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# Fluoxetine vs. clomipramine in depressed patients: a controlled multicentre trial

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**Summary**

A sample of 120 patients, all of whom met DSM-III criteria for major unipolar depressive disorder, were randomly allocated to two treatment groups. Sixty patients were treated with fluoxetine and 60 with clomipramine during a 6-week period. No significant difference was found in antidepressant efficacy, with improvement occurring on both drugs. Important differences were found in the side-effects profile of each group, their incidence being significantly lower and tending to disappear during the course of treatment in the group of patients treated with fluoxetine.

*Key words:* Fluoxetine vs. clomipramine; Antidepressant effect; Side effects; Major depression

## Introduction

Over the years research on the two main neurotransmitters involved in depressive illness, noradrenaline (Schildkraut, 1965) and 5-hydroxytryptamine (5-HT; serotonin; Van Praag, 1977), has greatly improved our understanding of the biochemical process which take place at the synaptic level as well as providing a possible explanation of how antidepressant compounds work.

The mode of action of classical tricyclic antidepressants (TCA) is primarily based upon their combined action on noradrenergic and serotonergic systems.

The introduction of compounds with a specific noradrenergic or serotoninergic uptake inhibitory action has given physicians not only a valuable tool for the treatment of depressive illness, but also a useful instrument for the better under-

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standing of the relationship between a particular neurotransmitter and a wide variety of psychiatric conditions, in spite of the great methodological difficulties involved in this line of research.

Fluoxetine, a highly selective serotonin reuptake inhibitor (Wong et al., 1974, 1975), has been shown in several controlled trials to have antidepressant efficacy equivalent to amitriptyline (Chouinard, 1985) and imipramine (Stark and Hardison, 1985). It has also been claimed that fluoxetine has a different side-effects profile to that of tricyclic antidepressant drugs. This is possibly due to a minimal affinity for muscarinic, histaminergic, dopaminergic, noradrenergic and serotonergic receptors (Stark and Hardison, 1985) of both fluoxetine and its active metabolite desmethyl fluoxetine (Fuller and Wong, 1977).

We considered it interesting to undertake a double-blind study of fluoxetine versus clomipramine. We particularly wanted to know if the antidepressant efficacy of fluoxetine was similar to that of clomipramine and compare their side-effects profile.

We chose clomipramine as the control drug because of all the available tricyclic antidepressant drugs it has the greatest effect on the reuptake of serotonine. Also, although clomipramine is a widely prescribed antidepressant, this comparison has not been made before.

## Method

As required by the protocol, a total of 120 patients, who met all inclusion criteria, were randomly allocated to either fluoxetine or clomipramine treatment. The trial was carried out simultaneously in three different centres. The investigators had previously agreed on the inclusion and exclusion criteria, rating scales, measuring criteria and the remaining study procedures.

Patients had to meet DSM-III criteria for major unipolar depressive disorder and be between 18 and 65 years of age. Severity of the depression had to be at least 17 points on the first 17 items of the Hamilton rating scale at the initial interview and also after the placebo wash-out period, during which a maximum decrease of 20% in Hamilton score was allowed, thus eliminating possible placebo responders. A score of at least 8 on the Raskin scale was required and this had to be greater than the Covi Anxiety Scale score.

Exclusion criteria were: a previous history of manic episodes, pregnancy, lactation, or women of child-bearing age without adequate contraceptive measures, glaucoma and chronic urinary retention, brain or other significant organic illness including hyperthyroidism, hypertension treated with guanethedine, reserpine, clonidine or methyldopa, schizophrenia, other mental illness or severe suicidal risk, recent history (less than 1 year) of drug or alcohol abuse, concurrent treatment with other psychotropic drugs including lithium, use of monoamine oxidase inhibitors less than 2 weeks prior to the start of the trial and a family history of phospholipidosis.

All patients were informed of the scope of the study and agreed to sign a consent form.

Patients considered to be potentially suitable for inclusion in the study started with a placebo wash-out period of 5–10 days. After eliminating the placebo responders, the remaining 120 patients were randomly allocated to either the fluoxetine or the clomipramine group. The trial lasted for 6 weeks and efficacy was measured at weekly visits at which patients were scored by means of the Hamilton Rating Scale for Depression (HRS-D), Raskin Depression Scale, Covi Anxiety Scale, Clinical Global Impression (CGI) and Patients Global Impression (PGI). To evaluate safety, all adverse experiences were recorded and vital signs measured at each visit. Any concomitant medication was also controlled. Occasionally 10 mg of clorazepate was allowed for transitory insomnia. In addition, on weeks 0, 3 and 6, biochemical, haematological and urine clinical laboratory tests were monitored. Chest X-rays were performed at the beginning and the end of the study period.

Active treatment lasted for 6 weeks. All patients were given a weekly supply of apparently identical capsules in seven double envelopes marked 'morning' and 'midday' dose, the contents of one envelope to be taken daily. Boxes had to be returned at the following visit, together with what was left of the weekly clorazepate allowance. For the first 4 weeks, patients received a fixed daily dose of either 20 mg of fluoxetine or 100 mg of clomipramine, after a gradual increase

in dosage lasting for the first week in the case of the clomipramine group. During the last 2 weeks of the study unresponsive patients could be given more capsules, bringing the dosage in the fluoxetine group up to 40 mg daily, whilst in the clomipramine group active dosage was unchanged, patients receiving more placebo capsules.

## Results

The final data refer to a pool of 120 patients from three different centres. Analysis of variance showed no significant interaction among these centres.

No significant differences were found between the two treatment groups each of which consisted of 60 patients, 25% males, 75% females in the fluoxetine group, 30% males, 70% females in the clomipramine group. Mean age was 46.3 years, range 26–65 in the fluoxetine group and 46.0 years, range 24–65 in the clomipramine group. The initial HRS-D score was $25.0 \pm 5.3$ in the fluoxetine group and $26.4 \pm 4.9$ in the clomipramine group. There were no significant differences in demographic characteristics, history of previous episodes, length and severity of current episode, subtype of depression and vital signs.

Fig. 1 presents the mean values of the HRS-D total scores at weekly control visits of patients

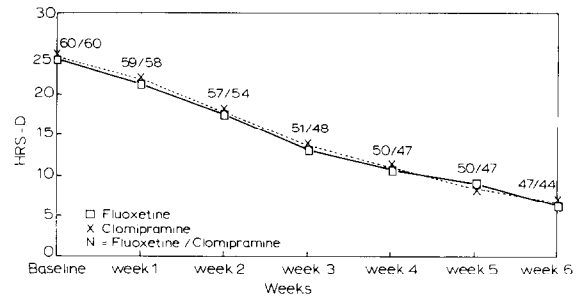


Fig. 1. Weekly mean HRS-D scores.

remaining in the study, showing a similar improvement in both treatment groups. The scores obtained on the scales used to evaluate the efficacy of both treatments at weeks 0, 2, 4 and 6 of active treatment are shown in Table 1.

Fig. 2 shows the mean differences between baseline and final score in different measuring scales: HRS-D, Raskin and CGI-severity. All patients, including those who had discontinued treatment, were included in this statistical analysis, last visit scores being carried forward to the final assessment.

Both treatments proved to be effective and generally similar. During treatment, a significant decrease in the HRS-D scores was observed in the two groups. After 6 weeks of active treatment the mean values decreased by 16 points from the baseline. There were no significant differences

TABLE 1

BASELINE MEANS AND MEAN CHANGES IN EFFICACY MEASURES FOR ALL PATIENTS

| Variable | Drug | Week 0 (mean ± SD) | Week 2 (mean ± SD) | Week 4 (mean ± SD) | Week 6 (mean ± SD) |
|---|---|---|---|---|---|
| HRS-D | FLX | 24.30 ± 4.90 | 17.53 ± 6.35 * | 10.68 ± 5.94 * | 6.21 ± 4.57 * |
| | CLM | 24.60 ± 5.15 | 17.93 ± 6.71 * | 11.04 ± 5.93 * | 6.66 ± 4.93 * |
| Raskin | FLX | 10.25 ± 1.44 | 7.96 ± 2.06 * | 6.06 ± 2.14 * | 4.55 ± 1.78 * |
| | CLM | 10.40 ± 1.84 | 8.31 ± 2.28 * | 6.30 ± 2.17 * | 4.64 ± 1.69 * |
| Covi | FLX | 7.15 ± 2.03 | 6.46 ± 2.3 * | 5.01 ± 1.7 * | 4.26 ± 1.4 * |
| | CLM | 7.80 ± 2.28 | 6.35 ± 2.3 * | 5.06 ± 2.0 * | 4.27 ± 1.7 * |
| CGI-severity | FLX | 4.48 ± 0.67 | 3.70 ± 1.07 * | 2.68 ± 1.17 * | 1.81 ± 1.10 * |
| | CLM | 4.66 ± 0.75 | 3.85 ± 1.05 * | 2.85 ± 1.18 * | 1.75 ± 0.99 * |
| CGI-improvement | FLX | 3.98 ± 0.62 | 2.86 ± 1.15 * | 1.84 ± 0.91 * | 1.36 ± 0.70 * |
| | CLM | 3.82 ± 0.70 | 3.11 ± 2.80 * | 2.08 ± 1.08 *# | 1.41 ± 0.72 * |
| PCI | FLX | 4.1 ± 0.8 | 3.24 ± 1.04 * | 3.22 ± 0.97 * | 2.95 ± 1.07 * |
| | CLM | 4.0 ± 1.0 | 3.37 ± 1.00 * | 3.41 ± 1.13 | 2.79 ± 0.98 * |

* Significantly different from baseline ($P < 0.01$), Wilcoxon signed-rank test (unilateral).

\# Significant difference between the treatment groups ($P < 0.05$), Wilcoxon rank-sum test (bilateral).

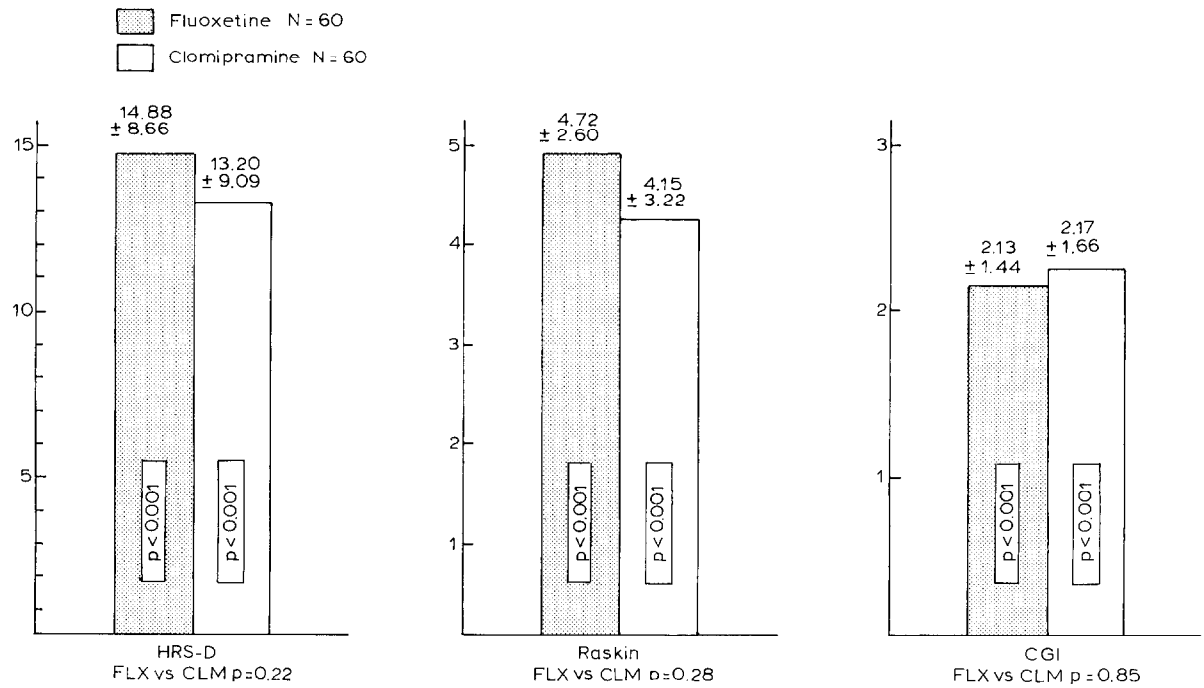


Fig. 2. HRS-D, Raskin and CGI-severity scores: mean improvement from baseline to final visit. The treatment groups were compared using the two-tailed Wilcoxon rank test. Improvement for each group was analysed with the one-tailed Wilcoxon signed-rank sum test.

between the two groups at any time. From the second week of active treatment, a significant improvement was found in all efficacy measures in both groups. A slight advantage in favour of the fluoxetine group could be seen at week 4, when a significant difference compared to baseline in the PGI score in the fluoxetine group ($P < 0.001$) was not found in the clomipramine group. Differences between the two groups were only found at week 4 in the CGI. In the CGI, a significantly improved response was observed in the fluoxetine group as compared with the clomipramine group ($P < 0.05$). These differences were not maintained at week 6.

At week 6, 83% of the patients in the fluoxetine group scored 1 or 2 on the 7-point Severity of Illness scale of the CGI, compared with only 50% in the clomipramine group. This difference is significant at the $P < 0.002$ level on the Wilcoxon test.

Important differences were found between the two groups in the number of adverse effects and their profile. Patients taking fluoxetine reported significantly fewer side effects than those taking clomipramine, this difference becoming increasingly significant in the later weeks of the study.

Table 2 shows the percentages of side effects most commonly reported, including the statistical difference between groups and between weeks 1 and 6 of the study. At week 6, only the absence of side effects reported in the fluoxetine group and the nausea reported in both groups showed statistically significant differences in relation to week 1. There were also statistically significant differences between the two groups at week 6 in the number of patients free of side effects (fluoxetine 57.4%, clomipramine 31.8%, $P < 0.05$) and the incidence of dry mouth (fluoxetine 6.4%, clomipramine 40.9%, $P < 0.001$), in favour of fluoxetine.

Discontinuations are shown in Table 3. There were no significant differences in number of and reasons for discontinuation between groups and severe adverse effects were not the cause of this in either group. The use of clorazepate showed no significant differences between the two groups.

TABLE 2

MOST COMMON ADVERSE EFFECTS IN FLUOXETINE- AND CLOMIPRAMINE-TREATED PATIENTS: DIFFERENCES BETWEEN WEEKS 1 AND 6 AND BETWEEN GROUPS OF TREATMENT

| | | Week 1 | Week 6 |
|---|---|---|---|
| Absence | FLX | 29.30 | 57.40 * |
| | CLM | 15.50 | 31.80 # |
| Anxiety | FLX | 10.30 | 0.00 |
| | CLM | 1.70 | 0.00 |
| Insomnia | FLX | 1.70 | 0.00 |
| | CLM | 3.40 | 0.00 |
| Nausea | FLX | 37.90 | 0.00 * |
| | CLM | 27.60 | 2.30 * |
| Nervousness | FLX | 5.20 | 4.30 |
| | CLM | 8.60 | 6.80 |
| Constipation | FLX | 5.20 | 2.10 |
| | CLM | 24.10 | 11.40 |
| Dry mouth | FLX | 20.70 | 6.40 |
| | CLM | 55.20 | 40.90 # |
| Headache | FLX | 13.80 | 6.40 |
| | CLM | 13.80 | 11.40 |
| Sweating | FLX | 3.40 | 0.00 |
| | CLM | 12.10 | 9.10 |
| Tremor | FLX | 10.30 | 4.30 |
| | CLM | 6.90 | 11.40 |

* $P < 0.05$ week 6 vs. week 1, $\chi^2$ test with Yates' correction.
\# $P < 0.05$ fluoxetine vs. clomipramine, $\chi^2$ test with Yates' correction.

With regard to vital signs, patients on fluoxetine experienced a significant mean weight loss of 1.04 kg during the 6 weeks of active treatment. Both treatments caused a decrease in diastolic pressure and clomipramine treatment also produced a significant decrease in systolic pressure.

Laboratory studies showed no significant variations for either treatment group.

TABLE 3

ANALYSIS OF DISCONTINUATIONS

| | Fluoxetine ($n$) | Clomipramine ($n$) |
|---|---|---|
| Baseline | 60 | 60 |
| Completers | 47 | 44 |
| Dropouts due to: | 13 * | 16 * |
| adverse reactions | 2 | 6 |
| lack of efficacy | 3 | 0 |
| patient decision | 1 | 4 |
| protocol violation | 7 | 6 |

* $P = 0.669$ (NS), $\chi^2$ test.

## Discussion

Our data are in agreement with the results of other previously published papers (Altamura et al., 1988; Wernicke et al., 1987) which suggest that a single daily dose of 20 mg of fluoxetine has a clear antidepressant effect. Our results support this conclusion and demonstrate that the antidepressant efficacy of a daily dose of 20 mg of fluoxetine is comparable to that of a daily dose of 100 mg of clomipramine in the treatment of outpatients with major depressive disorders.

After 4 weeks' treatment, the dosage could be increased on the investigator's criteria. In the fluoxetine group the dosage was increased in 18 patients to 40 mg daily, whilst eight patients on clomipramine continued to take the same dosage plus placebo. The fact that there were, at the time of setting up the trial, prior to the work of Wernicke et al. in 1987 and Altamura et al. in 1988, no generally agreed criteria as to what represented the most effective therapeutic dosage of fluoxetine justified this, whilst it was considered that a fixed daily dose of 100 mg of clomipramine is therapeutically effective and within the manufacturer's recommended dosage range. Previous studies have shown that as little as 75 mg daily of clomipramine in healthy volunteers results in a marked 5-HT platelet uptake inhibition (Waldmeier et al., 1976). A similar 5-HT platelet uptake inhibition was found in our own study of melancholic depressive patients treated with a daily dose of 100 mg of clomipramine (Sarrias et al., 1987). We consider that patients who fail to improve on 100 mg daily of clomipramine derive more clinical benefit from the addition of drugs such as lithium salts to this treatment than from an increased dosage of clomipramine. However, in many countries a larger dose is used. A larger dose of clomipramine might have increased side effects to the extent of seriously endangering the double-blind nature of the trial. No significant differences were found on any of the scales as a result of the increase in fluoxetine dosage.

The incidence of side effects was significantly lower in the group of patients treated with fluoxetine and most of these (nausea, anxiety, headache, etc.) tended to disappear during treat-

ment. On the other hand, in patients from the clomipramine group, the cholinergic effects were present throughout treatment. We believe that the different side-effects profile could explain the greater proportion of totally recovered patients (scores 1 and 2 in Severity of Illness in the CGI) in the fluoxetine group by the end of the study, as patients tend to confuse side effects from antidepressant drugs with symptoms of their illness. This could also be the reason for the differences shown between the two groups at week 4 in the closer analysis.

Fluoxetine appears to be a valid alternative to the classic antidepressant drugs and somehow emphasises the possible role of the serotonergic system in depressive disorders.

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