ORIGINAL ARTICLE

Psychosocial Disability in the Course of Bipolar I and II Disorders

A Prospective, Comparative, Longitudinal Study

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Context: Evidence of psychosocial disability in bipolar disorder is based primarily on bipolar I disorder (BP-I) and does not relate disability to affective symptom severity and polarity or to bipolar II disorder (BP-II).

Objective: To provide detailed data on psychosocial disability in relation to symptom status during the long-term course of BP-I and BP-II.

Design: A naturalistic study with 20 years of prospective, systematic follow-up.

Setting: Inpatient and outpatient treatment facilities at 5 US academic centers.

Patients: One hundred fifty-eight patients with BP-I and 133 patients with BP-II who were followed up for a mean (SD) of 15 (4.8) years in the National Institute of Mental Health Collaborative Depression Study.

Main Outcome Measures: The relationship, by random regression, between Range of Impaired Functioning Tool psychosocial impairment scores and affective symptom status in 1-month periods during the long-term course of illness from 6-month and yearly Longitudinal Interval Follow-up Evaluation interviews.

Results: Psychosocial impairment increases significantly with each increment in depressive symptom severity for BP-I and BP-II and with most increments in manic symptom severity for BP-I. Subsyndromal hypomanic symptoms are not disabling in BP-II, and they may even enhance functioning. Depressive symptoms are at least as disabling as manic or hypomanic symptoms at corresponding severity levels and, in some cases, significantly more so. At each level of depressive symptom severity, BP-I and BP-II are equally impairing. When asymptomatic, patients with bipolar disorder have good psychosocial functioning, although it is not as good as that of well controls.

Conclusions: Psychosocial disability fluctuates in parallel with changes in affective symptom severity in BP-I and BP-II. Important findings for clinical management are the following: (1) depressive episodes and symptoms, which dominate the course of BP-I and BP-II, are equal to or more disabling than corresponding levels of manic or hypomanic symptoms; (2) subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment; and (3) subsyndromal hypomanic symptoms appear to enhance functioning in BP-II.

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BIPOLAR DISORDER HAS BEEN found to be associated with the following types of disability: increased suicidal behavior,[1] increased health care use and costs,[1,2] higher unemployment,[3,4] higher dependence on public assistance,[1] lower annual income,[5] increased work absenteeism owing to illness,[2,5,6] decreased work productivity,[5] poorer overall functioning,[7-9] lower quality of life,[2,10] and decreased life span.[11] Although informative, the conclusions are limited by methodological shortcomings such as reliance primarily on cross-sectional rather than longitudinal designs, generally small samples, using screening rather than research diagnostic methods, combining bipolar I disorder (BP-I) and bipolar II disorder (BP-II), or omitting BP-II altogether. To our knowledge, no study has examined disability in relation to all of the levels of affective symptom severity that occur over time, has compared disability for manic and depressive symptoms, or has examined disability separately for BP-I and BP-II.

In previous studies,[12-14] we established that BP-I and BP-II are dimensional illnesses in which patients experience, during their long-term course of illness, fluctuating levels of severity of manic and depressive symptoms interspersed with symptom-free (euthymic) pe-

riods. Studies are needed to characterize the link between degrees of disability and the various levels of affective symptom severity that subjects with bipolar disorder experience over time. The present investigation addresses this challenge.

The National Institute of Mental Health Collaborative Depression Study (CDS)[15,16] provides a unique opportunity to investigate psychosocial disability associated with bipolar disorders during all of the phases of the illness. This study was designed to answer 4 research questions: (1) In line with our previous findings for unipolar major depressive disorder (MDD),[17] does psychosocial impairment in BP-I and BP-II increase significantly in a progressive stepwise fashion with each increment of symptom severity in the manic or depressive spectrum? (2) The scientific literature primarily describes the management of manic episodes and symptoms. Are symptoms in the manic spectrum associated with more psychosocial disability than symptoms in the depressive spectrum at corresponding levels of severity? (3) Is BP-II less impairing than BP-I at corresponding levels of symptom severity? (4) When patients with BP-I or BP-II are completely free of affective symptoms, do they return to good psychosocial functioning, as we found in patients with unipolar MDD,[17] and how does their psychosocial functioning compare with a currently well control group?

METHODS

SUBJECTS

Subjects entered the CDS[15,16] as inpatients or outpatients at 1 of 5 tertiary care centers from 1978 to 1981 while experiencing an active affective episode. All of the patients in the CDS were required to be white (to test genetic hypotheses), speak English, have an IQ score of at least 70, and have no evidence of any organic brain syndrome or terminal medical illness. Written informed consent was obtained for participation in research. Patients in the CDS received a diagnosis using the Research Diagnostic Criteria,[18] based on Schedule for Affective Disorders and Schizophrenia interviews[19] and on a review of medical records. They were included in the present analysis if they met criteria for BP-I (definite) or BP-II (definite or probable) at entry. In a prior article,[13] we found no difference in clinical, demographic, or follow-up characteristics of patients with BP-II with hypomanic episodes lasting at least 1 week (definite BP-II) vs 3 to 6 days (probable BP-II), so we combined both groups. Consistent with *DSM-IV* criteria,[20] we excluded patients who had only manic or hypomanic episodes without any MDD by the end of follow-up. Patients who switched from unipolar MDD to 1 of the 2 bipolar disorders during follow-up were included in the analysis starting at the time of their first lifetime manic or hypomanic episode.[20] Patients who ever met Research Diagnostic Criteria for schizophrenia or schizoaffective disorder were excluded. As described later, forms with poor or very poor reliability of symptom status or psychosocial impairment (3%) were excluded from the analysis. The resulting analysis sample included 158 patients with BP-I and 133 patients with BP-II.

PSYCHIATRIC SYMPTOM RATINGS

As described in previous publications,[12-14,17,21] trained professional raters interviewed patients every 6 months for the first 5 years and then yearly thereafter, using variations of the Longitudinal Interval Follow-up Evaluation (LIFE).[22] The CDS raters underwent rigorous training, resulting in intraclass correlation coefficients of 0.90 for reliability of psychiatric symptom ratings, 0.95 for recovery from major affective episodes, and 0.88 for subsequent appearance of affective symptoms.[22] Weekly psychiatric symptom ratings were aggregated into 1 of 10 mutually exclusive categories representing the most severe level of symptom severity that occurred during any week of each 1-month period: symptoms in the pure depressive spectrum (MDD, minor depression or dysthymia, or subsyndromal depression) with no manic or hypomanic symptoms; symptoms in the pure manic spectrum (mania, hypomania, or subsyndromal hypomanic symptoms) with no depressive symptoms; symptoms of cycling or mixed polarity (owing to either change in polarity or coexistence of both manic and depressive symptoms within a given month, coded according to the most severe level in either spectrum); or asymptomatic status (no affective symptoms, return to usual self for the entire month). Because of the small number of person-months in the 9 combinations of cycling or mixed symptoms, these were analyzed as a single category at the subsyndromal level of severity (accounting for 2.0% of person-months for BP-I and 0.5% for BP-II), a combination of 3 categories at the minor depression and/or hypomanic level of severity (2.4% of person-months for BP-I and 1.0% for BP-II), and a combination of 5 categories at the MDD and/or mania level of severity (1.0% of person-months for BP-I and 0.3% for BP-II). The 6 categories of pure depression, mania, or hypomania and the asymptomatic status are the primary focus of this article, and they were not collapsed with one another or with any cycling or mixed states.

LIFE–RANGE OF IMPAIRED FUNCTIONING TOOL PSYCHOSOCIAL IMPAIRMENT SCORES

Each monthly symptom severity category described earlier was matched with psychosocial disability ratings for the same month. Using the LIFE forms, trained interviewers made ratings of each patient's worst level of psychosocial impairment due to psychopathological abnormalities (ie, excluding extraneous factors such as life events). Psychosocial functioning assessments were obtained for every month from 25 months to 5 years of follow-up and for the final month of follow-up in years 6 to 20. Ratings in 9 specific functional domains as well as a global rating of overall psychosocial functioning were made using 2 5-point Likert scales with behavioral anchors for each area of function.[17] The LIFE–Range of Impaired Functioning Tool (LIFE-RIFT) score was created by adding ratings for the most impaired role function (work, household, or school), the most disrupted area of interpersonal relationships (with spouse or mate, children, other relatives, or friends), limitations in recreation or hobbies, and overall negative subjective satisfaction. Scores on the LIFE-RIFT can range from 4, indicating very good functioning (no impairment) in all of the 4 component areas, to 20, indicating very poor functioning (severe impairment) in all of the 4 areas. A LIFE-RIFT score of approximately 8 represents psychosocial functioning in the good range; 12, fair functioning; 16, poor functioning; and 20, very poor functioning. The LIFE-RIFT score has been shown to have good reliability and validity in patient samples.[23,24] In addition, it had a high correlation (r=0.86) with raters' independent ratings of overall psychosocial impairment within the current analysis samples.

Months in which any component of the LIFE-RIFT score was missing (2.0% of patients and 2.7% of months that otherwise qualified for the analyses) were excluded. Although both groups of patients with bipolar disorder participated in the CDS fol-

Table 1. Demographic and Clinical Characteristics of Patients With Bipolar I and II Disorders*

Characteristic	BP-I (n = 158)	BP-II (n = 133)	Significance Test	*P* Value
Demographics at Intake				
Sex, No. (%)				
Female	95 (60.1)	90 (67.6)	$\chi^2_1 = 1.77$	.18
Male	63 (39.9)	43 (32.3)		
Age, y				
Mean (SD)	38.2 (12.6)	35.2 (12.7)	$t_{289} = 2.02$	.04
Median	36.5	31.0		
Range	17-79	17-74		
Marital status, No. (%)				
Married/living together	71 (44.9)	56 (42.1)	$\chi^2_2 = 0.25$	.88
Separated/divorced/widowed	38 (24.1)	33 (24.8)		
Never married	49 (31.0)	44 (33.1)		
Education, No. (%)				
High school or less	63 (39.9)	57 (42.9)	$\chi^2_1 = 0.27$	.61
College or more	95 (60.1)	76 (57.1)		
Clinical History				
Total lifetime affective episodes (including intake episode), No. (%)				
Median	5.5	5.0	$z = 0.65$†	.52†
0-1	15 (9.5)	18 (13.5)		
2-3	37 (23.4)	33 (24.8)		
≥4	106 (67.1)	82 (61.6)		
Age at onset of first lifetime affective episode, y				
Mean (SD)	23.6 (10.4)	22.1 (10.5)	$t_{289} = 1.22$	.22
Median	21.0	20.0		
Range	1-62	1-64		
Characteristics of Intake Episode				
Patient status at intake, No. (%)				
Inpatient	140 (88.6)	89 (66.9)	$\chi^2_1 = 20.26$	$P<.001$
Outpatient	18 (11.4)	44 (33.1)		
Severity of intake episode, worst-week GAS Scale score				
Mean (SD)	33.6 (10.7)	37.1 (9.2)	$t_{289} = 2.90$	.004
Median	32.0	35.0		
Range	10-67	5-61		
Amount of Follow-up Data				
Latest available follow-up, y				
Mean (SD)	15.2 (4.7)	15.2 (4.9)	$t_{289} = 0.14$	.89
Median	17.0	17.0		
Range	2.5-20.0	2.5-20		
Months with LIFE-RIFT psychosocial assessments, No.‡				
Mean (SD)	28.5 (14.5)	27.3 (15.5)	$t_{289} = 0.66$	.51
Median	29.5	29.0		
Range	1-50	1-50		

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; GAS, Global Assessment of Severity; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool.

*Patients from the National Institute of Mental Health Collaborative Depression Study were included in the analyses if they had a diagnosis of BP-I (definite) or BP-II (definite or probable) at entry to the study, or if they switched from unipolar major depressive disorder to 1 of the 2 bipolar disorders during follow-up (in which case, only data after the switch were analyzed). Patients with schizophrenia or schizoaffective disorder were excluded. Only those patients with 1 or more months with the required data were used in the analyses.

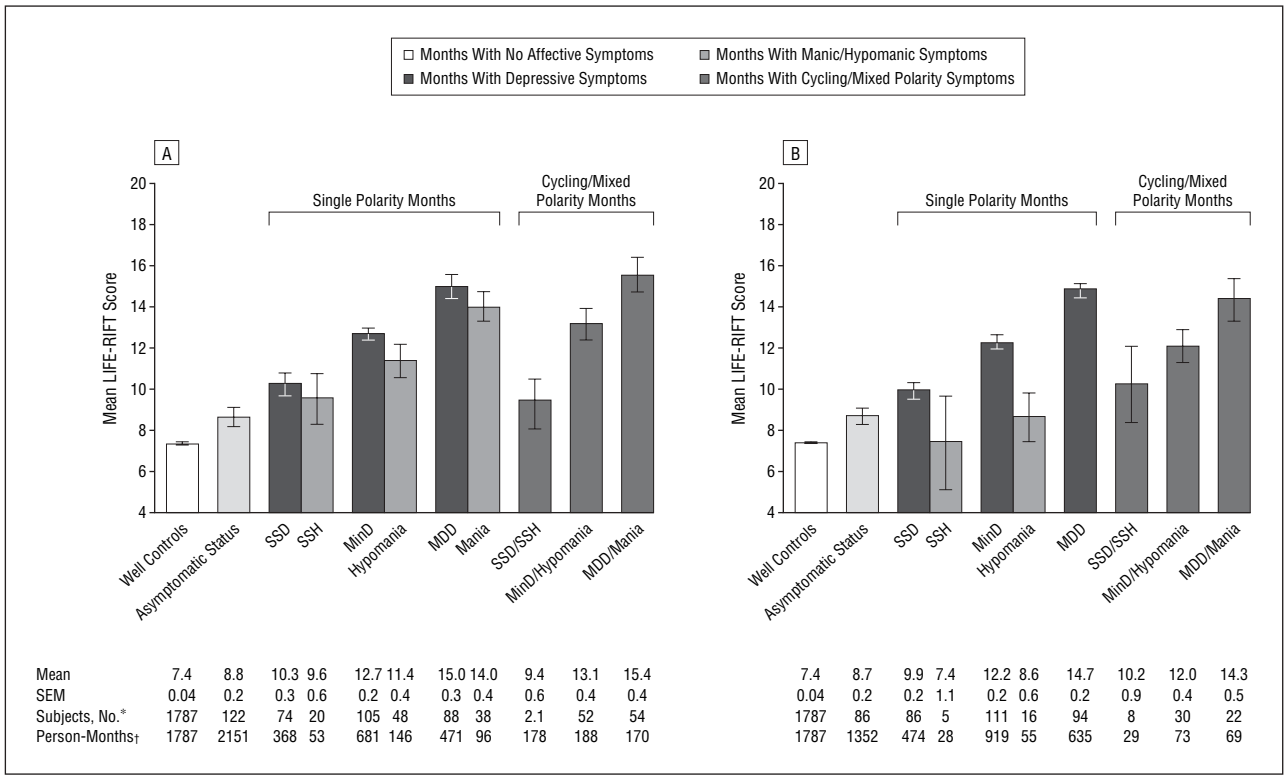
†Two-group comparison by Wilcoxon rank sum test on discreet (ungrouped) values for number of lifetime episodes.

‡Psychosocial assessments were obtained for all of the months from 25 months to 5 years of follow-up and for the final month of follow-up from years 6 to 20. Months were included in the analyses only if psychiatric symptom status and all of the 4 ratings composing the LIFE-RIFT score were present and rated at least fair in terms of accuracy.

low-up for a mean of 15.2 years (182.4 months), the mean (SD) number of months with LIFE-RIFT scores was 28.5 (14.5) for patients with BP-I and 27.3 (15.5) for those with BP-II (**Table 1**) during the period from 25 months to 20 years of follow-up.

STATISTICAL ANALYSES

All of the analyses were performed with SAS version 8.2 software (SAS Institute Inc, Cary, NC). The currently well comparison sample comprised 1817 relatives, spouses, and family acquaintances with no current Research Diagnostic Criteria psychiatric or substance abuse disorders as of their 6-year follow-ups, at which time they were evaluated for psychosocial functioning in the prior month. A simple *t* test was used to compare the single-month impairment rating for all of the subjects in the well comparison group with those patients with BP-I and BP-II who had 1 or more months' data in a given symptom category. Using a procedure described previously,[17] the *t* tests were conducted using 1 randomly selected month for patients with



	A									
Mean	7.4	8.8	10.3	9.6	12.7	11.4	15.0	14.0	9.4	13.1	15.4
SEM	0.04	0.2	0.3	0.6	0.2	0.4	0.3	0.4	0.6	0.4	0.4
Subjects, No.*	1787	122	74	20	105	48	88	38	2.1	52	54
Person-Months†	1787	2151	368	53	681	146	471	96	178	188	170

	B									
Mean	7.4	8.7	9.9	7.4	12.2	8.6	14.7	10.2	12.0	14.3
SEM	0.04	0.2	0.2	1.1	0.2	0.6	0.2	0.9	0.4	0.5
Subjects, No.*	1787	86	86	5	111	16	94	8	30	22
Person-Months†	1787	1352	474	28	919	55	635	29	73	69

Figure. Mean Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool (LIFE-RIFT) psychosocial impairment scores per symptom severity category, adjusted for within-subject variation through mixed regression analysis, by monthly symptom status categories for well controls (n=1787) and patients with bipolar I (n=158) (A) or bipolar II (n=133) (B) disorder. Weekly psychiatric symptom ratings obtained through LIFE follow-up interviews were aggregated into 1 of the following 10 mutually exclusive categories representing the most severe level of symptom severity during each 1-month period of follow-up data independent of episode status in that month: asymptomatic status (no depressive or manic symptoms [return to usual self] for the entire month); depressive spectrum symptoms at 1 of 3 levels of severity with no manic spectrum symptoms—namely, major depressive disorder (MDD) depressive symptoms at the threshold for MDD), minor depression (MinD) depressive symptoms at the threshold for MinD or dysthymia but not as severe as MDD), or subsyndromal depressive symptoms (SSD) subsyndromal depressive symptoms below the threshold for MinD); manic spectrum symptoms at 1 of 3 levels of severity with no depressive spectrum symptoms—namely, mania (manic spectrum symptoms at the threshold for mania), hypomania (manic spectrum symptoms at the threshold for hypomania but not as severe as mania), or subsyndromal hypomanic symptoms (SSH) manic spectrum symptoms below the threshold for hypomania); or 1 of 3 categories of cycling or mixed polarity symptoms classified according to the worst severity level of symptoms in either spectrum—namely, MDD/mania (symptoms in both the manic and depressive spectra reaching the level of MDD and/or mania), MinD/hypomania (symptoms in both the manic and depressive spectra reaching the level of MinD and/or hypomania), and SSD/SSH (symptoms in both the manic and depressive spectra, below the level of MinD or hypomania). The SEM values are from mixed regression analysis. Error bars above and below the top of bars indicate the upper and lower 95% confidence intervals for the means (based on mean + t x SEM, where t is the t value resulting in $\alpha = .05$ for the corresponding df); asterisk, the number of subjects with 1 or more months of impairment ratings in this symptom severity category; and dagger, total number of months with impairment ratings in this symptom severity category, where a given subject (except well controls) may contribute multiple months to the analysis.

multiple evaluations in a particular symptom category, or using the single rating for patients with only 1 month at that level.

Random regression analysis (using SAS MIXREG software[25]) was used to model the relationship between LIFE-RIFT ratings of psychosocial impairment and monthly severity and polarity of affective symptoms. The regression models included a random intercept term to account for correlated observations within patients over time. A compound symmetry covariance structure was used to model within-subject variation because it yielded a better (higher) model-fitting criteria than autoregressive or unstructured covariance. Means and standard errors of the means of impairment ratings were obtained for each symptom category after adjusting for within-subject correlation. The significance of contrasts between specific pairs of symptom categories (to assess impairment associated with incremental steps in symptom severity and with depression vs mania at comparable levels of severity) within each diagnostic group was determined from post hoc paired symptom category comparisons performed within full mixed regression models that included all of the 10 BP-I or 9 BP-II categories of monthly symptom status after first determining that the overall models were statistically significant. This provided a conservative test of significance since within-subject variation was calculated across all of the symptom categories. Comparisons of BP-I vs BP-II disability were made by performing a separate 2-group mixed regression run within each symptom category. Degrees of freedom for all mixed regression main effects and contrasts were calculated using the Satterthwaite method.[25]

An α level of .05 (2-tailed) was used to assess the significance of each statistical test. Bonferroni adjustments to the α level were not made because most of the contrasts were derived from only 2 overall mixed regression models that were designed to provide conservative tests of paired group contrasts (as described earlier). Furthermore, each research question in this study is addressed by examining the pattern of findings across multiple symptom categories (eg, across 3 stepwise increments in depressive or manic symptom severity); adjusting the α level could increase type II errors and mask findings relevant to the study questions.

RESULTS

Intake demographic and clinical characteristics of the patient samples are presented in Table 1. The **Figure** shows

Table 2. Significance of Mixed Regression Comparisons of Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool Psychosocial Impairment Scores by Symptom Status Categories During 1-Month Assessment Periods in the Long-term Follow-up of Collaborative Depression Study Patients With Bipolar I Disorder*

Comparison of Symptom Severity Categories	Significance of Comparison of Symptom Severity Categories From Mixed Regression		
	t	*df*	*P* Value
Stepwise increments in symptom severity			
Severity levels of pure depressive symptoms			
SSD>asymptomatic	4.10	576	<.001
MinD>SSD	6.30	601	<.001
MDD>MinD	6.16	590	<.001
Severity levels of pure manic symptoms			
SSH = asymptomatic	1.29	701	.20
Hypomania>SSH	2.52	721	.01
Mania>hypomania	4.68	685	<.001
Severity levels of cycling/mixed polarity symptoms			
SSD/SSH = asymptomatic	1.04	595	.30
MinD/hypomania>SSD/SSH	5.60	619	<.001
MDD/mania>MinD/hypomania	4.53	649	<.001
Depression vs mania at comparable levels of symptom severity			
SSD = SSH	1.04	708	.30
MinD>hypomania	2.97	655	.003
MDD = mania	1.84	656	.07

Abbreviations: MDD, major depressive disorder; MinD, minor depression; SSD, subsyndromal depressive symptoms; SSH, subsyndromal hypomanic symptoms.

*For mean Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool impairment ratings per symptom severity category adjusted for within-subject variation through mixed regression analysis, see the Figure, A. The significance of contrasts between specific pairs of symptom categories within each diagnostic group was determined from post hoc paired group comparisons performed within full mixed regression models that included all of the 10 bipolar I disorder categories of symptom status per month.

Table 3. Significance of Mixed Regression Comparisons of Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool Psychosocial Impairment Scores by Symptom Status Categories During 1-Month Assessment Periods in the Long-term Follow-up of Collaborative Depression Study Patients With Bipolar II Disorder*

Comparison of Symptom Severity Categories	Significance of Comparison of Symptom Severity Categories From Mixed Regression		
	t	*df*	*P* Value
Stepwise increments in symptom severity			
Severity levels of pure depressive symptoms			
SSD>asymptomatic	3.91	433	<.001
MinD>SSD	7.19	456	<.001
MDD>MinD	8.02	440	<.001
Severity levels of pure manic symptoms			
SSH = asymptomatic	–1.15	530	.25
Hypomania = SSH	0.96	548	.34
Severity levels of cycling/mixed polarity symptoms			
SSD/SSH = asymptomatic	1.68	591	.09
MinD/hypomania = SSD/SSH	1.86	615	.06
MDD with SSH or hypomania>MinD/hypomania	3.57	580	<.001
Depression vs mania at comparable levels of symptom severity			
SSD>SSH	2.30	534	.02
MinD>hypomania	5.75	564	<.001

Abbreviations: MDD, major depressive disorder; MinD, minor depression; SSD, subsyndromal depressive symptoms; SSH, subsyndromal hypomanic symptoms.

*For mean Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool impairment ratings per symptom severity category adjusted for within-subject variation through mixed regression analysis, see the Figure, B. The significance of contrasts between specific pairs of symptom categories within each diagnostic group was determined from post hoc paired group comparisons performed within full mixed regression models that included all of the 9 bipolar II disorder categories of symptom status per month.

mean LIFE-RIFT psychosocial impairment scores for each affective symptom severity category for patients with BP-I and BP-II after adjusting for within-subject variation through mixed regression. Significance levels for all of the statistical comparisons relevant to the study questions are presented in **Table 2** for subjects with BP-I, **Table 3** for subjects with BP-II, and **Table 4** for the comparison of subjects with BP-I vs subjects with BP-II.

In both BP-I and BP-II, each increase or decrease in depressive symptom severity is associated with a highly significant ($P<.001$) stepwise increase or decrease in psychosocial disability (Table 2 and Table 3). Patients with BP-I show a similar pattern of significant stepwise change in impairment as their level of manic symptom severity changes between mild subsyndromal symptoms and hypomania ($P=.01$) or between hypomania and mania ($P<.001$). As patients with BP-I move between the asymptomatic status and subsyndromal hypomanic symptoms, impairment scores do not change significantly ($P=.20$). In patients with BP-II, the pattern of significant stepwise changes in psychosocial impairment is seen only in relation to changes in depressive symptom severity. As symptom severity changes from asymptomatic to subsyndromal hypomanic to hypomanic, or the reverse, significant changes in psychosocial impairment are not found; in fact, there is a slight but nonsignificant improvement ($P=.25$) in psychosocial functioning as patients with BP-II go from the asymptomatic status to periods with subsyndromal hypomanic symptoms.

At each level of depressive symptom severity (ie, subsyndromal, minor depressive, or major depressive symptoms), psychosocial impairment is equal to or significantly greater than the corresponding level of manic symptom severity in BP-I (Figure and Table 2) and BP-II (Figure and Table 3). In BP-I, minor depression is associated with significantly more psychosocial disability than

hypomania ($P=.003$). In patients with BP-II, subsyndromal depressive symptoms are more disabling than subsyndromal hypomanic symptoms ($P=.02$), and minor depressive symptoms are more disabling than hypomanic symptoms ($P<.001$).

Psychosocial impairment in BP-I vs BP-II is shown in Table 4. Within 8 of the 9 symptom severity categories, levels of psychosocial impairment are not significantly different for patients with BP-I and patients with BP-II ($P=.07$-$.81$). While experiencing hypomanic symptoms, patients with BP-II have significantly better psychosocial functioning (lower impairment scores) than patients with BP-I ($P=.003$), probably owing to the slightly enhanced functioning of patients with BP-II during hypomania. There is no significant difference in psychosocial impairment between BP-I and BP-II at any level of depressive symptom severity or the asymptomatic status.

The LIFE-RIFT psychosocial impairment scores at each symptom status category were also compared with those of well controls. As we found for patients with unipolar MDD,[17] patients with BP-I and BP-II at each level of depressive symptom severity are significantly more impaired than the well controls ($P<.001$). For patients with BP-I, each level of manic or hypomanic and cycling or mixed polarity symptom severity is associated with significantly greater impairment than in the well comparison group ($P<.001$ to $P=.004$). Patients with BP-II and hypomanic or subsyndromal hypomanic symptoms are not significantly more impaired than well controls ($P=.11$ and $P=.77$, respectively). When patients with either BP-I or BP-II are asymptomatic in terms of their mood disorders, their psychosocial functioning normalizes, and LIFE-RIFT scores return to the good range. However, both groups of patients show a small but significant decrement in functioning during asymptomatic periods as compared with the well comparison control group ($t_{127}=5.74$, $P<.001$ for the BP-I group; $t_{108}=5.33$, $P<.001$ for the BP-II group).

Table 4. Significance of Mixed Regression Comparisons of Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool Psychosocial Impairment Scores by Symptom Status Categories During 1-Month Assessment Periods in the Long-term Follow-up of Collaborative Depression Study Patients With Bipolar I vs Bipolar II Disorder*

BP-I vs BP-II Within Each Symptom Severity Category	Significance of Comparison of Symptom Severity Categories From Mixed Regression: *t*	*df*	*P* Value
Asymptomatic status			
BP-I = BP-II	0.24	218	.81
Severity levels of pure depressive symptoms			
SSD: BP-I = BP-II	0.99	146	.32
MinD: BP-I = BP-II	1.45	224	.15
MDD: BP-I = BP-II	0.80	177	.43
Severity levels of pure manic symptoms			
SSH: BP-I = BP-II	1.90	20.2	.07
Hypomania: BP-I>BP-II	3.15	56.3	.003
Severity levels of cycling/mixed polarity			
SSD/SSH: BP-I = BP-II	−0.65	30.6	.52
MinD/Hypomania: BP-I = BP-II	1.82	82.8	.07
MDD/Mania: BP-I = BP-II	1.59	72.4	.12

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; MDD, major depressive disorder; MinD, minor depression; SSD, subsyndromal depressive symptoms; SSH, subsyndromal hypomanic symptoms.

*For mean Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool impairment ratings per symptom severity category adjusted for within-subject variation through mixed regression analysis, see the Figure. Comparisons of BP-II vs BP-I disability were made by performing a separate 2-group mixed regression run within each symptom severity category.

COMMENT

To our knowledge, this is the first investigation that has examined psychosocial impairment associated with every level of affective symptom severity and periods of euthymia in a large clinical cohort of patients with BP-I and BP-II followed prospectively, naturalistically, and systematically for many years. These data provide an unusually detailed documentation of psychosocial disability in patients with BP-I and BP-II.

DEPRESSIVE SPECTRUM IN BP-I AND BP-II

Consistent with the pattern we previously described for unipolar MDD,[17] with every increase or decrease in depressive symptom severity, there is a corresponding significant and stepwise increase or decrease in psychosocial disability in both BP-I and BP-II. When patients with BP-I or BP-II have no mood disorder symptoms, their psychosocial functioning normalizes and is rated as good; when they are experiencing subsyndromal depression, psychosocial functioning is between good and fair; when minor depressive or dysthymic symptoms are present, functioning is fair; and when patients have symptoms at the threshold for major depression, functioning is poor.

Much of the research and clinical attention in bipolar disorders has been focused on syndromal manic and major depressive episodes. However, we have shown previously[12-14] that the course of bipolar illness is dominated by affective symptoms below the threshold of MDD and mania. We have now shown in 3 separate diagnostic groups (BP-I, BP-II, and unipolar MDD[17]) that minor and subsyndromal depressive symptoms are associated with significant psychosocial disability as compared with months when the same patients have no symptoms of a mood disorder. Altshuler et al[26] found that in a sample of male patients with BP-I who recovered from syndromal manic, hypomanic, or MDD episodes for at least 3 months, the degree of residual depressive symptoms measured by scores on the Hamilton Depression Scale was positively associated with the level of psychosocial impairment as measured by the Global Assessment of Functioning Scale. While the direction of causality is not clear, it is important to note that the goal of treatment is not only to reduce symp-

toms but also to promote normalization of psychosocial functioning. We therefore submit that it is important to reduce, to the extent possible, all of the levels of depressive symptoms in bipolar illness.

MANIC SPECTRUM IN BP-I AND BP-II

Patients with BP-I have a significant, stepwise progression in disability associated with each increment in manic or hypomanic symptom severity, except for the asymptomatic status vs subsyndromal level of hypomanic symptoms. The situation for hypomanic symptoms in BP-II is quite different. Patients with BP-II actually experience a nonsignificant improvement in psychosocial functioning as they go from the asymptomatic status to subsyndromal hypomanic symptoms ($P=.25$). When patients with BP-II are hypomanic, psychosocial functioning is rated the same as when they are asymptomatic. Our present finding that hypomania and its milder levels are not significantly impairing in BP-II is consistent with other studies[27-30] indicating that hypomania is not necessarily disruptive and may even be adaptive. Benazzi and Akiskal[31] found that several key signs and symptoms of hypomania in a clinical sample featured behaviors that potentially improve functioning even in short-term hypomanias (2-4 days, which is shorter than the *DSM-IV*[20] threshold for frank hypomania). According to Akiskal,[30] these positive hypomanic signs and symptoms include increased cheerfulness, jocularity, gregariousness, confidence, sexual drive, and vitality. This makes diagnosis of hypomania difficult since psychosocial functioning may be sufficiently good during hypomania so that it is not experienced as a period of illness. In fact, in *DSM-IV*,[20] psychosocial impairment is not required for a diagnosis of hypomania whereas it is for mania. Hypomania in BP-II presents not only a diagnostic challenge but also a therapeutic challenge to clinicians since the hypomanic symptom status per se is not associated with significant psychosocial impairment.

DEPRESSIVE VS MANIC OR HYPOMANIC SYMPTOMS

Treatment of patients with BP-I has focused on management of the more dramatic manic episodes and symptoms, not on depression. In this study, we found that depressive symptoms are at least as disabling, and sometimes significantly more disabling, than manic symptoms at comparable levels of severity. For patients with BP-I or BP-II, minor depression or dysthymia is associated with significantly more psychosocial disability than hypomania ($P=.003$ and $P<.001$, respectively). In addition, subsyndromal depressive symptoms are more disabling than subsyndromal hypomanic symptoms in BP-II ($P=.02$). It is noteworthy that major depression is marginally rated as more disabling than mania in patients with BP-I ($P=.07$). This is consistent with the findings by Vojta et al,[10] who, despite considerable methodological differences from our present study, found self-reported quality of life to be highest in patients with bipolar disorder who were euthymic, significantly lower in patients who were manic or hypomanic, and significantly lower yet in patients with bipolar disorder who were in major depressive or mixed polarity episodes. Our article underscores the clinical significance of all of the severity levels of depressive symptoms in BP-I and BP-II as well as the need for greater attention to depressive symptoms in the diagnosis and treatment of bipolar disorders.

BP-I VS BP-II

In this study, we show that BP-II is comparable to BP-I in terms of psychosocial disability at corresponding levels of affective symptom severity. Only during hypomania are patients with BP-I significantly more impaired than patients with BP-II ($P=.003$) owing to the nonsignificant improvement in psychosocial functioning of BP-II during subsyndromal hypomania as compared with when the same patients are asymptomatic. When patients with BP-II are hypomanic, psychosocial functioning is rated as good, the same as when they are asymptomatic. This highlights an important difference in psychosocial functioning between BP-I and BP-II.

DISABILITY COMPARED WITH CURRENTLY WELL SUBJECTS

It is encouraging to find that when patients with bipolar disorder are asymptomatic, their psychosocial functioning normalizes and is rated as good. At the same time, it is sobering to learn that, even when asymptomatic, their psychosocial functioning is slightly but significantly worse than that of a well control group ($P<.001$). Even subsyndromal depressive or manic symptoms in BP-I or subsyndromal depressive symptoms in BP-II are associated with clinically significant worsening of psychosocial dysfunction. This has implications for both diagnosis and treatment.

CYCLING OR MIXED POLARITY

Based on prior CDS descriptions of poorer long-term outcomes in patients entering the study with cycling or mixed polarity symptoms,[32] we anticipated that psychosocial impairment would be significantly worse during months with symptoms of cycling or mixed polarity than during periods with pure depression or pure mania. A more definitive analysis would examine every combination of manic and depressive symptom severity separately. However, from the present analysis, it does not appear that symptoms of cycling or mixed polarity are more disabling than symptoms of pure depression or pure mania. Thus, these data confirm the prior findings by Vojta et al[10] that disability associated with cycling or mixed symptoms appears to be determined by the severity level of the depressive symptoms.

METHODOLOGICAL ISSUES

The LIFE interviews have been shown to yield good interrater reliability (intraclass correlation coefficients >0.88) for symptom severity and psychosocial impairment.[22] Differential patterns of psychosocial disability found in relation to symptom severity levels within this

National Institute of Mental Health Collaborative Program on the Psychobiology of Depression–Clinical Studies

This study was conducted with current participation of the following investigators: M. B. Keller, MD (Chairperson, Providence, RI); W. Coryell, MD (Co-chairperson, Iowa City, Iowa); D. A. Solomon, MD (Providence); W. A. Scheftner, MD (Chicago, Ill); J. Haley (Iowa City); J. Endicott, PhD, A. C. Leon, PhD, J. Loth, MSW (New York, NY); and J. Rice, PhD (St Louis, Mo). Other current contributors include: H. S. Akiskal, MD, J. Fawcett, MD, L. L. Judd, MD, P. W. Lavori, PhD, J. D. Maser, PhD, and T. I. Mueller, MD.

This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement. The data for this manuscript came from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression–Clinical Studies (*Am J Psychiatry*. 1979;136:49-51). The Collaborative Program was initiated in 1975 to investigate nosologic, genetic, family, prognostic, and psychosocial issues of mood disorders, and it is an ongoing, long-term, multidisciplinary investigation of the course of mood and related affective disorders. The original principal and co-principal investigators were from 5 academic centers and included Gerald Klerman, MD (Co-chairperson),† Martin Keller, MD, Robert Shapiro, MD† (Massachusetts General Hospital and Harvard Medical School, Boston); Paula Clayton, MD, Theodore Reich, MD,† Amos Wellner, MD† (Washington University Medical School, St Louis, Mo); Jean Endicott, PhD, Robert Spitzer, MD (Columbia University, New York, NY); Nancy Andreasen, MD, PhD, William Coryell, MD, George Winokur, MD† (University of Iowa, Iowa City); Jan Fawcett, MD, William Scheftner, MD (Rush-Presbyterian–St Luke's Medical Center, Chicago, Ill). The National Institute of Mental Health Clinical Research Branch was an active collaborator in the origin and development of the Collaborative Program with Martin M. Katz, PhD, branch chief as the co-chairperson, and Robert Hirschfeld, MD, as the program coordinator. Other past contributors include J. Croughan, M. T. Shea, R. Gibbons, M. A. Young, and D. C. Clark.

†Deceased.

study provide encouraging evidence of the validity of symptom status and psychosocial impairment ratings.

Correlations between psychiatric symptom rating severity levels and LIFE-RIFT impairment scores were moderately high ($r=0.70$ for patients with BP-I; $r=0.67$ for patients with BP-II). However, this explains only half or less of the variance of each measure, indicating that there is a substantial amount of unique information in each.

Psychiatric symptom rating coding rules for the CDS specify that once an affective episode is resolved to the asymptomatic level, subsyndromal affective symptoms are generally not recorded unless they at least meet the threshold for minor depressive or hypomanic episodes. However, prodromal or isolated subsyndromal symptoms are recorded in the *DSM-III* categories of atypical depression, adjustment disorder with depressed mood, or cyclothymic personality.

Since the LIFE-RIFT is a composite of 4 domains of function, we conducted mixed regression analysis for all of the specific domains assessed by the LIFE interview. We found that work role function is the most sensitive to disruption by affective symptoms, even at the subsyndromal level, indicating that it could possibly serve as an early warning sign of depression in BP-I and BP-II or of mania in BP-I. This warrants further study.

To shed light on the cumulative, long-term personal disability and public health impact of these disorders, we are preparing a separate article that integrates the total cumulative level of psychosocial impairment in BP-I and BP-II during long-term follow-up, incorporating all of the mood states and levels of symptom severity experienced during that time.

It is beyond the scope of this article to explore the effect of comorbid diagnoses, psychotic features, or other relevant characteristics that may affect psychosocial disability. In light of the findings by Solomon et al[33] that patients with euthymic BP-I with higher lithium levels had better psychosocial functioning than those with lower levels, it is likely that the type(s), dosage, timing, and individual response to treatment affect psychosocial impairment during all of the phases of bipolar illness. We previously found that patients with BP-II were prescribed somatic treatment (medication or electroconvulsive therapy) significantly less often than patients with BP-I at the same symptom severity levels ($P<.01$ for all except hypomania, for which $P=.07$).[14] This strongly suggests that clinicians underrecognize the highly chronic and depressive nature of BP-II and, consequently, underprescribe for this disorder in both acute and maintenance treatment. It is hoped that the present article will bring attention to the high level of psychosocial disability associated with BP-I and BP-II, especially during periods of depression.

CONCLUSIONS

The longitudinal symptomatic course of bipolar disorders is expressed as a dimensional continuum of affective symptom severity. Symptom severity and psychosocial disability fluctuate together during the course of illness. Depressive symptoms in both bipolar subtypes are at least as disabling as, and sometimes more disabling than, manic or hypomanic symptoms. Subsyndromal depressive symptoms are associated with significant impairment in BP-I and BP-II as compared with the asymptomatic status ($P<.001$). Subsyndromal hypomanic symptoms are not associated with significant increases in impairment for either disorder ($P=.20$ and $P=.25$, respectively), and they may even enhance functioning in BP-II. When patients with BP-I or BP-II are asymptomatic, their psychosocial functioning is good, but not as good as that of well controls. These findings indicate that the depressive phase of bipolar illness is equal in importance to the manic or hypomanic phase, and they confirm the advantage of studying BP-I and BP-II separately.

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Additional Information: This study was conducted with participation of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression–Clinical Studies. For a complete listing of participants, see the box on page 1329.

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