Fluoxetine in Early Poststroke Depression
A Double-Blind Placebo-Controlled Study
L. Wiart, MD; H. Petit, MD; P.A. Joseph, MD; J.M. Mazaux, MD; M. Barat, MD

Background and Purpose—Early poststroke depression (PSD) is a frequent and specific entity that impairs the rehabilitation and functional recovery of hemiplegic patients. This trial was designed to study the efficacy and tolerance of fluoxetine (FLX) in the treatment of early PSD.

Methods—This was a multicenter, double-blind, placebo-controlled study. Recent hemiplegic patients (<3 months) suffering from major depressive disorder (determined by International Classification of Diseases, 10th Revision, and Montgomery-Asberg Depression Rating Scale [MADRS] >19) were randomized to receive either 20 mg/d fluoxetine (FLX) or placebo for 6 weeks. Patients were evaluated by use of the Motricity Index, Mini-Mental State Examination, Functional Independence Measure, and MADRS. Statistical analysis was performed by using an intent-to-treat approach comparing the 2 groups at day 0 (baseline) and days 15, 30, and 45 (end point).

Results—Of 121 patients screened, 31 were included in the study, 16 in the FLX group and 15 in the placebo group. There were no significant differences in baseline characteristics among the 2 groups. The FLX-treated patients compared with placebo-treated patients demonstrated significant improvement in mean MADRS scores at end point (11.8±6.7 [mean±SD] versus 18.7±10.0, respectively; P=0.05). FLX-treated patients compared with placebo-treated patients also demonstrated greater response rate (62.5% versus 33.3%, respectively) and greater mean decrease of MADRS (16.6 versus 8.4, respectively; P=0.02). There were no differences in motor, cognitive, or functional improvement and no significant side effects after FLX treatment, except for a patient with a moderate and transient increase of transaminases.

Conclusions—FLX is an efficacious and well-tolerated treatment for early PSD. Further research is needed to evaluate the efficacy and safety of long-term treatment in this population. (Stroke. 2000;31:1829-1832.)

Key Words: antidepressant agents ▪ cerebrovascular disorders ▪ depression ▪ fluoxetine

Poststroke depression (PSD) is a common disorder, affecting 30% to 50% of hemiplegic patients within 1 year of their cerebral infarction.1–4 In the early stage, ie, during the first 3 to 4 months after a stroke, PSD poses serious problems, such as worsened functional1,7 and vital prognoses1,6 as well as worsened quality of life of the patient and caregiver.7 Psychological factors that may contribute to PSD include the grieving process and adaptation to the handicap.1,8 Moreover, the area of infarction may affect brain regions that have been empirically associated with depression.1,2,8–10 This distinguishes PSD from depression in healthy subjects and indicates the need for special controlled studies in this population. Surprisingly, few such studies,4 controlled11–14 and 4 open label,15–18 have been conducted with antidepressants.2 In our previous open-label trial,18 15 recent (<3 months) hemiplegic patients treated with fluoxetine (20 mg/d) showed a response rate of 73% at end point (day 45). The present study reports the results of a controlled study undertaken to verify our open-label results.

Subjects and Methods
The trial was a multicenter, double-blind, controlled study comparing fluoxetine (20 mg/d) with placebo. The study protocol was approved by the ethics committee of the University of Bordeaux Medical School Hospital Center. The study was designed by a group of university hospital doctors, including a neurorehabilitation specialist, a neurologist, a psychiatrist, and a statistician.

Patients selected for the present study had been hospitalized in a rehabilitation unit. Each one was evaluated 15 days after his/her arrival by a neuropsychiatrist previously trained in clinical and psychiatric evaluation. The patients had a recent (<3-month) single ischemic or hemorrhagic stroke, which was documented by cerebral CT scanning or MRI before enrollment. Patients exhibited major depressive disorder depression, as assessed by the International Classification of Diseases, 10th Revision (ICD-10) and the Montgomery-Asberg Depression Rating Scale (MADRS).19 Inclusion required a MADRS >19 because of the high rate of organic symptoms in this population. All antidepressant or neuroleptic drugs were stopped 10 days before enrollment. Each patient signed an informed consent.

Exclusion criteria were severe cognitive deficit assessed by a Mini-Mental State Examination (MMS)20 <23, severe aphasia, contraindication to the use of fluoxetine, history of severe psychiatric problems (which required hospitalization), chronic alcoholism, previous stroke, or chronic associated handicapping pathology.

Treatment lasted up to 45 days (end point) and was given in the form of identical white capsules containing 20 mg of either fluoxetine or placebo, delivered in boxes coded by the central pharmacy of the University Hospital complex of Bordeaux. Evaluation was...
TABLE 1. General Characteristics of Fluoxetine and Placebo Groups at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine (N=16)</th>
<th>Placebo (N=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.3±7.1</td>
<td>68.9±11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Time since stroke, d</td>
<td>47.1±21.6</td>
<td>47.7±19.9</td>
<td>NS</td>
</tr>
<tr>
<td>Side of lesion, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>12</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td>4</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Impairment, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphasia</td>
<td>4</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Neglect</td>
<td>10</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>MI, /100</td>
<td>29.6±23</td>
<td>43.4±25.5</td>
<td>NS</td>
</tr>
<tr>
<td>MMS, /30</td>
<td>23.5±3.5</td>
<td>24.1±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>FIM, /126</td>
<td>62.7±17.6</td>
<td>72.3±20.9</td>
<td>NS</td>
</tr>
<tr>
<td>MADRS, /60</td>
<td>28.5±7.7</td>
<td>27.2±6.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of patients. Cutoff scores are as follows: MMS, <23; FIM, <90; and MADRS, >19.

Conducted at day 0 (the day before the start of the treatment, baseline) and then at days 15, 30, and 45 (the last day of treatment, end point). This evaluation included a clinical interview, a clinical examination, and the following standardized tests: Motricity Index (MI), MMS, Functional Independence Measure (FIM), and MADRS. Side effects were assessed qualitatively and quantitatively, and a complete blood count, liver test, and renal function test were carried out at each visit. An intent-to-treat statistical analysis was conducted in which the last visit recorded was used as an end point. Baseline-to-endpoint changes were compared between the 2 groups. The primary outcome measure was the mean change in MADRS. The secondary outcome measures were percentage of responders (patients whose MADRS improved by >50% at end point) and mean changes in MI, MMS, and FIM at end point. The nonparametric Mann-Whitney test was used for continuous variables, and the χ² or Fisher test was used for categorical variables. The significance level was set at P<0.05.

Results

Of 121 screened patients, 31 met inclusion criteria and were consecutively randomized in the study. Sixteen patients received fluoxetine and 15 received placebo. Two fluoxetine-treated patients were discontinued, one for increased hepatic alanine aminotransferase and aspartate aminotransferase levels and the other for noncompliance. The end-point evaluation for these 2 patients was at day 15.

At baseline, the 2 groups were similar (Table 1), without any clinically relevant differences. Patients had a major depressive disorder and severe hemiplegia with substantial motor, cognitive, and functional deficits.

Table 2 and Figure 1 show that fluoxetine-treated patients demonstrated significantly greater improvement in mean MADRS scores at end point than did placebo-treated patients (11.8±6.7 [mean±SD] versus 18.7±10.0, respectively; P=0.05). Fluoxetine-treated patients also demonstrated significantly greater mean changes (baseline to end point) on MADRS than did the placebo-treated patients (16.6±8.1 versus 8.4±7.8, respectively; P=0.02). Figure 2 shows a trend for greater response in the fluoxetine group than in the placebo group (62.5% versus 33.3%, respectively; P=0.1). There was a global improvement of MI, MMS, and FIM.

TABLE 2. Clinical Course in Fluoxetine and Placebo Groups

<table>
<thead>
<tr>
<th>Days of Treatment</th>
<th>Fluoxetine (N=16)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MADRS, /60</td>
<td>ΔMADRS</td>
</tr>
<tr>
<td>0</td>
<td>28.5±7.7</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>20.9±8</td>
<td>7.6±5.2</td>
</tr>
<tr>
<td>30</td>
<td>15±8.9</td>
<td>13.4±9.6</td>
</tr>
<tr>
<td>45</td>
<td>11.8±6.7†</td>
<td>16.6±8.2†</td>
</tr>
</tbody>
</table>

Values are mean±SD. ΔMADRS indicates difference of MADRS between days 0, 15, 30, and 45. Cutoff scores are as follows: MADRS, >19; responders, decrease of MADRS score >50%; MMS, 23 (general cognitive impairment if <23); and FIM, 90 (independent if >90).

* P=0.05; † P=0.02.
scores in each group (Table 2); however, there were no significant differences between the 2 groups. Side effects (Table 3) were reported in both groups. The side effects were reported early and abated after 2 patients had a seizure. The treatment was continued in the latter 2 patients without any new seizure.

Discussion

This placebo-controlled study showed fluoxetine to be an effective and safe antidepressant treatment for early PSD. We confirmed the results of our preliminary open-label trial18 and of other studies15–17 showing that fluoxetine (20 mg/d) improved depression in 60% to 75% of the patients. In a recent review, Robinson2 discussed an unpublished study comparing fluoxetine, nortriptyline, and placebo that also reported successful antidepressant treatment of PSD. However, few details of the responses were reported.

The placebo-controlled studies of other antidepressants in PSD found evidence for a good activity of nortriptyline,11 trazodone,12 citalopram,13 and methylphenidate14 on depressive symptoms. Side effects were frequent with tricyclic drugs1,11 and were problematic with long-term methylphenidate use.14 As a result, many authors2,13,15–17 advise the use of selective serotonin recapture inhibitors. The response latency is from 4 to 6 weeks for all of these agents except methylphenidate, whose mechanism of action is different. This corresponds to typical response latencies of antidepressants in able-bodied subjects. Of note is the high level of placebo response (33.3%) at end point, which can be explained in part by the spontaneous neurological improvement and by the rehabilitation care received by the patients. This rate of placebo response is typical of many controlled trials of antidepressants and illustrates the importance of including a placebo control to determine the true potential antidepressant efficacy in the actively treated group.

Surprisingly, we did not observe a significant difference between the 2 groups in motor function, overall cognitive activity, or functional independence. The improvement between baseline and end point was significant in both groups but not different between the 2 groups. One might have expected a general improvement in performances related to the regression of depressive psychomotor inhibition. The literature on this subject is still insufficient. It is widely believed that PSD has a negative impact on rehabilitation.1,2,23 Effective treatment of this depression is believed to contribute to the recovery of stroke-induced deficits. In a trial comparing fluoxetine and nortriptyline, Dam et al15 reported an improvement of motor function and autonomy in the fluoxetine group. Gonzales et al16 observed an improvement of cognitive abilities. However, in both studies, the tricyclic agent used for comparison with fluoxetine could induce a decrease of motor or cognitive performances due to anticholinergic effects.24 In the present study, we hypothesize that at this early stage of stroke, spontaneous improvement and rehabilitation may lead to larger gains in these parameters than the improvement of depression itself. It would be interesting to test this hypothesis in neurologically and functionally stabilized vascular hemiplegia (eg, after the sixth month after stroke).

Side effects were rare but typical of those previously reported (Table 3). Only one patient was discontinued because of a subclinical but moderate elevation of transaminases, which reversed after discontinuation. Although significant elevations in transaminases are rarely seen in clinical trials using depressed patients from the general community,25 poststroke patients (such as the one in the present study) may be at greater risk because of polymedication. Medications frequently include hepatotoxic antiepileptic agents (carbamazepine) or muscle relaxants (dantrolene). This may warrant the monitoring of blood transaminases on the second week of treatment in hemiplegic patients. The other side effects were typical for this type of patient and were reported at similar incidence in both treatment groups, so it was difficult to attribute all of them to the treatment. Nevertheless, the overall safety and tolerability are better than with tricyclic antidepressants.

A major limitation of the present study was the small number of patients included: 31 of 121 patients screened. This was partly due to the difficulty in obtaining patients willing or able to consent to a study using placebo and partly to the restrictiveness of inclusion criteria. Nonetheless, use of strict criteria furnished us a very homogeneous population of early hemiplegic patients, typical of those seen in rehabilita-

![Figure 2. Percentage of responders.](http://stroke.ahajournals.org/)

### TABLE 3. Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are number of patients.
tion units during the early phase. The similarity of the 2
groups on critical baseline characteristics supports the valid-
ity of the results. Another limitation of the present study is the
exclusion of severe aphasic patients, who can be more prone
to depression. In the next study, we will try to include aphasic
patients using special scales tested by Gainotti et al.26

Our use of a strict statistical intent-to-treat method could
have biased our results against finding a differential treatment
effect in the other efficacy measures. The 2 fluoxetine-treated
patients who stopped the study early had their evaluations at
day 15. This period of treatment would generally be too short
to have a significant antidepressant effect. Thus, the analysis
of those completing the study showed better results (end-
point MADRS, 10.2 for fluoxetine versus 18.7 for placebo;
P=0.01) and a significant difference between the percentage
of responders (76.9% for fluoxetine versus 33.3% for pla-
cebo, P=0.02). Despite this bias, we found a significant effect in
the MADRS scores that supports our hypothesis that
fluoxetine is an effective antidepressant in early PSD.

In conclusion, fluoxetine appears to be an effective and
well-tolerated treatment for early PSD. Further trials are
needed to study the long-term efficacy and safety of fluox-
etine treatment in these patients to evaluate more precisely
the optimal duration of treatment of early PSD.

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