

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

CME Background

Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

To obtain credit, read the article, correctly answer the questions in the Posttest, and complete the Evaluation. A \$10 processing fee will apply.

CME Objective

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

Accreditation Statement

The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.



Credit Designation

The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note: The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*[™] from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 1 hour of Category I credit for completing this program.

Release, Expiration, and Review Dates

This educational activity was published in November 2020 and is eligible for *AMA PRA Category 1 Credit*[™] through December 31, 2022. The latest review of this material was October 2020.

Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Marlene P. Freeman, MD, Editor in Chief, has received research funding from JayMac and Sage; has been a member of the advisory boards for Otsuka, Alkermes, and Sunovion; has been a member of the Independent Data Safety and Monitoring Committee for Janssen; has been a member of the Steering Committee for Educational Activities for Medscape; and, as a Massachusetts General Hospital (MGH) employee, works with the MGH National Pregnancy Registry, which is sponsored by Teva, Alkermes, Otsuka, Actavis, and Sunovion, and works with the MGH Clinical Trials Network and Institute, which receives research funding from multiple pharmaceutical companies and the National Institute of Mental Health. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

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

Estela Salagre, MD^{a,b}; Iria Grande, MD, PhD^{a,b,*}; Eduard Vieta, MD, PhD^{a,b,*}; Gisela Mezquida, PhD^{b,c}; Manuel J. Cuesta, MD, PhD^d; Carmen Moreno, PhD^{b,e}; Miquel Bioque, MD, PhD^{b,c,f}; Antonio Lobo, MD, PhD^{b,g}; Ana González-Pinto, MD, PhD^{b,h}; Dolores María Moreno, MD, PhD^{b,e}; Iluminada Corripio, MD, PhD^{b,i}; Norma Verdolini, MD, PhD^{a,b,f}; Josefina Castro-Fornieles, MD, PhD^{b,e,j}; Anna Mané, MD, PhD^{b,k}; Justo Pinzon-Espinosa, MD^a; Caterina del Mar Bonnin, PhD^{a,b}; Miquel Bernardo, MD, PhD^{b,c,e}; and PEPs Group^l

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.

J Clin Psychiatry 2020;81(6):19m12996

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.

To cite: Salagre E, Grande I, Vieta E, et al. Predictors of bipolar disorder versus schizophrenia diagnosis in a multicenter first psychotic episode cohort: baseline characterization and a 12-month follow-up analysis. *J Clin Psychiatry*. 2020;81(6):19m12996.

To share: <https://doi.org/10.4088/JCP.19m12996>

© Copyright 2020 Physicians Postgraduate Press, Inc.

^aBipolar and Depressive Disorders Unit, Psychiatry and Psychology Department of the Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, Barcelona, Spain

^bBiomedical Research Networking Center for Mental Health (CIBERSAM), Barcelona, Spain

^cBarcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, University of Barcelona, Barcelona, Spain

^dDepartment of Psychiatry, Complejo Hospitalario de Navarra, Instituto de Investigaciones Sanitarias de Navarra, Pamplona, Spain

^eDepartment of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IISGM, School of Medicine, Universidad Complutense, Madrid, Spain

^fAugust Pi I Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

^gDepartment of Medicine and Psychiatry, Zaragoza University, Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain

^hDepartment of Psychiatry, Hospital Universitario de Álava, University of the Basque Country (UPV/EHU), Vitoria, Spain

ⁱDepartment of Psychiatry, Hospital de Sant Pau, Barcelona, Spain

^jDepartment of Child and Adolescent Psychiatry and Psychology, 2017SGR881, Institute of Neurosciences, Hospital Clinic of Barcelona, University of Barcelona, Spain

^kHospital del Mar Medical Research Institute, Autonomous University of Barcelona, Barcelona, Spain

^lPEPs Group members are listed at the end of the article.

*Corresponding authors: Eduard Vieta, MD, PhD, and Iria Grande, MD, PhD, Department of Psychiatry and Psychology, Clinical Institute of Neuroscience, Hospital Clinic of Barcelona, Villarroel, 170, 08036 Barcelona, Spain (evieta@clinic.cat and igrande@clinic.cat).

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 pediatric² 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 al²¹ 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

It is illegal to post this copyrighted PDF on any website.

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)* criteria²⁴; (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 B⁴³); (3) attention (Continuous Performance Test-II⁴⁴); (4) processing speed (categorical [Animal Naming] and phonemic [F-A-S] components of the Controlled Oral Word Association Test⁴⁵ and Trail Making Test, form A⁴⁶); (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-III³⁹ and WISC-IV⁴⁰); 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 $P < .050$.

You are prohibited from making this PDF publicly available.

Table 1. Comparison of Sociodemographic Characteristics at Baseline

Characteristic	Bipolar Disorder (n=47)		Schizophrenia (n=105)		Mann-Whitney U	P ^a
	Mean	SD	Mean	SD		
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

^aBoldface indicates statistical significance at the $P < .05$ level.

^bIncludes eating disorders, personality disorders, or substance use.

^cIncludes 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

It is illegal to post this copyrighted PDF on any website.

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 <i>U</i>	
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

^aBoldface 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

You are prohibited from making this PDF publicly available.

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

	Bipolar Disorder (n=47)	Schizophrenia (n=105)	Statistic	P ^a
	Mean (SD)	Mean (SD)		
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

^aBoldface indicates statistical significance at the $P < .05$ level.

^bStudent t test.

^cMann-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			

^aBoldface indicates statistical significance at the $P < .05$ level.

^bThe 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 ($\text{OR} = 0.913$ [0.857–0.972]; $P = .004$) and DUP ($\text{OR} = 0.995$ [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 al⁵⁷ 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

You are prohibited from making this PDF publicly available.

It is illegal to post this copyrighted PDF on any website.

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 level⁶¹ or age at onset⁵⁸ 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

You are prohibited from making this PDF publicly available.

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.

Submitted: July 11, 2019; accepted June 29, 2020.

Published online: November 3, 2020.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents or device therapies that is outside US Food and Drug Administration–approved labeling has been presented in this article.

PEPs Group: Bibiana Cabrera, PhD; Silvia Amoretti, PhD; Laura Pina-Camacho, MD, PhD; Elisa Rodríguez, PsyD; Anna Alonso-Solís, PhD; Mireia Rabella, PhD; Purificación López, MD, PhD; Iñaki Zorrilla, MD, PhD; Concepción De-la-Cámara, MD, PhD; Fe Barcones, MD, PhD; Julio Sanjuán, MD, PhD; Esther Lorente-Rovira, PhD; Patricia-Carolina Garnier, MD; Purificación Salgado, MD; Jose Sanchez-Moreno, PsyD; Susana Gomes-da-Costa, MD; Immaculada Baeza, MD, PhD; Elena de la Serna, PhD; Fernando Contreras-Fernández, MD, PhD; Cristina Saiz-Masvidal; María Paz García-Portilla, MD, PhD; Lorena De la Fuente-Tomás, PsyD; Miguel Gutiérrez-Fraile, MD, PhD; Mónica Dompablo, PsyD; Roberto Rodríguez-Jiménez, MD, PhD; Judith Usall, MD, PhD; Anna Butjosa, PhD; Salvador Sarró, MD, PhD; Edith Pomarol-Clotet, MD, PhD; Ángela Ibáñez, MD, PhD; Ana Sánchez-Torres, PhD; and Vicent Balanzá-Martínez, MD, PhD.

Financial disclosure: Dr Grande has received grants and served as consultant, advisor, or CME speaker for Angelini, AstraZeneca, CasenRecordati, Ferrer, Janssen Cilag, Lundbeck, Lundbeck-Otsuka, SEI Healthcare, Spanish Ministry of Economy and Competitiveness, and Instituto de Salud Carlos III (ISCIII). Dr Vieta has received grants and served as consultant, advisor, or CME speaker for AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Galenica, Janssen, Lundbeck, Novartis, Otsuka, Sage, Sanofi-Aventis, and Takeda. Dr Mezquida reports grants from European Union Funds, ISCIII, and Spanish Ministry of Economy and Competitiveness and declares honoraria for participating in advisory boards, data safety monitoring boards, or symposia from Janssen, Servier, Nuvelution, Otsuka, Lundbeck, and Angelini. Dr Bioque has received honoraria for

talks and consultancy from Adamed, Lundbeck, and Otsuka; received honoraria for consultancy from Ferrer; received research support and honoraria for talks and consultancy from Janssen-Cilag; received honoraria for talks from Neuraxpharm; and received a research prize from Pfizer. Dr González-Pinto has received grants from and served as consultant, advisor, or CME speaker for Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Exeltis, Ferrer, Nutrición Médica, Angelini, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Instituto de Salud Carlos III), the Basque Government, and the Stanley Medical Research Institute. Dr D. M. Moreno has received honoraria from Rubió and Rovi. Dr Pinzon-Espinosa has served as a CME speaker for Lundbeck-Otsuka. Dr Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of AB-Biotics, Adamed, Angelini, Casen Recordati, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda, and Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union. Drs Salagre, Cuesta, C. Moreno, Lobo, Corripio, Verdolini, Castro-Fornieles, Mané, and Bonnin and the remaining members of the PEPs group have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This study was supported by Ministerio de Economía y Competitividad (ref. ISCIII 2009-2011: PEPs study PI 080208); Instituto de Salud Carlos III, Fondo Europeo de Desarrollo Regional, Unión Europea, "Un manera de hacer Europa"; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), by the CERCA Programme/Generalitat de Catalunya and Secretaria d'Universitats i Recerca del Departament

d'Economia i Coneixement (2014SGR441). Dr Vieta acknowledges the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283) integrated into the Plan Nacional de I+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365); and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya. Dr Grande acknowledges the support of the Spanish Ministry of Economy, Industry and Competitiveness (PI16/00187, PI19/00954) integrated into the Plan Nacional de I+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER). Dr Salagre is supported by the Instituto de Salud Carlos III through a "Rio Hortega" contract (CM19/00123) co-financed by the European Social Fund. Dr González-Pinto acknowledges the support of the national grant PI14/01900. Dr Bonnin acknowledges the Departament de Salut de la Generalitat de Catalunya for the PERIS grant (SLT002/16/00331). Dr Ibáñez acknowledges the support of Madrid Regional Government (B2017/BMD-3740 AGES-CM 2, and Fondo Social Europeo y Fondo Europeo de Desarrollo Regional, 2014-2020. Dr Balanzá-Martínez is supported by the national grant PI16/01770 (PROBILIFE Study), from the Instituto de Salud Carlos III.

Role of the sponsor: The funding providers had no role in the conduct of the study or the publication of the results.

Previous presentation: Poster presented at the 31st ECNP Congress; October 6–9, 2018; Barcelona, Spain • XXI Congreso Nacional de Psiquiatría; October 18–20, 2018; Granada, Spain.

REFERENCES

- Grande I, Berk M, Birmaher B, et al. Bipolar disorder. *Lancet*. 2016;387(10027):1561–1572.
- Castro-Fornieles J, Baeza I, de la Serna E, et al.

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

- Two-year diagnostic stability in early-onset first-episode psychosis. *J Child Psychol Psychiatry*. 2011;52(10):1089–1098.
3. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Primers*. 2018;4(1):18008.
 4. Kessing LV. Diagnostic stability in bipolar disorder in clinical practice as according to ICD-10. *J Affect Disord*. 2005;85(3):293–299.
 5. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord*. 1994;31(4):281–294.
 6. Altamura AC, Buoli M, Caldiroli A, et al. Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: a naturalistic study. *J Affect Disord*. 2015;182:70–75.
 7. Baca-García E, Perez-Rodriguez MM, Basurte-Villamor I, et al. Diagnostic stability and evolution of bipolar disorder in clinical practice: a prospective cohort study. *Acta Psychiatr Scand*. 2007;115(6):473–480.
 8. Musliner KL, Østergaard SD. Patterns and predictors of conversion to bipolar disorder in 91,587 individuals diagnosed with unipolar depression. *Acta Psychiatr Scand*. 2018;137(5):422–432.
 9. Salvatore P, Baldessarini RJ, Khalsa HM, et al. Predicting diagnostic change among patients diagnosed with first-episode DSM-IV-TR major depressive disorder with psychotic features. *J Clin Psychiatry*. 2013;74(7):723–731.
 10. Zhang L, Yu X, Fang YR, et al. Duration of untreated bipolar disorder: a multicenter study. *Sci Rep*. 2017;7(1):44811.
 11. Gonzalez-Pinto A, Gutierrez M, Mosquera F, et al. First episode in bipolar disorder: misdiagnosis and psychotic symptoms. *J Affect Disord*. 1998;50(1):41–44.
 12. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. *J Clin Psychiatry*. 2009;70(4):458–466.
 13. Jauhar S, Ratheesh A, Davey C, et al. The case for improved care and provision of treatment for people with first-episode mania. *Lancet Psychiatry*. 2019;6(10):869–876.
 14. Vieta E, Salagre E, Grande I, et al. Early intervention in bipolar disorder. *Am J Psychiatry*. 2018;175(5):411–426.
 15. Drancourt N, Etain B, Lajnef M, et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatr Scand*. 2013;127(2):136–144.
 16. Haahr U, Friis S, Larsen TK, et al. First-episode psychosis: diagnostic stability over one and two years. *Psychopathology*. 2008;41(5):322–329.
 17. Schimmelmann BG, Conus P, Edwards J, et al. Diagnostic stability 18 months after treatment initiation for first-episode psychosis. *J Clin Psychiatry*. 2005;66(10):1239–1246.
 18. Schwartz JE, Fennig S, Tanenberg-Karant M, et al. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Arch Gen Psychiatry*. 2000;57(6):593–600.
 19. Heslin M, Lomas B, Lappin JM, et al. Diagnostic change 10 years after a first episode of psychosis. *Psychol Med*. 2015;45(13):2757–2769.
 20. Kim JS, Baek JH, Choi JS, et al. Diagnostic stability of first-episode psychosis and predictors of diagnostic shift from non-affective psychosis to bipolar disorder: a retrospective evaluation after recurrence. *Psychiatry Res*. 2011;188(1):29–33.
 21. Arrasate M, González-Ortega I, Alberich S, et al. Affective dimensions as a diagnostic tool for bipolar disorder in first psychotic episodes. *Eur Psychiatry*. 2014;29(7):424–430.
 22. Bernardo M, Bloque M, Parellada M, et al; PEPs Group. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). *Rev Psiquiatr Salud Ment*. 2013;6(1):4–16.
 23. Salagre E, Arango C, Artigas F, et al. CIBERSAM: ten years of collaborative translational research in mental disorders [in Spanish]. *Rev Psiquiatr Salud Ment*. 2019;12(1):1–8.
 24. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition. Washington, DC: American Psychiatric Association; 1995.
 25. First MB, Gibbon M, Williams JBW. *SCID-II: Guía del Usuario para la Entrevista Clínica Estructurada para los Trastornos de la Personalidad*. Barcelona, Spain: Masson; 1999.
 26. First MB, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders—Administration Booklet*. Washington, DC: American Psychiatric Press; 1994.
 27. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
 28. Ulloa RE, Ortiz S, Higuera F, et al. Interrater reliability of the Spanish version of Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL) [in Spanish]. *Actas Esp Psiquiatr*. 2006;34(1):36–40.
 29. Hollingshead AB, Redlich FC. Social class and mental illness: a community study. 1958. *Am J Public Health*. 2007;97(10):1756–1757.
 30. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
 31. Peralta V, Cuesta MJ. Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia. *Psychiatry Res*. 1994;53(1):31–40.
 32. Lobo A, Chamorro L, Luque A, et al; Grupo de Validación en Español de Escalas Psicométricas (GVEEP). Validation of the Spanish versions of the Montgomery-Asberg Depression and Hamilton Anxiety Rating scales [in Spanish]. *Med Clin (Barc)*. 2002;118(13):493–499.
 33. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
 34. Colom F, Vieta E, Martínez-Arán A, et al. Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale [in Spanish]. *Med Clin (Barc)*. 2002;119(10):366–371.
 35. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
 36. Cannon M, Jones P, Gilvarry C, et al. Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. *Am J Psychiatry*. 1997;154(11):1544–1550.
 37. Rosa AR, Sánchez-Moreno J, Martínez-Arán A, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clin Pract Epidemiol Ment Health*. 2007;3(1):5.
 38. Rosa AR, Reinares M, Amann B, et al. Six-month functional outcome of a bipolar disorder cohort in the context of a specialized-care program. *Bipolar Disord*. 2011;13(7-8):679–686.
 39. Wechsler DW. *Adult Intelligence Scale-III (WAIS-III)*. San Antonio, TX: Psychological Corporation; 1997.
 40. Wechsler DW. *Intelligence Scale for Children-IV (WISC-IV)*. San Antonio, TX: The Psychological Corporation; 2003.
 41. Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Chicago, IL: Stoelting Co.; 1978.
 42. Heaton RK. *Wisconsin Card Sorting Test Manual*. Odessa, FL: Psychological Assessment Resources; 1981.
 43. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(3):271–276.
 44. Conners CK. *Conners' Continuous Performance Test*. Toronto, Canada: Multi-Health System; 2002.
 45. Benton ALHK. *Multilingual Aphasia Examination Manual*. Iowa City, IA: University of Iowa; 1976.
 46. Reitan RM, Wolfson DW. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. Tucson, AZ: Neuropsychology Press; 1993.
 47. Benedet MJ, Alejandre MA. *Test de Aprendizaje Verbal Española-Complutense (TAVEC)*. Madrid, Spain: Tea Ediciones; 1998.
 48. Benedet MJ, Alejandre MA, Pamos A. *Test de Aprendizaje Verbal Española-Complutense Infantil (TAVECi)*. Madrid, Spain: Tea Ediciones; 1998.
 49. Brackett MA, Salovey P. Measuring emotional intelligence with the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT). *Psychothera*. 2006;18(suppl):34–41.
 50. Extremera N, Fernández-Berrocal P, Salovey P. Spanish version of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Version 2.0: reliabilities, age and gender differences. *Psychothera*. 2006;(suppl 18):42–48.
 51. Cuesta MJ, Sánchez-Torres AM, Cabrera B, et al; PEPs Group. Premorbid adjustment and clinical correlates of cognitive impairment in first-episode psychosis: the PEPsCog Study. *Schizophr Res*. 2015;164(1-3):65–73.
 52. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361–387.
 53. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York: John Wiley & Sons, Inc; 2000.
 54. Swann AC, Bowden CL, Calabrese JR, et al. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am J Psychiatry*. 1999;156(8):1264–1266.
 55. Colom F, Reinares M, Pacchiarotti I, et al. Has number of previous episodes any effect on response to group psychoeducation in bipolar patients? a 5-year follow-up post hoc analysis. *Acta Neuropsychiatr*. 2010;22(2):50–53.
 56. Amoretti S, Cabrera B, Torrent C, et al; PEPsGroup. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. *Acta Psychiatr Scand*. 2018;138(5):441–455.
 57. Peña J, Ojeda N, Segarra R, et al. Executive functioning correctly classified diagnoses in patients with first-episode psychosis: evidence from a 2-year longitudinal study. *Schizophr Res*. 2011;126(1-3):77–80.
 58. Kapila A, Fisher HL, Johnson S, et al. Clinical and demographic differences between patients with manic, depressive and schizophrenia-spectrum psychoses presenting to Early Intervention Services in London. *Early Interv Psychiatry*. 2019;13(3):509–516.
 59. Bromet EJ, Kotov R, Fochtmann LJ, et al. Diagnostic shifts during the decade following first admission for psychosis. *Am J Psychiatry*. 2011;168(11):1186–1194.
 60. Maggioni E, Bellani M, Altamura AC, et al. Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder. *Epidemiol Psychiatr Sci*. 2016;25(4):312–316.

- It is illegal to post this copyrighted PDF on any website.**
61. Zanelli J, Reichenberg A, Morgan K, et al. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. *Am J Psychiatry*. 2010;167(1):78–85.
 62. Mojtabai R, Bromet EJ, Harvey PD, et al. Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. *Am J Psychiatry*. 2000;157(9):1453–1460.
 63. Daros AR, Ruocco AC, Reilly JL, et al. Facial emotion recognition in first-episode schizophrenia and bipolar disorder with psychosis. *Schizophr Res*. 2014;153(1–3):32–37.
 64. Rosen C, Marvin R, Reilly JL, et al. Phenomenology of first-episode psychosis in schizophrenia, bipolar disorder, and unipolar depression: a comparative analysis. *Clin Schizophr Relat Psychoses*. 2012;6(3):145–151.
 65. Jauhar S, Krishnadas R, Nour MM, et al. Is there a symptomatic distinction between the affective psychoses and schizophrenia? a machine learning approach. *Schizophr Res*. 2018;202:241–247.
 66. Subramaniam M, Pek E, Verma S, et al. Diagnostic stability 2 years after treatment initiation in the early psychosis intervention programme in Singapore. *Aust N Z J Psychiatry*. 2007;41(6):495–500.
 67. Preisig M, Strippoli MF, Castelao E, et al. The specificity of the familial aggregation of early-onset bipolar disorder: a controlled 10-year follow-up study of offspring of parents with mood disorders. *J Affect Disord*. 2016;190:26–33.
 68. Hafeman DM, Merranko J, Axelson D, et al. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry*. 2016;173(7):695–704.
 69. Duffy A, Goodday S, Keown-Stoneman C, et al. The emergent course of bipolar disorder: observations over two decades from the canadian high-risk offspring cohort. *Am J Psychiatry*. 2019;176(9):720–729.
 70. Maggioni E, Crespo-Facorro B, Nenadic I, et al, ENPACT group. Common and distinct structural features of schizophrenia and bipolar disorder: the European Network on Psychosis, Affective disorders and Cognitive Trajectory (ENPACT) study. *PLoS One*. 2017;12(11):e0188000.
 71. Parellada M, Gomez-Vallejo S, Burdeus M, et al. Developmental differences between schizophrenia and bipolar disorder. *Schizophr Bull*. 2017;43(6):1176–1189.
 72. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. Diagnostic stability of ICD/DSM first episode psychosis diagnoses: meta-analysis. *Schizophr Bull*. 2016;42(6):1395–1406.
 73. Fiedler K, Kutzner F, Krueger JI. The long way from α -error control to validity proper: problems with a short-sighted false-positive debate. *Perspect Psychol Sci*. 2012;7(6):661–669.
 74. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203–213.



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