ORIGINAL ARTICLE

A Prospective Investigation of the Natural History of the Long-term Weekly Symptomatic Status of Bipolar II Disorder

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Background: This is the first prospective longitudinal study, to our knowledge, of the natural history of the weekly symptomatic status of bipolar II disorder (BP-II).

Methods: Weekly affective symptom status ratings for 86 patients with BP-II were based on interviews conducted at 6- or 12-month intervals during a mean of 13.4 years of prospective follow-up. Percentage of weeks at each symptom severity level and the number of shifts in symptom status and polarity were examined. Predictors of chronicity for BP-II were evaluated using new chronicity measures. Chronicity was also analyzed in relation to the percentage of follow-up weeks with different types of somatic treatment.

Results: Patients with BP-II were symptomatic 53.9% of all follow-up weeks: depressive symptoms (50.3% of weeks) dominated the course over hypomanic (1.3% of weeks) and cycling/mixed (2.3% of weeks) symptoms. Subsyndromal, minor depressive, and hypomanic symptoms combined were 3 times more common than major depressive symptoms. Longer intake episodes, a family history of affective disorders, and poor previous social functioning predicted greater chronicity. Prescribed somatic treatment did not correlate significantly with symptom chronicity. Patients with BP-II of brief (2-6 days) vs longer (≥7 days) hypomanias were not significantly different on any measure.

Conclusions: The longitudinal symptomatic course of BP-II is chronic and is dominated by depressive rather than hypomanic or cycling/mixed symptoms. Symptom severity fluctuates frequently within the same patient over time, involving primarily symptoms of minor and subsyndromal severity. Longitudinally, BP-II is expressed as a dimensional illness involving the full severity range of depressive and hypomanic symptoms. Hypomania of long or short duration in BP-II seems to be part of the same disease process.

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EWALD HECKER (1898)[1] was one of the first to describe what is now diagnosed as bipolar II disorder (BP-II),[2] emphasizing its chronic, fluctuating, ambulatory course characterized by depressions with occasional hypomanic periods. Later, Kraepelin[3] described hypomanic episodes in the course of manic-depressive illness, and Dunner et al[4] described a specific course pattern in which hypomanic episodes were interspersed with major depressive episodes (MDEs). Otherwise, descriptions of hypomania are sparse in the literature. They are largely based on cross-sectional studies and focus on duration,[5] seasonal occurrence,[6] depressive admixtures,[7,8] or polarity shifts in relation to antidepressant drug therapy.[9] A variety of descriptions characterizing BP-II have reported both commonalties and differences among BP-II, BP-I, and unipolar major depressive disorders (MDDs).[10-20] Previous studies on the course of BP-II have concentrated primarily on the prevalence and nature of syndromal MDEs and hypomanic episodes. We[21-25] already demonstrated that detailed analysis of the full range of affective symptom severity and polarity presents a more complete picture of the long-term symptomatic structure of mood disorders. We[21-25] found that unipolar disorders and bipolar disorders (BP-I) are both expressed, over time, as dimensional illnesses featuring the full range (spectrum) of affective symptom severity and polarity and that subsyndromal and syndromal affective symptoms fluctuate frequently within the same patient.

We report herein the weekly symptomatic analysis of a cohort of patients with BP-II followed prospectively, naturalistically, and systematically for up to 20 years in the National Institute of Mental Health Collaborative Depression Study (CDS).[26,27]

Table 1. Demographic and Clinical Characteristics of 86 CDS Patients With Bipolar II Disorder at Intake*

Age, mean ± SD (range), y	36.2 ± 13.4 (18-76)
Female, No. (%)	54 (62.8)
Education, No. (%)	
High school or less	40 (46.5)
College or more	46 (53.5)
Marital status, No. (%)	
Married/living together	40 (46.5)
Separated/divorced/widowed	22 (25.6)
Never married	24 (27.9)
Total No. of lifetime affective episodes (including intake episode), No. (%)	
1 (Intake episode)	4 (4.7)
2-3	17 (19.8)
4-10	31 (36.0)
>10	34 (39.5)
Age at onset of first lifetime affective episode, mean ± SD (range), y	20.9 ± 9.6 (1-64)
Early onset of first lifetime affective episode (age ≤20 y), No. (%)	51 (59.3)
Severity of intake episode (worst week prior to intake, Global Assessment of Severity score), mean ± SD (range)	36.6 ± 9.8 (5-61)
Inpatient status (intake), No. (%)	54 (62.8)
Polarity of affective episode before intake, No. (%)	
Depressive Dx only	48 (55.8)
Hypomania Dx only	0
Cycling/mixed Dx†	38 (44.2)
Polarity of entire intake episode, No. (%)	
Depressive Dx	34 (39.5)
Manic Dx only	0
Cycling/mixed Dx†	52 (60.5)
All follow-up weeks, mean ± SD (range)‡	
Weeks (median = 884)	745.8 ± 318.8 (104-1040)
Years (median = 17.0)	14.3 ± 6.1 (2-20)
Follow-up weeks with Psychiatric Status Rating scale scores of "fair" or better accuracy, mean ± SD (range)‡	
Weeks (median = 832)	694.2 ± 308.9 (104-1040)
Years (median = 16.0)	13.4 ± 5.9 (2-20)
Follow-up with Psychiatric Status Rating scale scores of "fair" or better accuracy, No. (%)‡	
15-20, y	53 (61.6)
10-<15, y	12 (14.0)
5-<10, y	5 (5.8)
2-<5, y	16 (18.6)

Abbreviations: CDS, Collaborative Depression Study; Dx, diagnosis.

*Patients in the National Institute of Mental Health CDS were included in the analyses if they had a history of Research Diagnostic Criteria (RDC) hypomania and depression (RDC major, minor, intermittent, or dysthymic depressive disorder) as of intake; no history of RDC mania, schizophrenia, or schizoaffective disorder as of intake or during follow-up; and at least 104 weeks (2 years) of weekly Psychiatric Status Rating scale scores with "very good," "good," or "fair" accuracy.

†Cycling/mixed diagnosis is based on the occurrence of hypomania plus depression (major, minor, or intermittent depression or dysthymia) in either cycling or mixed affective patterns during the intake episode.

‡Analyses are based on Longitudinal Interview Follow-up Evaluation (LIFE) and LIFE-II interviews conducted at 6-month intervals during the first 5 years of follow-up plus Streamlined Longitudinal Interval Continuation Evaluation interview covering 1-year intervals during years 6 to 20 of follow-up. Weekly affective symptoms status based on Catch-Up Form interview covering greater than 1-year gaps in patient contact during follow-up years 3 to 5 was excluded from the analyses and is part of the 6.1% of weeks with missing data. Gaps in patient contact requiring Catch-Up Form interviews occurred during the period before the CDS protocol was extended past 2 years of follow-up.

Two new measures of chronicity previously described in BP-I[25] were evaluated for BP-II: (1) the total percentage of follow-up weeks during which patients experienced the full syndromal level of major depression and (2) the total percentage of follow-up weeks during which patients experienced any affective symptoms, regardless of severity level.

Controversy exists about the duration of hypomanic episodes necessary for the diagnosis of BP-II. For example, the Research Diagnostic Criteria (RDC)[28] divides BP-II into definite vs probable categories based on the duration of hypomanic episodes (≥7 days is definite and 2-6 days is probable). The RDC and *DSM-IV*[2] duration criteria were not established empirically but rather by consensus. To develop data on this issue, the BP-II cohort was subdivided into patients with short (2-6 days) vs longer (≥7 days) hypomania, and these groups were compared on all variables.

METHODS

PATIENTS

The analysis sample of 86 patients with BP-II entered the CDS from 1978 through 1981, at 1 of 5 academic health centers ([1] Massachusetts General Hospital and Harvard Medical School, Boston; [2] Rush–Presbyterian–St Luke's Medical Center, Chicago, Ill; [3] University of Iowa College of Medicine, Iowa City; [4] New York State Psychiatric Institute and Columbia University, New York; and [5] Washington University School of Medicine, St Louis, Mo) during an affective episode.[26,27] Patients had experienced MDEs and hypomanic episodes as of intake without any evidence, at intake or during follow-up, of mania, schizophrenia, or schizoaffective disorder. The diagnosis of BP-II was based on the *Schedule for Affective Disorders and Schizophrenia*[29] using the RDC.[28] Of 86 patients, 69 were RDC BP-II, definite (hypomania for ≥7 days), and 17 were RDC BP-II, probable (hypomania for 2-6 days) disorder. Patients were white (this was a criterion because genetic hypotheses were being tested), spoke English, had an IQ score of at least 70, and had no evidence of an organic mental disorder or terminal medical illness. All patients gave informed consent at the 5 academic sites at which the follow-up data were gathered. Demographic and clinical characteristics of the analysis sample are summarized in **Table 1**.

FOLLOW-UP PROCEDURES

Trained raters interviewed patients every 6 months for the first 5 years of follow-up, and yearly thereafter (ongoing), using variations of the Longitudinal Interval Follow-up Evaluation (LIFE).[30] 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, research, or other records, and all information was integrated into a weekly symptom severity rating for each affective and nonaffective psychiatric disorder. Weekly symptom ratings were made using LIFE Psychiatric Status Rating (PSR) scales, which are anchored to diagnostic thresholds for RDC mood disorders. The CDS raters regularly undergo rigorous training and monitoring, 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).[30]

The trained interviewers systematically rated the accuracy of the PSR data obtained from each interview by using a 5-point Likert scale. The overall rating was based on the quality of the patient's recall, the internal consistency of information provided, and any evidence of denial or distortion due to illness status. If a patient is severely depressed or psychotic at the scheduled time of follow-up, the interview is generally rescheduled. Of the 1503 rating forms available for the analysis sample, 22.7% were rated "excellent," 58.8% "good," 17.5% "fair," 0.7% "poor," and 0.3% "very poor" in terms of accuracy of the weekly PSR information. There was no significant difference between accuracy ratings for interviews conducted at 6-month intervals (46.4% of forms) vs 1-year intervals (54.6% of forms) (Wilcoxon rank sum test $Z=0.30$; $P=.77$). Specific follow-up weeks were excluded from the analyses because of poor or very poor accuracy ratings (1.0% of weeks) or missing data (6.1% of weeks). Owing to frequent changes in symptom status, it was considered inappropriate to impute illness status during periods of inaccurate or missing data.

The potential analysis sample consisted of 89 patients with BP-II who were followed for up to 20 years. Because the present study focused on long-term course, 1 patient (1.1%) with less than 2 years of weekly PSR data with fair or better accuracy was eliminated from the analyses. In addition, to make the sample consistent with the *DSM-IV* definition of BP-II,[2] 2 patients (2.2%) who had never experienced a full MDE were also omitted, leaving 86 patients with BP-II in the final analysis sample.

CLASSIFICATION OF WEEKLY SYMPTOM STATUS (SEVERITY AND POLARITY)

Methods[33] reported previously were used to assign each weekly affective symptom severity level. Levels were based on the 6-point PSR scale for major depression plus the 3-point PSR scale for rating minor depression/dysthymia, hypomania, *DSM-III* atypical depression, *DSM-III* adjustment disorder with depressed mood, and RDC cyclothymic personality. Affective symptom severity levels are anchored to the diagnostic thresholds for all affective conditions, including MDE, minor depressive/dysthymic disorder, and hypomania, but weekly levels were assigned regardless of whether the patient was in an RDC-defined episode. Affective symptoms below the thresholds of these RDC disorders were classified as subsyndromal depression or subsyndromal hypomania. Weeks with no affective symptoms were classified as asymptomatic. Weeks with affective symptoms were then categorized into levels of pure depression (no hypomania) or pure hypomania (no depression) or a combination of hypomanic and depressive symptoms (cycling/mixed affective symptoms). Weeks with prominent psychotic symptoms were counted based on a PSR score of 6 on the 6-point PSR scale for MDE.

CLASSIFICATION OF WEEKLY SOMATIC TREATMENT

The CDS is designed as a naturalistic follow-up study; somatic treatments were prescribed naturalistically at each of the 5 academic data collection sites. The CDS is not an experimentally controlled treatment study, although weekly treatments received were recorded systematically by the interviewers. For analysis, weekly treatments received were assigned to 3 categories: antidepressants (eg, imipramine hydrochloride, monoamine oxidase inhibitors, fluoxetine hydrochloride, sertraline hydrochloride, bupropion hydrochloride, and electroconvulsive therapy), mood stabilizers (eg, lithium carbonate, carbamazepine, Depakote [Abbott Laboratories Inc, Abbott Park, Ill], and electroconvulsive therapy), and antipsychotics (typical and atypical).

STATISTICAL ANALYSES

Follow-up weeks spent at 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. Course chronicity was defined in 2 ways: (1) the total percentage of follow-up weeks spent with symptoms at the full syndromal MDE level and (2) the total percentage of follow-up weeks spent with any affective symptoms (any level other than the asymptomatic status). In addition, the percentages of follow-up weeks with symptoms in the depressive spectrum only, the manic spectrum only, or both the depressive and the manic spectrum were computed. These percentages were also correlated with percentages of follow-up weeks during which patients were prescribed *any* somatic treatment (antidepressant, mood stabilizer, or antipsychotic agents), a combination of some antidepressant and some mood stabilizer, some antidepressant without any mood stabilizer, or some mood stabilizer without any antidepressant.

The analysis sample was subdivided into patients with BP-II and hypomania of short (2-6 days) vs longer (≥7 days) duration who were compared on all measures evaluated in this investigation. Subgroups of patients with BP-II were also analyzed based on potential predictors of chronicity previously identified in the BP-I and BP-II literature: age,[31] age at onset of the first lifetime affective episode,[31] number of lifetime affective episodes,[32] poor social functioning in the 5 years before intake,[33] family history of affective disorder,[32] alcoholism,[33] and the duration,[34] polarity,[34,35] and presence of psychotic features in the intake episode.[30] Although not previously identified as robust predictors of chronicity in BP-II, we also examined sex, severity of the intake episode, comorbid drug use disorders, and comorbid anxiety disorders. Group comparisons were made, as appropriate, using analysis of variance, χ^2 tests, Fisher exact tests, or Wilcoxon rank sum tests. A 2-tailed α level of $P=.05$ was used to define statistical significance. Where appropriate, data are given as mean±SD.

RESULTS

SYMPTOM STATUS DURING THE COURSE OF ILLNESS

Patients were symptomatically ill during more than half of the follow-up weeks (53.9%±32.9%; median, 56.0%) and asymptomatic the remainder of follow-up (46.1%±32.9%; median, 44.0%). Weeks when patients were symptomatic included 15.7%±16.8% (median, 9.0%) of weeks with subsyndromal affective symptoms beneath the threshold of hypomania or minor depression, 25.2%±22.4% (median, 20.5%) of weeks with minor depression/dysthymia or hypomanic symptoms, and 13.0%±16.4% (median, 7.5%) of weeks at the syndromal threshold of MDE. The 5 CDS academic health centers did not differ significantly in the mean percentage of weeks patients with BP-II spent with affective symptoms or in the asymptomatic state ($F_{4,81}=2.21$; $P=.08$), although patients in New York, NY, and St Louis, Mo, tended to be symptomatic during fewer follow-up weeks (38.7%±26.4% and 39.8%±29.1%, respectively) than patients in Boston, Mass (60.0%±32.6%), Iowa City, Iowa (57.1%±38.7%), or Chicago, Ill (64.4%±29.3%).

Table 2. Follow-up Weeks Spent at Specific Affective Symptom Severity Levels Divided by Polarity During Long-term Follow-up of 86 CDS Patients With Bipolar II Disorder*

Severity Level	Follow-up Weeks, %†		
	Mean ± SD	Median	Range
Asymptomatic (no depression or hypomania)	46.1 ± 32.9	44.0	0-100
Pure depression (no hypomania)	50.3 ± 32.3	51.0	0-100
Pure subsyndromal depression	13.9 ± 15.5	8.0	0-77
Pure minor depression/ dysthymia threshold	23.5 ± 22.4	19.0	0-94
Pure major depression threshold	12.9 ± 16.4	7.5	0-85
Pure hypomania (no depression)	1.3 ± 4.3	0	0-29
Pure subsyndromal hypomania	0.4 ± 1.4	0	0-9
Pure hypomania threshold	0.9 ± 3.1	0	0-20
Cycling/mixed affective symptoms‡	2.3 ± 7.4	0	0-62

Abbreviation: CDS, Collaborative Depression Study.

*Patients in the National Institute of Mental Health CDS were included in the analyses if they had a history of Research Diagnostic Criteria (RDC) hypomania and depression (RDC major, minor, intermittent, or dysthymic depressive disorder) as of intake; no history of RDC mania, schizophrenia, or schizoaffective disorder as of intake or during follow-up; and at least 104 weeks (2 years) of weekly Psychiatric Status Rating scale scores with "very good," "good," or "fair" accuracy.

†Analyses are based on Longitudinal Interview Follow-up Evaluation and LIFE-II interviews conducted at 6-month intervals during the first 5 years of follow-up plus Streamlined Longitudinal Interval continuation Evaluation interviews covering 1-year intervals during years 6 to 20 of follow-up. Weekly affective symptom status based on Catch-Up Form interviews covering greater than 1-year gaps in patient contact during follow-up years 3 to 5 was excluded from the analyses and is part of the 6.1% of weeks with missing data. Gaps in patient contact requiring Catch-Up Form interviews occurred during the period before the CDS protocol was extended past 2 years of follow-up.

‡Weeks with cycling/missed affect reached levels of major depressive disorder an average of 0.1% of follow-up weeks; minor depressive disorder, dysthymia, or hypomania an average of 0.8% of follow-up weeks; and subsyndromal levels of depression or hypomania an average of 1.4% of follow-up weeks.

Table 3. Characteristics of Affective Symptom Status and Polarity During Long-term Follow-up of 86 CDS Patients With Bipolar II Disorder*

Characteristic	Value
Per patient No. of changes in symptom status, mean ± SD (median) [range]†	
During all of follow-up	42.5 ± 41.0 (34.5) [1-266]
Per year	3.8 ± 4.6 (2.6) [0.2-36.5]
Per patient No. of changes in polarity, mean ± SD (median) [range]‡	
During all of follow-up	13.1 ± 28.6 (2.0) [0-197]
Per year	1.3 ± 3.9 (0.2) [0-32]
No. (%) of patients with	
≥1 wk asymptomatic	76 (88.4)
≥1 wk in depression spectrum (major, minor, or subsyndromal)	85 (98.8)
≥1 wk at all 3 depressive symptom levels	69 (80.2)
≥1 wk in manic spectrum (hypomania or subsyndromal hypomania)	39 (45.3)
≥1 wk at both hypomanic symptom levels	19 (22.1)
≥1 wk of cycling/mixed polarity	27 (31.4)

Abbreviation: CDS, Collaborative Depression Study.

*Patients in the National Institute of Mental Health CDS were included in the analyses if they had a history of Research Diagnostic Criteria (RDC) hypomania and depression (RDC major, minor, intermittent, or dysthymic depressive disorder) as of intake; no history of RDC mania, schizophrenia, or schizoaffective disorder as of intake or during follow-up; and at least 104 weeks (2 years) of weekly Psychiatric Status Ratings with "very good," "good," or "fair" accuracy.

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

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

Patients experienced approximately 39 times more depressive symptoms (50.3% of all follow-up weeks) than hypomanic symptoms (1.3% of all follow-up weeks), and depressive symptoms were 22 times more frequent than cycling/mixed symptoms (2.3% of all follow-up weeks) (**Table 2**). Subsyndromal, minor depressive/dysthymic, and hypomanic symptoms (combined) were 3 times more prevalent (40.9% of all follow-up weeks) than full MDE-level symptoms (13.0% of all follow-up weeks). Patients with BP-II spent only 0.9% of all follow-up weeks with psychotic symptoms during MDEs.

CHANGES IN SYMPTOM STATUS

A change in symptom status was defined as any week-to-week change in symptom severity level or polarity. Patients experienced 42.5±41.0 changes in symptom status during follow-up, or 3.8±4.6 changes per year (**Table 3**). Only 19.8% of patients averaged 1 or fewer changes in affective symptom status per year. Most of the sample (62.8%) changed status more than 2 times per year; 24.4% changed status more than 5 times per year.

SHIFTS IN AFFECTIVE SYMPTOM POLARITY

Some of the symptom status changes involved shifts in symptom polarity, that is, between some level of depression and some level of hypomania. This occurred 13.1±28.6 times during extended follow-up, or 1.3±3.9 times per year. Three fourths of all patients (74.4%; n=64) shifted polarity an average of once a year or less. A relatively small percentage of patients (5.8%; n=5) averaged more than 5 polarity changes per year during follow-up.

PATIENT COMBINATIONS OF AFFECTIVE SYMPTOM STATUS CATEGORIES

Eighty-five patients (98.8%) spent 1 or more weeks with depressive symptoms, and 39 (45.3%) had some weeks with manic spectrum symptoms during follow-up (Table 3). Less than one third of the patients (31.4%; n=27) had 1 week with cycling/mixed affective symptoms. In addition, 69 patients (80.2%) spent weeks during follow-up in 4 or more of the 6 separate symptom status categories (ie, 3 levels of depressive symptom severity, 2 levels of hypomanic severity, and the asymptomatic status).

Table 4. Follow-up Weeks Spent With Symptoms at the Threshold for MDD or Any Level of Affective Symptoms During the Long-term Follow-up of 86 CDS Patients With Bipolar II Disorder by Various Predictors of Chronicity*

Predictor of Chronicity	Follow-up Weeks With Symptoms at MDD Threshold: Percentage, Mean ± SD	*t*	*df*	*P* Value	Follow-up Weeks With Any Level of Affective Symptoms: Percentage, Mean ± SD	*t*	*df*	*P* Value
Sex								
M (n = 32)	13.3 ± 16.4	0.11	84	.91	57.0 ± 34.1	0.68	84	.50
F (n = 54)	12.9 ± 16.5				54.5 ± 32.4			
Age at intake, y								
≤40 (n = 58)	13.9 ± 17.0	0.71	84	.48	53.1 ± 33.2	0.32	84	.75
>40 (n = 28)	11.2 ± 15.2				55.5 ± 33.0			
Age at onset of first lifetime affective episode, y								
1-20 (n = 51)	13.8 ± 16.8	0.15†	2, 83	.86	59.7 ± 32.6	2.04†	2, 83	.14
21-40 (n = 32)	11.9 ± 16.3				44.8 ± 32.6			
>40 (n = 3)	11.3 ± 11.5				52.3 ± 30.0			
Lifetime affective episodes (including intake episode), total No.								
1-3 (n = 21)	10.8 ± 15.0	0.65†	2, 83	.52	49.0 ± 29.4	1.17†	2, 83	.32
4-10 (n = 31)	11.9 ± 13.0				50.0 ± 32.0			
>10 (n = 34)	15.5 ± 19.7				60.6 ± 35.5			
Best level of social functioning in the 5 y before intake								
Fair or better (n = 76)	11.6 ± 15.6	2.22	84	.03§	52.7 ± 31.9	0.93	84	.36
Poor/very poor/grossly inadequate (n = 10)	23.6 ± 19.0				63.0 ± 40.5			
Any affective disorder Dx in first-degree relatives‡								
Yes (n = 46)	14.0 ± 15.1	2.62	45.8§	.01§	58.1 ± 30.5	2.43	56	.02§
No (n = 12)	6.6 ± 6.1				34.4 ± 28.1			
Total duration of intake episode								
<6 mo (n = 11)	5.4 ± 6.1	4.18†	2, 83	.02§	41.8 ± 34.2	6.13†	2, 83	.003§
6 mo to <2 y (n = 30)	9.0 ± 9.5				41.5 ± 30.2			
≥2 y (n = 45)	17.6 ± 20.1				65.1 ± 30.9			
Polarity of entire intake episode								
Depressive Dx only (n = 34)	12.6 ± 15.9	0.17	84	.85	51.1 ± 35.4	0.72	84	.72
Cycling/mixed (n = 52)	13.3 ± 16.8				55.8 ± 31.4			
Severity of intake episode (worst week Global Assessment of Severity score before intake)								
11-30 (n = 12)	14.9 ± 23.2	0.09†	2, 83	.91	54.0 ± 33.4	0.29†	2, 83	.75
31-40 (n = 50)	12.7 ± 15.1				55.9 ± 33.2			
41-67 (n = 24)	12.7 ± 15.7				49.7 ± 13.2			
Psychotic features intake episode (based on intake SADS)								
Yes (n = 20)	15.2 (17.6)	0.69	84	.49	56.4 (38.3)	0.39	84	.70
No (n = 66)	12.3 (16.0)				53.1 (31.4)			
Comorbid substance use disorders								
Ever met RDC alcoholism Dx§								
Yes (n = 33)	10.1 ± 12.6	1.43	83.1‖	.16	49.5 ± 29.8	0.98	84	.33
No (n = 53)	14.8 ± 18.2				56.6 ± 34.7			
Ever met RDC drug use disorder Dx¶								
Yes (n = 15)	9.9 ± 8.8	1.21	41.3‖	.23	56.4 ± 25.3	0.32	84	.75
No (n = 71)	13.7 ± 17.5				53.4 ± 34.4			

Abbreviations: CDS, Collaborative Depression Study; Dx, diagnosis; MDD, major depressive disorder; RDC, Research Diagnostic Criteria; SADS, Schedule of Affective Disorders and Schizophrenia.

*Patients in the National Institute of Mental Health CDS were included in the analyses if they had a history of RDC hypomania and depression (RDC major, minor, intermittent, or dysthymic depressive disorder) as of intake; no history of RDC mania, schizophrenia, or schizoaffective disorder as of intake or during follow-up; and at least 104 weeks (2 years) of weekly Psychiatric Status Rating scale scores with "very good," "good," or "fair" accuracy.

†F test.

‡Data not available for 28 patients.

§Statistically significant value.

‖Adjusted for unequal group variances.

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

PREDICTORS OF CHRONICITY DURING FOLLOW-UP

Chronicity was defined by the 2 new measures: the total percentage of follow-up weeks with symptoms at the full syndromal MDE level and the total percentage of follow-up weeks with any level of affective symptoms (**Table 4**).[25] Of the 12 predictors of chronicity previously reported for BP-II, only 3 were significantly associated with increased chronicity based on one or both of the new measures: longer duration of the intake episodes, a history of affective disorder in first-degree relatives, and poor or very poor social functioning in the 5 years before intake. Variables not predicting significantly greater chronicity by either measure were sex, age, age at onset of first lifetime affective episode, total num-

Table 5. Follow-up Weeks With Different Types of Prescribed Somatic Treatment Received Correlated With Follow-up Weeks With Different Types of Affective Symptoms During Long-term Follow-up of 86 CDS Patients With Bipolar II Disorder*

Type of Somatic Treatment Received†	Follow-up Weeks With Each Type of Somatic Treatment, Mean ± SD (Median), %	% of Follow-up Weeks With: Any Affective Symptoms		Depressive Symptoms (Major, Minor, or Subsyndromal) With No Hypomania		Hypomanic Symptoms (Hypomania or Syndromal Hypomania) With No Depression		Cycling/Mixed Symptoms (Symptoms in Depressive and Manic Spectrum)	
		Pearson *r*	*P* Value	Pearson *r*	*P* Value	Pearson *r*	*P* Value	Pearson *r*	*P* Value
Any somatic treatment	48.5 ± 39.7 (35.3)	0.178	.10	0.147	.18	0.048	.66	0.121	.27
Antidepressant plus mood stabilizer	21.6 ± 32.2 (2.8)	0.028	.80	0.002	.99	0.170	.12	0.015	.89
Antidepressant without mood stabilizer	26.0 ± 30.9 (13.0)	0.200	.07	0.182	.09	−0.111	.31	0.145	.18
Mood stabilizer without antidepressant	0.9 ± 3.3 (0.0)	0.034	.76	0.049	.66	−0.033	.76	−0.041	.71

Abbreviation: CDS, Collaborative Depression Study.

*Patients in the National Institute of Mental Health CDS were included in the analyses if they had a history of Research Diagnostic Criteria (RDC) hypomania and depression (RDC major, minor, intermittent, or dysthymic depressive disorder) as of intake; no history of RDC mania, schizophrenia, or schizoaffective disorder as of intake or during follow-up; and at least 104 weeks (2 years) of weekly Psychiatric Status Rating scale scores with "very good," "good," or "fair" accuracy.

†For more information, see the "Classification of Weekly Somatic Treatment" subsection in the text.

ber of lifetime affective episodes, severity and polarity of the intake episode, psychotic features in the intake episode, comorbid alcoholism, substance use disorders, and comorbid anxiety disorders.

RELATIONSHIP OF SOMATIC TREATMENT TO CHRONICITY OF AFFECTIVE SYMPTOMS

These patients with BP-II received some form of somatic treatment (antidepressants, mood stabilizers, or antipsychotic medications) during slightly less than half of their long-term follow-up (48.5%±39.7%) (**Table 5**). They received treatment 53.5%±38.3% of all weeks when they were symptomatic and 42.4%±42.5% of all weeks when they were asymptomatic. Follow-up weeks when antidepressants were prescribed without mood stabilizers (26.0%±30.9% of follow-up weeks) slightly exceeded weeks when antidepressants together with mood stabilizers were received (21.6%±32.2% of follow-up weeks). Mood stabilizers without antidepressants were only received during 0.9%±3.3% of follow-up weeks for this BP-II sample. There were low, nonsignificant correlations between the percentage of follow-up weeks that somatic treatments were received and the percentage of follow-up weeks with any affective symptoms or with depressive symptoms only, hypomanic symptoms only, or symptoms of cycling/mixed polarity (Table 5).

COMPARISON OF PATIENTS WITH HYPOMANIC EPISODES OF SHORT VS LONG DURATION

Patients with BP-II and short (n=17) vs longer (n=69) hypomanic episodes were compared on the 33 measures evaluated in this study (the measures are given in Tables 1-4). Of these, only 1 measure was significantly different. Hypomania of longer duration (≥7 days) was associated with more weeks with minor depressive symptoms (25.9%±23.8%) compared with hypomania of short duration (2-6 days) (16.6%±13.6%) ($t_{43.6}$=2.14, adjusted for unequal group variances; P=.04), a difference that could be attributable to chance alone given the number of variables on which the 2 groups were compared. There were no other significant differences on measures involving demographic characteristics, age at onset, clinical presentation or severity of the intake episode, previous clinical history, comorbidity with anxiety or substance use disorders, family history of affective disorder, polarity shifts, or other patterns of affective symptom severity during long-term follow-up.

COMMENT

To our knowledge, this is the first prospective study describing the long-term natural history of the symptomatic course of BP-II in terms of the full range of severity of affective symptoms. Evaluation of the weekly symptom status complements past approaches of epoch-based analyses focusing primarily on syndromal MDE and hypomanic episodes.[37-40] The present analyses give the most detailed picture to date of the entire longitudinal symptomatic structure of BP-II based on summary (aggregate) measures of weekly symptom status when patients are in and out of RDC affective episodes.

During mean follow-up of 13.4 years, the symptomatic course of BP-II fluctuates relatively frequently within the same patient. Thus, BP-II, like BP-I[25] and unipolar[21] disorders, presents longitudinally as a dimensional illness. The modal symptomatic expression is dominated by depressive rather than hypomanic or cycling/mixed symptoms. Symptom severity is principally in the minor and subsyndromal range rather than at the full syndromal level of major depression. Without the weekly symptomatic analysis, it would not have been possible to characterize BP-II as primarily a depressive disorder of subsyndromal to moderate severity whose course is punctuated by occasional MDEs and relatively infrequent weeks of hypomanic or cycling/mixed symptoms.

Using the total percentage of weeks symptomatic during the entire course as a measure of chronicity depicted a chronic picture of BP-II. This BP-II cohort, with a total of 54% of follow-up weeks symptomatic, falls between those with BP-I and those with unipolar MDD (47% and 60%, respectively),[21,25] which suggests a continuum of chronicity among the affective disorders. Previous studies[31,36,40] of course chronicity of affective disorder have generally focused on recurrence, number, severity, and characteristics of syndromal episodes, but, as shown in this and a previous study,[25] the exclusive focus on syndromal episodes, although essential, does not delineate the full picture of bipolar course and chronicity. For example, Coryell et al[36] reported a high level of chronicity of major depressive and hypomanic episodes in BPs; to these observations we add high overall *symptomatic* chronicity for BP-I[25] and BP-II (the present study) during long-term follow-up. Intake episodes of 2 years' duration or longer, family history of affective disorder, and poor previous social functioning predicted significantly greater chronicity in BP-II based on the total percentage of weeks with any affective symptoms or symptoms at the MDE threshold. Comorbid anxiety disorders, comorbid alcoholism and substance use disorders, and the other previously identified predictors were not significantly associated with increased chronicity using the new measures. The failure to replicate earlier predictors of chronicity may be due to using a new and complementary approach to defining chronicity. The CDS is the only prospective, long-term study of the course of affective disorders that is available today; it has been our experience that data from the CDS may not always replicate findings from studies based on retrospective clinical observations, cross-sectional analyses, or short-term prospective observations. In another CDS study,[41] more lifetime substance abuse and anxiety disorder was found in patients with BP-II than in those with BP-I. What we report herein is that these comorbidities did not predict the tendency toward chronicity in BP-II, suggesting that the chronicity identified in these analyses is largely due to the BP-II disease process itself rather than the associated comorbid conditions.

Patients with BP-II had substantially fewer changes in weekly symptom status (mean, 3.8 times per year) than was reported for patients with BP-I (mean, 5.9 times per year)[25] but more changes than were found for patients with unipolar MDD (mean, 1.8 times per year).[21] The symptomatic course of BP-II fluctuates frequently over time within the same patient. This means that longitudinally BP-II is expressed symptomatically as a dimensional illness involving the full range of symptom severity of depression and hypomania. These findings indicate that if any level of BP-II symptoms is present, the disease process continues to be active.

To our knowledge, there are no other recent prospective studies of BP-II based on symptom status. However, in a cross-sectional study, Benazzi and Akiskal[42] reported that hypomanic admixtures occurred during up to 46.3% of MDEs; this is somewhat higher but still within the same range as the finding reported herein that 31.4% of patients with BP-II experienced 1 or more weeks with cycling/mixed affective states during long-term follow-up. Baldessarini et al[43] reported a rate of 30.3% for full-blown rapid cycling in BP-II, but we have not directly addressed this in the present analyses. Benazzi[44] found that residual depressive symptoms occurred in 43.3% of patients with BP-II; in support of this finding, we found that the most frequent symptom status for patients with BP-II was subsyndromal and minor affective symptoms, accounting for 40.9% of all follow-up weeks. All these studies, including the present study, converge in identifying a strong tendency for BP-II to have a fluctuating and very chronic course.[42,45,46] Cyclothymic temperament may underlie such a course,[20] including rapid cycling tendencies.[43]

There has been uncertainty about the duration of hypomanic episodes necessary for a diagnosis of BP-II, especially the clinical significance of short (2- to 3-day) hypomania. The RDC requires at least a 7-day duration of hypomania for the diagnosis of BP-II, definite, and a 2- to 6-day duration for BP-II, probable, which overlaps the *DSM-IV* requirement of 4 or more days of hypomania. The duration criteria for hypomania in the RDC and *DSM-IV* were derived by consensus, not by empirical data. Only 1 of the 33 measures compared for patients with BP-II divided by short vs longer hypomania reached significance, which could be due to chance alone. This finding supports the proposition that hypomania of 2 to 6 days' duration, frequently observed in patients with BP-II, seems to be part of the same disease process as hypomania of longer duration. These data are consistent with the idea that more liberal diagnoses of BP-II, to include hypomania with durations as short as 2 days, are appropriate.[47,48] This has major implications for revision of the *DSM-IV*.

The CDS is a natural history study of the longitudinal course of BP-II and other affective disorders. The CDS is not an experimentally controlled treatment investigation. Treatments received at each of the 5 academic sites were prescribed naturalistically and were recorded systematically. This perspective should be kept in mind in interpreting the somatic treatment data reported in this study. We generally found low, nonsignificant correlations between the percentage of follow-up weeks when patients with BP-II were receiving somatic treatments and the percentage of follow-up weeks when they had affective symptoms. The fact that symptomatic chronicity occurred even in the context of relatively more (rather than less) medication therapy leads us to conclude that we are describing the true naturalistic expression of BP-II as it unfolds across the life cycle.

The CDS patients were enrolled at academic health centers; therefore, generalization to other samples of BP-II may be limited. Nonetheless, the demographic and clinical characteristics of this cohort closely resemble those of cohorts in other studies involving patients with BP-II. Although interrater agreement for levels of affective symptom severity was excellent, it is possible that in a naturalistic follow-up study of up to 20 years' duration there may be some degree of error in assigning weekly symptom severity levels. It is well-known that patients with BP-II, especially when interviewed during a depressive state, tend not to recall periods of hypomania.[47] Repeated prospective evaluation at frequent intervals, such

Study Investigators

The National Institute of Mental Health Collaborative Program on the Psychobiology of Depression–Clinical Studies was conducted with the participation of the following investigators: Dr Keller (co-chairperson, Providence, RI); Dr Coryell (co-chairperson, Iowa City); T. I. Mueller, MD (Providence); J. Fawcett, MD, W. A. Scheftner, MD (Chicago); J. Haley (Iowa City); J. Loth, MSW (New York); and J. Rice, PhD, T. Reich, MD (St Louis). Other contributors include N. C. Andreasen, MD, PhD; P. J. Clayton, MD; J. Croughan, MD; R. M. A. Hirschfeld, MD; M. M. Katz, PhD; P. W. Lavori, PhD; M. T. Shea, PhD; R. L. Spitzer, MD; M. A. Young, PhD (deceased); G. L. Klerman, MD; E. Robins, MD; R. W. Shapiro, MD; and G. Winokur, MD.

as that used by the CDS, is the best—although not a foolproof—method for identifying hypomanic periods. Given the nature of this illness, however, it is likely that the percentage of time patients with BP-II spend with hypomanic and subsyndromal hypomanic symptoms was underestimated. If a patient was severely depressed at the time of a scheduled interview, it was generally rescheduled for a time when the patient's symptomatic state would be less distorting and distracting. Thus, a systematic procedure was used to reduce the potential impact of distorted recall during depressive phases. It is reassuring that the overall ICC for changes in affective symptoms was 0.92, for identifying episode recovery was 0.95, and for subsequent symptom onset was 0.88.[30] Weeks with subsyndromal affective symptoms may also have been underestimated and the time asymptomatic overestimated because PSR coding rules do not allow for subsyndromal symptoms to be coded after fully asymptomatic episode recovery until such time as symptoms again reach syndromal levels. Subsyndromal affective symptoms in patients with mood disorder are common; as a result, we proposed that when any affective symptoms are present in patients with mood disorder, the disorder continues to be active. In support of this proposition, we reported significant risk of early episode relapse[22,23] and increased psychosocial impairment[24] associated with subsyndromal depressive symptoms in patients with unipolar MDD. Our picture of the long-term symptomatic structure of BP-II needs to be considered in light of the possibility that patients with the most severely depressive course were disproportionately retained in the study. On the other hand, it is also possible that missing data (6.1% of all follow-up weeks) is heavily weighted toward times when patients were more severely ill. These 2 factors may counterbalance each other in terms of producing an accurate estimate of the percentage of time patients with BP-II spend with symptoms at the full MDE level.

In conclusion, longitudinally, BP-II is a chronic affective disorder expressed within each patient as a fluctuating dimensional symptomatic continuum, which includes the full severity range of depressive and hypomanic symptoms, but dominated primarily by minor and subsyndromal depression. Thus, the long-term symptomatic structure of BP-II, like that of BP-I[25] and unipolar MDD,[21] is expressed as a dimensional illness. To rephrase it within the framework of Kraepelin,[3] this study of BP-II prospectively documents the existence of long periods of subthreshold or "cyclothymic" fluctuations of symptoms between relatively short syndromal affective episodes. To paraphrase Kraepelin,[3] the nature of this deceptively "milder" form of manic-depressive illness is so chronic as to seem to fill the entire life.

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