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A DOUBLE-BLIND CONTROLLED CLINICAL TRIAL COMPARING FLUVOXAMINE WITH IMIPRAMINE

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1 The effects of fluvoxamine to a maximum of 300 mg daily were compared with those of imipramine to a maximum of 200 mg daily, in 151 patients with primary major depression.

2 Four weeks of treatment with fluvoxamine resulted in 67.2% improvement (± s.d. 21.6) on the Hamilton Rating Scale for Depression (26 items). Treatment with imipramine showed 62.1% improvement (± s.d. 29.5) on this scale.

3 Fluvoxamine had no untoward effects on the cardiovascular system, while imipramine produced systematic increases in the postural fall in blood pressure. Dry mouth, nausea, daytime somnolence and tremor were seen with fluvoxamine treatment, while imipramine was associated with dry mouth, daytime somnolence, dizziness and tremor.

4 We conclude that fluvoxamine seems to have the same general antidepressant efficacy as imipramine. It was not associated with any safety problems and was generally well tolerated.

Introduction

Fluvoxamine maleate is a compound in the series of 2-aminoethyl oximethers of aralkylketones. It is a potent 5-hydroxytryptamine (5-HT) re-uptake inhibitor with little or no effect on noradrenergic processes (Claassen, 1974). Animal pharmacology studies revealed no anticholinergic activity, no sedative or amphetamine-like stimulating activity and no inhibition of monoamine-oxidase (Claassen *et al.*, 1977). A role for fluvoxamine in the treatment of depressive illness was postulated on account of the growing knowledge of the involvement of 5-HT in depression (Shaw *et al.*, 1967; van Praag *et al.*, 1970; Coppen *et al.*, 1972) and thus further studies were undertaken, both in healthy volunteers and in depressed patients. A study using both quantitative pharmaco-EEG and computer-EEG techniques confirmed the expected antidepressant activity of fluvoxamine and predicted a profile similar to that of the 'stimulant' antidepressants (Itil *et al.*, 1977). Acceptable efficacy as an antidepressant has been shown in several studies with a maximum dose of 300 mg/day and non-significant toxicity or unwanted effects have been observed (Saletu *et al.*, 1977; Itil *et al.*, 1977, Wright & Denber, 1978). In particular, no severe adverse effects on the cardiovascular system and no anticholinergic symptoms were noted.

A drug disposition study in healthy volunteers showed that maximum plasma levels after a single 100 mg dose were reached 2–8 h after drug administration. The mean plasma half-life was approximately 15 h (de Bree & van der Schoot, 1976).

The tricyclic antidepressant imipramine hydrochloride (Tofranil®) was selected as the comparative drug because of its known efficacy and its similar half-life of 14.2 h (Ziegler *et al.*, 1978).

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Methods

Study design

This was a prospectively randomized, double-blind, comparative, clinical study, conducted in 22 psychiatric centres in France. The study drug administration period was 4 weeks immediately following a 'wash-out' period of at least 3 days. During the wash-out period patients were not to receive any psychotropic drugs except: placebo *ad libitum*; flunitrazepam (2–4 mg orally at night for insomnia);

diazepam (intramuscular, maximally 20 mg/day only in cases of agitation or severe anxiety).

Psychometric evaluations were done on entry to the study, at the end of the wash-out period and weekly thereafter. Physical examinations, laboratory tests, EEG and ECG were done on day 0 and at the end of treatment. Concurrent signs and symptoms were recorded on a checklist at the weekly interview.

Subjects

Depressed patients, male or female, who had been hospitalised for a clear and relatively persistent major depression were eligible for the study. A score of 25 or more on the NIMH 26-item version of the Hamilton Rating Scale for Depression (HAMD; Guelfi *et al.*, 1981) was required at the end of the wash-out period.

Exclusion criteria were: pregnancy, non-stabilised organic illnesses, EEG and ECG abnormalities, serious abnormalities of the laboratory test results and structured psychotherapy started within the last 3 months.

The declaration of Helsinki (1964) was signed by the investigators of this study.

Drug treatment

According to the order of inclusion into the study, the patients randomly received identical capsules of either fluvoxamine maleate (supplied by Duphar B.V., Weesp, The Netherlands) or imipramine hydrochloride. Treatment was given in twice daily dosing in the range of 100–300 mg daily for fluvoxamine and of 50–200 mg daily for imipramine. Fluvoxamine capsules contained 50 mg of active drug, while for imipramine this was 25 mg. The doses were progressively increased during the first 3 days of treatment, to reach four capsules per day.

Initial doses were administered as follows: first day—two capsules, one in the morning, one in the evening; second day—three capsules, one in the morning, two in the evening; third day—four capsules, two in the morning, two in the evening. This schedule remained unchanged until day 7. If the patient was sufficiently improved according to the investigator's clinical global impression, the same dosage was continued. If the patient was suffering from undesirable or uncontrollable side-effects, the dosage was reduced by one capsule to 150 mg fluvoxamine or 75 mg imipramine. If the patient was insufficiently improved, the dosage could be increased by two extra capsules to 300 mg fluvoxamine or 150 mg imipramine.

At day 14, the investigators proceeded in the same way. The effective dose was either maintained, decreased by one capsule or increased by two capsules. The maximum dosage was eight capsules per day. This was 300 mg fluvoxamine (six capsules active drug + two capsules placebo) or 200 mg imipramine.

At day 21, if again a decrease in dosage was necessary, treatment was interrupted and final assessments were done.

Dosage changes were only permitted at the weekly clinical evaluation sessions.

Psychometric tests

The efficacy of both drugs was measured by means of the modified 26-item HAMD (Hamilton, 1967; Guelfi *et al.*, 1981). In addition, the Clinical Global Impression Scale was used (CGI; Guy, 1976).

Concomitant medication

During the treatment period the following psychotropic medication was allowed: flunitrazepam (Rohypnol®) 2 mg, 1 or 2 tablets at night before bed; diazepam (Valium ®) 5 mg, 1 tablet in case of anxiety with a maximum of 4 tablets per day; alimemazine (Théralène ®), a neuroleptic sedative, up to 50 drops per day only for emergencies.

Other medication allowed was: phenylephrine (Neosynephrine ®) in 1% solution, 200 drops per day for hypotension; anethole trithione (Sulfarlem S25 ®) 4–8 tablets per day for dry mouth.

Drugs given chronically for somatic complaints were allowed to be continued if they did not have any psychotropic effect. As far as possible, concomitant somatic treatment was maintained at a constant dose level during the study.

Early termination

Termination of the study drug treatment prior to the end of the fourth week was permitted for the following reasons: a third successive decrease in dose required at day 21 psychiatric assessment; significant worsening of condition during the study; hypomanic swing; serious side-effects and non-observance or refusal of treatment.

Statistical methods

Mostly non-parametric methods were adopted, treating the data as a homogenous sample. In this study, 'statistically significant' means significant at the 5% level. Only two-sided statistical tests have been employed. Patients qualified for the end-point analysis provided they had at least 14 days study medication. Recovery or lack of efficacy were given the best or the worst rank numbers, respectively.

Table 1 Reasons for early termination of treatment (before day 28)

Reason	*Fluvoxamine*	*Imipramine*
No apparent study drug related reason	13[a]	6[b]
Recovered	1[c]	1[c]
Ineffectiveness (for patients who received at least 14 days study drug)	0	3[c]
Hypomanic swing	1 (17th day)	1 (20th day)
Severe threat of suicide	2	0
Side-effects	2	5
Leaving hospital	0	1[c] (26th day)
No data available	0	1 (3rd day)
Total number of patients terminating prematurely	19	18
n	77	81
Patients included in efficacy analysis	59	68

[a]Includes three patients excluded from all analyses, see text.
[b]Includes four patients excluded from all analyses, see text.
[c]Patients included in efficacy analysis; recovery or lack of efficacy were given the best or worst rank numbers, respectively.

Results

Study subjects

One hundred and fifty-eight primary depressed in-patients, aged between 21 and 71 years, entered the study. Seven patients were excluded from all analyses (see under Premature terminations below), leaving 74 patients in the fluvoxamine group and 77 in the imipramine group. The diagnoses of depression were: unipolar endogenous: 52; unipolar non-endogenous: 79; bipolar: 18, and two unclear diagnoses. The diagnostic groups were evenly split between the two treatment groups.

Premature terminations

A total of 37 patients stopped study drug treatment prematurely (19 on fluvoxamine, 18 on imipramine). Table 1 shows the reasons why study drug intake was stopped. The reasons for premature termination seemed not to be very different in the two treatment groups. Seven cases were excluded from all statistical analyses (three in the fluvoxamine group and four in the imipramine group): four for protocol non-compliance, two because only baseline data were available and one for early drop-out (day 3) with no data available.

Drug dosage

The mean doses of drug received were 221 mg/day for fluvoxamine (74 patients) and 112 mg/day for imipramine (77 patients).

Efficacy

The severity of depression prior to treatment, as measured by the total HAMD score (26 items) tended to be slightly greater in the imipramine group. The mean total score was 33.2 (± s.d. 6.2) for the fluvoxamine group *vs* 35.0 (± s.d. 6.3) for the imipramine group ($P = 0.052$, Wilcoxon test).

The mean total score on the HAMD showed a steady decline in both study groups. At the final assessment the mean total score (± s.d.) in the fluvoxamine group was 11.0 (± 9.0), equivalent to a mean improvement of 67.2% (± 21.6). In the imipramine group the mean total score at the final assessment was 13.6 (± 11.2), equivalent to a mean improvement of 62.1% (± 29.5). On no occasion was there a statistically significant treatment difference between the two groups with respect to the HAMD scores. The course of the depressive illness as recorded by the HAMD percentage improvement can be seen in Table 2.

The patient's condition as judged on the CGI also improved gradually. The groups were comparable at pretreatment ($P = 0.17$, Wilcoxon test) with a tendency for the patients in the imipramine group to be slightly more ill. The median severity score in the fluvoxamine group was 5.5 which meant that the majority of the patients were between markedly and severely ill. The median severity score in the

Table 2 Percentage improvement from pretreatment total scores on the HAMD (25* items)

	Week 1		*Week 2*		*Week 3*		*Week 4*	
	Flu	*Imi*	*Flu*	*Imi*	*Flu*	*Imi*	*Flu*	*Imi*
Mean %	26.4	32.5	42.0	45.1	52.4	54.7	67.2	62.1
s.d.	22.5	27.7	33.0	28.1	22.7	31.0	21.6	29.5
n	74	77	70	74	64	73	58**	67**
P (Wilcoxon test)	0.14		0.92		0.31		0.57	

Flu = fluvoxamine; Imi = imipramine
*the item 'loss of weight' was omitted
**one patient in each group missed their end-of-treatment HAMD assessment

imipramine group was 6, thus the majority of patients were severely ill. Tables 3 and 4 illustrate the course of the CGI severity-of-illness scores.

Onset of action

The apparent onset of therapeutic action was mostly during the second treatment week. There were no noteworthy differences between the two treatments at any time ($P = 0.59$, Wilcoxon test).

Early terminators did not materially affect the efficacy pattern of either drug.

Cardiovascular effects

The effects of both drugs on the heart rate (upright position), systolic and diastolic blood pressure (upright and recumbent position) were measured at weekly intervals. The appropriate calculations were made for postural changes in blood pressure, i.e. recumbent minus upright. At the start and the end of the study ECGs were done. No drug-induced changes towards abnormality were found in this study population. Neither drug had an appreciable effect on heart rate.

Patients on imipramine showed a systematic tendency towards a decrease in systolic blood pressure in the upright position ($P < 0.01$, trend test) which was not seen in fluvoxamine patients. The mean decrease was 14.2 mm Hg ± s.d. 25.1. This resulted in a treatment difference in favour of fluvoxamine ($P = 0.01$, multivariate test).

Treatment with imipramine was associated with a decrease in mean diastolic blood pressure in the upright position (8.8 mm Hg ± s.d. 18.4). A statistically significant treatment difference was seen in favour of fluvoxamine at week 4 ($P = 0.02$, Wilcoxon test). Neither drug had any appreciable effect on blood pressure in the recumbent position.

At pretreatment, patients in the fluvoxamine group showed a decrease in systolic blood pressure upon changing posture of 6.5 mm Hg ± 13.5 (mean ± s.d.). In the imipramine group the mean postural decrease was 1.0 mm Hg ± 12.6. During the course of

Table 3 Frequency distributions of the CGI severity-of-illness scores

	Week 1		*Week 2*		*Week 3*		*Week 4**	
Category	*Flu*	*Imi*	*Flu*	*Imi*	*Flu*	*Imi*	*Flu*	*Imi*
Normal	2	4	4	6	3	10	17	21
Borderline mentally ill	2	4	9	12	18	20	16	18
Mildly ill	9	10	20	16	12	19	13	11
Moderately ill	29	23	21	20	19	12	9	8
Markedly ill	14	15	10	11	10	5	2	2
Severely ill	16	19	6	8	1	5	2	5
Extremely ill	2	2	3	2	1	2	0	3
n	74	77	73	75	64	73	59	68
P-value**	0.94		0.82		0.14		0.84	

*In cases of early termination due to inefficacy or recovery, extreme rank numbers were given.
**Wilcoxon test
Flu = fluvoxamine; Imi = imipramine

Table 4 End-point analysis of the CGI severity-of-illness scores

Category	*Pretreatment* Flu	Imi	*End of treatment** Flu	Imi
Normal	0	0	17	21
Borderline mentally ill	0	0	16	18
Mildly ill	0	0	13	11
Moderately ill	13	10	9	8
Markedly ill	16	16	2	2
Severely ill	26	34	2	5
Extremely ill	4	8	0	3
n	59	68	59	68
P (Wilcoxon test)	0.15		0.84	

*In cases of early termination due to inefficacy or recovery, extreme rank numbers were given.
Flu = fluvoxamine; Imi = imipramine

the study, the postural decrease in systolic blood pressure became less in the fluvoxamine group and was only 4.0 mm Hg ± 12.2 (mean ± s.d) by week 4.

In the imipramine group, the reverse happened and by week 4 the postural decrease was 9.7 mm Hg ± 17.7 (mean ± s.d.). This resulted in a statistically significant difference in favour of fluvoxamine during all 4 weeks ($P < 0.01$, multivariate test).

A similar picture was seen for the postural change in diastolic blood pressure, but to a lesser degree. Again a statistically significant treatment difference occurred in favour of fluvoxamine ($P = 0.04$, multivariate test).

EEG results

Two patients with normal EEG tracings at pretreatment showed some abnormality at day 28. One patient (on fluvoxamine) displayed an overall slowing of electrical activity. The other patient (on imipramine) showed some evidence of focalisation of slow-wave activity.

Laboratory tests

Routine laboratory tests for haematology and blood biochemistry were performed at baseline and at the end of the study. Statistically significant changes occurred in platelet count, creatinine, SGOT and SGPT.

Treatment with fluvoxamine was associated with a mean decrease in platelet count of $11.8 \times 10^9/1 \pm 54.8$ (mean ± s.d.; $P = 0.05$, signed rank test). Imipramine showed the opposite effect, i.e. a mean increase in platelet count of $17.3 \times 10^9/1 \pm 67.5$ ($P = 0.02$, signed rank test).

Creatinine values increased in the fluvoxamine group by 6.4 μmol/l ± 23.8 ($P < 0.01$, signed rank test). With imipramine the increase was 2.4 μmol/l ± 15.1 over the study period ($P = 0.07$, signed rank test).

For the SGOT there was a negligible trend towards a decrease in the fluvoxamine group. In the imipramine group the mean increase was 3.7 iu/l ± 11.7 ($P = 0.03$, signed rank test). The opposing trends resulted in a statistically significant difference between the two groups ($P = 0.01$, Wilcoxon test).

The SGPT in the fluvoxamine group showed a mean increase of 2.7 iu/l ± 12.4 ($P = 0.052$, signed rank test). The mean increase in the imipramine group was 10.7 iu/l ± 38.2 ($P < 0.01$, signed rank test).

Concomitant medication

In this study there was in general a large amount of concomitant medication given, particularly for

Table 5 Treatment-emergent symptoms (%)

	Pretreatment Flu	Imi	*Week 1* Flu	Imi	*Week 2* Flu	Imi	*Week 3* Flu	Imi	*Week 4* Flu	Imi
Constipation	49	49	51	55	50	47	43	37	31	41
Dizziness	32	19	36	27	36	29	33	31	33	17
Dry mouth	31	35	50	58	57	68	60	76	57	65
Nausea	19	19	26	6	20	7	21	7	10	3
Somnolence	27	19	36	30	37	21	46	24	34	17
Syncope	15	6	14	13	10	12	11	10	2	9
Taste perversion	15	22	23	21	20	32	30	24	26	23
Tremor	19	18	31	27	39	34	43	32	28	21
Urinary retention	8	13	14	14	13	15	16	14	14	14
Vomiting	1	5	7	5	3	1	3	1	2	6

Flu = fluvoxamine; Imi = imipramine

symptoms of the nervous system, e.g. anxiety, agitation and insomnia. Ninety-five percent of the patients in each group received medication for these symptoms during the wash-out period. In week 4, 85% of fluvoxamine patients and 94% of the imipramine patients received medication for symptoms of the nervous system.

Concomitant medication for treatment of symptoms of the digestive tract mainly consisted of treatment for dry mouth. By week 4, 17% of fluvoxamine patients and 18% of imipramine patients received medication for dry mouth.

In several of the study centres, an antihypotensive agent was routinely co-prescribed during treatment with an antidepressant. In week 4, 31% of fluvoxamine patients and 21% of imipramine patients received medication for hypotension.

Prescription for other signs and symptoms was minimal. There were no statistically significant differences between the two study groups with regard to prescription of concomitant medication.

Tolerance

A checklist with 54 somatic signs and symptoms was used at the patient's weekly interview. It was the impression that the majority of the concomitant signs and symptoms were directly related to the depressive illness. There were, however, a few symptoms which in each drug group appeared to be treatment related.

The symptoms that increased by more than 5% during the treatment period were considered to be treatment-emergent and are shown in Table 5. In the fluvoxamine group these were: dry mouth, nausea, somnolence, taste perversion, tremor, urinary retention and vomiting. In the imipramine group these were: constipation, dizziness, dry mouth, somnolence, syncope and tremor.

Twenty-seven of the 54 reported signs and symptoms showed a decrease during the study period. A few of these symptoms showed a steeper decline in one study group than in the other, resulting in statistically significant differences.

Anorexia showed a steeper decline with imipramine. In week 2 there was a statistically significant treatment difference ($P = 0.02$, Fisher exact test). Nervousness decreased faster with fluvoxamine, which resulted in a treatment difference in week 4 ($P = 0.02$, Fisher exact test).

From the start of treatment, the number of reports of nausea dropped steeply with imipramine, but with fluvoxamine there was an initial increase. This resulted in statistically significant treatment differences between the two treatment groups in the first three treatment weeks ($P \leq 0.04$, Fisher exact test).

Patients in the imipramine group complained during a longer period in the study of early morning insomnia ($P = 0.056$, Wilcoxon test).

With both study drugs, the incidence of daytime somnolence increased slightly in the first treatment week. With imipramine, but not with fluvoxamine, this was followed by a decline to baseline level. This resulted in statistically significant treatment differences in favour of imipramine in weeks 2, 3 and 4 ($P \leq 0.04$, Fisher exact test).

There were more anticholinergic symptoms reported in the imipramine treatment group. However, treatment differences failed to reach statistical significance.

Discussion

This double-blind, controlled, multicentre trial compared fluvoxamine with imipramine in 151 primary major depressed in-patients during 4 weeks treatment.

Both treatment groups showed good improvement of depressive illness as measured by the HAMD and CGI scales. Imipramine was associated with a systematic postural fall in systolic and diastolic blood pressure. No such effects were seen with fluvoxamine.

Dry mouth, tremor, nausea and daytime somnolence were the most common treatment-associated symptoms in the fluvoxamine group. Dizziness, dry mouth, daytime somnolence and tremor were the most common in the imipramine group. There were more anticholinergic effects reported in the imipramine group.

A fall in platelet count and a rise in serum creatinine without an increase in blood urea nitrogen was observed in the fluvoxamine group. A rise in both liver enzymes SGPT and SGOT was observed in the imipramine group. However, most patients had values falling well within the normal reference values.

The therapeutic effects of imipramine in this study were similar to those reported for this standard treatment in a general population with major depressive disorders (Martindale, 1977), as measured by the HAMD and CGI. It therefore may be expected that the results found with fluvoxamine will be projectable to a larger population than that of our study.

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