ORIGINAL ARTICLE

The Long-term Natural History of the Weekly Symptomatic Status of Bipolar I Disorder

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Background: To our knowledge, this is the first prospective natural history study of weekly symptomatic status of patients with bipolar I disorder (BP-I) during long-term follow-up.

Methods: Analyses are based on ongoing prospective follow-up of 146 patients with Research Diagnostic Criteria BP-I, who entered the National Institute of Mental Health (Bethesda, Md) Collaborative Depression Study from 1978 through 1981. Weekly affective symptom status ratings were analyzed by polarity and severity, ranging from asymptomatic, to subthreshold levels, to full-blown major depression and mania. Percentages of follow-up weeks at each level as well as number of shifts in symptom status and polarity during the entire follow-up period were examined. Finally, 2 new measures of chronicity were evaluated in relation to previously identified predictors of chronicity for BP-I.

Results: Patients with BP-I were symptomatically ill 47.3% of weeks throughout a mean of 12.8 years of follow-up. Depressive symptoms (31.9% of total follow-up weeks) predominated over manic/hypomanic symptoms (8.9% of weeks) or cycling/mixed symptoms (5.9% of weeks). Subsyndromal, minor depressive, and hypomanic symptoms combined were nearly 3 times more frequent than syndromal-level major depressive and manic symptoms (29.9% vs 11.2% of weeks, respectively). Patients with BP-I changed symptom status an average of 6 times per year and polarity more than 3 times per year. Longer intake episodes and those with depression-only or cycling polarity predicted greater chronicity during long-term follow-up, as did comorbid drug-use disorder.

Conclusions: The longitudinal weekly symptomatic course of BP-I is chronic. Overall, the symptomatic structure is primarily depressive rather than manic, and subsyndromal and minor affective symptoms predominate. Symptom severity levels fluctuate, often within the same patient over time. Bipolar I disorder is expressed as a dimensional illness featuring the full range (spectrum) of affective symptom severity and polarity.

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KRAEPELIN[1] HAD described manic-depressive insanity as a cyclical illness. Until recently, following his lead, clinical and research attention concerning mood disorders was concentrated on the most severe syndromal manifestations of these disorders, ie, manic and major depressive episodes (MDE).[2-9] However, recent evidence suggests that the concept of bipolar I disorder (BP-I) with episode-free periods of euthymia punctuated by syndromal MDE and mania is inadequate.[10-12] Analyses of weekly symptomatic status during the long-term course of another mood disorder, unipolar MDD,[12] has shown that, although this illness has traditionally been examined primarily in terms of the onset, remission, and relapse of MDEs, minor and subsyndromal depressive symptoms dominate its long-term course by nearly a 3:1 ratio (43% vs 15% of follow-up weeks). Patients with unipolar MDD were found to be symptomatic during 60% of the follow-up period and to experience a changeable course in which major, minor, and subsyndromal depressive symptoms alternated within the same patient over time. In brief, unipolar MDD is expressed longitudinally as a dimensional illness involving the full spectrum of depressive symptom severity.

This new understanding of the long-term symptomatic structure of unipolarity stimulated us to carry out a similar analysis of the longitudinal symptom structure of BP-I, based on weekly levels of symptom severity and polarity in a large cohort of patients with BP-I who entered the National Institute of Mental Health (Bethesda, Md) Collaborative Depression Study (CDS)[13,14] during a major

SUBJECTS AND METHODS

SUBJECTS

The analysis sample consisted of 146 patients with BP-I entering the CDS from 1978 through 1981 at 1 of 5 academic centers during an affective episode.[13,14] Patients experienced both depressive and manic episodes as of intake or during follow-up, with no evidence of schizophrenia or schizoaffective disorder. Bipolar I diagnosis was based on the Schedule of Affective Disorders and Schizophrenia[15] using Research Diagnostic Criteria (RDC).[16] Subjects were white (genetic hypotheses were being tested), spoke English, had an IQ score of at least 70, and had no evidence of organic mental disorder or terminal medical illness. All patients gave informed consent at the 5 academic sites where the data were gathered. Demographic and clinical characteristics are presented in **Table 1**.

FOLLOW-UP PROCEDURES

Trained raters interviewed patients every 6 months for the first 5 years of follow-up and are still continuing to interview them yearly thereafter, using variations of the Longitudinal Interval Follow-up Evaluation (LIFE).[17] Patient interviews were the primary information source for LIFE data, with chronological memory prompts used to obtain information on changes in weekly symptom severity for all mood and other mental disorders. Interviews were supplemented by detailed review of available medical records and all information was integrated into a final rating algorithm score. Weekly symptom ratings were obtained using LIFE Psychiatric Status Rating (PSR) scales, which are anchored to diagnostic thresholds for RDC mental disorders. Collaborative Depression Study 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).

Interviewers assign a 5-point rating of the accuracy of weekly PSR information based on their overall impression of the subject's recall, the internal consistency of information provided, and evidence of denial or distortion of illness status. If a subject is severely manic or depressed at the scheduled time of follow-up, the interview is rescheduled at a later time. Of the 2516 forms available for the analysis sample, 25.8% were rated "excellent," 50.4% "good," 20.7% "fair," 2.7% "poor," and 0.4% "very poor" in their accuracy of weekly PSR information. Specific follow-up weeks were not included in the analyses if accuracy ratings were "poor" or "very poor" (9.0% of follow-up weeks accounting for 77 forms) or if there were missing data (0.9% of weeks). Due to frequent changes in symptom status, it was inappropriate to impute illness status during a period of inaccurate or missing data.

A total of 157 CDS patients met diagnostic criteria for BP-I and were followed up for up to 20 years. Because our study focused on the long-term course, we eliminated from the analyses 11 patients (7.0%) with less than 2 years of weekly PSR data with "fair" or better accuracy. Nine of these patients dropped out before 2 years; the remaining 2 excluded subjects were followed up for exactly 2 years but had missing data or forms with "poor" or "very poor" accuracy for some portion of that time. This left 146 patients with BP-I with at least 2 years of weekly follow-up data rated "fair" or better accuracy.

CLASSIFICATION OF WEEKLY SYMPTOM SEVERITY LEVELS

We have extended the methodology used in our previous work, describing the course of unipolar MDD,[12] to include symptom severity levels of mania as well as depression. Each weekly symptom severity level was assigned as presented in **Table 2**, based on the 6-point PSR scale for major depression and mania plus the 3-point PSR scale for rating minor depression/dysthymia, hypomania, *DSM-IV* atypical depression, *DSM-III* adjustment disorder with depressed mood, and RDC cyclothymic personality. While affective symptom severity levels are anchored to the diagnostic thresholds for all depressive and manic conditions, including MDE, minor depressive/dysthymic disorder, mania, and hypomania, weekly levels were assigned regardless of whether the patient was in an RDC-defined episode. Affective symptoms below the thresholds of the foregoing RDC conditions were classified as subsyndromal depression or subsyndromal mania. Weeks with no affective symptoms were classified as asymptomatic. Weeks with some affective symptoms were then categorized into levels of pure depression (no mania/hypomania), pure mania/hypomania (no depression), or a combination of manic and depressive symptoms (cycling/mixed affect). Weeks with prominent psychotic symptoms were counted based on a PSR score of 6 on the 6-point PSR scale for mania or MDE.

STATISTICAL ANALYSES

Follow-up weeks spent in the different symptom status categories were computed for each patient as percentages of the total number of follow-up weeks with PSR ratings of "fair" or better accuracy. Total and average yearly numbers of changes in symptom status categories and shifts in symptom polarity were also computed per patient. Subgroups of patients with BP-I were defined based on predictors of chronicity previously identified in the BP-I literature: age; age at onset of first lifetime affective episode; number of lifetime affective episodes; poor social functioning in the 5 years prior to intake; family history of affective disorder; alcoholism; and duration, polarity, and presence of psychotic features in the intake episode. Although not previously identified as robust predictors of chronicity in BP-I, we also examined sex, severity of the intake episode, drug-use disorder, and comorbid anxiety disorders. We defined long-term chronicity in 2 ways: (1) the total percentage of follow-up weeks spent with symptoms at the full-syndromal MDD/manic level, and (2) the total percentage of follow-up weeks spent with any affective symptoms (at any level other than the asymptomatic status). Comparisons were made by analyses of variance, with a 2-tailed α level of .05 defining statistically significant group comparisons.

Table 1. Demographic and Clinical History Characteristics of Patients With Bipolar I Disorder at CDS Intake*

Age, mean (SD) [range], y	39.2 (13.7) [17-79]
Female	81 (55.5)
Education	
High school or less	58 (39.7)
College or more	88 (60.3)
Marital status	
Married/living together	63 (43.2)
Separated/divorced/widowed	35 (24.0)
Never married	48 (32.9)
Total No. of lifetime affective episodes (including intake episode)	
1 (intake episode)	8 (5.5)
2 or 3	32 (21.9)
4-10	61 (41.8)
>10	45 (30.8)
Age at onset of first lifetime affective episode, mean (SD) [range], y	22.9 (10.0) [1-59]
Early onset of first lifetime affective episode (age ≤20 y)	72 (49.3)
Severity of intake episode (worst week GAS score), mean (SD) [range]	32.9 (10.6) [11-67]
Inpatient status (intake)	132 (90.4)
Polarity diagnosis of affective episode prior to intake	
Depressive only	29 (19.9)
Mania only	45 (30.8)
Cycling/mixed†	72 (49.3)
Polarity diagnosis of entire intake episode	
Depressive only	20 (13.7)
Manic only	31 (21.2)
Cycling/mixed†	95 (65.1)
All follow-up, mean (SD) [range]	
Weeks (median, 884)	738.0 (295.1) [104-1040]
Years (median, 17.0)	14.2 (5.7) [2-20]
Follow-up with psychiatric status ratings of "fair" or better accuracy, mean (SD) [range]	
Weeks (median, 806)	665.0 (296.6) [104-988]
Years (median, 15.5)	12.8 (5.7) [2-19]
Years of follow-up with psychiatric status ratings of "fair" or better accuracy	
15-19	82 (56.2)
10-14	17 (11.6)
5-9	26 (17.8)
2-4	21 (14.4)

*Data are given as number (percentage) of patients unless otherwise indicated. Patients in the National Institute of Mental Health Collaborative Depression Study (CDS) who, as of intake or any time during follow-up, have Research Diagnostic Criteria (RDC) mania and depression but no schizophrenia or schizoaffective disorder, and who have at least 104 weeks (2 years) of weekly psychiatric status ratings with "very good," "good," or "fair" accuracy, which were the basis for the analyses. GAS indicates Global Assessment Scale.

†Diagnosis of RDC major, minor, intermittent, or dysthymic depressive disorder, plus mania or hypomania.

affective episode. We hypothesized that BP-I would also be expressed longitudinally as a dimensional illness in which patients typically experience frequent changes in polarity and severity of affective symptoms covering the full range of severity of depression and mania.

We also examined 2 new potentially useful measures of chronicity in relation to predictors of chronicity previously identified for BP-I, as follows: (1) the total percentage of follow-up weeks that patients experienced the full-syndromal level of major depressive or manic symptoms and (2) the total percentage of follow-up weeks they experienced *any* affective symptoms at any level of severity. We anticipated greater chronicity for BP-I than we previously found for unipolar MDD, and we predicted that our 2 new indices, characterizing chronicity during the entire follow-up period, would provide a somewhat different but complementary picture than previously reported for BP-I.

RESULTS

SYMPTOM STATUS DURING THE COURSE OF ILLNESS

Patients were symptomatically ill about half of the time (mean [SD], 47.3% [34%]; median, 38%) and asymptomatic for the remainder of follow-up (52.7% [34%]; median, 62%). Fourteen patients (9.6%) of 146 were symptomatic during all of their prospective follow-up (a finding not attributable to these patients having a shorter follow-up period). Symptomatically ill weeks (47.3% of follow-up) included a mean ([SD]; median) of 14.8% ([18.7%]; median, 7.5%) of all follow-up weeks with subsyndromal symptoms of mania or depression; 20.2% ([21.0%]; median, 12%) of total follow-up with minor depression/dysthymia or hypomanic symptoms, and only 12.3% ([14.2%]; median, 7%) of follow-up spent at the syndromal

Table 2. Classification of Affective Symptom Severity Levels Based on Weekly PSR Scale Scores Across All 4 Groups of Affective Disorders*

Affective Symptom Severity Level	MDD/Mania†	Minor Depression/ Hypomania‡	*DSM-III* Depressive Conditions‡§	RDC Cyclothymic Personality‡
1. Asymptomatic: no depressive or manic spectrum symptoms whatsoever; return to usual self	1	1	1	1
2. Subsyndromal: depressive spectrum symptoms	1	1	2 or 3	2 or 3
below minor depression level or manic spectrum	1	2	...	...
symptoms below hypomania level	2	1 or 2	...	...
3. Affective symptoms at the minor depression or	1	3	...	...
hypomania level	2	3	...	...
	3	...	...	...
	4	...	...	...
4. Affective symptoms at the MDD or mania level	5	...	...	...
	6	...	...	...

*Weekly symptom severity level is assigned based on each week's ratings on all affective conditions regardless of whether the patient was in a Research Diagnostic Criteria (RDC) episode at that time. Rated affective conditions including RDC major depressive disorder (MDD), RDC minor or intermittent depression or dysthymia, RDC mania, RDC hypomania, RDC cyclothymic personality, and *DSM-III* atypical depression (code 296.82) and adjustment disorder with depressed mood (code 309.00). Weekly symptom severity levels are mutually exclusive. Read across the table for combinations of Psychiatric Status Rating Scale (PSR) values that result in classifying a particular week at a given symptom severity level. For example, a patient would be classified at the minor depression/dysthymia level for the week they were rated as PSR 3 or 4 on the 6-point major depression scale or PSR 3 on the 3-point minor depression/dysthymia scale with a PSR score of 1 or 2 on the 6-point major depression scale. Ellipses indicate any PSR value of this affective condition qualifies for the given symptom severity level, in conjunction with the values shown for other affective conditions. For example, a given week is classified at the MDD/mania level based on a PSR of 5 or 6 for MDD and/or mania, regardless of PSR values on any other affective condition(s).

†Six-point weekly PSR values: 1 = asymptomatic, returned to usual self; 2 = residual/mild affective symptoms; 3 = partial remission, moderate symptoms or impairment; 4 = marked/major symptoms or impairment; 5 = definite criteria without prominent psychotic symptoms or extreme impairment; 6 = definite criteria with prominent psychotic symptoms or extreme impairment.

‡Three-point weekly PSR values: 1 = asymptomatic, returned to usual self; 2 = probable criteria (mild symptoms); 3 = definite criteria (severe symptoms).

§Includes *DSM-III* atypical depression (code 296.82) and adjustment disorder with depressed mood (code 309.00).

threshold level of mania and/or MDE. Notably, the 5 CDS centers did not differ in the percentage of weeks patients with BP-I spent with some affective symptoms or asymptomatic ($F_{4,141} = 1.06$; $P = .38$).

As presented in **Table 3**, patients experienced 3 times more depressive symptoms (31.9% of total follow-up weeks) than manic symptoms (9.3% of weeks), and depressive symptoms were 5 times more frequent than cycling/mixed symptoms (5.9% of weeks). Subsyndromal and minor depressive/dysthymic symptoms were much more prevalent than MDE-level symptoms (22.9% vs 8.9% of weeks); subsyndromal manic and hypomanic symptoms were 3 times more common than symptoms at the threshold for mania (7.0% vs 2.3% of weeks). Overall, most of all symptomatic weeks involved subsyndromal, minor depressive, and hypomanic symptoms (74.0%). Only 12.3% of all follow-up weeks were spent with symptoms at the threshold for MDE or mania. During RDC-defined MDEs, patients with BP-I had symptoms at the full symptomatic threshold for only 32.6% of weeks; during RDC-defined manic episodes, they experienced the full manic symptom threshold for only 20.5% of weeks.

PERCENTAGE OF WEEKS WITH PSYCHOTIC SYMPTOMS

Patients with BP-I spent 2.3% of total follow-up weeks with psychotic symptoms—1.3% of weeks occurred during mania and 0.9% weeks during MDE. Throughout their entire course, approximately half of patients (47.3%) had some weeks with psychotic symptoms—26.0% had psychotic symptoms during MDEs and 28.1% during manic episodes.

CHANGES IN SYMPTOM STATUS

A change in symptom status was defined as any week-to-week change in symptom severity level and/or polarity. As presented in **Table 4**, patients experienced a mean (SD) of 74.3 (115.1) changes in symptom status during the entire follow-up, or 5.9 (7.6) times per year. Only 9.6% patients averaged 1 or fewer changes in affective symptom status per year. More than half of the sample (54.1%) changed affective symptom status more than 3 times per year, 34.9% more than 5 times per year, 11.6% more than 10 times per year, and 5.5% more than 20 times per year.

CHANGES IN AFFECTIVE SYMPTOM POLARITY

A substantial portion of the symptom status changes involved shifts in symptom polarity, that is, between some level of depression and some level of mania/hypomania. This occurred a mean (SD) of 47.2 (110.8) times during extended follow-up, or 3.5 (7.4) times per year. About 60% of patients changed polarity once per year or less, while 19.2% changed polarity an average of more than 5 times per year, 8.2% changed polarity more than 10 times per year, and 4.1% changed polarity more than 20 times per year.

PATIENT COMBINATIONS OF SYMPTOM STATUS CATEGORIES

Overall, 90% of patients spent 1 or more weeks during follow-up with depressive symptoms and 86.3% had 1 or more weeks with manic/hypomanic symptoms. Only

Table 3. Percentage of Follow-up Weeks Spent at Specific Affective Symptom Categories Defined by Symptom Polarity and Severity During Long-term Follow-up of 146 Patients With Bipolar I Disorder in the CDS*

Affective Symptom Severity Level	Percentage of Follow-up Weeks Spent at Each Level: Mean (SD)	Median (Range)
Weeks asymptomatic (no depression or mania/hypomania)	52.7 (34.0)	62 (0-99)
Weeks with pure depression (no mania/hypomania)	31.9 (29.9)	23 (0-99)
Pure subsyndromal depression	9.4 (14.7)	3 (0-82)
Pure minor depression/dysthymia threshold	13.5 (17.3)	7 (0-82)
Pure major depression threshold	8.9 (12.5)	5 (0-63)
Weeks with pure mania/hypomania (no depression)	9.3 (15.6)	2.5 (0-82)
Pure subsyndromal mania/hypomania	2.4 (6.8)	0 (0-38)
Pure hypomania threshold	4.6 (9.9)	1 (0-81)
Pure mania threshold	2.3 (4.0)	1 (0-37)
Weeks with cycling/mixed affective symptoms†	5.9 (14.2)	0 (0-94)

*Patients in National Institute of Mental Health Collaborative Depression Study (CDS) who, as of intake or any time during follow-up, have lifetime Research Diagnostic Criteria mania and depression but no schizophrenia or schizoaffective disorder, and who have at least 104 weeks (2 years) of weekly psychiatric status ratings with "very good," "good," or "fair" accuracy.

†Weeks with cycling/mixed affect reached levels of major depressive disorder or mania an average of 1.0% of follow-up weeks; levels of minor depressive disorder, dysthymia, or hypomania an average of 2.0% of follow-up weeks; and subsyndromal levels of depression or mania an average of 2.9% of follow-up weeks.

Table 4. Affective Symptom Severity Characteristics During Long-term Follow-up of 146 Patients With Bipolar I Disorder in the CDS*

No. of changes in symptom status per patient,† mean (SD); median [range]	
During all of follow-up	74.3 (115.1); 33.0 [2-273]
Per year	5.9 (7.6); 3.4 [0.2-49.3]
No. of changes in polarity per patient,‡ mean (SD); median [range]	
During all of follow-up	47.2 (110.8) 7.5 [0-752]
Per year	3.5 (7.4) 0.6 [0.0-48.7]
Patients, No. (%)	
≥1 wk asymptomatic	132 (90.4)
≥1 wk in depression spectrum	132 (90.4)
≥1 wk at all 3 depressive symptom levels	105 (79.5)
≥1 wk in manic spectrum	126 (86.3)
≥1 wk at all 3 manic symptom levels	61 (48.4)
≥1 wk cycling/mixed polarity	71 (48.6)

*Patients in National Institute of Mental Health Collaborative Depression Study (CDS) who, as of intake or any time during follow-up, have Research Diagnostic Criteria mania and depression but no schizophrenia or schizoaffective disorder, and who have at least 104 weeks (2 years) of weekly psychiatric status ratings with "very good," "good," or "fair" accuracy.

†Any week-to-week change in level of depressive and/or manic/hypomanic symptoms, or change from/to the asymptomatic status counts as +1. Weeks with symptoms of both depression and mania/hypomania add +1.

‡Change in polarity is defined as a change from some level of depression to some level of mania/hypomania or vice versa with or without intervening weeks at the asymptomatic status. Weeks with symptoms of both depression and mania/hypomania add +1 to the count.

approximately half (48.6%) had 1 or more weeks with cycling/mixed affective symptoms (Table 4). In addition, 35 patients (24.0%) spent 1 or more weeks during follow-up in all 7 possible symptom categories (ie, 3 levels of depressive symptom severity, 3 levels of manic/hypomanic severity, and the asymptomatic status). Another 41 patients (28.1%), during their course of illness, experienced 6 of the 7 symptom categories (and of these patients, 10% had no weeks asymptomatic); 27 (18.5%) spent 1 or more weeks at 5 symptom categories, 29 (19.9%) at 4 categories, 11 (7.5%) at 3 categories, and only 8 (2.1%) in 2 symptom categories. Of the 132 patients with 1 or more weeks symptomatic in the depressive spectrum, 105 (79.5%) experienced all 3 levels of depressive severity. Of the 126 patients with manic symptoms, 61 (48.4%) experienced all 3 levels of the manic symptom spectrum.

PREDICTORS OF CHRONICITY DURING FOLLOW-UP

Greater chronicity, defined in terms of a significantly higher percentage of follow-up weeks with symptoms at the full-syndromal MDE/mania level, as well as weeks with *any* level of affective symptom severity, was significantly associated with 4 predictors: poor social functioning in the 5 years prior to intake, a longer total duration of the intake episode, depressive-only or cycling/mixed (vs manic-only) polarity of the intake episode, and having an RDC diagnosis of drug-use disorder as of intake or during follow-up. Sex, age at intake, age of onset of first affective episode, total number of affective episodes, history of affective disorder in first-degree relatives, severity of intake episode, psychotic features of the intake episode, and RDC diagnosis of alcoholism were not significantly associated with increased chronicity (**Table 5**). Research Diagnostic Criteria–diagnosed anxiety disorders (generalized anxiety disorder, panic disorder, phobic disorder, and obsessive-compulsive disorder), considered individually as well as in the aggregate, also did not predict an overall more chronic course.

COMMENT

Previous reports[3-9,18] on the long-term picture of BP-I have largely focused on the course of MDE and manic episodes or have examined it from the perspective of patterns of successive epochs of illness, such as the "kindling" model.[18-20] These epoch-based analyses of major affective episodes have informed us about this illness. However, we had a different objective: to document the long-term symptomatic structure of this disorder based on summary (aggregate) measures of weekly affective symptom status. To the best of our knowledge, this is the first article describing the entire long-term weekly naturalistic course of BP-I in terms of the *full* range of affective symptoms. We believe that the measures examined here provide a more complete picture of the longitudinal structure of BP-I, which complements past approaches focusing only on major depressive/manic episodes, and provide valuable new information about the long-term course of this illness.

Table 5. Percentage of Follow-up Weeks Spent With Symptoms at the Disorder Threshold for MDD/Mania or Any Level of Affective Symptom Severity During Long-term Follow-up of 146 Patients With Bipolar I Disorder in the CDS by Various Predictors of Chronicity*

Predictor of Chronicity	% of Follow-up Weeks With Symptoms at MDD/Mania Threshold†	% of Follow-up Weeks With Any Level of Affective Symptoms†
Sex		
Male (n = 65)	12.1 (14.3)	42.9 (33.4)
Female (n = 81)	12.4 (14.2)	50.8 (34.2)
	$t_{144} = 0.10$; $P = .92$	$t_{144} = 1.41$; $P = .16$
Age at intake, y		
≤40 (n = 88)	11.9 (12.7)	45.2 (33.7)
>40 (n = 58)	12.8 (16.3)	50.4 (34.4)
	$t_{101.1}$† = 0.36; $P = .72$	$t_{144} = 0.91$; $P = .37$
Age at onset of first lifetime affective episode, y		
1-20 (n = 72)	13.9 (15.6)	48.6 (34.6)
21-40 (n = 63)	11.4 (13.3)	46.3 (34.2)
>40 (n = 11)	6.4 (6.2)	43.9 (30.8)
	$F_{2,143} = 1.56$; $P = .21$	$F_{2,143} = 0.13$; $P = .87$
Total No. of lifetime affective episodes (including intake episode)		
1-3 (n = 40)	9.4 (12.6)	39.3 (34.0)
4-10 (n = 61)	12.1 (13.5)	48.7 (32.9)
>10 (n = 45)	15.0 (16.1)	52.5 (34.8)
	$F_{2,143} = 1.65$; $P = .20$	$F_{2,143} = 1.70$; $P = .19$
Best level of social functioning in 5 y prior to intake		
Fair or better (n = 136)	11.3 (13.4)	45.9 (33.9)
Poor/very poor/grossly inadequate (n = 8)	28.9 (20.0)	74.4 (26.8)
	$t_{142} = 3.51$; $P < .001$	$t_{142} = 2.33$; $P = .02$
Any affective disorder Dx in first-degree relatives		
Yes (n = 47)	11.7 (12.1)	51.0 (33.3)
No (n = 15)	6.7 (8.8)	38.8 (33.4)
	$t_{60} = 1.46$; $P = .15$	$t_{60} = 1.23$; $P = .22$
Total duration of intake episode		
<6 mo (n = 50)	5.5 (6.8)	29.4 (30.4)
6 mo to <2 y (n = 60)	11.9 (12.3)	50.8 (29.8)
≥2 y (n = 35)	21.9 (18.7)	66.4 (34.2)
	$F_{2,142} = 16.93$; $P < .001$ (a<b<c)‡	$F_{2,142} = 15.22$; $P < .001$ (a<b<c)‡
Polarity of entire intake episode		
Depressive Dx only (n = 20)	14.8 (14.5)	46.9 (29.5)
Manic Dx only (n = 31)	5.2 (5.9)	30.0 (30.5)
Cycling/mixed (n = 94)	13.8 (15.3)	52.9 (34.5)
	$F_{2,142} = 5.07$; $P = .008$ (b<a,c)‡	$F_{2,142} = 5.56$; $P = .005$ (b<c)‡
Severity of intake episode (worst-week GAS score prior to intake)		
11-30 (n = 55)	13.8 (14.8)	46.3 (36.0)
31-40 (n = 65)	11.3 (14.9)	48.6 (34.1)
41-67 (n = 26)	11.5 (11.0)	46.1 (30.2)
	$F_{2,143} = 0.51$; $P = .60$	$F_{2,143} = 0.08$; $P = .92$
Psychotic features in intake episode (based on intake SADS)		
Yes (n = 78)	14.1 (16.7)	48.3 (35.0)
No (n = 68)	10.1 (10.4)	46.1 (33.0)
	$t_{131.0}$† = 1.78; $P = .08$	$t_{144} = 0.39$; $P = .70$
Comorbid substance abuse disorders		
Ever met RDC alcoholism Dx§		
Yes (n = 58)	14.3 (15.5)	46.8 (34.3)
No (n = 88)	10.9 (13.2)	47.6 (34.0)
	$t_{144} = 1.44$; $P = .15$	$t_{144} = 0.13$; $P = .90$
Ever met RDC drug-use disorder Dx§		
Yes (n = 29)	19.1 (16.7)	63.9 (34.0)
No (n = 117)	10.6 (13.0)	43.2 (32.8)
	$t_{144} = 2.99$; $P = .003$	$t_{144} = 3.02$; $P = .003$

*Data are given as mean (SD) patients unless otherwise indicated. Patients in National Institute of Mental Health Collaborative Depression Study (CDS) who, as of intake or any time during follow-up, have Research Diagnostic Criteria (RDC) mania and depression but no schizophrenia or schizoaffective disorder, and who have at least 104 weeks (2 years) of weekly psychiatric status ratings with "very good," "good," or "fair" accuracy, which were the basis for the analyses. MDD indicates major depressive disorder; Dx, diagnosis; GAS, Global Assessment Scale; and SADS, Schedule of Affective Disorders and Schizophrenia.

†Degrees of freedom adjusted for unequal group variances.

‡Significant differences based on post hoc group comparisons.

§Ever met diagnosis, at probable or definite level, as of intake or during follow-up.

While BP-I is less chronic than unipolar MDD, which did not support our a priori hypotheses of increased chronicity of BP-I, these patients were nonetheless symptomatically ill nearly half of their long-term follow-up. Although BP-I is traditionally described in terms of episodes of MDE and mania, we found that subthreshold, minor depressive/dysthymic, and hypomanic symptoms were the modal expressions of BP-I during its prospective

course. Symptoms in the depressive spectrum predominated substantially over manic (3:1) or cycling/mixed symptoms (5:1). We cannot, however, rule out the possibility that patients with more distressing depressive symptoms may be more likely to enter and remain in a long-term prospective study. Bipolar I is often regarded as a psychotic disorder, yet slightly more than half of the patients had no weeks with psychotic symptoms during the entire course of illness; psychotic symptoms occurred relatively more frequently during manic than MDD episodes. Patients experienced frequent changes in symptom status and polarity in a dynamically fluctuating course. The full range of subsyndromal, minor depressive/dysthymic, hypomanic, MDE, and manic symptoms were observed commonly within the same patients over time. In sum, these data strongly support the idea that the longitudinal course of BP-I is expressed as a dimensional spectrum involving the complete range of severity of depressive and manic symptoms. We therefore submit that longitudinal descriptions of the BP-I course that do not include all levels of affective symptom severity and polarity are incomplete.

The definitions of chronicity we have used in this article, namely, the percentage of all follow-up weeks spent at the highest level of affective symptom severity or with any affective symptoms, are new but provide a complementary perspective of the long-term course of BP-I. Other analyses of chronicity in BP-I have used a variety of definitions based on specific epochs of time,[4-8] such as time to recovery from the intake episode, time to first prospectively observed MDE or manic episode relapse, relapse to MDE/manic episode(s) within a specified period of time, occurrence of an MDE/manic episode during a particular follow-up interval,[5] or level of morbidity during a particular period. Only Turvey et al[8] analyzed predictors of the overall percentage of follow-up spent in major affective episodes. However, their analyses, as all other studies of the long-term course of BP-I, focused only on MDE and manic episodes rather than the more frequent periods of minor depression, dysthymia, or hypomania. To the best of our knowledge, our study is the first to characterize *all* of long-term follow-up based on the full range of syndromal and subsyndromal levels of affective symptom severity. Our approach presents a definitive picture of the overall chronic nature of BP-I compared with other definitions based only on selected follow-up intervals, which have produced inconsistent findings. We also found that 2 indices of past chronicity, namely, poor social functioning in the 5 years prior to intake and a longer intake episode, predicted significantly greater symptomatic chronicity during all of follow-up. To earlier findings that cycling in the intake episode predicted greater chronicity,[4,7] we now add that a purely depressive intake episode also predicts greater chronicity compared with purely manic intake episodes. Unlike Coryell et al,[5] who found that alcoholism predicted chronicity, defined as being in an MDE or manic episode during the 15 years of follow-up, we found that drug abuse but not alcoholism predicted greater chronicity of both MDE and manic symptoms, and these affective symptoms remain during long-term follow-up. Inconsistent findings in chronicity underscores the need for reliable and meaningful definitions of chronicity, such as the ones we have proposed.

Generalization to other samples of BP-I may be limited because the CDS cohort consisted of severely ill, tertiary care, white patients. We do not know the extent to which the history and intake status of our sample are representative of other patients with BP-I seeking treatment. Although interrater agreement for changes in episode status has been shown to be high, there may be some degree of error in assigning weekly symptom severity levels. We may have underestimated the time with subsyndromal symptoms and overestimated the asymptomatic time since PSR coding rules do not allow for subsyndromal symptoms to be coded following fully asymptomatic episode recovery until such time as symptoms again reach syndromal levels. Cycling/mixed expressions may have been relatively uncommon because a universally accepted definition of these forms did not exist when the Schedule of Affective Disorders and Schizophrenia instrument was developed in the late 1970s; thus, our analyses cannot shed light on the question of dysphoric mixed states using contemporary definitions. Nonetheless, the CDS is a unique database for the perspective symptomatic study of the long-term symptomatic structure of BP-I. Now that the Zurich Study[2,21] has closed, the CDS is the only available, ongoing prospective naturalistic follow-up study of a large cohort of patients with affective disorder of which we are aware.

Algorithms to summarize the dose intensity of mood stabilizers, antidepressants, and antipsychotic medications have been created and updated over the years to reflect new treatments that have become available since the study began in 1978.[22] However, the CDS is a naturalistic follow-up study of mood disorders, not a controlled treatment investigation. Meaningful analyses of the adequacy, intensity, and effect of antidepressant, antimanic, and antipsychotic medications on the various levels of affective symptom severity would be extremely complex and are beyond the scope of this article. The predominance of depressive over manic/hypomanic symptoms should not be interpreted as suggesting the need for more aggressive use of antidepressant medications in the absence of a mood stabilizer since there is some evidence that antidepressants may induce mania or cycle acceleration in some bipolar patients.[23]

Analyses of within-subject trends over time for particular subgroups of interest, such as patients with BP-I with various patterns of cycling or comorbid substance abuse, are also beyond the scope of our study. The focus of this article is on characterizing in the aggregate the overall long-term symptomatic status of BP-I based on the sample as a whole. The relatively large variation around the means of the long-term outcome measures we have presented suggests that these indices may be useful for identifying and characterizing clinically meaningful subgroups of patients with BP-I , which we intend to address in future manuscripts.

While these data support the idea that bipolar disorder is best characterized as a spectrum of affective symptom severity,[24] they do not imply a continuum between BP-I and BP-II, which may have rather distinct course patterns.[25,26] Nor can we comment on contemporary imaginative proposals to extend the bipolar spectrum to "softer"

expressions, such as pharmacologic hypomania, cyclothymic, and impulse-control disorders.[27-29] Our data more properly pertain to a dimensional continuum of bipolar symptom severity from subsyndromal to full-blown syndromal levels *within* the course of rigorously defined BP-I. Kraeplin,[1] who wondered why manic-depressive episodes erupted periodically, had suggested that someday the origin of the illness would be understood from relatively inconspicuous subsymptomatic foundations that persist between episodes. These data provide support for his conceptualization.

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