Risk Factors for and Correlates of Poststroke Depression Following Discontinuation of Antidepressants

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The authors randomly assigned nondepressed patients at least 3 months poststroke to receive nortriptyline, fluoxetine, or placebo for 3 months using double-blind methodology. Patients were followed at 3, 6, 9, and 21 months for new onset of depression. In patients treated with antidepressants, lesion volume and degree of social impairment were associated with subsequent late-onset of poststroke depression at 6 and 9 months. In the placebo group, severity of impairment in activities of daily living, at 3 and 9 months, was associated with late onset poststroke depression. Differences in the clinical/pathological correlates may reflect subtle differences in the pathophysiology of poststroke depression following prophylactic antidepressants.

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In a longitudinal study of 142 acute stroke patients, 39% of patients not depressed during the acute in-hospital evaluation developed major or minor depression between 3 months to 2 years after stroke.[1] Several other investigators have also shown that a significant proportion of poststroke depressions begin after the acute stroke period.[2] In a prior study, we reported that late-onset poststroke depression, defined as occurring more than 3 months following stroke, was associated with more severe social impairment than acute onset depression.[3] Late-onset poststroke depression has received relatively little attention compared with acute-onset depressions,[4] warranting further study.

The effectiveness of prophylactic antidepressants to prevent or delay late-onset poststroke depression continues to be debated. Several studies have examined this issue.[5–7] Palomaki et al.[6] administered mianserin (60 mg/day) to 100 consecutive acute stroke patients during 1 year using a placebo-controlled double-blind design; they found no difference in the rate of late-onset depression comparing mianserin and placebo. Rasmussen et al.[5] examined the utility of sertraline in preventing

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depression in 137 patients randomly assigned to 12 months of sertraline (N = 70) or placebo (N = 67). Using a Hamilton Rating Scale for Depression (HAM-D) score of >18 as an indication of clinically significant depression, the frequency of depression at the end of 52 weeks of treatment was 8.2% (95% CI 2.4–13.9%) in the sertraline-treated group versus 22.8% (95% CI 13.7–32.0%) in the placebo group. The 17-item HAM-D scores were significantly lower in the sertraline group than the placebo group from 21 weeks to 52 weeks following treatment.

Narushima et al.[7] found that fluoxetine and nortriptyline prevented or delayed the onset of poststroke depression compared with placebo during a 12-week period of administration. After 12 weeks of treatment, patients receiving nortriptyline had significantly higher rates of depression and higher mean HAM-D scores at 9 months (i.e., 6 months after treatment ended) than patients given placebo. At 12- and 24-month follow-up, there were no intergroup differences in the frequency of depression. This study did not examine the clinical or pathological characteristics of the patients who developed late-onset poststroke depression (i.e., after the 12-week treatment period) to see if any factors predicted or were associated with late-onset poststroke depression.

The present study was undertaken, using these data cited above from 12 weeks to 24 months, to determine whether there are identifiable risk factors which would predict the onset of depression after antidepressant medications are discontinued. Based on the results of our previous studies, we hypothesized that prior treatment with antidepressants,[7] left frontal lesion location,[8,9] and social impairment[3] would all be associated with late-onset poststroke depression.

METHOD

This study sample was described in our previous publication.[7] It consisted of 48 nondepressed patients, 18 to 85 years of age, with acute thromboembolic stroke or intracerebral hemorrhage, admitted to Younkers Rehabilitation Center at Iowa Methodist Medical Center in Des Moines, IA (N = 41); the department of neurology at University of Iowa Hospitals and Clinics in Iowa City (N = 1), or the VAMC in Iowa City (N = 2), or the Raul Carrea Neurological Institute in Buenos Aires, Argentina (N = 4).

Patients were randomly assigned to 12 weeks of treatment with fluoxetine (N = 23), nortriptyline (N = 16), or placebo (N = 17), unless one of the active drugs was contraindicated. Nortriptyline was contraindicated in patients (N = 7) with cardiac conduction abnormalities, and fluoxetine was contraindicated in patients (N = 5) with intracerebral hemorrhage. These patients were subsequently randomly assigned to receive the noncontraindicated medication or placebo. Doses of nortriptyline were 25 mg/day for week 1, 50 mg/day for weeks 2 to 3, 75 mg/day for weeks 3 to 6, and 100 mg/day for the final 6 weeks. Doses of fluoxetine were 10 mg/day for the first 3 weeks, 20 mg for weeks 4 to 6, 30 mg for weeks 7 to 9 and 40 mg for weeks 10 to 12. At the end of the treatment period, patients and raters were no better than chance at guessing whether they received active or placebo medication.[10] Patients were seen for follow-up at 3, 6, 9, and 12 weeks during treatment, and 3, 6, 9, and 21 months following treatment with the exception of the Argentinian patients, who had no follow-up after 12 weeks.

Some of the initially nondepressed patients were given antidepressants by their primary care physicians during the naturalistic 21-month follow-up. Three placebo patients, four nortriptyline and four fluoxetine patients took antidepressants during the follow-up. The mean duration of continued treatment for these 11 patients was 6 months. There were no intergroup differences in the frequency or duration of receiving antidepressants after the treatment period.

Assessment

Psychiatric assessment included administration of a version of the Present State Examination (PSE)[11] that is reliable and valid in patients with stroke[12] and modified to identify DSM-IV-TR[13] symptoms of depression and anxiety disorder at the initial and final treatment evaluation (i.e., 12 weeks), and 3, 6, 9, and 21 months following treatment. Initially and at each 3-week evaluation during treatment, the 17-item form of the HAM-D[14] was administered. We have previously demonstrated the reliability and validity of the HAM-D in patients with stroke.[12,15]

The Hamilton Rating Scale for Anxiety (HAM-A)[16] has demonstrated reliability and validity in poststroke patients.[17] The Johns Hopkins Functioning Inventory (JHFI)[12] quantifies activities of daily living and was administered at each evaluation. The JHFI is a 10-item, 44-point scale on which higher scores indicate greater levels of impairment. We have previously demonstrated the reliability and validity of the JHFI in this patient population.[18] The Mini-Mental State Examination (MMSE) is

a brief cognitive examination[19] with demonstrated reliability and validity in patients with stroke.[20] The Social Functioning Exam (SFE)[21] is a 28-item scale that assesses patients' satisfaction with their social functioning before the stroke (assessed at the in-hospital evaluation) or during the 2 weeks before each follow-up examination. Scores on the SFE range from 0.00 to 1.00, with higher scores indicating greater severity of social impairment. The reliability and validity of this instrument has also been previously demonstrated.[22,23]

Imaging

Computerized tomography or magnetic resonance scans were obtained from the treating hospital as part of the patient's clinical care and transferred onto standardized templates using the method of Damasio.[24] Images were evaluated for the anatomical location and size of the brain injury by a neuroradiologist or a neurologist who was blind to any of the psychiatric findings. Lesion volume, expressed as a percentage of the total brain volume, was calculated from the ratio of the largest cross-sectional area of the lesion on any computed tomography (CT) scan slice to the cross-sectional area of the whole brain on the slice passing through the body of the lateral ventricle.[25] The reliability of this measurement of lesion volume and its subsequent utility in stroke patients have previously been demonstrated.[26]

Statistical Analysis

Frequency distributions of background and neuropsychiatric categorical variables were analyzed using a chi-square test (or Fisher's exact test if the cell size was prohibitively small). We analyzed continuous variables using Wilcoxon test based on the median.

Participants were stratified by initial treatment status, and those who did not develop depression were contrasted with those who developed minor or major depression on measures from the JHFI, the MMSE, and the SFE. An exploratory data analysis was employed for these comparisons. Measures which demonstrated significant differences between groups were then modeled in multiple regression to control for potential confounds and assess for any initial treatment status by depression outcome interactions.

RESULTS

The background characteristics of the patients included in the study are shown in Table 1. There were no significant differences on any of the variables presented in Table 1, with the exception of lesion volume, which was significantly larger with late-onset poststroke depression than in those who were never depressed. There were no significant differences in time since stroke. The depressed group was composed of patients who met DSM-IV criteria for major or minor depressive disorder at some time during the 3 to 24 month follow-up. Among the treated patients, three developed depression at 3 months, two at 6 months, three at 9 months, three at 12 months and none at 24 months. Among the untreated (placebo) patients there were six depressed at 3 months, two at 6 months, none at 9 months, one at 12 months, and one at 24 months. There were no differences in the probability of depression over 24 months related to treatment over the first 3 months (Wilcoxon chi-square = 3.61, df = 2, p = 0.165).

There were no significant differences between the depressed and never-depressed groups in family history of depression, personal history of depression, history of alcohol abuse, or time since stroke. The structural imaging findings are also listed in Table 1. There was no significant difference between the depressed and never-depressed groups regarding lesion location. There was, however, a significantly larger lesion volume among treated depressed compared with the treated never-depressed patients (Table 1) (Wilcoxon tests; chi-square = 5.338, df = 1, p = 0.021). The SFE demonstrated significantly greater impairment among the treated depressed patients compared with the treated never-depressed patients at 6 (Wilcoxon, df = 1, p = 0.0355) and 9 (Wilcoxon, df = 1, p = 0.0280) months (Table 2). Of 13 depressive episodes observed in this group, eight began at 6 months or later. Similarly, the mean scores on the JHFI revealed significantly greater impairment in the placebo-treated depressed group compared with the placebo-treated never-depressed group at 3 (Wilcoxon, df = 1, p = 0.0207) and 9 (Wilcoxon, df = 1, p = 0.0319) months (Table 2). All of the eight depressions in this group began at 3 months or later.

From the comparisons above, we found associations between JHFI scores and the development of depression in untreated patients (months 3 and 9) as well as associations between SFE scores and the development of depression in treated patients (months 6 and 9). These results are summarized in Table 2.

We employed multiple regression with an interaction term to assess whether the differences between depressed and never depressed patients on these measures

(JHFI and SFE) indeed significantly related to the presence or absence of initial treatment. Because of significant differences in lesion volume between depressed and never depressed groups, we controlled for lesion volume in the regression model. Other potential confounding variables such as age and gender were considered in the model, although they were not included as they did not significantly contribute to the model or affect the results. The initial treatment status by depression outcome interaction was not significant for JHFI scores at 3 months or SFE scores. There was a significant effect of initial treatment by depression outcome interaction for JHFI scores at 9 months ($F = 7.6$, $df = 1$, $p = 0.0147$).

DISCUSSION

In this analysis, we found no differences in the probability of depression between the active and placebo-treated groups during the 21 months of follow-up after this 12-week double-blind randomized controlled trial. Among patients who received active antidepressants, the occurrence of depression after stopping the antidepressant was related to larger lesion volume and greater impairment in social function as measured by the SFE. Among patients given placebo, the onset of depression after the placebo period was associated with greater impairment of activities of daily living as measured by the JHFI. Controlling for lesion volume in multiple regression, the association of ADL impairment and depression significantly differed based on the presence or absence of initial treatment.

Before further discussion of these findings, it is important to acknowledge the limitations of this study. Patients enrolled in this study agreed to participate in a double-blind, placebo-controlled treatment trial. Thus, the patients enrolled in this study may not represent a random cross-section of nondepressed patients with stroke. Furthermore, the patients were followed in a naturalistic design from 3 to 24 months following enroll-

TABLE 1. Characteristics of Depressed and Never Depressed Patients Who Received Antidepressant Treatment During the First 3 Months Following Stroke

	Treated Patients		Untreated Patients	
Number (%)	**Never Depressed (N = 20)**	**Developed Depression, Minor or Major (N = 11)**	**Never Depressed (N = 7)**	**Developed Depression, Minor or Major (N = 10)**
Age, median year	68.5	66.0	66.0	70.5
Sex, male	14 (70.0)	9 (81.8)	6 (85.7)	7 (70.0)
Race, white	17 (94.4)	11 (100.0)		
Education, median year	12.5	12.0	10.0	12.0
Marital status, married	14 (70.0)	8 (72.7)	6 (85.7)	5 (50.0)
SES, IV or V	6 (30.0)	5 (45.5)	3 (42.9)	4 (40.0)
Handedness, right	17 (94.4)	11 (100.0)	5 (100.0)	9 (90.0)
Family history of depression	3 (17.7)	1.0 (9.1)	1.0 (20.0)	1.0 (10.0)
Personal history of depression	1 (5.9)	0	0	2 (20.0)
Personal history of alcohol abuse	6 (35.3)	3 (27.3)	1 (20.0)	3 (30.0)
Diagnosis: ischemic	15 (83.3)	9 (81.8)	5 (100.0)	9 (90.0)
Days since last stroke	64.5 (102.0)	39.0 (37)	79.3 (29.0)	25.6 (27.0)
Location of Single Lesion:				
Left side	7 (38.9)	3 (27.3)	3 (60.0)	4 (40.0)
Right side	11 (61.1)	6 (54.6)	2 (40.0)	4 (40.0)
Brainstem	0	2 (18.2)	0	0
Lesion Location:				
Corticalsubcortical	9 (52.9)	6 (54.6)	4 (80.0)	8 (88.9)
Cortical	1 (5.88)	1 (9.1)	0	1 (11.1)
Subcortical	7 (41.2)	2 (18.2)	4 (80.0)	4 (44.4)
Mixed (cortical & subcortical)	1 (5.9)	3 (27.3)	0	3 (33.3)
Left-hemisphere	2 (11.8)	1 (9.1)	3 (60.0)	2 (22.2)
Left-anterior	0	1 (9.1)	1 (20.0)	1 (11.1)
Vascular Distribution:				
MCA	6 (35.3)	5 (45.5)	2 (40.0)	6 (66.7)
PC	4 (25.0)	3 (27.3)	1 (20.0)	0
Mixed (MCA & PC)	2 (11.8)	0	2 (40.0)	2 (22.2)
Lesion volume (%), median*	0.795	7.105	0.83	1.03

*Significantly larger with late-onset poststroke depression than among never depressed (Wilcoxon, $\chi^2 = 5.3382$, $df = 1$, $p = 0.0209$)
Abbreviations: MCA = middle cerebral artery, PC = posterior circulation

ment in the study. During this time, some of the patients received antidepressant medication, and the intensity of physical or speech therapy likely varied and may have affected the outcome. However, the fact that 30% of the active and 20% of the placebo patients received active antidepressants after the treatment period would not likely explain why the clinical correlates of depression were different between the active and placebo groups. Our assessment of lesion volume was limited by the use of different scanners in the course of treatment and the use of an approximation to lesion volume rather than the automated segmentation method currently used.[27] Additionally, we conducted 28 comparisons among depressed and never depressed groups in this exploratory data analysis. At least one comparison would be expected to reach statistical significance by chance, and some findings may have indeed occurred by chance. We did, however, replicate a finding from a previous study[3] using an entirely different population which supported our hypothesis that impaired social function would be related to delayed onset depression.

It is difficult to establish whether impairments in social functioning or activities of daily living are predictors, causes, or consequences of poststroke depression. Because of sample size, the current analysis has limited power to address this challenging, albeit important, question. However, potentially salient clinical predictors were indeed identified. Our power was further limited to assessing whether associations observed truly differed significantly based on treatment status. Despite this limitation, we were able to demonstrate that the association between activities of daily living impairment (JHFI) and depression at 9 months in untreated patients indeed differed significantly by initial treatment status.

Given these caveats, how might these findings be construed to indicate which patients are at highest risk for the development of delayed onset poststroke depression? Lesion volume, activities of daily living impairment and social impairment were all significantly associated with the development of late-onset poststroke depression. These findings are supported by other studies. Sharpe et al.[28] also reported that lesion volume predicted depression in long-term survivors of stroke. Pohjasvaara et al. showed an association between delayed onset depression and functional physical impairments.[29]

This study found that patients who received prophylactic antidepressants may be at greater risk for future depression with large lesions and impaired social func-

TABLE 2. Impairment Variables of Patients Based on Depression and Treatment Status

	Treated Patients			Untreated Patients		
	Never Depressed (N = 14)*	Developed Depression, Minor or Major (N = 11)	Level of Significance (p value), df = 1	Never Depressed (N = 6)*	Developed Depression, Minor or Major (N = 10)	Level of Significance (p value), df = 1
Johns Hopkins Functioning Inventory						
3 months	1.0	2.0	0.2367	1.0	4.5	**0.0207**
6 months	2.0	2.0	0.7136	1.0	5.5	0.0862
9 months[†]	2.0	2.0	0.3484	2.0	5.0	**0.0319**
21 months	2.0	3.0	0.5093	4.0	5.0	0.3921
Mini-Mental State Examination						
3 months	28.0	28.5	0.5349	27.0	27.0	0.7382
6 months	27.5	28.0	0.8230	28.0	25.0	0.8699
9 months	27.0	28.0	0.3243	28.0	27.0	0.2817
21 months	27.0	26.5	0.4802	27.0	27.5	0.1266
Social Functioning Exam						
3 months	0.053	0.046	0.5371	0.024	0.075	0.1523
6 months	0.000	0.043	**0.0355**	0.013	0.125	0.1476
9 months	0.039	0.119	**0.0280**	0.026	0.101	0.6014
21 months	0.078	0.078	0.6165	0.000	0.030	0.1483
Hamilton Depression Scale[#]						
3 months	5.56	8.44	0.1396	3.33	8.33	**0.0478**
6 months	4.80	10.50	0.0885	3.67	10.44	0.1001
9 months	5.17	13.20	**0.0253**	8.00	9.70	0.5733

The Social Functioning Exam was analyzed using nonparametric (Wilcoxon Rank Sum) analysis

*The numbers are reduced based on patients who dropped out between 3 and 21 months follow-up

[†] A significant treatment by depression outcome interaction was present on multiple regression, controlling for total lesion volume

[#] Analysis performed to assess mean depression indices at critical time points for interpretation of other findings, p values based on two-tailed, independent samples t-test

tioning, whereas those who did not receive prophylactic antidepressants may be at greater risk for depression with functional activities of daily living impairment. The latter suggestion (those who did not receive prophylactic antidepressants may be at greater risk for depression with functional impairment in activities of daily living) represents the strongest finding since the interaction between the presence or absence of initial treatment and depression outcome was significant in multiple regression, even after controlling for lesion volume. Though it is possible that the differences observed simply reflect selection bias for a more treatment-resistant group among those who develop depression following prophylactic treatment with an antidepressant, these findings may further imply etiologic heterogeneity of depression in the chronic poststroke period. One may speculate that exposure to antidepressants leads to physiological brain changes and increased sensitivity to the social concerns of chronic illness, whereas placebo does not produce such physiological brain changes and depression is more related to perception of physical impairment. Although this issue will require further research, antidepressants may alter the ischemic brain in a manner that modifies the mechanisms of subsequent depression. If confirmed by future studies, these findings may suggest the need for emphasis on increased social support for those who were treated with prophylactic antidepressants for poststroke depression and physical and occupational therapy for those who do not receive prophylactic antidepressants.

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