Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomised comparison

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A double-blind, multinational study was conducted to compare the efficacy and safety of fluvoxamine and fluoxetine in outpatients with major depressive episode; 184 patients were randomised to fluvoxamine (100 mg/day) or fluoxetine (20 mg/day) for 6 weeks. Both drugs were effective and there were no statistically significant differences between them in the area under the curve of change from baseline in the Hamilton depression rating scale (HAMD) total score. However, the percentage of HAMD responders (≥50% decrease in HAMD total score) at week 2, the clinical global improvement severity of illness score at week 2 and the depression subscale of the irritability, depression and anxiety scale at weeks 1, 2 and 4, all showed significant advantages for fluvoxamine. During the last 2 weeks, fluvoxamine was significantly more effective in improving the HAMD sleep disturbance scale. Both drugs were well tolerated and there were no marked differences in their side effect profiles which were typical of SSRIs. Fluvoxamine and fluoxetine have similar efficacy and safety profiles in the treatment of major depressive episode; the findings of this study indicate that fluvoxamine may have a faster onset of action with respect to resolution of depressive symptoms and result in a better improvement in sleep quality.

INTRODUCTION

Although tricyclic antidepressants are effective in the treatment of depression, they are associated with a number of adverse events (such as dry mouth, tremor, low blood pressure and cardiovascular effects) that hinder compliance and may occasionally be dangerous. Selective serotonin reuptake inhibitors (SSRIs) generally show comparable efficacy to the tricyclic antidepressants (Anderson and Tomenson, 1994) but have a more benign safety profile (Montgomery et al., 1994). Despite a wealth of studies comparing the SSRIs with other classes of antidepressant and placebo, there have been few studies directly comparing one SSRI with another. However, available evidence suggests that all SSRIs do not share the same profile (Leonard, 1992; van Harten, 1993; Montgomery et al., 1994; Wilde et al., 1993; DeVane, 1995; Hindmarch, 1995; van den Berg, 1995; Price et al., 1996; Lane, 1997; Waldinger et al., 1998). For example, there are considerable differences in their chemical structures (van den Berg, 1995) and in their pharmacological (Leonard, 1992) and pharmacokinetic (van Harten, 1993) behaviour. Findings from meta-analyses have suggested there may be differences in efficacy between the SSRIs in certain patient subgroups, such as those with severe depression (Anderson and Tomenson, 1994). There is also evidence that there are differences in their safety profiles, with paroxetine and sertraline being associated with more sexual side-effects (Nemeroff et al., 1995; Lane, 1997; Waldinger et al., 1998) and fluoxetine being associated with more anxiety and nervousness (Aguglia et al., 1993).

This study, the results have which have not previously been published in full, was designed to directly compare the efficacy and safety of two widely
prescribed SSRIs, fluvoxamine and fluoxetine, in a large, multicentre, randomised, double-blind study in patients with a major depressive episode.

SUBJECTS AND METHODS

This was a prospectively randomised, double-blind, fixed-dose, parallel-group study conducted according to the principles of good clinical practice in 24 European centres.

Patients

Outpatients of either sex, aged 18–70 years old, meeting DSM-III-R (American Psychiatric Association, 1987) criteria for major depressive episode and having a total score of 17 or more on the 17-item Hamilton depression rating scale (HAMD) (Hamilton, 1967) were included in the study. Patients were excluded if they had: acute suicidal ideation or a serious suicide attempt in the previous 6 months; dementia; a history of epilepsy or seizures; concurrent or recent (6 months) alcoholism, other psychoactive substance abuse or drug-induced psychosis; were pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures; or if they had clinically uncontrolled hepatic, renal, pulmonary, endocrine or collagen disease. Also excluded were patients who had previously failed SSRI therapy or who required concomitant lithium, warfarin, heptatically metabolised antivitamin K agents, carbamazepine, theophylline, insulin or hypoglycaemic agents. Patients were required not to receive monoamine oxidase inhibitors or electroconvulsive therapy (ECT) in the 2 weeks prior to the study. All patients provided written or verbally witnessed informed consent.

Treatment

All patients entered a 7-day placebo run-in period that enabled previous antidepressant therapy to be withdrawn and identified any patients who were likely to respond to placebo. Eligible patients were then randomised to receive oral fluvoxamine (100 mg/day) or fluoxetine (20 mg/day) for 6 weeks; fluvoxamine (Solvay Pharmaceuticals) was given at a dose of 50 mg/day for the first 7 days of the study. Doses were as recommended by the respective manufacturers for the treatment of major depressive episode.

Oxazepam or nitrazepam were permitted as necessary for night-time sedation; no other psychotherapeutic treatments or ECT were permitted during the study.

Assessments

The primary efficacy parameter was the area under the curve (AUC) of the change in 17-item HAMD total score from baseline (expressed as HAMD weeks). Secondary efficacy variables comprised: 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 clinical global impression (CGI) (Guy, 1976) severity of illness and global improvement scores; the clinical anxiety scale (CAS) score; the irritability, depression and anxiety scale (IDAS) total score and subscores; the Beck’s scale for suicide ideation (SSI) score; sleep evaluation and the 17-item HAMD total and subtotal scores.

The 17-item HAMD was determined at screening, baseline and after 1, 2, 4 and 6 weeks (or upon premature termination) of treatment; all other efficacy variables were determined at all visits except screening. Adverse events were documented at baseline and at each subsequent visit; vital signs and weight were measured at baseline and at the final visit and a physical examination was conducted at screening and at the final visit.

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) and the per-protocol (PP) sample (i.e. subset of ITT patient sample who did not have any serious deviation from the study protocol). Analyses of secondary efficacy variables were performed on the ITT efficacy sample only. All analyses were performed using visit-wise (observed cases; OC) and last observation carried forward (LOCF) data. The Wilcoxon two-sample test was used to analyse both the primary and the secondary efficacy variables. All tests were two-sided. Differences with $p$ values $\leq 0.05$ were considered to be statistically significant.

RESULTS

One-hundred and eighty-four patients were randomised to treatment, 90 to fluvoxamine (33 male, 57 female; mean age 42 years) and 94 to fluoxetine (35 male, 59 female; mean age 42.1 years); there were no significant differences between the two treatment groups with respect to gender, race, age distribution, body weight or height. Four patients in the fluvoxamine group and three in the fluoxetine group had no
post-baseline assessment and were therefore excluded from the ITT efficacy sample (86 fluvoxamine patients and 91 fluoxetine patients). A further four patients in the fluvoxamine group and seven in the fluoxetine group had major deviations from the protocol and were excluded from the PP sample (82 fluvoxamine patients and 84 fluoxetine patients). Reasons for exclusion were failure to meet inclusion or exclusion criteria (3 fluvoxamine, 3 fluoxetine patients), disallowed prior medication (1 fluvoxamine and 3 fluoxetine patients) and baseline HAMD less than 17 (1 fluoxetine patient). Sixteen patients in the fluvoxamine group and ten in the fluoxetine group withdrew from the study prematurely.

Efficacy

Fluvoxamine and fluoxetine both resulted in a significant improvement in depressive symptoms.

Primary variable. The mean AUC of the change from baseline in 17-item HAMD total score decreased progressively during the study in both groups. After 6 weeks of treatment, the mean AUC value was −189 HAMD weeks in the fluvoxamine group and −175 HAMD weeks in the fluoxetine group. HAMD scores were reduced from a mean of 22.3 and 22.2 at baseline in the fluvoxamine and fluoxetine groups respectively to 10.0 and 11.3, respectively, at day 42. There were no statistically or clinically significant differences between the treatments at any point or in any of the population samples analysed.

Secondary variables. The secondary efficacy variables confirmed the overall effectiveness of fluvoxamine and fluoxetine, but revealed some benefits of fluvoxamine over fluoxetine. The data are presented for the LOCF analysis; similar results were obtained from the OC analysis.

Percentage of 17-item HAMD responders. A patient was considered to be a responder if they had a reduction in 17-item HAMD total score of at least 50% from baseline. Patients appeared to respond better to fluvoxamine than to fluoxetine, especially during the early stages of treatment (Figure 1); after 2 weeks of treatment, the percentage of patients who responded was significantly higher with fluvoxamine than with fluoxetine (29% vs 16%; \( p \leq 0.05 \)). At the end of the study, the majority (approximately 60%) of patients in both groups were considered to be responders (Figure 1).

CGI severity of illness score. The overall severity of illness was progressively reduced in both groups from ‘moderately to markedly ill’ to ‘borderline to mildly ill’. However, the reduction in the mean score was greater with fluvoxamine than with fluoxetine at all assessments, the difference achieving statistical significance (\( p \leq 0.05 \)) at week 2 (Figure 2).

CGI global improvement score. Again, a continuous improvement was seen in both groups; at the end of the study, the mean score was 2.0 (much improved) in the fluvoxamine group and 2.2 (minimally to much improved) in the fluoxetine group. There were no significant differences between the treatments at any point.
CAS total score. The mean score decreased progressively in both groups. In the fluvoxamine group, the mean score fell from 12.6 at baseline to 6.9 at the end of the study; the corresponding reduction in the fluoxetine group was from 13.1 to 7.7. There were no significant differences between the treatments at any point.

IDAS total score and subscores. The IDAS total and subscores, which assess levels of irritability, depression and anxiety, all fell progressively during the study. As shown in Table 1, the reduction in the mean total score was greater with fluvoxamine than with fluoxetine at all time points. Mean changes in the anxiety, irritability and depression subscores were also greater with fluvoxamine at all time points; a statistically significant difference being achieved with the depression subscore at weeks 1, 2 and 4.

Beck’s SSI score. The mean score decreased progressively in both groups; at the end of the study, it had fallen from 4.7 to 1.6 in the fluvoxamine group and from 5.4 to 2.1 in the fluoxetine group. There were no significant differences between the treatments at any point.

Sleep evaluation. There was a gradual improvement in mean sleep evaluation scores in both groups over the course of the study. As shown in Figure 3, the improvement in the quality of sleep was more pronounced with fluvoxamine at weeks 4 and 6, although the differences did not achieve statistical significance. Overall, slightly more than half of all patients (51% in both groups) used a hypnotic drug during the study. The most frequently used hypnotic was oxazepam (25% in the fluvoxamine group and 30% in the fluoxetine group) which was allowed in the protocol.

17-item HAMD total and subtotal scores. The mean total score decreased progressively in both groups; at the end of the study, the mean score had fallen from 22.3 to 10.0 in the fluvoxamine group and from 22.2 to 11.3 in the fluoxetine group. There were no significant differences between the treatments at any point.

Fluvoxamine was associated with a greater reduction in anxiety/somatization and cognitive disturbance subscores, although there were no statistically significant differences between the groups. The improvement in the retardation subscore was similar in each group. However, in agreement with the sleep evaluation score, fluvoxamine was more effective than fluoxetine at improving the quality of sleep. The improvement in the sleep disturbance subtotal was statistically significantly greater with fluvoxamine than with fluoxetine at week 4 (−2.3 vs −1.6; \( p \leq 0.05 \)) and at the end of the study (−2.4 vs −1.8; \( p \leq 0.05 \)) and was of borderline significance \( (p = 0.052) \) at week 1 (Figure 4).

Safety

Fluvoxamine and fluoxetine were both well tolerated. There was a similar incidence of adverse events in each group, the majority of which were mild or moderate. The most frequently reported treatment-emergent signs and symptoms (TESS) in both groups were nausea (24% with fluvoxamine and 20% with fluoxetine) and headache (13% with fluvoxamine and 14% with fluoxetine). No other TESS occurred in more than

| Table 1. Mean change in IDAS total and subscores (ITT sample; LOCF analysis) |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                           | 1            | 2            | 4            | 6            |
| **Total score**           |              |              |              |              |
| Fluvoxamine (n = 66)      | −3.8         | −7.9         | −11.6        | −12.4        |
| Fluoxetine (n = 76)       | −2.5         | −4.7         | −8.4         | −10.7        |
| **Anxiety**               |              |              |              |              |
| Fluvoxamine (n = 68)      | −1.0         | −2.0         | −3.5         | −3.8         |
| Fluoxetine (n = 77)       | −0.8         | −1.6         | −2.9         | −3.6         |
| **Irritability**          |              |              |              |              |
| Fluvoxamine (n = 67)      | −1.6         | −3.4         | −4.6         | −4.7         |
| Fluoxetine (n = 76)       | −1.3         | −2.4         | −3.8         | −4.6         |
| **Depression**            |              |              |              |              |
| Fluvoxamine (n = 67)      | −1.2\( ^a \)  | −2.3\( ^a \)  | −3.3\( ^a \)  | −3.6         |
| Fluoxetine (n = 78)       | −0.4         | −0.8         | −1.7         | −2.5         |

\( ^a p \leq 0.05 \) fluvoxamine versus fluoxetine.
10% of patients in either group. Sexual dysfunction was reported by one patient in the fluvoxamine group (ejaculatory abnormality) and two in the fluoxetine group (ejaculatory abnormality and impotence).

There were four patients with serious adverse events. One (anxiety and alcohol intoxication) occurred in the fluvoxamine group and was considered unrelated to treatment and three occurred in the fluoxetine group (anorexia and stomach complaints that were considered highly probably related to treatment in one patient, a suicide attempt that was considered possibly related to treatment in another and a suicide attempt that was considered unrelated to treatment in a third patient).

There were no clinically significant changes in vital signs, body weight or physical condition in either group.

DISCUSSION

Fluvoxamine (100 mg/day) and fluoxetine (20 mg/day) both resulted in a progressive, clinically significant improvement in 17-item HAMD total score over the course of treatment. However, analysis of secondary efficacy parameters indicated that fluvoxamine may have some advantage over fluoxetine during the early phase of treatment: the percentage of 17-item HAMD responders, the CGI severity of illness score and the IDAS depression subscore all showed a significantly greater improvement with fluvoxamine after 2 weeks of treatment. However, whilst the differences between the two treatments were maintained after 4 weeks of treatment, they remained statistically significant only for the IDAS depression subscore.

Fluvoxamine also appeared to have a more beneficial effect on sleep quality, especially after 4 weeks of treatment. The reduction in sleep disturbance was significantly greater with fluvoxamine than with fluoxetine from week 4 onwards according to the 17-item HAMD sleep disturbance score. Moreover, fluvoxamine was clearly superior to fluoxetine on the sleep evaluation score from week 4 onwards. Patients treated with fluvoxamine showed a progressive improvement in sleep quality throughout the study, whilst those given fluoxetine showed little improvement after the second week. These findings are consistent with clinical experience suggesting that fluvoxamine causes less sleep disturbance and is less activating than fluoxetine (Baldessarini and Marsh, 1990; Rickels and Schweizer, 1990; Freeman, 1991; Aguglia et al., 1993; Lane et al., 1995).

Both treatments improved anxiety symptoms, irritability, suicidal ideation, retardation and cognitive disturbance. A somewhat greater improvement in anxiety, irritability and cognitive disturbance was observed with fluvoxamine, but these differences did not achieve statistical significance. Again, this is consistent with the propensity of fluoxetine to cause activation (Baldessarini and Marsh, 1990; Rickels and Schweizer, 1990; Aguglia et al., 1993; Lane et al., 1995).

There are a number of clear differences between fluvoxamine and fluoxetine. They have completely different chemical structures and pharmacokinetic and pharmacological profiles. For example, fluoxetine has a considerably longer half-life than fluvoxamine (2–4 days vs 17–22 h) (Preskorn, 1997) and is the only SSRI with a metabolite that has significant clinical activity (Lane et al., 1995). In addition, fluoxetine reduces dopamine synthesis (Baldessarini and March, 1990) whilst fluvoxamine has no effect on dopaminergic neurotransmission.

However, there have been very few studies directly comparing the efficacy of one SSRI with another. This direct, double-blind comparison of fluvoxamine and fluoxetine in patients with a major depressive episode was therefore designed to provide data on potential areas of differentiation between the efficacy of the two treatments. Thus, a wide range of variables were selected in order to assess all the characteristic symptoms of major depressive episode including depression, sleep disturbance, irritability, anxiety, cognitive disturbance, retardation and suicidal ideation.

A number of previous studies have suggested that the SSRIs may show some differences in their safety profiles. Thus, sertraline (Nemeroff et al., 1995) and paroxetine (Waldinger et al., 1998) appear to be
associated with more sexual side-effects than fluvoxamine, whilst fluoxetine (Aguglia et al., 1993; Stokes, 1993; DeVane, 1995) has been reported to cause more anxiety and nervousness than the other SSRIs. Similarly, in accordance with its pharmacological profile, paroxetine (Dunbar, 1989; Kiev and Feigher, 1997) tends to be associated with a higher incidence of anticholinergic effects (such as sedation, sweating and dry mouth) than the other SSRIs. However, neither fluvoxamine nor fluoxetine have adverse cardiac side-effects, as measured using both ECG and echocardiography, a more direct reflection of cardiac functioning (Strik et al., 1998). In the current study, fluvoxamine and fluoxetine were equally well tolerated and had very similar safety profiles. Nausea and headache were the most common adverse events and were reported by similar proportions of patients in each group.

In conclusion, fluvoxamine 100 mg/day is at least as effective and safe as fluoxetine 20 mg/day in the treatment of major depressive episode and may be superior in terms of onset of action and improvement in sleep quality.

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REFERENCES


