Key Words: bipolar disorder, depression, psychosocial function, personality

Correlates of Functioning in Bipolar Disorder

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ABSTRACT ~ ***Objectives:*** *Our primary aim was to describe unique correlates of functioning in bipolar disorder (BD).* ***Experimental Design:*** *The study included the first 500 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Patients were 41.9 ± 12.7 years old, and diagnosed with bipolar I, II or NOS, verified by structured interview. Overall functionality was determined by the Range of Impaired Function Tool (LIFE-RIFT). Stepwise multiple regression analysis tested the non-redundant-independent- association of 28 variables on functioning.* ***Principal Observations:*** *Severity of depression symptoms was significantly and uniquely correlated with impaired functioning in the context of a wide variety of demographic and clinical variables, contributing 60.9% to the total variance in overall functioning (*$\beta = 0.254$, $p = 0.0001$*). Substantial variance in function remains unexplained.* ***Conclusions:*** *Intensity of depressive symptoms is the major determinant of impaired functioning in bipolar disorder, but longitudinal analyses may further explain the substantial variance in function not explained by this large and comprehensive model. Treatments and outcome assessment for patients with bipolar disorders should consider both functional and symptomatic change.* Psychopharmacology Bulletin. *2008;41(4):51–64.*

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INTRODUCTION

Bipolar disorder (BD) is associated with impaired psychosocial functioning, in both symptomatic and recovered states (1–3). Beyond symptom intensity, there is no clear agreement as to which variables are most highly correlated with functioning (4). The variability in results may be due to diverse assessment methods of functioning (5), different patient selection criteria or different independent correlates used across studies (1,4).

The presence of depression has been uniformly identified as a major correlate of function in bipolar disorder (2–4,6–8). Few studies have investigated the unique effect of the severity of current depression on overall functioning (3,9) in the context of other confounding clinical variables (for example, co-morbid psychiatric illnesses, illness course, demographic variables). Some studies have shown that acute manic and/or hypomanic symptoms are also correlated with psychosocial functioning (9,10). Nevertheless, the intensity of affective (9), manic (4,9,10), depressive symptoms or cumulative morbidity (4,7,11) do not explain all of the variance in the functional domains of patients with bipolar disorder. Indeed, co-existing substance use (12–14) or anxiety disorders (15), history of psychosis (16), number of lifetime episodes (17) and rapid cycling course (18) also correlate with impairment in functioning. Euthymic patients with co-existing bipolar disorder and personality disorders have more impaired psychosocial functioning than patients with bipolar disorder without personality disorder diagnoses (19). Personality factors (extraversion, neuroticism) affect work performance (11) in patients with bipolar disorder. Attributional styles interact with life events in predicting the intensity of both manic and depressive symptomatology (20). The direct effect of attributional style on function is not known.

The current study examines the association of a large number of demographic, clinical, affective, course, and personality variables on function in a cohort of persons with bipolar disorder. In previous studies the relatively modest sample size may have limited the number of independent correlates of functioning included in multivariate analyses (3,9). Our primary goals were to determine correlations between psychosocial functioning and (1) severity of depression symptoms, after controlling for a large number of other putative explanatory variables (2), the severity of (hypo) mania, history of co-morbid psychiatric illnesses, previous illness course, and personality traits.

Our major exploratory hypotheses were as follows:

1. The intensity of current depression will be the strongest unique correlate of psychosocial impairment even after controlling for other explanatory clinical variables.

2. History of severe morbidity (past depressive morbidity, anxiety disorders, frequent past mood episodes) as well as personality factors will also be uniquely associated with impaired functioning.

MATERIALS AND METHODS

Study Overview

This cross-sectional study describes the association of demographic, clinical course characteristics, and mood state on functioning in the first 500 participants enrolled in the Systematic Enhancement Program for Bipolar Disorders (STEP-BD). STEP-BD is a large, NIMH-funded, disease management program, which shares a battery of common assessments and practice procedures, consistent with effectiveness research. At its largest, STEP-BD had 21 active clinical sites across the US, some with associated community partner sites. More information about methods and assessment procedures utilized in STEP-BD are described elsewhere (21).

Inclusion and Exclusion Criteria

Eligibility criteria were non-restrictive in order to maximize the generalizability of study results. Patients were at least 15 years of age, met DSM-IV criteria for bipolar I, bipolar II, bipolar NOS, or schizoaffective disorder with manic or bipolar subtypes. Patients entered the study in any mood state. Exclusion criteria were limited to the unwillingness or inability to comply with study assessments, or inability to give informed consent. The study was approved by the institutional Human Subject Review Board of each site and all patients gave written informed consent before enrollment in the study.

Measures and Procedures

All clinician- and patient-rated instruments examined in this report were collected cross-sectionally at study entry as part of the intake assessment. Investigators and clinicians at all study sites received extensive standardized training and met certification requirements on the study measures and assessment tools. To prevent rater drift, every six months randomly selected clinical status ratings (see below) were reviewed, and remedial training was administered as necessary.

DSM-IV Axis I diagnoses were confirmed using the Mini International Neuropsychiatric Interview (MINI Version 4.4) (22). The current clinical status of the patients at intake was determined by a semi-structured diagnostic instrument, the "Clinical Monitoring Form" (CMF) (21) based on DSM-IV criteria. The eight operationally defined

clinical states were *depression, mania, hypomania,* or mixed episode, *recovering, recovered, continued symptomatic, and roughening* (worsening). The categories of continued symptomatic and roughening are viewed as subsyndromal states (21).

The Affective Disorders Evaluation (ADE), a semi-structured interview (21), was used to obtain baseline information about the previous course of illness, duration of illness, number of affective (hypomanic, manic, mixed and depressed) episodes over the last 12 months, the longest period of continuous euthymia in the past two years, as well as history of hospitalizations, co-morbid medical conditions, history of psychosis, the current medications and participation in psychotherapy. Intensity of manic and depressive symptoms was assessed using the Young Mania Rating Scale (YMRS, range 0–60) (23) and Montgomery-Asberg Depression Rating Scale (MADRS, range 0–60) (24).

Functional impairment over the last 7 days prior to evaluation was assessed with the Range of Impaired Function Tool (LIFE-RIFT) (25,26). The LIFE-RIFT is a brief, semi-structured, clinician administered scale that assigns scores from 1–5 (1-no impairment, 3-moderate/fair and 5-severe impairment) to four areas of function (work/role performance, interpersonal relationships, recreation and satisfaction with activities). Overall function score ranges from 4 to 20. The reliability and validity of the LIFE-RIFT has been established in BD with high interrater reliability (intraclass correlation coefficient, ICC: 0.99) and concurrent validity (correlation between LIFE-RIFT total score and GAS ($b = -0.03$; 95% CI: –0.04 to –0.02; $z = 4.88$, $p<0.001$; $R^2 = 0.39$; $N = 153$ subjects; observations = 538) (25). LIFE-RIFT total score showed good internal consistency (Cronbach coefficient, α was 0.83).

Personality characteristics were assessed by the NEO-Five Factor Inventory (NEO-FFI) (27,28), which measures five domains of personality; Neuroticism, Extraversion, Openness to Experience, Conscientiousness, and Agreeableness. Other measures included the Attributional Style Questionnaire (ASQ) (29,30), a self-report measure for three dimensions of attribution to causes of events: internal-external, stable-unstable, and global-specific. We included both the scores of attributions for negative events (ASQ–) and positive events (ASQ+). The total score Personality Disorder Questionnaire (PDQ) (31) was used to provide additional information of potential personality disorders.

Based upon a literature review, we identified a list of putative correlates of functioning in patients with bipolar disorder. These included

demographic and clinical variables characterizing illness type, course, severity, co-existing psychiatric and medical conditions and personality traits, (3,4,6,9–13,15,16,18–20,32–40) and can be found in Table 3. Several variables that had not been explored to date were also included after consensus for inclusion by three authors (LGy, MSB, LBM). We have not included variables which themselves can directly represent functioning such as education, social class, and marital status, among others.

Data Analysis

Means and standard deviations (SDs) were calculated for all continuous variables and percentages for discrete variables.

We utilized two analytic strategies to investigate the association between putative correlates and functional impairment variables. First, using bivariate linear regression models we explored the associations between each putative independent variables and the LIFE-RIFT total score (dependent variable). Correlation coefficients (R), beta, F values and p are presented. We did not employ Bonferroni corrections of the p values for multiple comparisons because of the exploratory goals of the univariate analyses.

Second, for the functional indices, we utilized stepwise regression analyses to identify independent variables that contributed uniquely to the variance. The significance level for entry in to the models was ≤ 0.15 and for retention in the models was ≤ 0.05, consistent with the exploratory approach. As in the stepwise analysis, no adjustments to p-values were made for multiple comparisons, so results must be interpreted accordingly.

RESULTS

Sample Characteristics

Table 1 summarizes the demographic and clinical characteristics of the patient sample.

The majority of the patients had Bipolar I disorder and less than one fourth had Bipolar II disorder. Women were only slightly more represented than males. The most frequent comorbid psychiatric illnesses were anxiety disorders. Overall, the severity of depressive symptoms was in the mild-to-moderate range (MADRS = 14.8 ± 11.3). The severity of the manic symptoms was very mild (the average YMRS = 6.0 ± 6.5).

At entry into the study, 51% of the participants had a clinical status of *recovered* or *recovering*, 25% were currently in a major depressive episode, and 12% met criteria for a current manic, hypomanic or mixed episode.

TABLE 1

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTRISTICS

	N OF TOTAL SAMPLE	PARAMETER VALUE
Demographic Features		
Age (years) mean (S.D.)	492	41.9 (12.7)
Gender Male/Female (%)	492	40.7/59.3
Race (%)	500	
Caucasian		90.4
African American		3.9
Other		5.7
Unemployed/Disabled %	499	37.7
Diagnostic Features		
Bipolar I (%)	499	74.2
Bipolar II (%)	499	22.7
Bipolar NOS (%)	499	3.2
Co-Morbidities		
Current Anxiety Disorder (%)	473	30.2
Current Alcohol/Drug Use Disorder (%)	472	9.7
Attention Deficit/Hyperactivity Disorder (%)	471	7.0
Other Axis I morbidity (%)*	473	5.3
Any Personality Disorder (DSM-IV) (%)	500	11.0
Any Medical Co-Morbidities-current (%)	500	42.0
Course Features		
History of psychosis (%)	477	43.8
Number of (Hypo)manias last year mean (S.D.)	460	1.9 (3.4)
Number of Depressions last year mean (S.D.)	424	1.9 (2.6)
Duration of illness mean (S.D.)	496	24.0 (13.0)
Illness years (ratio of years ill: age) mean (S.D.)	488	0.56 (0.21)
Longest time euthymic last 2 years (days) mean (S.D.)	474	209.9 (220.6)
Number of medications at baseline mean (S.D.)	500	1.65 (1.31)
Mood State at Baseline		
MADRS mean (S.D.)	478	14.8 (11.3)
YMRS mean (S.D.)	480	6.0 (6.5)
Personality Features		
ASQ negative score mean (S.D.)	340	14.0 (1.9)
ASQ positive score mean (S.D.)	334	14.5 (1.9)
NEO-FFI Neuroticism mean T score (S.D.)	418	62.9 (10.4)
NEO-FFI Extraversion mean T score (S.D.)	414	43.4 (12.2)
NEO-FFI Openness mean T score (S.D.)	420	54.7 (11.3)
NEO-FFI Agreeableness mean T score (S.D.)	420	45.2 (12.4)
NEO-FFI Conscientiousness mean T score (S.D.)	417	39.7 (11.5)

NEO-FFI: NEO Five Factor Inventory; Score of 50 is the population standard *: "Other Axis I morbidity" includes (hypo)manic episodes, anxiety disorders or psychotic disorders due to substance use or medical conditions, current psychotic disorders, schizoaffective disorder, bulimia and anorexia nervosa.

Abbreviations: BD, bipolar disorders; ADHD, attention deficit hyperactivity disorder; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale.

TABLE 2

FUNCTIONAL STATUS OF PATIENTS AT INTAKE

	N OF SAMPLE	MEAN (S.D.)
LIFE-RIFT Total Score	467	11.1 (3.9)
LIFE-RIFT Satisfaction	481	2.7 (1.1)
LIFE-RIFT Recreation	481	2.6 (1.3)
LIFE-RIFT Work	470	3.0 (1.5)
LIFE-RIFT Relationship	483	2.8 (1.2)
Work Days Missed	167	11.5 (10.0)

The remainder of the sample met criteria for subsyndromal states. LIFE-RIFT scores of patients during the week before enrollment indicated on average a moderate impairment in functioning (Table 2).

Thirty-one percent of the sample missed on average 11.5 ± 10.0 days of work due to symptoms of bipolar illness or other psychiatric condition in the past 30 days.

Bivariate Analyses

Of 28 independent variables, 20 were significantly associated with the LIFE-RIFT total score (Table 3).

The total MADRS score showed the strongest positive correlations with LIFE-RIFT total score (i.e., the higher the MADRS score was the larger the functional impairment). The score of YMRS positively correlated with the LIFE-RIFT total score: those with increased symptoms of (hypo) mania at baseline tended to have more functional impairments. There was a strong positive correlation between the longest time of being continuously euthymic over the last 2 years and the LIFE-RIFT total score (a longer the euthymic period was associated with less functional impairment).

There was no correlation between the type of bipolar disorder (Bipolar I or II) and functioning. There was a strong negative correlation between having a comorbid anxiety disorder and functioning.

Greater neuroticism was associated with more functional impairment, while greater extraversion, conscientiousness and agreeableness were associated with less functional impairment. The ASQ- score was positively associated with LIFE-RIFT total score.

Factors Uniquely Associated with Function

Factors uniquely contributing to the variability of function are presented in Table 4.

Only 3 variables (MADRS, "other" Axis I morbidities, and extraversion) contributed uniquely to LIFE-RIFT total score (Table 4) in

TABLE 3

UNIVARIATE ASSOCIATIONS BETWEEN DEMOGRAPHIC AND ILLNESS CHARACTERISTICS AND FUNCTIONAL IMPAIRMENTS AS ASSESSED BY THE LIFE-RIFT

INDEPENDENT VARIABLES	LIFE-RIFT TOTAL B, (F), P
Age (years)	+0.01, (0.50), 0.4788
Gender (female)	−0.370, (1.01), 0.315
Race (white)	+0.328, 0.30, 0.5859
Bipolar I	+0.656, (2.63), 0.1057
Bipolar II	−0.605, (2.05), 0.1528
Anxiety Disorders-Current	+2.707, (51.12), <0.0001
Drug and Alcohol Abuse/Dependence-Current	+1.594, (6.61), 0.0104
ADD/ADHD	+2.239 (9.47), 0.0022
Other Axis I morbidities	+2.661, (10.89), 0.0010
Any Personality Disorders	+1.690, (9.11), 0.0027
Any medical co-morbidity	−0.002, (0.00), 0.9949
History of Psychosis	−0.564, (2.36), 0.1255
Years of ill/Age	+2.57, (8.59), 0.0036
Rapid cycling last year	+1.301, (9.63), 0.0021
Number of (hypo)manic episodes last year	+0.207, (12.59), 0.0004
Number of depressive episodes last year	+0.308, (16.66), <0.0001
Longest time period of continued euthymia	−0.006, (66.72), <0.0001
MADRS Score at intake	+0.239, (426.7), <0.0001
YMRS Score at intake	+0.169, (41.54), <0.0001
NEO-FFI neuroticism	+0.155, (81.58), <0.0001
NEO-FFI extraversion	−0.114, (56.56), <0.0001
NEO-FFI openness	−0.034, (4.26), 0.0397
NEO-FFI agreeableness	−0.65, (18.43), <0.0001
NEO-FFI conscientiousness	−0.089, (28.69), <0.0001
ASQ−	+0.412, (5.89), <0.0001
ASQ+	+0.148, (1.63), 0.2027
Psychotherapy-Additional	+1.039, (8.44), 0.0038
Current number of medications taken	+0.619, (21.22), <0.0001
Total number of significant explanatory variables	**20**

the stepwise multiple regression analysis. MADRS scores were strongly associated with LIFE-RIFT total scores; a one unit increment in MADRS score is associated by 0.254 unit increment in the LIFE-RIFT. Total LIFE-RIFT score was also positively associated with the presence of "Other Axis I morbidities." NEO-FFI Extraversion had a negative relationship with overall functional impairment (the more extraverted patients functioned better); a one unit increase in the extraversion score was associated with 0.0367 unit decrease in LIFE-RIFT Total score. The presence of MADRS scores alone explained 60.9% of the variance in the total LIFE-RIFT score,

TABLE 4

FACTORS UNIQUELY ASSOCIATED WITH FUNCTION-SUMMARY OF STEPWISE SELECTION

PREDICTOR VARIABLES:	LIFE-RIFT, TOTAL BETA , (F VALUE), P
Symptom Levels	
MADRS	+0.254, (248.39), <0.0001
Axis I Morbidity	
"Other" Axis I morbidities	+2.666, (12.21), <0.0001
Personality Characteristics	
Extraversion	−0.0367 (0.009), 0.0089
Total Variance accounted for %	63.9
Number of uniquet explanatory variables	3

whereas the other 2 variables explained only 3.0% of the total explainable variance (63.9%).

DISCUSSION

The current study examines correlates of function in BD using, a broad array of putative correlates in a large cohort of patients with bipolar disorders in a wide range of mood states. Unique aspects of the current study design include the assessment of personality traits in addition to demographic, course, and clinical variables.

Several findings are novel, while others underscore and extend data in the published literature. The intensity of baseline depressive symptoms was strongly associated with impairment in functioning. This finding confirms previous findings in the literature (2–4,6,8,9), although now examined in the context of an extensive array of demographic and clinical variables in a large cohort.

We did not analyze the association of functional impairment with depressive symptoms in categorically defined DSM-IV (hypo) manic, mixed or pure depressive episodes, respectively. Thus, we can not draw definitive conclusions whether the intensity of depressive symptoms correlates with functioning in all mood states equally or differentially. In STEP-BD, the majority of patients spent their time in either recovered/recovering or depressed states, versus mixed or (hypo)manic states The interactions between affective episodes and symptom intensity on function will need to be tested in the future.

Intensity of current (hypo) manic symptoms did not correlate independently with overall functioning when other variables were controlled. A self-report community based survey (6) found that while both depressive and manic symptoms negatively affected social life and family life, depression was most harmful. Their findings are only partially consistent

with our findings, perhaps due to the different methodologies used. For example, Calabrese et al (6) used self report and days of hyper/energetic feelings over 4-weeks time for quantifying hypomanic/manic states while we used clinician-administered symptom intensity ratings with YMRS over a 1 week period. In light of more depressive morbidity, with the low frequency of (hypo) manic and mixed episodes and the low average YMRS score in this cohort, the representativeness of our findings to those in (hypo) manic states is limited.

This study is the first to examine the effect of personality traits on functioning in BD using a full structural model of personality (28,29). The finding that extraversion was mildly associated with overall functioning is novel and has heuristic value. Assessment of this personality trait may help predict treatment prognosis. Additionally, interventions to improve social and communication skills may assist patients in experiencing better functional outcomes. While extraversion added little variability to overall function, this finding is consistent with a positive relationship between extraversion and subjective well being, life satisfaction or functioning in healthy volunteers (37,38).

It is surprising that specific co-morbid Axis I illnesses did not uniquely correlate with overall functioning in the context of other clinical variables. The presence of depression may have diminished effect on the independent contribution of other Axis I illnesses to function (for example anxiety disorders). This notion is supported by other work utilizing the same cohort (Simon et al (15)) indicating that the presence of current anxiety disorder affected function most strongly when those patients were recovered or recovering from depression, (hypo)mania or mixed states.

It is possible that other factors, not included in this analysis, determine function in BD. These may include social class (39), insight and coping with problems of mania or depression (40), self-esteem (41), positive family environment (42,43), social support and availability of resources (40).

Limitations of the Study

This study is cross-sectional, and course variables were collected retrospectively and thus subject to recall bias. The inclusion of BD I, BD II and BD NOS and schizoaffective disorder patients enhanced the representativeness of the sample, but also introduced heterogeneity. In addition, racial and ethnic minorities were not well-represented in this sample, and hence the potential predictive significance of this characteristic could not be assessed. Most patients entered as outpatients, which limited the range of pathology examined and representativeness of our findings for patients with bipolar disorder in general. The study was largely exploratory and the

predictive validity of the unique independent correlates will be tested on the prospective data collected in the STEP-BD cohort.

The direction of causality cannot be determined by associational studies. These analyses therefore cannot determine whether depression causes loss of function or vice versa—causation may well be bidirectional and iterative. Affective morbidity may lead to impaired psychosocial function which in turn leads to worse affective outcome (7) and low self esteem (41). Thus, functional impairments could perpetuate a vicious cycle between psychosocial impairments and affective morbidity.

Relevant to this, and consistent with the substantial amount of unexplained variance in functional status, Bauer and McBride (44) proposed that function is not simply a sequelae of disease processes or other pathology, but it is modulated by an individual's "host factors" such as illness management skills, knowledge base, socioeconomic status and attitudes and preferences. Such characteristics modulate function, and also treatment participations, and ultimately illness expression. By this model chronic treatment aimed at directly influencing function and illness management skills will be required in addition to purely symptomatic treatment in order to optimize social role and work function in bipolar disorder. These treatment modalities may include vocational counseling, family interventions (42,43), self-management training (44), education (45) and psychotherapy (46,47).

CONCLUSIONS

The cohort of 500 patients with diagnoses of bipolar disorders had moderately impaired functioning as measured by the LIFE-RIFT. Of the large number of clinical and demographic variables assessed, the intensity of depression was the dominant unique contributor to the variance in overall functioning. Despite the inclusion of a many potential predictive variables, 36.1% of the variance in functioning remained unexplained. Future studies need to address the role of other clinical and social variables as explanation for the variability on functioning patients with bipolar disorder. Treatments and outcome assessments for patients with bipolar disorders should consider both functional and symptomatic change.✤

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Additional detail on STEP-BD can be located at http://www.nimh.nih.gov/health/trials/practical/step-bd/questions-and-answers-for-the-systematic-treatment-enhancement-program-for-bipolar-disorder-step-bd-study-background.shtml.

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DECLARATION OF INTEREST

None.

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