Recovery From Multiple Episodes of Bipolar I Depression

David A. Solomon, MD; Jess G. Fiedorowicz, MD, PhD; Andrew C. Leon, PhD†; William Coryell, MD; Jean Endicott, PhD; Chunshan Li, MA; Robert J. Boland, MD; and Martin B. Keller, MD

ABSTRACT

Objective: To describe the duration of bipolar I major and minor depressive episodes and factors associated with time to recovery.

Method: As part of the National Institute of Mental Health Collaborative Depression Study, 219 participants with bipolar I disorder based on Research Diagnostic Criteria analogs to *DSM-IV-TR* criteria were recruited at 5 academic medical centers from 1978 to 1981 and followed for up to 25 years with the Longitudinal Interval Follow-Up Evaluation. The probability of recovery over time from depressive episodes, the primary outcome measure, was examined with mixed-effects grouped-time survival models.

Results: The median duration of major depressive episodes was 14 weeks, and over 70% of participants recovered within 12 months of episode onset. The median duration of minor depressive episodes was 8 weeks, and approximately 90% of participants recovered within 6 months of onset of the episode. Aggregated data demonstrated similar durations of the first 3 major depressive episodes. However, for each participant with multiple episodes of major depression or minor depression, the duration of each episode was not consistent (intraclass correlation coefficient = 0.07 and 0.25 for major and minor depression, respectively). The total number of years in episode over follow-up with major plus minor depression prior to onset of a major depressive episode was significantly associated with a decreased probability of recovery from that episode; with each additional year, the likelihood of recovery was reduced by 7% (hazard ratio = 0.93; 95% CI, 0.89–0.98; $P = .002$).

Conclusions: Bipolar I major depression generally lasts longer than minor depression, and the duration of multiple episodes within an individual varies. However, the probability of recovery over time from an episode of major depression appears to decline with each successive episode.

J Clin Psychiatry 2013;74(3):e205–e211

Submitted: *July 25, 2012; accepted October 25, 2012 (doi:10.4088/JCP.12m08049).*
†Deceased.
Corresponding author: *Jess G. Fiedorowicz, MD, PhD, Departments of Psychiatry and Internal Medicine, Carver College of Medicine, Department of Epidemiology, College of Public Health, University of Iowa, 200 Hawkins Drive W278GH, Iowa City, IA (jess-fiedorowicz@uiowa.edu).*

Depression occurs more often in bipolar I disorder than manic and mixed states.[1–3] Bipolar I depressive states are associated with poor short-term[4] and long-term[5] symptomatic outcome, psychosocial functioning is significantly worse during periods of depression than mania or hypomania,[6–10] and suicidality is greatest during depressive and mixed states.[8,11–14] Despite these implications, few reports have described the duration of depressive episodes.

The National Institute of Mental Health Collaborative Depression Study (CDS) is the only long-term observational study to have previously examined the duration of depressive episodes in bipolar I disorder.[15] An early report from this study examined 66 participants with bipolar I disorder followed for up to 5 years and found that the median time to recovery from the first 2 prospectively observed episodes of major depression was 20 weeks and 24 weeks.[16] A subsequent report described 82 participants with bipolar I disorder followed for 10 years; the median duration of major and minor depressive episodes was 12 and 5 weeks, respectively.[17] These results are limited by the relatively short duration of follow-up, which is problematic, as bipolar I disorder has a mean age at onset of 18 years,[18] and the risk of suffering recurrent mood episodes remains high for at least 40 years after onset.[19] These 2 reports also lacked the analytic methods required to study the effect of successive mood episodes given correlated observations.[20]

We sought to utilize longer-term data from the CDS to describe recovery from episodes of bipolar I major and minor depression. Using a mixed-effects grouped-time survival model, we analyzed the effect of multiple depressive episodes on episode duration and examined factors associated with time to recovery. The model also facilitated determination of within-subject variability in time to recovery across depressive episodes.

METHOD

Subjects

From 1978 to 1981, the CDS recruited patients with active mood disorders at academic medical centers in Boston, Massachusetts; Chicago, Illinois; Iowa City, Iowa; New York, New York; and St Louis, Missouri. Inclusion criteria included age of at least 17 years, IQ greater than 70, ability to speak English, white race (genetic hypotheses), knowledge of biological parents, and no evidence that the mood disorder was secondary to a medical condition. The study was approved by each respective institutional review board, and participants provided written informed consent.

A total of 955 patients entered the study, all of whom met Research Diagnostic Criteria (RDC)[21] for a major mood episode. The sample for the present analysis consists of the 219 subjects who (1) met RDC for either bipolar I disorder or schizoaffective disorder, mainly affective subtype; (2) had recovered from the mood episode present at study intake; and (3) had subsequently suffered at least 1 depressive episode. Of the 269 subjects who met diagnostic criterion 1 above, 4 were lost to follow-up before the 6-month assessment, 46 did not suffer a recurrence

Clinical Points

- The median duration of major and minor depressive episodes in bipolar I disorder is 14.0 and 8.0 weeks, respectively.
- A more chronic course of illness is associated with a delayed recovery from depressive episodes in bipolar I disorder, although duration of discrete episodes is variable within individuals.

of major depression, and 219 recovered from the intake mood episode and suffered at least 1 subsequent depressive episode. The 46 subjects with at least 1 follow-up who did not suffer a repeat depressive episode following recovery were followed for a mean (SD) of 10.7 (9.4) years and, compared with the 219 subjects, experienced a nonsignificantly greater persistence of clinically significant depressive symptoms as defined by previous methods[22–28] (median of 35% vs 14% of follow-up, Wilcoxon rank sum $P = .07$) but otherwise did not differ from the sample on sociodemographic or clinical variables. Research Diagnostic Criteria for bipolar I disorder fall within *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*) criteria.[20] Research Diagnostic Criteria for schizoaffective disorder, mainly affective subtype, are very similar to the *DSM-IV-TR* criteria for bipolar I disorder, demanding that relevant psychotic symptoms develop simultaneously with or following manic or depressive symptoms and not be present for a week or more in the absence of manic or depressive symptomatology. Previous analyses further show similar course of illness.[29] The inclusion of subjects with the predominantly affective subtype of schizoaffective disorder is consistent with other longitudinal studies of bipolar I disorder.[19,26,27,29–32]

Of the 219 subjects, 156 (71%) were diagnosed with bipolar I disorder at study intake, 25 (11%) were diagnosed with unipolar major depressive disorder at intake but subsequently suffered at least 1 episode of mania over follow-up, 14 (6%) were diagnosed with bipolar II disorder at intake but subsequently suffered an episode of mania over follow-up, and 24 (11%) were diagnosed at study intake with schizoaffective disorder, mainly affective subtype. Compared with the other subjects, those with unipolar major depressive disorder on intake experienced a greater persistence of clinically significant depressive symptoms as defined by previous methods[22–28] (median of 33% vs 11% of follow-up, Wilcoxon rank sum $P = .001$) but otherwise did not differ from the remaining sample on sociodemographic or clinical variables. Subjects with bipolar II disorder or schizoaffective disorder, mainly affective subtype, did not differ from other subjects on any of the sociodemographic or clinical variables.

Assessments and Procedures

At intake, raters interviewed patients about their current and past psychiatric history using the Schedule for Affective Disorders and Schizophrenia.[33] Raters also reviewed medical records and, whenever feasible, interviewed physicians and other informants.

Over prospective follow-up, raters assessed the level of psychopathology through direct interviews conducted every 6 months for the first 5 years of the study and annually thereafter, using variations of the semistructured Longitudinal Interval Follow-Up Evaluation (LIFE).[34] In the current study, participants were prospectively followed for up to 25 years. At each assessment, the interviewer rated the weekly level of psychopathology for each mood syndrome that had occurred since the time of the last interview and assigned a separate weekly score for each mood syndrome. To accomplish this, the rater utilized chronological anchor points to aid recollection and whenever possible obtained corroborative data from medical records. Level of psychopathology for major depression was quantified on a 6-point scale. A rating of 1 corresponded to no symptoms, while 6 indicated full criteria for the disorder with psychosis or extreme impairment in functioning. For minor depression, psychopathology was quantified on a 3-point scale.

Minor depression was defined as at least 2 weeks of depressed mood accompanied by at least 2 other symptoms, without psychosis or the threshold of major depression. Minor depression included episodes identified within the RDC[35] nosology as lasting "for less than 2 years" or "for 2 or more years" (analogous to the *DSM-IV-TR* construct of dysthymia).[20] If, at any point during a minor depressive episode, the participant met criteria for major depression, the entire episode was considered major depression.

Recovery from episodes of major or minor depression was defined according to RDC,[20] which require ≥ 8 consecutive weeks with either no symptoms or only 1 or 2 mild symptoms with no functional impairment. A major depressive episode may thus include periods of minor depression and euthymia shorter than 8 weeks. Recurrence or onset of a new depressive episode was defined as the reappearance of major depression at full criteria for at least 2 consecutive weeks or minor depression at the definite level for at least 2 consecutive weeks. By definition, recurrence occurred only after recovery from the preceding episode.

Raters received rigorous training before being certified to conduct interviews, and consequently the interrater reliability of the LIFE was excellent, with high intraclass correlation coefficients (ICCs) for rating changes in symptoms (ICC = 0.92), recovery from mood episodes (ICC = 0.95), and reappearance of symptoms (ICC = 0.88).[34] Additionally, the test-retest reliability of the LIFE was very good, with ICCs ranging from 0.85 to 0.93.[36]

Treatment

The CDS was an observational study in that treatment was not assigned. Over time, the intensity of treatment varied both within subjects and between subjects. The type and dose of all prescribed somatic treatment were collected with the LIFE[34] and corroborated with available medical records.

Data Analytic Procedures—Time to Recovery

The Kaplan-Meier product limit[37] estimated the cumulative probability of recovery over time from each of the first

3 prospectively observed major depressive episodes per subject. The probability of recovery over time from each of the major depressive episodes was the primary outcome measure. The intake depressive episode was excluded from these analyses because it was previously described[38] and was not entirely prospective. Survival time was defined as the number of weeks until recovery from the depressive episode and began with the first week of each depressive episode. Survival analyses estimated the cumulative probability of recovery, and survival time ended with recovery from the episode or, for censored cases, end of the follow-up period (25 years), withdrawal from study, or death.

Data Analytic Procedures—Factors Associated With Recovery

A mixed-effects grouped-time survival model[39] estimated the magnitude of the association between various clinical predictors and the probability of recovery over time from episodes of bipolar I major depression. The predictors included

(1) Severe episode onset: full criteria for major depression along with psychosis or extreme impairment in functioning in week 1 of the episode;

(2) Number of prior depressive episodes: number of major and minor depressive episodes observed during prospective follow-up, beginning with the intake mood episode and ending with the depressive episode immediately prior;

(3) Number of years in episode with depression: cumulative number of years in episode (symptomatically ill) with major depression plus minor depression during prospective follow-up, beginning at study intake and ending with the week prior to onset of the referent episode; and

(4) Comorbid anxiety disorder: generalized anxiety disorder, panic disorder, phobic disorder, or obsessive-compulsive disorder.

A second mixed-effects grouped-time survival model[39] estimated the magnitude of any association between various predictors and recovery from bipolar I minor depression over time. The predictors included number of prior depressive episodes, number of years ill with depression, and comorbid anxiety disorder. The mixed models also calculated an ICC that estimated the consistency in duration of depressive episodes across multiple within-subject episodes.

The mixed-effects models accounted for the correlation among multiple, within-subject depressive episodes. In the grouped-time survival model for recovery from major depression, the episode durations were categorized as follows (in weeks): 1 to 4, 5 to 8, 9 to 13, 14 to 17, 18 to 21, 22 to 26, 27 to 52, and > 52. For minor depression, the episode durations were categorized as follows (in weeks): 1 to 4, 5 to 8, 9 to 13, 14 to 26, and > 26. The choice of survival time intervals was guided by clinical relevance while avoiding sparse cells. The hazard ratio was assumed to be constant within any categorized time interval. Each statistical test used a 2-tailed $\alpha = .05$.

Table 1. Sociodemographic and Clinical Characteristics at Study Intake for Subjects With Bipolar I Disorder (N = 219)

Characteristic	
Age, mean (SD), y	37 (13)
Sex, n (%)	
Male	97 (44)
Female	122 (56)
Marital status, n (%)	
Never married	84 (38)
Married/live together	85 (39)
Divorced, separated, or widowed	50 (23)
Socioeconomic status, n (%)[a,b]	
I	8 (4)
II	32 (15)
III	69 (32)
IV	63 (29)
V	47 (21)
Intake medical center, n (%)	
Boston	34 (16)
Chicago	43 (20)
Iowa City	62 (28)
New York	31 (14)
St. Louis	49 (22)
Status at intake, n (%)	
Inpatient	196 (89)
Outpatient	23 (11)
Polarity of mood state at study intake, n (%)	
Mania	142 (65)
Major depression	62 (28)
Mixed	15 (7)
Psychosis, n (%)	
Present	121 (55)
Absent	98 (45)
Global Assessment Scale score, mean (SD)[c]	32 (11)
Age at onset for first lifetime mood episode (major depression, minor depression, mania or hypomania), mean (SD), y	24 (10)
Number of mood episodes prior to intake episode, n (%)	
0	27 (12)
1	20 (9)
2	26 (12)
3 or more	146 (67)

[a]Hollingshead-Redlich scale[40]: I = highest, V = lowest.
[b]Percentages do not sum to 100 because of rounding.
[c]The range for the Global Assessment Scale[41] is 1 to 100, with higher numbers indicating less psychopathology and better psychosocial functioning.
Abbreviation: SD = standard deviation.

RESULTS

Subjects and Length of Follow-Up

The sample consisted of 219 subjects with bipolar I disorder who each recovered from the study-intake mood episode and then suffered at least 1 depressive episode. The mean (median; SD) length of follow-up was 17.3 (20; 7.9) years. Of the 219 subjects, 169 (77%) were followed for at least 10 years, and 122 (56%) were followed for at least 20 years. Those with ≥ 20 years of follow-up tended to be younger at intake ($P = .001$) but did not otherwise differ. Data for the 39 (18%) who died during follow-up are included. Table 1 displays the sociodemographic and clinical characteristics of participants at study intake.

Time to Recovery—Bipolar I Major Depression

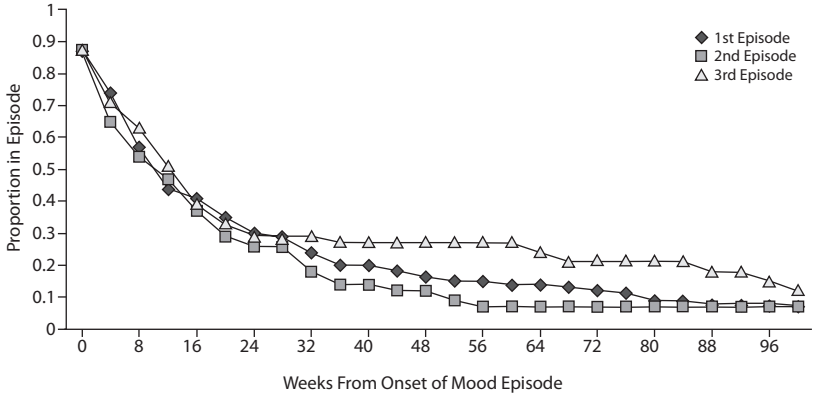
A total of 373 major depressive episodes were prospectively observed during the 25-year follow-up. Table 2 displays

Table 2. Proportion of Subjects Recovering From Successive Prospectively Observed Episodes of Bipolar I Major Depression[a]

Major Depressive Episode, no.	Subjects at Start of Episode, n	Time From Onset of Major Depressive Episode[b]					
		1 Month	3 Months	6 Months	1 Year	2 Years	5 Years
1	130	0.130 (0.045–0.345)	0.460 (0.287–0.674)	0.670 (0.486–0.842)	0.840 (0.668–0.952)	0.930 (0.784–0.990)	Not estimated[c]
2	80	0.120 (0.028–0.433)	0.480 (0.265–0.750)	0.720 (0.485–0.913)	0.880 (0.664–0.984)	Not estimated[c]	Not estimated[c]
3	52	0.120 (0.021–0.534)	0.370 (0.149–0.733)	0.710 (0.425–0.937)	0.730 (0.439–0.949)	Not estimated[c]	Not estimated[c]

[a]Recovery from an episode of major depression was defined according to Research Diagnostic Criteria,[21] which require at least 8 consecutive weeks with either no symptoms or only 1 or 2 symptoms at a mild level of severity and no impairment of functioning.
[b]Proportions derived from Kaplan-Meier product limit estimates (95% confidence interval).
[c]Estimate was not calculated because of limited number of subjects at risk for recovery.

Figure 1. Time to Recovery From First 3 Major Depressive Episodes



the proportion of subjects who recovered over time from each of the first 3 episodes of major depression. These first 3 episodes comprised 262 (70%) of the 373 major depressive episodes. There were 130 subjects who suffered at least 1 prospectively observed major depressive episode. On the basis of Kaplan-Meier estimates, 84% recovered from this first episode within 1 year of onset of the episode. Of the 80 subjects with a second major depressive episode, 88% recovered within 1 year. Among subjects with a third episode, 73% recovered within 1 year. The corresponding Kaplan-Meier survival curves for the duration of the first 3 major depressive episodes are shown in Figure 1. The 3 curves are similar, indicating that time to recovery in the sample as a whole was consistent across multiple episodes.

The quartiles for duration of the first 3 prospectively observed major depressive episodes were also analyzed. Across all 3 episodes, 25% of the subjects (ie, the first quartile) recovered within 6.0 (SE = 0.8) weeks of onset of the episode, 50% of the subjects (ie, the median) recovered within 14.0 (SE = 1.4) weeks, and 75% (ie, the third quartile) recovered within 35.0 (SE = 3.4) weeks.

Factors Associated With Recovery From Bipolar I Major Depression Over Time

In mixed-effects grouped-time survival analysis, a greater number of years in episode (symptomatically ill) with major depression plus minor depression during prospective follow-up was associated with a significantly decreased probability of recovery. With each additional year in episode prior to onset of a major depressive episode, the likelihood of recovery from that episode was reduced by approximately 7% (hazard ratio = 0.93; 95% CI, 0.89–0.98; $z = -3.08$, $P = .002$), controlling for number of prior depressive episodes, severe onset of episode, and comorbid anxiety. Number of prior depressive episodes (hazard ratio = 0.99; 95% CI, 0.94–1.04; $z = -0.50$, $P = .62$), severe onset of episode (hazard ratio = 1.08; 95% CI, 0.65–1.77; $z = 0.28$, $P = .78$), and comorbid anxiety disorder (hazard ratio = 1.01; 95% CI, 0.64–1.62; $z = 0.05$, $P = .96$) were not significantly associated with the probability of recovery from an episode of major depression.

The mixed-effects model also examined within-subject variability in time to recovery. The model yielded an ICC of 0.07, meaning that, for each subject with 2 or more prospectively observed episodes of major depression, the duration of these multiple episodes was not consistent.

Time to Recovery—Bipolar I Minor Depression

A total of 157 bipolar I minor depressive episodes were prospectively observed during the 25-year follow-up. Table 3 displays the proportion of subjects who recovered over time from each of the first 3 episodes of minor depression. These first 3 episodes comprised 140 (89%) of the 157 minor depressive episodes. There were 80 subjects who suffered at least 1 prospectively observed minor depressive episode. On the basis of Kaplan-Meier estimates, 70% recovered from this first episode within 3 months of onset of the episode. Of the 40 subjects with a second minor depressive episode, 70% recovered from that episode within 3 months of onset. Among subjects with a third minor depressive episode, 60% recovered within 3 months.

The corresponding Kaplan-Meier survival curves for the duration of the first 3 minor depressive episodes are shown in Figure 2. The 3 curves are again similar, suggesting consistency in aggregate time to recovery across multiple mood episodes.

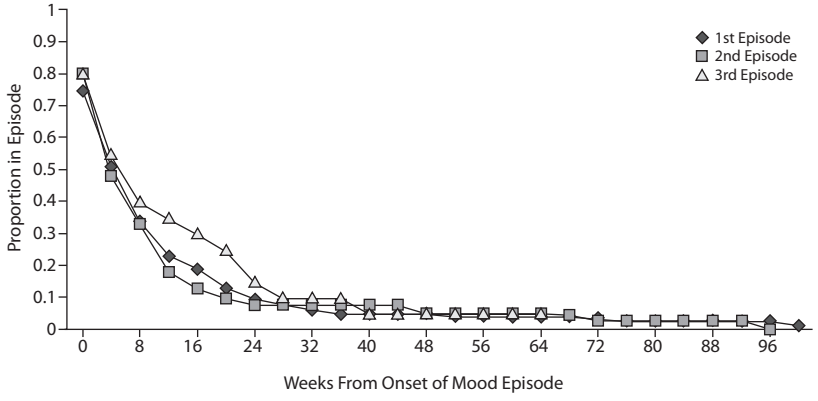
The quartiles for duration of the first 3 prospectively observed bipolar I minor depressive episodes were also analyzed. Overall, across all 3 episodes, 25% of the subjects (the first quartile) recovered within 4.0 (SE = 0.4) weeks of onset of the episode, 50% of the subjects (the median) recovered

Table 3. Proportion of Subjects Recovering From Successive Prospectively Observed Episodes of Bipolar I Minor Depression[a]

Minor Depressive Episode, no.	Subjects at Start of Episode, n	Time From Onset of Minor Depressive Episode[b]			
		1 Month	3 Months	6 Months	1 Year
1	80	0.250 (0.099–0.550)	0.700 (0.471–0.898)	0.890 (0.687–0.985)	Not estimated[c]
2	40	0.200 (0.044–0.668)	0.700 (0.385–0.949)	0.920 (0.608–0.999)	Not estimated[c]
3	20	0.200 (0.023–0.882)	0.600 (0.212–0.971)	Not estimated[c]	Not estimated[c]

[a]Recovery from an episode of minor depression was defined according to Research Diagnostic Criteria,[21] which require at least 8 consecutive weeks with either no symptoms or only 1 or 2 symptoms at a mild level of severity and no impairment of functioning.
[b]Proportions derived from Kaplan-Meier product limit estimates (95% confidence interval).
[c]Estimate was not calculated because of limited number of subjects at risk for recovery.

Figure 2. Time to Recovery From First 3 Minor Deressive Episodes



within 8.0 (SE = 0.9) weeks of onset of the episode, and 75% (the third quartile) recovered within 15 (SE = 1.9) weeks.

Factors Associated With Recovery From Bipolar I Minor Depression Over Time

With mixed-effects grouped-time survival analysis, the number of years of episodic depression (hazard ratio = 0.94; 95% CI, 0.86–1.02; $z = -1.54$, $P = .12$), number of prior depressive episodes (hazard ratio = 1.09; 95% CI, 0.98–1.22; $z = 1.63$, $P = .10$), and comorbid anxiety disorder (hazard ratio = 0.59; 95% CI, 0.18–1.91; $z = -0.88$, $P = .38$) were not significantly associated with the probability of recovery from an episode of minor depression.

The mixed-effects model also examined within-subject variability in time to recovery from one minor depressive episode to the next. The model yielded an ICC of 0.25.

Treatment

Treatment was categorically defined as at least 8 consecutive weeks of somatic therapy or treatment for the entire episode in the case of episodes lasting fewer than 8 weeks. Over one-half of the depressive episodes were treated with a mood stabilizer, and roughly one-quarter of the depressive episodes were treated with a mood stabilizer plus an antidepressant. Nearly one-quarter of the bipolar I major depressive episodes were treated with an antidepressant in the absence of a mood stabilizer.

DISCUSSION

In a large prospective cohort with bipolar I disorder over long-term follow-up, the median duration of major depression was 14 weeks and minor depression was 8 weeks. Within episodes, the rate of recovery decreased over time, underscoring the significance of persistent depressive episodes. Across episodes, the cumulative duration of previous depressive episodes was associated with a significantly decreased probability of recovery from a new episode of major depression, such that with each additional year of depressive illness prior to onset of a major depressive episode, the likelihood of recovery from that episode was reduced by approximately 7% (consistent with a previous finding).[38] For any single patient with multiple episodes of major and minor depression, the duration of the episodes was inconsistent, although those with a more chronic course had delayed recovery as noted above.

Only a few observational studies such as the CDS have prospectively collected data on samples of this size over decades to describe recovery from multiple mood episodes of bipolar I disorder. The length of follow-up allowed the investigators to analyze 402 depressive episodes and to better assess subjects with relatively long mood episodes and subjects with a long interval of wellness between mood episodes. This reduced the likelihood that length of follow-up would condition or bias the results. Other strengths of

the present study included frequent assessment of subjects through direct interviews using standardized diagnostic and follow-up instruments. In addition, the study met the need for evaluating course of illness in patients treated in the community rather than specialty mood disorder clinics.[8]

For the entire sample of subjects analyzed collectively, time to recovery from the 3 prospectively observed episodes of bipolar I major depression was similar (see Figure 1 and Table 2). Likewise, recovery from the 3 prospectively observed episodes of minor depression was uniform (see Figure 2 and Table 3). This consistency across multiple depressive episodes in bipolar I disorder is strikingly similar to the uniformity in time to recovery across multiple depressive episodes in unipolar major depressive disorder.[42,43]

However, the regularity in recovery across multiple episodes that was observed when the data were analyzed collectively for the entire sample was not observed at the level of individual subjects. For each participant with 2 or more prospectively observed episodes of major depression, the duration of these multiple episodes was highly inconsistent. Similarly, for each subject with 2 or more prospectively observed episodes of minor depression, the duration of these multiple episodes was inconsistent. These findings are at odds with the idea that the duration of episodes is relatively constant in a given individual[8] and, in contrast to prior findings of long-term stability in consistency of overall symptom burden or persistence,[44] suggest perhaps that chronicity of illness but not episode duration may be stable. In this analysis, those with a more chronic course of illness over prospective follow-up were less likely to recover from major depressive episodes.

There are several limitations to this study. A majority of participants were inpatients at academic medical centers at the time of enrollment into the study, although participants spent a significant amount of time as outpatients, and hospitalization is relatively common in patients with bipolar disorder.[45] The recruitment location may have selected for higher acuity than a representative community sample. While our use of prospectively observed episodes minimized recall bias related to any estimation of the duration of intake episode, almost one-fifth of those with bipolar I did not have a recurrence following a remission. Our results may not generalize to this subset of individuals with a chronic course that does not remit. Our results related to duration of depressive episodes in bipolar I are further presented in aggregate form, and it is not clear the extent to which the aggregate results apply to those for specific subgroups. Another limitation is that subjects were recruited at varying points in their course of illness, with some subjects enrolled closer to onset of their illness. The mixed-effects model thus systematically and differentially underestimated the number of years in episode with depression, because the analyses did not capture depressive illness prior to intake. Treatment was not controlled and may not have been optimal. The analyses were not designed to appropriately assess treatment effects akin to prior analyses of these observational data.[46,47] Prior work highlighted the importance of clinical variables such as the nature, severity, and trajectory of mood symptoms,[46–49] which if not adequately addressed could yield misleading results. Future study of treatment will use models with treatment intervals, rather than mood episodes, as the unit of analysis and use propensity scores to address confounding factors that determine treatment selection.

Additional questions remain regarding duration of bipolar I mania, hypomania, and cycling and mixed episodes. Further analyses of the CDS data will improve our knowledge of the prognosis for bipolar I disorder.

Author affiliations: Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, Rhode Island (Drs Solomon, Boland, and Keller); UpToDate, Waltham, Massachusetts (Dr Solomon); Department of Psychiatry, Weill Cornell Medical College, New York, New York (Dr Leon and Mr Li); Department of Psychiatry, Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, and Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City (Dr Fiedorowicz); and New York State Psychiatric Institute, New York (Dr Endicott).

Study participants: Conducted with the current participation of the following investigators: M. B. Keller, MD (Chairperson, The Warren Alpert Medical School of Brown University, Providence, Rhode Island); W. Coryell, MD (Cochairperson, University of Iowa, Iowa City); D. A. Solomon, MD (The Warren Alpert Medical School of Brown University, Providence, Rhode Island); W. Scheftner, MD (Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois); J. Endicott, PhD; A. C. Leon, PhD†; and J. Loth, MSW (Weill Medical College of Cornell University, New York, New York); and J. Rice, PhD (Washington University Medical School, St. Louis, Missouri). Other current contributors include H. S. Akiskal, MD (Department of Psychiatry, University of California, San Diego), J. Fawcett, MD (Department of Psychiatry, University of New Mexico, Albuquerque), L. L. Judd, MD (Department of Psychiatry, University of California, San Diego), and J. D. Maser, PhD (Department of Psychiatry, University of California, San Diego). The original principal and coprincipal investigators were from 5 academic centers and included Gerald Klerman, MD† (Cochairperson); Martin B. Keller, MD; Robert Shapiro, MD†; (Massachusetts General Hospital, Harvard Medical School, Boston), Eli Robbins, MD†; Paula Clayton, MD; Theodore Reich, MD†; Amos Wellner, MD† (Washington University Medical School, St. Louis, Missouri); Jean Endicott, PhD; Robert Spitzer, MD (Columbia University, New York, New York); Nancy Andreasen, MD, PhD; William Coryell, MD; George Winokur, MD† (University of Iowa, Iowa City, Iowa); Jan Fawcett, MD; and William Scheftner, MD (Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois). The NIMH Clinical Research Branch was an active collaborator in the origin and development of the Collaborative Program with Martin M. Katz, PhD, Branch Chief, as the Cochairperson 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.

†Deceased.

Potential conflicts of interest: **Dr Solomon** serves as Deputy Editor at UpToDate.com. In the past 36 months, **Dr Endicott** has received research support from the New York State Office of Mental Hygiene, the US National Institute of Mental Health, and Cyberonics and has served as a consultant or advisory board member to Amgen, AstraZeneca, Bayer Heathcare, Berlex, Shire, and Wyeth-Ayerst. In the past 36 months, **Dr Keller** has received research support from Pfizer; has served as a consultant or received honoraria from CeNeRx, Medtronic, and Sierra Neuropharmceuticals; and served on an advisory board for CeNeRx. **Drs Fiedorowicz, Leon, Coryell,** and **Boland** and **Mr Li** have no potential conflicts of interest to disclose.

Funding/support: Funding for this study was provided by National Institute of Mental Health (NIMH) grant MH25478-29A2. This study was funded by NIMH grants 5R01MH025416-33 (W. Coryell), 5R01MH023864-35 (J. Endicott), 5R01MH025478-33 (M. Keller), 5R01MH025430-33 (J. Rice), and 5R01MH029957-30 (W. A. Scheftner). The NIMH had no further role in the design or conduct of this study; in the collection, management, analysis, and interpretation of the data; and in the preparation, review, or approval of the manuscript.

Additional information: This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement. The data for this manuscript came from the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression—Clinical Studies. The Collaborative Program was initiated in

1975 to investigate nosologic, genetic, family, prognostic, and psychosocial issues of mood disorders and is an ongoing, long-term multidisciplinary investigation of the course of mood and related affective disorders.

REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002; 59(6):530–537.
2. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
3. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163(2): 217–224.
4. Mysels DJ, Endicott J, Nee J, et al. The association between course of illness and subsequent morbidity in bipolar I disorder. *J Psychiatr Res*. 2007;41(1–2):80–89.
5. Coryell W, Turvey C, Endicott J, et al. Bipolar I affective disorder: predictors of outcome after 15 years. *J Affect Disord*. 1998;50(2–3):109–116.
6. Bauer MS, Kirk GF, Gavin C, et al. Determinants of functional outcome and healthcare costs in bipolar disorder: a high-intensity follow-up study. *J Affect Disord*. 2001;65(3):231–241.
7. Calabrese JR, Hirschfeld RM, Frye MA, et al. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. *J Clin Psychiatry*. 2004;65(11):1499–1504.
8. Goodwin FK, Jamison KR. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*, 2nd Edition. New York, NY: Oxford University Press; 2007:120, 128, 263-264, 340.
9. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry*. 2005;62(12):1322–1330.
10. Simon GE, Bauer MS, Ludman EJ, et al. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *J Clin Psychiatry*. 2007;68(8):1237–1245.
11. Dilsaver SC, Chen YW, Swann AC, et al. Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure-mania. *Psychiatry Res*. 1997;73(1–2):47–56.
12. Hawton K, Sutton L, Haw C, et al. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry*. 2005;66(6): 693–704.
13. Isometsä ET, Henriksson MM, Aro HM, et al. Suicide in bipolar disorder in Finland. *Am J Psychiatry*. 1994;151(7):1020–1024.
14. Valtonen HM, Suominen K, Haukka J, et al. Differences in incidence of suicide attempts during phases of bipolar I and II disorders. *Bipolar Disord*. 2008;10(5):588–596.
15. Katz MM, Secunda SK, Hirschfeld RM, et al. NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression. *Arch Gen Psychiatry*. 1979;36(7):765–771.
16. Coryell W, Keller M, Endicott J, et al. Bipolar II illness: course and outcome over a five-year period. *Psychol Med*. 1989;19(1):129–141.
17. Judd LL, Akiskal HS, Schettler PJ, et al. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J Affect Disord*. 2003;73(1–2):19–32.
18. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
19. Angst J, Gamma A, Sellaro R, et al. Recurrence of bipolar disorders and major depression: a life-long perspective. *Eur Arch Psychiatry Clin Neurosci*. 2003;253(5):236–240.
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
21. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782.
22. Coryell W, Fiedorowicz J, Leon AC, et al. Age of onset and the prospectively observed course of illness in bipolar disorder [published online ahead of print October 10, 2012]. *J Affect Disord*. 2012.
23. Fiedorowicz JG, Endicott J, Solomon DA, et al. Course of illness following prospectively observed mania or hypomania in individuals presenting with unipolar depression. *Bipolar Disord*. 2012;14(6):664–671.
24. Fiedorowicz JG, Coryell WH, Rice JP, et al. Vasculopathy related to manic/hypomanic symptom burden and first-generation antipsychotics in a subsample from the Collaborative Depression Study. *Psychother Psychosom*. 2012; 81(4):235–243.
25. Fiedorowicz JG, Palagummi NM, Behrendtsen O, et al. Cholesterol and affective morbidity. *Psychiatry Res*. 2010;175(1-2):78–81.
26. Fiedorowicz JG, Solomon DA, Endicott J, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosom Med*. 2009;71(6):598–606.
27. Fiedorowicz JG, Leon AC, Keller MB, et al. Do risk factors for suicidal behavior differ by affective disorder polarity? *Psychol Med*. 2009;39(5): 763–771.
28. Persons JE, Coryell WH, Fiedorowicz JG. Cholesterol fractions, symptom burden, and suicide attempts in mood disorders [published online ahead of print July 11, 2012]. *Psychiatry Res*. 2012;200(2–3):1088–1089. doi:10.1016/j.psychres.2012.06.039.
29. Solomon DA, Leon AC, Endicott J, et al. Empirical typology of bipolar I mood episodes. *Br J Psychiatry*. 2009;195(6):525–530.
30. Nolen WA, Luckenbaugh DA, Altshuler LL, et al. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. *Am J Psychiatry*. 2004;161(8):1447–1454.
31. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2003;53(11):1028–1042.
32. Solomon DA, Leon AC, Coryell WH, et al. Longitudinal course of bipolar I disorder: duration of mood episodes. *Arch Gen Psychiatry*. 2010;67(4): 339–347.
33. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry*. 1978;35(7):837–844.
34. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-Up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry*. 1987;44(6):540–548.
35. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *J Clin Psychiatry*. 2002;63(9):807–811.
36. Warshaw MG, Keller MB, Stout RL. Reliability and validity of the Longitudinal Lnterval Follow-up Evaluation for assessing outcome of anxiety disorders. *J Psychiatr Res*. 1994;28(6):531–545.
37. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457–481.
38. Keller MB, Lavori PW, Coryell W, et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. *JAMA*. 1986;255(22):3138–3142.
39. Hedeker D, Siddiqui O, Hu FB. Random-effects regression analysis of correlated grouped-time survival data. *Stat Methods Med Res*. 2000;9(2): 161–179.
40. Hollingshead AB, Redlich FC. *Social Class and Mental Illness: A Community Study*. New York, NY: John Wiley & Sons; 1958.
41. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*. 1976;33(6):766–771.
42. Coryell W, Akiskal HS, Leon AC, et al. The time course of nonchronic major depressive disorder: uniformity across episodes and samples. National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. *Arch Gen Psychiatry*. 1994;51(5):405–410.
43. Solomon DA, Keller MB, Leon AC, et al. Recovery from major depression: a 10-year prospective follow-up across multiple episodes. *Arch Gen Psychiatry*. 1997;54(11):1001–1006.
44. Coryell W, Fiedorowicz J, Solomon D, et al. Age transitions in the course of bipolar I disorder. *Psychol Med*. 2009;39(8):1247–1252.
45. Peele PB, Xu Y, Kupfer DJ. Insurance expenditures on bipolar disorder: clinical and parity implications. *Am J Psychiatry*. 2003;160(7):1286–1290.
46. Leon AC, Solomon DA, Li C, et al. Antidepressants and risks of suicide and suicide attempts: a 27-year observational study. *J Clin Psychiatry*. 2011; 72(5):580–586.
47. Leon AC, Solomon DA, Li C, et al. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. *Am J Psychiatry*. 2012;169(3):285–291.
48. Prabhakar M, Haynes WG, Coryell WH, et al. Factors associated with the prescribing of olanzapine, quetiapine, and risperidone in patients with bipolar and related affective disorders. *Pharmacotherapy*. 2011;31(8):806–812.