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Functional outcomes in first-episode patients with bipolar disorder: a prospective study from the Systematic Treatment Optimization Program for Early Mania project

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Abstract

Background: Bipolar disorder causes substantial psychosocial morbidity, as it frequently affects independent living, vocational, and social activities. However, there is a relative dearth of research on functional outcomes and their predictors in first-episode manic patients from prospective studies early in the course of bipolar disorder.
Methods: The Systematic Treatment Optimization Program for Early Mania (STOP-EM) project recruited 53 patients who recently experienced their first episode of mania with or without psychosis. Multidimensional Scale of Independent Functioning (MSIF) was used as the main measure of functional outcome. Of the 53 patients recruited, 35 completed the 6-month follow-up assessment.
Results: At entry, 62.3% of patients had met criteria for full remission of mood symptoms. Despite this, the mean baseline MSIF score was 4.5 points; 62.3% of the patients had at least moderate disability. A significant improvement in functioning was noted at 6 months relative to entry as indicated by the reduction in mean MSIF scores from 4.5 to 2.6 ($t = 4.1$, $df = 34$, $P < .001$). The proportion of patients with at least moderate disability was reduced from 62.3% to 25.7% at 6 months. Remission of depressive symptoms at 6 months was associated with better functioning ($P < .01$). In a regression model, only depressive symptoms were significantly correlated with the MSIF global functional scores at 6 months. Even subsyndromal depressive symptoms were significantly correlated with disability ($r = 0.3$, $P < .05$).
Conclusion: The findings highlight the deleterious impact of depressive symptoms on functional recovery after a first manic episode even when they are subsyndromal. Considered together, these results emphasize the importance of an aggressive treatment of subsyndromal depressive symptoms for functional recovery.

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1. Introduction

Bipolar disorder (BD) causes substantial psychosocial morbidity, as it frequently affects independent living, vocational, and social activities. The onset of the illness most commonly occurs in adolescence or early adulthood, which contributes to pervasive functional impairment and socioeconomic burden. Bipolar disorder has been reported to be the sixth leading cause of disability in young adults in market economies worldwide [1]. Achieving functional recovery has proven to be more challenging than symptomatic improvement in the treatment of patients with BD [2]. Even treatment-responsive patients, who remain well syndromally for extended periods of time, frequently demonstrate subthreshold symptoms and continuing psychosocial morbidity and cognitive impairment [3], suggesting that functional deterioration occurs and may be enduring. However, there is a relative dearth of research about functional outcomes from prospective studies in patients with BD who recently had their first manic episode. An understanding of predictors of functional outcome in the early stages of the BD illness is highly needed, as this strategy is more likely to take into account the course of the illness and may contribute to the development of effective preventive interventions for psychosocial morbidity in BD.

Diverse cross-sectional and prospective studies have investigated the clinical correlates and predictors of outcome in BD, but they have not yielded consistent findings. The observed discrepancies are likely related to the fact that most of the studies used diverse or nonspecific functional assessment instruments [4,5]; initiated the follow-up with patients at different stages of the illness [2]; or included patients with psychosis, combining BD and schizophrenia [6]. Despite these limitations, data from these studies showed that rates of syndromic and symptomatic recovery are greater than functional recovery, with rates of 60% to 85% and of 33% to 68%, respectively, after 6 to 12 months of follow-up [4,5,7]. Among prospective studies, the most consistently reported predictors of functional impairment are psychiatric and medical comorbidity [8] and persistent interepisode subsyndromal symptoms, particularly depressive symptoms [2,9]. More recently, studies that have focused on the population of patients with first-episode (manic) BD confirmed that poor functional outcomes are common [5,6,10]. These studies suggested that worse premorbid functioning, lower social economic status [5], drug abuse, family history of affective disorder [10], persistent mood symptoms, longer hospitalization, earlier age of onset [6], and cognitive impairment [11] were associated with worse functional outcome. However, the above studies recruited patients after their first psychotic episode from inpatient units or from early psychosis intervention programs. The observed unfavorable outcomes could be related to selection of the most severe cases of BD with psychosis. As far as we are aware, none of these first-episode cohorts were designed to recruit both psychotic and nonpsychotic patients, hospitalized or not, in their first manic episode.

Although functional outcomes are of great interest, the appropriate measurement of disability is challenging. Initial studies assessed functioning using records of objective information such as employment status or used conventional scales with one overall rating such as the Global Assessment of Functioning (GAF) [12]. There are limitations with these strategies. First, productive activity can occur in various environments, such as at work, at school, or in the household, and can be impacted by cultural and contextual factors. Second, scales like the GAF do not permit a clear differentiation between clinical and functional outcomes, as the GAF also includes symptoms in its anchor points. The Premorbid Adjustment Scale was developed to provide a better measure of disability; but despite including multiple domains, it still evaluates broad areas of living skills and includes symptoms in its scores, such as energy level and interest in life [13]. Other studies have used the Psychosocial Functioning Scales of the Longitudinal Interval Follow-up Evaluation and the Social Adjustment Scale II, which include ratings for major life roles. However, they do not account for the influence of contextual factors, such as the level of support available and the tolerance to performance decrements [14]. These may be of particular importance in the study of first-episode samples, considering they are a younger group.

The Multidimensional Scale of Independent Functioning (MSIF) was developed to overcome these limitations. The MSIF is designed to rate independently the dimensions of role responsibility, level of support, and performance in each of 3 environments: work, education, and residential. The MSIF was first validated in 114 psychiatric outpatients with schizophrenia and schizoaffective disorder [15] and was recently validated in 143 patients with BD [14]. The advantages of this instrument are the independent rating of its domains and the ability to accommodate sources of external variability, such as level of support and tolerance. These characteristics of the scale provide a measure focused on the performance rather than on the objective socioeconomic (employment) condition. In studies with first-episode patients, it is particularly important to capture subtle differences in functional outcomes, which permit more accurate identification of the risk factors as well as effective treatments for disability.

The Systematic Treatment Optimization Program for Early Mania (STOP-EM) project provides a unique opportunity to investigate clinical correlates of functional outcomes in the early phase of the bipolar illness. The objectives of the current work were to prospectively assess functional outcome with the MSIF and to investigate its clinical correlates in patients with BD who recently experienced their first manic episode.

2. Methods

The STOP-EM project recruited 53 consecutive patients who recently experienced their first episode of mania with

or without psychosis, as per protocol described in a previous report [16]. Briefly, STOP-EM is a naturalistic, prospective study of patients after their first manic episode and their clinical and functional outcomes, health status, and brain morphology. *All* patients were clinically diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria [12] based on information obtained through the clinical interview *and* the Mini International Neuropsychiatric Interview [17]. Patients were recruited from University of British Columbia and Vancouver General Hospitals and affiliated sites as well as through referrals from physicians and psychiatrists. Patients were eligible for program entry if they were 14 to 35 years old and have experienced a manic episode, with or without psychosis, with or without any comorbidity, within the 3 months preceding enrolment. Those who had previously undiagnosed or untreated manic symptoms were excluded. Patients could be referred after hospitalization for mania, but also could be referred as outpatients. The STOP-EM program was initiated in July 2004 and has been active continuously since then. Subjects enrolled in the program received open-label maintenance treatment of BD from clinicians with expertise in management of mood disorders and familiar with the most recent clinical guidelines. Any new mood episodes were treated using best evidence-based practices. In addition to regular assessment of psychiatric status and medication monitoring, they received supportive therapy and psychoeducation to improve adherence to treatment. Subjects enrolled in the program were assessed as clinically indicated, and at a minimum of every 6 months for research purposes, over a 5-year follow-up period. We report here the functioning assessment for the first 6 months. Of the 53 patients recruited to date, 35 completed the 6-month follow-up visit and 12 are not due for 6-month follow-up visit yet. There were 6 dropouts (2 moved out of commutable distance, 2 withdrew consent, 2 were lost to follow-up).

Clinical and sociodemographic variables were assessed using a standardized protocol. Mood symptoms were quantified using Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), and Young Mania Rating Scale (YMRS). The criteria for full symptomatic remission were a YMRS score of less than 7 and a HAM-D score of less than 8 [18]. Scores higher than these were considered subsyndromal symptoms if the DSM-IV criteria for mood episode diagnosis were not present. The comorbidities were diagnosed according to DSM-IV criteria and confirmed with the Mini International Neuropsychiatric Interview. For analysis purposes, all current and lifetime anxiety disorders were grouped. Only current psychosis was included in the analysis. The drug abuse category included cannabis, opiate, stimulant, and alcohol abuse. The length of illness was considered the length of time since first mood episode, including previous depressive episodes. As well, age of onset refers to age of onset of first mood episode. Age and age of onset of mania overlap because patients were recruited after their first manic episode.

The MSIF was used as the main measure of functional outcome [15]. The MSIF ratings capture the modal state during the month before the interview. We used the global ratings across all 3 role dimensions, that is, performance, support, and role position, and an overall global rating. The global ratings within each role domain reflect the overall level of role responsibility, support, or performance across environments (work, school, and residential). Ratings on the MSIF were given based on the following anchors: (1) essentially normal; (2) very mild disability or low end of reference range; (3) somewhat disabled; (4) moderately disabled; (5) significantly disabled; (6) extremely disabled; and (7) totally disabled. For analysis purposes, in this work, scores from 1 to 3 were considered as none or minimal impairment; and scores of 4 to 7 were considered moderate to extreme impairment. The GAF was also used as a measure of disability.

All procedures described in this report received approval from the University of British Columbia Clinical Research Ethics Board. Written informed consent was obtained from all patients before any study procedures taking place.

2.1. Statistics

All analyses were performed with the Statistical Package for Social Sciences version 13.0 (SPSS Inc, Chicago, IL). Each subject was first designated as with or without moderate to extreme disability, as per scores in the MSIF scale. We compared the demographic variables and clinical features between those with and without disability using t tests and χ^2 tests, as indicated in Tables 2 and 4. Differences in medication use were compared using χ^2 test, as shown in Table 3. We did not control for multiple testing because these were exploratory analyses.

Multiple linear regressions were conducted to determine which factors significantly predicted the continuous outcome variable (MSIF scores). The selection of variables as potential predictors of the outcome was based on the findings of previous literature [2,8,19,20]. Predictors examined included continuous variables (age, years of education, number of previous depressive episodes, number of days depressed/manic, length of illness, age of onset, YMRS and HAM-D scores at baseline and at 6 months, number of suicide attempts, duration of first manic episode) and dichotomous variables (sex, psychosis, drug abuse and anxiety comorbidity, hospitalization in the first episode, depressive or manic relapse). First, a simple Pearson correlation was carried out to find out which variables were likely to correlate with the functional outcome. Afterward, those variables that were more likely to contribute substantially to the model's ability to predict the outcome—that is, those significantly correlated with the outcome—were entered in the regression model. These results are shown in Table 4. All statistical tests were 2-tailed

and were carried out using a significance level of $\alpha = .05$. Data are presented as means ± standard deviation (SD).

3. Results

Twenty-seven male and 26 female subjects have been recruited into the STOP-EM project to date. The age at first manic episode ranged from 17 to 32 years, and the mean number of years for education was 14.0 years for the whole sample. Eighty-eight percent of the patients (n = 47) were hospitalized for their first manic episode. Descriptive statistics for the entire sample showed that, at program entry, patients had minimal symptoms (mean MADRS = 6.2, YMRS = 3.8, HAM-D = 6.9) and 62.3% of patients had met criteria for remission of mood symptoms. Despite this, the MSIF mean score at entry was 4.57; and 62.3% of the patients had at least moderate disability.

At the 6-month assessment, 88.6% of patients met remission criteria for manic symptoms; and none had a manic relapse. However, 20% did not meet criteria for remission of depressive symptoms; and 28.6% of patients had experienced a depressive relapse at some point between program entry and 6-month assessment. A significant improvement in functioning was noted at 6 months relative to entry as indicated by the reduction of mean MSIF scores from 4.5 to 2.6, ($t = 4.1$, $df = 34$, $P < .001$). The proportion of patients with at least moderate disability was reduced from 62.3% to 25.7% at 6 months. The functional profile of patients with BD according to MSIF anchor points at entry and at 6 months is shown in Table 1. The GAF confirmed these findings, as the mean scores increased from 64.5 (SD = 12.9) at baseline to 76.4 (SD = 9.5) at 6 months ($t = -5.48$, $df = 32$, $P < .001$).

Table 2 shows the demographic variables for patients with and without functional impairment. There were no significant differences between those with and without disability regarding sex, age, years of education, and ethnicity. There was a statistical trend toward more male subjects having disability at baseline ($\chi^2 = 3.2$, $df = 1$, $P = .07$), which was significant at 6-month assessment ($\chi^2 = 5.8$, $df = 1$, $P = .02$). There were no significant differences in medication use between patients with or without functional impairment. At entry, 90.9% (n = 30) of patients with and 80% of those without disability were taking a mood stabilizer (ie, lithium, divalproex, or carbamazepine); 78.8% (n = 26) of patients with and 75% (n = 15) of patients without disability were taking antipsychotics; and only 3 patients were taking antidepressants, one without disability and two in the disability group. At 6 months, 100% (n = 9) of patients with and 84% (n = 21) of those without disability were taking a mood stabilizer; 44.4% (n = 4) of patients with and 57.7% (n = 15) of those without disability were on antipsychotics; and only 4 patients were on antidepressants, two in each group.

Table 1
Functional profile for the entire sample at entry and at 6 months

Variable	Entry (n = 53)	6-mo follow-up (n = 35)
Normal functioning	9.4%	22.9%
Very mild disability	17.0%	28.6%
Somewhat disabled	11.3%	22.9%
Moderately disabled	9.4%	14.3%
Significantly disabled	9.4%	5.7%
Extremely disabled	9.4%	5.7%
Totally disabled	34.0%	0%

Table 2
Sociodemographic variables among patients with and without disability at entry and at 6-month visit

Variable	Entry bipolar patients (53)		P	6-mo follow-up bipolar patients (35)		P
	None-mild disability 37.7% (20)	Moderate-extreme disability 62.3% (33)		None-mild disability 74.3% (26)	Moderate-extreme disability 25.7% (9)	
Sex						
Male	35.0% (7)	60.6% (20)	.07[a]	42.3% (11)	88.9% (8)	.02[c]
Female	65.0% (13)	39.4% (13)		57.7% (15)	11.1% (1)	
Age (y)*	22.15 (3.1)	22.21 (4.0)	.28[b]	21.88 (3.2)	23.88 (3.9)	.35[b]
Education (y)*	14.10 (1.9)	13.93 (2.5)	.20[b]	13.96 (2.0)	13.22 (2.7)	.70[b]
Ethnicity						
White	75.0% (15)	78.8% (26)	.89[a]	69.2% (18)	100% (9)	.16[a]
Asian	20.0% (4)	15.2% (5)		26.9% (7)	0%	
Other	5.0% (1)	6.1% (2)		3.8% (1)	0%	

[a] χ^2 test.
[b] t test.
[c] Fisher exact test.
* Mean (SD).

Table 3 shows differences in clinical features between those with and without moderate to extreme disability at entry and at 6-month visit. At entry, there were no significant clinical differences between those with and without disability. The remission of depressive symptoms was associated with better functioning at the 6-month visit ($\chi^2 = 9.5$, $df = 1$, $P = .006$). Six-month HAM-D and MADRS scores were significantly higher in those with moderate/extreme disability at the 6-month follow-up ($t = -3.8$, $df = 33$, $P = .001$ and $t = -3.3$, $df = 33$, $P = .002$, respectively). Interestingly, neither remission of symptoms at entry nor HAM-D scores at entry were different between those with or without disability at entry or at 6-month visit. There were no significant differences between patients with or without disability at 6-month follow-up with respect to any other clinical variables examined, such as age at illness onset, length of illness, number of previous mood episodes, type of index episode, psychosis, anxiety comorbidity, drug abuse, or number of suicide attempts.

There was a positive correlation between depressive symptoms and global scores of MSIF ($r = 0.58$, $P < .001$), as

Table 3
Clinical features among patients with and without disability at entry and at 6-month follow-up

Variable	Entry BD (53)		P	6-mo follow-up BD (35)		P
	None-mild disability (20)	Moderate-extreme disability (33)		None-mild disability (26)	Moderate-extreme disability (9)	
Age onset illness						
Mean (SD)	19.20 (3.3)	19.37 (4.9)	.891[a]	19.03 (3.7)	20.55 (7.3)	.565[a]
Length of illness						
Mean (SD) (y)	2.95 (3.5)	2.9 (3.2)	.985[a]	2.8 (3.3)	3.3 (4.6)	.736[a]
No. of previous depression						
Mean (SD)	1.3 (1.7)	1.0 (1.2)	.477[a]	1.2 (1.5)	1.3 (1.7)	.919[a]
No. of previous hypomania						
Mean (SD)	0.70 (1.8)	0.48 (1.6)	.654[a]	0.5 (1.6)	0.1 (0.3)	.480[a]
Lifetime index episode						
Mania	52.6% (10)	43.8% (14)	.139[b]	46.2% (12)	55.6% (5)	.685[b]
Depression	47.4% (9)	56.3% (18)		53.8% (14)	44.4% (4)	
Psychosis	5.0% (1)	21.2% (7)	.234[c]	7.7% (2)	22.2% (2)	.238[b]
Drug abuse	57.9% (11)	51.6% (16)	.665[b]	48.0% (12)	75.0% (6)	.242[c]
Anxiety	11.1% (2)	9.4% (3)	.884[c]	8.0% (2)	25.0% (2)	.241[c]
Suicide attempts						
Mean (SD)	0.30 (0.9)	0.06 (0.24)	.269[a]	0.27 (0.8)	0 (0)	.341[a]
YMRS mean (SD)						
Baseline	3.1 (7.2)	4.36 (4.7)	.448[a]	3.58 (5.7)	3.33 (4.1)	.908[a]
6 mo	0.60 (1.4)	0.55 (1.0)	.907[a]	0.62 (1.3)	0.44 (0.8)	.723[a]
HAM-D mean (SD)						
Baseline	8.1 (10.0)	6.2 (8.3)	.459[a]	6.5 (8.9)	7.56 (11.0)	.784[a]
6 mo	3.07 (5.1)	4.90 (5.4)	.324[a]	2.3 (3.4)	9.1 (6.8)	.001[a]
MADRS mean (SD)						
Baseline	7.7 (9.4)	5.4 (6.8)	.315[a]	5.9 (8.3)	6.7 (8.5)	.804[a]
6 mo	3.1 (5.2)	4.8 (6.2)	.397[a]	1.3 (3.0)	9.0 (8.0)	.002[a]
Mood symptoms						
Remission baseline	60.0% (12)	63.6% (21)	.791[b]	66.7% (6)	65.4% (17)	.944[b]
Remission 6 mo	86.7% (13)	75.0% (15)	.672[c]	44.4% (4)	92.3% (24)	.006[c]

[a] *t* test.
[b] χ^2 test.
[c] Fisher exact test.

shown in Fig. 1. This correlation remained significant when only patients with subsyndromal symptoms were taken into account (HAM-D scores <15, n = 32) ($r = 0.30$, $P < .05$). In a correlation matrix, only HAM-D and MADRS scores were significantly correlated with MSIF global scores. There was no significant correlation of the other variables (age, number of previous depressive episodes, number of days depressed/manic, length of illness, age of onset, number of suicide attempts, duration of first manic episode, sex, psychosis, drug abuse and anxiety comorbidity, hospitalization in the first episode, depressive or manic relapse) with the global MSIF scores. The HAM-D scores were chosen to be entered in the regression model because this scale has been widely used in previous studies and demonstrated a strong correlation with the outcome. Despite initial lack of correlation with the outcome, variables such as sex, years of education, length of illness, and age of onset were entered in the model because of consistent evidence from previous reports indicating an association with functional outcomes. When entered in the linear regression model, only depressive symptoms at 6 months (HAM-D) were significantly correlated with the global functional scores at 6 months (Table 4). In the model, HAM-D scores explained 53% of the variance in the MSIF global scores ($\beta = .66$, $R^2 = .53$, $P < .001$) (Table 4). Depressive symptoms significantly predicted

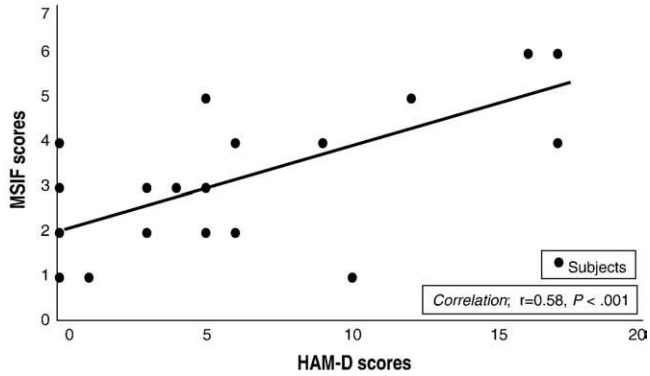

Fig. 1. Correlation between depressive symptoms and MSIF scores (functional outcome) at 6-month follow-up.

Table 4
Predictors of functional outcome at 6 months entered in a regression model in relation to MSIF scores—global scores and dimensions of performance, support, and role position

Model	MSIF							
	Global (total)		Performance		Support		Role position	
	Coefficient	R^2	Coefficient	R^2	Coefficient	R^2	Coefficient	R^2
Sex	−.16	.08	−.10	.00	−.30	.08	−.21	.15*
Education	−.21	.08	.07	.02	.10	.11	−.33	.18*
Length illness	−.04	−.01	.08	.02	.26	−.14	.18	.30**
Age onset	.23	.16	.06	.03	−.14	.31	−.02	.20
YMRS	−.16	.16	.22	.13	−.07	.31*	−.25	.21
HAM-D	.66	.53***	.53	.37*	.29	.38*	.71	.64***

* $P < .05$.
** $P < .01$.
*** $P < .001$.

scores in all domains of the MSIF scale and were particularly correlated with scores in the role position dimension, accounting for about 64% of the variance. The manic symptoms (YMRS) showed a negative correlation with the MSIF scores in the support domain ($\beta = -.07$, $R^2 = .31$, $P < .05$). There was also a negative correlation between years of education, sex, and the scores in the role position, as expected ($\beta = -.33$, $R^2 = .18$, $P < .05$). The length of illness was predictive of the level of support required to perform activities as expected ($\beta = .26$, $R^2 = .30$, $P < .01$).

4. Discussion

Our results show that within 3 months of onset of a first manic episode, most of the patients in our sample have achieved symptomatic but not functional recovery. The functioning did appear to improve with longer follow-up because by the 6-month visit, the rates of disability decreased significantly. Of all the clinical features analyzed, only depressive symptoms and lack of remission at the 6-month visit were associated with a worse functional outcome. Furthermore, in a regression model, depressive symptoms strongly predicted overall functional outcome; and even subsyndromal depressive symptoms were correlated with disability. As the MSIF does not include depressive symptoms in the anchor points, this association is unlikely to reflect solely an overlap of the HAM-D and MSIF assessment scales. Surprisingly, none of the variables examined at entry were predictive of disability at entry or at 6-month follow-up. Given that MSIF scores capture the modal level of functioning over the previous 30 days, the fact that most of the patients had been hospitalized for their first manic episode within the previous 3 months may have been a confounding factor reflected in the lack of associations of clinical features with disability assessed at entry. However, none of the clinical features assessed at entry were associated with MSIF scores at the 6-month visit either. In fact, neither remission nor HAM-D scores at entry were predictive of functional outcome at 6 months in a regression model.

These findings could be interpreted in 2 ways: first, they may reflect a time lag between symptomatic recovery and functional recovery; second, they may suggest that the consistent and sustained improvement of symptoms at 6 months may be the most important variable for functional recovery as compared with early response (within 3 months). In addition, we found that more years of education predicted a better functioning in role position, which was expected. Manic symptoms were associated with better functioning; however, it is worth noting that none of the patients experienced a full manic relapse. Therefore, the positive impact of manic symptoms on functional outcomes was actually due to subsyndromal symptoms. This finding confirms results from previous reports in which manic symptoms were associated with worse functioning, whereas subsyndromal hypomanic symptoms were reported to be associated with a slight improvement in functioning [2]. Alternatively, this could represent the fact that short-term observation after a manic episode restricts the ability to detect the deleterious effects of mania.

Extensive research supports the association of subsyndromal depressive symptoms with functional impairment [2,3,10,21,22]. For instance, in a cohort of patients with BD followed for 20 years, each increase or decrease in depressive symptom severity was associated with a highly significant increase or decrease in psychosocial disability [2]. In a 10-year prospective follow-up study, sustained remission predicted levels of psychosocial adjustment to a greater extent than polarity of index episode [23]. In the same study, persistent mood symptoms were more strongly associated with subsequent outcome than the diagnosis of unipolar or bipolar and than comorbid alcohol dependence. Our results confirm that these findings also hold true in the early phase of BD. In a previous study of first-episode psychotic mania sample, in which all patients experienced psychotic symptoms, symptomatic remission at 6 months predicted better outcome at 12 months [10]. Interestingly, that study found that recovery at 6 months was predictive of

better symptomatic and functional outcome at 12 months, but did not find significant associations with baseline variables, which is in line with our results. Symptomatic remission and functional restoration have been proposed as a marker of wellness in BD [18] and may be of particular importance in a vulnerable phase, after a first manic episode, when optimal treatment could prevent further damage.

Compared with previous studies with first-episode samples, our patients showed impressively better rates of functional recovery at 6 months. For instance, Tohen et al (2000) reported only 29.2% and Conus et al (2006) reported 34% achieving functional recovery at 6 months. In another study of patients with a first psychotic episode, 33% of those with affective psychosis achieved functional recovery after 3 years of follow-up, whereas only 22% of those with schizophrenia had functional improvement [24]. In our sample, 74.3% had none to mild disability at 6 months. However, if we use more stringent definition of recovery, for example, percentage of patients that achieved 1 or 2 in the MSIF global score—that is, essentially normal functioning or very mild disability that could be in the low end of the reference range—the rate of functional recovery at 6 months falls to 51.5%, which is still higher but closer to those previously reported. A reason for a better outcome in our sample could be the entry inclusion of both psychotic and nonpsychotic manic episodes, whereas previous studies only included psychotic manic episodes [6,10,24], thereby recruiting a more severely ill sample of patients. In fact, only 8 patients in this sample were currently with psychosis (Table 3); and of these, 7 were in the group with disability at baseline. Other factors associated with better outcomes in this sample may be the low rates of comorbidities and the absence of significant medical condition. The relatively short length of illness may also contribute to a better short-term outcome. Studies with patients with BD at different phases in the course of the illness reported work disability rates as high as 68% during a 12-month observation period [25]. In a sample of older adults, BD was associated with substantial disability, similar in severity to schizophrenia; and 51% were in the low-functioning category [26]. The sum of these findings raises the perspective of BD as a developmental disorder. Without early intervention, patients with BD may deteriorate over time, sometimes irrevocably, in social, vocational, cognitive, and neurobiological development [27].

The lack of association in our sample of previously reported predictors such as psychiatric and physical comorbidities [8] with functional outcomes may be due to the fact that this is a first-episode sample—a very young group with no significant medical illness and low rates of psychiatric comorbidities. Despite considerable rates of substance abuse, very few patients fulfilled the criteria for dependence, which precluded meaningful analysis (data not shown). Psychosis also has been previously reported to be linked with poor outcome. The low rate of psychosis in our sample probably limited the statistical power for finding significant associations. Furthermore, there was no association between medication use and functional outcome. The fact that most patients in our sample were medicated limited the findings about the effects of medication on functional outcomes. Previous reports suggested that higher lithium levels were associated with better psychosocial functioning [28]. It was beyond the scope of this article to explore such specific associations; but it is likely that medication type, dosage, and compliance affect functional outcomes [5].

Our results should be interpreted with caution in light of some limitations. The sample size may have restricted the ability to detect smaller effect sizes of other variables in the regression model. Furthermore, we did not evaluate premorbid level of functioning or comorbid personality disorder, which have been reported to affect functioning in previous studies [5,10,29]. However, previous studies also showed that depressive symptoms predicted functional outcomes independent of personality disorders or premorbid status [10,29]. In addition, it was beyond the scope of this article to investigate other possible predictors of disability, such as cognitive impairment [11,30,31]. These and other factors not examined here may explain the other 47% of the variance in the functional scores that was not explained by depression. Finally, taking into account the short period of follow-up, our conclusions should be limited to the early recovery phase of first manic episodes.

The results discussed here reflect some clinical challenges in the treatment of BD: syndromal remission is easier to achieve than to maintain; symptomatic remission is common in BD, but relapse and residual symptoms are very common. Furthermore, persistent subsyndromal symptoms in patients with BD are associated with worse outcomes and may have considerable short-term prognostic importance. Patients who have recovered from a manic episode are often left with residual depressive symptoms. The treatment of bipolar depression remains a challenge to clinicians because of the risk of precipitating a manic switch. However, there is mounting evidence that depression, whether it is fully syndromal or subsyndromal, affects wellness, quality of life, and functioning [9,32,33]. Our results highlight that these residual symptoms may exert an important role in functional outcomes even early after the first manic episode. We emphasize the importance of consistent treatment of residual depressive symptoms starting at early phases of BD.

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