Clinical Staging in Bipolar Disorder: Focus on Cognition and Functioning

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ABSTRACT

Objective: Clinical staging has increasingly been considered suitable for psychiatric disorders such as bipolar disorder. A staging model of bipolar disorder could help clinicians understand the mechanisms underlying the course of the illness and guide prognosis and therapy. This study aimed to investigate differences in functional status and cognitive functioning in patients in different clinical stages of bipolar disorder.

Method: Subjects who met *DSM-IV* criteria for bipolar disorder (n = 54) were recruited from the Bipolar Disorders Program at Hospital de Clínicas de Porto Alegre (Brazil) from October 2012 to October 2013. All patients had been in remission (score < 7 on the 17-item HDRS and the YMRS) for at least 1 month before assessment. They were classified into 4 clinical stages according to the model described by Kapczinski et al and compared to 43 healthy controls. Functional status was assessed by using the Functioning Assessment Short Test (FAST). Neuropsychological measures were performed to investigate cognitive functioning.

Results: Significant differences in functional status were found between patients in all stages compared to controls ($F = 33.014$, $P < .001$), except for stage I ($P = .104$). Additionally, a very strong linear association was found between FAST scores and clinical stages, with FAST scores increasing from stage I to IV ($F = 149.55$, $P < .001$). In the bipolar group, stage I was associated with better occupational functioning than stage II ($F = 48.344$, $P = .003$). Stage IV patients experienced greater impairment in autonomy than stage III patients ($F = 26.646$, $P = .004$), and stage III patients experienced poorer autonomy than those in stage II ($P = .004$). With regard to cognitive measures, patients in late stages (stages III and IV) were more impaired than healthy controls ($P < .001$). A similar performance was found between patients in early stages (stages I and II) and healthy controls.

Discussion: This study showed progressive functional changes from stage I to stage IV of bipolar disorder, with a greater impairment in patients in later stages of the illness. FAST scores seem to have a good discriminant ability to distinguish between patients in early versus late stages of bipolar disorder and could therefore contribute to the development of a bipolar disorder staging system.

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Bipolar disorder is a chronic, recurrent illness that represents a major public health concern and often shows incomplete recovery and increased mortality.[1,2] Bipolar disorder is one of the leading causes of years lost due to disability in young adults,[3] and it is also associated with high direct medical costs, exceeding by far the costs for the general population.[4,5]

Patients with bipolar disorder may suffer from marked cognitive impairment, even when euthymic.[6–8] In this regard, a follow-up study[9] conducted in the United States found that 98% of first-episode manic patients with bipolar disorder remitted within 2 years, whereas only 38% of them achieved functional recovery. Moreover, functional and symptomatic recoveries are not always associated in bipolar disorder.[9,10] Psychosocial functioning describes a person's ability to function socially and occupationally and to live independently.[11,12] Patients with bipolar disorder may experience serious dysfunction in distinct life domains, such as work productivity, social activities, and autonomy.[13–16] Important dysfunction may be present early in the course of illness[17–19] but tends to become more severe in later stages.[20,21]

The natural history of bipolar disorder progression involves relapses, an increasing severity of subclinical symptoms, and comorbidity with other psychiatric and medical conditions.[22–24] Repeated illness episodes have an impact not only on illness severity but also on the level of disability.[25,26]

Staging models are widely used in medicine, helping to optimize treatments according to anatomic, clinical, and functional characteristics of progressive diseases. Staging is particularly useful when it is able to distinguish between early, milder clinical phenomena and those that accompany illness progression and chronicity.[27] In bipolar disorder, staging models could not only help understand illness progression from a heuristic perspective but also, and especially, help estimate prognosis and guide therapy. In this sense, a functional staging model in bipolar disorder could be a practical criterion to assess the progressive course of the illness.[28]

While there is now a theoretical basis for illness staging in bipolar disorder, the models currently available are still in need of empirical substantiation. The aim of the present study was to assess functional status and neurocognitive performance as major dimensions of clinical staging in bipolar disorder. To that end, we report differences and relevant cutoff points obtained in patients in different clinical stages of bipolar disorder using a validated instrument for the assessment of functioning.

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Clinical Points

- Current evidence supports a progressive functional decline from initial to late stages in some patients with bipolar disorder.
- A functional staging model in bipolar disorder may be useful to guide treatments according to individual needs.

METHOD

Subjects

Outpatients were recruited from the Bipolar Disorders Program at Hospital de Clínicas de Porto Alegre, in southern Brazil from October 2012 to October 2013. Inclusion criteria were (1) being > 18 years of age, (2) fulfilling *DSM-IV* criteria for bipolar I disorder, and (3) meeting remission criteria, defined as a score < 7 on both the 17-item Hamilton Depression Rating Scale (HDRS-17)[29] and the Young Mania Rating Scale (YMRS)[30] for at least 1 month before the assessment. All patients received pharmacologic treatment according to previously determined protocols.

This study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre. Patients were informed of the goals and procedures of the study and were included only after signing an informed consent form.

For the purpose of this study, patients were classified according to the staging model described by Kapczinski et al.[22] The model includes a latent phase and 4 clinical stages; patients were classified along the 4 clinical stages. To that end, a semistructured interview was administered to each patient by 2 psychiatrists previously trained in the model. The clinicians collected data on course of illness, presence or absence of psychiatric comorbidities, subjective assessment of work activity and social interactions, and self-care. Even though functioning is an important aspect of bipolar disorder staging, this variable was assessed separately, using the Functioning Assessment Short Test (FAST), as described below. Therefore, patients were stratified into 4 clinical stages by the clinicians, regardless of functional status results, as follows: stage I, individuals who present the same premorbid status in the interepisodic period as they did before the onset of bipolar disorder; stage II, individuals whose interepisodic period is marked by psychiatric comorbidities or residual symptoms that require changes in pharmacologic treatment but who are able to maintain daily activities; stage III, individuals who require occupational and social rehabilitation and face difficulties in their daily activities; and stage IV, individuals who are unable to maintain personal self-care and to live autonomously. Medical charts were carefully checked, and the clinician responsible for each patient was consulted in cases of interrater disagreement so that a final decision on clinical staging could be reached. Both clinicians were blind to the results of the clinical evaluation, as well as of neurocognitive and functional assessments. The same method has been successfully used previously by Reinares et al[31]; those authors were able to differentiate between patients in early and in late stages of bipolar disorder (only the former benefited from psychoeducation).

The control group consisted of healthy subjects selected from the pool of volunteers at the hospital. They had no current or previous history and no first-degree family history of major psychiatric disorders, including dementia or mental retardation, assessed by the nonpatient version of the Structured Clinical Interview for *DSM-IV* (SCID).

Assessments

The SCID for *DSM-IV* Axis I and Axis II Disorders (SCID-I and SCID-II) were administered to patients to confirm diagnosis.[32,33] Sociodemographic, clinical, and pharmacologic data were collected by using a structured interview and examining the patients' clinical records. The HDRS-17 and the YMRS were administered by experienced raters to assess depressive and manic symptoms, respectively.

Functional Status

The FAST, used to assess functional impairment, is a 24-item scale that covers 6 specific areas of functioning: namely, autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Items are rated using a 4-point Likert scale, where 0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty, and 3 = severe difficulty. Overall FAST scores may range from 0 to 72, with higher scores indicating greater disability and a threshold score of 11 indicating significant disability.[13,34,35] The FAST has been validated for use in the Brazilian population, with good psychometric properties (validity, internal consistency, and interrater reliability).[15]

Neurocognitive Performance

Neuropsychological measures were obtained from all subjects by experienced psychologists on the same day of the clinical assessment. This assessment included different tasks of attention, verbal learning and memory, working memory, and executive function—cognitive tasks defined as appropriate for use in bipolar disorder assessment according to the International Society for Bipolar Disorders.[36] The following tests were used: Stroop Test-Interference Measure,[37,38] Hopkins Verbal Learning Test-Revised (HVLT-R),[39,40] and Digit Span and Letter-Number Sequencing subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III).[41]

Statistical Analysis

Demographic and clinical characteristics were analyzed by using the χ^2 test, analysis of variance (ANOVA), or Kruskal-Wallis. Descriptive analysis results were expressed as mean (SD) or median (interquartile range). A receiver operating characteristic (ROC) curve was performed to analyze the discriminant validity of the FAST scale.

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Table 1. Subject Characteristics

Characteristic	Healthy Controls (n = 43)	Bipolar Disorder Subjects				P Value
		Stage I (n = 16)	Stage II (n = 11)	Stage III (n = 13)	Stage IV (n = 14)	
Gender, n						.401[a]
Male	19	4	2	4	4	
Female	24	12	9	9	10	
Age, y[b]	45.7 (10.6)	41.8 (13.6)	46.1 (14.2)	52.6 (14.2)	52.1 (11.6)	.065[c]
Years at school[b]	9.6 (3.4)	9.9 (3.5)	9.5 (2.7)	7.3 (3.9)	8.3 (2.0)	.163[d]
Illness duration, y	…	9.0 (8.3)	11.0 (16.0)	26.0 (15.5)	18.0 (23.75)	.001[d]
No. of mood episodes[e]	…	5.0 (4.0)	6.5 (11.25)	9.0 (9.0)	16.0 (26.5)	.005[d]
Suicide attempts[e]	…	2.0 (0)	1.0 (1.0)	2.0 (1.0)	1.0 (1.0)	.492[d]
No. of hospitalizations[e]	…	2.0 (2.5)	1.0 (4.5)	4.5 (3.5)	3.0 (4.0)	.094[d]
HDRS score[e]	…	0.5 (2.0)	3.0 (3.0)	3.0 (3.0)	5.0 (2.5)	.019[d]
YMRS score[e]	…	0 (2.5)	1.0 (2.0)	1.0 (2.0)	1.0 (2.5)	.747[d]
Marital status, n (%)						.206[a]
Single	4 (9.3)	4 (25.0)	3 (27.3)	2 (15.0)	5 (35.7)	
Married	31 (72.0)	9 (56.3)	5 (45.4)	6 (46.6)	6 (42.8)	
Divorced	6 (14.0)	1 (6.2)	2 (18.2)	2 (15.4)	2 (14.3)	
Widow(er)	2 (4.7)	2 (12.5)	1 (9.1)	3 (23.0)	1 (7.2)	
Work situation, n (%)						< .0001[a]
Employed	43 (100)	13 (81.3)	4 (36.3)	4 (30.8)	2 (14.3)	
Unemployed	0	3 (18.7)	3 (27.3)	3 (23.0)	2 (14.3)	
Medical benefits	0	0	2 (18.2)	2 (15.4)	3 (21.4)	
Invalidity	0	0	2 (18.2)	4 (30.8)	7 (50.0)	
Medication, n (%)						
Lithium	…	9 (56.3)	4 (36.4)	5 (38.5)	5 (35.7)	
Anticonvulsants	…	10 (62.5)	6 (54.5)	10 (76.9)	7 (50.0)	
Atypical antipsychotics	…	5 (31.3)	4 (36.4)	4 (30.8)	10 (71.4)	
Typical antipsychotics	…	0	4 (36.4)	8 (61.5)	2 (14.3)	
Antidepressants	…	4 (15.4)	4 (36.4)	3 (23.1)	2 (14.3)	
Benzodiazepines	…	0	5 (45.5)	3 (23.1)	3 (21.4)	

[a]χ^2.
[b]Shown as mean (SD).
[c]Analysis of variance.
[d]Kruskal-Wallis.
[e]Shown as median (interquartile range).

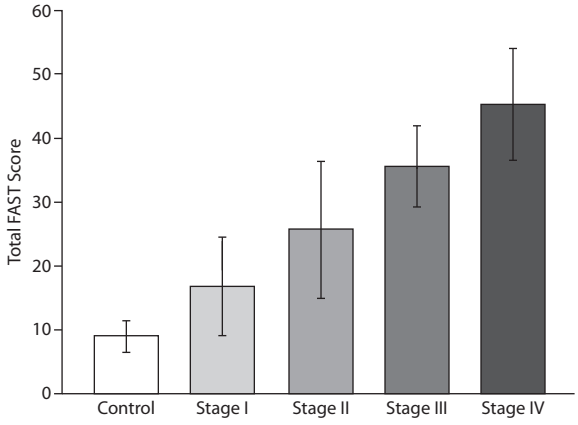
RESULTS

The sample included 43 healthy controls and 54 patients with bipolar disorder, classified into stages I (n = 16), II (n = 11), III (n = 13), and IV (n = 14). Sample characteristics are summarized in Table 1. Regarding pharmacologic treatment, our results showed that 16.7% (n = 9) of the patients were on monotherapy. Among the patients on polypharmacy, 46.3% (n = 25), 25.9% (n = 14), and 11.1% (n = 6) of the patients received 2, 3, and 4 psychotropic medications, respectively. The percentages of mood stabilizers, antipsychotics, antidepressants, and benzodiazepines used in patients according to their clinical stages are presented in Table 1.

Functional Status

Patients versus controls. Overall functioning results (as measured by mean ± SD FAST score) were similar in patients in stage I (16.94 ± 14.25) and in healthy controls (9.20 ± 7.70; $P = .104$). Patients in stage II (25.70 ± 14.74), stage III (35.36 ± 9.48), and stage IV (44.91 ± 12.56) experienced greater functional impairment than healthy controls ($F = 33.014$, $P < .001$). These differences are illustrated in the very strong linear association shown in Figure 1, with FAST scores increasing from stage I to IV ($F = 149.55$, $P < .001$) (Figure 1).

Figure 1. Mean Total Functioning Assessment Short Test (FAST) Scores in Patients in Distinct Stages and Healthy Controls[a]



[a]Error bars of FAST scores represent mean (SD).

Patients in different clinical stages. Significant differences were found in distinct domains of the FAST between patients in different clinical stages. Specifically, patients in stage I showed improved occupational functioning when compared with patients in stage II ($F = 48.344$, $P = .003$; Figure 2). Stage II patients experienced higher levels of autonomy than stage III patients ($F = 26.646$, $P = .004$; Figure 2). Patients in stage

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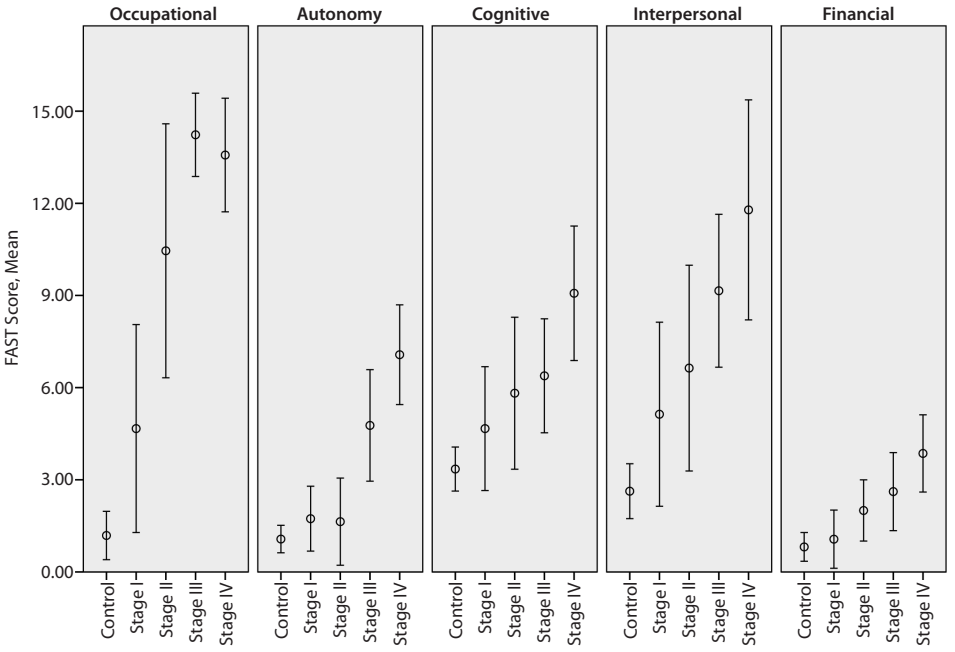
Figure 2. Mean Functioning Assessment Short Test (FAST) Domain Scores in Distinct Stages and Healthy Controls[a]



[a]Error bars of FAST scores represent mean, indicated by circles, and SD.

Table 2. Mean Differences in Functioning Assessment Short Test Scores Between Bipolar Stages in Patients and Healthy Controls

Domain	Group Differences
Overall	Stage I < stage III**
	Stage I < stage IV**
	Stage II < stage IV**
Autonomy	Stage I < stage III*
	Stage I < stage IV**
	Stage II < stage III*
	Stage II < stage IV**
	Stage III < stage IV*
Occupational functioning	Stage I < stage II*
	Stage I < stage III**
	Stage I < stage IV**
Cognitive functioning	Stage I < stage IV*
Interpersonal relationships	Stage I < stage IV**
	Stage II < stage IV*
Financial issues	Stage I < stage IV**

*$P < .05$ (1-way analysis of variance with Tukey correction for multiple comparisons).
** $P < .005$.

IV showed more severe impairment in autonomy than stage III patients ($F = 26.646$, $P = .004$; Figure 2). With regard to overall functioning, patients in stage I showed better results than those in stages III or IV ($F = 42.550$, $P < .001$), and stage IV patients were more impaired than stage II patients ($F = 42.550$, $P < .001$). Other functioning differences between patients in different clinical stages are shown in Table 2.

We also divided patients into early (stage I/stage II) and late (stage III/stage IV) stages of bipolar disorder to assess the clinical utility of FAST scores. The area under the curve was 0.83 (95% CI, 0.714–0.938), which indicates good discriminant ability. We suggest that a cutoff point of 36 could be useful to distinguish between patients in early versus late stages of bipolar disorder, with a good balance between sensitivity (69%) and specificity (77%).

Neurocognitive Performance

Patients in stages III and IV performed poorly in neuropsychological tests when compared with healthy controls, especially in executive function (Stroop Interference), verbal learning and memory (HVLT-R), and working memory and attention (WAIS-III-Digit Span forward and backward). No statistically significant differences were found in neurocognitive measures between individuals in stages I/II and healthy control subjects (Table 3).

DISCUSSION

As far as we are aware, this is the first study to assess functional status and cognitive functioning using a comprehensive staging model in bipolar disorder. Our results showed that patients in stage I and healthy controls had similar functioning patterns. In addition, a strong linear association was found between total FAST scores and clinical stages, suggesting a progressive functional decline from stage I through to stage IV of bipolar disorder. These findings provide further support to the clinical staging model in bipolar disorder, indicating that bipolar patients lie on a continuum of disorder progression ranging from periods of favorable functioning to others of incomplete functional recovery.

In regard to specific domains, our results showed that patients in stage II showed more severe impairment in

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Table 3. Neurocognitive Performance in Bipolar Staging

Test	Control, Mean ± SD	Stage I (1), Mean ± SD	Stage II (2), Mean ± SD	Stage III (3), Mean ± SD	Stage IV (4), Mean ± SD	*F*	*P*	Group Differences
Executive function								
Stroop (interference)	64.59 ± 37.72	65.31 ± 39.60	69.50 ± 39.42	101.92 ± 52.45	112.38 ± 76.04	4.129	.004	Control = 1 = 2 < 3 = 4
Verbal learning and memory								
Hopkins Verbal Learning Test								
Total recall	23.74 ± 4.92	20.19 ± 4.92	20.73 ± 4.43	17.86 ± 4.04	16.43 ± 4.15	9.537	< .0001	Control = 1 = 2 > 3 = 4
Delayed recall	8.11 ± 2.42	6.25 ± 2.35	7.09 ± 3.36	4.79 ± 2.39	4.14 ± 2.32	10.119	< .0001	Control = 1 = 2 > 3 = 4
Recognition	10.30 ± 2.17	9.06 ± 2.43	10.00 ± 2.41	8.00 ± 2.42	7.57 ± 2.79	5.562	.001	
Working memory attention								
WAIS-III–Digit Span	13.83 ± 4.24	11.38 ± 3.10	10.18 ± 2.93	10.5 ± 3.13	9.36 ± 2.47	6.546	< .0001	Control = 1 = 2 = 3 > 4
WAIS-III–Letter-Number Sequencing	8.02 ± 3.16	6.31 ± 2.55	6.45 ± 2.46	5.71 ± 2.70	5.36 ± 2.10	3.947	.005	Control = 1 = 2 > 3 = 4

Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-III.

occupational functioning than those in stage I. This finding may explain, at least in part, the high rates of unemployment observed among patients with bipolar disorder, who tend to face serious difficulties in maintaining work activities, even at early stages of the illness.[13] In addition, lower levels of autonomy were found in patients in stage IV, followed by patients in stage III, and finally stage II. The autonomy domain consists of simple tasks such as household activities, shopping, living alone, and self-care. Despite the preliminary nature of these findings, they do suggest that the assessment of functional status, especially occupational functioning and autonomy, may help identify patients in distinct clinical stages of bipolar disorder.

Our patients with bipolar disorder in stages II, III, and IV presented poorer functioning than healthy controls, which underscores the negative impact of bipolar disorder on functional outcomes. Previous reports[16,17] had already shown a strong association between functional impairment and bipolar disorder severity (ie, number of episodes). For instance, a 1-year follow-up study[20] reported higher levels of functional and symptomatic recovery in patients experiencing their first episodes when compared to those with multiple episodes. First-episode patients were usually younger and had received less complex treatment regimens, which may have been associated with fewer cognitive complaints and better functioning, than patients with multiple episodes.[9,42]

Cognitive deficits may also limit long-term psychosocial functioning,[43,44] which means that patients with greater cognitive impairment are more likely to experience poorer outcomes. In this regard, Bonnín et al[45] found that variables measured with the California Verbal Learning Test, especially free delayed recall, were good predictors of long-term psychosocial functioning in a euthymic sample. Other follow-up studies[46,47] have also demonstrated that patients with executive and memory dysfunctions tend to show greater impairment in daily life activities. Comparing neurocognitive performance between patients with low and high functioning scores, Martínez-Arán et al[48] showed that patients with poor functioning had significantly more severe impairment in memory tasks, inhibitory control, and working memory. Indeed, patients with verbal memory and learning dysfunctions have serious difficulties remembering long-term information, which may be strongly associated with poor occupational functioning and interpersonal relationships.[48] In a recent study,[49] clinical variables, including episode density (illness duration/number of episodes) and residual depressive symptoms, as well as cognitive deficits (estimated verbal intelligence and inhibitory control), were shown to be good predictors of poor outcomes in bipolar disorder.

In addition to psychosocial functioning, we found a similar pattern of cognitive functioning between patients in stages I and II and healthy controls. In contrast, patients in stages III and IV performed worse than healthy controls in 3 neurocognitive domains. These findings are consistent with previous findings that indicate an association between cognitive deficit and illness severity.[50,51] In particular, number of manic episodes seems to predict cognitive impairment.[52] Lopez-Jaramillo et al[52] observed worse neurocognitive performance in euthymic patients who had had at least 3 manic episodes versus patients who had had only 1, and they suggested that manic relapses are a strong predictor of unfavorable cognitive functioning. Other clinical features, such as subsyndromal depressive symptoms,[53] illness duration,[6] psychotic symptoms,[48] number of hospitalizations,[51] and psychiatric comorbidities,[48] have also been correlated with cognitive impairment.

Taken together, our findings suggest a course of illness in which early intervention would be crucial to prevent illness progression. In this scenario, primary prevention could be used to treat individuals at ultra high risk for developing psychiatric disorders[54] and also patients in stage I. There is evidence supporting the neuroprotective benefits of early interventions for stage I patients, as this subgroup would be able to preserve cognitive and psychosocial functioning.[24] In this regard, Reinares et al[31] reported that psychoeducation for caregivers of patients with bipolar disorder in stage I is an effective therapy to improve long-term outcomes in terms of time to recurrence.[31] Another study has reported that patients with less than 10 mood episodes on lithium therapy showed higher response rates than those with more than 10 episodes, suggesting a strong relationship between number of episodes and treatment response.[55]

Our results must be interpreted in light of some limitations. First, the FAST is an interviewer-administered instrument and provides a clinical evaluation of the functional

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impairment. This assessment leaves out the subjective evaluation made by the patient, which can often differ significantly from the clinician's.[21] Although functioning is a relevant part of staging, FAST scores were obtained without knowledge of patient stage. Second, regarding the neurocognitive assessment, the present study focused specifically on the cognitive deficits most commonly related to bipolar disorder (eg, memory and executive dysfunctions), but a more comprehensive neuropsychological battery, for instance, including distinct executive function measures, should be considered for further research. Third, nearly all patients were on polypharmacy, which may have influenced the outcomes as a result of side effects.[6] Fourth, our sample was recruited at a single tertiary hospital in Porto Alegre, southern Brazil, which limits the generalization of findings to other cultures and countries as well as to populations from other areas of Brazil. Longitudinal studies with larger samples are warranted to confirm the validity of the functional staging model in bipolar disorder. Nevertheless, our results do provide an initial overview of the potential use of this model.

In conclusion, the present study suggests a progressive functional decline from stage I to stage IV of bipolar disorder, as well as differences in specific functional domains (work and autonomy) according to clinical stage. The FAST scores showed a good discriminant ability to distinguish between patients in early versus late stages of bipolar disorder, and could contribute useful information to a bipolar disorder staging system. In this sense, a functional staging model could be clinically meaningful in bipolar disorder, especially to guide therapeutic approaches according to individual needs.

Drug names: lithium (Lithobid and others).

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