Progress Reviews

Predictors of Depression after Stroke
A Systematic Review of Observational Studies

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Background and Purpose—Although depression is common after stroke, there is uncertainty over its etiology and risk factors, which complicates management. Knowledge of the predictors of depression associated with stroke may allow for the better targeting of therapy, both prevention and treatment.

Methods—We undertook a systematic review of all published, nonexperimental, population-, hospital-, and rehabilitation-based stroke studies (to June 2004) with prospective, consecutive patient recruitment undertaken to identify variables associated with depressive symptoms (or “illness”) after stroke. Assessments were made of the quality of studies including the validity of prognostic models.

Results—Data were available from 3 population-based studies including 492 patients, 8 hospital-based studies including 15 272 patients, and 9 rehabilitation-based studies including 2170 patients. Physical disability, stroke severity and cognitive impairment were consistently associated with depression. In addition to the common problem of selection bias, major limitations of these studies included variable selection and poor statistical quality and reporting; small sample sizes meant that only a limited range of variables were analyzed in multivariate models.

Conclusions—There is a paucity of well-designed studies of sufficient size to allow stable multivariate predictive models of depression after stroke to be developed. Other than showing that depression is associated with more severe strokes, current evidence does not allow for ready identification of patients most at risk of developing this important complication of stroke. (Stroke. 2005;36:2296-2301.)

Key Words: depression ■ epidemiology ■ stroke ■ systematic review

Although depression is recognized as an important complication of stroke, there is uncertainty regarding its etiology, risk factors, and management, both prevention and treatment. Thirty years ago, a strong case was made regarding the importance of the location of the cerebral lesion in determining the onset of “poststroke depression” as a specific clinical entity related to a focal disturbance of neurotransmitter pathways. Subsequent research has focused on providing clinical entity related to a focal disturbance of neurotransmitting the importance of the location of the cerebral lesion in determining the onset of “poststroke depression” as a specific clinical entity related to a focal disturbance of neurotransmitter pathways. This literature is complicated by methodological limitations, including the use of small and highly selected groups of patients. Much less effort has been given to explorations of other potential personal or environmental risk factors. We performed a systematic review of published population-, hospital-, and rehabilitation-based nonexperimental studies to collate data on predictive factors for depression after stroke. These data may be helpful in identifying potentially high-risk patients who may be targeted for therapy.

Methods
This review was restricted to published research articles, abstracts, and letters of patients with a clinical diagnosis of stroke where an attempt was made to assess the variables associated with, or predictive of, the development of depressive illness or depressive symptoms. The methods used for article selection and analysis have been published previously. In brief, the review included incidence studies, case-control studies, and case series that had prospective, consecutive patient recruitment within clearly defined geographical- and time-limited boundaries. There were no restrictions on the basis of language, sample size, or duration of follow-up, but we excluded studies of mixed populations unless separate results for stroke patients were identified. Studies were also excluded if they had any of the following: limited to specific patient characteristics, such as sex or location of stroke lesion; convenience sampling; retrospective recruitment; or if there was only unstructured assessment of mood.

For the purposes of these analyses focused on multivariate modeling, we accepted the diagnostic category of depression as applied by the authors of each study, which included the following: (1) the presence of depressive disorder, depressive symptoms, or “psychological distress,” as defined by scores above a cut point for abnormality on a standard mood scale; (2) severity of depressive disorder, depressive symptoms, or psychological distress, as defined by scores on a standard mood scale; and (3) the presence of major depression or minor depression (or dysthymia) according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IIIR, DSM-IV, or other standard psychiatric diagnostic criteria.

Data for this review were identified from the following computerized databases: MEDLINE, EMBASE, CINAHL, PsychINFO, Applied Science and Technology Plus, Biological Abstracts, General

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Science Plus, Arts and Humanities Index, Science Citation Index, Social Sciences Citation Index, Sociofile, and Digital Dissertations using terms and strategy based on the Cochrane Stroke Group methodology (full details available on request; last searched June 2004). Studies were grouped into 3 categories that represented degrees of case selection. The first group, “population-based studies,” considered the highest (least biased) quality, consisted of studies that attempted to recruit all stroke patients, including those who were not admitted to hospital for acute care. The other 2 groups were “hospital-based” studies, which included all inpatients with stroke recruited from acute care medical wards in general hospitals, and “rehabilitation-based” studies, which included inpatients from rehabilitation wards or hospitals (including stroke units).

For each study, data were collected on all of the variables considered for analyses, as well as those that were shown to be significantly associated with or predictive of depression after stroke. Additional data were collected to assess the quality of each multivariate model according to accepted criteria, which include: external validity (were the patients representative; how generalizable was the model?), internal validity (were the assessments appropriate; how biased was the model?), statistical validity (including the calculation of the “events per variable” ratio: the number of outcome events per independent variable entered into the model; the minimum number is 10 persons for logistic regression that predicted the presence of depression and 20 persons per independent variable for linear regression predicting the severity of depression), evaluation (how are the model’s predictions?), and practicality (how easy the model is to use?).

Results
Three population-based studies including 492 patients, 8 hospital-based studies including 15 272 patients, and 9 rehabilitation-based studies including 2170 patients assessed factors potentially associated with or predictive of depression after stroke (Figure 1). Most studies excluded patients with subarachnoid hemorrhage, transient ischemic attack, and communication difficulties (eg, aphasia, confusion, or dementia). The multivariate models were developed on between 442 and 13 999 patients. A variety of methods were used to diagnose depression and assess the degree of depressive symptoms or depressive symptom burden. DSM criteria were used to define the dependent variable in 7 studies using information from completed mood scales and occasionally from structured interviews. Six mood scales and 1 single simple question were used to define the presence or severity of depression across studies.

Figure 1 summarizes the quality of analyses in the included studies. There was little variation in relation to external and internal validity across the studies. The main difference was that the hospital- and rehabilitation-based studies had several exclusion criteria that may have restricted their generalizability (eg, in the exclusion of patients with a history of depression or psychiatric illness or by having age limits for inclusion), and the baseline assessment was seldom conducted within 7 days of stroke.

Statistical quality and the presentation of methods and results was poor in many studies. Potentially important predictors of depression, age, sex, and personal history of depression, were seldom all included in the multivariate models. Although it is common practice to include only variables that are significant in univariate analyses in a multivariate model, ideally it is important to also include variables that are theoretically associated with or have been shown in other studies to be associated with the dependent variable. Few studies limited variables to those assessed at stroke onset; however, it was difficult to determine exactly when many variables were assessed in the studies. When variables were assessed at more than one time point (ie, prestroke, immediately after stroke, and after the acute recovery phase), studies seldom stated at which time point the included variable was assessed. Most of the models presented in this review are explanatory (they describe the relationship of predictor variables to the presence or severity of depression) rather than predictive (describing the probability than depression will occur). Therefore, it would appear that most of the models are not clinically practical for identifying, before hospital discharge, those at high risk of later depression.

Six studies included too few patients for the model to be stable (events per variable ratio), only 4 studies clearly stated that collinearity (ie, a high degree of correlation between ≥2 predictor variables) was assessed, and only 3 studies validated their model on the data used to generate the model (internal validation). No models were validated on another dataset (external validation) or assessed in clinical practice to establish whether their predictions were better than unstructured, clinical judgment. However, 11 studies used stepwise techniques to select predictor variables, and studies with a sufficient “events per variable ratio” were able to explain between 22% and 85% of the variance (ie, goodness of fit) in the presence or severity of depression.

As shown in Figure 2, a total of 87 different variables were assessed across the studies, although only 15 variables (17%) were assessed in ≥5 studies. Of those, only physical disability after stroke showed a consistently positive association with depression (9 of 11; ie, a significant association in 9 of 11 studies which assessed this variable). Stroke severity (5 of 5) and cognitive impairment (4 of 5) were also positively associated with depression. When considered together, social factors after stroke (living alone, place of residence, social support, and social isolation) were also consistently associated with depression. Among the other variables considered, older age showed no association (13 of 17; ie, no association in 13 of 17 studies), nor did female sex (7 of 17); education level (5 of 7); living alone at stroke onset (5 of 7); personal history of diabetes (4 of 5); stroke (4 of 7); or depression (3 of 8); or stroke subtype (6 of 7). No variable was shown to be protective for future depression.

Discussion
We have shown that, although a wide range of variables have been considered across studies, only physical disability, stroke severity, and cognitive impairment were most consistently identified as being associated with depression after stroke. However, the ability to draw firm conclusions is restricted by methodological heterogeneity and limitations of the literature. Only 4 studies accounted for >50% of the total variation in depressive symptom burden, only 2 of those models were developed in samples large enough to be reliable, and no model was validated in another population.

Several basic problems were identified in the statistical methods used to produce many of the models. In the general population, the risk of depression is known to increase with age and is about twice as common in women than in men. However, stroke patients are more often elderly, female, have
concomitant illness, and have experienced bereavement and other major life events. Furthermore, between 35% and 60% of people with depression will eventually have another episode, whereas major depressive disorder is up to 3 times more common among first-degree relatives of depressed people than in the general population. Yet, few stroke studies included in this review forced age, sex, and history of depression into their multivariate analyses.

A recent systematic review of depression among elderly community-dwelling people found that disability was 1 of 5 key risk factors that were identified (the others were bereavement, sleep disturbance, prior depression, and female sex). Our data would suggest that clinicians should be particularly vigilant to the detection of depression among patients with severe strokes and stroke-related disability. Other confounders that may need to be considered in future predictive modeling are cognitive impairment (which may modify any psychological reaction), physical disability, and social support.

The presence of depression and physical and cognitive impairment in stroke patients should be of particular concern

| Criteria | FINNSTROKE 
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<th>Study details</th>
<th>Stroke subtype included</th>
<th>External validity</th>
<th>Internal validity</th>
<th>Statistical validity</th>
<th>Evaluation of model</th>
<th>Practicality of model</th>
<th>Confidence intervals given</th>
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<td>Time of assessment</td>
<td>Ischemic</td>
<td>Inception cohort</td>
<td>Age</td>
<td>Events per variable ratio sufficient</td>
<td>Variance in prevalence of depression (%)</td>
<td>Face validity variables</td>
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<td>Subarachnoid haemorrhage</td>
<td>Not assessed</td>
<td>Sex</td>
<td>Stepwise analysis</td>
<td>24</td>
<td>Actual model given</td>
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<tr>
<td>1 y 1 m 2 w 3 m</td>
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<td>Assessed at 7 days post-stroke</td>
<td></td>
<td>Collinearity assessed</td>
<td>35</td>
<td>Variance in severity of depression (%)</td>
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<tr>
<td>6-12 m</td>
<td>Undetermined</td>
<td>&lt;10% cohort excluded or lost to follow-up</td>
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<td>6 m</td>
<td>Timing of outcomes</td>
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<td>2 m</td>
<td>Fixed time points used for assessment</td>
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Abbreviations: -- an approximation of numbers, actual value not provided in published paper; d: day; m: month; w: week; y: year; disch: at discharge from the rehabilitation facility, no average time since stroke provided in the published paper.

Figure 1. Quality of multivariate modelling in studies of depression following stroke.
Figure 2. Variables associated with, or predictive of, depressed mood following stroke.
to physicians. It is likely that depression reduces the desire and capacity to participate in rehabilitation, and affected people are less inclined to socialize (socialization is thought to be protective of mood disorders, and low social support was associated with depression in 4 of 4 studies in this review). Other social factors after stroke, such as place of residence (especially living alone or in an institution), also warrant additional attention. Social isolation may be complicated by the stigma associated with acknowledging a mental health problem, with some people “masking” symptoms so that their family and doctor are unaware of any problems. Depression and social isolation may put people at a greater risk of adverse health behaviors, such as poor adherence to medications and increased alcohol and drug intake. In turn, loss of physical ability and decreased cognitive function after stroke may also lead to depression.

Current models of depression after stroke are not accurate, have not been rigorously developed and validated, are not

### Recommendations for Future Studies of Predictors of Depression After Stroke

Selection bias kept to a minimum; ideally studies should be population- or hospital-based.

Mood assessment is by a semi-structured psychiatric interview or with a validated mood scale.

Dependent variable selection and analytic method clearly described: the presence of depression (logistic regression), depression severity (linear regression), or the time to depression (proportional hazards regression).

**Intended purpose** of the model is adequately explained:
- Is the model intended to be useful in clinical practice? It is therefore a predictive model (aims to calculate the probability that an event will occur) and should only include readily available pre- and acute stroke variables.
- Is the model intended to explain the relationship between each independent variable and depression? It is therefore explanatory and can also include variables collected at the same time as depression was assessed.

Sample size should be adequate to build the model. The guideline is 10 outcome events per independent variable entered into a logistic regression model or proportional hazards model, and 20 persons per independent variable entered into a linear regression model. The number of cases with the outcome of interest and the total number of cases in the sample should be reported.

Independent variables (or risk factors) must be clearly described, including when the variable was measured, how it was measured and coded, and in what form it was entered into the model (was transformation of the variable required). There must also be an adequate number of persons with each risk factor being entered into the model.

Process of variable selection and development of the model should be clearly described, including testing for high correlation, co-linearity, and interaction between predictor variables, the use of stepwise, or change in estimate methods to build the model.

Important confounders must be included, or forced, into the model.

Automated methods of building models must be checked to determine that the data are clinically meaningful and useful, and not simply ‘statistically significant’.

Reporting the usefulness of the model should include confidence intervals around odds ratios and regression coefficients, and the amount of variance ($R^2$, adjusted $R^2$, C statistic) explained by the model should be reported, which is more important than the “$p$” value.

Clinically meaningful models should be validated internally (on the sample used to derive it), externally (on another sample), and in clinical practice to determine whether the use of the predictor variables is better than unstructured clinical assessment.
well described, predominantly describe variables associated with depression presence and severity, and are not clinically useful for predicting the occurrence of depression after stroke. We have provided some recommendations for the methods and reporting of future studies (see Table 1).9,31,41 In summary, no reliable data are currently available to allow the easy identification of those patients at the greatest risk of experiencing depression at any time after the onset of stroke. Additional research in this area would be of considerable importance not only in terms of increasing our understanding of etiological risk factors for depression in the setting of stroke but also in advancing health care delivery to improve stroke rehabilitation outcomes.

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References

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