. Onset of antidepressant activity, as inferred from the statistically significant reduction in depressive symptomatology during the first week of treatment, was considered rapid for both drugs. Extending the duration of the trial to 42 days did not result in increasing improvement; rather it demonstrated maintenance of the improvement level already achieved.

Analyses of the unipolar sample alone did not produce results that differ significantly from those described above. Extensive analyses of the small sample of bipolars were not performed; but it was observed that, on most variables, they were more severely ill at baseline and that their overall improvement across time was substantially less than that of the unipolar depressives. In fact, the mean HAMD total score at termination for bipolar patients as a whole remained sufficiently high enough to meet the entrance criteria for the trial.

Treatment-Emergent Symptoms

A treatment-emergent symptom is defined here as one that was not present in a patient at baseline, but which was subsequently cited on at least one assessment period. A persistent treatment-emergent symptom is one cited at two or more assessment periods. Symptoms present at baseline and unchanged throughout the treatment period were deleted from analyses. Information on adverse symptomatology was obtained by spontaneous patient report, direct observation including ward staff reports, and a general, nonspecific inquiry.

The percent of patients exhibiting the most frequently cited treatment emergent symptoms on at least one occasion under each treatment is presented in Figure 2. Significant treatment differences were obtained for two of these symptoms: dizziness, more frequent under imipramine ($\chi^2 = 7.69$, $P < .01$); nonspecific complaints, more frequent under fluvoxamine ($\chi^2 = 4.03$, $P < .05$). Nonspecific complaints were general expressions of malaise that could not be more clearly delineated despite direct probing. They are reported here because of their

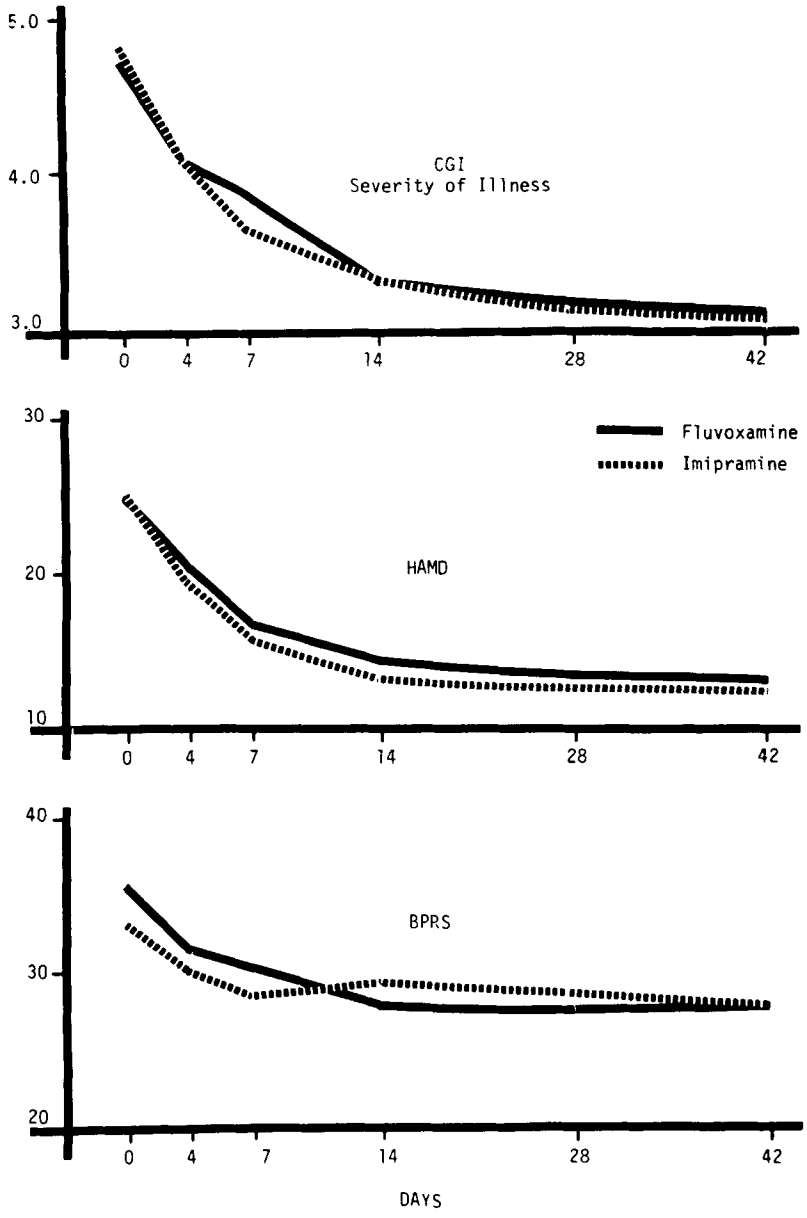

Fig. 1. Mean total scores for treatment groups across assessment periods.

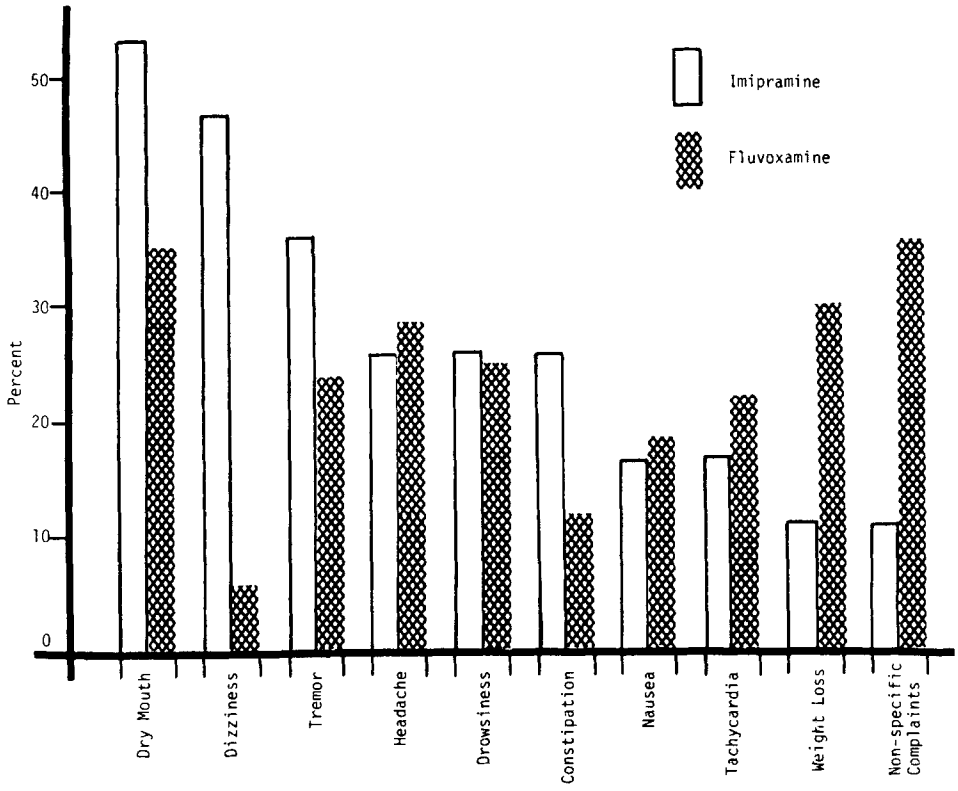

Fig. 2. Most frequently cited treatment emergent symptoms.

prevalence in the fluvoxamine group. Although not significantly so, dry mouth, tremor, and constipation occurred more frequently in the imipramine group, while tachycardia—i.e., complaints of "heart pounding"—and weight loss were more frequently cited with fluvoxamine. Subjectively reported tachycardia for both groups was verified by vital signs measurements in less than 50% of the cases. Actual weight loss was slightly higher for those fluvoxamine patients reporting it; but for the sample as a whole, the mean weight loss was under 5 lb. For the most part, symptoms in both groups were rated "Mild" or "Moderate" and did not impair function or produce unacceptable discomfort.

When persistent treatment-emergent symptoms are inspected, however, there is a more distinct separation of effects between the two treatments (Fig, 3). Persistency in this trial means that a symptom was reported "present" at assessment periods covering a total of at least 2 wk of observation, but not necessarily continuously "present" throughout that period. First, the overall frequency of citations is reduced by approximately one-half. Second, persistency for several symptoms appears to be confined to one of the treatment groups or is present in changed ratios. Tremor, dizziness, and constipation are reported only with imipramine; and tachycardia, only with fluvoxamine. While persistent dry mouth is reduced in both treatment groups, the frequency ratio of approximately 2:1 (imipramine to fluvoxamine) is maintained. The marked decline in persistent weight loss citations under fluvoxamine (26% single citations to 6% persistent citations) is not seen under imipramine, where the percent of patients exhibiting the symptom persistently remains at 11%. Conversely, headaches in the fluvoxamine

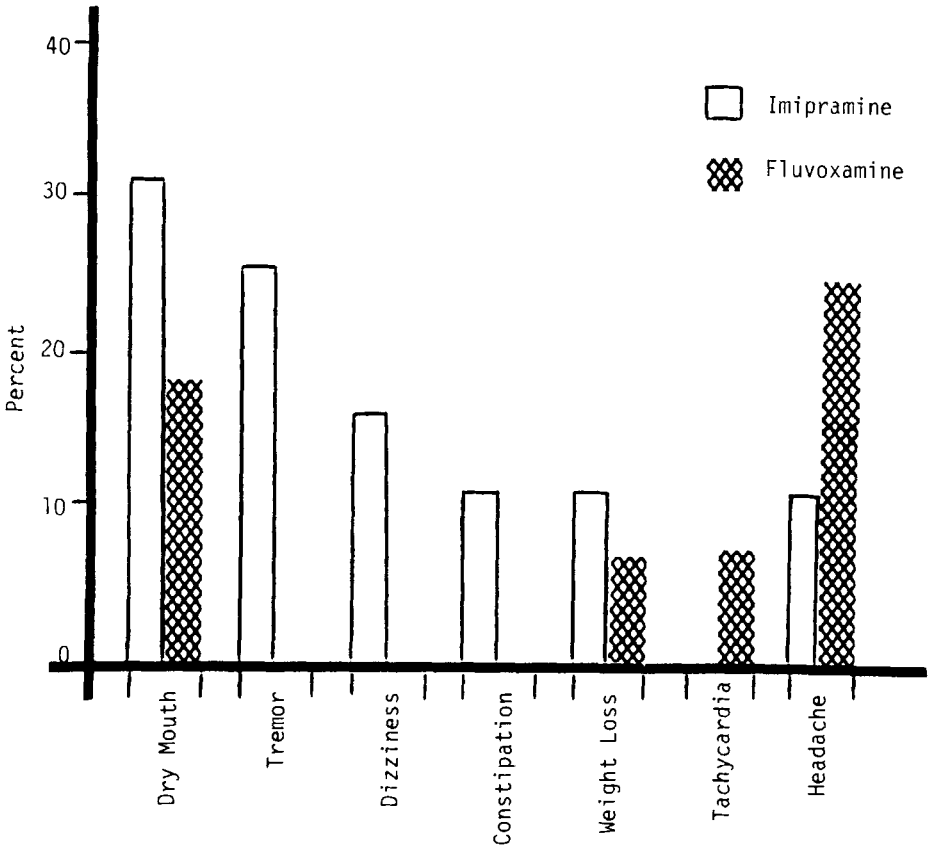

Fig. 3. Persistent treatment emergent symptoms.

group appear to persist at the same level as single citations (25%), while there is a substantial reduction of persistent headaches in the imipramine group (26% to 11%).

The intensity rating of "Severe" was given almost exclusively to those treatment-emergent symptoms that necessitated termination of treatment. In the fluvoxamine group, one patient, a 45-yr-old bipolar female, was terminated on day 21 because of agitation, excitement, increased appetite, and increased motor activity. These symptoms were not considered to be a "bipolar switch." Two imipramine-treated patients, a 34-yr-old unipolar and a 44-yr-old bipolar female, were terminated because of complaints of dizziness within the first 14 days of treatment. A third imipramine patient, a 48-yr-old unipolar female, was terminated on day 13 for psychotic behavior and stereotypy.

There were no clinically significant laboratory findings reported for either treatment group. ECG recordings were scored according to criteria prepared by Robles de Medina [1972], with comparisons being made to baseline ECG. Presented in Table 4 are the data from patients who were judged to have normal ECGs at baseline (score of 1 or 2) and who subsequently exhibited ECG changes indicating development of an abnormality. Also included are patients whose ECG diagnosis was borderline (2) or slightly abnormal (3) at baseline and whose later tracings indicated an increase in abnormality. Four of the five fluvoxamine-treated

TABLE 4. Abnormal ECG Findings*

Patient	Abnormality	Baseline diagnosis	Final diagnosis	Comparison final to baseline
Fluvoxamine				
34F	T wave	1	1	2
37F	T wave	1	2	3
21F	T wave	1	1	2
37F	ST-T wave	1	2	3
42F	T wave	3	3	3
Imipramine				
44M	T wave	1	2	1
30F	T wave	1	3	1
20F	T wave	1	2	1
47F	ST-T wave	3	4	3

*Robles de Medina scoring [1972]: Diagnostic rating — 1 = normal limits, 2 = borderline, 3 = slightly abnormal, 4 = abnormal. Comparison rating — 1 = no change from baseline, 2 = improving from baseline, 3 = worsening from baseline.

patients (26% of the total group) had normal baseline ECGs, developed S-T- or T-wave changes during the trial, but were judged to have tracings that were within normal limits by termination. Two of these patients, however, showed changes that suggested increasing abnormality compared to baseline. The fifth fluvoxamine patient had an abnormal ECG at baseline, and on final tracing, it was still slightly abnormal, with increasing changes. Three of the four imipramine patients (20% of total group) had normal baseline ECGs and developed S-T or T-wave changes. Two of these were judged within normal limits on the final ECG tracing and one was judged slightly abnormal. The fourth imipramine patient had a slightly abnormal tracing at baseline that was judged to be abnormal on the final reading. Termination from treatment was not considered necessary in any of these cases.

CONCLUSIONS

In a sample whose demographic characteristics were fairly typical of depressive populations, both fluvoxamine and imipramine produced statistically significant reductions in depressive symptomatology over the 4–6-wk course of treatment. For both drugs, the onset of therapeutic action was within the first week of treatment. Most of the overall improvement took place in the first 2 wk of treatment and was maintained at that level for the duration of the study. No definitive treatment differences between fluvoxamine and imipramine were obtained in the statistical analyses of efficacy. Data on the small sample of bipolar depressives reflected a less favorable outcome for this group than that obtained in the unipolar group.

Generally, adverse reactions, particularly anticholinergic ones, were less frequently observed in the fluvoxamine group. Headache and tachycardia were the two persistent symptoms seen more frequently in the fluvoxamine group, while dry mouth, tremor, dizziness, and constipation were more frequent and persistent under imipramine treatment. No clinically significant laboratory abnormalities were reported for either treatment, but minor ECG irregularities were reported in both treatment groups.

The findings of this study appear to mirror the results obtained in previous comparative clinical trials. Significant treatment differences between fluvoxamine and standard tricyclic antidepressants were not obtained here or in the previous studies; but comparable significant reductions in depressive symptomatology were found for both the investigational and standard

drug. Similarly, this study and previous studies suggest that fluvoxamine is less likely to produce anticholinergic effects and to exert few—if any—deleterious ECG effects.

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