Increased Frequency of First-Episode Poststroke Depression After Discontinuation of Escitalopram

Katsunaka Mikami, MD, PhD; Ricardo E. Jorge, MD; David J. Moser, PhD; Stephan Arndt, PhD; Mijin Jang, MS; Ana Solodkin, PhD; Steven L. Small, PhD, MD; Pasquale Fonzetti, MD; Mark T. Hegel, PhD; Robert G. Robinson, MD

Background and Purpose—The purpose of this study was to compare escitalopram, problem-solving therapy, and placebo to prevent poststroke depression during 6 months after discontinuation of treatment.

Methods—We examined for depression 33 patients assigned to placebo, 34 to escitalopram, and 41 to problem-solving therapy.

Results—After controlling for age, gender, prior mood disorder, and severity of stroke, new-onset major depression and Hamilton Depression scores were significantly higher 6 months after escitalopram was discontinued compared with the problem-solving therapy or placebo groups.

Conclusions—Discontinuation of escitalopram may increase poststroke depressive symptoms.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00071643.

Key Words: depression ■ stroke

We previously reported that nondepressed patients given placebo over 1 year after stroke were 4.5 times more likely to develop new-onset depression than patients given escitalopram and 2.2 times more likely than patients given problem-solving therapy (PST).1

In the current study, we examined the frequency of major depression and changes in Hamilton Depression Rating Scale (HDRS)2 in this population 6 months after discontinuation of treatment. We hypothesized if preventive benefit of escitalopram and PST compared with placebo would continue after cessation.

Patients and Methods

The patient population was described in detail in prior publications.1 Nondepressed patients aged 50 to 90 years were enrolled within 3 months of an index stroke from the University of Iowa, the University of Chicago, and Burke Rehabilitation Hospital.

In a randomized controlled design, patients were assigned for 12 months to escitalopram (10 mg/day ≤65 years; 5 mg/day >65 years), placebo, or PST. The PST, developed for treating medically ill patients with depression,3 consisted of 12 sessions in which the patient selected a problem and used a 7-step process to arrive at a course of action. Using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis4 and the HDRS,2 patients were assessed for major depression and its severity 6 months after cessation of treatment. Secondary outcome measures included activities of daily living using the Functional Independence Measure.5

Escitalopram, PST, and placebo groups were compared using Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. Changes in HDRS were compared using a linear regression model with covariates of age, gender, history of mood disorder, treatment received (escitalopram versus nonescitalopram), and Functional Independence Measure at 12 months because we assumed these variables might influence the HDRS during the 6-month follow-up.

Results

A total of 33 patients randomized to placebo, 34 to escitalopram, and 41 to PST were examined 6 months after cessation. Baseline characteristics showed no significant intergroup differences (Table 1). Frequency of major depression was 4 cases for escitalopram (11.8%) versus 0 for placebo (Fisher exact test; \( P=0.1139 \)) and 0 for PST (Fisher exact test; \( P=0.0382 \)).

The escitalopram group showed significantly increased HDRS scores only at 18 months (Kruskal-Wallis test; \( \chi^2 [2] \)
Table 1. Baseline Characteristics of Poststroke Patients in the Placebo, Escitalopram, or Problem-Solving Therapy Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Escitalopram</th>
<th>Problem-Solving Therapy</th>
<th>Test Results</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(SD), y</td>
<td>67.5 (12.5)</td>
<td>63.7 (13.9)</td>
<td>66.1 (10.6)</td>
<td>Kruskal-Wallis ($\chi^2 [2] = 1.90$)</td>
<td>0.3870</td>
</tr>
<tr>
<td>Male, %</td>
<td>63.6</td>
<td>61.8</td>
<td>48.8</td>
<td>Fisher exact</td>
<td>0.3825</td>
</tr>
<tr>
<td>Married, %</td>
<td>51.5</td>
<td>55.9</td>
<td>51.2</td>
<td>Fisher exact</td>
<td>0.9128</td>
</tr>
<tr>
<td>Previous history of depression, %</td>
<td>0</td>
<td>8.8</td>
<td>2.4</td>
<td>Fisher exact</td>
<td>0.1942</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>13.3 (3.2)</td>
<td>13.9 (2.6)</td>
<td>14.0 (3.0)</td>
<td>Kruskal-Wallis ($\chi^2 [2] = 0.62$)</td>
<td>0.7351</td>
</tr>
<tr>
<td>Stroke characteristics, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>30.3</td>
<td>29.4</td>
<td>29.3</td>
<td>Fisher exact</td>
<td>1.000</td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>30.3</td>
<td>20.6</td>
<td>34.1</td>
<td>Fisher exact</td>
<td>0.4117</td>
</tr>
<tr>
<td>Cardioembolism/other</td>
<td>30.3</td>
<td>44.1</td>
<td>29.3</td>
<td>Fisher exact</td>
<td>0.3627</td>
</tr>
<tr>
<td>Left-sided lesions</td>
<td>45.5</td>
<td>55.9</td>
<td>34.1</td>
<td>Fisher exact</td>
<td>0.1665</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

A linear regression model covaried for age, gender, history of mood disorder, escitalopram versus nonescitalopram, and severity of stroke as measured by Functional Independence Measure at 12 months showed a β coefficient for change in HDRS for “escitalopram versus nonescitalopram” of 1.87 (95% CI, 0.41 to 3.32; $P = 0.0125$). There was no effect of treatment on change in Functional Independence Measure score ($\beta = -0.64$; 95% CI, 2.23 to 0.94; $P = 0.42$).

Discussion and Conclusions
This study found that nondepressed patients with stroke, who discontinued escitalopram after 12 months, were more likely to develop major depression and increased HDRS scores during the next 6 months than patients given placebo or PST.

This study is limited by not including patients with acute stroke such as those with severe comorbid illness. Furthermore, the number of new major depressions was relatively small. Thus, our findings should be considered preliminary.

For clinicians, the most important implication of our finding is that patients, given antidepressants after stroke, may be more prone to develop depressive symptoms than untreated patients once their antidepressants are stopped. They may need to be monitored for depression for at least 6 months. Furthermore, treatment for >1 year may be needed or slow tapering of antidepressants. Because PST effectively prevented poststroke depression and no new depressions occurred after cessation, should PST be the first treatment? Perhaps, but the lack of general availability of PST and administration of 12 therapy sessions will probably limit its use.

Cessation of escitalopram may have led to increased depressive symptoms because drugs like escitalopram produce changes in enzymes involved in synthesis and metabolism of biogenic amines and receptors and neuroplastic changes in the hippocampus and prefrontal cortex. Abrupt withdrawal of escitalopram may have led to neural system dysfunction and depression. Increased depressive symptoms after cessation of antidepressants has been reported in other studies. It is important to remember that antidepressants may improve cognitive and physical recovery after stroke.

Sources of Funding
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Disclosures

Table 2. Scores of HDRS and FIM at Baseline, 12 Months, and 18 Months

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=33)</th>
<th>Escitalopram (n=34)</th>
<th>Problem-Solving Therapy (n=41)</th>
<th>Test Results</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDRS score at baseline</td>
<td>5.9 (2.8)</td>
<td>7.1 (3.9)</td>
<td>5.9 (2.9)</td>
<td>2.02</td>
<td>0.3635</td>
</tr>
<tr>
<td>12 mo</td>
<td>5.0 (2.8)</td>
<td>5.6 (3.3)</td>
<td>4.7 (3.8)</td>
<td>2.40</td>
<td>0.3010</td>
</tr>
<tr>
<td>18 mo</td>
<td>4.5 (2.3)</td>
<td>6.9 (4.6)</td>
<td>4.0 (2.9)</td>
<td>10.05</td>
<td>0.0066</td>
</tr>
<tr>
<td>FIM score at baseline</td>
<td>117.4 (10.5)</td>
<td>113.4 (18.6)</td>
<td>113.0 (14.8)</td>
<td>1.21</td>
<td>0.5468</td>
</tr>
<tr>
<td>12 mo</td>
<td>121.6 (4.5)</td>
<td>118.3 (11.6)</td>
<td>121.6 (4.2)</td>
<td>1.45</td>
<td>0.4837</td>
</tr>
<tr>
<td>18 mo</td>
<td>121.4 (4.5)</td>
<td>117.4 (13.6)</td>
<td>121.3 (4.7)</td>
<td>3.38</td>
<td>0.1842</td>
</tr>
</tbody>
</table>

HDRS indicates Hamilton Depression Rating Scale; FIM, Functional Independence Measure; SD, standard deviation.
# References


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