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After studying this article, you should be able to:

- Identify patients with first-episode psychosis who have clinical features that are associated with a diagnosis of bipolar disorder as opposed to schizophrenia

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Predictors of Bipolar Disorder Versus Schizophrenia Diagnosis in a Multicenter First Psychotic Episode Cohort: Baseline Characterization and a 12-Month Follow-Up Analysis

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ABSTRACT

Objective: The aim of this study was to identify predisposing factors and clinical features at baseline that might help predict diagnosis of bipolar disorder vs schizophrenia in a first-episode psychosis (FEP) cohort.

Methods: In this prospective, naturalistic study, we evaluated a cohort of 335 subjects with FEP recruited from April 2009 to April 2012. Baseline features were compared between subjects with a final *DSM-IV* diagnosis of bipolar disorder and schizophrenia at 12-month follow-up. A binary logistic regression model was used to assess predictors of diagnosis of bipolar disorder at follow-up.

Results: At 12-month follow-up, 47 of the 335 subjects included in the study received the diagnosis of bipolar disorder and 105, of schizophrenia. Subjects with a final diagnosis of bipolar disorder had a higher prevalence of family history of mood disorders (38.2% vs 18.0%, $P=.02$), better baseline premorbid adjustment (Premorbid Adjustment Scale [PAS]: 38.4 vs 50.6, $P<.01$) and psychosocial functioning (Functional Assessment Short Test [FAST]: 23.6 vs 33.7, $P=.001$), better cognitive flexibility (number of perseverative errors on the Wisconsin Card Sorting Test [WCST]: 14.2 vs 19.7, $P=.01$), more manic symptoms (Young Mania Rating Scale [YMRS]: 14.1 vs 7.3, $P<.01$), lesser negative symptoms (Positive and Negative Syndrome Scale negative scale [PANSS-N]: 15.0 vs 22.3, $P<.001$), and shorter duration of untreated psychosis (144.2 vs 194.7 days, $P<.01$) than subjects with a schizophrenia diagnosis. Binary logistic regression model revealed that lower FAST scores (odds ratio [OR] = 0.956; $P=.015$), lower PANSS-N scores (OR = 0.93; $P=.048$), and lower number of perseverative errors on the WCST (OR = 0.946; $P=.035$) were significantly related to diagnosis of bipolar disorder at follow-up.

Conclusions: In our FEP cohort, better psychosocial functioning, lesser negative symptoms, and better cognitive flexibility were related to diagnosis of bipolar disorder at 12-month follow-up.

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Clinical Points

- Early diagnosis in bipolar disorder can be challenging due to its heterogeneous clinical presentation, which can be in the form of first-episode psychosis (FEP).
- In those FEP patients presenting with good baseline psychosocial functioning, less severe negative symptoms, and less cognitive impairment, differential diagnosis with bipolar disorder should be considered.

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Bipolar disorder is a polymorphic psychiatric condition that can exhibit diverse clinical symptomatology, particularly in its early stages.[1] Therefore, the diagnosis of bipolar disorder at these stages can be extremely challenging,[2,3] as reflected in previous reports describing misdiagnosis rates of around 30%–60% in pediatric[2] and adult bipolar samples.[4–7] In its early stages, bipolar disorder is most commonly misdiagnosed as major depressive disorder when the onset of the disorder is a depressive episode.[2,8,9] However, bipolar disorder can also be misdiagnosed as schizophrenia when incongruent psychotic symptoms are evident in first-episode psychosis (FEP).[2,10,11] In the McLean-Harvard International First-Episode Project,[12] more than 500 patients with a first-lifetime psychotic episode had their diagnosis reassessed over 2 years, and it was reported that around 16% of the patients with a final diagnosis of bipolar disorder had been diagnosed with a nonaffective psychotic disorder at baseline.

An early distinction between bipolar disorder and nonaffective psychotic disorders has important treatment implications, as pharmacologic and psychological treatment regimens, as well as prognoses, differ between the groups.[13] Moreover, an early start of mood stabilizers in bipolar disorder is usually associated with a better response to treatment.[14,15] Research efforts to date in FEP samples have mainly focused on the identification of those factors related to conversion to schizophrenia.[16–19] However, fewer available data exist on particular factors related to the diagnostic shift to bipolar disorder. One of the few studies was carried out by Kim et al.[20] In their retrospective study, they found that female gender, shorter duration of untreated psychosis (DUP), better premorbid functioning, and religious or grandiose delusions were associated with diagnostic shift to bipolar disorder after FEP. A second study done by Arrasate et al[21] found that activation and manic symptoms predicted a diagnosis of bipolar disorder at 5 years of follow-up and that the presence of depressive symptoms predicted misdiagnosis. Due to the limited prospective data on the topic, the aim of the present study was to investigate baseline differences in sociodemographic, clinical, and neuropsychological variables between schizophrenia and psychotic bipolar disorder subjects included in a FEP cohort. Moreover, we sought to identify baseline features potentially useful to predict diagnosis of bipolar disorder at 12-month follow-up.

METHODS

The current work is part of the project "Phenotype-Genotype and Environmental Interaction: Application of a Predictive Model in First Psychotic Episodes" (PEPs study). The detailed protocol of the study has been published elsewhere.[22] The PEPs study was a multicenter, longitudinal, naturalistic follow-up study with a total of 16 participating centers throughout Spain. Fourteen of these centers are members of the Biomedical Research Networking Center for Mental Health (CIBERSAM),[23] and 2 are collaborator centers.[22]

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was approved by the investigation ethics committees of each participating center. Written, informed consent was obtained from all participants, or their legal guardians in case of underage participants, after providing them with a full explanation of the study.

Sample

A total of 335 subjects with FEP were recruited by the 16 participating centers, from April 2009 to April 2012. The inclusion criteria were (1) age between 7 and 35 years; (2) presence of first lifetime psychotic symptoms for at least

1 week in the last 12 months; (3) fluency in the Spanish language; and (4) provision of signed informed consent. The exclusion criteria were (1) intellectual disability according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) criteria[24]; (2) history of head trauma with loss of consciousness; and (3) presence of an organic disease with mental repercussions.

Patients had been receiving antipsychotic treatment for less than 12 months at study entry. Follow-up evaluations were performed at 2 months, 6 months, 12 months, and 24 months. For the purpose of the present study, we decided to focus on the 12-month follow-up assessment to establish the diagnostic groups, as we considered it a reasonable time frame to observe changes in diagnosis with better retention rates than at 24-month follow-up.

Diagnostic and Sociodemographic Assessment

Adults were evaluated using the Structured Clinical Interviews for *DSM-IV* Axis I and II Disorders (SCID-I and -II),[24–26] and children and adolescents were evaluated using the Spanish translation of the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL).[27,28] Sociodemographic data, including gender, age, education, current living situation, and occupation, were gathered from all participants at baseline. Parental socioeconomic status was recorded using the Hollingshead Two-Factor Index of Social Position.[29] A complete personal and family history of psychiatric disorders was also compiled.

Clinical and Functional Assessment

Psychopathology was evaluated using the Spanish validated versions of the Positive and Negative Syndrome Scale (PANSS),[30,31] the Montgomery-Asberg Depression Rating Scale,[32,33] and the Young Mania Rating Scale (YMRS).[34,35] The retrospective Premorbid Adjustment Scale (PAS)[36] was used to estimate premorbid adjustment. Functional outcome was determined using the Functional Assessment Short Test (FAST).[37,38] In all scales, higher scores are indicative of greater clinical severity or functional impairment.

Days spent in the hospital and DUP were also registered. DUP was defined as the number of days elapsed between the onset of positive psychotic symptoms and the initiation of the first appropriate treatment for psychosis. Apart from the interviews with the patient, multiple sources of information (including medical records and interviews with relatives) were used to establish the onset of positive psychotic symptoms (defined as the first week with the PANSS items P1, P3, P5, P6, or G9 scoring 4 or more).

Neuropsychological Assessment

Trained neuropsychologists evaluated cognition in the first 2 months after the inclusion of the participant in the study to ensure clinical stability. No minimum years of education were required. The neuropsychological assessment included the following cognitive domains: (1) estimated Intelligence Quotient (IQ) (calculated based on the performance on the Vocabulary subtest from the Wechsler Adult Intelligence Scale [WAIS-III][39] or from the Wechsler Intelligence Scale for Children [WISC-IV][40]); (2) executive function (Stroop Color-Word Interference Test,[41] Wisconsin Card Sorting Test [WCST],[42] and Trail Making Test, form B[43]); (3) attention (Continuous Performance Test-II[44]); (4) processing speed (categorical [Animal Naming] and phonemic [F-A-S] components of the Controlled Oral Word Association Test[45] and Trail Making Test, form A[46]); (5) verbal memory (Spanish version of the California Verbal Learning Test, the Test de Aprendizaje Verbal España-Complutense[47,48]); (6) working memory (Digit and Letters and Numbers subtests of WAIS-III[39] and WISC-IV[40]); and (7) social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test[49,50]). Direct scores were used for the analysis. The battery is explained in detail in the PEPsCog study.[51]

Statistical Analysis

First, we analyzed diagnosis distribution in our sample at 12-month follow-up in order to determine which patients had a well-established diagnosis of bipolar disorder or schizophrenia (determined by expert clinicians using *DSM-IV* criteria) at that point. We decided not to include in either group (bipolar disorder or schizophrenia) patients keeping a provisional diagnosis (ie, psychotic disorder not otherwise specified, acute and transient psychotic disorder, schizophreniform disorder, or substance-induced psychotic disorder) at 12-month follow-up, as we could not be certain whether their diagnosis would shift to affective psychosis or stay as nonaffective psychosis. In consequence, for subsequent analyses we only focused on those patients with a confirmed diagnosis of bipolar disorder or schizophrenia at 12-month follow-up in order to obtain more homogeneous groups.

Next, the Kolmogorov-Smirnov test was used to examine the normality of variables. Differences in baseline sociodemographic, clinical, and neuropsychological features between FEP subjects with a diagnosis of bipolar disorder and schizophrenia at 12-month follow-up were assessed using the χ^2 test for categorical variables and the *t* test or the Mann-Whitney *U* test, as appropriate, for continuous variables. A binary logistic regression was performed to determine the impact of sociodemographic, clinical, and neuropsychological variables on the likelihood of having a diagnosis of bipolar disorder vs schizophrenia at 12-month follow-up. For the regression analyses, we only entered those baseline variables that were significantly different between the 2 groups in the initial bivariate comparison and supported by prior evidence. Diagnosis of bipolar disorder was used as the dependent variable. Models were created according to Hosmer and Lemeshow, introducing a variable for every 10 observed cases of the dependent variable to avoid overfitting.[52,53] A direct approach was used to build the models. Data were analyzed using the IBM Statistic Package for Social Sciences (SPSS) v.23. Significance level was set at $P < .050$.

Table 1. Comparison of Sociodemographic Characteristics at Baseline

Characteristic	Bipolar Disorder (n = 47) Mean	SD	Schizophrenia (n = 105) Mean	SD	Mann-Whitney *U*	*P*[a]
Age, y	22.34	6.3	23.94	5.8	2,856.5	.12
	n	%	n	%	χ^2	
Gender					0.72	.79
Female	12	25.5	29	27.6		
Male	35	74.5	76	72.4		
Civil status					2.63	.11
Single	40	85.1	98	93.3		
Other	7	14.9	7	6.7		
Education					2.47	.12
Basic education	27	57.4	74	70.5		
Bachelor's degree or university degree	20	42.6	31	29.5		
Living situation					1.13	.57
Family of origin	36	77.0	88	83.8		
Independent	9	19.1	14	13.3		
Other	2	4.3	3	2.9		
Employment situation					3.61	.16
Student	26	55.3	44	41.9		
Active	8	17.0	15	14.3		
Other	13	27.7	46	43.8		
Parental socioeconomic status					2.52	.77
High	9	19.2	20	19.0		
Medium-high	5	10.6	9	8.6		
Medium	14	29.8	24	22.8		
Medium-low	12	25.5	36	37.0		
Low	7	14.9	14	13.3		
Unknown	0	0.0	2	1.9		
Previous psychiatric diagnoses	n = 19		n = 28			
Anxiety disorders	3	15.8	9	32.1	1.59	.31
Affective disorders	9	47.4	9	34.6	0.74	.54
Behavioral/learning disorders	4	21.1	5	17.9	0.08	1.00
Others[b]	3	15.8	7	25.0	0.57	.72
Family history of psychiatric disorder	n = 34		n = 89			
Affective disorders	13	38.2	16	18.0	5.6	**.02**
Anxiety disorders	5	14.7	11	12.4	0.12	.73
Psychotic disorders	4	11.8	14	15.7	0.31	.58
Substance misuse	4	11.8	12	13.5	0.06	.80
Others[c]	4	11.8	7	7.9	0.46	.50

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]Includes eating disorders, personality disorders, or substance use.
[c]Includes eating disorders, personality disorders, or autism spectrum disorder.

RESULTS

A total of 335 subjects with FEP were included in the study. Of these, a total of 47 subjects (14.0%) were diagnosed with bipolar disorder at 12-month follow-up, and 105 subjects (31.3%) were diagnosed with schizophrenia. 29.6% of subjects retained a provisional diagnosis or received a diagnosis of schizoaffective disorder, and the remaining 25% of the sample dropped out of the study. The most frequent diagnoses in the dropout group were psychotic disorder not otherwise specified, acute and transient psychotic disorder, and schizophreniform disorder. No significant differences were found between those subjects who remained in the study and those who dropped out except for civil status and living situation (patients who were in the dropout group lived more often independently from their families of origin), the number of days in the hospital (lower in the dropout group), and the number of perseverative errors in the WCST (again, lower in the dropout group). These differences suggest that the dropout group might be a better preserved group.

Comparisons Between Groups on Baseline Characteristics

Sociodemographic characteristics. As displayed in Table 1, no differences in sociodemographic variables were found between both groups. Among those patients with a positive personal history of psychiatric disorders, the prevalence of previous diagnoses did not differ between both groups. With regard to family history of psychiatric disorder, the prevalence of mood disorders encompassing major depressive disorder and bipolar disorder was higher among patients diagnosed with bipolar disorder (38.2% vs 18.0%; $P = .02$).

Clinical and functioning features. At baseline, patients diagnosed with bipolar disorder exhibited significantly more manic symptoms (mean YMRS score: 14.1 vs 7.3; $P < .01$) and lesser negative symptoms (mean PANSS negative

Table 2. Comparison of Clinical Characteristics and Functioning at Baseline

	Bipolar Disorder (n = 47) n (%)	Schizophrenia (n = 105) n (%)	χ^2	P^a
Substance misuse	36 (77.0)	80 (76.0)		
Tobacco use	30 (63.8)	65 (61.9)	0.05	.86
Cannabis use	14 (29.8)	43 (40.9)	1.72	.19
Alcohol use	27 (57.4)	45 (42.9)	2.77	.10
Cocaine use	3 (6.4)	12 (11.4)	0.93	.34
	Mean (SD)	Mean (SD)	Mann-Whitney *U*	
PANSS				
Total positive	19.0 (8.5)	18.7 (7.2)	2,466	.99
Total negative	15.0 (6.7)	22.3 (8.5)	3,662.5	**<.001**
Total general	36.7 (14.1)	39.7 (13.2)	2,774	.22
Total PANSS	70.7 (24.5)	80.7 (24.4)	3,007	**.03**
YMRS	14.1 (14.1)	7.3 (7.9)	1,820	**<.01**
MADRS	12.6 (11.7)	13.5 (9.3)	2,752	.26
FAST				
Autonomy	3.6 (3.1)	5.4 (3.5)	2,843.5	**<.01**
Occupational functioning	5.4 (5.3)	8.3 (5.9)	2,821	**<.01**
Cognitive functioning	5.5 (3.9)	6.6 (3.8)	2,581.5	.10
Financial issues	1.7 (1.9)	2.0 (1.9)	2,389	.41
Interpersonal relationships	5.6 (5.1)	8.5 (4.7)	2,963.5	**.001**
Leisure time	1.7 (1.9)	2.9 (1.9)	3,001.5	**<.001**
FAST total	23.6 (16.6)	33.7 (15.0)	2,993	**.001**
PAS				
Childhood	6.2 (4.5)	6.0 (4.1)	2,261.5	.96
Early adolescence	7.8 (4.7)	9.0 (5.1)	2,449.5	.22
Late adolescence	7.9 (5.1)	10.8 (6.2)	2,313	**.03**
Adulthood	2.4 (2.3)	3.9 (3.3)	1,757.5	**.03**
General questions	15.9 (8.1)	22.9 (10.9)	3,067.5	**<.001**
PAS total	38.4 (19.0)	50.6 (22.9)	2,933.5	**<.01**
Duration of untreated psychosis, d	144.2 (156.5)	194.7 (133.6)	3,037.5	**<.01**
No. of days spent in the hospital	23.7 (14.6)	31.6 (26.5)	1,743.5	.20

[a]Boldface indicates statistical significance at the $P < .05$ level.
Abbreviations: FAST = Functioning Assessment Short Test, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, PAS = Premorbid Adjustment Scale, YMRS = Young Mania Rating Scale.

scale [PANSS-N] score: 15.0 vs 22.3; < .001) than patients diagnosed with schizophrenia (Table 2). No significant differences were found in the total PANSS positive scale (PANSS-P), although, when focusing on specific items, patients diagnosed with bipolar disorder showed higher scores in grandiosity and lower scores in hallucinatory behavior (data not presented). Both groups showed functional impairment, but premorbid adjustment (mean PAS score: 38.4 vs 50.6; $P < .01$) and psychosocial functioning (mean FAST scale score: 23.6 vs 33.7; $P = .001$) were better in the group diagnosed with bipolar disorder, in particular in the areas of autonomy, interpersonal relationships, and leisure time. DUP was longer in the group diagnosed with schizophrenia (mean DUP: 144.2 vs 194.7 days; $P < .01$). There were no differences in substance misuse between both groups.

Neuropsychological measures. As described in Table 3, patients diagnosed with bipolar disorder and patients diagnosed with schizophrenia differed in the estimated premorbid IQ, with patients diagnosed with bipolar disorder exhibiting a mean estimated premorbid IQ of 98.7 compared to 90.9 in the patients diagnosed with schizophrenia ($P = .01$). Both groups also showed differences in the executive function domain in the first neuropsychological assessment (2-month follow-up), in particular in cognitive flexibility, as patients diagnosed with bipolar disorder performed significantly better in the perseverative error measure of the WCST.

Factors Related to Diagnosis of Bipolar Disorder at Follow-Up: Logistic Regression Model

A logistic regression analysis was performed to investigate the impact of baseline characteristics in the diagnostic group membership at 12-month follow-up. The full model containing the variables baseline PANSS-N, FAST, perseverative errors, and family history of affective disorder as predictors was statistically significant ($B = 2.3$; $P = .009$; $\text{Exp}(B) = 9.979$). The model as a whole explained between 21.1% (Cox and Snell R^2) and 30.2% (Nagelkerke R^2) of the variance and correctly classified 76.8% of cases. Baseline negative symptoms (OR = 0.930 [0.866–0.999]; $P = .048$), functioning (OR = 0.956 [0.922–0.991]; $P = .015$), and the number of perseverative errors on the WCST (OR = 0.946 [0.899–0.996]; $P = .035$) significantly contributed to the model (Table 4), indicating that higher scores on the PANSS-N, FAST, and perseverative errors were associated with a lower probability of bipolar disorder diagnosis.

As included subjects had a wide age range, we decided to explore whether predictors of bipolar disorder would be different in subjects < 18 years old (pediatric sample) and in subjects ≥ 18 years old (adult sample). In the pediatric

Table 3. Comparison of Neuropsychological Characteristics at 2-Month Follow-Up

	Bipolar Disorder (n = 47) Mean (SD)	Schizophrenia (n = 105) Mean (SD)	Statistic	P[a]
Estimated premorbid IQ				
WAIS vocabulary	98.7 (17.7)	90.9 (14.5)	2.78[b]	**.01**
Executive function				
WCST				
Errors	29.3 (16.1)	34.9 (16.9)	2,466[c]	.05
Perseverative responses	17.5 (11.4)	23.1 (17.3)	2,395[c]	.08
Perseverative errors	14.2 (9.0)	19.7 (13.4)	2,609.5[c]	**.01**
Categories	4.98 (1.7)	4.6 (1.8)	1,743.5[c]	.13
SCWT				
Interference	1.4 (13.3)	−1.1 (11.7)	164[c]	.74
TMT				
Trails B	93.3 (41.4)	97.5 (49.1)	2,243.5[c]	.75
Attention				
CPT-II				
Omissions	9.2 (14.4)	10.9 (13.1)	1,873.5[c]	.42
Commissions	16.1 (8.2)	16.5 (8.2)	−0.26[b]	.80
Mean hit RT	386.7 (98.3)	405.0 (62.7)	−1.1[b]	.28
Mean hit RT SE	8.6 (5.9)	7.9 (3.1)	0.69[b]	.50
Processing speed				
COWAT				
FAS	30.2 (10.6)	27.0 (9.4)	1.74[b]	.08
Animal naming	18.1 (5.2)	16.4 (4.2)	1,694.5[c]	.08
TMT				
Trails A	38.9 (22.4)	42.4 (19.9)	2,637[c]	.09
Verbal learning and memory				
TAVEC				
List A (total)	46.2 (12.5)	45.0 (12.8)	0.5[b]	.60
Free short-recall	9.9 (3.6)	9.2 (3.4)	1.15[b]	.25
Cued short-recall	10.5 (3.4)	10.0 (3.4)	1,855.5[c]	.46
Free delayed-recall	10.2 (3.8)	9.6 (3.4)	1[b]	.32
Cued delayed-recall	10.4 (3.4)	10.3 (3.5)	0.25[b]	.80
Recognition	14.6 (1.5)	14.0 (2.1)	1,588[c]	.10
Working memory				
WAIS-III				
Digit-symbol coding	14.4 (3.3)	13.7 (2.9)	1.27[b]	.21
Letter-number sequencing	9.6 (3.4)	8.9 (3.1)	1,852[c]	.19
Emotional intelligence				
MSCEIT				
Managing emotions	93.2 (8.5)	93.3 (10.0)	−0.75[b]	.94

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]Student *t* test.
[c]Mann-Whitney *U*.
Abbreviations: COWAT = Controlled Oral Word Association Test, CPT-II = Conners Continuous Performance Test, Mean hit RT = mean hit reaction time, Mean hit RT SE = mean hit RT standard error, MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test, SCWT = Stroop Color and Word Test, TAVEC = Test de Aprendizaje Verbal España-Complutense, TMT = Trail Making Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

Table 4. Impact of Baseline Factors in Diagnosis of Bipolar Disorder at Follow-Up: Logistic Regression Model

	B (SE)	OR	95% CI	P[a]
Constant	2.3 (0.884)	9.979		**.009**
Negative symptoms[b] (baseline PANSS-N score)	−0.072 (0.036)	0.930	0.866–0.999	**.048**
Functioning[b] (baseline FAST score)	−0.045 (0.018)	0.956	0.922–0.991	**.015**
Perseverative errors (baseline)[b]	−0.055 (0.026)	0.946	0.899–0.996	**.035**
Family history of affective disorders	0.761 (0.533)	2.140	0.753–6.081	.153
R^2 Nagelkerke	0.302			
−2 log	103.872			

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]The results show that higher scores in the PANSS-N, FAST, and perseverative errors are associated with a lower probability of bipolar disorder diagnosis.
Abbreviations: FAST = Functioning Assessment Short Test, OR = odds ratio, PANSS-N = Positive and Negative Syndrome Scale–Negative scale, SE = standard error.

sample, only the model containing the variable baseline FAST as predictor of bipolar disorder was statistically significant ($B = 1.875$; $P = .040$; $\text{Exp}(B) = 6.523$). Regarding the adult sample, the full model containing the variables baseline PANSS-N, FAST, and DUP as predictors was statistically significant ($B = 2.079$; $P = .005$; $\text{Exp}(B) = 8.000$). Baseline negative symptoms (OR = 0.913 [0.857–0.972]; $P = .004$) and DUP (OR = 0.995 [0.992–0.999]; $P = .020$) significantly contributed to the model.

DISCUSSION

Our results indicate that subjects with FEP and further diagnosed with bipolar disorder or schizophrenia at 12-month follow-up display some clinical and cognitive differences from early baseline. Better baseline psychosocial functioning, lower PANSS negative score, and better executive performance—specifically, better cognitive flexibility, as measured by the perseverative errors on the WCST—were related to diagnosis of bipolar disorder at 12-month follow-up. Identification of features suggesting the diagnosis of bipolar disorder in a person with FEP has important clinical implications, as mood stabilizers and nonpharmacologic interventions like psychoeducation have proven to be more effective when started earlier in the course of bipolar disorder.[54,55] In addition, early interventions such as those aimed at improving cognitive reserve might need to be designed differently for patients with bipolar disorder and patients with schizophrenia.[56]

These results replicate previous findings from FEP samples, where better psychosocial functioning, less severe negative symptoms, or better executive functions were associated with a future diagnosis of bipolar disorder.[20,57–59] Besides, the relationship between more negative symptoms, lower functioning, and diagnosis of schizophrenia at follow-up has been consistently reported in previous studies examining diagnosis stability in adult and pediatric FEP samples.[2,16–19,59] Moreover, our results support the findings from Peña et al[57] on the potential of executive functioning to predict diagnostic shift to bipolar disorder or schizophrenia after FEP. Using a multinomial logistic regression model, they found that baseline performance on the WCST tasks "number of categories completed" and "perseverative errors" was able to distinguish between those patients with a final diagnosis of schizophrenia, those with a final diagnosis of other psychoses, and those with a final diagnosis of bipolar disorder with an overall accuracy rate

of 84.4%.[57] The findings of better cognitive flexibility in FEP patients with a final diagnosis of bipolar disorder compared to FEP patients with a final diagnosis of schizophrenia, along with higher IQ in the former group, may be linked to findings from neuroimaging studies that reported more pronounced and generalized gray matter deficits in patients with schizophrenia compared to patients with bipolar disorder,[60] suggesting that more severe neuronal alterations in frontotemporal brain regions in schizophrenia can be considered a biological trait related to the poor cognitive performance and clinical negative symptoms typical of the schizophrenia diagnosis.

In contrast to previous FEP studies, we found neither gender differences[61,62] nor differences in educational level[61] or age at onset[58] between the 2 groups. Yet, our findings confirm the presence of more manic symptoms and lesser negative symptoms in FEP patients with a final diagnosis of bipolar disorder, in consonance with prior studies comparing first-episode schizophrenia and first-episode psychotic bipolar disorder.[58,63,64] We did not find differences in the PANSS-P between the 2 groups except for grandiosity and hallucinatory behavior, on which the patients diagnosed with bipolar disorder scored higher and lower, respectively. This finding reflects the overlap between the PANSS-P and the YMRS—as does the fact that the group diagnosed with schizophrenia showed YMRS scores compatible with subclinical manic symptoms—and may suggest that the PANSS-P might not be sensitive enough to distinguish when positive symptoms like excitement or irritability are due to manic symptoms or due to psychotic symptoms. As so, it highlights the importance of completing the evaluation of subjects with FEP by carefully checking for the presence of "core" manic symptoms using the YMRS, especially among those subjects with high scores in grandiosity and low scores in negative symptoms and hallucinatory behavior. Our results are in consonance with those reported by Jauhar et al,[65] who found that clinical psychopathology syndromes could differentiate affective vs nonaffective psychosis with reasonable accuracy using machine learning techniques. These novel techniques are expected to better capture the complex relationship between variables included in prediction models than traditional statistical models, especially in large data sets.

We also found a shorter DUP in patients diagnosed with bipolar disorder compared to patients diagnosed with schizophrenia, in keeping with the results of previous reports.[20,58,64] The shorter DUP in patients diagnosed with bipolar disorder might be a consequence of more abrupt and noticeable behavioral changes in this group, with lesser predominance of negative symptoms, hence motivating an earlier contact with mental health services. Together with the fact that longer DUP has been related to a future diagnosis of schizophrenia spectrum disorder after FEP,[16,66] our evidence suggests that DUP might be a useful measure to differentiate between schizophrenia and bipolar disorder.

In our cohort, family history of affective disorder was more frequent in patients diagnosed with bipolar disorder than in patients diagnosed with schizophrenia. Nevertheless, this significance was not maintained in the regression model, even though a positive family history of bipolar disorder—especially early onset bipolar disorder—has been found as the strongest predictive factor for bipolar disorder in bipolar offspring cohort studies.[14,67] We did not find any differences in personal history of psychiatric disorder between the 2 groups. Caution is needed in interpreting these results due to the small number of patients reporting previous psychiatric disorders. Still, evidence arising from high-risk populations suggests that subjects at high risk for bipolar disorder and for schizophrenia might initially present with rather unspecific symptoms,[65] whereas more specific symptoms would appear shortly before the development of the full-blown bipolar or psychotic syndrome.[68,69] Thus, the presence or absence of a particular premorbid psychiatric disorder might be less informative than the evolution of psychiatric symptoms over time.

Lastly, previous studies have already reported that subjects with schizophrenia present a more marked premorbid deterioration in functionality than subjects with bipolar disorder,[36] as supported by our findings. In relation to the fact that common and different neural bases between schizophrenia and bipolar disorder have been identified,[70] some authors theorize that both disorders might share developmental pathologies, though of different nature and more severe or frequent in schizophrenia.[71] Taking that into account, although differences in premorbid adjustment and psychosocial functioning could be a consequence of an earlier start of attenuated clinical symptoms in the group of patients diagnosed with schizophrenia, as suggested by a longer DUP, they might also be due to more pronounced neurodevelopmental vulnerability in this group.

Strengths and Limitations

Some limitations should be mentioned when interpreting these results. First, the follow-up period was short, and only a small percentage of subjects received a diagnosis of bipolar disorder or schizophrenia at 12-month follow-up. Additionally, the sample size in the group of patients diagnosed with bipolar disorder was half of that in the group of patients diagnosed with schizophrenia. Third, due to this short follow-up, the subgroup of nonaffective psychosis patients included in the study might comprise those with a more severe clinical course, and, therefore, differences between patients diagnosed with bipolar disorder and patients diagnosed with schizophrenia might be more pronounced, influencing our results. Still, our findings are in line with other studies with longer follow-up.[20,59] Fourth, we cannot rule out that some of the patients diagnosed with bipolar disorder or schizophrenia might still change diagnosis, for instance, to schizoaffective disorder. However, a high diagnostic stability for both bipolar disorder and schizophrenia has been reported,[9,59,72] suggesting that the numbers of diagnostic shifts in both groups are expected to be minimal. Also, the significance threshold of our model was not corrected for multiple testing, which may be taken

into account when interpreting it. Nevertheless, this is a controversial issue due to the risk of increasing β error,[73] and our results are supported by previous literature, which makes them less likely to be due to chance. Lastly, as the study design was constructed prior to 2009, specific scales for negative symptoms such as the Brief Negative Symptom Scale or the Clinical Assessment Interview for Negative Symptoms were not used.

Despite these limitations, it must be underlined that this is a naturalistic study that includes a large sample of patients with a wide age range of inclusion, from adolescence to mid-adulthood, recruited in multiple Spanish psychiatric admission centers for acute psychosis. As such, the sample is expected to be representative of the FEP population in Spain. Furthermore, subjects included in the study were very well characterized, as they underwent a comprehensive protocol that explored in detail sociodemographic, clinical, and neuropsychological variables. Moreover, psychopathology was assessed with well-validated instruments, and cognition was measured using an extensive neuropsychological battery based on the National Institute of Mental Health MATRICS consensus.[74]

CONCLUSIONS

Our results indicate that subjects meeting diagnostic criteria for bipolar disorder or schizophrenia after FEP differ in clinical and neuropsychological variables from patients in the early phases of illness. In particular, we found that better psychosocial functioning, lesser negative symptoms, and better executive performance are related to diagnosis of bipolar disorder at 12-month follow-up. Future prediction models would ideally use a combination of clinical and biological factors. Meanwhile, disentangling which clinical features represent the most differential elements between affective and nonaffective psychosis even at early stages may represent a starting point to guide research in biological markers.

Further studies with larger sample sizes and longer follow-up periods are needed to confirm our results. Even so, our findings support the notion that there are some baseline features that are easily measurable in a clinical setting and useful for identifying patients at high risk of a shift in diagnosis to bipolar disorder after FEP, hence making it possible to design early interventions tailored to these patients.

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POSTTEST

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: December CME) to take this Posttest and complete the Evaluation.** A $10 processing fee is required.

1. **Bipolar disorder is associated with initial misdiagnosis rates in pediatric and adult samples of around:**
   a. 1–2%
   b. 5–10%
   c. 30–60%
   d. 80–90%

2. **Which of the following neurocognitive tests/tasks would you preferentially administer to a patient after a first psychotic episode to help you in the differential diagnosis between bipolar disorder and schizophrenia?**
   a. Conners' Continuous Performance Test-II
   b. Wisconsin Card Sorting Test perseverative error measure
   c. Stroop Color-Word Interference Test
   d. Wechsler Adult Intelligence Scale III Letter-Number Sequencing

3. **When assessing a patient with first-episode psychosis, which of the following scales would prove less informative for the differential diagnosis between bipolar disorder and schizophrenia?**
   a. Young Mania Rating Scale
   b. Functional Assessment Short Test
   c. Positive and Negative Syndrome Scale-Negative Symptoms Subscale
   d. Positive and Negative Syndrome Scale-Positive Symptoms Subscale

4. **Marquita, a 23-year-old woman, was admitted 2 months ago for a first psychotic episode characterized by delusional ideation without hallucinatory behavior. She was diagnosed with schizophrenia. In the last 2 weeks, Marquita has shown low mood, insomnia, clinophobia, refusal to shower or eat, ideas of guilt, and slowness of movement and speech. Current symptomatology, together with a family history of affective disorder, makes you rethink the diagnosis. To evaluate Marquita for a possible diagnosis of bipolar disorder, based on the results of this study, you should collect information on all of the following items *except*:**
   a. Severity of negative symptoms during the first-episode psychosis
   b. Psychosocial functioning prior to the first psychotic episode
   c. Manic symptoms during the first-episode psychosis
   d. History of cocaine use