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A Belgian multicentre study of fluvoxamine in depressive outpatients

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ABSTRACT

Fluvoxamine, a new antidepressant that specifically inhibits serotonin reuptake, was studied in 272 outpatients in a six-week multicentre trial in Belgium. On the Hamilton Depression Scale, the mean score dropped from 25.2 to 8 after six weeks ($p < 0.00001$). The Clinical Global Impression scores showed similar evolution.

Fluvoxamine is a real antidepressant with a marked effect on mood. Its effective dosage is 100 mg to 200 mg/day. Its tolerance, notably at the cardiovascular level, is excellent [Acta psychiat. Belg., 85, *636-643 (1985)*].

Key words: fluvoxamine, depression.

Introduction

Fluvoxamine is a new antidepressant that is quite distinct from all other categories of antidepressants. It specifically inhibits serotonin reuptake. A large number of open as well as double-blind clinical trials have clearly shown its efficacy to be at least comparable with imipramine and clomipramine and its tolerance to be excellent, particularly with respect to cardiovascular effects (Klok *et al.*, 1981 ; Lapierre *et al.*, 1981 ; De Wilde and Doogan, 1982 ; Feldmann and Denber, 1982 ; Claassen, 1983 ; De Wilde *et al.*, 1983 ; Dick and Ferrero, 1983 ; Geukens-Foppen *et al.*, 1983 ; Guelfi *et al.*, 1983 ; Itil *et al.*, 1983 ; Roos 1983 ; Saletu and Grunberger, 1983 ; Wilson *et al.*, 1983 ; Guy *et al.*, 1984); 650 patients have been treated with fluvoxamine under strict protocol conditions involving rigorous methodological criteria.

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The objective of this study was to confirm the efficacy and tolerance of fluvoxamine in a population of outpatients. It is generally accepted that there is a marked difference between inpatients and outpatients as regards conditions of treatment. Outpatients tend to comply less strictly with the prescription (number of daily doses, interaction with other drugs, alcohol intake, etc.). In view of this, a multicentre open trial appeared to be the best way of assessing a drug in daily clinical practice.

Subjects and methods

The trial included 272 patients over a six-week period, with clinical assessments before treatment and after 1, 2, 4 and 6 weeks of treatment. Patients were of either sex, aged over 18 years and diagnosed as suffering from depression with somatic symptoms either with or without anxiety.

Exclusion criteria were : pregnancy or risk of pregnancy ; lactation ; clinically relevant impairment of renal or hepatic function ; high suicide risk ; concurrent treatment with MAOI or lithium (a washout period of 2 and 1 week respectively was required).

The initial daily dose was 100 mg fluvoxamine divided into 50 mg in the morning and 50 mg at night. After 1 or 2 weeks of treatment this dosage could be raised to a maximum of 300 mg/day in function of the therapeutic response. When additional medication proved to be necessary, only benzodiazepines were allowed.

The following clinical assessments were carried out before treatment and after 1, 2, 4 and 6 weeks of treatment : Hamilton Depression Scale — 17 items ; Hamilton Anxiety Scale — 7 somatic items ; Clinical Global Impression ; vital signs (heart rate, blood pressure); side effects ; concurrent medication.

The average age of the patients was 45.9 ($\pm$ 13); 29.5 % were male and 70.5 % were female.

The results were analysed by means of a one-way analysis of variance with repeated measures.

Results

On the 272 patients entering the study, 58 dropped out and 214 completed the trial. The efficacy results relate to the patients who have completed the trial. The drop-outs will be considered separately.

1. **Efficacy.**

a) *Hamilton depression scale* (17 items).

The scores (fig. 1) showed an improvement from the first week of fluvoxamine treatment, with a 19 % decrease between the mean pretreatment score and the mean score after one week of treatment ($p < 0.00001$). After six weeks of treatment, the mean score dropped from 25.2 to 8, which represents an improvement of 68.3 % ($p < 0.00001$).

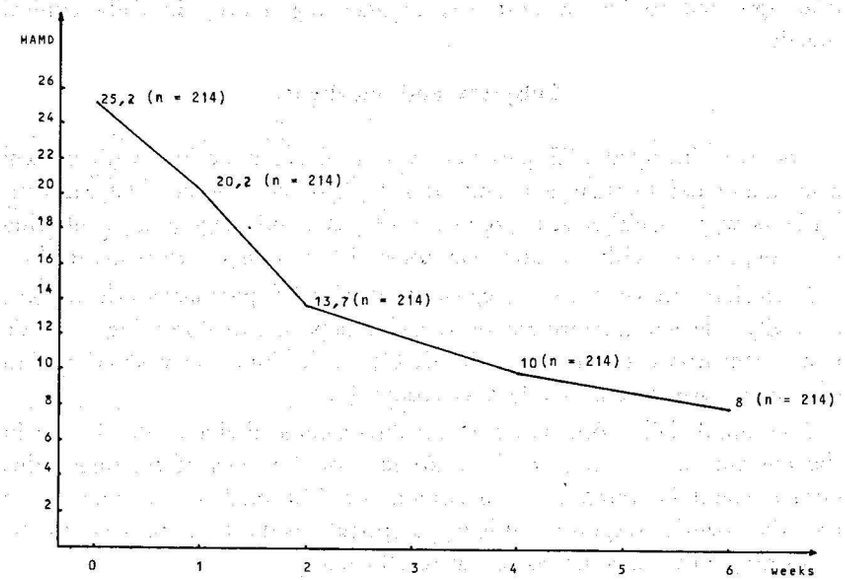

FIG. 1. — Mean scores on the Hamilton Depression Scale before, during and at the end of treatment ($p < 0.00001$).

b) *Somatic symptoms scores.*

This 7-item scale is made us of the somatic symptoms of the Hamilton Anxiety Rating Scale. The mean scores are shown in table I. There was a striking parallelism between the scores on this scale and those on the Hamilton Depression Scale.

c) *Clinical Global Impression scores.*

The scores are shown in table II. An adjusted percentage of improvement has been added because the minimum score of this scale is 1 instead of 0 as on the previous two scales. This adjustment allows a stricter comparison between the various scores. The improvement in time again

TABLE I

Mean scores on the Somatic Symptoms Scale

	Score	*SD*	*% improvement*
Pretreatment	10,5	5,2	
1 week	8,5	5,0	19 ($p < 0.00001$)
2 weeks	5,9	4,6	44
4 weeks	4,3	3,7	59
6 weeks	3,7	3,8	64 ($p < 0.00001$)

TABLE II

Mean Clinical Global Impression Scores

	Mean score	*SD*	*% improvement*	*% adjusted*
Pretreatment	4,5	0,94		
1 week	4,05	1,1	10	13
2 weeks	3,1	1,2	22	40
4 weeks	2,6	1,2	43	55
6 weeks	2,3	1,2	49	63

corresponded strikingly with the one recorded on the Hamilton Depression Scale, the statistical significance being identical (after 7 days $p < 0.0001$; after 6 weeks $p < 0.00001$).

2. **Dosage.**

Most investigators started the treatment by prescribing the recommended dosage of 100 mg/day in 2 intakes of 50 mg (morning and night). The mean dosage throughout the trial is shown in table III.

In interpreting this table, it must be added that after one week of treatment the majority of patients were in fact prescribed either 100 mg or 200 mg fluvoxamine, which explains the mean dosage of 150 mg

TABLE III

Mean daily dosage

	Mean dosage	*SD*
Start of treatment	101,6	13,3
Start of 2nd week	154,4	49,9
Start of 4th week	157,3	64,2
Start of 6th week	152,9	64

throughout the trial. Practically, this means that actually only few patients took 150 mg/day.

3. **Side effects.**

Among the 272 patients included in the trial, 80 (30 %) never showed any untoward effects.

Table IV lists the 19 most frequent symptoms and differentiates the patients who completed the trial from the drop-outs. It should be added that two patients shifted into a manic episode

TABLE IV

Side effects

	Total (n=272) n(%)	Completed (n = 214) n/%	Drop-outs (n = 58) n/%
Nausea	48 (17,6)	27/ 12,6	21/ 36,2
Gastric Pain	42 (15,4)	25/ 13	14/ 24
Somnolence	25 (9,1)	20/ 9,3	5/ 8,6
Dry mouth	21 (7,7)	19/ 4,8	2/ 3,4
Dizziness	14 (5,8)	10/ 4,6	6/ 10,3
Headaches	14 (5,1)	12/ 5,6	2/ 3,4
Vomiting	13 (4,7)	6/ 2,8	7/ 12
G.I. complaints	11 (4 %)	6/ 2,8	5/ 8,6
Tachycardia	10 (3,6)	7/ 3,7	2/ 3,4
Perspiration	7 (2,5)	6/ 2,8	1/ 1,7
Tremor	7 (2,5)	5/ 2,3	2/ 3,4
Agitation	7 (2,5)	5/ 2,3	2/ 3,4
Insomnia	6 (2,2)	6/ 2,8	
Anxiety	5 (1,8)	4/ 1,9	1/ 1,7
Constipation	5 (1,8)	5/ 2,3	
Diarrhoea	5 (1,8)	4/ 1,9	1/ 1,7
Fatigue	5 (1,8)	5/ 2,3	
Pyrosis	5 (1,8)	4/ 1,9	1/ 1,7
Hypotension	5 (1,8)	4/ 1,9	1/ 1,7

4. **Drop-outs.**

Fifty-eight patients failed to complete the trial :

— 6 for administrative reasons (they failed to return);
— 10 (i.e. 27 % of the drop-outs) because of gastro-intestinal complaints alone ;
— 6 because of inefficacy ;
— 2 because of gastro-intestinal complaints and inefficacy ;

— 13 because of the following symptoms : paranoid development (1), epilepsy (1), impotence (1), prostate complaints (1), suicide attempt (1), suicidal thoughs (2), anxiety (1), nervousness (1), agitation (1), euphoria (1), somnolence (1), coma (1) (the coma was a consequence of the patient's general condition and must not be attributed to the action of fluvoxamine);
— 9 for several symptoms.

All side effects causing the discontinuation of the treatment appeared in the first two weeks of the treatment, the majority even during the first week. It was impossible in the course of this study to relate the side effects with the dosage, because 32 patients (55 % of the drop-outs) took only 100 mg fluvoxamine per day.

Discussion

The essential question whether fluvoxamine is a real antidepressant, in regard to the three target scheme proposed by Kielholz, is answered straightaway by stating that fluvoxamine has an undeniably excellent effect on mood. Its effect on the other two target symptoms, i.e. anxiety and psychomotor inhibition, is observed within the context of mood improvement. Consequently fluvoxamine is a real antidepressant. Fluvoxamine is similar to other antidepressants as to the types of depression that respond best to it. It appears that major depressions with anxiety and somatisation are doubtless those that respond best to fluvoxamine.

However, fluvoxamine has been successfully tested on severe depressed neurotics. Its good tolerance in those patients makes it an important tool in the treatment of neurosis. Although 70 % of the patients in the study combined fluvoxamine with benzodiazepines, the investigators believe that fluvoxamine can be prescribed as monotherapy. The high incidence of benzodiazepine intake is not the consequence of the fluvoxamine treatment, but of the fact that prior to the fluvoxamine treatment, most patients were already on 1 or 2 benzodiazepines and a withdrawal is not recommended in view of the risk of rebound anxiety. On the other hand, in the course of the fluvoxamine treatment, a decreased demand for benzodiazepines has been observed. Patients treated solely with fluvoxamine have not developed differently from the others.

The majority of the investigators have found the tolerance for fluvoxamine quite satisfactory. The gastro-intestinal side effects are probably related to the fluvoxamine treatment, although here the depressive context and its usual somatisation must be taken into account. The ad-

ditional prescription of a classic anti-emetic may generally suppress this untoward effect.

The excellent cardiovascular tolerance is appreciated by all investigators. Sleep seems to be favourably affected by fluvoxamine. Patients fall readily asleep and their sleep is not agitated.

In conclusion, fluvoxamine can be regarded as a good antidepressant, with a marked effect on mood, complemented by a light anxiolytic component. The drug is well tolerated in spite of the relatively frequent incidence of nausea at the start of the treatment, which in most cases, however, recedes spontaneously. Besides, its cardiovascular tolerance is remarkable. The efficient dosage is about 150 mg/day (100 mg to 200 mg).

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RESUME

Etude multicentrique belge de la fluvoxamine chez des patients ambulants déprimés.

Un nouvel antidépresseur, la fluvoxamine, inhibiteur spécifique du recaptage de la sérotonine, a été étudié en Belgique au cours d'un essai multicentrique incluant 272 patients traités ambulatoirement. L'étude portait sur une durée de six semaines. La note à l'échelle de Hamilton pour la dépression est passée d'une moyenne de 25,2 à 8 en fin de traitement ($p < 0.00001$) ; l'échelle d'impression clinique globale suivit la même évolution. La fluvoxamine est un antidépresseur vrai à action évidente sur l'humeur, efficace à une dose variant de 100 à 200 mg par jour, bien toléré, notamment sur le plan cardiovasculaire.

SAMENVATTING

Een belgische multicenter studie met fluvoxamine bij ambulante depressieve patiënten.

Fluvoxamine, een nieuw antidepressivum dat specifiek de serotonine reuptake inhibeert werd in België bestudeerd bij 272 ambulante patiënten tijdens een multicenter onderzoek. De studie duurde zes weken. De score van de Hamilton depressie schaal daalde van gemiddeld 25,2 naar 8 na zes weken ($p = 0.00001$) ; de clinical global impression schaal volgde dezelfde evolutie. Fluvoxamine is een echt antidepressivum met uitgesproken effect op het gemoed, werkzaam bij een dosering van 100 à 200 mg per dag, zeer goed getolereerd, onder andere op cardiovasculair gebied.

BIBLIOGRAPHY

CLAASSEN V. Review of the animal pharmacology and pharmacokinetics of fluvoxamine. *Brit. J. clin. Pharmacol., 15,* 349-355 (1983).

DE WILDE J.E, DOOGAN D.P. Fluvoxamine and chlorimipramine in endogenous depression. *J. Aff. Dis., 4,* 249-259 (1982).

DE WILDE J.E., MERTENS C., WAKELIN J.S. Clinical trials of fluvoxamine vs chlorimipramine with single and three times daily dosing. *Brit. J. clin. Pharmacol., 15,* 427-431 (1983).

DICK P., FERRERO E. A double-blind comparative study of the efficacy of fluvoxamine and chlorimipramine. *Brit. J. clin. Pharmacol., 15,* 419-425 (1983).

FELDMANN H.S., DENBER H.C.B. Long-term study of fluvoxamine : a new rapid-acting antidepressant. *International Pharmacopsychiatry, 17,* 114-122 (1982).

GEUKENS-FOPPEN F.H., RAPWORTH S J., PECK A.W. Fluvoxamine, a new antidepressant. *Brit. J. clin. Pharmacol., 15,* 347 (1983).

GUELFI J D., DREYFUS J.F., PICHOT P., GEPECEP. A double-blind controlled clinical trial comparing fluvoxamine with imipramine. *Brit. J. clin. Pharmacol., 15,* 411-417 (1983).

GUY W., WILSON W.H., BAN T.A., KING D L., MANOY G., FJETLAND O.K. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. *Drug Development Research, 4,* 143-153 (1984).

ITIL T.M., SHRIVASTAVA R K., MUKHERJEE S., COLEMAN B.S., MICHAEL S.T. A double-blind placebo study of fluvoxamine and imipramine in out-patients with primary depression. *Brit. J. clin. Pharmacol., 15,* 433-438 (1983).

KLOK J.C., BROUWER G.J., VAN PRAAG H.M., DOOGAN D. Fluvoxamine and clomipramine in depressed patients. *Acta psychiat. scand., 64,* 1-11 (1981).

LAPIERRE Y.D., OYEWUMI L.K., COLEMAN B. The efficacy of fluvoxamine as an antidepressant. *Clin. Trials J., 18,* 313-320 (1981).

ROOS J.C. Cardiac effects of antidepressant drugs. A comparison of the tricyclic antidepressants and fluvoxamine. *Brit. J. clin. Pharmacol., 15,* 439-445 (1983).

SALETU B., GRUNBERGER. Pharmaco-EEG profiles of antidepressants. Pharmacodynamic studies with fluvoxamine. *Brit. J. clin. Pharmacol., 15,* 369-384 (1983).

WILSON W.H., HIGANO H., PAPADATOS Y., KELWALA S., BAN T.A. A double-blind placebo controlled study to compare the autonomic effects of fluvoxamine with those of amitriptyline and doxepin in healthy volunteers. *Brit. J. clin. Pharmacol., 15,* 385-392 (1983).

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