Predictors of Relapse in Major Depressive Disorder

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• **Risk of relapse into an affective episode was high in the months immediately after recovery from a major depressive disorder (MDD) in 141 subjects with nonbipolar depression, without a preexisting dysthymic disorder. The probability of relapse then declined steadily during the duration of the follow-up (median follow-up, 62 weeks from recovery). In patients entering the study during their first affective episode, the Research Diagnostic Criteria secondary subtype of MDD and an older age of onset predicted a significantly greater likelihood of relapse. Three or more prior episodes of depression predicted a significantly shorter time to the first and second prospectively observed relapses and, thus, a significantly greater likelihood of subsequent multiple affective episodes.**

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IN 1979, Zis and Goodwin[1] reviewed ten of the most frequently quoted studies on the natural history of affective illness in an effort to assess the empirical support for the widely accepted hypothesis that affective disorders may be distinguished from other psychiatric conditions by their having a cyclic course. Despite the major differences in design and samples of the studies that contributed to the substantial variation in reports of relapse rates, number of episodes, and duration of episodes, they concluded that the majority of patients with major affective disorders do experience several episodes of illness in their lifetime. By applying life-table methods to reanalyze the original data presented in a number of the studies in this literature, we were able to strengthen Zis and Goodwin's conclusion and to document further the almost universal impression that the probability of relapse after recovery from a depressive episode is highest in the months immediately after recovery and then declines steadily during the ensuing year.[2]

Given this general pattern of recurrence in patients with affective disorders, clinicians and researchers would further benefit from identification of the factors that predict relapse after recovery and the likelihood of subsequent recurrences. Most[3-5] but not all[6] studies in the literature report that patients with bipolar depression experience a substantially greater number of episodes than do those with nonbipolar depression. Furthermore, recent work indicates that the presence of a coexisting chronic or intermittent minor depression of at least two years' duration (dysthymic disorder) obscures the power of clinical variables to predict the course and outcome of episodic major depression.[7]

Patients with depression but without a history of mania or a preexisting dysthymia who have recovered from an episode of major depressive disorder form a clinically meaningful group. This group includes the majority of patients who have experienced severe depression some time in their lives. The prevention of relapse, especially multiple relapse, in such patients is a goal of considerable importance to clinical practice.

This article combines life-table and regression methods to report on relapse patterns in a sample of nonbipolar, nondysthymic patients after their recovery from an episode of major depression, with particular focus on the identification of predictors of the speed and likelihood of relapse.

RESEARCH PLAN AND METHODS

Design of the Collaborative Depression Study

Patients were recruited for the National Institute of Mental Health (NIMH)-Clinical Research Branch Collaborative Program on the Psychobiology of Depression (Collaborative Depression Study)[8] when

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Table 1.—Clinical and Sociodemographic Characteristics of Patients (N=141)

Geographic region where patient was studied (admitting center)	
17.7% New York	
30.8% St Louis	
12.3% Boston	
26.2% Iowa City	
13.1% Chicago	
Hospitalization status at intake	
73.8% inpatient	
26.2% outpatient	
No. of episodes of depression before index episode	
35.0% none	
22.9% one	
17.1% two	
9.3% three	
15.7% four or more	
Duration of episode before intake to study	
19.9% <2 mo	
15.6% 2 mo to <3 mo	
19.9% 3 mo to <6 mo	
14.9% 6 mo to <1 yr	
29.8% 1 yr or more	
Severity of depressive syndrome at worst during index episode before entry (extracted Hamilton)	
25±7.5 (mean ±SD)	
Time since first impairment or treatment to intake	
Median, 4 yr; quartiles, 0.8 and 10	
RDC subtypes of major depressive disorder	
Endogenous, 88.7%	
Current primary, 69.5%	
Psychotic, 14.9%	
Sociodemographic characteristics	
Age at intake	
Median, 34 yr; quartiles, 27 and 54	
Sex	
36.9% male	
63.1% female	
Marital status at intake	
48.9% married	
16.3% divorced	
7.1% widowed	
27.0% single	
0.7% other	

they sought psychiatric treatment through the usual referral mechanisms at inpatient and outpatient psychiatric units in public and private settings associated with each of the five collaborative centers in Boston, Chicago, Iowa City, New York, and St Louis. Patients included in the Collaborative Depression Study had a current Research Diagnostic Criteria (RDC)[9] diagnosis of major depressive disorder (MDD), mania, or schizoaffective disorder; were at least 17 years of age at entry, white, and spoke English; had an IQ above 70; and were without evidence of organic brain syndrome.

This was a naturalistic, prospective, longitudinal follow-up study, and subjects were not randomly assigned to different treatment groups. Treatment was prescribed as a result of joint decisions by clinicians and patients and was not controlled in any way by the investigators. However, a detailed record of all treatment received during the course of the study was kept.

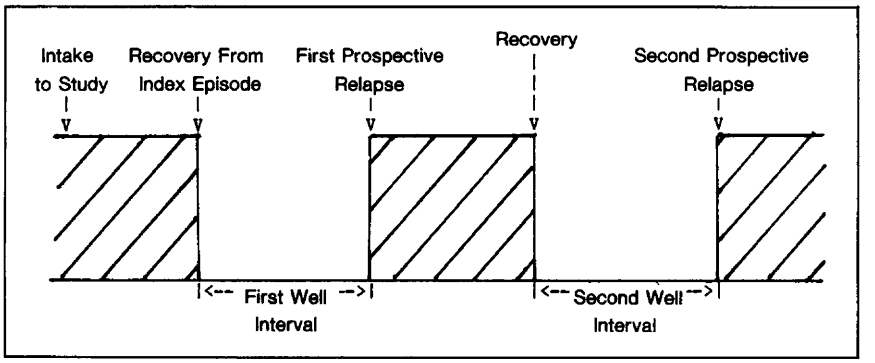

Fig 1.—Time line for recovery and relapse.

Subjects for This Report

This article reports on the first 141 subjects who entered the study with a current episode of nonbipolar MDD, without a preexisting chronic minor depression or a chronic intermittent depressive disorder of at least two years' duration and who recovered from this depression within two years after intake into the study. Sociodemographic and clinical characteristics of this sample and the RDC subtyping of the index episode of MDD are given in Table 1. We have previously reported some aspect of the follow-up for 40 of these patients who constituted part of the sample in an earlier set of analyses.[10] This report is based on considerably longer follow-up for those patients and completely new data for the other 101 patients.

Procedures and Assessments

All patients were evaluated with the Schedule of Affective Disorders and Schizophrenia (SADS),[11] the RDC, and a number of other standardized evaluations that are described elsewhere.[8] According to the RDC, a minimum of five depressive symptoms lasting for at least two weeks are required for a definite diagnosis of MDD. In addition, the person must seek help or have some impairment in functioning and have no evidence of certain specific psychotic symptoms. The diagnosis of major depression in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM III*)[12] is very similar, and the reader is referred to a recent article by Williams and Spitzer[13] for a detailed annotated comparison of the RDC and *DSM III*. Details of the intake and follow-up assessments and the overall goals and background of the research program have been described previously.[8,14]

Subjects are reinterviewed at six-month intervals using the Longitudinal Interval Follow-up Evaluation.[15] Change points in psychopathological state are recorded by completing week-by-week psychiatric status ratings on a quantitative scale of severity for each separate RDC disorder diagnosed at entry or at any time during the follow-up period.

Recovery and Relapse

To be considered recovered from an episode of MDD or any other RDC condition during the follow-up, a patient must have had only mild symptoms of that disorder for eight consecutive weeks. Subjects may continue to have symptoms of another preexisting psychiatric disorder.

Patients were considered to have relapsed into an affective disorder when they met the RDC for definite MDD, minor depressive disorder, mania, hypomania, schizoaffective disorder-manic, or schizoaffective disorder-depressed.

Since these patients were followed up prospectively for considerable time after recovery from the index episode, we could potentially observe more than one relapse. Figure 1 illustrates the time line for recovery and relapse after entry into the study. We refer to the relapse after recovery from the index episode as the "first prospective relapse" and to the relapse after recovery from the first prospective relapse as the "second prospective relapse." The "first well interval" is the time in weeks from the recovery from the index episode to the first prospective relapse, and the "second well interval" is the time in weeks from the recovery from the first prospective relapse to the second prospective relapse.

Predictor Variables

Each of the sociodemographic and clinical characteristics and RDC subtypes of MDD listed in Table 1 was examined to determine if it was predictive of the length of either the first or second well interval.

Statistical Methods

To compare the times from recovery to relapse among groups of patients and estimate the probability of relapse at each time at risk, we used a combination of life-table (survival) methods and regression models. Since both the total follow-up

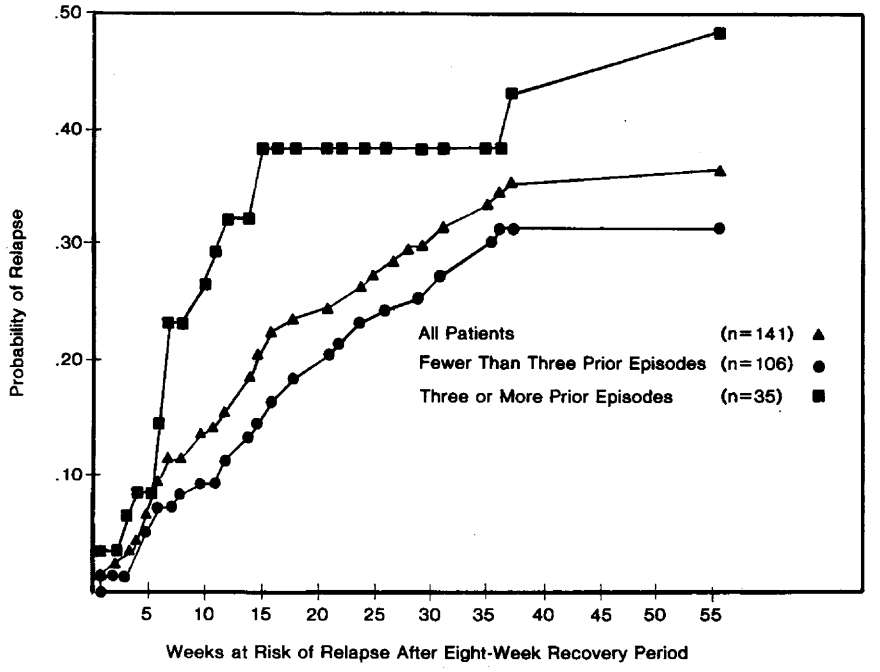

Fig 2.—Cumulative probability of relapse by weeks since recovery from index episode.

time and the time from entry to recovery vary among patients, the total time-on-study that each patient was at risk for relapse (after recovery from the index episode) varied, with a median of 62 weeks and quartiles of 28 and 84 weeks. After recovery from this relapse, patients were followed up for a median of 39 weeks and quartiles of 26 and 53 weeks. To take account of the different times-on-study in this group of patients, we used the Kaplan-Meier product-limit estimate[16] for the cumulative probability of relapse as a function of time and compared relapse curves with the Mantel-Haenszel test.[17] Since the stability of an estimate of relapse probability depends on the number of patients still at risk, we present comparisons between groups only as long as approximately half of the patients remain at risk, ie, to about 15 months for the first relapse and about ten months for the second relapse. All P values are from two-sided tests.

To analyze the effects of covariates on relapse, we modeled the natural logarithm of time to relapse after the eight-week recovery period as a linear function of covariates, with a logistic error distribution.[18] In these models, the covariate acts to shorten (or lengthen) the time to relapse, by acting linearly in the logarithm of time and, therefore, multiplicatively in the time. From the hazard-function estimates provided by the fitted model, the interval-specific rates of relapse were calculated, providing a profile of relapse risk adjusted for influential covariates. These profiles allowed adjusted comparison of the first and second prospectively observed times between episodes of affective illness.

RESULTS

Risk of Relapse in the Whole Sample

The cumulative probability of relapse by time from recovery from the index episode of MDD is shown in Fig 2. The minimum well interval is eight weeks, since a patient must have only mild symptoms for at least eight consecutive weeks to be considered recovered. The monthly risk of relapse (in patients still well) is highest in the period immediately after recovery and declines steadily. There was a total of 43 relapses observed, of which 24 were into MDD, one into mania, three into hypomania, and 15 into minor depression. One of the hypomanias developed into mania, and four of the minor depressions developed into MDD.

Predictors of the First Prospective Relapse

All Patients.—Figure 2 illustrates that in the entire group of 141 patients, those with three or more prior episodes of depression had significantly shorter times from recovery to relapse than the patients with fewer than three episodes before entry (log-logistic regression model, P=.044). None of the other variables described in Table 1 had a substantial effect on time to relapse for the whole sample.

First Episode Patients.—Since patients whose index episode of MDD was their first lifetime major affective episode form a clinically interesting group, we conducted a separate multivariate analysis on those 49 subjects.

Patients whose first lifetime affective episode is preceded by a nonaffective psychiatric condition are diagnosed as having a secondary MDD according to the RDC, and therefore the designation "secondary depression" refers to a temporal relationship and does not imply causality.

Patients with the primary RDC subtype of MDD had longer well intervals and, thus, lower relapse rates than secondary patients (P=.014). According to the log-logistic model, being secondary shortens the time to relapse by a factor of about 5. The cumulative relapse rate in primary patients was 15% at six months after recovery compared with 35% in the secondary patients. By one year the gap widened to 22% in the primary v 67% in the secondary patients. The overall difference was statistically significant by the nonparametric Mantel-Haenszel test (χ^2=5.53, 1 df; P=.02).

Of the 14 patients whose first major depression was secondary to a nonaffective psychiatric disorder, three were alcoholic at entry, another six had past diagnoses of alcoholism but no current nonaffective condition at entry, two had drug dependence at entry (one with a past diagnosis of schizotypal features and one with schizotypal features at entry), one had a past diagnosis of other psychiatric disorder (OPD) and schizotypal features at entry, and the remaining two had past diagnoses of phobia and drug dependence, respectively, with no current nonaffective condition at entry. Thus, 93% (13/14) of these secondary subjects had a previous history of alcoholism or drug dependence.

There were six relapses in these first-episode secondary patients, of which four occurred in the six patients who had current nonaffective conditions at entry, and two occurred in the eight patients with only past nonaffective conditions. In

all of the four patients with current nonaffective conditions at entry who relapsed, the nonaffective condition either continued through the well interval or returned before the affective relapse. All patients whose nonaffective condition returned then had a relapse into an affective episode.

Age at entry (which virtually coincides with age at onset of first affective episode in first-episode patients) was negatively associated with duration of the well interval, so that younger subjects had longer well intervals, hence, lower relapse rates (P=.043), ie, patients who are older are more likely to relapse sooner. According to the log-logistic model, each decade of age decreases the predicted time from the end of the eight-week recovery to relapse by about 40%.

None of the other variables described in Table 1 had a substantial effect on relapse rates in the first-episode patients.

Patients With at Least One Episode Before Entry

For these 92 patients, we used the log-logistic regression model in a stepwise method to test the predictive value of the clinical variables presented in Table 1. Only the number of episodes before entry was a statistically significant predictor of time to relapse, as we found that patients with more episodes before entry had shorter relapse time (P=.043) after adjusting for the duration of the well interval just before the index episode and the duration of the index episode. Doubling the number of prior episodes has the effect of halving the predicted time from recovery to relapse.

Predictors of Time to the Second Prospective Relapse in All Patients

Thirty patients recovered from the index episode, relapsed, and recovered again and were at risk for the second relapse. Patients who entered the study with two or fewer prior episodes (cohorts 1 through 3) had only an 18% second relapse rate by 26 weeks after the recovery from the first relapse, compared with 73% for the patients entering with three or more episodes before the index (cohort 4). By the 70th week after the recovery from the first relapse, 37% of the cohorts 1 through 3 had relapsed, compared with 100% of the cohort 4 group. In the regression analysis, episode cohort was a significant predictor of relapse (more episodes before entry predicted faster relapse) (P=.04). None of the other variables described in Table 1 had a substantial effect on time to relapse after recovery from the first prospectively observed episode.

Comparison of the Time to Relapse From the First and Second Prospectively Observed Recoveries

Table 2 illustrates that after recovery from the index episode of depression, the risk of relapse (in patients not yet relapsed) falls steadily with elapsed well time, while the corresponding risk of *second* relapse after recovery from the *first* relapse rises to a maximum between the fourth and seventh month at risk. These risks of relapse have been corrected for the effects of number of episodes of depression before entry by adjusting them to the predicted values for a hypothetical population of patients, half with three or more episodes of depression before entry and half with fewer than three. Since these risks have been adjusted for the effects of number of episodes before entry, they measure the effect of one more episode before recovery on risk of relapse, thus separating the selection variable (number of episodes before entry) from the clinical variable (number of episodes before the recovery). The typical second time to relapse is significantly shorter than the typical first time to relapse (P=.011, comparing the general location parameter in the log-logistic model) even after adjusting for the number of episodes of depression before entry.

Table 2.—Adjusted Monthly Probabilities of Relapse by Time at Risk After Recovery Comparison of Risks of First and Second Relapses*

Month at Risk of Relapse	Probability of Relapse, % After Recovery From Index Episode	Probability of Relapse, % After Recovery From First Relapse
1	7	5
4	4	10
7	3	10
13	2	Not available

*The table gives the probability that a patient who has not yet relapsed will relapse during the indicated month. The month at risk refers to the time since the end of the eight-week period required for recovery. All probabilities have been adjusted (using the regression model) for the number of episodes of depression before entry into the study. The risk during the 13th month after the second recovery could not be estimated, due to the end of follow-up.

Treatment

As described previously, the treatment that these patients received was a result of decisions made by the clinicians and the patients and was not under the control of the investigators at any time during the study, including the period immediately preceding the week of relapse in the 43 patients who relapsed. We have investigated the treatment that these patients were receiving up to the time of relapse, with the following results. Forty-seven percent (20/43) were receiving no antidepressant somatotherapy at the time of relapse. Of these 20 patients, 11 were not receiving any treatment, while nine received psychotherapy or psychotropic medication other than an antidepressant. Twenty-nine percent (12/43) were receiving moderate to high levels of maintenance antidepressant medication (at least 150 mg of imipramine hydrochloride or its equivalent) before relapse, and 21% (9/43) received between 75 and 100 mg of imipramine hydrochloride or its equivalent. For two subjects (5%), information was inadequate to construct an accurate treatment profile.

All of the treatment levels described previously herein were stable for at least four weeks before relapse, and many patients had been on a single maintenance regimen for several months before relapse.

COMMENT

These results indicate that the highest rate of relapse into an affective disorder was in the period immediately after recovery from an episode of MDD and that the probability of relapse declined steadily during the course of a two-year prospective follow-up of 141 patients with a nonbipolar depression and without a preexisting dysthymia.

This same pattern of risk of relapse in the postrecovery period was reported previously in a one-year follow-up of 75 patients with an MDD, of

whom 19% (n=14) had a bipolar disorder and 31% (n=23) had a preexisting dysthymic disorder.[10] In the current study, we found a longer time to relapse by excluding patients with bipolar affective illness or dysthymia.

Predictors of Relapse

All Patients.—In the entire sample described in this report, a history of at least three episodes of depression before entry into the study was the only clinical variable that had a significant (P=.044) association with a shorter time to relapse after recovery from the index episode of depression. This extends a similar finding in an overlapping sample of 52 patients with nonbipolar *or* bipolar MDD and without dysthymia, whose cases were reported after one year of follow-up.[10]

First-Episode Patients.—In the patients who entered the study in their first major depressive episode, our results are consistent with several earlier studies[19,20] that found an increased rate of relapse in patients who are older when they experience their first affective episode.

We also found that first-episode patients whose depression occurred after the onset of a nonaffective psychiatric condition (RDC secondary subtype of MDD) had a substantially higher rate of relapse. The magnitude of this association makes the primary-secondary distinction a useful prognostic indicator for clinicians to assess risk of relapse in patients who have recovered from their first episode of depression. Ninety-three percent of the patients with a secondary depression had a prior history of alcoholism or drug dependence. This also provides an example of the usefulness of follow-up studies in establishing the predictive validity of nosological subtypes of MDD.

The relationship between the nonaffective psychiatric disorder that preceded the first depression and the first prospective relapse is of clinical and theoretical interest. In those subjects in whom the nonaffective disorder persisted after recovery from the first index depression or recurred before the next relapse into an affective episode, it is possible that the nonaffective condition was a strong predisposing influence on the development of the subsequent affective episode. Another consideration is the extent to which the previous nonaffective episode might have been an earlier manifestation of the affective disorder that followed. Similarly, it is possible that the persisting nonaffective condition represented a residuum of the index depression that was manifested in nonaffective symptoms.

The Predictive Importance of Number of Previous Episodes

Clinical follow-up studies attempt to answer questions such as: Given a patient in his or her first, second, or other episode of affective illness, what are the probabilities of recovery? of relapse? of chronicity? of well being? and of one or more recurrences? These questions can only be answered by data derived from prospective study of subjects whose histories of affective disorder represent the different histories of patients seen by clinicians. The results of this study show that a crucial component of the patient's history is the number of episodes of depression that the patient has had before coming to the clinician for treatment.

The strength of the association between the number of episodes of depression before entry into the study and time to relapse into the first and second prospectively observed episodes and the fact that other clinical predictors of time to relapse only emerge in subjects with no prior episodes show that it would be incorrect to base prognosis for a patient with three or more prior episodes on data from patients in their first depressive episode. Our results indicate that the clinician can make two predictions with some confidence.

1. If the clinician sees patients with different histories and follows them until recovery, the patients who were initially seen with three or more prior episodes will probably have shorter well intervals and will be more likely to relapse than similar patients with fewer prior episodes.

2. If the clinician treats a patient until recovery and then observes a subsequent relapse and again the patient recovers, the clinician may expect on average that the patient's current recovery will not last as long as the previous recovery.

CONCLUSION

Our analyses indicate that patients with nonbipolar disorders who recover from their first major depressive episode are at a crucial point in the development of their course of illness. They have a substantial probability of prompt relapse, and should they relapse, they have approximately a 20% chance of remaining chronically depressed.[21] With each subsequent relapse, the chance of repeated relapse becomes greater, and thus the patient is at risk for a "chronic course" marked by fluctuations between new episodes of illness and recovery.

On the basis of these findings from this naturalistic research study (that assesses but does not assign treatment), we suggest two hypotheses that should be tested in clinical trials. First, since the patient has the highest risk of relapse in the months immediately after recovery, treatment after recovery may substantially reduce both the initial and the overall risk of relapse. This could be tested in a six- to eight-month controlled treatment study, as our results indicate a sharp reduction in relapse hazard after only a few months of remission. Second, since patients with primary MDD do substantially better than patients with secondary MDD, and relapse seems particularly inevitable after the reappearance of nonaffective symptoms, it may be that treatment of the preexisting nonaffective condition will be effective in moderating the course of the affective disorder. This could also be tested in a treatment study.

Controlled clinical trials have shown that the relapse rate into subsequent affective disorders is reduced when patients are treated after recovery with tricyclic antidepressant medication[22] or lithium carbonate[23] and that some benefit is also derived by continued treatment with psychotherapy.[22] In view of this suggested efficacy of various treatments in reducing relapse, and the high risk of relapse in patients with three or more prior episodes of depression and in first-episode depressed patients who have a secondary MDD and an older age of onset, we recommend that clinicians consider continuing somatic treatment after recovery and that vigorous treatment should be insti-

tuted at the first onset of new affective or nonaffective symptoms. We hope that empirical results from the types of clinical trials suggested earlier will help determine whether such rapid treatment interventions are effective, either in postponing or preventing relapse. Although the relative weight of the consequences of side effects and overuse of medication *v* relapse requires empirical research, we have established that recovery is particularly fragile in these patients and that the period of greatest risk occurs in the immediate postrecovery period.

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References

1. Zis AP, Goodwin FK: Major affective disorder as a recurrent illness: A critical review. *Arch Gen Psychiatry* 1979;36:835-839.

2. Lavori PW, Keller MB, Klerman GL: Relapse in affective disorders: A reanalysis of the literature using life table methods. *Psychiatr Res*, in press.

3. Stenstedt A: A study in manic-depressive psychosis: Clinical, social and genetic investigations. *Acta Psychiatr Neurol Scand Suppl* 1952; 79:1-111.

4. Bratfos O, Haug JO: The course of manic-depressive psychosis: A follow-up investigation of 215 patients. *Acta Psychiatr Scand* 1968; 44:89-112.

5. Perris C, D'Elia G: A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses: IX. Therapy and prognosis. *Acta Psychiatr Scand Suppl* 1966;42:153-171.

6. Pollock HM: Recurrence of attacks in manic-depressive psychoses. *Am J Psychiatry* 1931;11:567-574.

7. Keller MB, Lavori PW, Endicott J, et al: Double depression: A two year follow-up. *Am J Psychiatry* 1983;140:689-694.

8. Katz MM, Secunda SK, Hirschfeld RMA, et al: NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression. *Arch Gen Psychiatry* 1979;36:765-771.

9. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: Rationale and reliability. *Arch Gen Psychiatry* 1978;35:773-782.

10. Keller MB, Shapiro RW, Lavori PW, et al: Relapse in major depressive disorder: Analysis with the life table. *Arch Gen Psychiatry* 1982; 39:911-915.

11. Spitzer RL, Endicott J: *Schedule for Affective Disorders and Schizophrenia (SADS)*, ed 3. New York, Biometric Research, New York State Psychiatric Institute, 1979.

12. American Psychiatric Association Committee on Nomenclature and Statistics: *Diagnostic and Statistical Manual of Mental Disorders*. ed 3. Washington, DC, American Psychiatric Association, 1980.

13. Williams JBW, Spitzer RL: Research Diagnostic Criteria and DSM III: An annotated comparison. *Arch Gen Psychiatry* 1982;39:1283-1289.

14. Shapiro RW, Keller MB: Initial six month follow-up of patients with major depressive disorder: A preliminary report from the NIMH Collaborative Study of the Psychobiology of Depression. *J Affective Disord* 1981;3:205-220.

15. Shapiro RW, Keller MB: *Longitudinal Interval Follow-up Evaluation (LIFE)*. Boston, Massachusetts General Hospital, 1979.

16. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.

17. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959;22:719-748.

18. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*. New York, John Wiley & Sons Inc, 1980.

19. Angst J, Weiss P: Periodicity of depressive psychoses, in Brill H, Cole JO, Deniker P, et al (eds): *Proceedings of the Fifth International Medical Foundation*, International Congress series 129. Amsterdam, Excerpta Medica, 1967, pp 703-710.

20. Zis AP, Grof P, Webster M, et al: Prediction of relapse in recurrent affective disorders. *Psychopharmacol Bull* 1980;16:47-49.

21. Klerman GL: Other specific affective disorders, in Freedman AM, Kaplan HI, Sadock BJ (eds): *The Comprehensive Textbook of Psychiatry*. Baltimore, Williams & Wilkins Co, 1980.

22. Klerman GL, Dimascio A, Weissman M, et al: Treatment of depression by drugs and psychotherapy. *Am J Psychiatry* 1974;131:186-191.

23. Prien RF, Klett CJ, Caffey EM Jr: Lithium prophylaxis in recurrent affective illness. *Am J Psychiatry* 1974;131:198-203.