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Controlled Comparison of Paroxetine and Fluvoxamine in Major Depression

M. ANSSEAU[1]*, A. GABRIËLS[2], J. LOYENS[3], F. BARTHOLOMÉ[4], J. L. EVRARD[5], A. DE NAYER[5], R. LINHART[6], J. WIRTZ[7], F. BRUYNOOGHE[8], K. SURINX[9], H. CLARYSSE[10], R. MARGANNE[11] AND P. PAPART[1]

[1]Psychiatric Unit, C.H.U. du Sart Tilman, B-4000 Liège; [2]Onze Lieve Vrouw Ziekenhuis, B-9300 Aalst; [3]Sint Jozef ziekenhuis, B-8400 Oostende; [4]Hôpital Saint-Joseph, B-4000 Liège; [5]Clinique Sainte-Thérèse, B-6080 Montignies sur Sambre; [6]Sint Jozef ziekenhuis, B-2300 Turnhout; [7]Hôpital Neuropsychiatrique de l'Etat, L-9012 Ettelbruck; [8]Sint Lucasziekenhuis, B-8200 Brugge; [9]Stedelijk Ziekenhuis Virga Jesse, B-3500 Hasselt; [10]Kliniek van het Heilige Hart, B-8800 Roeselare; [11]Centre Médical de Serbie, B-4000 Liège, Belgium

A multicentre study compared the antidepressant efficacy and the tolerance of two selective serotonin reuptake inhibitors, paroxetine (20–30 mg/d) and fluvoxamine (50–200 mg/d) in two parallel groups of respectively 56 and 64 patients with major depression, as defined by DSM-III-R criteria. The duration of the study was six weeks, with assessments at baseline and at the end of weeks 1, 2, 4, and 6. For efficacy the Hamilton depression, the Hamilton anxiety scales and the clinical global impressions were used; adverse events were assessed by means of a non-leading question. Results showed a similar improvement in both groups on all rating instruments. The total number of patients reporting adverse events did not significantly differ between paroxetine (52 per cent) and fluvoxamine (64 per cent); severe adverse events were however significantly less frequently reported with paroxetine than with fluvoxamine (13 per cent versus 28 per cent), and resulted less frequently in the discontinuation of treatment (5 per cent versus 17 per cent).

KEY WORDS—Paroxetine, fluvoxamine, selective serotonin reuptake inhibitors, antidepressant, major depression.

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRI's) represent a very successful new class of antidepressant drugs (Boyer and Feighner, 1991a). Several compounds, such as fluvoxamine, fluoxetine, citalopram, sertraline, and paroxetine, have clearly demonstrated an antidepressant efficacy superior to placebo and equivalent to reference tricyclics, with a significantly better safety profile (Boyer and Feighner, 1991a,b; Kasper *et al.*, 1994). Among SSRIs, several differences exist regarding their potencies, their levels of selectivity, and their pharmacokinetic characteristics (Johnson, 1991; Kasper *et al.*, 1994). Few studies have however compared the antidepressant efficacy and the tolerability of SSRIs. These comparisons are important in order to better define the respective profile of the efficacy and tolerability of the representatives of this new class (Benfield and Ward, 1986). In this context, our study focused on paroxetine and fluvoxamine. Paroxetine is the more potent inhibitor of serotonin reuptake, with an inhibition constant of 1·1 nmol/l compared with 6·2 nmol/l for fluvoxamine (Dechant and Clissold, 1991). The selectivity of paroxetine is higher than fluvoxamine, with an inhibition constant for the reuptake of serotonin 320 times greater than for noradrenaline, compared to a ratio of 180 for fluvoxamine (Dechant and Clissold, 1991). The mean terminal elimination half-lives are approximately 24 h for paroxetine and 16 h for fluvoxamine, without active metabolites (DeVane, 1992). Therefore, the purpose of the present study was to assess if these biochemical and pharmacological differences had clinical implications.

SUBJECTS AND METHOD

Design of the study

The study was performed between July 1991 and August 1992 in 10 Belgian and one Luxemburgian centres (see affiliations). The trial used a double-blind design with two parallel groups of patients randomly assigned to either paroxetine or fluvoxamine. Paroxetine was administered at an initial dose of 20 mg in the morning. This dose could

* Author to whom correspondence should be addressed.

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Table 1. Demographic and clinical characteristics of the sample

	Paroxetine group ($n = 56$)	Fluvoxamine group ($n = 64$)
Gender (M/F) (n)	30/26	21/43
Mean age (years) (SD)	43·7 (11·5)	43·4 (9·9)
Age range (years)	20–65	27–64
Inpatient/outpatient (%)	36/64	33/67
Previous depressive episode (%)	73	77
Family history of depression (%)	46	38
Duration of present episode (n) (%)		
< 1 month	9 (16·1)	7 (10·9)
1–3 months	14 (25·0)	20 (31·3)
3–6 months	11 (19·6)	18 (28·1)
6–12 months	11 (19·6)	6 (9·4)
> 12 months	11 (19·6)	13 (20·3)

be increased to 30 mg after 2 weeks in case of a lack of response. Fluvoxamine was administered at an initial dose of 50 mg in the evening during the first week and 100 mg in the evening during the second week; this dose could be increased to 200 mg (100 mg in the morning and 100 mg in the evening) after two weeks in case of a lack of response. The drug administration period was preceded by a one week run-in period on placebo. Patients who had received benzodiazepines for at least two weeks prior to entering the study were permitted to continue these agents, providing the dose remained unchanged throughout the study period. In addition, low dose lormetazepam or chloral hydrate were permitted in case of severe insomnia.

The duration of the study was six weeks, with assessments at baseline and after 1, 2, 4 and 6 weeks of treatment.

Subjects

A total of 135 patients were included in the study, of whom 120 were evaluated on an intent-to-treat basis : 56 in the paroxetine group and 64 in the fluvoxamine group. All subjects were depressed in- or outpatients, aged 18–65 years who fulfilled DSM-III-R criteria for a major depressive episode and scored at least 18 on the 21-item Hamilton depression scale (Hamilton, 1960), without an improvement higher than 20 per cent during the placebo run-in period. The demographic characteristics of the two treatment groups are presented in Table 1. Patients presenting with clinically significant co-existing diseases or other psychiatric disorders were excluded as well as those with a history of alcohol or drug abuse. Women of child-bearing potential not employing adequate contraception were similarly excluded. Recent treatment with monoamine oxidase inhibitors, neuroleptics, or lithium, and current treatment with oral anticoagulants and type 1C antiarythmics were also reasons for patients exclusion. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients were fully informed of the purpose of the study and gave written or witnessed oral consent to participate.

Assessments

Efficacy assessments were performed by means of the 21-item Hamilton depression scale including five subscales (anxiety, cognitive disturbance, retardation, sleep disturbance, melancholia) (Guy, 1976), the Hamilton anxiety scale including subscales for psychic and somatic anxiety (Hamilton, 1959) and the clinical global impressions (Guy, 1976). The safety evaluation included physical examination, vital signs, routine laboratory tests, and evaluation of adverse events via a non-leading question.

Data analysis

The treatment groups were compared using Fisher's exact tests, Mantel-Haenszel Chi-square test, or two-sample t-tests. The intent-to-treat population was analysed using an endpoint dataset as well as a visitwise dataset. All statistical procedures were obtained using the SAS statistical package.

Table 2. Reasons for dropouts *n* (%)

	Paroxetine group ($n = 56$)	Fluvoxamine group ($n = 64$)
Lack of efficacy (relapse)	2 (3·6)	3 (4·7)
Lack of efficacy and adverse events	0	2 (3·1)
Adverse events	3 (5·4)	11 (17·2)
Improvement	1 (1·8)	0
Other reasons	10 (17·9)	7 (10·9)

RESULTS

Dropouts

A total of 39 patients were withdrawn during the study : 16 in the paroxetine group (11 with 20 mg and six with 30 mg) and 23 in the fluvoxamine group (eight with 50 mg, five with 100 mg, and 10 with 200 mg). The reasons for these dropouts are summarized in Table 2. Significantly more patients in the fluvoxamine group left the study due to adverse events ($p = 0{\cdot}05$).

Dosage

In the paroxetine group, 26 (46 per cent) patients took a maximum dose of 20 mg and 30 (54 per cent) patients a maximum dose of 30 mg; in the fluvoxamine group, eight (13 per cent) patients took a maximum dose of 50 mg, 19 (30 per cent) patients a maximum dose of 100 mg and 37 (58 per cent) patients a maximum dose of 200 mg.

Hamilton depression scale

The changes over time on the Hamilton depression in the two groups are presented in Figure 1. No significant differences between drugs were present. The paroxetine group had a baseline mean total score (SD) of 26·0 (4·2) and a mean improvement at endpoint (SD) of 12·9 (6·5) and the fluvoxamine group a baseline mean total score (SD) of 26·5 (4·5) and a mean improvement at endpoint (SD) of 12·4 (7·1). There was no evidence of any significant difference between the treatment groups at weeks 1, 2, 4 and 6, and endpoint. Twenty-four (53 per cent) paroxetine patients and 21 (44 per cent) fluvoxamine patients had reduced their 21-item total Hamilton depression score by 50 per cent at week 4 (n.s.); by week 6, 19 (50 per cent) paroxetine patients and 24 (56 per cent) fluvoxamine patients had achieved this response (n.s.), and for the endpoints, 24 (53 per cent) paroxetine patients and 24 (50 per cent) fluvoxamine patients (n.s.). Both treatment groups also showed a similar consistent pattern of improvement for the five Hamilton depression subscales.

Mean scores (SD) on the suicide item (item 3) improved similarly with both antidepressants, from 1·4 (0·9) to 0·2 (0·5) with paroxetine and from 1·4 (1·0) to 0·4 (0·8) with fluvoxamine (n.s.).

The changes from baseline in total Hamilton depression scores showed no significant differences whether the in- or outpatient treatment groups were considered.

Hamilton anxiety scale

The changes over time on the Hamilton anxiety scale in the two treatment groups are presented in Figure 2. No significant differences between drugs were present. The paroxetine group had a baseline mean score (SD) of 22·0 (6·7) and a mean improvement at endpoint (SD) of 9·4 (6·9); the fluvoxamine group had a baseline mean score (SD) of 22·6 (6·1) and a mean improvement at endpoint (SD) of 9·7 (7·2) (n.s.). There was no evidence of any significant difference between treatment groups at weeks 1, 2, 4 and 6 and endpoint. For the psychic and somatic anxiety subscales, both treatment groups showed similar consistent patterns of improvement during the study, without any significant difference between the groups at weeks 1, 2, 4 and 6 and endpoint.

CGI

The CGI severity of illness showed a consistent pattern of improvement in the two treatment groups during the study. The paroxetine group had a baseline mean score (SD) of 5·0 (0·7) and a mean improvement from baseline to endpoint (SD) of 2·0 (1·3) and the fluvoxamine group a baseline mean score (SD) of 5·1 (0·7) and a mean improvement at endpoint (SD) of 2·1 (1·5). There was no evidence of any significant difference between the treatment groups at weeks 1, 2, 4 and 6 and endpoint.

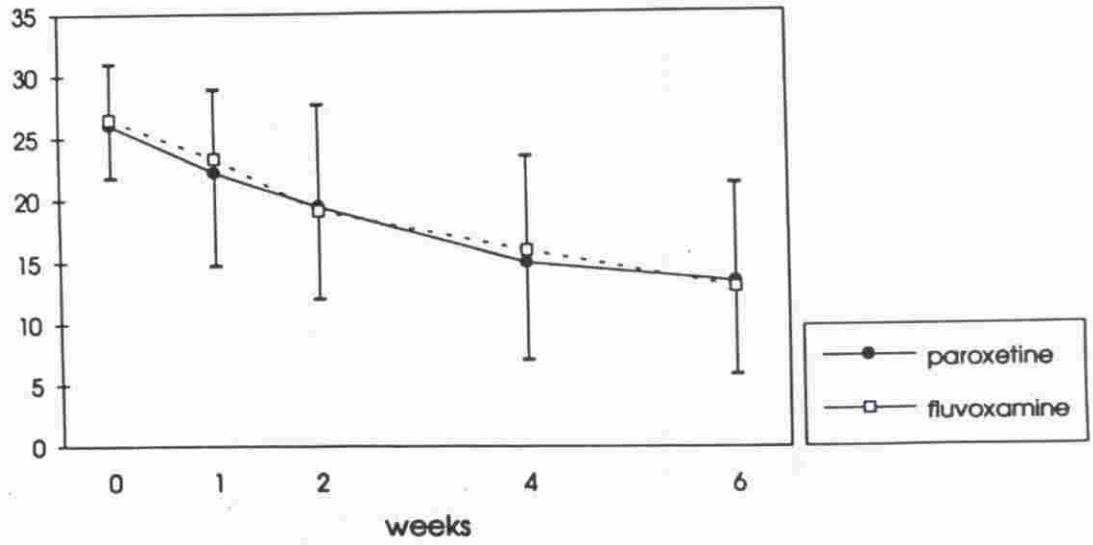

Figure 1. Changes over time in mean scores (±SD) on the Hamilton depression scale among patients treated by paroxetine (20–30 mg/d) or fluvoxamine (100–200 mg/d)

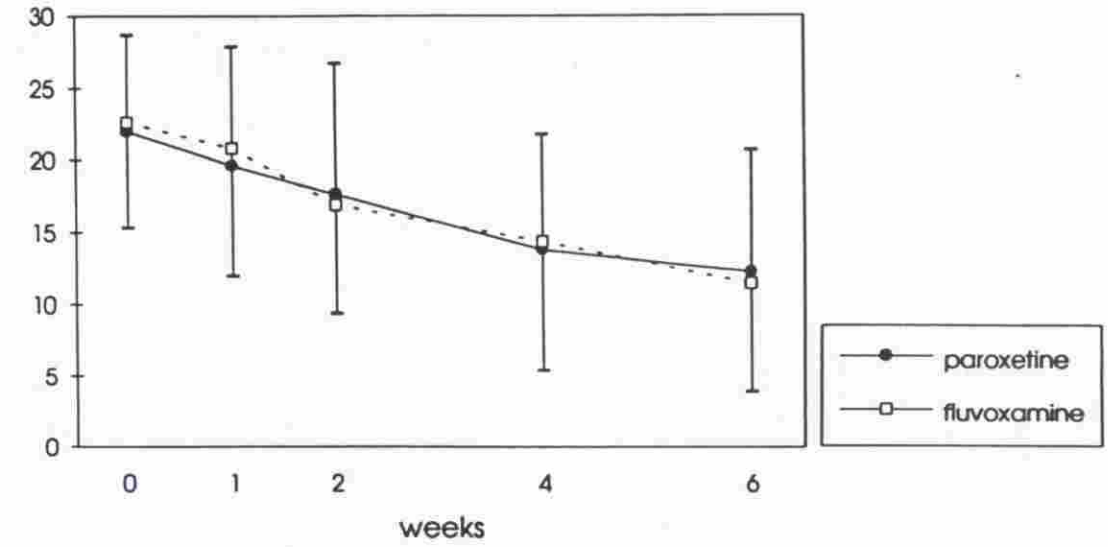

Figure 2. Changes over time in mean scores (±SD) on the Hamilton anxiety scale among patients treated by paroxetine (20–30 mg/d) or fluvoxamine (100–200 mg/d)

The CGI improvement scores of the two treatment groups showed also similar consistent patterns of improvement during the study. At week 6, the paroxetine group exhibited a mean score (SD) of 1·8 (1·0) and the fluvoxamine group a mean score (SD) of 2·0 (1·2) and at endpoint, mean scores (SD) of 1·9 (1·0) and 2·2 (1·3) respectively. There was no evidence of any significant difference between the treatment groups at weeks 1, 2, 4 and 6 and endpoint.

Adverse events

Twenty-nine patients (52 per cent) in the paroxetine group and 41 patients (64 per cent) in the the fluvoxamine group reported at least one adverse event during the study (n.s.). Their distribution by body system is presented in Figure 3. The most frequently reported adverse events in both groups related to the gastrointestinal system, particularly nausea (paroxetine 19·6 per cent, fluvoxamine 18·8 per cent). Significantly less patients treated with paroxetine as compared with fluvoxamine rated adverse events as severe, respectively seven (13 per cent) versus 18 (28 per cent) ($p < 0{\cdot}05$, Fisher's exact test). A total of 14 patients experienced adverse events which led to premature withdrawal from the study : 5 per cent with paroxetine versus 17 per cent with fluvoxamine ($p = 0{\cdot}05$) (Table 3).

Table 3. Adverse events leading to dropout*

Paroxetine: three patients	Fluvoxamine: 11 patients
Hiccups (1)	Nausea (3)
Trauma (1)	Abdominal pain (3)
Anxiety (1)	Vomiting (2)
Tremor (1)	Dyspepsia (1)
	Anxiety (1)
	Emotional lability (1)
	Headache (1)
	Manic reaction (1)
	Nervousness (1)
	Tachycardia (1)
	Vasodilatation (1)
	Palpitation (1)

*More than one event per patient could be recorded

Serious adverse events were reported by three patients in each treatment group. In the paroxetine group, these comprised hysterectomy, severe trauma requiring surgery, and hiccups, all of which necessitated hospitalization. In the fluvoxamine group, the serious events were anxiety/delusional beliefs, suicide attempt, and agitation, the latter two resulting in hospitalization.

Vital signs and laboratory tests

Mean sitting systolic and diastolic blood pressure (mmHg) decreased from 126·5/79·1 at baseline to 123·2/77·0 at week 6 in the paroxetine group and from 126·4/79·0 at baseline to 125·3/77·7 at week 6 in the fluvoxamine group, without any clinically significant differences.

Mean sitting pulse rate (beats/min) decreased from 79·4 at baseline to 77·5 at week 6 in the paroxetine group and from 79·9 at baseline to 79·6 at week 6 in the fluvoxamine group, without any significant difference.

Laboratory data did not reveal any significant alteration during the study.

DISCUSSION

The results of the present study show similar efficacy for the two SSRIs, paroxetine and fluvoxamine, in patients with major depression. Indeed, none of the rating scales used in this trial (Hamilton depression and anxiety scales including subscales, clinical global impressions) exhibit any significant difference in changes over time between the two drugs. In particular, the onset of improvement is very similar between the two groups. Moreover, the number of treatment responders does not differ between the drugs. Several limitations in these conclusions should however be acknowledged. First, the lack of a placebo-control group means the efficacy results should be considered with caution. Second, the number of patients included in each treatment cell (about 60), despite corresponding to international standards (Angst *et al.*, 1989), could have been too small to completely eliminate a possible type II error or to demonstrate subtle differences in efficacy. In fact the study was set up to detect a difference of four points between therapies using the mean change from baseline on the Hamilton depression scale with a power ($1 - \beta$) of 80 per cent and a significance level (α) of 0·05, assuming a within-group standard deviation of 7. This sensitivity could appear rather low since the mean improvement from baseline score to endpoint was 12·9 in the paroxetine group and 12·4 in the fluvoxamine group. This lack of differences is however confirmed on all efficacy variables including the number of treatment responders. Moreover, in two recent studies, our group was clearly able to differentiate active antidepressants, showing a significant superiority of amitriptyline over nefazodone in major depressive inpatients (Ansseau *et al.*, 1994b) and of fluoxetine over milnacipran in major depressive outpatients (Ansseau *et al.*, 1994a). In addition, the antidepressant efficacy of the two SSRI's has been well established in several placebo-controlled studies (Benfield and Ward, 1986; Dechant and Clissold, 1991); this efficacy has also been demonstrated as equivalent to reference tricyclics such as amitriptyline and imipramine in a

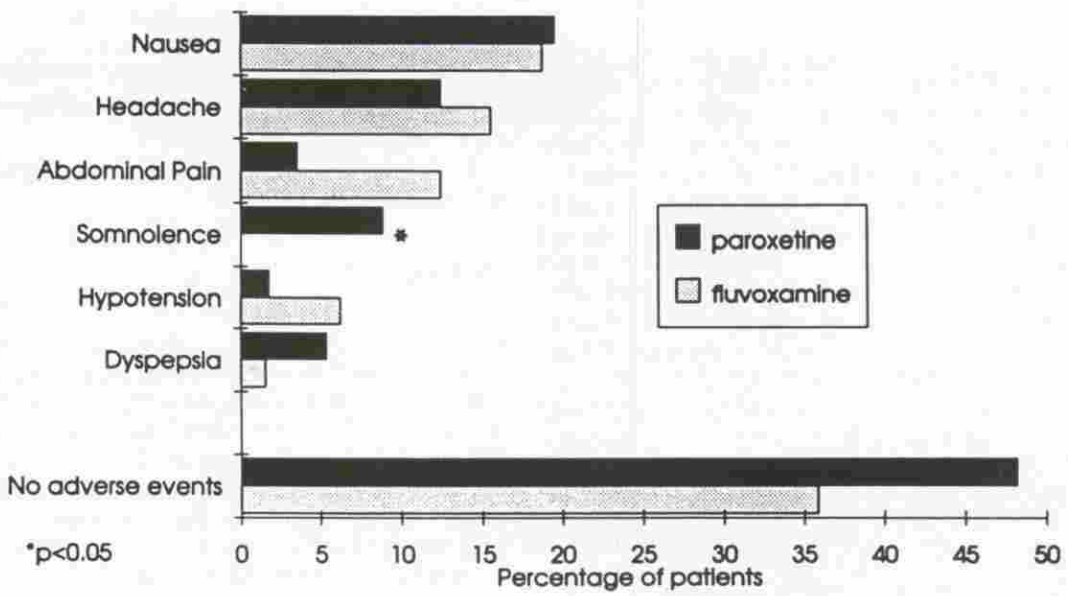

Figure 3. Incidence of adverse events (≥ 5 per cent) among patients treated by paroxetine (20–30 mg/d) or fluvoxamine (100–200 mg/d)

large number of controlled studies (Benfield and Ward, 1986; Dechant and Clissold, 1991).

Despite the fact that this study was not set up for this purpose, it is interesting to note that the rate of improvement of depression did not differ between in- and outpatients for both paroxetine and fluvoxamine. Depressive inpatients tend to be a much more homogeneous group, displaying increased levels of severity, endogenous features, and suicidal ideation and are less responsive to placebo, anxiolytic benzodiazepines, or to minor antidepressants (Ansseau, 1992). Inpatients are a particularly suitable group of patients for differentiating antidepressant compounds (Ansseau *et al.*, 1991). This trial supports the efficacy of SSRIs in both inpatients and outpatients suffering from major depression (Mendlewicz, 1992).

Concerning tolerability, the results of the present study did not show significant differences between the two drugs in the overall number of patients reporting emergent adverse events. Regarding individual events, only somnolence was significantly more frequently reported with paroxetine. This difference may have resulted from the opposed administration schedule of the two antidepressants, with paroxetine being taken in the morning and fluvoxamine in the evening (or morning and evening in case of a 200 mg daily dose). In both groups, the most frequently reported adverse events related to the gastrointestinal system, particularly nausea. These results reflect the characteristic profile of adverse events seen with SSRIs (Boyer and Feighner, 1991b). Concerning paroxetine, the incidence of nausea in the present study (19·6 per cent) was slighter lower than reported during short-term studies in 2963 depressive patients (23 per cent) (Jenner, 1992). Concerning fluvoxamine, the incidence of nausea in the present study (18·8 per cent) was much lower than in the initial studies with the drug (37 per cent). This better tolerability may depend on two factors. Firstly, initial studies with fluvoxamine generally used higher daily doses (200–300 mg); more recent trials using lower doses (100–200 mg) reported a lower incidence of nausea (15·7 per cent) (Wagner *et al.*, 1992). Secondly, in the present study, the rather conservative ascending dose schedule of fluvoxamine starting with 50 mg may have played a role in decreasing the incidence of adverse events, particularly digestive symptoms.

Despite this rather advantageous schedule, fluvoxamine was responsible for significantly more severe adverse events than paroxetine as well as for more adverse events leading to withdrawal from the study. The dropout rate does not appear to be related to the dosage of fluvoxamine since eight patients already left the study during the initial

week at 50 mg/d. The majority of adverse events leading to withdrawal on fluvoxamine related to the gastrointestinal system (nausea, abdominal pain, vomiting, dyspepsia) whereas none of the patients in the paroxetine group had to drop out from the study due to digestive symptoms. These findings suggest an overall advantage in tolerability favouring paroxetine over fluvoxamine, particularly regarding severe adverse events.

Concerning the dosage used in the present study, 54 per cent of patients treated with paroxetine had an increase from 20 to 30 mg and 58 per cent on fluvoxamine an increase from 100 to 200 mg. Results concerning paroxetine are well in line with published studies showing that if an overall 70 per cent of the patients respond to the initial 20 mg daily dose paroxetine 10 mg increments may be needed in a certain number of depressive patients, particularly in melancholics (Dunner and Dunbar, 1992). Concerning fluvoxamine, these results also agree with previous trials showing the initial 100 mg daily dose has to be increased to 200 mg or more in a significant number of depressive patients: in another multicentre study using flexible doses, the mean daily dose of fluvoxamine was 155 mg (Mendlewicz, 1992). The design used in this study however does not enable us to determine if the increase in paroxetine or fluvoxamine daily dose after 2 weeks at the initial dosage was actually beneficial. A response to the important issue of the optimal daily dose should come from trials using fixed dosage or comparing the responses of patients randomly assigned to either a continuation of the same dosage or to an increase in daily doses in case of a lack of response after an initial treatment period. A trial using fixed doses of paroxetine 10 mg, 20 mg, 30 mg, 40 mg/d or placebo over 6 weeks in 460 patients showed that 20 mg/d paroxetine is the minimum effective dose with a relatively flat dose–response curve across the range of 20 to 40 mg, suggesting that 20 mg/d is also the dose to which most patients respond (Dunner and Dunbar, 1992).

In conclusion, the results of the present study show similar efficacy of paroxetine and fluvoxamine in the treatment of major depressive patients but suggest an overall advantage in tolerability favouring paroxetine.

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