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Escitalopram and Problem-Solving Therapy for Prevention of Poststroke Depression
A Randomized Controlled Trial

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Prevention is a goal to which every field of medicine aspires because it reduces morbidity, may alleviate suffering, and reduces the cost of health care. Although the Commission on Chronic Illness proposed the classification of primary, secondary, and tertiary prevention1 in 1957, the Institute of Medicine Committee on Prevention of Mental Disorders recommended a new terminology2 in 1995. According to the new terminology, preventive intervention is defined as an intervention before the patient receives a diagnosis. Alternatively, treatment is an intervention for patients already with a diagnosis, and maintenance is the care of patients with chronic illnesses including relapse prevention. Furthermore, preventive interventions are categorized as (1) indicated, addressing high-risk individuals with premorbid signs or symptoms; (2) selective, for select individuals with demonstrated increased risk of developing illness; and (3) universal, for a whole population in a group with all levels of risk.

See also Patient Page.

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identifying a population at sufficiently high risk to justify the expense and risk of pharmacological or psychological intervention.

The annual incidence of stroke (ischemic and hemorrhagic cerebral infarction), which exceeds 700,000 in the United States, represents a major public health problem. Patients who survive acute stroke may constitute a particularly good population for preventive intervention for depression because of their high risk of developing depression. Among combined studies of 2178 patients hospitalized for acute stroke or rehabilitation, 22% were diagnosed with major depression and 17% were diagnosed with minor depression. Furthermore, among patients without depression during the acute stroke period, 14% developed major depression and 23% developed minor depression during the first 2 years following stroke. Thus, approximately 37% of stroke survivors developed depression after the acute stroke period and represent a sizeable population in which to assess a selective preventive intervention strategy.

Several investigators have previously attempted to prevent the development of poststroke depression without success. Palomäki et al conducted a randomized placebo-controlled study of 100 patients younger than 71 years who were admitted to the hospital for acute ischemic stroke. Patients received either mianserin (60 mg/d) or placebo for 1 year and were examined at 2, 6, 12, and 18 months follow-up. At no time during the 18-month follow-up did the prevalence rate for major depression according to the Diagnostic and Statistical Manual of Mental Disorders, (Third Edition, Revised) differ between treatment groups. Rasnussen et al, using double-blind methods and random assignment, treated 137 patients without depression over 12 months following acute stroke with sertraline (mean dose 63 mg/d; n=70) or placebo (n=67). The depression occurrence rate over the 12 months, based on a Hamilton-17 Depression Rating Scale score of greater than 18, was 8.2% for sertraline (90% confidence interval [CI], 2.4%-13.9%; 3 of 35 completers) vs 22.8% for placebo (90% CI, 13.7%-32.0%; 7 of 32 completers). Based on the number of completers, the power of this study to find significant intergroup differences was 0.44, which indicates that the study was underpowered.

The most recent report was by Almeida et al in which 111 patients within 2 weeks following stroke were randomized to treatment with sertraline (50 mg/d; n=55) or placebo (n=56) in a 24-week double-blind clinical trial. Results demonstrated no significant intergroup difference in the prevalence of scores of 8 or greater on the Hospital Depression and Anxiety Scale during the 24 weeks of treatment. Among sertraline-treated patients, 8 out of 48 (16.7%) developed depression compared with 11 out of 51 placebo-treated patients (21.6%) (rate ratio, 0.8; 95% CI, 0.3-2.1; P=.59). A recent meta-analysis, however, reported significant effect of antidepressants across 10 studies with duration of treatment ranging from 4 to 52 weeks. Some studies, however, were designed for prophylaxis while other studies were acute treatment studies in which nondepressed patients were assessed for measurement of recovery.

Although 3 double-blind trials failed to show a significant effect of active treatment in preventing poststroke depression, we undertook the current preventive treatment study to assess the efficacy of escitalopram or psychological problem-solving therapy. Our rationale included larger numbers of patients to increase statistical power, multisite enrollment to achieve a more varied sample, and comparison of both psychological and pharmacological interventions to prevent poststroke depression.

Problem-solving therapy was selected because it had been developed for use in elderly patients with depression and cognitive behavioral therapy had been shown to be unsuccessful in treating poststroke depression. We hypothesized that both escitalopram and problem-solving therapy would constitute effective preventive interventions.

**METHODS**

**Patients**

Patients were enrolled between July 9, 2003, and October 1, 2007, at the Department of Neurology, University of Iowa, Iowa City; the University of Chicago, Chicago, Illinois; and Burke Rehabilitation Hospital, White Plains, New York. Patients were also recruited for enrollment through newspaper advertisements. All patients were also within 3 months of an index stroke. The protocols were approved by the institutional review boards at each study site and written informed consent was obtained from each participant. A total of 200 patients were enrolled 28 from Burke Rehabilitation Hospital, 24 from the University of Chicago, and 148 from the University of Iowa. Inclusion criteria included age older than 50 years and younger than 90 years with clinical and neuroradiological findings consistent with either hemispheric, brainstem, or cerebellar stroke.

Patients with either ischemic or hemorrhagic stroke were entered in the study. Patients were excluded if they met DSM-IV diagnostic criteria for major or minor (research criteria) depressive disorder or had a score greater than 11 on the Hamilton-17 Depression Rating Scale. Patients with severe comprehension deficits, as demonstrated by inability to complete part 1 of the Token Test or patients with neuropsychological testing who showed impaired decision-making capacity, were excluded. Other exclusionary criteria included occurrence of stroke secondary to complications from an intracranial aneurysm, arterial-venous malformation, intracranial tumor or neoplastic process, stroke during the course of myocardial infarction, aortic dissection, or revascularization surgery. General exclusionary criteria included life-threatening heart or respiratory failure, renal or hepatic failure, severely disabling musculoskeletal disorder, cancer, and neurodegenerative disorders such as idiopathic Parkinson disease or Alzheimer disease. Patients were excluded if they experienced stroke due to complications of an intracranial an-
Neurological and Neuroradiological Evaluations
A complete physical and neurological examination was performed at the time of intake. The neurological findings were recorded using the National Institutes of Health Stroke Scale (NIHSS).19 Vital signs and body weight were recorded at baseline, 12 weeks, 6 months, 9 months, and 12 months follow-up. A 12-lead electrocardiogram, as well as laboratory measures of hemoglobin, hematocrit, white blood cell count, serum sodium, potassium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total protein, glucose, creatinine, blood urea nitrogen, and urinalysis were obtained at the beginning of the study. Neuroimaging scans were obtained from the treating hospital for analysis by a neuroradiologist who was blinded to the treatment assignment. There was no standardized imaging protocol.

Experimental Design and Treatment
Patients were centrally randomized at the University of Iowa study site by a team member who was not involved in any evaluation using a permuted blocks randomization scheme. Specifically, at the beginning of the study, the targeted sample size was divided randomly (200 patients) into block sizes of 3, 6, and 9 and within each block patients were randomly assigned 1 of the 3 treatments using computer-generated random numbers of 1, 2, or 3 to escitalopram (10 mg/d in the morning for patients <65 years and 5 mg/d for patients ≥65 years), placebo (all pills were identical), or problem-solving therapy. Escitalopram was selected, rather than citalopram, because of empirical evidence that citalopram may have greater efficacy and a faster onset of action than citalopram and successful patient tolerance over a 12-month administration.20,21 The problem-solving therapy used in this study is a manual-based intervention originally developed in England for treating medical patients with depression14 that has been elaborated for application in the United States.22 The problem-solving therapy was administered to patients at all sites (10 in Chicago, 41 in Iowa, and 8 in New York) and consisted of 6 treatment sessions over the first 12 weeks (weeks 1, 2, 3, 4, 6, and 10) and 6 reinforcement sessions (months 4, 5, 6, 8, 10, and 12). Prior to administering problem-solving therapy, therapists had to successfully complete 5 training cases under the supervision of one of the investigators (M.H.). All sessions were audiorecorded or videorecorded for supervision and adherence ratings by 1 investigator (M.H.). In patients without depression, the principles of therapy are the same as in patients with depression. The patient selects a problem and then goes through 7 steps to arrive at a course of action. Five patients were assigned to problem-solving therapy because they refused pharmacological treatment. Of these, 2 withdrew before treatment began and 3 were treated. None of these patients were included in the analysis of randomized patients. Patients were seen for evaluation by raters who were blinded to drug assignment or not involved in the administration of problem-solving therapy at 3, 6, 9, and 12 months follow-up. We have previously demonstrated reliability and validity of structured interviews like the Structured Clinical Interview for DSM-IV among patients with stroke.24,25 The diagnoses of “depression due to stroke with major depressive-like episode” and “minor depression” (research criteria) were based on symptoms elicited by the Structured Clinical Interview and DSM-IV criteria.18,23 At each follow-up interview or if a patient reported a problem, the patient was examined for depression. The examiners were unaware of each patient’s treatment assignment and double-blinded assessments were done for escitalopram and placebo. The patients receiving problem-solving therapy were aware of their treatment and, although they were asked not to tell the rater, all raters became aware of their problem-solving therapy treatment due to patients divulging their treatment. The diagnosis of depression was based on the patient meeting diagnostic criteria for major or minor depression (ie, symptom duration for 2 or more weeks) and having a Hamilton-17 Depression Rating Scale13 score of greater than 12. The Hamilton-17 Depression Rating Scale and the Hamilton Anxiety Rating Scale28 were administered at each of the initial and follow-up interviews. The Hamilton-17 Depression Rating Scale has been widely used and demonstrated to be a reliable and valid measure of depressive symptoms among patients with stroke.27 The Hamilton Anxiety Rating Scale is a 16-item instrument that measures severity of anxiety symptoms and has been shown to be valid and reliable in patients with stroke.26,29 Socioeconomic status was determined using the Hollingshead and Redlich classification.30 Secondary outcome measures included an assessment of activities of daily living using the Functional Independence Measure.31 The Functional Independence Measure is an 18-item, 7-level, activities of daily living scale developed to assess interpersonal, familial, and occupational functioning. The maximum
score is 122 points and higher scores indicate less impairment. The Functional Independence Measure has been widely used in rehabilitation settings and has been shown to be valid and reliable among patients with stroke.35 The Social Functioning Exam32 is a 28-item scale that assesses patients’ satisfaction with their social functioning prior to the stroke or during the 2 weeks prior to each examination. Scores on the Social Functioning Exam range from 0 to 1 with higher scores indicating greater severity of social impairment. Reliability and validity of this instrument have been demonstrated in a previous publication.33 Neuropsychological assessment included administration of the Line Bisection and Token Test at baseline to rule out significant hemispatial neglect and impaired ability to follow oral instructions. The remainder of the neuropsychological battery, which was administered at baseline and at the close of study, included the Repeatable Battery for the Assessment of Neuropsychological Status,34 a self-contained battery that includes tests of immediate and delayed memory, language, visuospatial/constructional ability, and attention; and additional tests of executive function. Detailed analysis of these data are beyond the scope of the current report.

Adverse Events
Patients, family members, and primary care physicians were asked about adverse events such as physical illnesses or medication adverse effects at 3-month intervals or sooner if an individual reported an adverse event—using a standardized checklist developed for this study. A data and safety monitoring board made up of investigators not involved in this trial assessed adverse events related to the 3 treatments.

Statistical Analysis
The study design was based on our a priori assumption that 35% of patients given placebo would develop a depressive disorder over 1 year. This was based on previous findings that 37% of stroke survivors developed depression after the acute stroke period and the mean rate of depression among placebo-treated patients in prior prevention treatment trials.9,10,12 We also predicted that 10% of patients who were given escitalopram would develop depression. This was based on the rate of depression in the sertraline group in the prevention trial by Rasmussen et al.12 Completer group sizes of 40 including new-onset cases of depression would, using an α of .05, give a power of 0.80 to detect significant intergroup differences.

Categorical data were analyzed using the Fisher exact test and logistic regression. Means and SDs were calculated for continuous measures and analyses were conducted using 1-way analysis of variance. Proportions, odds ratios (ORs), and hazard ratios (HRs) were reported along with their respective 95% confidence intervals. Size of the effect was assessed by reporting the number needed-to-treat along with the success rate difference and its CI following the recommendations by Kraemer and Kupfer.35 We used Wilson score CIs for success rate difference as recommended by Newcombe16 and Bender.37

In order to analyze the time-to-depression onset data, we built a proportional hazards Cox regression model using time-to-depression onset as the dependent variable and treatment group, site, and various baseline characteristics (eg, age, sex, prior history of mood disorder; Functional Independence Measure, Social Functioning Exam, and Repeatable Battery for the Assessment of Neuropsychological Status scores; hemispheric lesion location; and physical impairment) as independent variables. Only predictors that were significant were kept in the model. We tested all the 2-way interactions between these covariates and the treatment group. We used a robust estimate of the variance to account for the correlation of each data point within each site. This analysis included all the patients who completed the study as well as those who dropped out after randomization (ie, 176 patients). The latter were considered in the model as censored observations at the time they stopped participating in the study. The proportional hazards assumption was tested and met.

To investigate the effect of treatment on the secondary outcomes (ie, Functional Independence Measure, Social Functioning Exam, and Repeatable Battery for the Assessment of Neuropsychological Status global scores), we used a linear mixed model that included secondary outcome scores as the dependent variable, and treatment group, time, and site (random effect) as dependent variables. Other possible confounders such as change in Hamilton-17 Depression Rating Scale score between baseline and close out, sex, educational level, prior history of mood disorders, physical impairment, and age were considered in the model. Only significant predictors and interactions with the treatment group were considered in the final models. The mixed-model analytical approach allowed us not only to model the correlation of observations within sites, but also the correlation of patient outcomes over time while including all the available data during the course of this study.

All analyses were performed using R 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.1.3 for Windows (SAS Institute Inc, Cary, North Carolina). All the P values reported are 2-tailed. Significance level was set at P < .05.

RESULTS
Participants
The patient flow diagram is shown in Figure 1. A total of 200 patients signed informed consent, 176 were randomized, and 149 began randomized treatment. After signing informed consent, 24 patients (12.0%) dropped out of the study before randomization and 27 (13.5%) dropped out before receiving the first drug dose or problem-solving therapy session. Reasons for withdrawal prior to beginning treatment included 9 participants who did not want...
to commit the time to the study, 4 who developed a physical illness, 8 whose families withdrew consent, 4 who could not be reached and 2 who developed depression. Out of the total 149 patients who began treatment, 15 patients (10.1%) dropped out of the study, 5 within 90 days, 4 between 91 and 180 days, and 6 between 181 and 365 days. Of these drop-out patients, 3 died (sepsis, lung cancer, and severe traumatic brain injury following a motor vehicle crash), 4 developed an intercurrent disease that was judged to be incompatible with study continuation, 1 experienced adverse effects that might have been related to the study medication and requested to be withdrawn, 1 patient in the placebo group and 1 in the escitalopram group were excluded because of protocol violations, and 5 could not be reached for follow-up. We compared demographic and baseline variables (eg, age, sex, marital status, baseline Hamilton-17 Depression Rating Scale and Functional Independence Measure scores) for the group of patients who were randomized to treatment with those for patients who dropped out. A logistic regression analysis found no demographic or baseline impairment variables related to postrandomization dropout.

The demographic characteristics of the patients included in the intention-to-treat sample ($n = 176$) are shown in Table 1. There were 58 patients randomized to placebo, 59 to escitalopram, and 59 to problem-solving therapy. There were no significant differences between the groups in age, sex, years of education, marital status, or socioeconomic status. The overall illness severity, as well as the existence of comorbid illness for the 3 groups, is shown in Table 1. There were no significant intergroup differences in overall cumulative illness scores, coronary artery disease, low-density lipoprotein cholesterol, atrial fibrillation, chronic obstructive pulmonary disease, or systolic blood pressure. The patients randomized to escitalopram, however, had a significantly greater frequency of diabetes mellitus when compared with the placebo group (Fisher exact test $P$ value $= .01$).

**Stroke Characteristics and Impairment**

The type, location, and severity of stroke as well as severity of impairment in activities of daily living are shown in Table 1. There were no significant differences among the escitalopram, placebo, and problem-solving therapy groups in stroke characteristics, severity of stroke as measured by the National Institutes of Health Stroke Scale, or severity of impairment in activities of daily living, as measured by the Functional Independence Measure score. We found no evidence that these characteristics were different across the 3 participating centers.

**Effect of Preventive Intervention on Depression**

Using the 176 patients who were randomized to treatment, we built a Cox regression proportional hazards model using the time to depression onset as the dependent variable. Our final model included the type of treatment received and prior history of mood disorders as independent variables with data on the 27 patients who did not begin treatment cen-

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**Figure 1. Patients Assessed and Randomized to Receive Escitalopram, Problem-Solving Therapy, or Placebo**

799 Patients assessed for eligibility

563 Excluded
- 254 Did not meet inclusion criteria
- 168 Unwilling to participate
- 49 Lived in skilled nursing facility
- 35 Unwilling to commit the time
- 21 Physicians prescribed active antidepressant instead
- 36 Other reasons

176 Randomized

58 Randomized to receive placebo
- 51 Received placebo
- 7 Did not receive placebo
- 3 Family withdrew consent
- 2 Unwilling to commit the time
- 2 Developed physical illness

59 Randomized to receive escitalopram
- 50 Received escitalopram
- 9 Did not receive escitalopram
- 4 Could not be reached
- 3 Unwilling to commit the time
- 2 Developed depression

59 Randomized to receive PST
- 48 Received PST
- 11 Did not receive PST
- 5 Family withdrew consent
- 4 Unwilling to commit the time
- 2 Developed physical illness

58 Included in analysis

59 Included in analysis

59 Included in analysis

PST indicates problem-solving therapy. Of 149 patients who received at least 1 dose of escitalopram or 1 session of PST, 89.9% reached the study end points.

Study participation was not allowed at skilled nursing facilities.
sored at baseline (likelihood ratio test \( \chi^2 = 9.1; P = .03 \)). The interaction between type of treatment received and a history of mood disorders was not statistically significant. After adjusting for the previous history of mood disorders, participants who received placebo (11 major and 2 minor cases of depression, total 22.4%) were 4.5 times more likely to develop depression than patients who received escitalopram (3 major and 2 minor cases of depression, total 8.5%; adjusted HR, 4.5; 95% CI, 2.4-8.2; \( P < .001 \)) and 2.2 times more likely than patients who received problem-solving therapy (3 major and 2 minor cases of depression, total 11.9%; adjusted HR, 2.2; 95% CI, 1.4-3.5; \( P < .001 \); FIGURE 2). After adjusting for the treatment assignment, patients with a history of mood disorders were 5.2 times more likely to develop depression in the course of 1 year than patients without a previous history (adjusted HR, 5.2; 95% CI, 3.3-8.1; \( P < .001 \)).

Based only on the frequency of depression onset during the 1 year of treatment, 7.2 acute stroke patients (success rate difference, 0.14; 95% CI, 0.01-0.27) would need to be treated with escitalopram to prevent 1 case of depression and 9.1 acute stroke patients (success rate difference, 0.11; 95% CI, −0.03 to 0.24) would need to be treated with problem-solving therapy to prevent 1 case of depression.\(^{30,31}\) This latter effect did not reach statistical significance.

An alternative intention-to-treat conservative method of analyzing our data is to assume that all 27 patients who did not start randomized treatment would have developed depression. Using this assumption and controlling for prior history of mood disorders, escitalopram was superior to placebo (23.1% vs 34.5%; adjusted HR, 2.2; 95% CI, 1.2-3.9; \( P = .007 \)), while problem-solving therapy was not significantly better than placebo (30.5% vs 34.5%; adjusted HR, 1.1; 95% CI, 0.8-1.5; \( P = .51 \)).

The majority of patients who developed depression during the study experienced major depression (19 of 25, 76%). The baseline Hamilton-17 Depression Rating Scale scores in the patients who developed depression were not significantly different from the scores of patients who did not develop depression.

### Adverse Events and Adverse Effects

The frequency of adverse events or medication adverse effects is shown in **TABLE 2**. There were no significant differences between groups in the frequency of any of these events. Although this study was not designed to detect treatment-related differences in cardiovascular morbidity or other measures of morbidity related to the use of escitalopram, problem-solving therapy, or placebo, we did examine the number and cause of hospital admissions during the 1 year of treatment. A total of 5 patients receiving placebo and 5 patients receiving problem-solving therapy (8.6% of the combined group) and 2 receiving escitalopram (3.4%) sustained a cardiac event requiring hospitalization (OR, 2.7; 95% CI, 0.6-
12.6; Fisher exact test P = .34). There was no evidence that patients receiving placebo or problem-solving therapy were any more or less likely than patients receiving escitalopram to be hospitalized with cardiovascular illness. Also, there were no significant differences between the groups in the frequency of hospital admissions resulting from gastrointestinal bleeding or falls, which have been previously described as complications of selective serotonin reuptake inhibitor treatment (Table 2).

**Effect on Secondary Outcome Variables**

The effect of 1 year of treatment with escitalopram or problem-solving therapy or placebo on the longitudinal course of impairment in activities of daily living, assessed by the Functional Independence Measure, assessed the intention-to-treat sample (n = 176). All patients experienced improvement in activities of daily living over time, particularly during the first 3 months. Scores on the Functional Independence Measure at 3-, 6-, 9-, and 12-month evaluations were significantly improved compared with baseline values for all treatment groups (F [4166] = 9.49; P < .001). There was, however, no significant time × treatment interaction.

The assessment of social functioning over time revealed a significant effect of time on Social Functioning Exam scores (F[4167] = 4.33; P = .002), but the time × treatment interaction was not significant, again indicating that all groups showed improvement. Assessment of neuropsychological testing revealed that the total score on the Repeatable Battery for the Assessment of Neuropsychological Status showed no significant intergroup differences at baseline. In comparing initial and end-of-study performance, there were no significant time, treatment, or time × treatment interactions across the 2 treatment groups.

**COMMENT**

Although universal preventive intervention has been a long-standing goal in psychiatry, there has not been a double-blind study that has demonstrated prevention of a psychiatric disorder. However, this study has demonstrated that depression can be significantly decreased in frequency by preventive use of escitalopram compared with placebo over the first year following an acute stroke, using double-blind methodology. In an open treatment group, we also found that problem-solving therapy significantly increased the time to onset of depression during the first year following stroke. Based on these results, we calculated that 7.2 stroke patients would need to be treated with escitalopram or 9.1 patients with problem-solving therapy to prevent 1 case of depression. This could be compared with preventive intervention in cardiology in which 40 male patients with hypercholesterolemia would need to be treated with pravastatin for 5 years to prevent 1 myocardial infarction.38

Before discussing the implications of these findings, the limitations of this study are significant. There was no evidence that patients receiving escitalopram or problem-solving therapy were any more or less likely than patients receiving placebo to be hospitalized with cardiovascular illness. Also, there were no significant differences between the groups in the frequency of hospital admissions resulting from gastrointestinal bleeding or falls, which have been previously described as complications of selective serotonin reuptake inhibitor treatment (Table 2).

**Figure 2. Risk Comparison of Depression Onset for Patients Receiving Escitalopram, Problem-Solving Therapy (PST), or Placebo Over 1 Year**

After adjusting for previous history of mood disorders, participants who received placebo were 4.5 times more likely to develop depression than participants who received escitalopram (adjusted hazard ratio, 4.5; 95% confidence interval, 2.4-8.2; P < .001) and 3.2 times more likely than participants who received problem-solving therapy (adjusted hazard ratio, 2.2; 95% confidence interval, 1.4-3.5; P < .001).

**Table 2. Adverse Events in Poststroke Patients Randomized to Receive Escitalopram, Problem-Solving Therapy, or Placebo**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Escitalopram (n = 59)</th>
<th>Problem-Solving Therapy (n = 59)</th>
<th>Placebo (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17 (29)</td>
<td>23 (39)</td>
<td>27 (47)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (24)</td>
<td>16 (27)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>13 (22)</td>
<td>16 (27)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12 (20)</td>
<td>9 (15)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (12)</td>
<td>14 (24)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>9 (15)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (7)</td>
<td>10 (17)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Sexual adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased libido</td>
<td>12 (20)</td>
<td>17 (29)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Anorgasmia</td>
<td>4 (7)</td>
<td>3 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Ejaculation disorders</td>
<td>3 (10)</td>
<td>5 (23)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Impotence</td>
<td>3 (10)</td>
<td>5 (23)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Cardiovascular adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>38 (64)</td>
<td>42 (71)</td>
<td>36 (62)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8 (14)</td>
<td>12 (20)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5 (8)</td>
<td>7 (13)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>37 (63)</td>
<td>41 (69)</td>
<td>34 (59)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (41)</td>
<td>21 (36)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>12 (20)</td>
<td>17 (29)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

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Given these limitations, what are the implications of the current findings? Perhaps the first question is why this prevention trial worked while others failed to show a significant preventive effect. The mean age of the treated patients in the study by Rasmussen et al was 72 years (SD = 9.1) and in the study by Almeida et al was 67 years (SD = 13) while the mean age of our escitalopram-treated group was 62 years (SD = 13). Although the measures of physical impairment in those studies were different from ours, the severity appears somewhat greater than ours. Thus, it is possible that our population differed from those of the other studies, which could explain the differences in prevention rates. Conversely, our increased sample size, as well as the medication selected and the dosage prescribed, may have led to successful preventive treatment in this population that was elderly and sometimes very frail. For example, Andersen et al demonstrated that citalopram was superior to placebo in the treatment of acute poststroke depression. Patients aged 65 years and older were given 10 mg of citalopram and those younger than 65 years were given 20 mg of citalopram. These relatively low doses of citalopram may have been particularly well suited for this patient population. Furthermore, in our previous study of treatment of poststroke depression, we used doses of as much as 40 mg of fluoxetine for all patients in that treatment group and found no effect of fluoxetine vs placebo for depression, but did find that fluoxetine produced a mean (SD) weight loss of 6.8 (3.6) kg, which was not seen with nortriptyline or placebo.

The rates of gastrointestinal effects in the current study were not significantly different from placebo. It should also be acknowledged that the current study included a problem-solving therapy group that the other prevention studies did not have. It seems unlikely, however, that this influenced the overall study results. A recent 8-week nonblinded study of problem-solving therapy for preventing depression in older adults with macular degeneration also reported positive results for this treatment. The effects of problemsolving therapy, however, were lost over a 6-month follow-up period. In contrast to our study, the macular degeneration prevention protocol did not include reinforcement sessions. Thus, some form of maintenance problemsolving therapy may be necessary for long-term prevention.

The second logical question is what may be the consequence of prevention of poststroke depression? Since 1993, there have been at least 4 reports demonstrating an association of poststroke depression with increased mortality. For example, we reported in a 10-year follow-up of 103 patients with acute stroke that patients with acute-onset major or minor depression were more likely to die than patients who were without depression after the acute stroke, even after controlling for age, sex, marital status, socioeconomic status, cognitive impairment, activities of daily living impairment, previous and comorbid physical illness, stroke type, and stroke volume (adjusted OR, 3.7; 95% CI, 1.1-12.2; P = .03). Subsequently, House et al examined 448 patients with acute stroke and found that at 2 years follow-up, patients with 1 or more symptoms of depression on the General Health Questionnaire were significantly more likely to have died compared with patients with no depressive symptoms even after controlling for older age, lower Mini-Mental State Examination scores, lower Barthel score, prior stroke, and urinary incontinence (OR, 2.2; 95% CI, 1.2-4.0; P = .009). In a recent study of 104 acute stroke patients with or without depression, however, we found that 12 weeks of treatment with fluoxetine (20-40 mg) or nortriptyline (50-100 mg) significantly reduced the mortality rate at 7 to 9 years follow-up even after controlling for age, stroke type, comorbid physical illness, and diabetes mellitus. Whether prevention of poststroke depression might lead to increased survival is an important issue for further investigation.
Although the mechanism by which escitalopram and problem-solving therapy were able to decrease the frequency of poststroke depression is unknown, it is possible that the mechanism for the treatment of acute depression may be different. Antidepressants have been associated with enhanced recovery in executive function, as well as recovery in activities of daily living independent of depression. In addition, it has been hypothesized that antidepressant effects on neuroplasticity mediate both recovery from depression as well as motor and cognitive recovery through different mechanisms. Perhaps prevention of depression may be another example of this alternative mode of action. Alternatively, one might also hypothesize, based on the study of macular degeneration, that regaining ability to facilitate valued activities may have led to a preventive effect on depression in patients receiving problem-solving therapy.

In conclusion, this study has demonstrated that poststroke depression can be effectively prevented in a significant number of patients by administering escitalopram or problem-solving therapy during the first year following stroke. To our knowledge, this may be the first demonstration of selective prevention of a psychiatric disorder with adequate blinding for 2 of the 3 treatment groups. The 9 patients with prior history of depression clearly had maintenance intervention. However, the majority of patients had no prior history of mood disorder and this intervention protected them from depression. One might also question whether preventive intervention in all stroke survivors is superior to early detection and treatment. Although only a randomized controlled trial would answer this question, the major obstacle to early detection is that studies that have examined the detection of depression during standard stroke care have found that the vast majority of depression cases were overlooked by the treating physicians. The clinical implications of our findings are that patients who are given escitalopram or problem-solving therapy following acute stroke may be spared depression and perhaps its adverse consequences.

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Author Contributions: Dr Robinson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Robinson, Jorge, Solodkin, Fonzetti, Hegel. Acquisition of data: Robinson, Jorge, Solodkin, Small, Fonzetti. Analysis and interpretation of data: Robinson, Jorge, Moser, Acion, Small, Arndt. Drafting of the manuscript: Robinson, Jorge, Acion, Fonzetti, Hegel. Critical revision of the manuscript for important intellectual content: Moser, Acion, Solodkin, Small, Hegel, Arndt. Statistical analysis: Jorge, Acion, Arndt. Obtained funding: Robinson, Solodkin. Administrative, technical, or material support: Robinson, Solodkin, Small, Fonzetti. Study supervision: Moser, Hegel.

Financial Disclosures: All of the authors received salary contributions from the grant supporting this study. Over the past 5 years, Dr Robinson reports serving as a consultant to the former Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company; Dr Jorge reports receiving 2 travel awards to participate in national meetings from the former Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company; and Dr Small reports that he conducted a research study funded by Northstar Neuroscience that was unrelated to this prevention study. The former Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company had no financial interest in this prevention study. No other authors reported any financial disclosures.

Data and Safety Monitoring Board: Russell Noyes, MD, Harold Adams, MD, and Douglas Langbehn, MD, University of Iowa. 

Funding/Support: This work was supported solely by National Institute of Mental Health (NIMH) grant R01 MH-65134. All of the study medications were purchased using NIMH grant funds.

Role of the Sponsor: NIMH did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: We thank Stephanie Ro-sazza, BA, University of Iowa, for study coordination; Teresa Kopel, MA, University of Iowa, for administering problem-solving therapy; Jessica Thompson, BS, University of Chicago, for administering problem-solving therapy; and Mireya Montalvan, BA, Burke Rehabilitation Hospital, for performing neuropsychological assessment. None of these individuals received compensation for their work in association with this article.

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