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SPECIAL SECTION

Long-term symptomatic status of bipolar I vs. bipolar II disorders

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Abstract

Weekly affective symptom severity and polarity were compared in 135 bipolar I (BP I) and 71 bipolar II (BP II) patients during up to 20 yr of prospective symptomatic follow-up. The course of BP I and BP II was chronic; patients were symptomatic approximately half of all follow-up weeks (BP I 46.6% and BP II 55.8% of weeks). Most bipolar disorder research has concentrated on episodes of MDD and mania and yet minor and subsyndromal symptoms are three times more common during the long-term course. Weeks with depressive symptoms predominated over manic/hypomanic symptoms in both disorders (3:1) in BP I and BP II at 37:1 in a largely depressive course (depressive symptoms = 59.1% of weeks vs. hypomanic = 1.9% of weeks). BP I patients had more weeks of cycling/mixed polarity, hypomanic and subsyndromal hypomanic symptoms. Weekly symptom severity and polarity fluctuated frequently within the same bipolar patient, in which the longitudinal symptomatic expression of BP I and BP II is *dimensional* in nature involving all levels of affective symptom severity of mania and depression. Although BP I is more severe, BP II with its intensely chronic depressive features is not simply the 'lesser' of the bipolar disorders; it is also a serious illness, more so than previously thought (for instance, as described in DSM-IV and ICP-10). It is likely that this conventional view is the reason why BP II patients were prescribed pharmacological treatments significantly less often when acutely symptomatic and during intervals between episodes. Taken together with previous research by us on the long-term structure of unipolar depression, we submit that the thrust of our work during the past decade supports 'classic' notions of a broader affective disorder spectrum, bringing bipolarity and recurrent unipolarity closer together. However the genetic variation underlying such a putative spectrum remains to be clarified.

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Introduction

Previous studies of bipolar disorders have focused almost exclusively on full syndromal episodes of major depression (MDE) and mania (e.g. Angst, 1986; Cassano et al., 1989; Coryell et al., 1984; Koukopoulos et al., 1980; Winokur et al., 1994). However, our work has demonstrated the value of detailed analysis of the long-term weekly symptomatic status, in that the modal longitudinal symptomatic expression of the bipolar I (BP I) and bipolar II (BP II) disorders primarily involves symptoms at the minor and sub-syndromal level of severity rather than at the syndromal level of MDE or mania (Judd et al., 2002, 2003a). Looking at each disorder separately, it also appears that the longitudinal symptomatic expression of both BP I and BP II disorders is dimensional in character, featuring the full range of affective symptom severity and polarity.

Also, in a prior report, to help clarify further the relationship between these two disorders (Judd et al., 2003b), the frequency, duration and polarity of affective

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episodes of BP I and BP II disorders during the long-term course of these illnesses were compared. We now extend the findings of these earlier reports by comparing similarities and differences in the longitudinal weekly symptomatic status of BP I and BP II. This was also an opportunity to test the suggestion of others that BP I is more severe while BP II is more chronic (Ayuso-Gutierrez and Ramos-Brieva, 1982; Vieta et al., 1997). In the present paper, the weekly affective symptom severity and polarity was compared in two large cohorts of BP I and BP II patients who are being followed for up to 20 yr as part of the NIMH Collaborative Depression Study (CDS), which is an ongoing prospective, longitudinal investigation of the characteristics and course of affective disorders.

Subjects and methods

Subjects

Since the major purpose of this investigation was to contrast the long-term symptomatic status of BP I and BP II, the two analysis samples were constructed to be as diagnostically comparable as possible to ensure valid comparisons. Unlike prior studies we have reported (Judd et al., 2002, 2003a,b), the cohorts of BP I and BP II patients analysed herein were defined as follows: (1) Each patient met criteria for *definite* Research Diagnostic Criteria (RDC) bipolar disorder by virtue of having either a lifetime manic (BP I) or hypomanic episode of at least 1 wk duration, as well as a depressive episode of at least 2 wk duration (minor, major) or dysthymia. (2) Each patient had to meet bipolar diagnostic criteria at the time of intake into the study and at their last evaluation. The eliminated patients entering the study with unipolar depressive disorder who later converted to a bipolar diagnosis and BP II patients who converted to BP I. As a result, the analysis samples consisted of 135 BP I and 71 BP II patients entering the CDS from 1978 up to 1981 (Katz and Klerman, 1979; Katz et al., 1979) at one of five academic centres (Massachusetts General Hospital and Harvard University, New York Psychiatric Institute and Columbia University, University of Iowa, Rush Presbyterian – St Luke's Medical Center in Chicago, or Washington University in St Louis), during an index affective episode. Bipolar diagnosis was based on the Schedule of Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott, 1979) using RDC (Spitzer et al., 1977). Further, patients were eliminated from the analysis samples if they had any evidence of schizophrenia or schizoaffective disorder, at intake or during follow-up. Subjects were Caucasian (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 at intake. All patients gave informed consent at each academic site. Demographic and clinical characteristics of the BP I and BP II study samples are summarized in Table 1.

Assessment of follow-up course

Trained raters interviewed patients every 6 months for the first 5 yr of follow-up, and continue to interview them annually, using variations of the Longitudinal Interval Follow-up Evaluation (LIFE; Keller et al., 1987). Patient interviews are 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. Interview information, supplemented by available medical records is integrated into weekly symptom severity ratings using LIFE Psychiatric Status Rating (PSR) scales, which are anchored to diagnostic thresholds for RDC mental disorders. CDS raters routinely undergo rigorous training (Keller et al., 1987), resulting in high intra-class 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).

In addition, 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 scheduled time of follow-up, the interview is rescheduled at a later time. Of the 3550 LIFE forms available for the bipolar samples analysed in this paper, 25.0% were rated 'excellent', 53.2% 'good', 19.5% 'fair', 2.0% 'poor', and 0.3% 'very poor' in terms of accuracy of information of weekly psychiatric status. A total of 147 CDS patients met diagnostic criteria for BP I, and 77 met criteria for BP II disorder as of intake. Since the present analyses focused on weekly symptom status during long-term follow-up, we eliminated from the analyses 12 BP I patients (8.2%) and 6 BP II patients (7.8%) who had less than 2 yr of weekly PSR data rated 'excellent', 'good', or 'fair' in terms of accuracy, because they died or dropped out of the CDS study before 2 yr elapsed. This left 135 BP I and 71 BP II patients with between 2 and 20 yr of weekly prospective follow-up data rated 'fair' or better in terms of accuracy: BP I mean = 12.8 yr (S.D. = 5.7 yr, median = 15.5 yr) of follow-up, and BP II mean = 13.2 yr (S.D. = 6.2 yr,

Table 1. Demographic and clinical characteristics of BP I vs. BP II patients

Characteristics		BP I ($n=135$)	BP II ($n=71$)	Significance test and p value
Demographics				
Sex				
Female	*n* (%)	75 (55.6)	44 (62.0)	$\chi^2=0.78$, d.f. $=1$,
Male	*n* (%)	60 (44.4)	27 (38.0)	$p=0.376$
Age	Mean (S.D.)	39.2 (13.6)	37.4 (13.2)	$t=0.93$, d.f. $=204$,
	Median (range)	37 (17–79)	34 (19–76)	$p=0.352$
Marital status				
Married/Living together	*n* (%)	57 (42.2)	36 (50.7)	$\chi^2=2.12$, d.f. $=2$,
Separated/Divorced/Widowed	*n* (%)	33 (24.4)	18 (25.4)	$p=0.346$
Never married	*n* (%)	45 (33.3)	17 (23.9)	
Education				
High school or less	*n* (%)	54 (40.0)	32 (45.1)	$\chi^2=0.49$, d.f. $=1$,
College or more	*n* (%)	81 (60.0)	39 (54.9)	$p=0.483$
Clinical history				
Total number of lifetime affective episodes (including intake episode)	Mean (S.D.)	24.2 (45.5)	36.6 (51.2)	$t=1.78$, d.f. $=204$,
	Median (range)	6 (1–200)	8 (1–201)	$p=0.077$
Age at onset of first lifetime affective episode	Mean (S.D.)	23.1 (9.8)	20.8 (10.0)	$t=1.57$, d.f. $=204$,
	Median (range)	21 (1–59)	19 (1–64)	$p=0.118$
Polarity of first lifetime affective episode				
Depression	*n* (%)	82 (60.7)	45 (63.4)	$\chi^2=0.51$, d.f. $=2$,
Mania/hypomania	*n* (%)	42 (31.1)	19 (26.8)	$p=0.777$
Unknown	*n* (%)	11 (8.2)	7 (9.9)	

median = 16.0 yr) of follow-up ($t=0.43$, d.f. $=204$, $p=0.665$).

The CDS is a naturalistic follow-up study; it was not designed as a controlled treatment investigation. However, the nature and dose regimen of all somatic treatments (i.e. antidepressants, mood stabilizers, antipsychotics, ECT) was recorded regularly on a weekly basis on the LIFE forms.

Classification of weekly symptom severity levels

Methods previously reported in detail (Judd et al., 1998, 2002) were used to assign each weekly affective symptom severity level. Outlined in Table 2 are the four categories of affective symptom severity levels based on the 6-point PSR scale and 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. 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 separated in to weeks of pure depression (no mania/hypomania), pure mania or hypomania (no depression), or a combination of manic/hypomanic and depressive symptoms (cycling/mixed affective symptoms).

Statistical analyses

Statistical comparisons on background characteristics were made between the two bipolar groups by means of χ^2 or t tests. Follow-up weeks spent at the different symptom status categories were computed for each

Table 2. Classification of affective symptom severity levels based on combinations of weekly psychiatric status rating (PSR) scale scores across all four groups of affective disorders[a,b]

Affective symptom severity level	Major depressive disorder/mania (6-point PSR scale)[c]	Minor depression /hypomania (3-point PSR scale)[d]	DSM-III depressive conditions[e] (3-point PSR scale)[d]	RDC Cyclothymic Personality (3-point PSR scale)[d]
Level I				
Asymptomatic	1	1	1	1
No depressive or manic spectrum symptoms; return to usual self				
Level II	1	1	2 or 3	2 or 3
Syndromal symptoms	1	2	–[f]	–
Symptoms below the threshold of minor depression/dysthymia or hypomania	2	1 or 2	–	–
Level III	1	3	–	–
Minor depressive or	2	3	–	–
hypomanic symptoms	3	–	–	–
	4	–	–	–
Level IV	5	–	–	–
Major depressive or manic symptoms	6	–	–	–

[a] Weekly symptom severity level is assigned based on each week's ratings on all affective conditions regardless of whether the patient was in an RDC episode at that time. Rated affective conditions include RDC major depressive disorder (MDD); RDC minor or intermittent depressive or dysthymic disorder (MinD); RDC manic disorder; RDC hypomanic disorder; RDC Cylothymic 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.

[b] Read across the table for combinations of 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 1 or 2 on the 6-point major depression scale.

[c] 6-Point weekly Psychiatric Status Rating scale 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.

[d] 3-Point weekly Psychiatric Status Rating scale values: 1 = asymptomatic, returned to usual self; 2 = probable criteria (mild symptoms); 3 = definite criteria (severe symptoms).

[e] Includes DSM-III Atypical Depression (code 296.82) and Adjustment Disorder with Depressed Mood (code 309.00).

[f] – indicates 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 value of 5 or 6 for MDD and/or mania, regardless of PSR values on any other affective condition(s).

patient as percentages of the total number of follow-up weeks with PSR ratings of 'fair' or better accuracy; these were then compared for BP I vs. BP II by t tests. For subsets of patients who experienced one or more weeks in a given symptom status category, the percentage of weeks with some prescribed somatic treatment was computed; these were compared by Wilcoxon Rank Sum tests. A two-tailed α-level of $p = 0.05$ was used to define statistically significant group comparisons.

Results

Demographic characteristics and clinical history

As seen in Table 1, BP I and BP II patients did not differ in mean age, sex, marital status, or level of education. There were no significant differences in clinical history at intake, although BP II patients had a non-significant trend to have had more prior affective episodes (mean = 36.6, S.D. = 51.2) than BP I patients (mean = 24.2, S.D. = 45.5). Both cohorts experienced

Table 3. Percentage of follow-up weeks spent at three affective symptom severity levels and the asymptomatic status during long-term follow-up of BP I vs. BP II patients

Symptom severity level[a]	BP I ($n=135$)	BP II ($n=71$)	Significance test and p value[b]
% Weeks asymptomatic (no depression or mania/hypomania)			
Mean (S.D.)	53.4 (34.1)	44.2 (33.1)	$t=1.92$, d.f. $=204$,
Median (range)	62 (0–99)	43 (0–100)	$p=0.056$
% Weeks at the sub-syndromal depressive or sub-syndromal manic/hypomanic threshold of symptoms			
Mean (S.D.)	14.1 (18.3)	16.2 (17.9)	$t=0.68$, d.f. $=204$,
Median (range)	7 (0–94)	9 (0–78)	$p=0.496$
% Weeks at the minor depression/dysthymia or hypomania threshold of symptoms			
Mean (S.D.)	20.1 (21.2)	27.0 (23.3)	$t=2.12$, d.f. $=204$,
Median (range)	12 (0–86)	22 (0–94)	$p=0.036$
% Weeks at the major depression/mania threshold of symptoms			
Mean (S.D.)	12.3 (14.6)	12.6 (15.9)	$t=0.21$, d.f. $=204$,
Median (range)	7 (0–63)	8 (0–85)	$p=0.834$

[a] Weeks with cycling/mixed affective symptoms are classified at their highest (most severe) level.
[b] t tests were performed on arcsine of percentages of weeks.

their first affective episodes at approximately the same age and began their course of illness primarily with depressive episodes.

As reported elsewhere, for these samples (Judd et al., 2003b), BP I patients were more severely ill at intake as indicated by their significantly higher inpatient status ($\chi^2=38.4$, d.f. $=1$, $p=0.001$), lower Global Assessment scores ($t=3.06$, d.f. $=204$, $p=0.002$), and three times higher prevalence of psychotic features in the intake episode ($\chi^2=25.4$, d.f. $=1$, $p=0.001$). In addition, the median duration of the intake episode after admission to the CDS (from survival analysis) was about twice as long for BP II as for BP I patients (Wilcoxon $\chi^2=11.20$, $p=0.0008$).

Percentage of follow-up weeks spent at three symptom severity levels and at asymptomatic status

During their follow-up course (Table 3), BP II patients were symptomatic a higher percentage of weeks (mean $=55.8\%$, S.D. $=33.1\%$) than BP I patients (mean $=46.6\%$, S.D. $=34.1\%$) – a difference approaching statistical significance ($t=1.92$, d.f. $=204$, $p=0.056$). On average, the symptomatic course of both BP I and BP II primarily features moderate and subsyndromal symptoms (minor depressive, hypomanic) rather than symptoms at the syndromal threshold of MDE or mania. The two patient groups had similar percentages of follow-up weeks with subsyndromal affective symptoms and symptoms at the MDE/mania level. However, BP II patients spent a significantly higher percentage of weeks of minor depressive and hypomanic symptoms (BP I mean $=20.1\%$, S.D. $=21.2\%$; BP II mean $=27.0\%$, S.D. $=23.3\%$; $t=2.12$, d.f. $=204$; $p=0.036$).

Percentage of follow-up spent in affective symptom severity categories divided by polarity

Table 4 shows the percentage of weeks when the symptom severity levels are divided by polarity. BP II patients were found to spend significantly more follow-up weeks with depressive symptoms (major, minor and subsyndromal depressive) compared to the BP I ($t=4.45$, d.f. $=115.8$, $p=0.0001$). In fact, the BP II patients spent 37 times more weeks with depressive symptoms (51.9% of weeks) than hypomanic symptoms (1.4% of weeks). However, BP I patients also had three times as many weeks with depressive symptoms (30.6% of weeks) than with manic/hypomanic symptoms (9.8% of weeks).

Within the depressive symptom spectrum, BP II patients spent significantly more of follow-up weeks

Table 4. Percentage of follow-up weeks spent in specific affective symptom severity categories and the asymptomatic status during long-term follow-up of BP I vs. BP II patients, divided by polarity

Specific affective symptom category	BP I ($n=135$)	BP II ($n=71$)	Significance test and p value
% Weeks asymptomatic (no depression or mania/hypomania)			
Mean (S.D.)	53.4 (34.1)	44.2 (33.1)	$t=1.92$, d.f.= 204,
Median (range)	62 (0–99)	43 (0–100)	$p=0.056$
% Weeks with pure depression (no mania/hypomania)			
Mean (S.D.)	30.6 (29.6)	51.9 (32.5)	$t=4.45$, d.f.=115.8,
Median (range)	21 (0–99)	53 (0–100)	$p=0.0001$
% Weeks with sub-syndromal depression			
Mean (S.D.)	8.8 (14.2)	14.2 (16.4)	$t=2.37$, d.f.=204,
Median (range)	3 (0–82)	8 (0–77)	$p=0.019$
% Weeks at minor depression/dysthymia threshold			
Mean (S.D.)	13.1 (17.1)	25.1 (23.5)	$t=3.64$, d.f.=102.2,
Median (range)	6 (0–82)	20 (0–94)	$p=0.0004$
% Weeks at major depression threshold			
Mean (S.D.)	8.8 (12.7)	12.5 (15.9)	$t=1.71$, d.f.=113.3,
Median (range)	4 (0–63)	8 (0–85)	$p=0.091$
% Weeks with pure mania/hypomania (no depression)			
Mean (S.D.)	9.8 (16.1)	1.4 (4.7)	$t=5.48$, d.f.=167.3,
Median (range)	3 (0–82)	0 (0–29)	$p=0.0001$
% Weeks with sub-syndromal mania/hypomania			
Mean (S.D.)	2.6 (7.1)	0.4 (1.4)	$t=3.49$, d.f.=151.6,
Median (range)	0 (0–38)	0 (0–9)	$p=0.0006$
% Weeks at hypomania threshold			
Mean (S.D.)	4.8 (10.3)	1.0 (3.4)	$t=3.76$, d.f.=175.7,
Median (range)	1 (0–81)	0 (0–20)	$p=0.0002$
% Weeks at major mania threshold			
Mean (S.D.)	2.4 (5.0)	na	na
Median (range)	1 (0–37)		
% Weeks with cycling/mixed depression and mania/hypomania			
Mean (S.D.)	6.0 (14.3)	2.5 (8.1)	$t=2.18$, d.f.=204,
Median (range)	0 (0–94)	0 (0–62)	$p=0.030$

with subsyndromal symptoms ($t=2.37$, d.f.=204, $p=0.019$), and more weeks with minor depressive symptoms ($t=3.64$, d.f.=102.2, $p=0.0004$) than BP I patients. Within the manic/hypomanic symptom spectrum, BP I patients had significantly more time with hypomanic symptoms than BP II patients ($t=3.76$, d.f.=175.7, $p=0.0002$) and more weeks with sub-syndromal hypomanic symptoms ($t=3.49$, d.f.=151.6, $p=0.0006$). In addition, BP I patients had significantly more weeks with symptoms of cycling/mixed polarity than BP II patients ($t=2.18$, d.f.=204, $p=0.030$).

Changes in symptom status and polarity during follow-up

Changes in symptom status were defined as any week-to-week change in symptom severity level and/or polarity. As shown in Table 5, BP I patients had somewhat more annual changes in weekly symptom status (mean=5.9, S.D.=7.7) compared to BP II (mean=3.8, S.D.=4.9). Also, BP I patients experienced substantially more annual shifts in affective symptom polarity. Neither of these comparisons were subjected

Table 5. Per-patient changes in affective symptom status and polarity per year during long-term follow-up of BP I vs. BP II patients

Characteristics	BP I ($n=135$)	BP II ($n=71$)
Per patient number of changes in symptom status per year[a]		
Mean (S.D.)	5.9 (7.7)	3.8 (4.9)
Median (range)	3.3 (0.2–49.3)	2.7 (0.2–36.5)
Less than once per year, *n* (%)	14 (10.4)	11 (15.5)
More than 5 times per year, *n* (%)	48 (35.6)	16 (22.5)
More than 10 times per year, *n* (%)	21 (15.6)	4 (5.6)
More than 20 times per year, *n* (%)	7 (5.2)	1 (1.4)
Per patient number of shifts in symptom polarity per year[b]		
Mean (S.D.)	3.5 (7.5)	1.5 (4.2)
Median (range)	0.6 (0–48.7)	0.2 (0–32)
Less than once per year, *n* (%)	78 (57.8)	49 (69.0)
More than 5 times per year, *n* (%)	26 (19.3)	4 (5.6)
More than 10 times per year, *n* (%)	11 (8.1)	2 (2.8)
More than 20 times per year, *n* (%)	5 (3.7)	1 (1.4)

[a] 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 to the count.
[b] 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.

to statistical analyses, because it is possible that any differences might have been due to definitional issues whereby BP I, compared to BP II patients, can experience a greater number of possible changes in symptom status due to the absence of mania in BP II.

Somatic treatment during weeks at each symptom status category

As shown in Table 6, during weeks at most symptom severity levels BP I patients were prescribed significantly more somatic treatments (mood stabilizers, antipsychotics, antidepressants, ECT) as follows: weeks with subsyndromal depressive symptoms (Wilcoxon Rank Sum, $Z=4.09$, $p=0.0001$), weeks with minor depressive symptoms (Wilcoxon Rank Sum, $Z=4.30$, $p=0.0001$); and weeks with MDD symptoms (Wilcoxon Rank Sum, $Z=2.94$, $p=0.003$). BP I compared to BP II patients were also prescribed treatments during significantly more weeks of subsyndromal hypomanic (Wilcoxon Rank Sum, $Z=2.98$, $p=0.003$) symptoms but not during weeks with hypomanic or cycling mixed symptoms. Strikingly, BP I patients were prescribed treatment significantly more often during weeks when they were fully asymptomatic, than BP II patients (Wilcoxon Rank Sum, $Z=4.83$, $p=0.0001$).

Commentary

This is the first detailed comparison of the weekly symptomatic status of BP I and BP II patients during a mean of approx. 13 yr of follow-up. Both disorders were surprisingly chronic in that patients were symptomatic from their disorders about half the time – an average of 46.6% of follow-up weeks for BP I and 55.8% for BP II. It is of interest that weekly symptom severity for both BP I and BP II primarily involved symptoms of moderate severity (minor depression or hypomania) or subsyndromal affective symptoms which, taken together, were three times more common than symptoms at the syndromal level of major depression or mania. Virtually all previous research has been focused on syndromal episodes, and yet most of the long-term symptomatic course of these two disorders is expressed symptomatically below the full syndromal threshold.

The longitudinal weekly course of both cohorts primarily involves depressive – not manic and hypomanic

Table 6. Percentage of follow-up weeks in specific affective symptom severity categories with any prescribed somatic treatment during long-term follow-up of BP I vs. BP II patients[a]

Specific affective symptom category		BP I ($n=135$)	BP II ($n=71$)	Significance test and p value
Weeks asymptomatic (no depression or mania/hypomania)	Mean (S.D.)	73.7 (39.1)	43.5 (42.4)	Wilcoxon Rank Sum
	Median (range)	99.7 (0.0–100.0)	23.3 (0.0–100.0)	$Z=4.83$
	n	123	62	$p=0.0001$
Weeks with pure depression (no mania/hypomania)				
Weeks with sub-syndromal depression	Mean (S.D.)	75.9 (38.4)	51.9 (42.8)	Wilcoxon Rank Sum
	Median (range)	100 (0.0–100.0)	52.2 (0.0–100.0)	$Z=4.09$
	n	110	65	$p=0.0001$
Weeks at minor depression/dysthymia threshold	Mean (S.D.)	77.2 (34.0)	56.9 (36.7)	Wilcoxon Rank Sum
	Median (range)	100 (0.0–100.0)	58.9 (0.0–100.0)	$Z=4.30$
	n	119	69	$p=0.0001$
Weeks at major depression threshold	Mean (S.D.)	76.0 (32.5)	60.4 (39.9)	Wilcoxon Rank Sum
	Median (range)	97.2 (0.0–100.0)	76 (0.0–100.0)	$Z=2.94$
	n	110	67	$p=0.003$
Weeks with pure mania/hypomania (no depression)				
Weeks with sub-syndromal mania/hypomania	Mean (S.D.)	91.1 (26.2)	53.3 (51.6)	Wilcoxon Rank Sum
	Median (range)	100 (0.0–100.0)	100 (0.0–100.0)	$Z=2.98$
	n	83	15	$p=0.003$
Weeks at hypomania threshold	Mean (S.D.)	80.7 (33.8)	55.3 (46.7)	Wilcoxon Rank Sum
	Median (range)	100 (0.0–100.0)	79.8 (0.0–100.0)	$Z=1.83$
	n	114	25	$p=0.068$
Weeks at mania threshold	Mean (S.D.)	86.4 (22.8)	na	na
	Median (range)	100 (0.0–100.0)		
	n	99		
Weeks with cycling/mixed depression and mania/hypomania	Mean (S.D.)	79.9 (32.2)	58.8 (47.5)	Wilcoxon Rank Sum
	Median (range)	100 (0.0–100.0)	97.6 (0.0–100.0)	$Z=1.49$
	n	83	34	$p=0.137$

[a] Percentage of weeks with some form of prescribed somatic treatment (mood stabilizers, anti-psychotics, antidepressants, ECT, etc., was calculated and compared for each specific affective symptom category, only for those patients who spent some (i.e. one or more) follow-up weeks in that symptom category.

symptoms. BP I patients experienced weeks of depressive symptoms about three times more often than manic or hypomanic symptoms. However, it is striking that BP II patients were largely symptomatic with depression, in which weeks with depressive symptoms (51.9% of follow-up weeks) were 37 times more common than weeks with hypomanic or subsyndromal hypomanic symptoms (1.4% of follow-up weeks). In fact, BP II patients spent a significantly higher percentage of follow-up at the minor depressive (25.1 vs. 13.1% of weeks) and subsyndromal depressive levels (14.2 vs. 8.8% of weeks) than BP I patients. On the other hand, BP I patients had a seven times higher percentage of weeks with manic/hypomanic symptoms than BP II patients (9.8 vs. 1.4% of follow-up), as well as significantly more weeks with symptoms of cycling/mixed polarity (6.0 vs. 2.5% of follow-up).

The course of BP I fluctuated more than in BP II patients as evidenced by a higher number of annual shifts in symptom polarity and status during follow-up. The more frequent symptom status shifts for BP I patients might in part be accounted for by the fact that BP I patients can move into and out of more symptom status levels than the BP II patients who do not experience mania.

Despite the differences described above, BP I and BP II do share a number of similar characteristics. Both disorders feature primarily depressive symptoms during their course of illness. Even BP I, traditionally defined by its dramatic, explosive manic episodes, experienced depressive symptoms three times more

commonly during the course of illness than manic or hypomanic symptoms. The long-term symptomatic expression of both disorders is characterized by more moderate and subsyndromal affective symptoms. Also, both disorders are highly chronic in nature, with patients being symptomatically ill for approximately half of their long-term course of illness.

In prior analyses we have developed a new measure of chronicity, the total percentage of follow-up weeks with affective symptoms at any level which has proven to be a useful and sensitive measure of chronicity. In a previous report of the formal episode course of BP I and BP II patients (Judd et al., 2003b), we found that BP I patients were in a formal RDC affective episode an average of 24% of weeks during follow-up, compared to 32% of weeks for BP II. However, during an episode, patients spent the majority of their weeks below full syndromal threshold, and periods *between* formal episodes included substantial numbers of weeks with residual subsyndromal affective symptoms. Thus, analysis of the weekly symptom status during *all* of follow-up has provided a complementary and more detailed picture of chronicity of bipolar patients' during the long-term course of their illness.

Although it was not the purpose of this paper to investigate possible factors accounting for the greater chronicity of BP II, based on information in patients' psychiatric records, we did find an intriguing result relative to treatment. Overall, BP II patients were much less likely than BP I patients to have been prescribed *some* (i.e. any level or type) somatic treatment (antidepressants, mood stabilizers, antipsychotics, ECT, etc.) during weeks in most affective symptom severity categories. For example, BP II patients were prescribed some somatic treatment during only 60.4% of weeks when they were at the MDE threshold, whereas BP I patients had some treatment prescribed during 76.0% of weeks when experiencing MDE level symptoms. During weeks BP II patients spent with minor depressive/dysthymic symptoms, they were treated 56.9% of the time – far less than the 77.2% of weeks BP I patients were treated while at the same minor depressive symptom severity level. Interestingly, during weeks when patients were symptom-free between episodes, BP II had some somatic treatment prescribed 43.5% of the time, and BP I had treatment prescribed during 73.7% of the time. While these findings do not address the dosage, drug type, or adequacy of psychotropic medication or other somatic treatments for bipolar disorders, it makes a compelling case for the conclusion that clinicians may under-recognize or minimize the chronic and highly depressive nature of BP II and, consequently, under-prescribe for this disorder in both acute and maintenance treatment. It should be noted that the CDS is naturalistic (not designed as a treatment study), and these observations are based on treatment data that was recorded but not controlled.

Among others, our data confirm observations by Vieta et al. (1997) in a smaller clinical sample showing that BP II disorder tends to be more chronic, and BP I more severe cross-sectionally. Although BP I is uniquely characterized by its more severe manic episodes, whereas BP II is not, nonetheless both cohorts had virtually identical percentages of follow-up weeks at the syndromal episode threshold (i.e. BP I = 12.3% of weeks and BP II = 12.6% of weeks). However, the intensely chronic and the disabling nature of depressive symptoms which make up over 50% of the total course of BP II, highlights the fact that BP II is a serious chronic illness, and not necessarily the 'lesser' of bipolar disorders (Judd et al., 2003a,b). The present analysis of weekly symptom status goes beyond previous reports of the considerable chronicity of BP II (Akiskal, 1981; Benazzi, 2001; Coryell et al., 1989; Judd et al., 2003a) by emphasizing course similarities and differences with BP I and the need for enhanced treatment of BP II patients.

Although inter-rater agreement was high, there may be some degree of error in assigning weekly symptom status in retrospective interviews. There also may have been some tendency for CDS raters to focus on full syndromal symptoms of MDE and mania, and under-estimate symptoms at the minor depressive or hypomanic level. Also, the percentage of subsyndromal symptom weeks may be underestimated and the asymptomatic weeks overestimated, since PSR coding rules prohibit the recording of subsyndromal symptomatic symptoms following asymptomatic recovery until symptoms again reach syndromal levels. This could also result in an under-estimation of the number of polarity shifts into and out of the two subsyndromal symptom categories. Finally, it is uncertain how the differences in percentage of weeks at the various symptom severity levels were influenced by the unevenly distributed somatic therapies in BP I vs. BP II.

Combining data from the present analyses with previous findings in MDD (Judd et al., 1998; Kendler and Gardner, 1998), in BP I (Judd et al., 2002) and BP II (Judd et al., 2003a) cohorts suggest there may be an overall affective disorder spectrum which includes all three of these disorders. Commonalties between these disorders supporting this proposition include first, a high degree of long-term weekly symptomatic chronicity with MDD patients being symptomatic

approx. 60% of the weeks during the follow-up, BP II patients being symptomatic 57% of the weeks, and BP I patients symptomatic 47% of total weeks. Secondly, the long-term symptomatic course of all three affective disorders is dominated by depressive symptoms. Thirdly, despite the fact that all three affective disorders have traditionally been defined by their syndromal episodes, the long-term symptomatic course of all three is dominated by more moderate and subsyndromal affective symptoms. Fourthly, the longitudinal symptomatic expression of all three mood disorders is dimensional in that affective symptom severity levels ranging from subsyndromal to syndromal levels fluctuate frequently within the same bipolar patient over time. These considerations add further evidence for the position of those who have argued for a broad affective disorder spectrum indicating a closer relationship between bipolarity and highly recurrent unipolarity (e.g. Akiskal, 1983; Cassano et al., 1989; Gershon et al., 1982; Goodwin and Jamison, 1990). This proposal for a spectrum on the grounds of clinical psychopathological and course characteristics does not exclude the distinct possibility of underlying genetic variation (see e.g. Endicott et al., 1985; McMahon et al., 2001; MacKinnon et al., 2002; Rotondo et al., 2002).

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