Residual Symptom Recovery From Major Affective Episodes in Bipolar Disorders and Rapid Episode Relapse/Recurrence

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Context: Both bipolar disorder type I and type II are characterized by frequent affective episode relapse and/or recurrence. An increasingly important goal of therapy is reducing chronicity by preventing or delaying additional episodes.

Objectives: To determine whether the continued presence of subsyndromal residual symptoms during recovery from major affective episodes in bipolar disorder is associated with significantly faster episode recurrence than asymptomatic recovery and whether this is the strongest correlate of early episode recurrence among 13 variables examined.

Design: An ongoing prospective, naturalistic, and systematic 20-year follow-up investigation of mood disorders: the National Institute of Mental Health Collaborative Depression Study.

Setting: Five academic tertiary care centers.

Participants: Two hundred twenty-three participants with bipolar disorder (type I or II) were followed up prospectively for a median of 17 years (mean, 14.1 [SD, 6.2] years).

Main Outcome Measure: Participants defined as recovered by Research Diagnostic Criteria from their index major depressive episode and/or mania were divided into residual vs asymptomatic recovery groups and were compared according to the time to their next major affective episodes.

Results: Participants recovering with residual affective symptoms experienced subsequent major affective episodes more than 3 times faster than asymptomatic recoverers (hazard ratio, 3.36; 95% confidence interval, 2.25-4.98; \( P < .001 \)). Recovery status was the strongest correlate of time to episode recurrence (\( P < .001 \)), followed by a history of 3 or more affective episodes before intake (\( P = .007 \)). No other variable examined was significantly associated with time to recurrence.

Conclusions: In bipolar disorder, residual symptoms after resolution of a major affective episode indicate that the individual is at significant risk for a rapid relapse and/or recurrence, suggesting that the illness is still active. Stable recovery in bipolar disorder is achieved only when asymptomatic status is achieved.

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It is now well established that bipolar disorders are chronic, with a course characterized by frequent affective episode recurrence. Thus, we have proposed that it is no longer sufficient just to focus treatment on the symptoms of acute affective episodes; it is also necessary to reduce chronicity by preventing or delaying affective episode recurrence.

We have reported that residual subsyndromal depressive symptoms following recovery from a unipolar major depressive episode (MDE) are associated with a significantly faster recurrence compared with a fully symptom-free recovery (asymptomatic recovery). We designed our study to test the hypothesis that residual symptoms during recovery from a major affective episode in bipolar individuals are also associated with a significantly faster return to a major affective episode (ie, shorter well interval) compared with asymptomatic recovery. Based on our experience in unipolar depression, we also predicted that recovery status would be the strongest correlate of time to episode recurrence out of any clinical variable reported thus far.

The bipolar cohort from the Collaborative Depression Study (CDS) is uniquely appropriate for such a study, because the CDS prospectively captures a comprehensive battery of information,
including weekly symptom status on all psychiatric conditions for up to 30 years of systematic follow-up. Diagnosis and recovery from MDEs and manic episodes as well as the onset of subsequent affective episodes are obtained for CDS participants using a clear and specific criterion-based methodology recorded by the Schedule for Affective Disorders and Schizophrenia\textsuperscript{15} using Research Diagnostic Criteria (RDC).\textsuperscript{16}

**PARTICIPANTS**

The individuals studied were patients enrolled between 1978 and 1981 in the National Institute of Mental Health CDS,\textsuperscript{13,14} an ongoing prospective, naturalistic, longitudinal follow-up investigation of mood disorders at 5 academic tertiary care centers (Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; Rush-Presbyterian–St Luke’s Medical Center, Chicago, Illinois; University of Iowa College of Medicine, Iowa City, Iowa; New York State Psychiatric Institute and Columbia University, New York; and Washington University School of Medicine, St Louis, Missouri). Participants’ disorders were diagnosed by RDC\textsuperscript{16} based on Schedule for Affective Disorders and Schizophrenia\textsuperscript{15} interviews. The CDS participants were white (because genetic hypotheses were being tested), spoke English, had IQ scores of at least 70, and had no evidence of organic mental disorders or terminal medical illnesses. All participants gave informed consent at 1 of the entry sites.

The participants described entered the CDS during an episode of major depression and/or mania, with no evidence of schizoaffective disorder or schizophrenia before intake or during follow-up. Participants were included in the present analysis if they met criteria for bipolar disorder type 1 (BP-I, definite or probable) at entry. Participants with probable BP-II were included because we previously reported no significant differences in clinical, demographic, or follow-up characteristics of individuals with BP-II with hypomanic periods lasting at least 1 week (definite BP-II) vs 3 to 6 days (probable BP-II).\textsuperscript{3}

Of 132 participants with definite BP-I at intake, 16 were omitted from the analysis because they had censored data before the end of their intake MDE or mania. Of 107 participants with probable or definite BP-II at intake, 20 were omitted because they entered during an episode of minor depression or dysthymia (n=3), switched from BP-II to BP-I at some time during follow-up (n=12), or had censored data before the end of their intake MDE or manic episode (n=5). This left 136 participants with BP-I and 87 participants with BP-II, for a combined bipolar cohort of 223 participants entering the CDS in an MDE or manic episode, with continuous follow-up data through recovery from their index (intake) episode. Demographic and clinical characteristics of this sample are summarized in Table 1.

**FOLLOW-UP PROCEDURES**

Trained raters interviewed participants every 6 months for the first 5 years of follow-up and yearly thereafter, using variations of the Longitudinal Interval Follow-up Evaluation.\textsuperscript{17} Chronological memory prompts are used to obtain information on changes in weekly symptom severity for all mood and other mental disorders. Interview information, supplemented by available medical and research records, is integrated into weekly symptom ratings using Longitudinal Interval Follow-up

low-up Evaluation Psychiatric Status Rating scales, which are anchored to diagnostic thresholds for RDC mental disorders. The CDS raters routinely undergo rigorous training, resulting in high intraclass correlation coefficients (ICCs) for rating changes in symptoms (ICC=0.92), recovery from episodes (ICC=0.95), and subsequent reappearance of symptoms (ICC=0.88).\textsuperscript{15} If a participant is severely depressed or manic at the scheduled time of follow-up, the interview is generally rescheduled for a later time. The bipolar cohort analyzed in this study had a median of 17.0 years of follow-up data (mean, 14.1 [SD, 6.2] years). Because of the fluctuating nature of the course of bipolar disorders,\textsuperscript{4,5} affective symptom status was not imputed during periods when Longitudinal Interval Follow-up Evaluation assessments were missing (<1.0% of follow-up weeks) or when the accuracy of the weekly symptom status was rated poor or very poor (<2.0% of follow-up weeks).

**STATISTICAL ANALYSES**

Analysis focused on the period from the start of RDC-defined recovery until the onset of the first subsequent MDE or manic episode (first well interval). The RDC definition\textsuperscript{18} of recovery matches the current consensual definition—recovery from a major affective episode is achieved when symptoms of the disorder are either absent or are present in no more than a mild degree for 8 or more consecutive weeks. Participants were divided into 2 groups: those who recovered without symptoms for 8 or more consecutive weeks (asymptomatic recovery group) and those who retained ongoing residual subsyndromal affective symptoms, with no 8-week asymptomatic period during the first well interval (recovery group with residual affective symptoms). Recovery groups were compared on demographic, clinical, and outcome measures by t tests, Wilcoxon rank sum tests, or \(\chi^2\) tests.

Survival analysis (life table) methods\textsuperscript{19} were used to test the hypothesis that individuals with bipolar disorder who recover from their intake MDE or mania with residual affective symptoms return significantly faster to a subsequent major affective episode than those with asymptomatic recovery. The Kaplan-Meier product limit estimate\textsuperscript{17} was used to accommodate censored outcomes. Of the 223 bipolar participants meeting the current consensus definition for recovery from an intake MDE or mania, 126 (56.5%) experienced a major affective episode as their first prospectively observed relapse or recurrence, including 66 MDEs (29.6%), 26 manias (11.7%, all BP-I), and 34 MDEs/manic episodes with cycling/mixed polarity (15.2%). The first affective episode relapse or recurrence for 76 participants (34.1%) was minor depression, dysthymia, or hypomania rather than an MDE or mania; those participants were included in the analysis up to the start of the intervening episode and were censored at that point. For the remaining 21 participants (9.4%), follow-up data ended before they experienced any affective episode relapse or recurrence; those participants were included, with the length of their first well interval censored at that point.

Cox proportional hazards models\textsuperscript{18} were used to compare the overall likelihood (hazard) of experiencing a major affective episode recurrence in any given week during follow-up, for symmetric vs asymptomatic recovery groups as well as for a number of other variables potentially related to the duration of the first well interval. Predictors of bipolar relapse were considered if they have been reported in the literature and could be examined using the CDS database. These included sex\textsuperscript{3}; BP-I vs BP-II subtype\textsuperscript{2}; polarity of the index episode\textsuperscript{8,20,21}; polarity of the residual symptoms\textsuperscript{9,9}; severity of the intake episode\textsuperscript{22}; current comorbid axis I diagnoses\textsuperscript{23}; anxiety and substance abuse disorders\textsuperscript{4}; and various measures of social support.\textsuperscript{21,23} In ad
diation, we reexamined variables previously found not to be associated with time to relapse or recurrence: total number of lifetime affective episodes; duration of illness; and psychotropic medication use during the well interval. We also examined IV-TRs served as the basis for defining cyclothymic disorder in RDC, a condition of chronic subthreshold mood instability beginning at an early age. Since a number of the variables examined in this article, including the primary one (recovery status), are defined concurrent with the well interval that is the dependent variable in the analysis, we refer to the independent variables as correlates rather than risk factors for relapse.

To protect against the possibility of reporting variables as significant when they were in fact underpowered in our study sample, we conducted a post hoc power analysis. We found that 13 of 31 variables considered for inclusion in our presentation of results had at least 80% power to detect a group difference of 50% or more in the relative risk of relapse (hazard ratio [HR] > 1.5 or < 0.67), the minimum group difference we considered to be clinically meaningful, with a 5% risk of making a type I error. Each of these variables was evaluated 2 ways: first as an individual correlate of the length of the well interval, and then as a variable added after level of recovery was entered into the Cox proportional hazards model.

Instead of using a 2-tailed α level of 0.05 to define statistically significant group comparisons, a Bonferroni correction was employed to protect against a chance finding of significance based on the large number of variables examined. The 13 variables represent 12 relatively independent areas. Based on this number, P < .004 (ie, 0.05/12) was used to identify a variable as being a significant correlate of the length of the first well interval.

Consistent with our previous findings, CDS participants with BP-I have more severe intake episodes than those with BP-II. Nonetheless, rates of residual vs asymptomatic recovery for the 2 bipolar subtypes were not significantly different (35 of 136 [25.7%] BP-I participants and 25 of 87 [28.7%] BP-II participants).
Table 1. Characteristics of Individuals With Bipolar Disorder, Types I and II, by MDE/Mania Recovery Level\textsuperscript{a} (cont)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Bipolar Cohort (N=223)</th>
<th>Recovery Level From Intake MDE or Mania\textsuperscript{b}</th>
<th>Asymptomatic (n=163)</th>
<th>With Residual Affective Symptoms (n=60)</th>
<th>Asymptomatic vs Residual Symptom Recovery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid Diagnoses,\textsuperscript{b} No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>33 (14.8)</td>
<td>27 (16.6)</td>
<td>6 (10.0)</td>
<td>Fisher exact test</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>36 (16.1)</td>
<td>29 (17.8)</td>
<td>7 (11.7)</td>
<td>Fisher exact test</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>39 (17.5)</td>
<td>26 (15.9)</td>
<td>13 (21.7)</td>
<td>Fisher exact test</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>86 (38.6)</td>
<td>63 (38.6)</td>
<td>23 (38.3)</td>
<td>Fisher exact test</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>Cyclothymic disorder\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>20 (9.0)</td>
<td>6 (3.7)</td>
<td>14 (23.3)</td>
<td>Fisher exact test</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>28 (12.6)</td>
<td>13 (8.0)</td>
<td>15 (25.0)</td>
<td>Fisher exact test</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Any comorbid disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>83 (37.2)</td>
<td>61 (37.4)</td>
<td>22 (36.7)</td>
<td>Fisher exact test</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>144 (64.6)</td>
<td>104 (63.5)</td>
<td>40 (66.7)</td>
<td>Fisher exact test</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>% of Weeks during first well interval when participants received any psychotropic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>65.4 (41.1)</td>
<td>64.8 (41.2)</td>
<td>67.3 (41.0)</td>
<td>Wilcoxon rank sum, z=0.48</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>91.7 (0.0-100.0)</td>
<td>90.9 (0.0-100.0)</td>
<td>92.9 (0.0-100.0)</td>
<td>Wilcoxon rank sum, z=0.48</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative interviewed with a lifetime affective disorder, No. (%)\textsuperscript{d}</td>
<td>146 (64.4)</td>
<td>104 (63.5)</td>
<td>42 (68.3)</td>
<td>Fisher exact test</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>173</td>
<td>124</td>
<td>49</td>
<td>Fisher exact test</td>
<td>.75</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CDS, Collaborative Depression Study; GAS, Global Assessment Scale; MDE, major depressive episode; RDC, Research Diagnostic Criteria.
\textsuperscript{a}See text for description of participants.
\textsuperscript{b}The start of the recovery period (first well interval) following the intake episode of MDE or mania is defined, per RDC, as the first of 8 consecutive weeks with no symptoms or only residual symptoms of the MDE or mania (plus underlying dysthymia, if present). Recovery level during the first well interval was categorized as asymptomatic if the patient experienced 8 or more consecutive weeks with no affective symptoms before the start of the next major affective episode or the end of follow-up data (censoring); if no such symptom-free period occurred, the first well interval was characterized as recovery with residual affective symptoms.
\textsuperscript{c}After Satterthwaite adjustment for unequal group variances.
\textsuperscript{d}Polarity of the first lifetime affective episode could not be determined for 56 participants, whose age at onset of first depression and first manic or hypomanic episode were the same.
\textsuperscript{e}For the week before admission to the CDS. On a scale of 1 to 100, in which a higher score represents better functioning. A score of 31 to 40 represents marked impairment in several areas or impairment in reality testing.
\textsuperscript{f}Single vs dual polarity.
\textsuperscript{g}Dual-polarity episodes include those meeting diagnostic criteria for major depression along with mania (bipolar type I) or hypomania; or mania (bipolar type I) along with minor depression or dysthymia. Periods of depressed and elevated mood may be either alternating (cycling) or concurrent (mixed), such as in irritable mania.
\textsuperscript{h}Current RDC diagnoses are based on a probable or definite diagnosis recorded for current episode diagnosis on the intake-update RDC or any weekly Psychiatric Status Rating greater than 1 from intake to the end of the first well interval.
\textsuperscript{i}Research Diagnostic Criteria cyclothymic personality is nearly identical to DSM-IV-R cyclothymic disorder.
\textsuperscript{j}Family history of affective disorder among first-degree relatives (biological parents, siblings, or children) was determined by means of Lifetime Schedule for Affective Disorders and Schizophrenia interviews given at intake and again at 6-year follow-up; an affective diagnosis at either point was considered positive. Of the 223 participants in the sample, 50 did not have any first-degree relatives interviewed.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE ANALYSIS SAMPLE

As presented in Table 1, the analysis sample had a mean age of 37.4 (SD, 13.0) years, and 57.4% were female. More than half of participants (57.8%) had some college education, and 41.7% were married or living with a partner. Most participants in the sample (69.1%) had 3 or more lifetime affective episodes before their intake MDE or mania. Their mean age at onset of their first lifetime affective episode was 23.1 (SD, 10.1) years, with nearly half of the sample (48.9%) having their first episode before age 21 years. Three-fourths of the participants (78.5%) were hospitalized at intake. Mean Global Assessment Scale score for the worst week of the index episode was 34.6 (SD, 10.4), indicating major impairment in several areas of functioning. Of the analysis sample, 60 participants (26.9%) entered the study having an MDE, 37 (16.6%, all BP-I) entered during a manic episode, and 126 (56.5%) entered during an episode of mixed polarity.

LEVEL OF RECOVERY FROM INTAKE MDE AND/OR MANIA IN BIPOLAR PARTICIPANTS

All 223 participants met the RDC definition (current consensus criteria) for recovery from an MDE or manic epi-
Bipolar participants with asymptomatic recovery did not differ on any demographic characteristics from those with recovery with residual affective symptoms (Table 1). However, those who retained residual symptoms during recovery had significantly more lifetime affective episodes, lower rates of hospitalization at intake, more cycling and/or mixed intake episodes, and a higher rate of comorbid cyclothymic disorder. There were no other significant differences in clinical characteristics of the 2 recovery groups, nor did they differ in terms of their length of follow-up ($P = .9$, Wilcoxon 2-tailed).

As seen in Table 2 and the Figure, recovery with residual affective symptoms was associated with a significantly shorter well interval until the individual’s next major affective episode (Wilcoxon comparison of survival distribution curves, $\chi^2 = 35.81$; $P < .001$). Median time to episode recurrence for recoverers who retained residual symptoms of their index MDEs or manic episodes was 5 times faster than for asymptomatic recoverers (24 vs 123 weeks). Their overall risk of having a new major affective episode was 3.4 times higher across all weeks of follow-up (HR, 3.36; 95% confidence interval [CI], 2.25-4.98; $P < .001$). Stated differently, the relative risk of remaining free of a subsequent major affective episode was 3.4 times higher for the asymptomatic recoverers. There was a substantial and progressive disparity in the likelihood of remaining well over time: at 6 months, the Kaplan-Meier probability of remaining free of a major affective episode recurrence was approximately 2:1 for asymptomatic compared with symptomatic recoverers (81.4% vs 43.8%, respectively); at 1 year it was 3:1 (65.9% vs 20.6%, respectively); and at 2 years it was 5:1 (55.2% vs 10.6%, respectively). Even 10 years after resolution of the intake episode, 25.5% of those who recovered to asymptomatic status were still well, whereas all those who retained residual symptoms during recovery had a major affective episode recurrence by that time.

**Table 2. Survival Analysis of Weeks to First Prospective Major Affective Episode Relapse or Recurrence in Bipolar Individuals by Recovery Level**

<table>
<thead>
<tr>
<th>Level of Recovery From Intake MDE or Mania</th>
<th>Asymptomatic (n=163)</th>
<th>With Residual Affective Symptoms (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of weeks well, quartile estimates (95% confidence interval)</td>
<td>37 (27-48)</td>
<td>16 (12-20)</td>
</tr>
<tr>
<td>25%</td>
<td>123 (89-179)</td>
<td>24 (19-31)</td>
</tr>
<tr>
<td>50%, median</td>
<td>589 (365-725)</td>
<td>41 (29-83)</td>
</tr>
<tr>
<td>Probabilitya of remaining well by time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>0.919</td>
<td>0.800</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.814</td>
<td>0.438</td>
</tr>
<tr>
<td>1 y</td>
<td>0.659</td>
<td>0.206</td>
</tr>
<tr>
<td>2 y</td>
<td>0.552</td>
<td>0.106</td>
</tr>
<tr>
<td>5 y</td>
<td>0.344</td>
<td>0.045</td>
</tr>
<tr>
<td>10 y</td>
<td>0.255</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Abbreviation: MDE, major depressive episode.

aSee text for description of participants.

bThe start of the recovery period (first well interval) following the intake episode of MDE or mania is defined, per Research Diagnostic Criteria, as the first of 8 consecutive weeks with no symptoms or only residual symptoms of the MDE or mania (plus underlying dysthymia, if present). Recovery level during the first well interval was categorized as asymptomatic if the patient experienced 8 or more consecutive weeks with no affective symptoms before the start of the next major affective episode or the end of follow-up data (censoring); if no such symptom-free period occurred, the first well interval was characterized as recovery with residual affective symptoms.

cUpper limit of confidence interval cannot be computed.

dBy Kaplan-Meier method. Significance of difference in survival distributions to onset of first prospective relapse or recurrence to an episode of MDE or mania (major affective episode): Wilcoxon $\chi^2 = 35.81$; $P < .001$; hazard ratio, 3.36; 95% confidence interval, 2.25-4.98. Median weeks well: asymptomatic recovery, 123 (95% confidence interval, 89-179); recovery with residual affective symptoms, 24 (95% confidence interval, 19-31).

**Figure.** Survival analysis of weeks to first major affective episode relapse or recurrence in individuals with bipolar I or bipolar II disorder, comparing participants with asymptomatic recovery vs participants with recovery with residual affective symptoms from their intake major depressive episode (MDE) or mania. Significance of difference in overall survival distribution: Wilcoxon $\chi^2 = 35.81$; $P < .001$; hazard ratio, 3.36; 95% confidence interval, 2.25-4.98. Median weeks well: asymptomatic recovery, 123 (95% confidence interval, 89-179); recovery with residual affective symptoms, 24 (95% confidence interval, 19-31).

**RECOVERY GROUPS COMPARED USING TIME TO NEXT MAJOR AFFECTIVE EPISODE**

As seen in Table 2 and the Figure, recovery with residual affective symptoms was associated with a significantly shorter well interval until the individual’s next major affective episode (Wilcoxon comparison of survival distribution curves, $\chi^2 = 35.81$; $P < .001$). Median time to episode recurrence for recoverers who retained residual symptoms of their index MDEs or manic episodes was 5 times faster than for asymptomatic recoverers (24 vs 123 weeks). Their overall risk of having a new major affective episode was 3.4 times higher across all weeks of follow-up (HR, 3.36; 95% confidence interval [CI], 2.25-4.98; $P < .001$).

Stated differently, the relative risk of remaining free of a subsequent major affective episode was 3.4 times higher for the asymptomatic recoverers. There was a substantial and progressive disparity in the likelihood of remaining well over time: at 6 months, the Kaplan-Meier probability of remaining free of a major affective episode recurrence was approximately 2:1 for asymptomatic compared with symptomatic recoverers (81.4% vs 43.8%, respectively); at 1 year it was 3:1 (65.9% vs 20.6%, respectively); and at 2 years it was 5:1 (55.2% vs 10.6%, respectively). Even 10 years after resolution of the intake episode, 25.5% of those who recovered to asymptomatic status were still well, whereas all those who retained residual symptoms during recovery had a major affective episode recurrence by that time.

**Table 3 presents 2 summary statistics for each correlate, based on Cox proportional hazard regression models:**

1. The HR and its 95% CI for return to a major affective episode recurrence.

2. The HR and its 95% CI for return to a major affective episode recurrence in individuals with bipolar I or bipolar II disorder, comparing participants with asymptomatic recovery vs participants with recovery with residual affective symptoms from their intake major depressive episode (MDE) or mania. Significance of difference in overall survival distribution: Wilcoxon $\chi^2 = 35.81$; $P < .001$; hazard ratio, 3.36; 95% confidence interval, 2.25-4.98. Median weeks well: asymptomatic recovery, 123 (95% confidence interval, 89-179); recovery with residual affective symptoms, 24 (95% confidence interval, 19-31).
episode across all weeks of the first well interval and (2) a Wald χ² (and its chance probability). These are shown for the relationship between the dependent variable and each potential correlate entered into the regression model alone as well as the incremental values for each potential correlate after level of recovery was first entered into the model.

Of the 13 variables that had adequate power in this study sample, only 1 (recovery with residual affective symptoms) was statistically significant after applying the Bonferroni correction (Table 3). In fact, recovery status had a very robust association with duration of the first well interval (HR, 3.36; 95% CI, 2.25-4.98; P < .001). A history of 4 or more affective episodes (including the intake episode) had the next highest relationship with time to the next major affective episode (≥ 4 vs 0-3 episodes, HR, 1.73; 95% CI, 1.16-2.57; P = .007), but this was not significant after the Bonferroni correction. No other variable was significantly associated with the length of time that bipolar participants in this sample remained free of a major affective episode relapse or recurrence.

In our analysis of patients with unipolar major depressive disorder in the CDS, we found that incomplete recovery from the first lifetime MDE heralded not only a faster relapse to a subsequent MDE but also a more chronic overall symptomatic course. In the present study, participants with at least 2 years of follow-up who recovered from their intake MDE or mania with residual affective symptoms (n = 54) were symptomatic at some level during a mean of 57.7% (SD, 66.3%) of the remaining weeks of follow-up compared with a mean of 35.5% (SD, 40.5%) for asymptomatic recoverers (n = 146). A t test on the arcsine transformation of the percentage of follow-up weeks with symptomatic recovery for the 2 groups was significant at P < .001 (t199 = 4.53).

The faster rate of relapse associated with incomplete vs asymptomatic recovery in the study sample does not appear to be attributable to less frequent or less intensive treatment. We conducted analysis of the percentage of weeks during the intake episode and during the first well interval that the bipolar participants received any type of psychotropic treatment or any treatment in each of 3 modalities (antidepressant, antimanic, and antipsychotic). We also analyzed the mean per-person level of treatment intensity that participants received during each of the 2 periods. We found that the 2 recovery groups did not differ significantly on any measure of treatment frequency or intensity, either during their intake episode or during the first well interval.

**COMMENT**

This is the first investigation we are aware of that has tested a broad set of clinical and demographic variables in re-

### Table 3. Cox Proportional Hazards Model of the Probability of Experiencing a Major Affective Episode Relapse or Recurrence by Recovery Level and Other Putative Predictors in Individuals With Bipolar Disorder

<table>
<thead>
<tr>
<th>Measure</th>
<th>Variable Alone</th>
<th>Variable Added to Proportional Hazards Model After Level of Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Wald χ²</td>
</tr>
<tr>
<td>Recovery with residual affective symptoms</td>
<td>3.36 (2.25-4.98)</td>
<td>35.88</td>
</tr>
<tr>
<td>≥ 4 Lifetime affective episodes, including intake episode</td>
<td>1.73 (1.16-2.57)</td>
<td>7.25</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.00 (0.70-1.43)</td>
<td>0.00</td>
</tr>
<tr>
<td>Bipolar diagnosis, type I vs type II</td>
<td>1.07 (0.75-1.54)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cycling/mixed intake episode polarity</td>
<td>1.10 (0.77-1.56)</td>
<td>0.26</td>
</tr>
<tr>
<td>Psychotic features in intake episode</td>
<td>1.22 (0.86-1.74)</td>
<td>1.27</td>
</tr>
<tr>
<td>Lifetime substance use disorder by end of first well interval</td>
<td>0.92 (0.64-1.33)</td>
<td>0.18</td>
</tr>
<tr>
<td>Any comorbid disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime as of the end of first well interval</td>
<td>1.11 (0.76-1.61)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current during intake episode or first well interval</td>
<td>0.90 (0.62-1.30)</td>
<td>0.33</td>
</tr>
<tr>
<td>Social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can count on someone for all major things</td>
<td>0.72 (0.49-1.04)</td>
<td>3.00</td>
</tr>
<tr>
<td>Finds satisfaction with major life role most of the time</td>
<td>0.87 (0.61-1.23)</td>
<td>0.62</td>
</tr>
<tr>
<td>Low in 3 or 4 personal resource areas: social support, other support, life role satisfaction, and income</td>
<td>1.41 (0.94-2.13)</td>
<td>2.77</td>
</tr>
<tr>
<td>Received any psychotropic medication during &gt; 90% of weeks in well interval</td>
<td>1.05 (0.74-1.50)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

a Recovery level during the first well interval was categorized as asymptomatic if a participant experienced 8 or more consecutive weeks with no affective symptoms between the end of his or her intake major depressive episode or mania and the start of the next major affective episode or the end of follow-up data (censoring); if no such symptom-free period occurred, the first well interval was characterized as having residual subsyndromal affective symptoms.

b Participants from the National Institute of Mental Health Collaborative Depression Study were included if they had bipolar disorder type I (definite) or bipolar disorder type II (definite or probable) at entry to the study, had no evidence of schizophrenia or schizoaffective disorder at entry or during follow-up, entered the study in an episode of major depressive disorder or mania, and had weekly follow-up data present and rated fair or better in terms of accuracy for the 8-week Research Diagnostic Criteria–defined recovery period from the intake episode (period with no more than residual symptoms of the episode).

c The global Wald χ² is a test of the influence of risk factors on survival; unlike the Mantel-Haenszel χ² test, it does not assume homogeneity of risk across strata.

d Dual-polarity episodes include those meeting diagnostic criteria for major depression along with mania (bipolar type I) or hypomania; or mania (bipolar type I) along with minor depression or dysthymia. Periods of depressed and elevated mood may be either alternating (cycling) or concurrent (mixed), such as in irritable mania.

e Based on Personal Resources Inventory at intake.
lation to time to major affective episode recurrence in a large and well-defined cohort of participants with bipolar disorder during their long-term course of illness. Of 13 variables that had sufficient statistical power to detect a clinically meaningful difference in risk of relapse to a major affective episode, only the primary variable for this study, the presence of residual affective symptoms throughout a period of MDE or manic episode recovery, was significant after applying a Bonferroni correction to establish the required \( P \) value. Incomplete recovery was an extremely robust correlate of time to major episode relapse. Participants whose index episode recovery was characterized by ongoing residual subsyndromal affective symptoms had a far lower median time to relapse than asymptomatic recoverers \((24 \text{ vs } 123 \text{ weeks})\) and were more than 3 times as likely to experience a subsequent major affective episode during follow-up as those with asymptomatic recovery \((HR, 3.36; 95\% \text{ CI}, 2.25-3.98; P < .001)\).

In a related study, Keller et al.\(^{27}\) found that low serum lithium levels in 94 bipolar individuals were significantly associated with the presence of subsyndromal affective symptoms and a higher risk for major affective episode recurrence. Despite considerable differences in methodology and statistical analysis, our results are also fully consistent with the findings of Perlis et al.\(^{10}\) and Tohen et al.\(^{10}\) who have shown that initial residual mood symptoms predicted faster affective episode recurrence in individuals with BP-I. Thus, 4 different studies of bipolar disorder (including ours) concur that residual subsyndromal symptoms are robustly associated with more rapid episode recurrence. This association is consistent with our previous studies of unipolar major depressive disorder in which we concluded that ongoing residual affective symptoms following apparent MDE resolution indicate that the episode has not been fully resolved and the patient is at significant risk for rapid episode recurrence.\(^{11,12}\) We submit that a stabler and more lasting recovery from a major affective episode is achieved when the patient with bipolar or unipolar disorder has recovered to a completely symptom-free status.

The second strongest correlate of early recurrence was a history of 4 or more affective episodes \((P = .007)\), which was not statistically significant after making a Bonferroni correction for the number of correlates examined. We feel that this variable should not be overlooked, because the study by Perlis et al.\(^{10}\) also pointed to episode history as a predictor of earlier relapse. Studies based on the CDS cohort indicate that a history of 4 or more episodes (including the intake episode) is a significant risk factor for recurrence in unipolar major depressive disorder.\(^{11,12,27-29}\) Two studies now suggest that episode history may predict relapse in bipolar disorder as well.

We feel that it is not appropriate to conclude that results from this study either support or refute other published findings regarding predictors of bipolar relapse. The methodology of our study differs from that of any other published study in terms of samples, methods of ascertainment, definitions and timing of residual symptoms, and analytic methods. Most other studies have included only individuals with BP-I and most have limited their analysis to patients recovering from an index manic or mixed-polarity episode. All studies except for that by Tohen et al.\(^{10}\) have examined predictors of relapse separated by the polarity (depressive vs manic and/or mixed) of the subsequent episode. We did not analyze the data by polarity of the recurrent episode, because in the CDS bipolar cohort, we found a high degree of inconsistency \((47%-60\%)\) among the polarity of the index episode, residual symptoms after episode resolution, and the next affective episode. Since inconsistency of polarity was so common across these 3 affective states, we felt that conducting dual analyses of subsequent episodes separated by their polarity was not appropriate, nor would it advance our primary goal of identifying factors related to overall risk of episode relapse or recurrence.

For this investigation, we defined recovery status based on the level of recovery achieved during the entire first well interval, rather than on initial recovery status. Initial recovery status in our sample did not necessarily predict eventual recovery level, because some participants retained residual symptoms for a considerable time before becoming asymptomatic. Therefore, we felt it was better to characterize the highest level of recovery attained during the entire well interval and to examine this as a correlate of the length of that interval, which proved to be a valid and meaningful strategy.

The CDS follow-up is described as prospective. At each 6-month or yearly interview, however, data are collected based in large part on participants’ retrospective recall of their psychiatric status during the most recent interval. Although interrater agreement is high (rating changes in affective symptoms, ICC=0.92; recovery from episodes, ICC=0.95; and subsequent reappearance of symptoms, ICC=0.88\(^{17}\)), there may be some degree of error in assigning levels of weekly depressive symptom severity. One would expect such an error to attenuate systematic group differences, which were evident to a degree that suggests good symptom rating reliability.

Results presented here are from a moderately severely ill cohort of bipolar participants, 78% of whom were hospitalized at intake, though it should be noted that the standard practice from 1978 to 1981 was to treat MDE or mania on an inpatient basis. Participants had a mean (SD) Global Assessment Scale score of 34.6 (10.4), indicating impairment in several major areas of psychosocial functioning. These individuals may or may not be representative of all individuals with bipolar disorder who are treated for an MDE or mania at nonacademic psychiatric facilities or general medical outpatient settings.

The lower rate of hospitalization in the incomplete recovery group \((82\% \text{ vs } 68\%)\) does not appear to be a proxy for less intensive treatment, inasmuch as the 2 recovery groups did not differ significantly on any measure of treatment frequency or intensity, neither during their intake episode nor during the first well interval. Since the CDS is a naturalistic follow-up study, not a controlled treatment investigation, conclusions about the effects of specific treatments and MDE or mania recovery status were not examined. Definitive conclu-
sions about the effect of specific treatments of residual symptoms on recovery level and on the long-term course of bipolar disorders await results from prospective controlled treatment investigations. The medications available for acute and maintenance treatment of bipolar disorders have changed considerably since patients first entered the CDS; one may ask whether the findings of this report are generalizable to current clinical practice. Patients participated in the CDS at 1 of 5 university-affiliated medical centers, and we feel that the main finding from this study pertains regardless of the specific treatments available.

An issue raised by this research is whether the 2 groups of bipolar participants divided by recovery status are fundamentally different in the nature of their affective illnesses. Analysis of potential differences between the 2 recovery groups or specific treatment strategies used as well as investigation of the consistency of recovery status across successive episodes within individual participants will be the subject of future articles.

In summary, we have shown that in bipolar disorder, continuation of residual symptoms after resolution of major affective episodes, though meeting current consensus definitions of episode resolution, is a robust correlate of rapid relapse and a more chronic future symptomatic course of illness. A powerful confluence of scientific evidence has now emerged from 4 remarkably different studies, indicating that recovery with residual affective symptoms is a clinically useful marker for early bipolar relapse. This suggests that the presence of residual symptoms indicates that the illness is still active, thereby questioning the current consensual definition of major affective episode recovery. At the very least, this clinical characteristic indicates to the clinician that the patient has not fully recovered and should be considered as at risk and be monitored closely.

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nostic, and psychosocial issues of mood disorders and is an ongoing, long-term multidisciplinary investigation of the course of mood and related affective disorders. The original principal and co-principal investigators were from 5 academic centers and included Gerald Klerman, MD (co-chairperson; deceased), Martin Keller, MD, and Robert Shapiro, MD (deceased) (Massachusetts General Hospital, Harvard Medical School); Eli Robbins, MD (deceased), Paula Clayton, MD, Theodore Reich, MD (deceased), and Amos Wellner, MD (deceased) (Washington University Medical School); Jean Endicott, PhD, and Robert Spitzer, MD (Columbia University); Nancy Andreasen, MD, PhD, William Coryell, MD, and George Winokur, MD (deceased) (University of Iowa); and Jan Fawcett, MD, and William Scheftner, MD (Rush-Presbyterian–St Luke’s Medical Center). The National Institute of Mental Health Clinical Research Branch was an active collaborator in the origin and development of the program with Martin M. Katz, PhD, as the co-chairperson and Robert Hirschfeld, MD, as the program coordinator. Other past collaborators include J. Croughan, MD; M. T. Shea, PhD, R. Gibbons, PhD; M. A. Young, PhD; and D. C. Clark, PhD.

REFERENCES


