Two-Year Longitudinal Study of Poststroke Mood Disorders: Diagnosis and Outcome at One and Two Years

Robert G. Robinson, MD, Paula L. Bolduc, MS, and Thomas R. Price, MD

As part of a prospective study of mood disorders in stroke patients, interviews were obtained from 37 patients at 1 year and 48 patients at 2 years follow-up. In-hospital evaluations for these 65 follow-up patients found that 9 patients (14%) had symptom clusters of major depression, 12 patients (18%) had symptom clusters of dysthymic or minor depression, and 44 patients (68%) did not meet the DSM III diagnostic criteria for depression. Although overall prevalence of depression did not change significantly over time, the prognosis for individual patients, depending on diagnostic group, was different. All of the follow-up patients with major depression in-hospital were improved by 2 years, with a significant reduction in their mean depression scores and improvement in their activities of daily living, whereas only 30% of follow-up patients with dysthymic depression improved by this time. There was no significant improvement in their mean depression scores or mean activities of daily living score. Of the patients followed up who were not depressed in-hospital, 34% had developed major or minor depression by 2 years, and their mean depression scores were significantly increased. These data suggest that the prevalence of depression among the follow-up patients remains high (between 30 and 40%) for the first 2 years after stroke, but that untreated poststroke major depression has a natural course of about 1–2 years, with associated improvement in activity of daily living scores, whereas the prognosis for poststroke dysthymic depression is frequently unfavorable and often persists for >2 years. (Stroke 1987;18:837–843)

During the past few years, we have reported our findings from a group of 103 patients who were examined during their acute hospitalization for stroke and followed for 2 years. At 6 months follow-up, 10 of 13 patients with symptoms of major depression in hospital continued to have these symptoms, whereas 5 of 9 patients with minor (dysthymic) depression in-hospital continued to have these symptoms; the remaining 4 patients with dysthymic depression had developed symptoms of major depression. Of the 28 patients who were not depressed at the time of the initial in-hospital evaluation, 9 had developed either major or minor depressive symptoms by 6 months follow-up. Thus, based on our initial follow-up, 19 of 22 patients who were depressed in-hospital showed no significant improvement 6 months later, and another 32% of the follow-up patients developed depression after hospital discharge.

Although the Diagnostic and Statistical Manual III (DSM III) does not recognize more than 1 category of depression in patients with brain injury (i.e., organic affective disorder), our previous investigations have demonstrated that the diagnostic differentiation into major and dysthymic depression appears to be important. Major depression was strongly associated with left anterior lesion location, whereas dysthymic depression occurred primarily with posterior brain injury. The severity of depression, as measured by either the Zung or Hamilton Depression Rating Scales, was significantly different for patients with major compared with dysthymic depression. A positive dexamethasone suppression test (i.e., failure to suppress serum cortisol below 5 μg/ml following 1 mg of dexamethasone) was significantly associated with major but not dysthymic depression. Cognitive impairment associated with depression was also found only in stroke patients with major depression, whereas dysthymic depression did not appear to significantly affect cognitive impairment. Thus, there are several lines of evidence that suggest that the differentiation of major and dysthymic depression may be an important element in the evaluation of mood disorder associated with brain injury. In the present study, we examined whether in-hospital diagnosis of major depression, dysthymic depression, or no depression was significantly related to diagnostic status or physical or intellectual impairment at 1 and 2 years follow-up.

Subjects and Methods

Study Population

The sample population consisted of patients who were admitted to the University of Maryland Hospital for acute treatment of thromboembolic, atherosclerotic, or hemorrhagic stroke and gave informed consent.
for participation in this study. They were also included in the National Institute of Neurological and Communications Diseases and Stroke (NINCDS) Pilot Stroke Data Bank. A total of 154 consecutive admissions were evaluated; of these, 43 patients with severe comprehension deficits were excluded, as were 7 patients who were discharged before an interview could be done and 1 patient who refused examination. Thus, 103 patients were included in the prospective longitudinal study. During the 24-months follow-up, 8 patients died and 9 patients were lost completely, not having received any follow-up, while 86 patients were reexamined at either 3, 6, 12, or 24 months after stroke. The present study involves 65 patients, 37 seen at 12 months and 48 seen at 24 months follow-up (20 patients were seen at both times).

Evaluations

In-hospital and follow-up neurologic examinations were done by the attending neurologist using the standardized examination and rating criteria established by the NINCDS Pilot Stroke Data Bank. Neurologic diagnoses were made using the Stroke Data Bank criteria, which are based on both computed tomography (CT) scan and other laboratory tests as well as on clinical examination.

Psychiatric examination was done in the hospital by a psychiatrist or a social worker trained in the administration of these scales in the late morning so that any possible effect of diurnal mood variation on the interview outcome would be standardized. The psychiatric examination included 3 quantitative measures of mental state, the Present State Examination (PSE), the Hamilton Depression Scale, and the Zung Depression Scale. The reliability and validity of these measures in this brain-injured population has been demonstrated in previous publications.

In addition to these quantitative measures of depression, overall cognitive impairment was assessed using the Mini-Mental State Examination (MMSE). Scores range from 0 to 30, with scores < 23 indicating significant impairment. Functional physical impairment (i.e., activities of daily living, ADL) was quantified using the Johns Hopkins Functioning Inventory (JHFI). Scores range from 0 to 27, with higher scores indicating greater impairment. The quality of social functioning was determined using the Social Functioning Exam (SFE). This is a 28-item semistructured interview assessment of social functioning, with total scores reported as a fraction of the maximum possible score. We have demonstrated the reliability and validity of these instruments in this brain-injured population in previous publications.

At the follow-up evaluation, a detailed longitudinal medical and psychiatric history was taken. Any record of treatment for depression or intervening medical illness was carefully noted.

Diagnosis

Using the symptoms elicited from the PSE, DSM III diagnoses were generated. Although there is not an exact correspondence between PSE items and DSM III symptom criteria, we have shown in previous publications that there is a close correspondence between DSM III, Research Diagnostic Criteria, and PSE diagnoses. The conversion criteria for making DSM III diagnoses from PSE criteria is available upon request.

Statistical Analysis

Means and SDs were calculated for all quantitative measurement scales. Groups were compared using analysis of variance (ANOVA); a group was compared over time using repeated-measures ANOVA. If the ANOVA was significant, cells were compared using post-hoc planned orthogonal t tests. Nonparametric data were analyzed using χ2 statistics with Yates' modification for expected cell sizes of <5.

Results

Study Population and Neurologic Findings

Demographic characteristics for the 37 patients seen at 12 months and the 48 patients seen at 24 months are shown in Table 1. To determine whether the follow-up groups were in some way "aberrant samples" from our original group of 103, the no-follow-up group demographics were compared with the 2 follow-up groups (Table 1). There were no significant intergroup differences in any of the demographic data except age. The no-follow-up group was slightly younger (p < 0.05) than the follow-up groups.

Neurologic findings for patients evaluated at either 12 or 24 months as well as in-hospital findings in the no-follow-up group are shown in Table 2. There were no significant differences in neurologic findings between these groups. Almost all of the patients had a hemiparesis or monoparesis with or without sensory deficit.

Ten of the 65 patients seen at either 12 or 24 months had suffered subsequent strokes by the follow-up inter-

<table>
<thead>
<tr>
<th>Table 1. In-Hospital Demographic Characteristics of 12- and 24-Months Follow-Up and No-Follow-Up Groups</th>
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</thead>
<tbody>
<tr>
<td>12-Months follow-up</td>
</tr>
<tr>
<td>(n = 37)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
</tr>
<tr>
<td>Race (% black)</td>
</tr>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Marital status</td>
</tr>
<tr>
<td>% married</td>
</tr>
<tr>
<td>% widowed</td>
</tr>
<tr>
<td>% other</td>
</tr>
<tr>
<td>Socioeconomic status Hollingshead</td>
</tr>
<tr>
<td>Class I–III</td>
</tr>
<tr>
<td>Class IV–V</td>
</tr>
<tr>
<td>History of CVA</td>
</tr>
<tr>
<td>History of depression</td>
</tr>
</tbody>
</table>

*Significantly different from follow-up groups (p < 0.05); all other demographic variables not different by χ2.

CVA, cardiovascular accident.
views. Of these 10 patients, 6 were not depressed in-hospital or at follow-up. Two patients had symptoms of depression subsequent to a recurrent stroke; 1 had major depression, the other had dysthymic depression. One patient, who had an in-hospital diagnosis of major depression, had a 24-month follow-up diagnosis of dysthymic depression. One patient with dysthymic depression in-hospital had dysthymic depression subsequent to recurrent stroke.

In-Hospital Evaluation

In-hospital evaluations of the 37 patients seen at 12 months found 5 (14%) with symptom clusters of major depression and 7 (19%) with symptom clusters of dysthymic depression. Of the 48 patients seen at 24 months, in-hospital evaluations found 6 (13%) with symptom clusters of major depression and 10 (21%) with symptom clusters of dysthymic depression. In-hospital evaluations of the 38 no-follow-up patients revealed 11 (29%) with major depression and 9 (24%) with dysthymic depression. The frequency of depression in the no-follow-up group was not significantly different from either follow-up group ($\chi^2 = 3.62$, $df = 2$, not significant [NS] for 12-months follow-up; $\chi^2 = 4.34$, $df = 2$, NS for 24-months follow-up).

Mean in-hospital depression scores on the Hamilton ($F_{2,43} = 68.6$, $p < 0.001$), Zung ($F_{2,43} = 33.1$, $p < 0.001$), and PSE ($F_{2,43} = 69.2$, $p < 0.001$) for both the 12- and 24-months groups were significantly higher for patients with major compared with dysthymic depression or nondepressed patients (Table 3). Similarly, mean depression scores for patients with dysthymic depression were significantly higher than the nondepressed group (Table 3). The different depression groups, however, did not differ significantly in either MMSE ($F_{2,43} = 1.6$, NS) or SFE scores ($F_{2,43} = 1.7$, NS). Patients with major depression, however, had higher JHFI scores ($F_{2,43} = 3.5$, $p < 0.05$) than the non-depressed patients but were not significantly different from patients with dysthymic depression.

Patients with major, dysthymic, or no depression seen only in-hospital, at 12 months, or at 24 months did not differ in their mean in-hospital depression scores. In addition, in-hospital scores of physical (JHFI) and intellectual (MMSE) impairment or social functioning (SFE) did not differ significantly among the 12-months, 24-months, or no-follow-up groups. Thus, the no-follow-up group did not differ significantly from the follow-up groups in frequency or severity of depression or severity of impairment.

Follow-up Evaluation at 12 Months

Of the 37 patients interviewed at 12 months, 5 (14%) had major depressive symptoms, 7 (19%) had dysthymic symptoms, and 25 (67%) were not depressed. Although these were the same overall percentages found in-hospital (i.e., 14, 19, and 67%, respectively), the composition of the diagnostic groups had changed (Figure 1). Of the 5 patients with major depression in-hospital, only 1 continued to have major depression at 12 months, 2 had dysthymic depression symptoms, and 2 were not depressed (Figure 1). Of the 7 patients with dysthymic depression in-hospital, 2 had developed major depressive symptoms, 2 continued to have dysthymic symptoms, and 3 had no depression. Among the 25 patients who were not depressed in-hospital, 2 had developed major depression, 3 had developed dysthymic depression, and 20 patients remained not depressed.

Only 1 depressed patient (in-hospital diagnosis major depression, patient taking medication at 12-months interview) had received treatment with antidepressant medication. This patient was not depressed at 12 months. A hypothesis of unequal frequency of diagnostic change (i.e., 4 of 5 major depressions and 3 of 7 dysthymic depressions improved) based on in-hospital depression category was not substantiated ($\chi^2_{2-3} = 1.5$, $df = 1$, NS). Similarly, there was no significant change (using repeated-measures ANOVA) in mean scores over time or the diagnosis × time interaction for the Zung ($F_{2,34} = 0.57$, NS), Hamilton ($F_{2,34} = 0.54$, NS), or PSE ($F_{2,34} = 0.27$, NS) scores be-
Table 3: Scores Obtained In-hospital and at 12- and 24-Months Follow-Up

<table>
<thead>
<tr>
<th>In-hospital diagnosis</th>
<th>No-follow-up</th>
<th>12-Months follow-up</th>
<th>24-Months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In-hospital</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=11)</td>
<td>(n=5)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Major depression</td>
<td>60 ±14</td>
<td>53 ±13</td>
<td>51 ±15</td>
</tr>
<tr>
<td>Zung</td>
<td>14 ±7</td>
<td>15 ±3</td>
<td>15 ±3</td>
</tr>
<tr>
<td>Hamilton</td>
<td>25 ±10</td>
<td>22 ±5</td>
<td>23 ±4</td>
</tr>
<tr>
<td>PSE</td>
<td>16 ±5</td>
<td>22 ±7</td>
<td>23 ±6</td>
</tr>
<tr>
<td>MMSE</td>
<td>8 ±7</td>
<td>9 ±7</td>
<td>6 ±3</td>
</tr>
<tr>
<td>JHFI</td>
<td>0.25 ±0.07</td>
<td>0.10 ±0.06</td>
<td>0.20 ±0.13*</td>
</tr>
</tbody>
</table>

Dysthymic depression

|                       | In-hospital  | 12 months           |                     |
|                       | (n=9)        | (n=7)               | (n=7)               |
| Zung                  | 45 ±9        | 44 ±10              | 45 ±11              |
| Hamilton              | 9 ±6         | 9 ±3                | 12 ±8 (n=6)         |
| PSE                   | 13 ±5        | 14 ±7               | 13 ±11              |
| MMSE                  | 20 ±8        | 23 ±8               | 21 ±7               |
| JHFI                  | 10 ±8        | 6 ±6                | 4 ±4                |
| SFE                   | 0.28 ±0.21   | 0.24 ±0.1           | 0.31 ±0.13          |

Nondepressed

|                       | In-hospital  | 12 months           |                     |
|                       | (n=18)       | (n=25)              | (n=25)              |
| Zung                  | 34 ±6        | 35 ±6               | 40 ±11              |
| Hamilton              | 4 ±3         | 4 ±3                | 5 ±5                |
| PSE                   | 4 ±3         | 4 ±3                | 6 ±7                |
| MMSE                  | 22 ±5        | 23 ±7               | 25 ±6               |
| JHFI                  | 4 ±4         | 5 ±5                | 2 ±3*               |
| SFE                   | 0.22 ±0.14   | 0.19 ±0.11          | 0.21 ±0.14          |

Depression scores in-hospital and at 12-months follow-up are significantly different between each diagnostic category. F values for statistical analyses are given in text. PSE, Present State Examination; MMSE, Mini-Mental State Examination; JHFI, Johns Hopkins Functional Inventory; SFE, Social Functioning Exam.

*Significantly different from in-hospital scores.
†Significantly different from either major depression or nondepressed at 24-months follow-up.

There were no significant diagnosis X time interactions for any of the depression groups (F2,34 = 0.68, NS). In contrast, however, SFE scores were significantly worse at 12 months only for patients with major depression in-hospital (F1,25 = 7.26, p < 0.01) while patients with dysthymic or no depression did not deteriorate in social functioning. There were no significant diagnosis X time interactions in SFE scores (F2,34 = 1.10, NS).

Follow-up Evaluation at 24 Months

Of the 48 patients seen at 24 months, 10 (21%) had major depression, 10 (21%) had dysthymic depression symptoms, and 28 (58%) were not depressed. Although these percents were not significantly different from those found in-hospital (i.e., 14, 19, and 67%, respectively), the composition of the depression groups had changed (Figure 1). All patients with major depression at 24 months were different from patients with major depression in-hospital, and 7 of 10 patients with dysthymic depression were different from the patients with dysthymic depression in-hospital.

Of the 6 patients with major depression in-hospital, 4 had no depression and 2 had symptoms of dysthymic depression (Figure 1). In contrast, however, among the 10 patients with dysthymic depression in-hospital, at 24 months 4 had developed symptoms of major depression, 3 continued to have symptoms of dysthymic depression, and only 3 had recovered. Of the 32 patients who were not depressed at the initial evaluation, 6 had developed symptoms of major and 5 symptoms of dysthymic depression, whereas 21 remained nondepressed.

In this study, only 2 patients had a previous (i.e., prior to stroke) personal history of depression defined as seeing a health professional for evaluation or treatment of depression. These 2 patients were included in the 48 patients receiving 24-months follow-up. One patient had dysthymic depression in-hospital and remained depressed at 24 months, and the other had...
FIGURE 1. Diagnostic status in the hospital, 12 and 24 months after stroke, for individual patients indicated by a numbered bar; subsequent follow-up diagnosis is horizontally displayed.

major depression in-hospital but was not depressed by 24 months. Neither patient received a 12-months evaluation. Thus, a history of depression did not have a significant impact on the results of this study.

Remarkably, only 1 patient with dysthymic depression (this patient was being treated at the 6-months interview but still had dysthymic symptoms at 24 months) and 1 patient who was not depressed in-hospital but developed major depression by the 24-months follow-up (this patient was receiving treatment at 24 months) had received antidepressant medication.

In contrast to our findings at 12 months, at 24 months the hypothesis of unequal frequency of improvement (i.e., improvement was defined as in-hospital major depression going to dysthymic or no depression at follow-up, while in-hospital dysthymic depression was improved if no depression was found at follow-up) for in-hospital major vs. dysthymic depression was statistically substantiated ($\chi^2_{\text{expected}} = 4.35, df = 1, p < 0.025$). Thus, patients with major depression in-hospital were more likely to improve by 24 months than patients with dysthymic depression in-hospital.

The improvement in diagnostic status of patients with major depression between in-hospital and 24-months follow-up was also reflected by significant improvement in depression scores between in-hospital and 24-months follow-up using repeated-measures ANOVA of the diagnosis x time interaction for the Zung ($F_{3,45} = 10.1, p < 0.001$), Hamilton ($F_{3,45} = 12.6, p < 0.001$), and PSE ($F_{3,45} = 12.6, p < 0.001$). Post-hoc comparisons revealed that depression scores between in-hospital and 24-months follow-up significantly improved for patients with in-hospital major depression but were not improved in patients with dysthymic depression (e.g., Hamilton in-hospital vs. 24 months for major depression $t = 3.4, df = 5, p < 0.05$; Hamilton in-hospital vs. 24 months for dysthymic depression $t = 1.8, df = 9, NS$). On the other hand, by 24 months patients who were not depressed in the hospital had significantly worse scores on the Zung ($t = 3.7, df = 31, p < 0.05$), Hamilton ($t = 3.1, df = 31, p < 0.05$), and PSE ($t = 1.9, df = 31, p < 0.05$; one-tailed). At the 24-months follow-up, patients with dysthymic depression in-hospital had significantly higher scores on the Zung ($F_{3,45} = 4.6, p < 0.01$), Hamilton ($F_{3,45} = 5.9, p < 0.01$), and PSE ($F_{3,45} = 7.0, p < 0.01$) than patients with in-hospital diagnoses of either major or no depression, who were not significantly different from one another.

Patients showed significant improvements in their JHFI scores over 2 years ($F_{3,45} = 17.4, p < 0.05$), whereas post-hoc comparisons indicated that this occurred only in patients with major or no depression in-hospital and that patients with dysthymic depression in-hospital were not significantly improved. The diagnosis x time interaction was not significant ($F_{3,45} = 2.7, p < 0.08$). MMSE scores ($F_{3,45} = 2.3, NS$) and SFE ($F_{3,45} = 0.82, NS$) scores were not different between the in-hospital and 24-months evaluations for any diagnostic category.

Discussion

This study demonstrated that the prevalence of depression remains high but relatively stable for the first 2 years after stroke. The composition of the depressed groups, however, changed over the 2 years. All of the patients with major depression improved by 2 years, and their depression scores were significantly lower compared with their in-hospital evaluation. In contrast, however, only 30% of the patients with dysthymic depression improved in their diagnostic classification, and there was no significant improvement in their mean depression scores. As a group, patients who were not depressed in-hospital deteriorated in their mood state by 2 years, with more than a third of them developing clinically diagnosed depression and a significant increase in their mean depression scores.

The major uncertainties in this study are whether the
follow-up population is representative of the initial group and whether generalizations can be made to an overall stroke population based on the findings in this predominantly lower socioeconomic class population. Although these questions cannot be completely answered, we have shown that the follow-up patients did not differ in their diagnostic categories, severity of impairment, or demographic features from patients who were not followed up. Second, although the findings in these lower socioeconomic class patients may not always apply to the general stroke population, studies by other investigators have reported similar findings concerning the relation between severity of depression and lesion location, the association between failure to suppress serum cortisol following dexamethasone administration and the existence of depression, the lack of statistical association between severity of impairment (cognitive or functional physical) and severity of depression, and treatment response. Thus, although further studies will be needed to establish the general applicability and reproducibility of these findings, there appears to be some indication that this stroke population may provide some insights for the general stroke population.

The most important finding from this study was the poor prognosis of patients with an in-hospital diagnosis of dysthymic depression. This is in contrast to the improvement in depression scores and ADL scores (JHFI) seen in patients with major depression over the 2 years follow-up. This finding is certainly consistent with our previous reports demonstrating the importance of differentiating major from dysthymic post-stroke depression. It is also consistent with the findings of Jacoby et al. and Post, who found that depression in the elderly is frequently associated with a poor prognosis, particularly when there was associated ventricular enlargement.

Although this kind of differential prognosis for major and dysthymic depression might be expected for patients without brain injury, to find this same clinical differentiation within the brain-injured population surprised us. Both major and dysthymic depression recognized in-hospital generally met the DSM III diagnostic criteria of 2 weeks' duration of symptoms for major depression and 2 years' duration of symptoms for dysthymic disorder. It is possible, however, that some patients with dysthymic depression in-hospital improved and then relapsed by the 2-years follow-up. Although we do not know why major depressive disorder remits between 1 and 2 years after stroke, this spontaneous remission is consistent with the untreated course of major depression in patients without brain injury. It is also consistent with our previous suggestions of neurochemical or neurophysiological contributions to the development and remission of these depressive disorders. These major depressions may remit based on neural regeneration or biochemical compensatory mechanisms such as changes in receptor regulation or the rate of transmitter or enzyme synthesis.

The reason dysthymic depression disorders do not significantly improve over 2 years is uncertain. In a previous study, we examined patients with dysthymic depression in-hospital and compared them with those who developed dysthymic depression several months after discharge. Although we hypothesized that these delayed-onset dysthymic depressions might be "reactive" to the severity of physical or intellectual impairment, we found no significant relation of depression to severity of impairment. Thus, dysthymic depressions do not appear to be psychological reactions to the impairment. These depressions, however, might be related to premorbid personality vulnerabilities, and this "depressive" personality trait may lead to prolonged "characterological depressions." This is only one possibility, and others might be posed.

The other striking finding in this study was the association between improvement in ADL (JHFI) and the existence of depression. At the 12-months follow-up, only nondepressed patients significantly improved in JHFI scores. We have suggested in a previous publication that, although physical impairment does not cause depression, once depression occurs, there is an interaction that impacts significantly on the course of the recovery. It has been suggested by many clinicians that depression adversely affects stroke rehabilitation. These data provide some empirical support for this idea and also emphasize the need for ongoing clinical evaluation and treatment of depression in stroke patients. Although the demonstration of the efficacy of treatment of poststroke depressions by ourselves and others had not been published when this study was conducted (i.e., 1981), the lack of treatment of these disorders was striking.

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