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The Prediction of Recovery using a Multivariate Model in 1471 Depressed Inpatients

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Summary. Stepwise multiple logistic regression was used in an attempt to develop a statistical model which would predict "recovery" in a group of 1471 depressives admitted to a tertiary care hospital. Six variables identified by this approach included: Electroconvulsive therapy, personality disorder, chronicity, anxiety disorder, organic mental disorder, and dysthymia. The meaning and significance of the findings are discussed.

Key words: Depression – Electroconvulsive therapy – Dysthymia – Personality disorder – Anxiety disorder

Introduction

Approximately 50–60% of hospitalized depressives will experience marked short term improvement (i.e., recovery) with antidepressant medication or electroconvulsive therapy (ECT); between 70 and 80% will experience some improvement (Greenblatt et al. 1964; Avery and Lubrano 1979; Keller et al. 1984). Although antidepressant medication remains the treatment of choice for most patients, ECT is widely used in depressives who have not responded to medication, are acutely suicidal, or are refusing food or fluids (Crowe 1984). Other pharmacologic treatments (e.g., lithium carbonate) are often used to "augment" the response to antidepressants and appear to have promise as treatment strategies (Price et al. 1986). Nevertheless, 20–30% of depressed patients will have an unsatisfactory response to these treatments for reasons that are not entirely clear, and nearly 20% will develop a chronic depression (Keller et al. 1984). Over the past 30 years, researchers have attempted to explain these findings by studying treatment outcome from multiple perspectives (Hobson 1953; Kiloh et al. 1962; Carney et al. 1965; Deykin and Dimascio 1972; Hamilton and White 1960; Abrams et al. 1973; Nelson et al. 1982; Copeland 1983; Coryell and Zimmerman 1984; Clinical Research Center 1984; Robinson and Spiker 1985; Zimmerman et al. 1985; Rich et al. 1986; Lykouras et al. 1986; Coryell et al. 1988; Croughan et al. 1988). Their work has led to the identification of several demographic and clinical risk factors from both hospitalized and non-hospitalized samples. The results of these collective efforts, however, have often been inconsistent or contradictory.

The most important risk factor for treatment outcome appears to be the clinical distinction between "endogenous" and "neurotic" depression (Hobson 1953; Hamilton and White 1960; Kiloh et al. 1962; Carney et al. 1965). Outcome studies of both electrotherapy and antidepressant treatment have shown that, almost uniformly, "neurotic" patients respond more poorly than "endogenous" patients. Other risk factors predicting "good" outcome include a positive family history (i.e., of affective disorder) (Coryell and Zimmerman 1984), older age (i.e., generally 40 years or more; Carney et al. 1965), shorter duration of illness (Hobson 1953; Hamilton and White 1960), lower symptom severity (Croughan et al. 1988), and abnormal suppression to dexamethasone (Nelson et al. 1982; Coryell and Zimmerman 1984). Risk factors that have generated considerable disagreement include sex and psychotic features (Copeland 1983; Coryell and Zimmerman 1984; Robinson and Spiker 1985; Rich et al. 1986; Lykouras et al. 1986; Croughan et al. 1988). The reason for the inconsistency regarding psychosis is that findings tend to be treatment specific. Psychotic depression appears to respond well to ECT but not to antidepressant medication.

Recovery has also been associated with a diagnosis of primary depression and the absence of a personality disorder (Weissman et al. 1978; Davidson et al. 1980; Clayton and Lewis 1981; Tyrer et al. 1983; Pfohl et al. 1984; Coryell et al. 1985; Zimmerman et al. 1986; Zorumski et al. 1986). Both risk factors appear to represent a variation on the endogenous/neurotic distinction. The patient with a secondary depression and the depressed patient with a personality disorder each have a stormy lifestyle and an unstable personality – characteristics typical of a "neurotic" depression (Winokur 1985).

The matter of identifying predictors of response is important. Depression is a severe illness that leads to

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great emotional suffering by patients, their friends and family members, places the patient at risk socially and occupationally, and leads to excess morbidity and mortality (Kerr et al. 1969; Black et al. 1987b). For these reasons, it would be useful to find ways that would help physicians to predict treatment response more accurately.

The purpose of the present study was to develop a multiple logistic regression model utilizing demographic, clinical, and treatment data obtained from case notes of depressed inpatients in an attempt to develop a set of predictors of outcome in a high-risk population.

Methods

Between 1 January 1970 and 31 December 1981, 1471 depressives were admitted to the University of Iowa Psychiatric Hospital. These patients had a variety of clinical diagnoses including primary depression, secondary depression, neurotic depression, unipolar depression, bipolar depression, dysthymia, atypical depression, involutional melancholia, psychotic depression, involutional psychotic reaction, etc. The case notes of these patients were carefully reviewed by a master's level psychologist (A.N.). Demographic, clinical, treatment, and outcome data were abstracted using an instrument developed by two of the authors (D.W.B., G.W.). All patients were rediagnosed by applying DSM-III criteria (American Psychiatric Association 1980), the Research Diagnostic Criteria (Spitzer et al. 1978), and the Feighner criteria (Feighner et al. 1972). Patients were also classified according to Winokur's familial subtypes (Winokur 1979). Multiple diagnoses were allowed and data on medical illnesses were coded. Patients were described as having "recovered" if the case notes suggested that the patient had "markedly" improved or had been restored to his or her premorbid condition, and had no evidence of depression at the time of discharge. All others were considered not to have recovered. Further information on our methods are available elsewhere (Black et al. 1987a, 1989).

Categorical variables were compared by chi square, or Fisher's exact test when any expected cell count in a 2×2 table was less than 5. Multiple logistic regression analysis was performed using SAS software, and utilized a stepwise variable selection procedure (Schlesselman 1982; SAS Institute 1986). For the logistic regression analysis we defined outcome (recovered/non-recovered) as the dependent variable. The independent variables potentially to be included in this model are listed in Table 1.

This list of potential predictors consists mainly of those risk factors described in the literature review above for which data were available in this study. Because detailed family history data were not uniformly available from the case notes, the Winokur

Table 1. Variables potentially predictive of short-term outcome

Age (continuous)
Sex (male)
Marital status (divorced/not divorced)
Delusions (present/absent)
Number of previous hospitalizations (continuous)
Chronicity (duration of index episode >1 year vs <1 year)
Precipitating event (present/absent)
Hallucinations (present/absent)
ECT during index admission (any vs none)
Lithium treatment during index admission (any vs none)
Antipsychotic treatment during index admission (any vs none)
Antidepressant treatment during index admission (any vs none)
Organic features (present/absent)
Feighner primary depression (present/absent)
Feighner secondary depression (present/absent)
MDD, single episode (present/absent)
MDD, recurrent (present/absent)
Dysthymia (present/absent)
Unipolar familial pure depressive disorder (present/absent)
Unipolar depressive spectrum disorder (present/absent)
Unipolar sporadic depressive disorder (present/absent)
Unipolar depressive with family history of mania (present/absent)
Melancholia (present/absent)
Suicide attempt (none/ever)
Personality disorder (present/absent)

ECT, Electroconvulsive therapy; MDD, major depressive disorder

Table 2. Characteristics of study population

	Recovered ($n = 804$)	Non-recovered ($n = 667$)
Mean (SD) age at index admission, years (SD)	44.6 (17.4)	42.3 (17.0)
% female	62.4	63.0
% with hallucinations	6.6	5.7
% with delusions	14.1	9.8[b]
% reporting precipitating event	52.0	53.4
% hospitalized >1 month	44.0	37.8[b]
% chronically ill (ill >1 year at time of admission)	16.4	25.2[d]
% married	54.1	49.5[a]
% receiving antidepressants in the hospital	80.2	83.4
% receiving ECT in the hospital	41.3	28.2[d]
% receiving lithium in the hospital	17.4	19.3
% receiving neuroleptics in the hospital	20.2	18.4
% DSM-III, major depression, single episode	30.6	27.1
% DSM-III, major depression, recurrent	45.3	44.4
% DSM-III, bipolar depression	11.6	11.2
% DSM-III, dysthymia	0.4	2.6[d]
% DSM-III, atypical depression	12.2	14.7
% melancholia (DSM-III definition)	6.3	6.0
% with comorbid organic mental disorder	0.6	2.3[c]
% with comorbid substance abuse	5.5	8.6[b]
% with comorbid anxiety disorder	2.4	5.7[d]
% with comorbid somatoform disorder	2.0	3.0
% with comorbid personality disorder	5.0	10.8[d]
% with medical disorder	7.2	8.9
% Feighner primary depression	59.7	46.6[d]
% Feighner secondary depression	18.3	28.6[d]
% Winokur unipolar FPDD	15.9	15.6
% Winokur unipolar DSD	16.4	18.7
% Winokur unipolar SDD	34.5	29.2[b]

FPDD, familial pure depressive disorder; DSD, depressive spectrum disorder; SDD, sporadic depressive disorder

[a] $P < 0.01$ [c] $P < 0.005$
[b] $P < 0.05$ [d] $P < 0.001$

Table 3. Odds ratios (OR) and confidence intervals (CI) for each variable[a]

Variable	OR	CI (95%)
Electroconvulsive therapy	1.77	(1.41, 2.23)
Personality disorder	0.48	(0.32, 0.72)
Chronicity	0.64	(0.49, 0.84)
Anxiety disorder	0.45	(0.25, 0.80)
Organic mental disorder	0.28	(0.09, 0.84)
Dysthymia	0.38	(0.14, 1.01)

[a] Adjusted for effects of all other variables in model

familial subtypes shown in Table 1 were included as a substitute for family history of mental illness.

For a variable to enter as well as to remain in the model, the associated chi-square statistic, first prior to and then following its entry, had to be significant at the 0.10 level, controlling for all other variables in the model.

Results

Using our definition, 804 patients (54.6%) were recovered and 667 (45.4%) had not recovered at hospital discharge. Characteristics of the study population are shown in Table 2. The crosstabulations show that there were significant differences in age and marital status, but not gender. Patients having recovered were more likely than non-recovered patients to have had delusions, ECT, and a diagnosis of Feighner primary depression. Non-recovered patients were more likely to have a chronic (i.e., ill for more than 1 year) depression, a diagnosis of dysthymia, comorbid organic mental disorder, substance abuse, anxiety disorder, personality disorder, a diagnosis of Feighner secondary depression, and a diagnosis of Winokur's unipolar sporadic depressive disorder (SDD).

From that list of potential predictors, the following variables met significance level criteria for entry into and retention within the model: ECT, personality disorder; chronicity; anxiety disorder; organic mental disorder; and dysthymia. The odds ratios associated with these predictors, along with 95% confidence intervals, are shown in Table 3. The model chi square based on the likelihood ratio test with 6 *df* is highly significant (85.28, $P < 0.0001$).

Discussion

The variables that formed the final model were to some extent consistent with the literature, since they have been reported as being among the strongest predictors of recovery, especially chronicity, personality disorder, dysthymia, and ECT.

Multivariate Analysis

Chronicity, which we defined as a depression with a duration greater than 1 year, emerged in this multivariate analysis as militating against recovery. This finding was not unexpected, since longer duration of illness has been associated with poor response to both antidepressants and ECT in most (Hobson 1953; Hamilton and White 1960; Carney et al. 1965), but not all (Abrams et al. 1973) studies that address duration of illness. Anxiety disorders that occur along with depression, such as panic disorder or generalized anxiety, have also been associated with poor treatment response (Davidson et al. 1980; Coryell et al. 1988), although it is unclear how they impede recovery.

ECT was associated with good treatment response in the model, independent of other variables, such as hospital stay. ECT has consistently been demonstrated to be the most effective treatment for severe depression (Greenblatt et al. 1964; Avery and Lubrano 1979; Clinical Research Center 1984), so that this finding is not unexpected. In fact, these findings suggest that the treatment may be underutilized in tertiary care settings, and that many patients suffering severe depression who do not receive ECT could benefit from it.

Personality disorder, an operationally defined concept that seems to have displaced the term "neurotic," at least in reference to depression, emerges as predictive of outcome. That is, the patient with a comorbid personality disorder (e.g., antisocial, borderline, etc.) is 50% less likely to be recovered at hospital discharge than a depressive without the disorder. Personality disorder, like chronicity, has been linked to poor response to both antidepressants and ECT, and to predict both poor short- and long-term outcome (Weissman et al. 1978; Tyrer et al. 1983; Pfohl et al. 1984).

Dysthymia, like personality disorder, has became a contemporary synonym for "neurotic" (Winokur 1985; Winokur et al. 1987). In fact, depressive neurosis is an alternate term for dysthymia, according to DSM-III (American Psychiatric Association 1980). That the disorder would have a poor response is not surprising, since the condition lasts, by definition, more than 2 years, and has been associated with personality disorder (Akiskal 1983). Keller et al. (1983, 1984, 1986) have pointed out that poor treatment response is one of the most pernicious aspects of dysthymia, which they have termed, when combined with a superimposed major depression, a "double depression."

Organic mental disorders have rarely been mentioned as having an association with treatment response. In our data set, a patient fitting this category would have a pre-existing affective disorder (e.g., major depression, recurrent) and then have developed an organic disorder. However, much of the relevant literature concerns organic affective disorders, in which an affective disorder results from an organic insult, such as a stroke (Lipsey et al. 1984; Popkin et al. 1985). Although some work suggests that depression in stroke patients can be alleviated by antidepressants, there is little consensus. Clearly, additional studies are needed here.

Bivariate Analysis

From our bivariate analysis delusions and the Feighner et al. (1972) primary/secondary diagnostic scheme were

also associated with outcome in depression; patients who had recovered were more likely to be delusional than those who had not recovered, and patients experiencing recovery were more likely to have a primary depression than a secondary depression. Psychotic features have generally been associated with poorer outcome; yet these findings are deceptive, since psychotic depression responds relatively well to ECT, but not to antidepressants. A secondary depression is one that is chronologically preceded by a non-affective psychiatric disorder or serious medical illness. Secondary depression has been associated with both poor treatment response and greater chronicity than primary depression (Clayton and Lewis 1981; Davidson et al. 1980; Keller et al. 1984; Coryell et al. 1985; Zorumski et al. 1986). Although this diagnostic scheme is widely used in research settings, it has never attained clinical popularity, despite its apparent validity (Black et al. 1987c). The fact that the diagnosis of secondary depression is associated with poor clinical outcome gives this concept considerable credence, however.

Duration of hospital stay has not specifically been noted before as a predictor of outcome, and its positive association with recovery may be interpreted in several ways. This variable could, in part, represent the influence of ECT on outcome, since ECT is highly correlated with length of stay. However, length of hospital stay was not retained in our regression model, and ECT was independently significant; their interaction (ECT duration of hospital stay) was not significant. Hospital stay is also correlated with psychosis, and our crosstabulations reveal that delusional patients were more likely to have recovered. A more generous interpretation of the finding is that adequate treatment may take time, and that many non-recovered outcome patients are discharged too early.

Other findings from this analysis include the association of age, marital status, substance abuse, and Winokur's unipolar SDD with outcome. The fact that the patients who had recovered tended to be older and married has been noted previously (Carney et al. 1965; Coryell and Zimmerman 1984; Keller et al. 1984). It is possible that married persons are more likely to seek evaluation and early treatment at the instigation (or encouragement) of a spouse. This latter finding, however, must be viewed as preliminary, since it was only of trend significance. Substance abuse, including both alcoholism and drug abuse, are known to be associated with poor treatment response (Keller et al. 1984; O'Sullivan 1984). How these disorders interfere with recovery is still unknown. Winokur's unipolar SDD is a depression occurring in a person without a family history of depression, alcoholism, or antisocial personality; in other words, the depression is sporadic. Coryell and Zimmerman (1984) found an association with Winokur's familial subtypes of depression, but no other investigators have looked at this variable.

Methodologic Limitations

Several limitations of this study need to be considered. First, the study relied on case notes for determination of clinical and diagnostic variables, a method that is less desirable than personal interview and follow-up. We also made global assessments of outcome, instead of using accepted rating instruments, and ratings that were blind to clinical, treatment, or diagnostic material. However, in defense of chart studies, their results tend to be quite similar to more rigorously designed prospective studies (Black et al. 1987a). Using chart material may also lead to the underdiagnosis of comorbid personality disorder, organic mental disorder, anxiety and somatoform disorders. However, there is no reason to suspect differential misclassification on diagnostic variables. Therefore, any bias introduced by such errors would support the null hypothesis (i.e., minimizing differences among diagnostic categories).

We are also aware that the study population represents a select group of depressives hospitalized at a tertiary care facility. Clearly, these individuals were suffering from illnesses of such severity as to warrant the patient's admission to this setting. As such, the results probably cannot be generalized, except perhaps to other depressed patients at tertiary care hospitals.

The use of stepwise multiple logistic regression to develop a model which will predict short-term outcome represents a potential analysis-related limitation of the study. Stepwise procedures find the model which is the "best fit" to the data within a specified mathematical format. However, they cannot distinguish causal from non-causal associations, or from associations that are artifactual. Moreover, they depend on tests of significance which in turn depend on sample size. Therefore, in analyses of large samples, variables whose practical importance is minimal may be included in a model due to a small *P*-value and vice versa. As a result, the model which provides the best mathematical fit may not always be the model that makes the most practical clinical sense.

Conclusion

This study used multiple logistic regression in an attempt to predict short-term outcome in the treatment of depression, based on demographic and clinical data obtained from case records of depressed inpatients. Our model included six variables: ECT, personality disorder, chronicity, anxiety disorder, organic mental disorder, and dysthymia. Additional studies using large samples and employing careful clinical assessments, blind evaluations, and multivariate analyses will be needed to confirm and extend these observations.

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