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Original article

Spanish validation of the Empirically Developed Clinical Staging Model (EmDe-5) for patients with bipolar disorder

Lorena de la Fuente-Tomás[a,b,c,d,*], Belén Arranz[b,e], Pilar Sierra[f], Mónica Sánchez-Autet[e], Ana García-Blanco[f], Luis Gutiérrez-Rojas[g], Vicent Balanzá-Martínez[b,h], Sonia Vidal-Rubio[i], Eduard Vieta[b,j], Esther Jiménez[b,j], Carla Hernández[b,e], Manuel Arrojo[k], Jesús Gómez-Trigo[k], Yolanda Zapico-Merayo[l], Jose María Pelayo-Terán[b,l,m], Victor Pérez-Solà[b,n], Estanislao Mur[n], Narcís Cardoner[b,o], Ana González-Pinto[b,p], Iñaki Zorrilla[b,p], Miguel Ruiz-Veguilla[b,q], Ruben Catalán-Barragán[r], Gemma Safont[b,s], Clara Martínez-Cao[a,c], Pilar Sáiz[a,b,c,d], Julio Bobes[a,b,c,d], Maria Paz García-Portilla[a,b,c,d]

[a] *Department of Psychiatry, Universidad de Oviedo, Oviedo, Spain*
[b] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain*
[c] *Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*
[d] *Instituto Universitario de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain*
[e] *Parc Sanitari Sant Joan de Déu, Barcelona, Spain*
[f] *La Fe University and Polytechnic Hospital, Valencia, and University of Valencia, Valencia, Spain*
[g] *Department of Psychiatry and Psychiatry and Neurosciences Research Group (CTS-549), University of Granada, Granada, Spain*
[h] *Teaching Unit of Psychiatry, Department of Medicine, University of Valencia, Valencia, Spain*
[i] *Psychiatry Service, Ribera Deparment, Spain*
[j] *Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clínic of Barcelona, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain*
[k] *Psychiatry Service, Complejo Hospitalario Universitario de Santiago, Spain*
[l] *Servicio de Psiquiatría y Salud Mental. Hospital El Bierzo, Gerencia de Asistencia Sanitaria del Bierzo (GASBI), Gerencia Regional de Salud de Castilla y León (SACYL). Ponferrada (León), Spain*
[m] *Área de Medicina y Salud Pública, Departamento de Ciencias de la Salud, Universidad de León, León, Spain*
[n] *Department of Psychiatry, Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain; IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain*
[o] *Mental Health Department, Neuroscience and Mental Health Research Area, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain*
[p] *Department of Psychiatry UPV/EHU. BIOARABA, University Hospital Alava, País Vasco, Spain*
[q] *University Hospital Virgen del Rocío, Sevilla/ibis, University of Sevilla, Spain*
[r] *Llerena General Hospital, Hospitalization Unit, Badajoz, Spain*
[s] *Department of Psychiatry, Hospital Universitari Mútua Terrassa, University of Barcelona, Integrative and Conscious Health Institute, Barcelona, Spain*

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ABSTRACT

Introduction: Bipolar disorder (BD) has been reconceptualised as a progressive disorder that develops from mild to severe presentations. An empirical staging model – the Empirically Developed Clinical Staging Model for BD (EmDe-5) – was developed in a previous study. This study aims to further validate that model using a larger and more representative Spanish sample.
Material and methods: 183 BD outpatients were recruited at 11 sites in Spain. Assessment included clinical characteristics of the BD (number of hospitalisations, number of suicide attempts, comorbid personality disorders), physical health (BMI, metabolic syndrome, number of physical illnesses), cognition (SCIP), functioning (permanently disabled due to BD, FAST), and quality of life (SF-36). The CGI-S, VAS-S, and psychopharmacological treatment pattern were used as external validators.

* Corresponding author.
E-mail address: fuentelorena@cop.es (L. de la Fuente-Tomás).

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Results: Ten patients (51.5%) were classified as stage 1, 33 (18%) as stage 2, 93 (50 8%) as stage 3, 37 (20 2%) as stage 4, and 10 (5 5%) as stage 5. All profilers, other than number of suicide attempts ($p = 0.311$) and comorbid personality disorder ($p = 0.061$), exhibited worse scores from stage 1 to 5. As expected, VAS-S and CGI-S scores were worse in the later stages. Regarding treatment, early stages (1–2) were associated with the use of one to three drugs while late stages (4–5) were associated with four or more drugs ($p = 0.002$).
Conclusions: We confirm the EmDe-5 staging model's construct validity. The ease of obtaining the profilers, together with the operational criteria provided to quantify them, will facilitate the use of the EmDe-5 staging model in daily clinical practice.

Introduction

The clinical staging model, widely used in medicine, is a refined and practical system of classification for determining the position of an individual within a continuum of severity, taking into account the longitudinal course of the disease.[1] Several studies point to Bipolar Disorder (BD) as a lifelong progressive condition with different clinical, cognitive, and functioning manifestations throughout its recurrent course that would benefit from a staging model. Although different staging models for BD have been proposed, the majority have been developed from a theoretical perspective, and very few have been externally or longitudinally validated.[1]

In response to the growing interest in staging models for BD, since 2007, when the first theoretical staging model for BD was reported,[2] several more complex models have been proposed.[3–5] The first model proposed by Berk et al.[2] consisted of seven stages based on affective psychopathology. Then, Kapczinski et al.[3] suggested a similar model, with the addition of functioning, cognition, and biomarkers.[3,4] Duffy et al. later suggested a staging model that took into account the natural history of BD, and risk factors and behavioural changes during early stages of life.[5] Some of these models have been partially validated in other samples, but to our knowledge, only a modification of the model of Berk has been longitudinally validated.[6] Furthermore, the proposed models are rarely implemented in daily clinical practice.[6] One of the reasons for this may be the lack of replicated evidence on the biomarkers and behavioural boundaries of the proposed stages.[7]

The Empirically Developed Clinical Staging Model for BD (EmDe-5) is a staging model developed using k-means clustering.[8] It classifies patients into five stages according to their situation in twelve profilers grouped in five life domains (see Fig. 1). In addition to the clinical manifestations of BD, it includes information on cognition and functioning, as other models did.[3,4] However, this model is unique in incorporating information on physical health and self-reported information on the impact of BD on the patient's life. These findings confirm previous results which suggested these dimensions as markers that might help classify patients into clinical stages.[9–11] This model was created using data of outpatients from Oviedo, Barcelona, and Valencia (Spain),[8] and it was externally and longitudinally validated using the three-year follow-up data of these patients.[12] Concerning longitudinal validity of the proposed model, half of the patients remained at the same stage, more than a third progressed or regressed one stage and only 10% progressed or regressed two at three-year follow-up. Furthermore, this study showed that most patients who were euthymic remained at the same stage or regressed to a previous one.[12] The current study now aims to further validate this model using a different, larger and more representative Spanish national sample. To test the construct validity of the EmDe-5 staging model, we determined if: (1) the twelve profilers of the model behaved properly, that is, more severe scores on each profiler in late stages than in early stages and (2) our proposed external validators (CGI-S and VAS-S scores and pharmacological treatment patterns) also behaved properly. We hypothesised that, in late stages, the clinicians' perception of the disorder would be more severe and the prescribed pharmacological treatment more complex.

Methods

Study design

Naturalistic, cross-sectional, multicenter study of patients with BD in ambulatory treatment. Of a total of 214 outpatients recruited at 11 sites in Spain, 183 patients who had no missing data in any profiler of the EmDe-5 staging model were included in the study. Inclusion criteria were: (1) outpatients with a diagnosis of BD according to DSM-5[13] in treatment at any of the participating sites; (2) age ≥18 years, and (3) written informed consent to participate in the study. Exclusion criteria were designed to be minimal in order to obtain a heterogeneous and representative sample of all phases of the disorder and consisted of only refusal to participate.

Assessments

As the main objective of the study was to confirm the validity of the EmDe-5 staging model, evaluations were oriented mainly towards obtaining the 12 profilers of the model. Thus, the Spanish versions of the Scale for Cognitive Impairment in Psychiatry (SCIP),[14] Functioning Assessment Short Test (FAST),[15] and MOS 36-item Short-Form Health Survey (SF-36)[16] were employed. Information on clinical characteristics of the BD (lifetime number of hospital admissions, lifetime number of suicide attempts, and comorbidity with personality disorders) and patient physical health (height, weight, metabolic syndrome criteria,[17] and number of comorbid physical illnesses) was recorded. In addition, age, sex, and BD type were recorded for each patient.

Following our previous work on validation of the EmDe-5 staging model,[8,12] we decided to use clinician ratings of the severity of the disorder and patient pharmacological treatment regimen as external validators. For the measurement of the severity of the BD, we used the Clinical Global Impression (CGI-S),[18] and we developed a visual analogue scale (VAS-S). The VAS-S consists of a 16.5-cm-long vertical line divided into 100 units, ranging from 0 (no disease) to 100 (maximum possible severity). Clinicians mark the point on the line that they think best reflects the overall severity of their patient's BD.

The EmDe-5 staging model for BD[8]

The first step in the development of this staging model was to create a cluster-based method to classify BD patients using a cross-sectional sample from four sites in Spain. We made a dimensional reduction using k-means clustering, a technique that aims

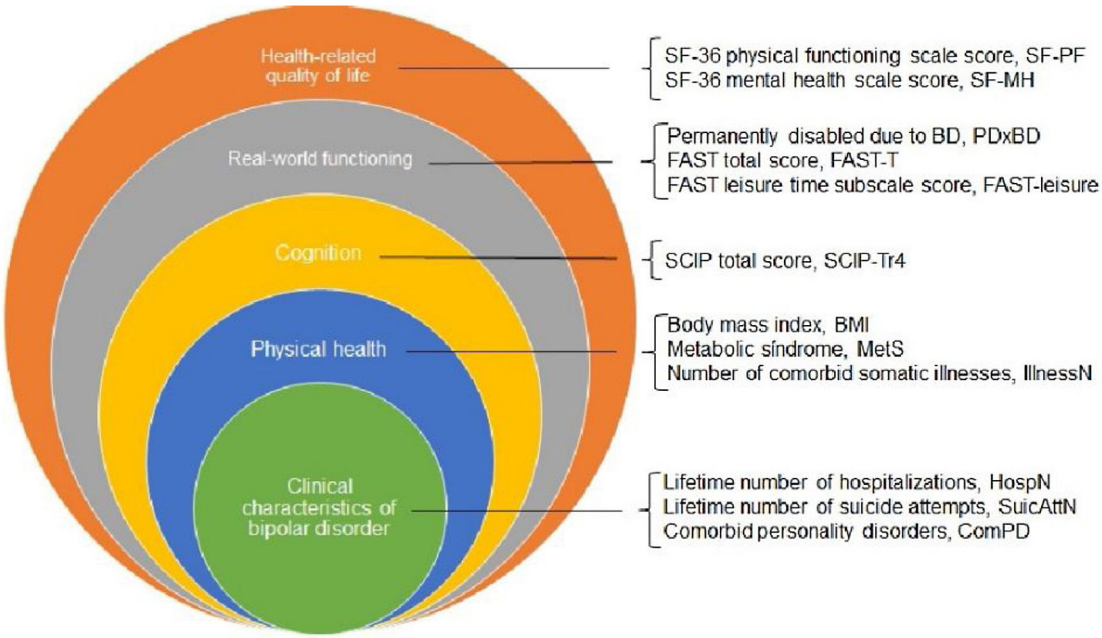

Figure 1. The EmDe-5 clinical staging model for bipolar disorder: Life domains and profilers. BD: Bipolar disorder; FAST: Functioning Assessment Short Test; SCIP: Screen for Cognitive Impairment in Psychiatry; SF-36: The MOS 36-item Short-Form Health Survey.

to partition n observations into k clusters in which each observation belongs to the cluster with the nearest mean. Comparisons of between-group variables were then performed by Chi-square and univariate ANOVA followed by Tukey's honestly significant difference post hoc testing. Those variables in which statistically significant between-group differences were found were selected to be part of the model along with other variables added by expert criteria based on previous findings and clinical practice. We used all these variables, hereafter called profilers, to calculate a global severity formula. The formula includes twelve profilers from the following five life domains shown in Fig. 1.

Using the severity formula below, we obtained a global severity score for each patient, which allowed us to assign that patient to one of the five clusters of the staging model.

$$Severity = \frac{10}{12}(HospN + SuicAttN + ComPD + BMI + MetS + IllnessN + SCIP\_Tr4 + PDxBD + FAST\_T + FAST\_T + FAST\_leisure + SF\_PF + SF\_MH) \quad (1)$$

All profilers have the same weight and may take values between 0 and 1, so the severity score ranges from 0 to 10. Categorical profilers, such as comorbid personality disorder, were given 0 for the absence and 1 for the presence of the profiler. Quantitative profilers, such as number of suicide attempts or those scores from psychometric scales, were divided according to the 5 stages. For further detail, see Fuente-Tomas et al.[8] Based on this score, we proposed cut-offs for delimiting the five clusters using the scores corresponding to the 5th, 25th, 50th, 75th, and 95th percentiles (1.70, 2.50, 4.50, and 6.10, and ≥6.11, respectively).

Statistical analysis

Analyses were performed using IBM SPSS Statistics for Windows, Version 24.0. The significance level was set at $p < 0.05$. Means and standard deviations and numbers and percentages were used to describe patient characteristics as appropriate. We used a chi-square test and ANOVA to identify associations between variables.

Ethical aspects

The study was conducted according to the ethical principles of the Declaration of Helsinki. The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (Ref. 36/12), and written informed consent was obtained from all participants before enrolment.

Results

Demographic and clinical characteristics

Patient demographic and clinical characteristics, including the profilers of the model, are shown in Table 1. Their mean age was 52.7, almost half were males (48.6%), 74.3% had a BD I diagnosis, and the mean illness-severity scores were 3.44 (range 1–7) for the CGI-S and 46.1 (range 5–100) for the VAS-S. Almost 40% of the patients did not have cognitive impairment, while 16.4% had mild, 19.7% moderate, and 25.1% severe cognitive impairment using the SCIP.

On average, patients were receiving a mean of 3.32 (SD 1.5) prescribed drugs. A total of 168 patients (91.8%) were taking classical mood stabilisers. Additionally, 119 patients (65.0%) were taking antipsychotics, 78 (42.6%) antidepressants, and 100 (54.6%) benzodiazepines.

Regarding stages, 10 (5.5%) were classified as stage 1, 33 (18%) as stage 2, 93 (50.8%) as stage 3, 37 (20.2%) as stage 4, and 10 (5.5%) as stage 5. The mean severity formula score of the sample was 3.64 (SD 1.4; range 0.85–7.39) and followed a normal distribution [Fisher skewness coefficient = 0.374 (standard error of skewness = 0.180), Fisher kurtosis coefficient = −0.469 (standard error of kurtosis = 0.357), K–S = 0.064, $p = 0.066$] (see Fig. 2).

Construct validity

All the profilers, other than number of suicide attempts and comorbid personality disorder, significantly worsened as the stages progressed (Table 2). The external validators proposed also behaved as hypothesised. On the one hand, VAS-S scores significantly worsened with the stages, ranging from 38.50 (SD 23.3) in stage 1–60.50 (SD 19.3) in stage 5, as did CGI-S scores (see

Table 1
Patient demographic and clinical characteristics.

Sample characteristics	(*n* = 183)
Mean age [Mean (SD)]	52.73 (13.2)
Sex, females [n (%)]	94 (51.4)
BD type, type 1 [n (%)]	136 (74.3)
CGI-S [Mean (SD)]	3.44 (1.2)
VAS-S [Mean (SD)]	46.09 (22.4)
FAST total score [Mean (SD)]	25.35 (16.1)
Profilers (direct scores)	
Lifetime number of hospitalisations [Mean (SD)]	2.53 (3.5)
Lifetime number of suicide attempts [Mean (SD)]	0.58 (1.7)
Comorbid personality disorder, yes [*n* (%)]	25 (13.7)
Body Mass Index [Mean (SD)]	30.11 (5.4)
Metabolic syndrome, yes [*n* (%)]	52 (28.4)
Number of comorbid physical illnesses [Mean (SD)]	1.60 (1.8)
SCIP category, no cognitive impairment [*n* (%)]	71 (38.8)
Permanently disabled due to BD, yes [*n* (%)]	83 (45.4)
FAST staging total score[a] [Mean (SD)]	23.10 (15.0)
FAST leisure subscale score [Mean (SD)]	2.25 (1.9)
SF-36 physical functioning scale *z*-score [Mean (SD)]	−0.34 (1.0)
SF-36 mental health scale *z*-score [Mean (SD)]	−0.53 (1.0)
Profilers (transformed scores 0–1) [Mean (SD)]	
Lifetime number of hospitalisations	0.40 (0.3)
Lifetime number of suicide attempts	0.11 (0.2)
Comorbid personality disorder	0.14 (0.3)
Body Mass Index	0.38 (0.3)
Metabolic syndrome	0.28 (0.4)
Number of comorbid physical illnesses	0.36 (0.3)
SCIP category, no cognitive impairment	0.43 (0.4)
Permanently disabled due to BD	0.45 (0.5)
FAST staging total score	0.35 (0.2)
FAST leisure subscale score	0.37 (0.3)
SF-36 physical functioning scale *z*-score	0.53 (0.1)
SF-36 mental health scale *z*-score	0.55 (0.1)

BD: Bipolar disorder; CGI-S: Clinical Global Impression, Severity, FAST: Functioning Assessment Short Test; SCIP: Scale for Cognitive Impairment in Psychiatry; SD: Standard deviation; SF-36: The MOS 36-item Short-Form Health Survey; VAS-S: Visual Analogue Scale-Severity.

[a] FAST staging total score = FAST total score – FAST leisure score (range = 0–66).

Table 3). On the other hand, regarding pharmacological treatment patterns, we found that early stages (1 and 2) were associated with the use of one to three-drug combinations while late stages (4 and 5) were associated with combinations of four or more drugs ($p = 0.002$). Also, patients in the late stages more frequently received antipsychotics and benzodiazepines, but only the latter achieved statistically significant differences (see Table 3).

Discussion

In this study, we further tested the EmDe-5 staging model, a cross-sectionally and longitudinally validated, empirically developed clinical staging model for patients with BD, in a sample from 11 sites across Spain. According to the hypothesis, the construct validity of the EmDe-5 staging model was appropriate; all profilers worsened from stages 1 to 5, although two profilers (number of suicide attempts and comorbid personality disorders) did not reach statistical significance. Its construct validity was also confirmed by the external validators used in this study, i.e., clinician assessment (CGI-S and VAS-S scores) and number of prescribed drugs.

Regarding the dimensions included in the EmDe-5 staging model, real-world functioning and cognition have been proposed by several authors.[3,4,19–21] However, the EmDe-5 staging model is the first to propose specific profilers for each of these dimensions and provides operational criteria for their quantification. In the case of real-world functioning, the model included three profilers: one pragmatic, permanently disabled due to BD, and two psychometrics, FAST total score and FAST leisure time subscale score. The fact that the model does not include the FAST occupational functioning subscale score may be seen as a limitation of the model; however, we thought that this construct is more accurately represented by the aforesaid pragmatic profiler. Cognition is represented by one unique profiler, SCIP total score. We employed the SCIP to assess cognition because this instrument has been recommended by the International Society for Bipolar Disorders (ISBD) Task Force[22] for screening and monitoring changes in cognitive performance over time, thus making it an ideal instrument for a staging model. In this study, we replicated previous findings,[8,12] and patients exhibited worse scores from stage 1 to stage 5 in all the profilers of these two dimensions. Thus, while only 10% of patients in stage 1 showed a decline in cognitive performance, 80% of those in stage 5 did. The same trend was seen in the three real-world dimension profilers. Our results in these two dimensions give empirical support to the Kapczinski et al.[3] staging model and confirm previous findings

Table 2
Construct validity of the EmDe-5 staging model: Values and distribution of profilers throughout the model.

Profilers	Stage 1 *n* = 10	Stage 2 *n* = 33	Stage 3 *n* = 93	Stage 4 *n* = 37	Stage 5 *n* = 10	Statistical test, *P*
Bipolar disorder						
Number of hospitalisations [Mean (SD)]	0.80 (1.2)	1.58 (1.9)	2.39 (2.8)	3.32 (5.1)	5.80 (5.1)	4.230[a], 0.003
Number of suicide attempts [Mean (SD)]	0.00 (0.0)	0.15 (0.5)	0.72 (2.2)	0.65 (1.1)	1.10 (1.4)	1.204[a], 0.311
Comorbid personality disorder, yes [*n* (%)]	0 (0.0)	1 (3.0)	13 (14.0)	8 (21.6)	3 (30.0)	9.003[b], 0.061
Physical health						
Body Mass Index [Mean (SD)]	24.73 (3.5)	27.42 (3.8)	29.78 (4.6)	33.47 (5.4)	35.0 (7.0)	13.092[a], <.0.001
Metabolic syndrome, yes [*n* (%)]	0 (0.0)	1 (3.0)	25 (26.9)	18 (48.6)	8 (80.0)	35.060[b], <.0.001
Number of comorbid physical illnesses [Mean (SD)]	0.20 (0.4)	0.61 (0.9)	1.32 (1.3)	3.27 (2.3)	2.60 (2.2)	19.964[a], <.0.001
Cognition						
SCIP category, cognitive impairment [*n* (%)]	1 (10.0)	11 (33.3)	60 (64.5)	32 (86.5)	8 (80.0)	33.715[b], <.0.001
Real-world functioning						
Permanently disabled due to BD, yes [*n* (%)]	1 (10.0)	8 (24.2)	37 (39.8)	27 (73.0)	10 (100.0)	35.578[b], <.0.001
FAST staging total score[c] [Mean (SD)]	5.40 (8.7)	12.30 (9.5)	22.01 (13.2)	34.86 (10.6)	43.10 (10.1)	29.407[a], <.0.001
FAST leisure subscale score [Mean (SD)]	0.70 (0.8)	1.00 (1.1)	2.00 (1.7)	3.70 (1.6)	5.20 (0.9)	26.855[a], <.0.001
Health-related quality of life						
SF-36 physical functioning scale *z*-score [Mean (SD)]	0.43 (0.2)	0.2 (0.8)	−0.30 (0.8)	−0.84 (1.0)	−1.32 (1.4)	11.005[a], <.0.001
SF-36 mental health scale *z*-score [Mean (SD)]	−0.06 (0.5)	−0.06 (0.8)	−0.48 (1.0)	−0.96 (1.2)	−1.44 (1.0)	6.391[a], <.0.001

[a] ANOVA test.

[b] Chi-square test. BD: Bipolar disorder; FAST: Functioning Assessment Short Test; SCIP: Scale for Cognitive Impairment in Psychiatry; SD: Standard deviation; SF-36: The MOS 36-item Short-Form Health Survey.

[c] FAST staging total score = FAST total score – FAST leisure score (range = 0–66).

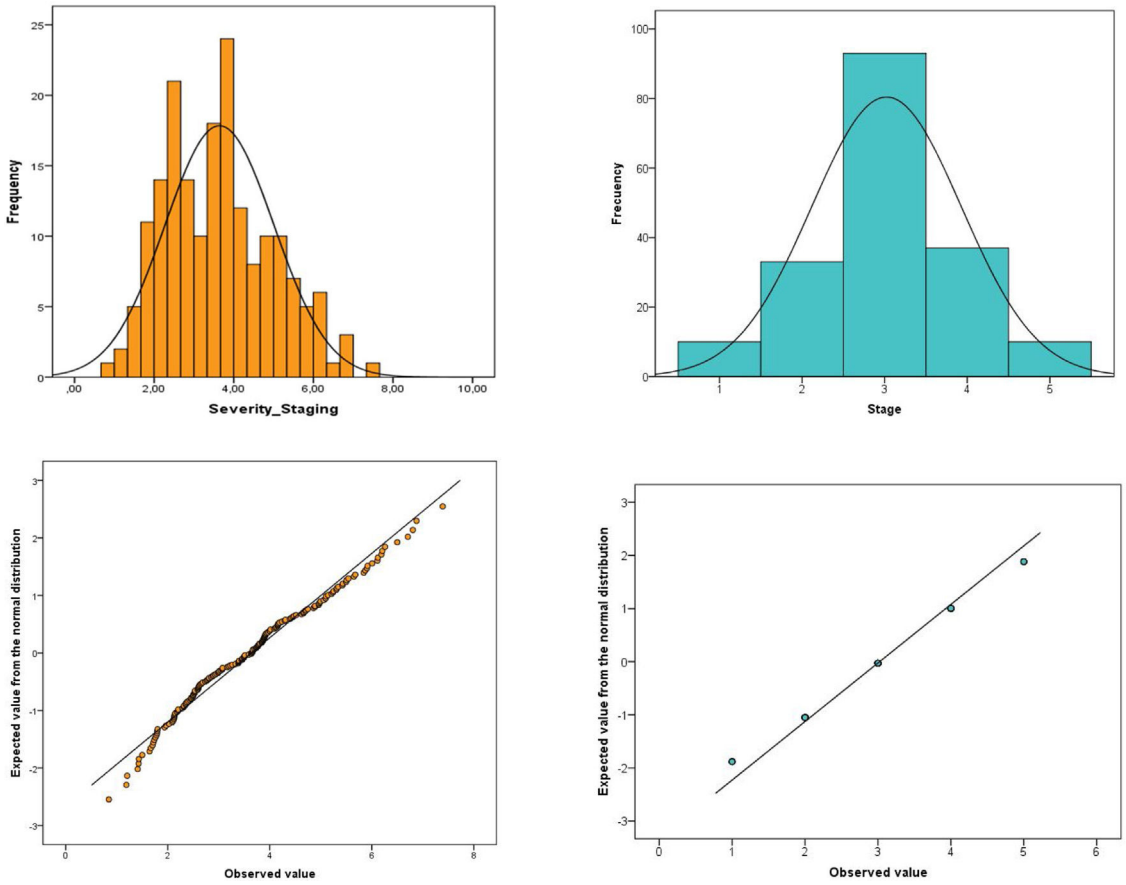

Figure 2. EmDe-5 staging model: Distribution of the sample and Kolgomorov–Smirnov test for normality according to severity formula score and stage.

Table 3
Construct validity of the EmDe-5 staging model: Values and distribution of external validators throughout the model.

	Stage 1 *n* = 10	Stage 2 *n* = 33	Stage 3 *n* = 93	Stage 4 *n* = 37	Stage 5 *n* = 10	Statistical test, *P*
CGI-S score [Mean (SD)]	2.50 (1.4)	2.67 (1.1)	3.49 (1.1)	3.97 (1.2)	4.50 (1.3)	9.518[a], <.0.001
VAS-S score [Mean (SD)]	38.50 (23.3)	35.61 (19.5)	47.05 (22.0)	51.19 (22.9)	60.50 (19.3)	3.880[a], 0.005
Number of prescribed drugs [n (%)]						43.202[b], 0.002
Zero	1 (10.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	
One	1 (10.0)	6 (18.2)	6 (6.5)	0 (0.0)	0 (0.0)	
Two	3 (30.0)	8 (24.2)	25 (26.9)	4 (10.8)	2 (20.0)	
Three	5 (50.0)	8 (24.2)	26 (28.0)	10 (27.0)	3 (30.0)	
Four	0 (0.0)	8 (24.2)	21 (22.6)	6 (16.2)	2 (20.0)	
Five or more	0 (0.0)	3 (9.1)	14 (15.1)	17 (45.9)	3 (30.0)	
Mean number of prescribed drugs [Mean (SD)]	2.20 (1.0)	2.85 (1.3)	3.18 (1.4)	4.30 (1.6)	3.70 (1.3)	7.352[a], <.0.001
Type of prescribed drugs [*n* (%)]						
Classical mood stabilisers[*]						8.092[b], 0.425
Zero	2 (20.0)	0 (0.0)	7 (7.5)	4 (10.8)	2 (20.0)	
One	7 (70.0)	27 (81.8)	66 (71.0)	27 (69.2)	10 (90.9)	
Two	1 (10.0)	6 (18.2)	20 (21.5)	7 (18.9)	1 (10.0)	
Antipsychotics	5 (50.0)	21 (63.6)	55 (59.1)	30 (81.1)	8 (80.0)	7.617[b], 0.107
Antidepressants	4 (40.0)	13 (39.4)	35 (37.6)	22 (59.5)	4 (40.0)	5.432[b], 0.246
Benzodiazepines	2 (20.0)	12 (36.4)	50 (53.8)	27 (73.0)	9 (90.0)	19.380[b], 0.001

CGI-S: Clinical Global Impression – Severity; SD: Standard deviation; VAS-S: Visual Analogue Scale-Severity.
[a] ANOVA test;.
[b] Chi-square test.
[*] Traditional mood stabilisers: Lithium, Valproate, Lamotrigine, and Carbamazepine.

suggesting that functioning and cognition may help to classify BD patients into different clinical stages.[23–25]

Partial validations of the Kapczinki et al.[3] staging model found statistically significant differences between early and late stages in several clinical BD variables such as number of the previous episodes,[24,27,28] age at onset,[23,28] and treatment response.[29] On the contrary, the EmDe-5 staging model did not include any of these variables in its clinical characteristics of the BD dimension. The three profilers selected in this dimension were lifetime number of hospitalisations, lifetime number of suicide attempts, and

comorbid personality disorders. Although two of these three profilers showed progressive worsening as the stages advanced, they did not reach statistical significance [number of suicide attempts and comorbid personality disorder ($p = 0.311$ and $p = 0.061$, respectively). The number of suicide attempts was one of the profilers included by expert criteria due to its clinical value. The presence of suicide attempts almost automatically confers upon the patient a greater level of severity and a different case-management approach with particular pharmacological and therapeutic interventions. The fact that it did not reach statistical significance may be related to its reduced range and its distribution in the sample. The majority of patients did not have previous suicide attempts (71%), 16.4% had 1 suicide attempt, 7.7% had 2, 2.7% had 3, and 4 patients (2.15) had more than 3 attempts. Also, it is necessary to point out that the average number of suicide attempts found in the initial sample was twice what was found in this sample, which could be one reason for this discrepancy. However, other authors also found no statistically significant relationship between a history of suicide attempts (yes, no) and clinical phases of BD.[24,26] Thus, this profiler may merit further analysis to confirm its utility in the model. Concerning comorbid personality disorder, Kapczinski et al.[3] included a current axis I or II diagnosis in their staging model, thus highlighting the importance of comorbidity with personality disorders in the clinical course of BD. Although comorbid personality disorders did not reach statistical significance in this study, there was a trend in that direction since the *p*-value was 0.061, and this could be explained by the lower prevalence of comorbid personality disorder found in this sample in comparison with the initial sample (13.7% vs 17.4%). However, further evidence is needed to support the inclusion of comorbid personality disorders in the model.

De la Fuente et al.[8] were the first to identify a new staging dimension in their EmDe-5 staging model, physical health, made up of three profilers: body mass index (BMI), metabolic syndrome (MetS), and number of comorbid physical illnesses. Although several lab test results, including C-reactive protein (CRP), were collected in the study for the development of the staging model,[8] the final EmDe-5 staging model does not include any. The lack of such objective biomarkers may be seen as one weakness of this model, particularly in an era of extensive searching for objective biomarkers in the field of psychiatry. There have been previous reports of related high levels of CRP with a great risk of developing physical comorbidities in patients with severe mental disorders,[30] even in first episode patients.[9] The EmDe-5 staging model selected physical comorbidities instead of one single biomarker partially underlying them, thus giving more concrete and pragmatic information to clinicians on the specific needs of each patient in this dimension and on the effectiveness of their interventions to address them. Furthermore, it is necessary to point out that two of the three profilers, BMI and MetS, rely on objective biomarkers (weight, height, abdominal circumference, blood pressure, and plasma levels of triglycerides, HDL cholesterol, and glucose) and are related to CRP levels, and other biomarkers of systematic inflammation. The results of the present study firmly support the three profilers of the EmDe-5 physical health dimension as they greatly worsened as the stages progressed. Thus, BMI smoothly progressed from normal in stage 0 to type II obesity in stage 5; the prevalence of MetS progressed from 0% in stage 0 to 80% in stage 5; and the mean number of physical comorbidities progressed from 0.2 in stage 0 to 2.6 in stage 5.

Finally, the fifth dimension of the EmDe-5 staging model, quality of life, represents the point of view of patients regarding the impact of BD on their lives, adding a valuable feature over the current models and confirming previous suggestions.[11] Both physical and mental health scales were selected, reflecting the importance that patients also place on effects on their physical health, and the results found in this study add evidence to support the inclusion of person-centred measurements in the model.

Concerning the external validators employed in this study, the number of psychopharmaceuticals prescribed behaved as expected; patients in late stages received a significantly greater number of drugs than did patients in early stages. This result is in agreement with previous reports on this issue.[8,12,25] However, when we analysed progression according to type of prescribed drugs, we found significant progression only in the case of benzodiazepines. The percentage of patients receiving this type of drug dramatically and progressively rose from 20% in stage 1 to 90% in stage 5. Antidepressants remained almost stable and without any identifiable pattern across the stages, ranging between 37.6% in stage 3 and 59.5% in stage 4. The results of the analysis of pattern of prescription for mood stabilisers and antipsychotics are much more complicated, since the latter may also be prescribed for mood stabilising. Between 50 and 80% of patients had been prescribed antipsychotics, and although the prevalence increased in later stages, it did not reach statistical significance. Both measures of clinician assessment, the CGI-S and the VAS-S, also behaved as expected; clinicians increased their patients' severity scores progressively from stage 1 to 5.

The main limitation of our study is that acute and extremely severe patients are underrepresented. However, it is necessary to point out that the inclusion of this type of patients involves several critical difficulties, including their ability to fully understand the nature of the study and, therefore, to give informed consent. Furthermore, the EmDe-5 staging model does not include the initial phases of the disorder, which prevents an accurate classification of these phases. This, however, is in agreement with the ISBD Task Force for Staging, which supported the use of staging models only in full-threshold disorders.[31] On the other hand, the study has several strengths. These include the relatively large sample size used and its multicentre design, which allow the generalisation of our results. With respect to the tested model, its multidimensional nature, which reflects the impact of BD on the different spheres of people's lives, and its psychometric robustness are other relevant strengths of our study. Furthermore, validated and accurate psychometric instruments for the study population were used to measure them. Therefore, this staging model provides a common language with well-defined, validated, and standardised criteria. Finally, we believe that the ease of obtaining the profilers included in the model, together with the operational criteria provided to quantify them, are other essential strengths that will facilitate the use of the EmDe-5 staging model in daily clinical practice.

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Conflict of interest

LGR has been a speaker for and advisory board member of Janssen-Cilag, Astra-Zeneca, Rovi, Lundbeck, Otsuka, Servier, and Pfizer. VBM has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following entities: Angelini, Ferrer, Lundbeck, Nutrición Médica, and Otsuka. VPS has been a consultant to or has received honoraria or grants from AstraZeneca, Bristol-Myers-Squibb, Janssen Cilag, Lundbeck, Otsuka, Servier, Medtronic and Exeltis. EV has received grants and served as a consultant, adviser, or CME speaker for the following entities: Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Janssen, Lundbeck, Novartis, Otsuka, Richter, Sage, Sanofi-Aventis, and Takeda. PAS has been a consultant to or has received honoraria or grants from Adamed, AstraZeneca, Brainpharma, Bristol-Myers Squibb, CIBERSAM, Esteve, European Comission, Ferrer inCode, GlaxoSmithKline, Instituto de Salud Carlos III, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas, Rovi and Servier. JB has received research grants and served as consultant, advisor or speaker within de last 5 years for: AB-Biotics, Acadia Pharmaceuticals, Alkermes, Allergan, Ambrosseti-Angelini, Biogen, Casen Recordati, D&A Pharma, Exeltis, Gilead, Indivior, GW Pharmaceuticals, Janssen-Cilag, Jazz Pharmaceuticals, Lundbeck, Mundipharma, Newron, Otsuka, Pfizer, Roche, Sage Therapeutics, Servier, Schwabe Farma Ibérica, Shire, Takeda, research funding from the Spanish Ministry of Economy and Competiveness –Centro de Investigación Biomedica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III-, Spanish Ministry of Health, Social Services and Equality – Plan Nacional sobre Drogas – and the 7th Framework Program of the European Union. MPGP has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and SAGE Therapeutics.

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