Article

Mortality and Poststroke Depression: A Placebo-Controlled Trial of Antidepressants

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Objective: Poststroke depression has been shown to increase mortality for more than 5 years after the stroke. The authors assessed whether antidepressant treatment would reduce poststroke mortality over 9 years of follow-up.

Method: A total of 104 patients were randomly assigned to receive a 12-week double-blind course of nortriptyline, fluoxetine, or placebo early in the recovery period after a stroke. Mortality data were obtained for all 104 patients 9 years after initiation of the study. Demographic and clinical measurements were collected at 3, 6, 9, 12, 18, and 24 months after the stroke. Survival data were analyzed by using the Kaplan-Meier method.

Results: Of the 104 patients, 50 (48.1%) had died by the time of the 9-year follow-up. Of 53 patients who were given full-dose antidepressants, 36 (67.9%) were alive at follow-up, compared with only 10 (35.7%) of 28 placebo-treated patients, a significant difference. Logistic regression analysis showed that the beneficial effect of antidepressants remained significant both in patients who were depressed and in those who were nondepressed at enrollment, after the effects of other factors associated with mortality (i.e., age, coexisting diabetes mellitus, and chronic relapsing depression) were controlled. There were no intergroup differences in severity of stroke, impairment in cognitive functioning and activities of daily living impairment, and other medications received.

Conclusions: Treatment with fluoxetine or nortriptyline for 12 weeks during the first 6 months poststroke significantly increased the survival of both depressed and nondepressed patients. This finding suggests that the pathophysiological processes determining the increased mortality risk associated with poststroke depression last longer than the depression itself and can be modified by antidepressants.

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Depression occurs in about 40% of patients with acute stroke and has been linked to poorer cognitive and physical recovery (1–3). An association between depressive symptoms and stroke mortality was reported in a community sample of 6,676 initially stroke-free adults who had five or more depressive symptoms at baseline, even after adjustment for demographic variables and physical illness comorbidity (4). Morris et al. (5) found that stroke patients with in-hospital depression were three-and-a-half times more likely to die during 10 years of follow-up than patients without depression (odds ratio=3.4, 95% confidence interval [CI]=1.8–5.4). Among 84 Australian patients in a rehabilitation hospital, Morris et al. (6) found that stroke patients with major depression were eight times more likely than nondepressed stroke patients to have died by 15-month follow-up.

Given the relationship between poststroke depression and mortality, an obvious question is whether adequate antidepressant treatment would reduce long-term mortality. Double-blind treatment trials have shown that poststroke depression responds to treatment with antidepressants (7, 8) and that antidepressant treatment improves cognitive and functional recovery (9). In the present study, we analyzed the demographic and clinical correlates of mortality occurring during long-term follow-up in a group of patients treated in a double-blind, placebo-controlled trial of antidepressants (7). We hypothesized that patients who received antidepressant medication after an index stroke would have significantly better long-term survival than patients who did not receive antidepressants and that this effect would be present independent of baseline depressive status.

Method

Patient Selection

The methods used for the double-blind, placebo-controlled trial have been extensively described elsewhere (7). Succinctly, patients were enrolled in the treatment study between June 1991 and June 1997 from Younkers Rehabilitation Center of Iowa Methodist Medical Center in Des Moines, Iowa (N=89), the neurological service at the University of Iowa Hospitals and Clinics in Iowa City (N=1), the Veterans Affairs Medical Center in Iowa City (N=2), and the neurological service of the Raúl Carrea Institute of Neurological Research in Buenos Aires, Argentina (N=12) (7).

Among 343 consecutive patients between ages 25 and 89 years who had had an acute stroke within the previous 6 months, 130 patients refused participation and 103 patients were excluded because of another life-threatening illness or because they were unable to undergo a verbal interview due to impairment of compre-

TABLE 1. Baseline Characteristics of Acute Stroke Patients Randomly Assigned to Receive a 12-Week Poststroke Course of Fluoxetine, Nortriptyline, or Placebo

Characteristic	Patients Receiving Fluoxetine (N=40)		Patients Receiving Nortriptyline (N=31)		Patients Receiving Placebo (N=33)	
	N	%	N	%	N	%
Male sex[a]	32	80.0	13	41.9	20	60.6
Socioeconomic status classes IV and V	17	42.5	13	41.9	12	36.3
Married	27	67.5	20	64.5	19	57.5
Personal history of mood disorder	4	10.0	4	12.9	3	9.1
Family history of mood disorder	7	17.5	9	29.0	3	9.1
	Mean	SD	Mean	SD	Mean	SD
Age (years)	68.6	13.7	66.0	11.9	70.4	9.0
Education (years)	12.3	2.4	12.4	2.4	11.5	2.9
Mini-Mental State Examination score	26.9	3.3	24.8	5.2	26.0	3.6
Functional Independence Measure score	57.5	10.9	53.9	15.7	52.7	10.4
Social Functioning Exam score	0.13	0.19	0.14	0.16	0.14	0.20
Social Ties Checklist score	3.1	1.2	2.8	1.5	3.6	1.9

[a] Significant difference among the three groups (χ^2=10.9, df=2, p=0.004).

TABLE 2. Characteristics of Stroke in Acute Stroke Patients Randomly Assigned to Receive a 12-Week Poststroke Course of Fluoxetine, Nortriptyline, or Placebo

Stroke Characteristic	Patients Receiving Fluoxetine (N=40)		Patients Receiving Nortriptyline (N=31)		Patients Receiving Placebo (N=33)	
	N	%	N	%	N	%
Type						
Infarction	39	97.5	24	77.4	30	90.9
Hemorrhage[a]	1	2.5	7	22.6	3	9.1
Location						
Left hemisphere	15	37.5	13	41.9	12	36.4
Right hemisphere	22	55.0	16	51.6	20	60.6
Brainstem and/or cerebellum	3	7.5	2	6.5	1	3.0
	Mean	SD	Mean	SD	Mean	SD
NIH Stroke Scale score	4.9	4.4	7.0	5.6	7.0	5.5

[a] Significant difference among groups (χ^2=7.6, df=2, p=0.02).

hension. In addition, two patients died before assignment to a treatment group, and four dropped out before starting treatment. Both depressed and nondepressed patients were randomly assigned to receive either active medication or placebo. Patients were also randomly assigned to either fluoxetine or nortriptyline treatment unless nortriptyline was contraindicated because of a cardiac conduction abnormality (e.g., bundle branch block) or a heart attack within the 3 months before the study (N=8). Fluoxetine was contraindicated for patients who had had an intracerebral hemorrhage (N=9). All patients provided signed informed consent for their participation in the study.

Depression was defined according to the DSM-IV criteria for depression due to stroke, with "major depressive-like episode" or "minor depressive disorder" specified (based on symptoms elicited by using the Present State Examination, a semistructured interview [10]), and a Hamilton Depression Rating Scale (11) score of 12 or greater. (See reference 7 for further details.)

Patients were seen at enrollment and at 3, 6, 9, and 12 weeks after beginning the medication. The doses of nortriptyline were 25 mg/day for the first week, 50 mg/day for weeks 2 and 3, 75 mg/day for weeks 3–6, and 100 mg/day for the final 6 weeks. Doses of fluoxetine were 10 mg/day for the first 3 weeks, 20 mg/day for weeks 4–6, 30 mg/day for weeks 7–9, and 40 mg/day for the final 3 weeks.

Of the 104 patients enrolled in the study, 23 dropped out before completing the 12-week treatment protocol (13 of the 40 patients who were receiving fluoxetine, five of the 31 patients who were receiving nortriptyline, and five of the 33 patients who were receiving placebo). The dropout rate was greater in the fluoxetine group than in the combined nortriptyline and placebo groups (χ^2=4.1, df=1, p=0.04). We obtained reliable mortality data on the 104 patients enrolled in the study. In addition, 63 of the 69 patients who completed the treatment protocol in the United States were followed up at 6, 9, 12, 18, and 24 months after enrollment, usually in the patient's home or long-term care facility. Of these 63 patients, 5 patients died during follow-up; therefore, 58 patients completed the 2-year follow-up evaluation. Patients enrolled in Argentina had clinical follow-up at the Neuropsychiatry Outpatient Clinic of the Raúl Carrea Institute of Neurological Research.

The background characteristics and baseline impairment variables of patients assigned to receive fluoxetine, nortriptyline, and placebo are shown in Table 1. No significant differences among the three groups were found for age, socioeconomic or marital status, degree of cognitive or functional impairment, psychosocial adjustment, or history of psychiatric disorders. However, the proportion of women was significantly higher in the nortriptyline group (χ^2=10.9, df=2, p=0.004).

Stroke characteristics for the three groups are summarized in Table 2. The frequency of hemorrhagic stroke was greater in the nortriptyline group than in the other two groups (χ^2=7.6, df=2, p=0.02). Overall, there were no significant differences among the three groups in stroke severity as measured by the National Institutes of Health (NIH) Stroke Scale (12).

No significant differences were found among the three groups in the frequency of coexistent physical illness (e.g., coronary

heart disease, diabetes mellitus, pulmonary disease) or in the frequency of mood or anxiety disorders.

We also compared the group of patients who completed the treatment protocol (N=81) with the group of patients who dropped out of the study (N=23). There were no significant differences between the groups in demographic variables (age, sex, race, socioeconomic status), type or severity of stroke, degree of cognitive or functional impairment, frequency of coexistent physical illness (e.g., coronary heart disease, diabetes mellitus, pulmonary disease), or frequency of mood or anxiety disorders.

Mortality

Information about cause of death was obtained in March 2001 from a combination of next-of-kin interviews, primary physician reports, and medical and autopsy records, as well as information conveyed by the National Death Registry. Cause of death was classified as cardiovascular causes (e.g., myocardial infarction, fatal arrhythmia, congestive heart failure), recurrent stroke (including the consequences of prostration such as aspiration pneumonia or pulmonary embolism), and other unrelated causes (e.g., cancer, pulmonary failure). Survival was ascertained by a research assistant who was not involved in the trial and was blind to the treatment status of the patients. Baseline characteristics for patients who had died by the time of the follow-up and those who were still alive are shown in Table 3.

Medical and Neurological Assessment

Medical history was obtained at each follow-up from the patient interview, caregiver or primary physician report, and analysis of medical records. Stroke severity was assessed by using the NIH Stroke Scale. We identified the following risk factors for the development of cardiovascular disorders: arterial hypertension, diabetes mellitus, smoking, obesity, and hypercholesterinemia.

Hypertension was considered to be present if systolic blood pressure was greater than 140 mm Hg, if diastolic blood pressure was greater than 90 mm Hg, or if antihypertensive medications were being used. Diabetes mellitus was defined as a fasting glucose of 126 mg/dl or higher, nonfasting glucose of 200 mg/dl or higher, or treatment for diabetes. Hypercholesterinemia was defined as low-density lipoprotein cholesterol greater than 140 mg/dl or the use of cholesterol-lowering agents. Finally, those patients with a body mass index equal to or greater than 30 kg/m^2 were considered to be obese.

In addition, we registered the presence of concurrent physical illnesses that have a significant effect on mortality and recurrent stroke rates. These included congestive heart failure, atrial fibrillation, coronary artery disease, and chronic obstructive pulmonary disease.

The number of risk factors for cardiovascular disease and the number of concurrent physical illnesses were used as composite scores in regression models. All participants were asked to bring to each follow-up visit all prescription and nonprescription medications taken in the previous 2 weeks.

Psychiatric Assessment

Severity of depression was assessed by using the 28-item form of the Hamilton depression scale (11, 13), a valid and reliable scale within this population (14). Treatment response was defined as a >50% reduction in the Hamilton depression scale score and no longer fulfilling the diagnostic criteria for major or minor depression.

Functional, Cognitive, and Psychosocial Functioning Assessment

Activities of daily living were assessed by using the Johns Hopkins Functioning Inventory (13) (lower scores indicate less impairment) and the Functional Independence Measure (15) (higher scores indicate less impairment). Cognitive functioning was assessed by using the Mini-Mental State Examination (MMSE) (16). Social functioning was measured by using the Social Ties Checklist (17), a 10-item questionnaire that quantifies the number of social connections available to the patient (higher scores indicate fewer connections). The reliability and validity of these scales (i.e., Johns Hopkins Functioning Inventory, Functional Independence Measure, MMSE, and Social Ties Checklist) in the stroke population have been previously demonstrated (14).

TABLE 3. Baseline Characteristics of Acute Stroke Patients, by Survival Status at 9-Year Follow-Up

Characteristic	Patients Alive at Follow-Up (N=54)		Patients Who Had Died by Follow-Up (N=50)	
	N	%	N	%
Male sex	34	63.0	31	62.0
White race	50	92.5	50	100.0
Socioeconomic status classes IV and V	22	40.7	20	40.9
Married	38	70.4	28	56.0
Personal history of mood disorder	9	16.7	4	8.0
Family history of mood disorder	10	18.5	9	18.0
	Mean	SD	Mean	SD
Age (years)[a]	64.6	11.2	72.5	11.2
Education (years)	12.1	2.4	12.1	2.7
Functional Independence Measure score	56.3	13.1	53.2	11.7
Mini-Mental State Examination score	25.9	4.3	26.0	4.0
NIH Stroke Scale score	6.2	4.5	6.3	4.4
Interval from intake to either death or survival (years)	7.1	1.2	3.8	2.1

[a] Significant difference between groups (F=13.0, df=1, 102, p=0.0005).

Statistical Analysis

For baseline comparisons, we used simple chi-square tests (or Fisher's exact test, if appropriate) for categorical variables and analysis of variance (ANOVA) for continuous variables. Survival data were analyzed by using the Kaplan-Meier method. A multiple logistic regression model was used to predict survival versus mortality status.

Results

Mortality

By a maximum time of 9 years after enrollment, 50 (48.1%) of the 104 patients had died. Of these 50 patients, 23 (46%) died from cardiovascular causes, 12 (24%) from recurrent stroke, and 15 (30%) from other causes (e.g., pulmonary disease, cancer). The mean time from enrollment to death was 3.8 years (SD=2.1). Patients who were alive at follow-up had a mean survival time of 7.1 years (SD=1.2).

Relationship of Mortality With Background and Impairment Variables and Comorbid Physical Illness

The patients who died were significantly older than the survivors (F=13.0, df=1, 102, p=0.0005) (Table 3), but no other background differences were significant. There were

TABLE 4. Risk Factors for Cardiovascular Disease and Concurrent Physical Illnesses of Acute Stroke Patients, by Survival Status at 9-Year Follow-Up

Risk Factor or Concurrent Illness	Patients Alive at Follow-Up (N=54)		Patients Who Had Died by Follow-Up (N=50)	
	Mean	SD	Mean	SD
Number of major cardiovascular risk factors	2.0	0.8	2.2	1.1
Number of concurrent physical illnesses	0.9	0.75	1.2	0.88
	N	%	N	%
Hypertension	36	66.7	27	54.0
Hypercholesterinemia	21	38.9	16	32.0
Smoking	19	35.2	19	38.0
Obesity	22	40.7	29	58.0
Diabetes mellitus[a]	10	18.5	22	44.0
Coronary artery disease	32	59.3	32	64.0
Congestive heart failure	7	13.0	8	16.0
Atrial fibrillation	3	5.6	8	16.0
Chronic obstructive pulmonary disease	10	18.6	13	26.0

[a] Significant difference between groups (χ^2=7.9, df=1, p<0.005).

no significant differences between the group of patients who died and the survivors' group in the type and severity of the index stroke measured by NIH Stroke Scale score, in the location of injury, or in the frequency of any specific neurological symptoms. However, patients who survived were more likely to have had a cerebral hemorrhage (p=0.03, Fisher's exact test).

No significant group differences were found between the patients who died and the survivors in baseline scores for impairment in activities of daily living as measured by the Johns Hopkins Functioning Inventory and the Functional Independence Measure, cognitive impairment as measured by the MMSE, or availability of social support as measured by the Social Ties Checklist (Table 3).

There were no significant differences between the group of patients who survived and the group of patients who died in the number of risk factors for cardiovascular disease or the number of concurrent physical illnesses (Table 4).

There were no significant between-group differences in the frequency of arterial hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, or chronic obstructive pulmonary disease. In addition, there were no significant between-group differences in the frequency of hypercholesterinemia, smoking, obesity, or alcohol use. However, patients who died were more likely to have a diagnosis of diabetes mellitus (χ^2=7.9, df=1, p<0.005) (Table 4).

Relationship of Mortality With Depressive Disorder

At baseline, 25 (50%) of the 50 patients who would die by the time of follow-up had a depressive disorder, compared with 31 (57.4%) of the 54 patients who would live. There was no significant association between depression at baseline and long-term mortality because many patients received adequate antidepressant treatment and experienced a sustained full remission of their symptoms. Initial Hamilton depression scale scores for placebo-treated patients who ultimately survived were not significantly different from initial Hamilton depression scale scores of placebo-treated patients who died (mean=7.3 [SD=3.7] and mean=6.4 [SD=5.1], respectively; F=0.24, df=1, 27, p=0.62). However, the small number of patients included in this comparison limits the statistical power to observe a significant difference.

Of the 58 patients who completed the 2-year follow-up evaluation, 22 developed a single episode of a depressive disorder that responded either to placebo or to antidepressant treatment. On the other hand, 14 patients had a chronic or relapsing course (i.e., no response to antidepressants or a response followed by a relapse or recurrence of depression). Twenty-two patients had no depressive disorder during the 2-year period. Of the 14 patients with relapsing depression, 10 patients (71.4%) died, compared with only six (27.3%) of 22 patients who responded and eight (36.4%) of 22 patients with no depressive disorder (χ^2=7.3, df=2, p=0.02). Thus, the deleterious effect of depression on mortality rates was observed in those patients who had a chronic or relapsing clinical course.

Relationship of Mortality to Treatment With Antidepressants

Intention-to-treat analysis showed that 42 of the 71 patients (59.2%) initially assigned to receive antidepressants were alive at 9-year follow-up, compared with 12 of the 33 patients (36.4%) who were assigned to receive placebo (χ^2=4.7, df=1, p=0.03). Kaplan-Meier survival analysis showed that the probability of survival was significantly greater in the patients assigned to receive antidepressant treatment (χ^2=4.7, df=1, p=0.03, log-rank test).

In the group of patients who completed the 12-week treatment protocol (N=81), 36 (67.9%) of the 53 patients treated with antidepressants were alive at the 9-year follow-up, compared with 10 (35.7%) of the 28 patients who received placebo (χ^2=7.7, df=1, p=0.005). The probability of survival was significantly greater in the patients who received antidepressant treatment (χ^2=8.2, df=1, p=0.004, Kaplan-Meier survival analysis, log-rank test) (Figure 1). Although decreasing the sample size has an effect on the power of statistical tests, the difference observed in survival rates between the patients receiving antidepressants and those receiving placebo continued to be significant after excluding the 12 patients recruited in Argentina (χ^2=3.8, df=1, p=0.05, Kaplan-Meier survival analysis, log-rank test).

Nineteen of the 27 patients (70.4%) treated with fluoxetine were alive at follow-up, compared with 17 of the 26 patients (65.4%) treated with nortriptyline.

Twenty-seven of the 53 patients (50.9%) treated with antidepressants had major or minor depression at baseline, compared to 13 of the 28 patients (46.4%) who received placebo. The probability of survival was higher in the pa-

tients who received antidepressants in both the depressed (χ^2=5.5, df=1, p=0.02, Kaplan-Meier survival analysis, log-rank test) and the nondepressed groups (χ^2=6.1, df=1, p=0.02, Kaplan-Meier survival analysis, log-rank test).

Of the 17 patients who received adequate antidepressant treatment and died during the 9-year follow-up period, five patients (29.4%) died from cardiovascular causes, one patient (5.9%) died from recurrent stroke, and 11 patients (64.7%) died from other unrelated causes. On the other hand, of the 33 patients who did not receive adequate antidepressant therapy and who died, 18 patients (54.5%) died from cardiovascular causes, 11 patients (33.3%) died from recurrent stroke, and four patients (12.1%) died from other unrelated causes. The frequency of deaths attributable to vascular causes (i.e., cardiovascular disease and recurrent stroke) was significantly higher in the nontreated group (χ^2=15.4, df=2, p=0.0005).

There were no significant differences between the group of patients who died and the group of patients who were still alive in the frequency of treatment with β blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, digitalis, diuretics, anticoagulants, hypoglycemic agents, insulin, α blockers, antiplatelet agents, benzodiazepines, or other psychotropic agents.

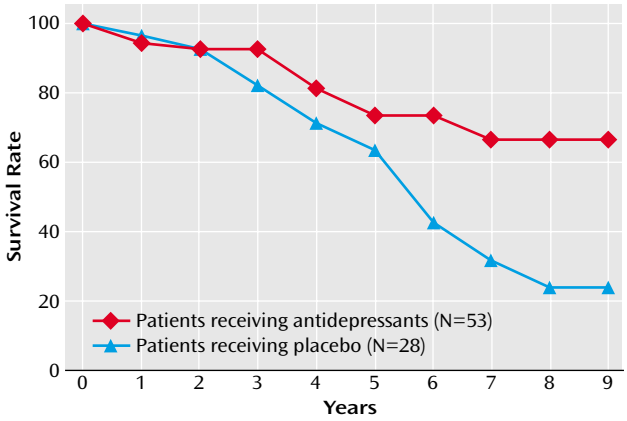
Finally, a logistic regression model analyzing the association of mortality with the variables that were significantly associated with increased mortality rates (i.e., age, stroke type, comorbid diabetes mellitus, relapsing depression, and antidepressant use) found that antidepressants remained significantly associated with the probability of survival (Wald χ^2=4.9, df=1, p=0.03), as did diabetes mellitus (Wald χ^2=5.3, df=1, p=0.02).

Discussion

This study analyzed the clinical correlates of long-term mortality in a population of patients treated with antidepressants after stroke. The most striking finding was that patients who had received active antidepressant treatment were more likely to survive, compared with patients who did not receive such treatment, regardless of whether they were initially depressed. The beneficial effect of antidepressants remained significant after the effects of age, stroke type, coexistent diabetes mellitus, and occurrence of a depressive disorder with a relapsing course were controlled. Mortality rates attributable to cardiovascular illness or recurrent stroke were significantly higher for patients who did not receive adequate treatment with antidepressants.

Before discussing these findings we need to address the limitations of the present study. The patients in the study were a selected group that reflected the demographic characteristics of the population in Iowa. Thus, these findings may not be applicable to other groups of stroke patients. During the past decade, there have been significant changes in stroke therapies, including the use of intravenous and intra-arterial thrombolytic medications. It is unclear how these developments would have affected the present findings. In addition, we did not obtain psychiatric follow-up data beyond the first 2 years after the index stroke, and additional data to further characterize the course of depressive illness would have been valuable.

FIGURE 1. Survival Rates Over 9-Year Follow-Up of Acute Stroke Patients Who Received a 12-Week Poststroke Course of Antidepressants or Placebo[a]



[a] Probability of survival was significantly greater in the patients receiving antidepressants (χ^2=8.2, df=1, p=0.004, Kaplan-Meier survival analysis, log-rank test).

Given these limitations, how can we construe these findings? Many explanations can be proposed to explain the increased risk of dying observed among patients with poststroke depression. Depressed patients might not comply with treatment recommendations for medication regimens or health-promoting behaviors. For instance, depressed diabetic patients may be poorly compliant with diet restrictions and use of hypoglycemic agents, resulting in increased blood glucose levels and more severe cardiovascular complications.

Depressive disorders might be characterized by the presence of abnormal positive feedback loops involving the prefrontal cortex, amygdala, hypothalamic-pituitary-adrenal axis, and noradrenergic brainstem nuclei. The medical consequences of these changes are widespread, including development of hypertension, hyperlipidemia, endothelial injury, and progressive atherosclerosis (19). Alterations in autonomic nervous system activity, as demonstrated by reduced heart rate variability, have been observed in depressed patients, compared with nondepressed patients, and these alterations may possibly predispose depressed patients to ventricular arrhythmias (20). Moreover, cardiovascular disease and major depression have been associated with increased serotonin-mediated platelet activation, activation of coagulation factors, and increased thrombus formation (21).

Antidepressants may enhance patient survival through their effect in these multiple pathophysiological mechanisms. Indeed, they may have different effects at different points in the longitudinal course of stroke patients.

We have observed that even a relatively short course of antidepressants early after an index stroke has a protective effect on long-term mortality. How can this effect be explained? There are two specific findings that must be addressed. The first is that the mortality risk exceeds the natural duration of depression. Our previous study and those of other investigators showed that patients who had acute poststroke depression were dying faster than those who were not depressed, even when the survivors and subsequent nonsurvivors had the same frequency and severity of depression (6). The second fact is that a 3-month treatment given within 6 months after a stroke was adequate to increase the likelihood of survival for up to 9 years. Although numerous explanations might be proposed, these findings suggest that there may be physiological abnormalities such as the ones previously mentioned that persist even after depression has remitted. Moreover, antidepressants must do something to reverse or correct these physiological abnormalities for prolonged periods, even after the antidepressants are stopped. It might be speculated that neurotrophic and neuroplastic changes associated with antidepressant treatment could produce long-lasting changes in cortical and hypothalamic networks mediating stress responses.

On the other hand, continuation treatment with antidepressants for prolonged periods may affect platelet function and progression of atherosclerosis and may also have an effect on the autonomic changes that make patients prone to severe cardiac arrhythmias.

Among the 58 patients who were followed for 2 years at our site, 36 received antidepressants during the first 12 weeks of the study. Of these 36 patients, 17 continued to receive therapeutic doses of antidepressants for approximately 12 months (mean=11.6 months, SD=5.9). At 9-year follow-up, 15 (88.2%) of the 17 patients who received continuation therapy with antidepressants were alive, compared with 10 (52.6%) of the 19 patients who received only 12 weeks of antidepressant treatment (p=0.02, Fisher's exact test).

Another important question is how antidepressants could prolong survival in patients who were initially not depressed. The most obvious answer is that early antidepressant treatment could modify the pathophysiological mechanisms associated with increased mortality independently of the effect of antidepressants on other behavioral measures. The fact that fluoxetine was not effective in treating acute poststroke depression (7) but was just as effective as nortriptyline in protecting against long-term mortality is consistent with this hypothesis. Furthermore, early antidepressant treatment could prevent the occurrence of delayed-onset depression or modify its pathophysiological correlates in order to provide for a better outcome.

In summary, although these findings require replication, the implications for the care of stroke patients are quite profound. Patients with depression need to be identified and treated, while those without depression should be carefully assessed and given antidepressants if they are at high risk for developing depressive disorders (e.g., if they have a family history or personal history of mood disorders). Because prior studies have shown that 40% of initially nondepressed patients will develop a depressive disorder, our data might be construed to suggest that all patients who survive acute stroke should receive antidepressant treatment because of the likelihood that it could prolong their survival.

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