ORIGINAL ARTICLE

Escitalopram and Enhancement of Cognitive Recovery Following Stroke

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Context: Adjunctive restorative therapies administered during the first few months after stroke, the period with the greatest degree of spontaneous recovery, reduce the number of stroke patients with significant disability.

Objective: To examine the effect of escitalopram on cognitive outcome. We hypothesized that patients who received escitalopram would show improved performance in neuropsychological tests assessing memory and executive functions than patients who received placebo or underwent Problem Solving Therapy.

Design: Randomized trial.

Setting: Stroke center.

Participants: One hundred twenty-nine patients were treated within 3 months following stroke. The 12-month trial included 3 arms: a double-blind placebo-controlled comparison of escitalopram (n=43) with placebo (n=45), and a nonblinded arm of Problem Solving Therapy (n=41).

Outcome Measures: Change in scores from baseline to the end of treatment for the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trail-Making, Controlled Oral Word Association, Wechsler Adult Intelligence Scale–III Similarities, and Stroop tests.

Results: We found a difference among the 3 treatment groups in change in RBANS total score ($P<.01$) and RBANS delayed memory score ($P<.01$). After adjusting for possible confounders, there was a significant effect of escitalopram treatment on the change in RBANS total score ($P<.01$, adjusted mean change in score: escitalopram group, 10.0; nonescitalopram group, 3.1) and the change in RBANS delayed memory score ($P<.01$, adjusted mean change in score: escitalopram group, 11.3; nonescitalopram group, 2.5). We did not observe treatment effects in other neuropsychological measures.

Conclusions: When compared with patients who received placebo or underwent Problem Solving Therapy, stroke patients who received escitalopram showed improvement in global cognitive functioning, specifically in verbal and visual memory functions. This beneficial effect of escitalopram was independent of its effect on depression. The utility of antidepressants in the process of poststroke recovery should be further investigated.

Trial Registration: clinicaltrials.gov Identifier: NCT00071643

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ALTHOUGH THERE HAS BEEN a significant decline in stroke-related mortality during the past 50 years, stroke remains a major health care problem, the third greatest cause of death in developed countries.[1] Worldwide, 5.5 million people die from stroke yearly.[1] The World Health Organization estimates that 60% of those in developed countries who have a stroke die or become dependent.[1] The World Health Organization has projected stroke burden to rise from around 38 million disability-adjusted life-years globally in 1990 to 61 million disability-adjusted life-years in 2020.[1] Thus, it is not surprising that the direct and indirect costs of stroke were estimated to be $65.5 billion per year in the United States.[2]

There have been significant advances in the treatment of acute stroke. The most significant of them are the implementation of organized stroke care and the use of acute thrombolytic therapy.[3-7] However, the latter needs to be administered within a narrow therapeutic window (ie, the first few hours after the onset of symptoms), which limits the number of patients effectively treated. Consequently, besides the efforts currently undertaken to increase the number of patients treated with thrombolytic agents, there is growing interest in restorative therapies that can be administered during the first few months after stroke, the period within which we observe the greatest degree of spontaneous recovery of initial motor and cognitive deficits. Restorative therapies include those based on the synergistic effect of a medication and a specific rehabilitation intervention, such as physical therapy or speech therapy[8-12] and those based on a more generalized effect of pharmaco-

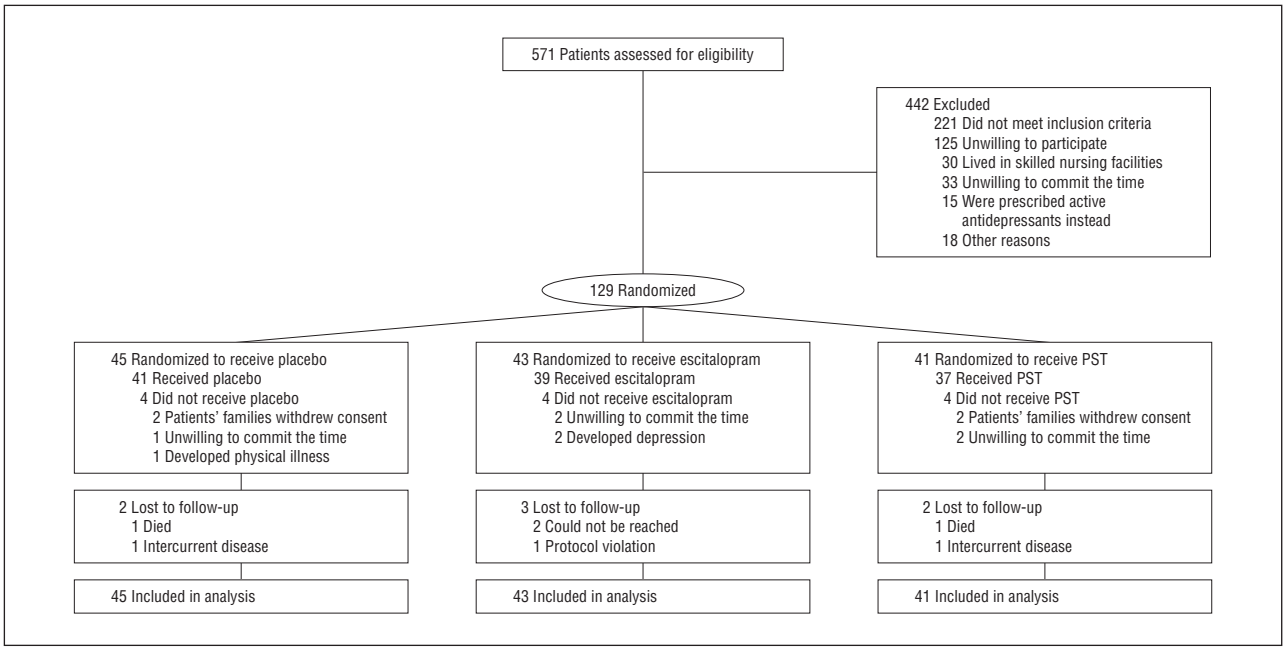

Figure 1. Patient flowchart. PST indicates Problem-Solving Therapy.

logical agents on widely distributed aminergic or cholinergic projection systems.[13-19] It is hypothesized that an intervention of this kind will improve stroke's physical and cognitive outcomes, reducing the number of patients who experience significant disability.[20]

Another line of research strongly suggests that antidepressants exert their therapeutic effects through complex signaling cascades that result in the increased expression of neurotrophic factors, the proliferation of neural and glial cell precursors, increased axonal sprouting, and the development of new synapses.[21-24] Furthermore, serotonin plays a role in neuroplastic changes associated with brain development,[25] and selective serotonin reuptake inhibitors (SSRIs) increase hippocampal neurogenesis, probably through serotonin$_{1A}$ receptor–mediated effects.[26-29] Overall, the neurotrophic effects of antidepressants and the fact that they are widely used medications of proven safety make them excellent candidates for use as restorative agents in the subacute phase of stroke and other forms of brain damage.[30]

We previously reported preliminary evidence that treatment with antidepressants in the subacute phase of stroke is associated with significant improvement in activities of daily living and cognitive functioning among patients who recovered from poststroke depression.[31-33] Other investigators have also observed the beneficial effects of antidepressants on motor and cognitive outcomes.[8,34] In addition, we reported that early antidepressant treatment was significantly associated with greater long-term survival rates among stroke patients both with and without depression.[35] Finally, we demonstrated that escitalopram oxalate, a widely prescribed SSRI, prevents the onset of depressive disorders among patients with an index stroke.[36] In the present study, we examine the effect of escitalopram on cognitive outcome. We hypothesized that patients treated with escitalopram would show more improved performance on neuropsychological tests assessing memory and executive functions than patients who received placebo or underwent Problem Solving Therapy (PST). In addition, we hypothesized that this improvement would be related to an effect of antidepressants on neural circuits that process cognitive information and, thus, would occur independently of a specific rehabilitation program or changes in depressive symptoms.

METHODS

PATIENTS

The 129 patients included in the present study were examined from July 9, 2003, to October 1, 2007, at the University of Iowa Stroke Center. These individuals represent most patients (571 of 799 [71.5%]) assessed for eligibility in our recent multicenter trial investigating the efficacy of escitalopram and PST to prevent the onset of poststroke depression. The characteristics of this trial have been extensively described elsewhere.[36] The participants whose data are reported in this article correspond to the Iowan subsample of that study. Patients recruited at the University of Iowa constitute our study group because they had a rigorous longitudinal follow-up of their cognitive status using complete neuropsychological evaluations performed by the same research assistant and supervised by the same neuropsychologist. Thus, these data correspond to the most complete and reliable information on cognitive outcome available for analysis.

All patients were randomized within 3 months of an index stroke (**Figure 1**). The protocol was approved by the University of Iowa institutional review board, and written informed consent was obtained from each participant. Inclusion criteria included age older than 50 and younger than 90 years and clinical and imaging findings consistent with cerebral hemisphere, brainstem, or cerebellar stroke. Participants with both ischemic and hemorrhagic strokes were included. Patients were excluded if they met *DSM-IV*[37] diagnostic criteria for major or minor (research criteria) depressive disorder or had a 17-item Hamilton Scale for Depression (HAM-D) score greater than 11.

Patients with severe comprehension deficits, as demonstrated by an inability to complete part 1 of the Token Test[38] or patients with neuropsychological testing showing impaired decision-making capacity were excluded. Other exclusion criteria included strokes secondary to complications from an intracranial aneurysm, arteriovenous malformation, or neoplastic process and stroke during the course of myocardial infarction or revascularization surgery. General exclusionary criteria included life-threatening organ failure, severely disabling musculoskeletal disorder, cancer, and neurodegenerative disorders, such as idiopathic Parkinson or Alzheimer diseases. In addition, patients were excluded if they met *DSM-IV* criteria for alcohol or substance abuse or dependence within the 12 months prior to enrollment or if they met *DSM-IV* criteria for a depressive disorder at the time of the index stroke.

NEUROLOGICAL AND NEURORADIOLOGICAL EVALUATIONS

A complete neurological examination was performed at the time of entry. We classified lesion location as right and left hemispheres or brainstem/cerebellar. Mechanism of ischemic stroke was categorized on the basis of the Trial of Org 10172 in Acute Stroke Treatment classification.[39] Therefore, stroke type was classified as hemorrhagic or ischemic, and the ischemic strokes were further categorized as large-artery atherosclerosis, cardioembolic, small-artery occlusion, or an undetermined or other cause. Severity of stroke was recorded using the National Institutes of Health Stroke Scale.[40] Neuroimaging scans were obtained from the treating hospital for analysis by a radiologist who was masked to the treatment assignment. There was no standardized imaging protocol.

EXPERIMENTAL DESIGN AND TREATMENT

Patients were randomized by 1 team member not involved in any evaluation. Specifically, we randomly assigned the 3 treatments using computer-generated random numbers of 1, 2, or 3 to escitalopram (10 mg, once daily in the morning, for patients $<$65 years and 5 mg for patients $\geq$65 years), placebo (all pills were identical), or PST. The PST used in this study was a manual-based intervention originally developed in the United Kingdom for treating medical patients with depression[41] that has been applied in the United States.[42] A rater masked to drug assignment and not involved in the administration of PST evaluated patients.

ASSESSMENT INSTRUMENTS

Patients were administered the Structured Clinical Interview for *DSM-IV*[43] at the initial evaluation and at 3-, 6-, 9-, and 12-month follow-ups. 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 for *DSM-IV* and *DSM-IV-TR* criteria.[37,43] The HAM-D, Hamilton Anxiety Rating Scale,[44] and Functional Independence Measure (FIM)[45] were administered at the initial and each follow-up interviews. Socioeconomic status was determined using the Hollingshead and Redlich classification.[46] Adverse effects were recorded using a detailed ad hoc instrument listing the described adverse effects of escitalopram.

NEUROPSYCHOLOGICAL TESTING

The test battery used in this study had an emphasis on memory and executive functioning. Neuropsychological testing was performed at baseline and at the end of the intervention phase for 70 to 85 minutes by a trained technician masked to the patient treatment status. Most of the tests had alternate forms to minimize practice effects during repeated testing, and administration of alternate forms were counterbalanced to prevent order effects. All tests were standardized instruments with published norms appropriate for use with the subjects in this study. The neuropsychological tests included:

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[47] This 25- to 30-minute battery assesses functioning in 5 domains (immediate memory, visuospatial/constructional, language, attention, and delayed memory). These domains are evaluated by 12 individual subtests, including List Learning, List Recall, List Recognition, Story Memory, Story Recall, Figure Copy, Figure Recall, Line Orientation, Picture Naming, Semantic Fluency, Digit Span, and Coding. This battery provides age-corrected norms for overall performance (total scale score) and scores in each domain.

Trail-Making Test Parts A and B.[48] This test assesses psychomotor processing speed and cognitive flexibility.

Controlled Oral Word Association.[49] This verbal fluency task assesses one's ability to initiate and maintain effort and requires the subject to rapidly produce words beginning with specified letters.

Wechsler Adult Intelligence Scale–III Similarities.[50] This test of abstract thinking requires the subjects to identify commonalities between word pairs.

Stroop Test.[51] This test of selective attention and response inhibition has 3 trials lasting 45 seconds each: (1) color naming, (2) color reading, and (3) color-word interference, also known as the Stroop effect.

STATISTICAL ANALYSIS

We conducted univariate analyses using 2 independent sample *t* tests or 1-way analysis of variance. Mann-Whitney or Kruskal-Wallis tests were used when data did not follow the statistical assumptions of the *t* test or analysis of variance, respectively. Categorical data were analyzed using the Fisher exact test or logistic or multinomial regression.

We assessed whether treatment predicted the change in neuropsychological scores between baseline and end of treatment evaluations after controlling for possible confounders. The confounders investigated were age, education, change in HAM-D scores, time elapsed between index stroke and start of treatment, baseline FIM score, and the stroke mechanism. The rationale for considering each of these variables as a confounder include the following: the change in HAM-D scores sought to control for the effect of depression on neuropsychological performance, particularly in the case of executive functions; the time from stroke to initiation of treatment sought to control for the spontaneous recovery of function that is observed during the subacute phase of stroke; stroke mechanism is related to the type and severity of cerebrovascular illness; and baseline FIM scores provide a measure of the severity of stroke when starting escitalopram treatment. We built several multiple linear regression models for each outcome of interest, including the aforementioned covariates. The models with the smallest corrected Akaike information criterion[52] were preferred for each of the neuropsychological outcomes. Models' assumptions were assessed with residual and influence analyses. Regression analyses were performed using the intent-to-treat sample. To this end, we assumed data were missing at random and imputed missing data 5 times using the Markov chain Monte Carlo method.[53] All regression results reported are adjusted according to the methods recommended by Rubin.[54]

All analyses were performed using SAS, version 9.1.3 (SAS Institute Inc, Cary, North Carolina). All *P* values reported are 2-tailed. Significance level was set at $P \leq .05$.

Table 1. Characteristics of Poststroke Patients Randomized to Receive Placebo, Escitalopram, or Problem-Solving Therapy

Characteristic	No. (%) by Treatment: Placebo (n=45)	Escitalopram (n=43)	Problem-Solving Therapy (n=41)	Kruskal-Wallis χ^2_2	*P* Value
Age, mean (SD), y	64.2 (13.9)	60.8 (14.4)	68.9 (11.7)	$F_{2,126}$=3.7	.03
Male sex	29 (64.4)	26 (60.5)	21 (51.2)		.78[a]
Married	27 (60.0)	23 (53.5)	19 (46.3)		.45[a]
Education, mean (SD), y	13.0 (2.9)	13.4 (3.1)	14.4 (2.9)	4.1	.13
Right-handed	42 (93.3)	35 (81.4)	32 (78.0)		.64[a]
Socioeconomic class IV-V[b]	13 (28.9)	12 (27.9)	10 (24.4)		.91[a]
Previous history of mood disorder	2 (4.4)	3 (7.0)	2 (4.9)		.47[a]
HAM-D score, mean (SD)					
Baseline	6.9 (3.5)	7.3 (3.9)	7.4 (3.4)	2.1	.36
Closeout	7.1 (6.1)	7.4 (5.0)	6.1 (5.2)	1.8	.40
Medical comorbidity					
Systolic blood pressure, mean (SD), mm Hg	144.0 (23.1)	137.8 (26.2)	146.8 (20.6)	$F_{2,126}$=2.0	.14
Hypertension	34 (75.6)	27 (62.8)	34 (82.9)		.04[a]
Low-density lipoprotein cholesterol, mean (SD), mg/dL	121.5 (48.1)	118.1 (41.1)	112.1 (42.8)	0.7	.70
Hypercholesterolemia	13 (28.9)	11 (25.6)	10 (24.4)		.94[a]
Diabetes mellitus	11 (24.4)	17 (39.5)	8 (19.5)		.14[a]
Coronary artery disease	10 (22.2)	13 (30.2)	14 (34.1)		.39[a]
Congestive heart failure	2 (4.4)	8 (18.6)	6 (14.6)		.09[a]
Atrial fibrillation	6 (13.3)	7 (16.3)	9 (22.0)		.49[a]
Chronic obstructive pulmonary disease	3 (6.7)	7 (16.3)	4 (9.8)		.35[a]
Cumulative illness rating scale total score, mean (SD)	1.8 (0.5)	1.9 (0.5)	1.8 (0.4)	0.8	.68
Stroke characteristics and functional impairment					
Hemorrhagic stroke	5 (11.1)	2 (4.7)	4 (9.8)	Likelihood ratio, χ^2_8=10.8	.22
Ischemic stroke					
Large-artery atherosclerosis	10 (22.2)	13 (30.2)	9 (22.0)		
Cardioembolic	8 (17.8)	13 (30.2)	6 (14.6)		
Small-artery occlusion	16 (35.6)	5 (11.6)	10 (24.4)		
Unidentified/other	6 (13.3)	10 (23.3)	12 (29.3)		
Supratentorial lesions	39 (86.7)	33 (76.7)	30 (73.2)		.27[a]
Left-side lesions	23 (51.1)	25 (58.1)	16 (39.0)		.21[a]
Lacunar infarctions	18 (40.0)	12 (27.9)	13 (31.7)		.49[a]
NIHSS score, mean (SD)	6.2 (2.1)	7.1 (3.0)	5.8 (2.4)	$F_{2,126}$=3.0	.06
Baseline FIM total score, mean (SD)	120.8 (5.6)	118.9 (12.7)	116.2 (12.4)	3.0	.23
Time from index stroke to treatment start, median (IQR), d	25.0 (14.0-43.0)	30.0 (19.0-60.0)	32.5 (23.5-53.5)	3.6	.17

Abbreviations: FIM, Functional Independence Measure; HAM-D, 17-item Hamilton Scale for Depression; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

SI conversion factor: To convert low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259.

[a] Fisher exact test.

[b] Class IV indicates some high school, completion of high school, or attainment of general educational development, and employment in an unskilled trade; and class V indicates completion of an eighth-grade education or less and employment at an unskilled trade or unemployment, per Hollingshead and Redlich classification.[46]

RESULTS

PARTICIPANTS

A total of 129 patients were randomized and 117 began treatment (Figure 1). Twelve (9.3%) patients dropped out before receiving the first drug dose or PST session for the following reasons: 5 participants did not want to commit the time, 4 patients' families withdrew consent, 2 developed depression, and 1 developed an illness. Of the total 117 patients who began treatment, 7 patients (6.0%) dropped out of the study, 3 within 90 days, 2 between 91 and 180 days, and 2 between 181 and 365 days. Of these dropouts, 2 patients died (sepsis and lung cancer), 2 developed an intercurrent illness judged to be incompatible with their continuation, 2 could not be contacted, and 1 violated the protocol. We compared demographic and baseline variables (eg, age, sex, and baseline HAM-D and FIM scores) in the group of patients who were randomized to treatment with those who dropped out. A logistic regression analysis found no demographic or baseline impairment variables related to postrandomization drop-out.

Demographic characteristics of the intent-to-treat sample (n=129) are shown in **Table 1**. There were 45 patients randomized to placebo, 43 to escitalopram, and 41 to PST.

BACKGROUND CHARACTERISTICS

Descriptive statistics of baseline demographic, neurological, psychiatric, and functional variables are presented in Table 1. Patients who received PST were older than patients randomized to escitalopram or placebo and

Table 2. Baseline and Closeout Neuropsychological Scores of Poststroke Patients Randomized to Receive Placebo, Escitalopram, or Problem-Solving Therapy

Characteristic	Mean (SD, Percentile) by Treatment			Kruskal-Wallis χ^2_2 for Change in Score	*P* Value
	Placebo	Escitalopram	Problem-Solving Therapy		
Age-corrected RBANS score					
Total scale score					
Baseline	85.3 (14.4, 16)	80.7 (16.8, 10)	88.2 (16.8, 21)	10.6	<.01
Closeout	91.0 (17.8, 27)	89.8 (15.1, 25)	89.1 (15.7, 23)		
Delayed memory					
Baseline	88.1 (17.7, 21)	84.2 (17.7, 14)	88.6 (19.8, 23)	13.4	.001
Closeout	94.2 (20.7, 34)	96.6 (14.3, 42)	89.1 (20.7, 23)		
Immediate memory					
Baseline	91.1 (19.8, 27)	83.4 (20.3, 13)	93.2 (17.2, 32)	8.4	.01
Closeout	98.5 (19.3, 47)	95.1 (17.3, 37)	94.9 (18.0, 37)		
Attention					
Baseline	86.2 (17.2, 18)	82.6 (18.4, 13)	90.0 (17.9, 25)	1.6	.44
Closeout	91.6 (16.0, 30)	89.2 (19.6, 23)	91.7 (16.4, 30)		
Language					
Baseline	91.4 (9.9, 27)	89.3 (16.3, 23)	94.7 (14.0, 37)	1.0	.61
Closeout	93.0 (10.3, 32)	93.8 (13.4, 34)	97.7 (11.9, 45)		
Visuospatial/constructional					
Baseline	87.4 (18.2, 19)	83.4 (20.7, 13)	88.2 (17.2, 21)	3.8	.15
Closeout	89.0 (19.8, 23)	86.9 (18.0, 19)	85.7 (16.9, 18)		
Trail-Making Test time					
Trail-Making Test B					
Baseline	146.1 (113.0, 9)	113.6 (76.3, 16)	147.2 (106.8, 16)		
Closeout	120.6 (75.1, 16)	122.0 (97.4, 9)	141.3 (95.1, 9)		
Trail-Making Test B – Trail-Making Test A, mean (SD)					
Baseline	82.5 (76.0)	58.9 (65.0)	87.2 (86.1)	1.7	.42
Closeout	60.9 (51.6)	65.4 (74.7)	94.5 (84.3)		
Controlled Oral Word Association raw score					
Baseline	28.8 (13.6, 25)	28.2 (14.4, 16)	28.9 (12.2, 37)	2.4	.30
Closeout	31.8 (13.8, 37)	33.6 (13.6, 37)	30.6 (12.5, 37)		
Stroop color-word trial raw score					
Baseline	26.1 (12.9, 8)	29.7 (14.4, 16)	24.3 (12.7, 27)	0.1	.96
Closeout	28.9 (12.5, 14)	30.4 (13.8, 16)	26.6 (11.3, 39)		
Age-corrected Wechsler Adult Intelligence Scale–III Similarities score					
Baseline	9.8 (3.2, 50)	9.2 (3.0, 37)	10.0 (3.4, 50)	2.8	.24
Closeout	10.3 (3.1, 50)	9.6 (2.9, 50)	10.7 (2.9, 63)		

Abbreviation: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

had hypertension more often than patients randomized to escitalopram. There were no differences between the 3 groups in the mechanism, type, severity, or location of stroke or baseline FIM scores. Overall, this group of patients had mild to moderate strokes.

One patient (2.2%) in the placebo group, 3 (7.0%) in the escitalopram group, and 2 (4.9%) in the PST group were receiving benzodiazepines. No patient in the placebo group, 1 (2.3%) in the escitalopram group, and 1 (2.4%) in the PST group were receiving cholinesterase inhibitors. We found no evidence of a difference between the 3 groups and the proportion of subjects receiving medications that could affect cognition.

NEUROPSYCHOLOGICAL VARIABLES

There were no differences between the 3 groups in baseline scores of neuropsychological tests probing memory and executive functioning (**Table 2**). We looked for differences between treatment groups in change in RBANS total score as well as in its attention, memory, language, and visuospatial/constructional domains. In addition, we examined the difference in Trail-Making Test B and Trail-Making Test A execution times, the Controlled Oral Word Association total score, the Stroop Color-Word interference score, and the Wechsler Adult Intelligence Scale–III Similarities score.

RBANS Total Score

Before controlling for other covariates, we found a difference in the change in RBANS total score between the 3 groups (Kruskal-Wallis $\chi^2_2 = 10.6$, $P < .01$). The change in score was higher among participants who received escitalopram compared with the participants in the other 2 groups. After controlling for change in HAM-D and the stroke mechanism, we found that the escitalopram group presented a higher change in score compared with the other 2 groups (adjusted mean change in score: escitalopram group = 9.9; PST group = 1.9, $P < .01$; placebo

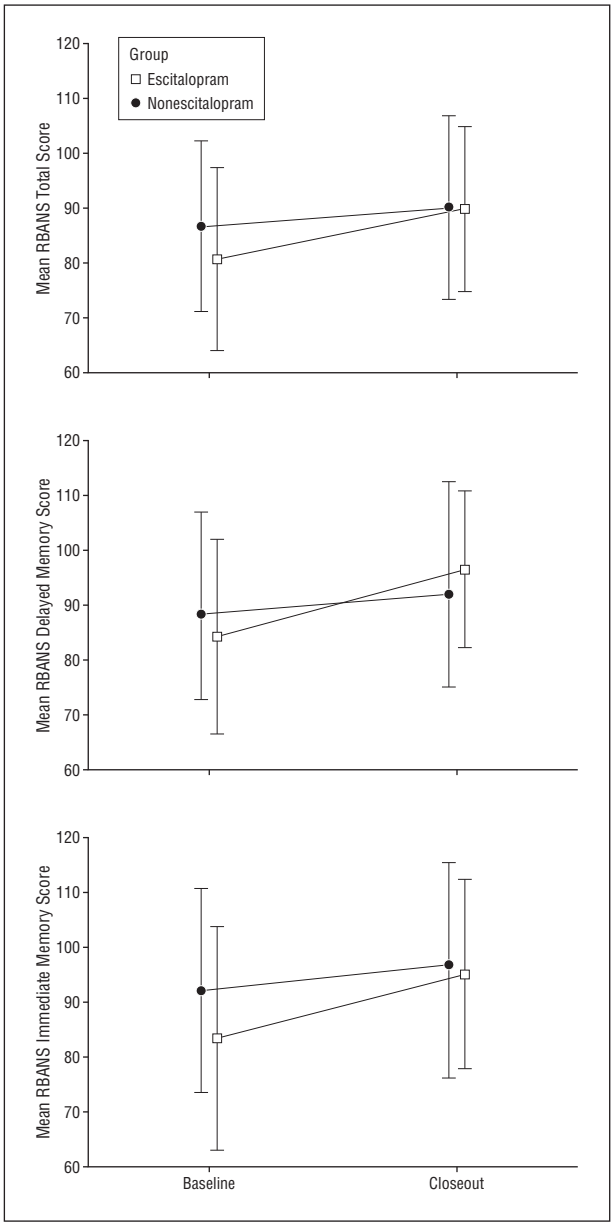

Figure 2. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores by patients receiving and not receiving escitalopram. Error bars indicate SDs.

group = 4.0, $P = .02$). Because the objective of this study was to determine the effect of escitalopram on the longitudinal course of cognitive variables, we collapsed the placebo and PST groups into a single group of patients not receiving escitalopram (referred to as the nonescitalopram group) and compared it with the group receiving escitalopram. After controlling for change in HAM-D score and stroke mechanism, there was an effect of escitalopram on the change in RBANS total score (adjusted mean change in score: escitalopram group = 10.0; nonescitalopram group = 3.1, $P < .01$) (**Figure 2**).

RBANS Delayed Memory Score

Before controlling for other covariates, we found a difference in the change in RBANS delayed memory score between the 3 groups (Kruskal-Wallis $\chi^2_2 = 13.4$, $P < .01$). The change in score was higher among participants receiving escitalopram compared with the participants in the other 2 groups. After controlling for time elapsed between the index stroke and treatment start, change in HAM-D score, stroke mechanism, and the interaction between treatment and change in HAM-D score (not significant), the group receiving escitalopram had a greater change in score than the other 2 groups (adjusted mean change in score: escitalopram group = 11.2, PST group = –0.7, $P < .001$; placebo group = 3.9, $P = .02$). When comparing the escitalopram group with the nonescitalopram group, we observed a significant effect of escitalopram on the change in RBANS delayed memory score after controlling for time elapsed between the index stroke and treatment start, change in HAM-D score, and stroke mechanism (adjusted mean change in score: escitalopram group = 11.3, nonescitalopram group = 2.5, $P < .01$) (Figure 2).

RBANS Immediate Memory Score

Before controlling for other covariates, we found a difference in the change in RBANS immediate memory score between the 3 groups (Kruskal-Wallis $\chi^2_2 = 8.4$, $P = .01$). The change in score was higher among participants who received escitalopram compared with the participants in the other 2 groups. After controlling for time elapsed between the index stroke and treatment start, change in HAM-D score, stroke mechanism, and the interaction between treatment and change in HAM-D score (not significant), the group receiving escitalopram presented a higher change in score than the other 2 groups (adjusted mean change in score: escitalopram group = 13.4, PST group = 2.0, $P < .001$; placebo group = 7.2, $P = .04$). We also observed an effect of escitalopram on the change in RBANS immediate memory score after controlling for time elapsed between the index stroke and treatment start, change in HAM-D score, and stroke mechanism (adjusted mean change in score: escitalopram group = 13.5, nonescitalopram group = 5.3, $P = .01$) (Figure 2).

We did not find an effect of treatment in the change in RBANS attention, language, or visuospatial/constructional domains, Trail-Making Test, Controlled Oral Word Association, Stroop Color-Word Trial, or Wechsler Adult Intelligence Scale–III Similarities scores before or after controlling for other covariates.

There was not an effect of age, lesion location, or type or mechanism of stroke on these outcome measures. There were no significant correlations of change in RBANS score with change in HAM-D or Hamilton Anxiety Rating Scale scores.

We examined if the reported changes in neuropsychological function had an impact on the functional status of stroke patients as measured by the FIM cognitive domain. We found a difference in changes in the FIM cognitive domain scores between the participants receiving escitalopram and those not receiving it (Mann-Whitney $U = 2181$, $P = .05$). Similarly, participants who received escitalopram showed greater changes in FIM memory scores than those receiving placebo or PST (Kruskal-Wallis $\chi^2_2 = 6.83$, $P = .03$). When change in FIM memory scores of those receiving escitalopram are compared with those not receiving it, the difference persists (Mann-Whitney

$U = 2291$, $P = .01$). Furthermore, there was a positive correlation between change in RBANS total scores and change in FIM total scores (Spearman $\rho = 0.25$, $P = .02$). Thus, the reported changes in neuropsychological test scores result in a measurable improvement in activities of daily living related to these changes.

We recorded living conditions before and after stroke for all participants. We also recorded occupational level data before and after the stroke. Most patients (92.2%) did not change living conditions after their stroke. Four (10.3%) participants receiving placebo, 2 (5.6%) participants receiving PST, and 1 (2.9%) participant receiving escitalopram started living in a more dependent environment after their stroke. Despite having slightly less severe strokes, patients receiving placebo were almost 4 times more likely to be in a more structured environment than patients receiving escitalopram after stroke, a difference that was not statistically significant.

There was no difference between groups in the change in occupational level before and after stroke. Eight (20.5%) patients in the placebo group, 5 (13.9%) in the escitalopram group, and 5 (14.3%) in the PST group had worse occupational levels after stroke, while 2 (5.6%) of the subjects receiving escitalopram augmented their occupational level after stroke.

ADVERSE EVENTS AND EFFECTS

The frequency of adverse events or medication adverse effects is shown in **Table 3** for all patients who received at least the first drug dose or PST session. There were no differences between groups in the frequency of any of these events. In addition, there were no differences between the groups in the frequency of hospital admissions resulting from gastrointestinal bleeding or falls, which have been previously described as complications of SSRI treatment.

Table 3. Adverse Events in Poststroke Patients Receiving at Least the First Drug Dose or PST Session

Adverse Effect	No. (%) by Treatment		
	Placebo (n=41)	Escitalopram (n=39)	PST (n=37)
Gastrointestinal			
Dry mouth	22 (53.7)	14 (35.9)	17 (45.9)
Constipation	11 (26.8)	13 (33.3)	13 (35.1)
Indigestion	9 (22.0)	11 (28.2)	15 (40.5)
Anorexia	5 (12.2)	12 (30.8)	7 (18.9)
Diarrhea	8 (19.5)	7 (17.9)	13 (35.1)
Abdominal pain	7 (17.1)	5 (12.8)	9 (24.3)
Nausea	4 (9.8)	4 (10.3)	8 (21.6)
Bleeding	1 (2.4)	1 (2.6)	1 (2.7)
Cardiovascular			
Tachycardia	32 (78.0)	34 (87.2)	32 (86.5)
Chest pain	5 (12.2)	8 (20.5)	9 (24.3)
Palpitations	3 (7.3)	3 (7.7)	4 (10.8)
Other			
Dizziness	31 (75.6)	33 (84.6)	31 (83.8)
Fatigue	18 (43.9)	22 (56.4)	15 (40.5)
Increased sweating	6 (14.6)	12 (30.8)	11 (29.7)
Falls	1 (2.4)	1 (2.6)	1 (2.7)
Sexual			
Decreased libido	9 (22.0)	11 (28.2)	12 (32.4)
Anorgasmia in women	2 (14.3)	2 (13.3)	2 (11.1)
Ejaculation disorders in men	2 (7.4)	2 (8.3)	3 (15.8)
Impotence in men	2 (7.4)	2 (8.3)	3 (15.8)

Abbreviation: PST, Problem-Solving Therapy.

COMMENT

We examined the effect of escitalopram treatment on cognitive recovery following stroke. Compared with patients receiving placebo or PST, patients receiving escitalopram showed higher scores in neuropsychological tests assessing global cognitive functioning and, specifically, neuropsychological measures probing verbal and visual memory. Importantly, the reported changes in neuropsychological performance resulted in an improvement in related activities of daily living. While one could argue that the findings are due to chance given the number of outcomes tested, most findings represent large effects that translate into P values that would remain significant even after applying a conservative approach of adjusting for multiple comparisons (eg, Bonferroni method).

The beneficial effect of escitalopram on cognitive recovery was independent of its effect on depressive symptoms and was not influenced by stroke type or mechanism of ischemic stroke. In addition, escitalopram was well tolerated and the frequency of adverse effects related to its administration was not different than that observed among patients receiving placebo.

Before discussing the implications of these findings, we must mention the limitations of the present study. First, we obtained reliable neuropsychological data on nondepressed patients with mild to moderate strokes recruited in a specialized unit; thus, the results cannot be extrapolated to other stroke patient groups with different characteristics. Second, patients receiving escitalopram were younger than patients in the other groups. However, age was not a significant factor in our statistical models, suggesting that it did not influence the results. Finally, though we examined initial clinical computed tomography and magnetic resonance imaging scans, we did not perform research studies that would have allowed us to examine the effect of important baseline neuroimaging variables (eg, hippocampal and white matter hyperintensity volumes) on cognitive outcomes.

Given these limitations, what are the implications of the present findings? Cognitive deficits are a major contributor to disability and decreased quality of life after stroke.[20] The presence of cognitive impairment has been associated with institutionalization and increased caregiver burden and health care costs.[55-58] Furthermore, it has been shown that dementia is a strong predictor of mortality after stroke.[59,60] A therapeutic intervention that fosters cognitive recovery of stroke patients has the potential to significantly reduce the burden of this disease.

There are several questions that require clarification before considering SSRI antidepressants as valuable candidates for restorative intervention. Is the cognitive enhancement effect of escitalopram a phenomenon observed only among stroke patients or should we expect a similar effect among other elderly populations? Selec-

tive serotonin reuptake inhibitors have a beneficial effect on cognitive functions among elderly patients with major depression.[61,62] It has also been reported that previous antidepressant use is associated with increased frontal gray matter volumes among elderly patients with depression.[63] Serotonin might have a regulatory effect on memory functioning among healthy controls, particularly in what relates to storage and consolidation of new information.[64] For instance, acute tryptophan depletion, an experimental paradigm that produces a reduction in serotonergic neurotransmission, has been associated with long-term memory impairment, an effect that is independent of mood or attentional changes.[64,65] On the other hand, acute intravenous administration of 10 mg of citalopram was shown to enhance verbal memory consolidation.[66] However, these acute effects might be qualitatively different than those related to the chronic administration of SSRIs among stroke patients. The early stages of recovery from stroke are characterized by increased expression of neurotrophic factors, increased expression of proteins involved in synaptogenesis and axonal sprouting, increased release of inflammatory cytokines, and proliferation of neural stem cells.[67-69] These changes might provide a unique biological environment that may enhance the effect of antidepressants.

We have hypothesized that escitalopram would have a beneficial effect on memory and executive functions. However, an effect was only observed in immediate memory and delayed recall. This is consistent with the literature on serotonergic modulation of cognitive functioning among healthy subjects. Acute tryptophan depletion impairs memory consolidation but does not affect executive functions associated with dorsolateral prefrontal circuits.[70-73] Conversely, tryptophan supplementation has been associated with improved performance in memory tests.[74,75] Although there is some evidence of serotonergic modulation of reversal learning and decision-making tasks related to ventromedial prefrontal circuits,[76,77] these types of tasks were not included in the neuropsychological battery used in the present study.

Previous studies show that drugs modulating aminergic transmission have a beneficial effect on stroke recovery.[16] However, a meta-analysis of the efficacy of amphetamine to enhance recovery after stroke could not reach a definitive conclusion on this issue and recommended further research.[78] As demonstrated in patients with neurodegenerative conditions, cholinesterase inhibitors improve their performance in memory tests. A similar beneficial effect has also been reported in patients with cerebrovascular disease.[14,15,18,19] Cholinergic agents, such as donepezil, may also improve fluency and comprehension among aphasic patients.[13]

The present findings suggest that chronic administration of SSRIs may also improve cognitive function in patients with stroke. The magnitude of this change appears to be greater for escitalopram than cholinesterase inhibitors (ie, 0.15-0.22 standard deviation [SD] units in the case of cholinesterase inhibitors vs 0.44-0.74 SD units for escitalopram).[79] We must acknowledge, however, that the efficacy of cholinesterase inhibitors was tested on multicenter trials, which usually present smaller effect sizes than single-center studies. In addition, SSRIs have a more benign adverse effect profile than cholinesterase inhibitors. For instance, mortality was significantly greater among stroke patients who received donepezil compared with patients who received placebo (odds ratio, 4.57; 95% confidence interval, 1.3-16.1).[79] Antidepressants, on the other hand, might increase survival after stroke.[35] Thus, long-term administration of SSRIs appears to be an effective and safe treatment option to improve cognitive outcomes among patients with cerebrovascular disease.

Another important question relates to the mechanisms involved in this effect of escitalopram. Cognitive function recovery following stroke is a complex process mediated by multiple mechanisms, including enhanced regional metabolism, resolution of diaschisis, and neuroplastic changes.[80] Serotonergic agents may exert their effects at different levels of the brain, interacting with other neurotransmitter systems (eg, modulation of cholinergic transmission in forebrain structures[81] or modulation of prefrontal function).[76] However, there is growing evidence that SSRIs produce neuroplastic changes in the hippocampus and the cerebral cortex. For instance, fluoxetine increases the proliferation of neuronal precursors in the subgranular zone of the dentate gyrus.[24] A recent study has also shown that fluoxetine restores cortical plasticity in the visual system of adult amblyopic rats, fostering the recovery of visual function. This effect is probably mediated by a decrease in intracortical inhibition and increased expression of brain-derived neurotrophic factor.[82] Similarly, sertraline appears to enhance plastic changes in the visual cortex of human subjects.[83] Furthermore, sertraline may prevent brain atrophy, improve motor performance, and delay mortality in a rat model of Huntington disease.[84] Although a causal relationship between structural changes and behavioral performance has not been established, we can speculate that the improvement in verbal and visual memory observed in the escitalopram group is probably related to increased dentate gyrus neurogenesis and remodeling of the hippocampal circuitry. In this sense, Dupret et al[85] reported that selective ablation of newly generated hippocampal neurons of transgenic mice results in severe deficits in spatial relational memory, suggesting that hippocampal neurogenesis is necessary for complex forms of learning.

Overall, whatever may be the mechanism of improved cognitive recovery, this study has shown, for the first time, that escitalopram, an SSRI, is associated with improved cognitive recovery following stroke compared with placebo and PST. The utility of antidepressants in the process of poststroke recovery deserves to be further investigated.

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