Regular Articles

Recurrence After Recovery From Major Depressive Disorder During 15 Years of Observational Follow-Up

Timothy I. Mueller, M.D., Andrew C. Leon, Ph.D., Martin B. Keller, M.D., David A. Solomon, M.D., Jean Endicott, Ph.D., William Coryell, M.D., Meredith Warshaw, M.S.S., M.A., and Jack D. Maser, Ph.D.

Objective: The recurrence of an affective disorder in people who initially recover from major depressive disorder was characterized by using the unique longitudinal prospective follow-up data from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. **Method:** Up to 15 years of prospective follow-up data on the course of major depressive disorder were available for 380 subjects who recovered from an index episode of major depressive disorder and for 105 subjects who subsequently remained well for at least 5 years after recovery. Baseline demographic and clinical characteristics were examined as predictors of recurrence of an affective disorder. The authors also examined naturalistically applied antidepressant therapy. **Results:** A cumulative proportion of 85% (Kaplan-Meier estimate) of the 380 recovered subjects experienced a recurrence, as did 58% (Kaplan-Meier estimate) of those who remained well for at least 5 years. Female sex, a longer depressive episode before intake, more prior episodes, and never marrying were significant predictors of a recurrence. None of these or any other characteristic persisted as a predictor of recurrence in subjects who recovered and were subsequently well for at least 5 years. Subjects reported receiving low levels of antidepressant treatment during the index episode, which further decreased in amount and extent during the well interval. **Conclusions:** Few baseline demographic or clinical characteristics predict who will or will not experience a recurrence of an affective disorder after recovery from an index episode of major depressive disorder, even in persons with lengthy well intervals. Naturalistically applied levels of antidepressant treatment are well below those shown effective in maintenance pharmacotherapy studies.

(Am J Psychiatry 1999; 156:1000–1006)

"Single episodes are extremely rare if the period of observation is significantly extended."

—Angst et al. (1)

For the majority of people with major depressive disorder, recurrence after recovery is the rule. Although resolution of the signs and symptoms of depression is the major goal of treatment, the maintenance of that state of well-being is one of the current challenges for the mental health field. Both naturalistic and treatment studies of major depression have highlighted the high rate of recurrence after recovery (2–6). A greater number of prior episodes of major depression is the strongest baseline predictor of the duration of the well interval; the greater the number of prior episodes, the more rapid the recurrence (4–6). Other factors that predict a more rapid recurrence are secondary subtype of depression (6) and the persistence of subsyndromal symptoms (L.L. Judd et al., 1998 unpublished paper). The literature is inconsistent regarding the effect of age on recurrence risk. Lower age has been

Presented in part at the 149th annual meeting of the American Psychiatric Association, New York, May 4–9, 1996. Received June 12, 1998; revision received Oct. 21, 1998; accepted Nov. 17, 1998. From the NIMH Collaborative Program on the Psychobiology of Depression—Clinical Studies; and the Department of Psychiatry and Human Behavior, Brown University School of Medicine. Address reprint requests to Dr. Mueller, Department of Psychiatry and Human Behavior, Brown University School of Medicine, c/o Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906; Timothy_Mueller@brown.edu (e-mail).

This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement.

The authors thank Rita Misek for manuscript preparation.

positively associated with greater risk in some studies of clinical samples (4, 7) and a nonclinical sample (8) and negatively associated with greater risk in other clinical samples (6).

The National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies is a prospective naturalistic study of a cohort of people who sought treatment for an affective disorder at one of five university medical centers between 1978 and 1981. This cohort has been followed since intake with attention to course and outcome of their mental disorders. We have reported (9) on the 10-year course of the index episode of major depressive disorder, focusing on the subjects who remained ill for 5 years of prospective follow-up. Over the 10 years of follow-up, 401 (93% by Kaplan-Meier estimate) out of 431 subjects eventually recovered. In the 35 subjects who were continuously ill for 5 years, 13 (38% by Kaplan-Meier estimate) subsequently recovered in the next 5 years.

The current report complements the description of 10 years of observation of the first cycle of major depressive disorder by describing the well interval following recovery from the intake episode, on the basis of 15 years of follow-up data, which have recently become available. In addition to the subjects who recovered at some point in the 15 years, we focus on the subgroup of subjects who recovered from the index episode of depression and subsequently remained well for at least 5 years. We chose 5 years to parallel the time frame used in the prior work (9). In this report we specifically address the following questions: 1) What proportion of subjects with major depressive disorder develop another episode of affective disorder? 2) Do subject age, number of prior episodes, and presence of secondary major depression persist as significant baseline predictors of recurrence? 3) What clinical or demographic features distinguish the group of subjects who recovered and then stayed well for at least 5 years after recovery? 4) Do subjects continue to experience recurrences after 5 years of recovery? and 5) What was the level of antidepressant treatment in the groups who stayed well for at least 5 years after recovery?

METHOD

Between the years 1978 and 1981, 955 patients who sought psychiatric treatment for a mood disorder at one of five U.S. medical centers (in Boston, Chicago, Iowa City, New York, and St. Louis) were entered into a prospective, naturalistic follow-up study. This report extends to 15 years of follow-up previous analyses on the 431 subjects with only major depressive disorder at intake who had no prior history of mania, hypomania, schizoaffective disorder, chronic intermittent depressive disorder, or minor depression of at least 2 years' duration at intake. After complete description of the study to the subjects, written informed consent was obtained. We have distinguished two nested groups. The first consists of the 380 subjects who recovered from the index episode at some time while still in active follow-up during the 15 years of observational follow-up. From them come the second group of 105, a subset who recovered from the index episode and subsequently remained well for at least 5 years.

Assessments

The details of the assessment procedures are described elsewhere (6, 9). Briefly, all subjects were assessed at intake with the Schedule for Affective Disorders and Schizophrenia (SADS) (10), and this information was used with medical records to make diagnoses according to the Research Diagnostic Criteria (RDC) (11). The subjects were interviewed every 6 months for the first 5 years and every year thereafter by means of the Longitudinal Interval Follow-Up Evaluation (12). This follow-up instrument measures the level of psychopathology for each RDC major affective disorder on a 6-point scale called the "psychiatric status rating" (9). A score of 1 denotes no symptoms of the disorders, and a score of 6 denotes fulfillment of the full diagnostic criteria with psychosis or severe impairment. For these 431 subjects with major depression, recovery was considered to begin with the first of 8 consecutive weeks of no or minimal symptoms (psychiatric status rating of 1 or 2). Until recovery occurred, a subject remained in an episode of major depressive disorder, with psychiatric status ratings of 1–6. The continuous string of psychiatric status ratings for major depressive disorder lasting up to 780 weeks was the source of data for the analyses of the course of illness.

Predictors of Course

We examined demographic and clinical characteristics determined at intake as predictors of the subsequent course of major depressive disorder. In addition, we used the extracted score on the Hamilton Depression Rating Scale (10) and the score on the Global Assessment Scale (GAS) from data collected at the 5-year point to reflect the "current" status for the subgroup of subjects who remained well for at least 5 years.

Treatment

Antidepressant treatment was coded weekly by using a 5-point composite antidepressant scale, which quantifies all antidepressant somatotherapy, including ECT and pharmacotherapy (9). A score of 0 means that no antidepressant somatic treatment was provided for that week. A score of 1 represents a daily dose of 1–99 mg of imipramine or its equivalent. A score of 2 represents a daily dose of 100–199 mg of imipramine or equivalent, 3 represents 200–299 mg of imipramine equivalent, and 4 represents 300 mg or more of imipramine equivalent. The study protocol did not influence the treatment provided by the patient's physician.

Statistical Methods

The outcome of interest in these analyses was recurrence of an affective disorder. The data were censored either by loss to follow-up or end of the assessment period. Survival analysis was used to analyze time until recurrence during the follow-up. The Kaplan-Meier product limit was used to estimate the cumulative probability of recurrence (13). Analyses were conducted for the entire group of 380 subjects with major depressive disorder at baseline who experienced a recovery and for the 105 subjects who subsequently remained well for at least 5 years after recovery from the index episode and for whom additional follow-up data were available.

For predictor analyses and to account for length of follow-up, clinical and demographic variables were entered into a Cox regression to evaluate the strength of their associations with recurrence after other variables in the model were controlled for. A two-tailed alpha of 0.05 was considered statistically significant. For analyses of treatment, the t test and Fisher's exact test were used. To account for multiple univariate tests, a two-tailed alpha of 0.01 was used to determine level of statistical significance.

RESULTS

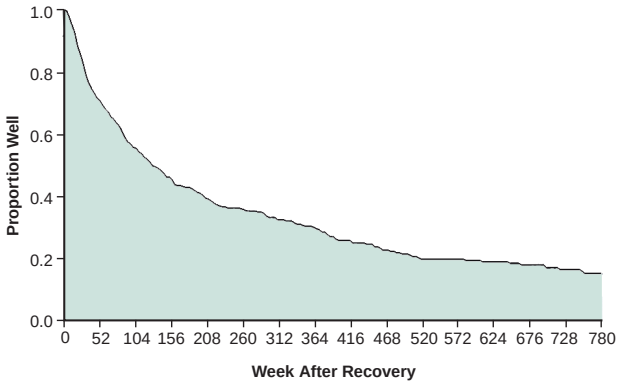
The results are organized to reflect the two groups that are the focus of this study: the complete cohort who recovered within 15 years (N=380) and the subset

TABLE 1. Relation of Clinical and Demographic Features to Recurrence Over 15 Years for 380 Subjects Who Recovered From an Index Episode of Major Depressive Disorder

Characteristic	No Recurrence (N=101)		Recurrence (N=279)		Adjusted Odds Ratio	95% CI	Wald χ^2 (df=1)	p
	Mean	*SD*	*Mean*	*SD*				
Age at intake (years)	39.6	14.2	37.7	14.7	1.00	0.99–1.01	0.18	0.67
Duration of depressive episode before intake (weeks) (odds ratio calculated per year)	50	85	68	108	1.11	1.05–1.18	12.59	0.0004
Hamilton depression score before intake[a]	19.4	7.3	20.3	7.1	1.01	0.99–1.03	0.80	0.37
GAS score before intake[a]	42.3	10.8	40.4	11.0	1.00	0.99–1.01	0.00	0.97
	N	*%*	*N*	*%*				
Female gender	52	51	178	64	1.43	1.10–1.86	7.20	0.007
Number of episodes of major depressive disorder before intake					1.18	1.06–1.31	9.51	0.002
0	48	48	93	33				
1	26	26	64	23				
2	10	10	40	14				
≥3	17	17	82	29				
Primary major depressive disorder at intake	60	59	164	59	0.80	0.62–1.03	2.91	0.09
Psychotic subtype at intake	7	7	29	10	1.17	0.77–1.79	0.53	0.47
Marital status at intake								
Married	58	57	133	48	1.00			
Divorced, separated, or widowed	24	24	56	20	1.01	0.73–1.40	0.00	0.96
Never married	19	19	90	32	1.55	1.14–2.10	7.83	0.005

[a] Owing to missing data, N=95 and N=271, respectively.

FIGURE 1. Time to Recurrence of Affective Disorder for 380 Subjects Who Recovered From an Index Episode of Major Depressive Disorder



of this group who subsequently remained well for at least 5 years (N=105).

Complete Cohort

Of the 380 subjects in this study group, 279 were followed until a recurrence, 66 remained well and were followed until "lost to follow-up," and 35 remained well and were followed to the 15-year point. In the survival analyses that follow, these last two groups are classified as censored. Table 1 summarizes the demographic and clinical features for the group who recovered and did not have a recurrence (N=101) and for those who recovered and eventually did experience a recurrence (N=279); it also presents the results of a Cox regression model that examined each variable as a predictor of recurrence. Women were 43% more likely to experience a recurrence. Those who had never married were 55% more likely to experience a recurrence than those in the other two categories of marital status. Longer duration of depressive episode before intake was associated with a higher risk, such that each additional year was associated with an 11% greater likelihood of recurrence. Similarly, each additional episode of major depression before intake was associated with an 18% increase in the risk of recurrence.

Figure 1 presents the survival curve for the 380 subjects. Subjects began their well intervals at different calendar dates and thus have different lengths of follow-up, from 28 weeks to 15 full years (780 weeks total). The median time to recurrence (length of the well interval) was 132 weeks, and the cumulative proportion (Kaplan-Meier) of recurrence at 15 years was 85%. The mean time to recurrence in the total group of subjects (including censored subjects) was 145 weeks (SD=160). Some of the 279 subjects with major depressive disorder at intake who had a recurrence received a different diagnosis during the recurrence: nine (3%) developed schizoaffective disorder (depressed, manic, or mixed); 17 (6%) developed mania; and 36 (13%) developed hypomania. For 78% (N=217), however, the recurrence was major depressive disorder.

To assess the level of naturalistic somatic antidepressant treatment, we determined the proportion of weeks during the episode of illness that any such treatment was received, the mean scores on the composite antidepressant scale during those weeks of treatment, and the proportion of subjects who received no antidepressant treatment. During their in-

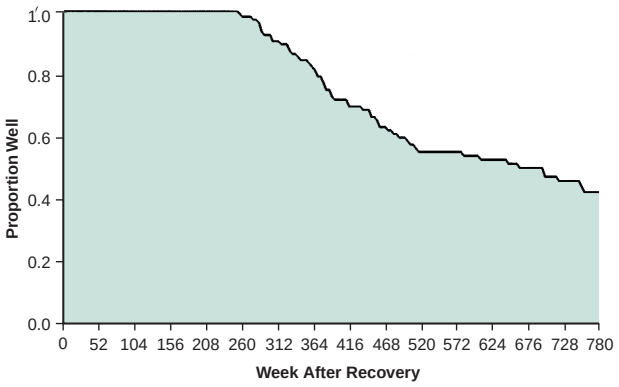
TABLE 2. Relation of Clinical and Demographic Features to Recurrence Over 15 Years for 105 Subjects Who Remained Well for at Least 5 Years After Recovery From an Index Episode of Major Depressive Disorder

Characteristic	No Recurrence (N=53)		Recurrence (N=52)		Adjusted Odds Ratio	95% CI	Wald χ^2 (df=1)	p
	Mean	*SD*	*Mean*	*SD*				
Age at intake (years)	39.5	12.8	38.5	15.8	1.01	0.98–1.03	0.40	0.52
Duration of depressive episode before intake (weeks) (odds ratio calculated per year)	56	103	42	50	0.97	0.73–1.29	0.05	0.82
Hamilton depression score before intake[a]	18.1	7.0	20.8	7.7	1.00	0.95–1.05	0.01	0.92
GAS score before intake	43.1	11.7	37.8	13.3	0.99	0.96–1.01	0.87	0.35
Hamilton depression score at 5 years[b]	4.1	3.8	4.8	3.9	1.08	0.97–1.19	1.96	0.16
GAS score at 5 years	77.0	9.7	72.7	11.8	0.99	0.96–1.03	0.11	0.74
	N	*%*	*N*	*%*				
Female gender	26	49	32	62	1.16	0.62–2.16	0.22	0.64
Number of episodes of major depressive disorder before intake					1.15	0.88–1.50	1.05	0.31
0	24	45	18	35				
1	13	25	11	21				
2	6	11	10	19				
≥3	10	19	13	25				
Primary major depressive disorder at intake	33	62	33	63	0.69	0.37–1.30	1.33	0.25
Marital status at intake								
Married	32	60	28	54	1.00			
Divorced, separated, or widowed	13	25	7	13	1.04	0.42–2.60	0.01	0.93
Never married	8	15	17	33	1.92	0.92–4.02	3.04	0.08

[a] Owing to missing data, N=51 and N=52, respectively.
[b] Owing to missing data, N=42 and N=49, respectively.

dex episode of major depressive disorder, the group with a recurrence (N=279) and the group without a recurrence (N=101) received antidepressant treatment for similar percentages of the weeks during follow-up (mean=68%, SD=36%, versus mean=70%, SD=40%, respectively) (t=0.40, df=378, p=0.69). These groups also received similar levels of antidepressant treatment, as represented by the score on the composite antidepressant scale (mean=1.70, SD=1.08, versus mean=1.64, SD=1.08) (t=–0.45, df=378, p=0.66). In addition, 11% of the group with a recurrence (30 of 279) versus 16% of the group with no recurrence (16 of 101) received no antidepressant treatment during the index episode of major depressive disorder (χ^2=1.81, df=1, p=0.18).

FIGURE 2. Time to Recurrence of Affective Disorder for 105 Subjects Who Remained Well for at Least 5 Years After Recovery From an Index Episode of Major Depressive Disorder



Subjects Who Remained Well for at Least 5 Years

In this subsample of 105 subjects, 52 were followed until a recurrence, 18 remained well and were followed until "lost to follow-up," and 35 remained well and were followed to the 15-year point. In the survival analyses that follow, these last two groups are classified as censored. Table 2 presents the demographic and clinical information for the 105 subjects who experienced a well interval of 5 years or longer and were followed for up to 10 additional years (15 years total). Many of these subjects remained well; however, 52 (58% Kaplan-Meier estimate) experienced a recurrence of an affective disorder during the subsequent prospective follow-up period. The subjects who did not experience a recurrence were followed for a mean of 676 weeks (SD=165), whereas those who did experience a recurrence were followed for 722 weeks (SD=116). Scores on the GAS and Hamilton depression scale at 5 years indicated a relatively high level of functioning and few depressive symptoms. The variables in table 2 were entered into a Cox regression model. None of these clinical or demographic variables predicted time to recurrence.

Figure 2 illustrates the survival curve for this subgroup of subjects. The median time to recurrence was 394 weeks, or 134 weeks beyond the requisite 260 weeks of recovery. Most of those who experienced a recurrence of an affective disorder after 5 years of wellness (N=52) developed only major depressive disorder (N=47, 90%). However, five (10%) developed hypomania; none developed schizoaffective disorder or mania. The pattern of recurrence of major affective disor-

TABLE 3. Relation of Recurrence Over 15 Years to Antidepressant Treatment Received During the Well Interval for 105 Subjects Who Remained Well for at Least 5 Years After Recovery From an Index Episode of Major Depressive Disorder

	No Recurrence (N=53)				Recurrence (N=52)				Analysis		
Period and Measure	N	%	Mean	SD	N	%	Mean	SD	t	df	p
Year 1 of well interval											
Subjects who received no antidepressant treatment	17	32			21	40					0.42[a]
Percentage of weeks in which antidepressant treatment was received	66	37					80	26	–1.68	65	0.10
Score on composite antidepressant scale for subjects receiving antidepressant treatment[b]			1.54	0.99			1.86	0.91	–1.39	65	0.17
Year 2 of well interval											
Subjects who received no antidepressant treatment	35	66			30	58					0.43[a]
Percentage of weeks in which antidepressant treatment was received	91	22					66	38	2.47	38	0.02
Score on composite antidepressant scale for subjects receiving antidepressant treatment[b]			1.99	0.95			1.37	1.10	1.89	38	0.07
Years 3–5 of well interval											
Subjects who received no antidepressant treatment	32	60			37	71					0.31[a]
Percentage of weeks in which antidepressant treatment was received	70	40					62	41	0.54	34	0.59
Score on composite antidepressant scale for subjects receiving antidepressant treatment[b]			1.49	1.09			1.34	0.95	0.43	34	0.67

[a] Fisher's exact test.
[b] A score of 1 represents 1–99 mg/day of imipramine or equivalent; 4 represents ≥300 mg/day of imipramine or equivalent.

der in this subgroup is similar to the overall pattern in the larger group of 279 subjects described earlier who recovered from the index episode and subsequently had a recurrence. Recurrence of major depressive disorder is the predominant pattern.

The antidepressant treatment for the group of subjects who stayed well for at least 5 years was examined. For the index episode of major depression we determined the proportion of weeks in which any antidepressant treatment was received, the mean level of antidepressant treatment in those weeks, and the proportion of subjects who received no antidepressant treatment. In addition, for all of these subjects we determined the same data at years 1, 2, and 3–5 of the well interval to gain a view of naturalistically applied "maintenance antidepressant treatment," and for the subjects with a recurrence we determined the antidepressant treatment during the 4 weeks just before recurrence. Those remaining well received antidepressant treatment for a mean of 63% (SD=44%) of the index episode of major depressive disorder, compared to 65% (SD=40%) for those who experienced a recurrence, and those who did and did not remain well had treatment levels corresponding to mean scores on the composite antidepressant scale of 1.48 (SD=1.15) and 1.59 (SD=1.15). Neither of these small differences was statistically significant. In addition, during the index episode, 21% of the well group (11 of 53) and 19% of the group who experienced a recurrence (10 of 52) received no antidepressant treatment (χ^2=0.04, df=1, p=0.85).

After recovery from the index episode, the subjects continued to receive antidepressant somatic therapy. Table 3 summarizes the antidepressant treatment received during the first 5 years of the well interval. Using a conservatively set alpha of 0.01 for statistical significance, we found no differences between those who did and did not have a recurrence in the proportion of weeks in which any antidepressant treatment was received, the mean score on the composite antidepressant scale for those who did receive treatment, or the proportion who received none. For the group who experienced a recurrence (N=52), we examined the level of antidepressant treatment during the month just before recurrence. The mean scores on the composite antidepressant scale for this time period were distributed as follows: score=0 (no treatment), N=40 (77%); score ≥1, N=12 (23%); score ≥2, N=8 (15%); score ≥3, N=1 (2%); score ≥4, N=0.

DISCUSSION

It may be that recurrence after recovery from major depressive disorder is not inevitable. These results extend our knowledge through careful prospective observation. It appears that some people with major depression do not develop another episode with observational periods of up to 15 years. What baseline characteristics distinguish these people from those who do have recurrences?

In the entire group of 380 subjects who recovered, a greater likelihood of recurrence of an affective disorder was associated with being female, having more prior episodes, never marrying, and having a longer duration of depression before intake. Age and primary versus secondary depressive episode did not distinguish the two groups in this long-term study, a finding contrary to the findings of reports from the collaborative depression study based on briefer follow-up periods (6). None of the other clinical or demographic characteristics assessed at baseline distinguished the two groups. Recent work by our group (unpublished 1998 paper), which broadens the strictly syndromal view of major depressive disorder to include subsyndromal

symptoms, illustrates that the persistence of subsyndromal symptoms in subjects who would classically be categorized as recovered predicts a threefold shorter time to recurrence than that seen in subjects who achieve a fully asymptomatic state (68 versus 231 weeks). In fact, this prospectively observed clinical characteristic appears to be a stronger predictor of recurrence than the aforementioned baseline measures.

The presence of psychotic features was not a significant predictor in this sample. Coryell and colleagues (14) demonstrated that the presence of psychotic features in subjects with depression in the collaborative depression study predicted greater psychosocial impairment, longer illness episodes, and shorter times to first and second recurrences. We did not find this to be the case in this group. The important distinction is that the current group was more restrictive and did not include any subjects with schizoaffective disorder, whereas the group in the study by Coryell et al. did.

A meaningful minority of subjects developed mania as the manifestation of their recurrent affective disorder. The rate of 6.1% for the larger group (N=380) is comparable to the 5.2% in the collaborative depression study (15), which was based on 10 years of follow-up data. As reviewed in the report on that study, previous investigators using widely differing methods and patient populations report a rate of switching from unipolar to bipolar depression that ranges from 0% to 37.5%, with a median of 9.7%. The longitudinal design of this study lends strength to our finding, which indicates a slight increase from 10 years of follow-up to the currently reported 15 years.

The gender difference in diagnosed major depressive disorder is well known. Most but not all studies reveal a 2:1 (female to male) ratio in prevalence and an earlier onset of depression and more recurrence for women than for men (16). The greater risk of recurrence for women is not universally reported; in fact, in studies using retrospectively collected data and sophisticated methods of analysis, no gender effect was apparent (17, 18). Earlier reports from the collaborative depression study on probands and family members (6, 8), including work on only subjects with a first episode of major depressive disorder (19), revealed no gender difference in time to recurrence. However, another analysis of data from the collaborative depression study, based on longer follow-up times, showed a gender difference among a group with heterogeneous numbers of episodes (20). That analysis indicates that a longer follow-up is needed to demonstrate a gender effect on recurrence. This effect disappears when the group is restricted to subjects with 5 years of recovery, suggesting that this subgroup "behaves" like the first-episode group in regard to the effect of gender on recurrence.

The second subject group in our study represents a unique collection of people. To our knowledge, this is the first report of a group of people with major depressive disorder who recovered from an episode of illness, subsequently remained well for 5 years, and were prospectively followed for up to 10 additional years. Our earlier work (8) demonstrated that although 67% (Kaplan-Meier estimate) recover from major depressive disorder within the first year, with a median time to recovery of 16 weeks (Kaplan-Meier), a small but meaningful fraction of people continue to recover for up to the 10-year follow-up point. The persistently well subjects (N=105) reported here recovered fairly promptly after intake (median time to recovery=13.27 weeks), and 80% were well at 1 year of follow-up. Even with the lengthy well interval, 58% (Kaplan-Meier estimate) subsequently experienced a recurrence. None of the baseline demographic and clinical characteristics that predicted recurrence in the larger group persisted as significant in this well group.

Our analysis of the antidepressant treatment received by the entire group of 380 subjects who recovered provides some insights into naturalistically applied treatments as prospectively observed over 15 years. The subjects who did and did not have a recurrence received similar amounts of antidepressant treatment during the index episode, and they received treatment for similar proportions of the index episode. Insofar as treatment is a reflection of clinical characteristics of the depression, the comparability of the treatment received lends further support to the clinical similarity of the index episodes of depression for the two groups.

The smaller group of 105 subjects who experienced at least 5 years of recovery provide another view of naturalistically applied treatments. As the well interval progressed, the proportion of weeks that any antidepressant treatment was received and the mean level of that treatment did not differ to a statistically significant degree between the group who did not experience a recurrence and the group who did. In addition, the proportion of subjects receiving no antidepressant treatment increased from around 35% to 65% over the 5 years.

Furthermore, of the subjects who eventually experienced a recurrence, 77% were receiving no antidepressant treatment during the month just before the recurrence. In the remaining 23% who did receive treatment, the modal level of treatment was between antidepressant scale scores of 2 and 3, or between 100 and 199 mg of imipramine equivalents per day. It appears that whether ill or well, this cohort of affectively ill subjects received roughly equivalent and rather low levels of somatic antidepressant therapy during the lengthy well interval, and the majority of subjects received no antidepressant therapy just before recurrence. Whether or not the recurrence rate would be reduced if the level of antidepressant treatment were greater cannot be determined by these data. Our data on nonsomatic therapies, such as psychotherapy or family therapy, are not systematic or comprehensive enough for us to comment on their application in this group.

Being female, having a longer episode of illness before seeking treatment, never being married, and having more prior episodes are characteristics that may

suggest to the treating clinician that a patient will have a recurrence after recovering from major depressive disorder. From the data we are reporting it was discouraging to find so little information with which to predict which subjects are still at risk for recurrence even after half a decade of recovery. Unfortunately, in this study group we found that people continue to experience recurrences even after long periods of wellness. The paucity of predictors and the persistent possibility of recurrence should guide clinicians and patients to be ever vigilant for a recurrence of depression and the pernicious subsyndromal symptoms of depression (our 1998 unpublished paper). This somewhat discouraging admonition is tempered by our report (9) that some people can recover after even extremely long and seemingly interminable episodes of major depressive disorder and by others' findings (2) that suggest that effective application of long-term antidepressant pharmacotherapy may maintain a state of well being.

ACKNOWLEDGMENTS

The NIMH Collaborative Program on the Psychobiology of Depression—Clinical Studies was conducted with the participation of the following investigators: M.B. Keller, M.D. (chairperson, Providence, R.I.); W. Coryell, M.D. (co-chairperson, Iowa City); J.D. Maser, Ph.D. (Washington, D.C.); T.I. Mueller, M.D., M.T. Shea, Ph.D. (Providence, R.I.); J. Haley (Iowa City); J. Endicott, Ph.D., A.C. Leon, Ph.D., J. Loth, M.S.W. (New York); and J. Rice, Ph.D., T. Reich, M.D. (St. Louis). Other contributors include H.S. Akiskal, M.D., N.C. Andreasen, M.D., Ph.D., P.J. Clayton, M.D., J. Croughan, M.D., R.M.A. Hirschfeld, M.D., M.M. Katz, Ph.D., P.W. Lavori, Ph.D., R.L. Spitzer, M.D., and M.A. Young, Ph.D. Deceased: G.L. Klerman, M.D., E. Robins, M.D., R.W. Shapiro, M.D., and G. Winokur, M.D.

REFERENCES

1. Angst J, Baastrup P, Grof P, Hippius H, Poldinger W, Weis P: The course of monopolar depression and bipolar psychoses. Psychiatr Neurol Neurochir 1973; 76:489–500
2. Frank E, Kupfer DJ, Peral JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990; 47:1093–1099
3. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D: The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 1985; 71:3–34
4. Gonzales LR, Lewinsohn PM, Clarke GN: Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. J Consult Clin Psychol 1985; 53:461–469
5. Maj M, Veltro F, Pirozzi R, Lobrace S, Magliano L: Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 1992; 149: 795–800
6. Keller MB, Lavori PW, Lewis CE, Klerman GL: Predictors of relapse in major depressive disorder. JAMA 1983; 250:3299–3304
7. Giles DE, Jarrett RB, Biggs MM, Guzick DS, Rush AJ: Clinical predictors of recurrence in depression. Am J Psychiatry 1989; 146:764–767
8. Coryell W, Endicott J, Keller MB: Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry 1991; 148:1353–1358
9. Mueller TI, Keller MB, Leon AC, Solomon DA, Shea MT, Coryell W, Endicott J: Recovery after five years of unremitted major depressive disorder. Arch Gen Psychiatry 1996; 53: 794–799
10. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
11. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978; 35: 773–782
12. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC: The Longitudinal Interval Follow-Up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987; 44:540–548
13. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481
14. Coryell W, Leon A, Winokur G, Endicott J, Keller M, Akiskal H, Solomon D: Importance of psychotic features to long-term course in major depressive disorder. Am J Psychiatry 1996; 153:483–489
15. Coryell W, Endicott J, Maser JD, Keller MB, Leon AC, Akiskal HS: Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 1995; 152:385–390
16. Pajer K: New strategies in the treatment of depression in women. J Clin Psychiatry 1995; 56(Feb suppl):30–37
17. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB: Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993; 29:85–96
18. Kessing LV: Recurrence in affective disorder, II: effect of age and gender. Br J Psychiatry 1998; 172:29–34
19. Simpson HB, Nee JC, Endicott J: First-episode major depression: few sex differences in course. Arch Gen Psychiatry 1997; 54:633–639
20. Winokur G, Coryell W, Keller M, Endicott J, Akiskal H: A prospective follow-up of patients with bipolar and primary unipolar affective disorder. Arch Gen Psychiatry 1993; 50:457–465