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Fluvoxamine as effective as clomipramine against symptoms of severe depression: results from a multicentre, double-blind study

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Background Although selective serotonin reuptake inhibitors (SSRIs) are better tolerated than tricyclic antidepressants, their efficacy in severe depression remains to be further elucidated.
Method A double-blind, multicentre study was conducted in 86 severely depressed inpatients (≥ 25 on the 17-item Hamilton depression rating scale [HAMD] total score) to compare the efficacy and safety of fluvoxamine with that of clomipramine. Following placebo run-in, 86 patients were randomised to receive fluvoxamine or clomipramine (100–250 mg/day) for 8 weeks.
Results Fluvoxamine and clomipramine both resulted in marked improvements; there were no statistically significant differences between them on the 17-item HAMD total score, the clinical global impression severity of illness or global improvement items or the Montgomery–Åsberg depression rating scale, at any visit. At the end of the study, 71% in the fluvoxamine group and 69% in the clomipramine group were responders ($\geq 50\%$ decrease in 17-item HAMD total score). However, fluvoxamine was better tolerated than clomipramine. Clomipramine was associated with a higher incidence of overall and treatment-related adverse events. In addition, the percentage of patients discontinued prematurely due to adverse events was more than twice as high with clomipramine than with fluvoxamine (24% vs 11%).
Conclusion Fluvoxamine and clomipramine are equally effective in severe depression, but fluvoxamine has a better safety and tolerability profile. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — fluvoxamine; clomipramine; severe depression; selective serotonin reuptake inhibitor

INTRODUCTION

Severe depression significantly impairs the patient's social and occupational functioning and an association between the increasing severity of depression and a history of suicide attempts has been proposed (Montgomery, 1992). Moreover, as depression is a chronic, relapsing and recurring disorder, it has been reported that each episode tends to become increasingly severe.

Until the advent of the selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants were the mainstay of treatment. However, the better tolerability and safety of the SSRIs has now greatly improved the treatment of depression (de Jonghe and Swinkels, 1992; Wagner *et al.*, 1994). Patients are significantly more likely to comply with SSRI treatment (Montgomery *et al.*, 1994; Steffens *et al.*, 1997), especially at the higher doses which may be necessary in severe depression, and they are not exposed to the potentially dangerous cardiovascular side effects (such as rhythm disturbances) of the tricyclic antidepressants (Laird *et al.*, 1993). The SSRIs are also considerably safer than the tricyclic antidepressants in overdose (Henry, 1991; Garnier *et al.*, 1993) and, provided they are of equal efficacy,

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should therefore be a first choice treatment for the severely depressed patient who may be at increased risk of suicide.

There have been concerns, however, that some SSRIs may be less effective than the tricyclic antidepressants and other antidepressants in the treatment of severe depression (Danish University Antidepressant Group, 1986; Danish University Antidepressant Group, 1990; Clerc *et al.*, 1994; Klieser *et al.*, 1995). For example, venlafaxine was significantly more effective than fluoxetine in a double-blind comparison in hospitalised melancholic depressed patients whilst tricyclic antidepressants were significantly more effective than fluoxetine in patients with a high initial Hamilton depression rating scale (HAMD) score and more effective than paroxetine in inpatients. This view is supported by the meta-analysis of Anderson and Tomenson (1994) which indicated that, although the SSRIs in general are as effective as the tricyclic antidepressants in treating depression, there is less certainty that they have equivalent efficacy in treating severe depression. Although the differences were relatively small, this meta-analysis found that tricyclic antidepressants were significantly more effective than fluoxetine in patients with high initial HAMD scores ($p < 0.05$) and that paroxetine was moderately less effective than tricyclic antidepressants in hospitalised depressed patients, although there were no significant differences between paroxetine and tricyclic drugs in patients with initially high HAMD scores. However, in the same meta-analysis (Anderson and Tomenson, 1995) fluvoxamine, citalopram and sertraline were as effective as tricyclic drugs in hospitalised or patients with high initial HAMD scores. Studies have shown that the efficacy of fluvoxamine appears to be superior to that of imipramine (Feighner *et al.*, 1989; Mendlewicz, 1992; Ottevanger, 1994; Kasper *et al.*, 1995; Fabre *et al.*, 1996) and at least equivalent to that of clomipramine (Ottevanger, 1995), amitriptyline (Gasperini *et al.*, 1992) and amineptine (Brunner, 1994). Moreover, fluvoxamine has been shown to be efficacious in patients with psychotic or delusional depression in an open (Gatti *et al.*, 1996; Serretti *et al.*, 2000) and a single double-blind study (Clerc *et al.*, 1994).

Although, there is no currently well-accepted definition of severe depression, a high initial HAMD score is clearly one component. In addition, in the current study as well as having an initial HAMD of at least 25, all patients were receiving therapy as inpatients and can therefore be considered as having depression at the more severe end of the spectrum. Hospitalisation represents an important independent indicator of severity and is based on the overall clinical judgement of the treating physician.

The current multicentre, double-blind study was designed to compare the efficacy and safety of fluvoxamine and clomipramine in severely depressed inpatients.

PATIENTS AND METHODS

Patients

This prospectively randomised, double-blind, parallel-group, multicentre (10 European centres) study was conducted in hospitalised patients of either sex, aged 18 to 70 years old, meeting the DSM-III-R (American Psychiatric Association, 1987) diagnosis of a severe major depressive episode, with or without mood congruent psychotic features not requiring antipsychotic treatment. Patients were also required to have a score of 25 or more on the 17-item Hamilton depression rating scale (HAMD) (Hamilton, 1967). All patients provided signed informed consent for participation in the study.

Patients were excluded if they had psychosis, a history of other psychiatric diagnosis, epilepsy or seizures, were a severe suicide risk, were pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures, or if they had clinically relevant/unstable disease which could affect the diagnosis and/or treatment of depression, hepatic or renal disease, severe heart disease, glaucoma, adrenal tumours, micturition disturbances, prostate hypertrophy, clinically relevant laboratory test abnormalities or multiple drug allergies. Also excluded were patients who had been treated unsuccessfully with two or more antidepressants, or with fluvoxamine or clomipramine, during the current episode of depression. Patients were required not to have received any antidepressants in the week prior to active treatment (5 weeks in the case of fluoxetine) or lithium, monoamine oxidase inhibitors, antipsychotics or electroconvulsive therapy (ECT) in the 2 weeks prior to active treatment.

Treatment

All patients entered a 7-day placebo run-in period that enabled previous antidepressant therapy to be withdrawn and to identify any patients who were likely to respond to placebo. Any patient who experienced a 20% or more improvement in the 17-item HAMD total score during this period was withdrawn from the study.

Patients were then randomly assigned to receive oral fluvoxamine (100–250 mg/day) (Solvay Pharmaceuticals) or clomipramine (100–250 mg/day) for 8 weeks.

Both treatments were started at a dose of 50 mg/day on days 1 to 3 followed by up-titration to 100 mg/day on days 4 to 7; from day 8 onwards, the dosage was adjusted between 100 and 250 mg/day according to efficacy and safety requirements.

With the exception of oxazepam, which could be given for night-time sedation or control of anxiety, no other psychopharmacological treatments or ECT were permitted during the study.

Assessments

The primary efficacy variables were the 17-item HAMD total score and the clinical global impression (CGI) (Guy, 1976) severity of illness score; the secondary efficacy variables were the Montgomery–Åsberg depression rating scale (MADRS) (Montgomery and Asberg, 1979), the CGI global improvement score and the number of 17-item HAMD responders (i.e. the number of patients with at least a 50% improvement in 17-item HAMD total score). The 17-item HAMD and MADRS were determined at screening, baseline and after 1, 2, 4, 6 and 8 weeks (or upon premature termination) of treatment; the CGI severity of illness score was obtained at all visits except screening and CGI global improvement score at all visits except screening and baseline.

Vital signs and self-reported adverse events were documented at screening and each subsequent visit. Laboratory evaluations, an ECG and a physical examination were conducted at screening and the final visit only.

Statistical analyses

Efficacy was assessed using the intent-to-treat (ITT) efficacy sample (i.e. patients who received at least one dose of study medication and provided at least one valid post-baseline efficacy evaluation on study medication). All analyses were performed using visit-wise (observed cases; OC) and last observation carried forward (LOCF) data. Primary efficacy variables were analysed using a two-way analysis of variance (ANOVA) model; the Wilcoxon two-sample test was used to analyse the secondary efficacy variables. Differences with p values ≤ 0.05 were considered statistically significant.

RESULTS

Eighty-six patients were randomised to treatment, 44 to fluvoxamine and 42 to clomipramine; the two treatment groups did not differ significantly with respect to demographic variables (Table 1). Premature withdrawal from the study occurred in eight patients in the fluvoxamine group (five due to adverse events, one due to inefficacy and two due to other reasons) and 13 in the clomipramine group (10 due to adverse events and three due to other reasons).

Table 1. Demographic characteristics (ITT population)

	Fluvoxamine ($n = 44$)	Clomipramine ($n = 42$)
Male/female	15/29	16/26
Mean ($\pm$ SD) age (years)	41.1 ± 14.6	41.9 ± 12.3
Mean ($\pm$ SD) weight (kg)	66.0 ± 14.5	64.5 ± 14.9

Table 2. Baseline severity characteristics (ITT efficacy population)

	Fluvoxamine ($n = 42$)	Clomipramine ($n = 42$)
Mean baseline HAMD	30.6 ± 4.8	30.5 ± 3.8
Mean baseline MADRS	37.6 ± 6.9	37.7 ± 5.4

Two patients in the fluvoxamine group had no post-baseline assessment and were thus excluded from the ITT efficacy sample (which comprised 42 fluvoxamine patients and 42 clomipramine patients). A further nine patients in the fluvoxamine group and 12 in the clomipramine group had major deviations from the protocol (see Table 2).

Dosage

After the start of flexible dosing at the beginning of week 3, mean doses climbed slowly in the fluvoxamine group (from 160.8 ± 49.6 mg/day at week 3 to 185.5 ± 55.1 mg/day at week 8). In the clomipramine group mean dosage declined slightly from 159.3 ± 44.1 mg/day at week 3 to 147.7 ± 57.5 by week 8. Fluvoxamine doses were higher then clomipramine doses at all weekly assessments.

Efficacy

Fluvoxamine and clomipramine were found to be equally effective in the treatment of severe depression, both resulting in a clinically significant improvement.

Primary variables. The mean 17-item HAMD total scores decreased progressively over the course of the study in both groups; the mean change with time (ITT sample, LOCF analysis) is shown in Figure 1. The mean score fell from 30.6 at baseline to 13.4 at the end of the study in the fluvoxamine group and from 30.5 to 12.3 in the clomipramine group.

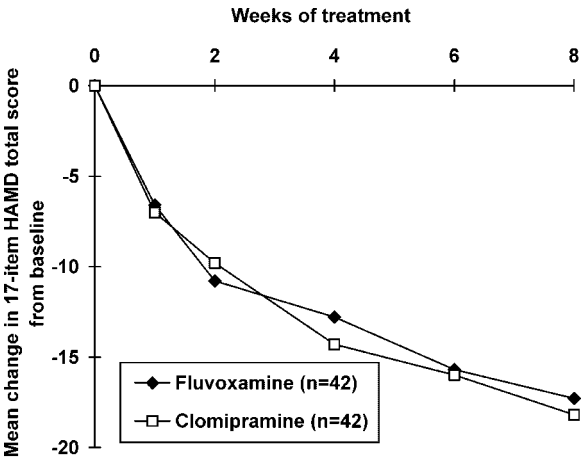

Figure 1. Mean change from baseline in 17-item HAMD total score over time (ITT sample; LOCF analysis)

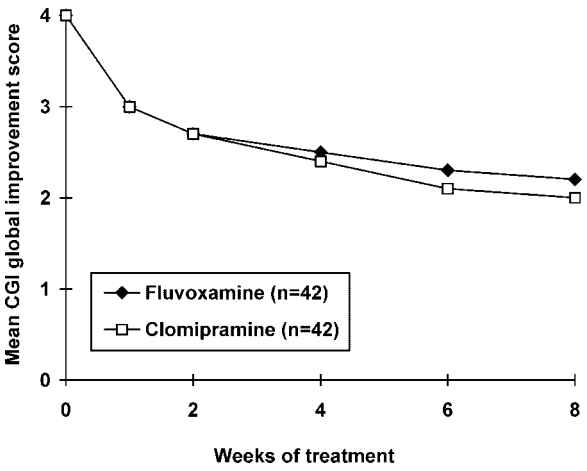

Figure 3. Mean CGI global improvement score over time (ITT sample; LOCF analysis)

A visit-wise analysis of the decrease in HAMD-17 similarly showed no significant differences between the treatment groups.

Similar results were obtained on the CGI severity of illness score, with a gradual improvement in both groups over time; the mean score over time (ITT sample, LOCF analysis) is shown in Figure 2. The mean score fell from 5.4 (markedly to severely ill) to 2.6 (borderline to mildly ill) in the fluvoxamine group and from 5.5 to 2.6 in the clomipramine group.

Neither the HAMD nor the CGI revealed any statistically or clinically significant differences between the treatments at any point or in any of the population samples analysed.

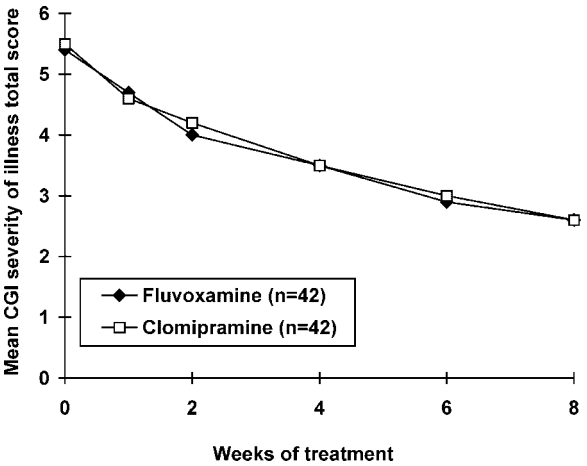

Figure 2. Mean CGI severity of illness score over time (ITT sample; LOCF analysis)

Secondary variables. The secondary efficacy variables supported the finding that fluvoxamine and clomipramine are equally effective in patients with severe depression.

The mean MADRS scores decreased progressively over the course of the study in both groups. In the ITT sample LOCF analysis, the mean score in the fluvoxamine group fell from a baseline value of 37.6 to 14.1 at the end of the study; the corresponding reduction in the clomipramine group was from 37.4 to 14.7. The CGI global improvement score revealed that both groups started to show improvement from as early as the first week of treatment and, by the end of the study, they were considered 'much improved' compared with their baseline condition. The mean score over time (ITT sample, LOCF analysis) is shown in Figure 3. The mean score at the end of the study was 2.2 in the fluvoxamine group and 2.0 in the clomipramine group. The number of 17-item HAMD responders also increased over time so that, by the end of the study, the majority of patients in both groups (71% in the fluvoxamine group and 69% in the clomipramine group; ITT sample, LOCF analysis) were considered to have responded to treatment.

There were no statistically or clinically significant differences between the treatments at any point, or in any of the population samples analysed, in any of the secondary efficacy variables.

Safety and tolerability

Fluvoxamine was better tolerated than clomipramine. The overall incidence of all adverse events, treatment-emergent signs and symptoms (TESS) and specifically

Table 3. Drug-related adverse events (i.e. considered at least possibly related to study treatment) occurring in 10% or more of patients in either group

	Clomipramine ($n=42$)	Fluvoxamine ($n=44$)
Dry mouth	22 (52.4%)	9 (20.5%)
Tremor	17 (40.5%)	4 (9.1%)
Constipation	12 (28.6%)	4 (9.1%)
Dizziness	11 (26.2%)	3 (6.8%)
Nausea	8 (19.0%)	13 (29.5%)
Sweating	7 (16.7%)	3 (6.8%)
Amblyopia	6 (14.3%)	1 (2.3%)
Tinnitus	5 (11.9%)	0

drug-related adverse events was higher with clomipramine than with fluvoxamine. Moreover, the percentage of patients who discontinued the study early due to adverse events was much higher with clomipramine (24%) than with fluvoxamine (11%).

Table 3 shows the individual drug-related adverse events occurring in 10% or more of patients in either group. As expected, anticholinergic events were markedly more common with clomipramine.

Reports of sexual side effects were not specifically sought in this study. Only one report each of anorgasmia and ejaculatory disturbance (present at baseline) in the clomipramine group and none in the fluvoxamine group was recorded.

There were four serious adverse events during the study in the fluvoxamine group (suicide, suicidal thoughts, suicide attempt and suicidal ideation) and three in the clomipramine group (suicide attempt, increased suicidal thinking and suicidal tendency). However, none were considered to be related to study treatment.

No clinically significant changes in laboratory parameters, vital signs, ECG measurements or physical condition were seen in either group. However, the percentage of patients with an increase in body weight of more than 7% was significantly ($p \leq 0.05$; Fisher's exact test) greater with clomipramine than with fluvoxamine (17% vs 5%), whilst the percentage of patients with a decrease in body weight of more than 7% was significantly greater with fluvoxamine than with clomipramine (15% vs 2%).

DISCUSSION

The definition of severe depression is based on a number of factors including diagnosis according to standard criteria, high scores on depression rating scales, hospitalisations, the presence of melancholic or psychotic features and the overall impairment of everyday functioning (Nierenberg, 1994; Schatzberg, 1996). However, as there is no standardised operational definition for severe depression, the criteria tend to vary considerably between studies. In the current study, a diagnosis of severe depression was carefully established based on DSM-III-R criteria and a baseline value of at least 25 on the 17-item HAMD total score. Moreover, all patients included in the study were hospitalised. These patients therefore have a degree of depression at the severe end of the severity spectrum.

Both fluvoxamine and clomipramine resulted in a rapid, progressive and clinically significant improvement in these severely depressed patients. There were no statistically or clinically relevant differences between the treatments. At the end of the study, almost three-quarters of the patients (71% with fluvoxamine and 69% with clomipramine) were considered to be responders (i.e. they had at least a 50% improvement in the 17-item HAMD total score). Moreover, the severity of the illness decreased progressively so that patients went from being markedly/severely ill at baseline to only borderline or mildly ill at the end of the study.

The major limitations of this study are the lack of a placebo control group and the small sample size. In the absence of a placebo comparison, the source of the improvement in HAMD scores cannot be definitively attributed to the medication. However, ethical considerations constrain the feasible methodologies in studies in which effective treatments are available for such a serious and potentially life-threatening illness. In the present study, fluvoxamine was compared with clomipramine, which has long-established efficacy in severe depression (Collins, 1970; Abenson, 1971; Collins, 1971). The small sample size requires that caution be exercised in concluding that the two treatments are equivalent.

A further potential source of bias is the distribution of dropouts between the groups. Twice as many patients dropped out for adverse effects in the clomipramine group compared with the fluvoxamine group and these patients might be expected to carry forward higher HAMD scores (since the onset of action of antidepressant therapy is generally delayed) and favour fluvoxamine. However, the observed case analysis does not bear this out; there were no significant differences between the groups in this analysis either.

Similar results were seen in an earlier small double-blind, multicentre study conducted in 40 hospitalised depressed patients (Ottevanger, 1995). This study differed somewhat in that patients were required to have

a baseline 17-item HAMD total score of at least 18 (as opposed to 25 in the current study); the actual mean values were 26.4 in the fluvoxamine group and 25.7 in the clomipramine group. After 4 weeks of treatment, both fluvoxamine (100–300 mg/day) and clomipramine (50–150 mg/day) resulted in a marked to moderate therapeutic effect, with similar improvements in 17-item HAMD total score and subscores and CGI scores.

A number of studies have also shown that fluvoxamine has superior efficacy to another of the tricyclic antidepressants, imipramine. In a double-blind study conducted in 60 hospitalised depressed patients, fluvoxamine (150–300 mg/day) was significantly more effective than imipramine (150–300 mg/day) and placebo on the CGI severity of illness score, the HAMD total score and the brief psychiatric rating scale after 6 weeks of treatment. Similarly, in a retrospective analysis of 338 patients enrolled in an earlier multicentre, double-blind study (Amin *et al.*, 1984), fluvoxamine (50–300 mg/day), but not imipramine (50–300 mg/day), was significantly more effective than placebo in the 103 patients with severe depression (baseline HAMD total score of 26 or more) as assessed by the HAMD total score and CGI global improvement score (Ottevanger, 1991; Kasper *et al.*, 1995). Interestingly, in the fluvoxamine group, the HAMD total score was reduced to a significantly greater extent in patients with severe depression than in those with moderate (baseline HAMD total score of 21–25) or mild (baseline HAMD score of 15–20) depression.

Hence, these findings are in line with the work of Anderson and Thomenson (1994) which also found that fluvoxamine as well as citalopram and sertraline were as effective as TCAs in hospitalised depressed patients and those with high initial HAMD scores. However, the dosage data in the present study shows that patients assigned to clomipramine found it more difficult to attain and sustain high doses of their therapy than did patients given fluvoxamine. On the one hand this finding implies that clomipramine-treated patients did not receive the full benefit of their medication, but on the other hand highlights the importance of good tolerability as a prerequisite for achieving compliance and a good therapeutic outcome.

The current study suggests that treatment with fluvoxamine is at least as effective as the tricyclic antidepressant clomipramine in patients with severe depression. However, whilst fluvoxamine and clomipramine were similar in terms of clinical efficacy, there were clear differences between the two treatments in terms of safety and tolerability.

As in previous studies, fluvoxamine was clearly better tolerated than clomipramine (Guelfi *et al.*, 1983; Guy *et al.*, 1984). Clomipramine was associated with more anticholinergic effects, including dry mouth, tremor, constipation and accommodation disturbances. Fluvoxamine was associated with some gastric disturbances, although these were almost always mild or moderate. In the previous study by Ottevanger (1995), clomipramine was associated with more anticholinergic side effects and orthostatic hypotension and was rated significantly worse by the investigator in terms of undesirable signs and symptoms. Such differences are to be expected from the pharmacological profiles of the drugs. In contrast to fluvoxamine, the lack of selectivity of clomipramine means it has marked effects at cholinergic, histaminergic and α_1-adrenoceptors and these effects are translated into the characteristic side effect profile of the tricyclic antidepressants.

Although severe suicide risk was an exclusion criterion for this study, there were seven suicide-related severe adverse events in the study (four in the fluvoxamine group including one completed and one uncompleted suicide attempt; and three in the clomipramine group). None of the events was considered to be related to the test medication. Despite the attempt to screen out patients who represented a severe suicide risk, it is to be expected that in such a severely depressed population as this (mean HAMD-17 of more than 30) some occurrences of suicidal ideation are likely.

In conclusion, fluvoxamine and clomipramine appear to be equally effective in this cohort of severely depressed patients; fluvoxamine, however, is better tolerated than clomipramine. With its better safety and tolerability profile, and hence probable superior compliance, fluvoxamine might be considered as a treatment of choice in this difficult-to-treat patient population.

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