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Mood instability and functional recovery in bipolar disorders

Strejilevich SA, Martino DJ, Murru A , Teitelbaum J, Fassi G, Marengo E, Igoa A, Colom F. Mood instability and functional recovery in bipolar disorders.

Objective: The aim of this study was to identify psychopathological factors associated with long-term functional outcome in euthymic bipolar disorder patients and to test new measures of mood instability and symptoms intensity.
Method: Fifty-five patients with more than 12 months of follow-up were included. In addition to traditional clinical variables, the time spent ill was documented using a modified life-charting technique based on NIHM life-charting method. New measures, Mood Instability Factor, and Mood Intensity Factor were defined and assessed. Functioning Assessment Short Test (FAST) was used to assess disability.
Results: The follow-up period was 3.00 ± 1.51 years. Weeks with subsyndromal depressive symptoms ($\beta = 0.133$, $t = 2.556$, $P = 0.014$), weeks with mild manic symptoms ($\beta = 1.441$, $t = 3.10$, $P = 0.003$), and the Mood Instability Factor ($\beta = 0.105$, $t = 3.593$, $P = 0.001$) contributed to approximately 46% of the FAST total score variance.
Conclusion: New methodologies including subsyndromal symptoms and mood instability parameters might contribute to understand the worse long-term functional outcome that affects a considerable percentage of BD patients even after episode remission. Concerns about therapeutic approaches are discussed.

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Key words: bipolar disorder; clinical aspects; methodology

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Significant outcomes

- Mood instability, even at a subclinical level, may be associated with long-term functional outcome.
- This study provides further support about the relationship between subsyndromal depressive symptoms and long-term functional outcome.
- The symptom intensity of past depressive or hypo/manic episodes might not impact on the level of functional outcome.

Limitations

- These are preliminary findings: the sample size was relatively small and results should be taken with caution.
- Some inclusion criteria of this work – namely euthymia and lack of drop-outs in the follow-up period – could have biased patients' enrollment toward those with a less severe course of disease.
- Some factors that could affect functional outcome such as psychosocial interventions, familiar support, and housing and financial resources were not controlled for.

Introduction

Bipolar Disorder (BD) represents a major public health problem. More than eighty per cent of their cost is related to the existing occupational and social impairment related to this condition. Several data confirm that 30%–60% of bipolar patients, even in syndromic remission, are unable to accom-

plish their sociovocational potential and many of them will be in need of care by others (1). Despite a large number of data supporting the efficacy of a growing arsenal of both psychological and pharmacological treatments for either acute treatment or prevention of mood episodes, the syndromic control of this condition seems to be dissociated from functional recovery in euthymic bipolar patients (2, 3). Consequently, translating the efficacy achieved in managing psychiatric symptoms into a significant improvement of functional outcome could be a turning point in BD treatment. Nevertheless, to reach such a challenge, new methods and clinical paradigms that correlate with functional evolution should be defined. This represents a critical problem that is yet to be solved (4).

Leaving aside the well-documented correlation between persistent cognitive impairment in euthymic bipolar I and II patients and overall functioning (5–7), at psychopathological level, only subsyndromic depressive symptoms (SSDS) have proven to be predictors of functional recovery (6, 8, 9). Other clinical variables, previously reported as functional predictors (i.e. number of previous episodes (10), number of previous hospitalizations (11), longer duration of the illness (12), mixed episodes (12, 13), psychosis (14), and symptom intensity (15, 16)) are not free from inconsistencies and discrepancies owing to several methodological caveats (1, 16). To mention a few, some studies have included non-euthymic patients (17, 18), others have used self-reported instruments for functional assessment (16), and, finally, with few exceptions (3, 16, 19, 20), there is a lack of control for potential confounders.

More recently, some pharmacological trials have incorporated SSDS as secondary outcomes, but, despite an improvement of these symptoms, no improvement in functioning was achieved (21, 22). A possible explanation of this is that other clinical features relating psychopathology and functional status have been neglected so far.

First, mood instability (MI), rather than mood episodes might be the core feature of BD. According to objective and self-reported observations, after achieving control of an episode many patients continue to experience daily or weekly subsyndromal mood swings (23). MI is significantly more prevalent in euthymic BD patients than in control subjects (24). Furthermore, pathological cyclothymic temperament (25) and mood liability (26) are more prevalent in unaffected relatives of BD patients than in the general population and would predict bipolar evolution (27).

Nonetheless, even if understanding of MI is critical when it comes to developing cognitive neuroscience-based treatments for BD, measures designed to assess this clinical dimension are ignored in current nomenclature (28). Recently, a number of new mathematical approaches have been proposed to assess MI in BD (23, 29, 30). These promising approaches have confirmed MI as a core feature of BD, yet some aspects of these proposals limit their application. First, they have been tested using non-common data gathering procedures such as chrono-records (29), self-reported data send by SMS (23), or simulated data (30). More importantly, to date no study has tested potential correlations between MI measures and functional outcomes.

On the other hand, BD has pleomorphic clinical presentations, ranging from very soft cases to full-blown psychotic – manic or depressive – episodes. Although previous studies have correlated mood symptom intensity with functional status (15, 16), to our knowledge none have examined the impact of past episodes' symptom intensity in the functional outcome of remitted bipolar patients.

Aims of the study

The main aim of this study was to determine the validity of mood instability and mood intensity parameters, and to understand its correlation with overall functioning. Our hypothesis was that a model combining full euthymia variables and mood stability parameters would correlate positively with functional status.

Material and methods

Sample selection

Out-patients in naturalistic conditions of treatment were retrospectively selected with the following inclusion criteria: i) diagnosis of bipolar disorder type I or II according to DSM-IV by Structured Clinical Interview for DSM-IV (SCID) (31); ii) age between 18 and 65 years old; iii) more than 12 months of treatment in our program; iv) no interruptions of treatment during the period of study; v) euthymia (defined by Hamilton Depression Rating Scale ≤ 8 and Young Mania Rating Scale ≤ 6 – Spanish validated versions (32, 33) for at least 8 weeks; vi) provided consent to participate to this study. Exclusion criteria were as follows: i) substance abuse or dependence within 12 months prior to entry; ii) other comorbid diagnoses for Axis I except for Generalized Anxiety Disorder; iii) untreated severe medical condition.

Clinical and symptomatic assessment

All participants were out-patients in the Bipolar Disorder Program of the Neuroscience Institute (Favaloro University, Buenos Aires). At study entry all eligible patients were interviewed to give conformity to participate, check inclusion criteria (including YMRS and HDRS scores), and run the functionality assessment. Clinical data and demographical information were obtained from clinical charts and direct patient interviewing (age, gender, years of education, age at illness onset, length of illness, bipolar subtype, previous manic/hypomanic, mixed and depressive episodes, lifetime history of psychosis, and number of hospital admissions). When possible, attempts were made to verify these historical data with third-party reports (medical records, family interview, etc.). The course of illness was retrospectively extracted from a modified life-charting technique routinely performed on each patient enrolled into our Program, by his/her psychiatrist, on a weekly basis. This life-chart technique was used in previous studies by our group (6, 34) and was developed without the knowledge or purpose of the present work. Our mood chart is based on the NIMH life-charting method and anchored by scores from both the Hamilton Depression Rating Scale and the Young Mania Rating Scale (Fig. 1). High inter-rater reliability was obtained for scores in YMRS (interclass correlation coefficient [ICC = 0.96]) and HDRS (ICC = 0.95).

For the purposes of this study, the included life charts of each patient were reviewed independently by two investigators (SAS & DJM) taking into account the proportion of time spent with a) subsyndromal, mild, moderate, and severe depressive, manic, and mixed symptomatology (Fig. 1). Mixed symptoms were considered: i) subsyndromal: when patients presented with coexisting subsyndromal manic and depressive symptoms; ii) mild: mild symptoms of one polarity with subsyndromal symptoms of opposite polarity; iii) moderate: mild symptoms of both polarities or moderate symptoms of one polarity with subsyndromal to mild symptoms of opposite polarity, or severe symptoms of one polarity with subsyndromal symptoms of opposite polarity; and iv) severe: moderate symptoms of both polarities, or severe symptoms of one polarity with mild to severe symptoms of opposite polarity. In addition, we assessed the number of episodes of depression (more than 2 weeks of at least mild depressive symptoms), hypomania or mania (more than 1 week of at least mild or moderately severe manic symptoms respectively), and mixed states (more than 2 weeks of mild, moderate, or severe symptoms of one polarity with at least subsyndromal symptoms of opposite polarity) during the follow-up period. Likewise, changes in polarity were computed when patients switched from at least mild depression to at least mild mania/mixed states, or alternatively, when patients switched from at least mild mania/ mixed states to mild depression or more. This approach allowed obtaining traditional measures of outcome (number of episodes and changes in polarity) as well as measurement of the time spent with each type of symptoms as well.

Finally, to assess the influence of symptomatic load, its intensity, and mood instability we considered three novel clinical factors, which were calculated as follows (Fig. 2):

i) Mood Instability Factor (MIF) = Number of mood changes/Number of weeks followed), Considering all mood changes including those from euthymia to subclinical symptoms or full-blown episodes and from full-blown episodes or subclinical symptoms to euthymia

	January	Etc.	
+4			Severe Mania (YMRS>26)
+3			Moderate Mania (YMRS>16 and <25)
+2			Mild Mania (YMRS>9 and <15)
+1			Subclinical Mania (YMRS>4 and <8)
0			Euthymic (YMRS<4 and HDRS<4)
–1			Subclinical Depression (HDRS>5 and <9)
–2			Mild Depression (HDRS>10 and <15)
–3			Moderate Depression (HDRS>16 and <25)
–4			Severe Depression (HDRS>26)

YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.

Fig 1. Criteria for assigning mood state scores in life charts.

ii) Mood Symptomatic Factor (MSF) = Number of weeks with symptoms/Number of weeks in follow-up. This score had the objective of assessing the proportion of weeks spent with mood symptoms independently of their polarity and intensity.
iii) Mood Intensity Factor (MIntF) = the summary score of symptomatic intensity extracted from mood chart in all symptomatic periods / Number of weeks of follow-up. MIntF was calculated by adding up each symptomatic week independently from polarity. In periods of mixed episodes joined scores of both manic and depressive symptoms were added.

Functional assessment

The Spanish version of the Functioning Assessment Short Test (FAST) was used to assess disability at study entry (35). The FAST comprises 24 items that investigate impairment or disability in the last 15 days in six specific areas of functioning: autonomy, work functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Each item scores in a 0–3 points range (0: no difficulty; 1: mild difficulty; 2: moderate difficulty; 3: severe difficulty) with total score ranging from 0 to 72 points (Higher score = higher disability). Due to the number of subjects included in this analysis, we only used the overall global rating of the scale.

Psychopharmacological assessment

Exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines was assessed by means of the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) (36). This scale provides a quantitative measure of exposure to different groups of psychotropic medications during a period of time (treatment period in this study) in a 0–5 point range (0 = no medication, 1 = sporadic low dose, 2 = continue low dose, 3 = middle dose, 4 = high dose, 5 = very high dose). Patients were under naturalistic conditions of treatment over the follow-up period, and the necessary psychotropic medications in accordance to published guidelines were prescribed.

Data analysis

First, Spearman bivariate correlations were computed to assess the relationship between FAST total score and both clinical-demographical variables and different measures at follow-up. A correction procedure for multiple correlations was applied (the suggested α level of significance was obtained after Bonferroni corrections). Second, the measures with significant correlation with disability level were considered as possible explanatory variables in a multiple linear regression model with FAST total score as dependent variable: antecedents of clinical-demographical variables (age, gender, years of education, age at illness onset, length of illness, bipolar subtype, previous manic/hypomanic and depressive episodes, history of psychosis, and hospital admissions) were entered into the model first, followed by follow-up measures (time spent ill in different illness condition and traditional measures of outcome such as number of episodes and changes in polarity) and then three mood factors: symptomatic, intensity, and instability factors. This order of variables

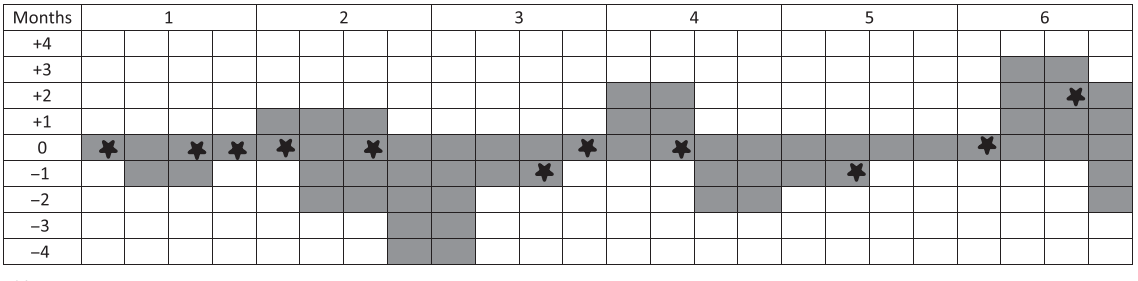

Fig 2. Examples of estimations of mood factors from mood charts.

allows for an examination of the independent contribution of symptomatic, intensity, and instability factors in the prediction of disability, while also correcting for the influence of antecedents of clinical-demographical variables as well as time spent ill and traditional measures of outcome during the follow-up. Homoscedasticity and normality of residuals of the multiple linear regression models were assessed with graphical (scatter plot of studentized residual by predicted values, as well as Normal Q-Q plot and Box Plot of studentized residual) and analytical (Kolmogorov–Smirnov and Shapiro–Wilk tests) approaches. Cases were excluded of the regression analysis if studentized residuals values were higher than 2, if leverage values were higher than 0.2, and if Cook's Distance was higher than 1.

Results

Fifty-five patients were included, 71.1% were female, 48.1% had BD type I, and 50% had history of psychotic symptoms. Mean age was 46.15 (17.45) years old; mean years of education were 14.81 (2.97); mean age at onset was 28.77 (13.69); mean length of illness was 17.40 (11.55) years; and they had 4.37 (4.95) previous manic/hypomanic episodes, 7.25 (9.80) previous depressive episodes, and 0.59 (1.01) hospital admissions. The mean YMRS score at the time of examination was 0.82 (1.22) points, and the mean HDRS 1.26 (1.87) points. The mean FAST total score was 8.81 (5.99). Thirty-four per cent of the sample ($n = 17$) were classified as over the 'impaired function' cut-off of 11 points (higher ratings imply higher impairment) (Table 1). The discriminate scores of FAST subitems are presented in table 1.

During follow-up, 96.2% of patients received mood stabilizers [IFD mean dose: 3.20 (0.79)], 53.8% benzodiazepines [IFD mean dose: 2.04 (0.77)], 63.5% antipsychotics [IFD mean dose: 2.13 (0.62)], and 33.7% antidepressants [IFD mean dose: 2.47 (1.07)]. Time of exposure to antipsychotics was significantly related to higher total FAST scores ($R = 0.437$; $P = 0.001$). No other significant correlations were found between exposure to medications and disability.

The follow-up period was 3.00 (1.51) years. Time spent ill is shown in table 2. Likewise, during each year of follow-up patients experimented a mean of 0.63 (0.69) depressive episodes, 0.13 (0.27) hypomanic episodes, 0.08 (0.19) manic episodes, 0.20 (0.32) mixed episode, and 0.31 (0.92) changes in polarity.

After correcting for multiple correlations any variable pertaining to clinical history or demographical information was significantly related to total FAST score. When considering correlations with time spent ill, disability was associated with weeks with subsyndromal depressive symptoms ($R = 0.503$; $P < 0.001$) and weeks with mild manic symptoms ($R = 0.535$; $P < 0.001$). Among traditional clinical variables of outcome, only the number of hypomanic episodes during follow-up was related with disability scores ($R = 0.503$; $P < 0.001$). Finally, all three novel mood factors considered correlated with FAST total score: symptomatic factor ($R = 0.473$; $P < 0.001$); intensity factor ($R = 0.358$; $P = 0.010$); and instability factor ($R = 0.604$; $P < 0.001$).

Taking into account variables with significant correlation with FAST total score, we conducted a multiple linear regression to find independent predictors of disability. Both weeks with subsyndromal depressive symptoms ($\beta = 0.181$, $t = 3.22$, $P = 0.002$) and weeks with mild manic symptoms ($\beta = 1.747$, $t = 3.422$, $P = 0.001$) predicted the level of disability (adjusted $R^2 = 0.326$; $F(2, 48) = 13.07$, $P < 0.001$). When we added the number of hypomanic episodes during follow-up, the model was modestly enhanced (adjusted $R^2 = 0.357$; $F(3, 47) = 10.24$, $P < 0.001$) yet it was a non-significant predictor ($\beta = 7.273$, $t = 1.818$, $P = 0.075$). Finally, we added the three factors which did

Table 1. Scores in functioning assessment short test (FAST)

FAST subitems	Mean	S.D.	Cut-off for Impairment*	% of patients over Cut-off
Total	9.25	6.828	>11	34
Autonomy	1.02	1.228	>1	14.3
Occupational Functioning	2.50	3.133	>1	50
Cognitive Functioning	2.29	2.147	>2	26.8
Financial Issues	0.39	1.021	>1	3.6
Interpersonal Relationship	2.02	2.308	>3	14.3
Leisure Time	1.04	1.560	>3	3.6

*Rosa et al. 2007.

Table 2. Percentage of time spent ill during follow-up period

	Mean	SD	Minimum	Maximum
Asymptomatic	65.17	22.83	2.63	100
Subsyndromal Depression	14.24	11.57	0	47.58
Mild Depression	7.33	7.79	0	36.92
Moderate Depression	2.95	5.62	0	29.95
Severe Depression	0.39	1.20	0	5.26
Subsyndromal Mania	4.19	6.12	0	30.00
Mild Mania	0.95	1.95	0	11.39
Moderate Mania	0.20	0.57	0	2.87
Severe Mania	0.11	0.55	0	2.63
Subsyndromal Mixed	1.23	2.12	0	8.78
Mild Mixed	1.48	2.54	0	10.96
Moderate Mixed	0.20	0.57	0	2.87
Severe Mixed	1.56	10.39	0	75.00

improve the model (adjusted $R^2 = 0.442$; $F(5, 45) = 8.76$, $P < 0.001$), although only the instability factor was an independent predictor ($\beta = 0.121$, $t = 3.26$, $P = 0.002$). The final model included weeks with subsyndromal depressive symptoms ($\beta = 0.133$, $t = 2.556$, $P = 0.014$), weeks with mild manic symptoms ($\beta = 1.441$, $t = 3.10$, $P = 0.003$), and the mood instability factor ($\beta = 0.105$, $t = 3.593$, $P = 0.001$) accounting for approximately 46% of the FAST total score variance (adjusted $R^2 = 0.460$; $F(3, 47) = 15.18$, $P < 0.001$). Two patients were excluded from the analysis because studentized residuals were higher than 2, and two patients were excluded because leverage values were higher than 0,2; therefore the final analysis was conducted over 51 patients. Kolmogorov–Smirnov and Shapiro–Wilk bring support to null hypothesis that studentized residuals were normally distributed ($P > 0{,}200$ and $P = 0{,}766$ respectively). The addition of exposure to antipsychotics did not modified the model (adjusted $R^2 = 0.443$; $F(4, 46) = 10.74$, $P < 0.001$), and was unrelated to the level of disability ($\beta = 0.575$, $t = 0.975$, $P = 0.335$).

Discussion

In this work we have found that nearly one third of our sample of strictly euthymic bipolar outpatients still presented with significant functional impairment. This finding agrees with some previous works and disagrees with others which found a higher percentage of patients with functional impairments in similar samples – for a review see MacQueen et al. (1). For example, whereas Carlson et al. (37) found in a follow-up study that one third of patients had some functional impairment, Rosa et al. (19) found, using the cross-examination instruments used in this study, a total score of FAST twice higher (18.68 ± 13.2) and twice as many patients (60%) with scores compatible with significant functional deficit. This heterogeneity regarding functional assessment results may be explained by sample characteristics. In our work, the patients included had higher educational levels and were less symptomatic at examination than in Rosa et al. sample (19), and in our center we assist patients from middle-up social classes and a mixture between first consult and tertiary level of reference patients.

Regarding the main objective of this work, we found, according to our hypothesis, that a model which takes into account i) percentage of weeks spent with subsyndromal depressive symptoms; ii) percentage of weeks spent with mild manic symptoms; and, iii) novel 'Mood Instability Factor' (MIF), showed a significant correlation with functional status after controlling for several other psychopathological variables.

The finding of a negative relationship between persistent subsyndromal depressive symptoms (SSDS) and overall functioning in remitted bipolar patients agrees with a large corpus of data from cross-sectional (20, 38) and follow-up studies (6, 16, 39, 40). In our sample, this negative association persisted although the percentage of time spent with SSDS was shorter than that found in other samples (41, 42), confirming its weight and specificity regarding functional outcome. Hence, SSDS should be taken into account in research and bipolar treatment as the strongest clinical predictor of functional recovery: It is the most prevalent symptomatic cluster in long-term bipolar evolution (41, 42) and their impact on functionality could be equivalent to a full depressive syndrome (39).

Another finding concerned the negative relationship between time spent with mild manic symptoms and overall functioning. In other words, manic symptoms have less influence in functional outcome than depressive symptoms and have no influence at subsyndromic level (16, 40, 43) even when manic symptoms coexist with depressive ones, as it is the case in mixed presentations (15). In The National Institute of Mental Health Collaborative Depression Study (CDS), manic symptoms showed a progressive impact on overall function according to their intensity from hypomania to full mania but, at subsyndromal level, manic symptoms had no effect. Furthermore, in Bipolar Disorder type II, hypomanic symptoms had no impact on the overall functioning and even subsyndromal manic symptoms showed nonsignificant correlation with increased functioning (16). Similar results were found in a secondary analysis of a trial designed to test a care management and psychoeducational intervention (40). Despite the obvious differences in duration of follow-up and sample size, other methodological dissimilarities could explain the discrepancies regarding the impact of manic symptoms in these studies compared with the present one. In our work, bipolar II patients and I were analyzed together. More importantly, whereas in the CDS and Simon et al. studies symptoms load was considered transversally, in the present one they were considered longitudinally. Here, accumulation of manic symptoms, rather than their mere presence, correlated with functional impairment, showing that the mild manic symptoms impact could be consequence of their accumulation and not an immediate effect. Probably, the correlation found with mild manic

symptoms but not with severe ones has to do with the fact that the mild form of manic symptoms was most prevalent in our follow-up. Another possible explanation may be that the number of previous manic episodes has been related with persistent cognitive impairments in euthymic patients (44) and their correlation with functional outcome (6). In clinical settings, manic symptoms could represent a psychopathological expression of persistent cognitive deficits and because of that more cognitively impaired patients already may suffer from more manic symptoms during their evolution, this justifying the correlation between manic symptoms and overall function in remitted patients. Future studies should also include a cognitive assessment to test this hypothesis.

Finally, the model is completed by the novel clinical measure Mood Instability Factor. MIF presents differences with other measures of mood instability as number of episodes or rapid cycling. MIF quantifies every change in mood, including those occurring during subclinical episodes or representing a return to euthymia. In our opinion, MIF depicts an improved and more realistic way of presenting this clinical feature, which has been previously described in remitted patients (23, 24). Socio-occupational functioning is not only determined by current status but also by a series of behaviours and skills. These need a mid- and long-time planning which can be hindered by mood instability. We added to MIF calculation swings to euthymia because this may produce behaviour mismatches with subsequent positive as well as negative repercussions regarding functionality. For example, people who spent some time in soft mania with a subsequent adjustment in their overall activity (i.e. working) could suffer a relative functional detriment when returning to euthymia. Similarly, people who adapted their social activity to a state of persistent SSDS would need to adjust themselves after having returned to euthymia. All these changes produce social and occupational disruptions. In a social and occupational regard, MIF is considered as a negative aspect of personality, even when representing a return to a better mood state. We did not find other works which have explored mood instability measures regarding functional outcomes. Although Judd et al. (16) found that cycling symptoms did not increase the impact on overall function, only swings to the opposite polarity were considered as mood change and, for statistical purposes, cycling symptoms were included in group together with mixed episodes.

Some negative findings deserve to be commented. In this study we tested several measures related to mood symptoms intensity (psychotic symptoms, number of hospitalizations, and the novel Mood Intensity Factor) which have not shown final correlation with functionality. Other studies have found a degree of functional impairments related to symptomatic intensity, especially to depressive ones. Nonetheless, as discussed above, in these studies functional status was assessed in concordance to symptomatic status of patients who were not in full euthymia (15, 16). In our study, symptom intensity and psychotic symptoms should be taken into account more as an antecedent because patients were strictly euthymic when functional status was evaluated. Similarly, the lack of correlation between previous symptoms intensity and functional outcome in remitted patients seems in line with the lack of differences in overall functional evolution among remitted patients with bipolar I or II reported in this study and others (16, 45). Finally, the lack of correlation between symptom intensity in previous episodes and functional outcome is compatible with the common observation of patients who achieve a complete functional recovery between episodes despite having suffered from serious and psychotic crisis, whereas others, which have been 'only' suffering mild episodes, cannot return to their previous level of functioning.

These findings show that it would be necessary to include measures of mood stability and subsyndromal symptoms in clinical constructs of bipolar disorders to have good correlation with functional recovery. A common assumption is that maintenance studies, through Kaplan–Meier Survival Analysis, assess efficacy of a treatment to restore mood stability. However, this kind of analysis assesses time until recurrence which appears as a poor measure of mood instability for a number of reasons elsewhere examined (46). Mood swings are normally present at subthreshold levels of symptom intensity, so that they are not properly assessed by this kind of study design (23). Paradoxically, at clinical levels survival design methodology may hide different kind of changes on mood instability and symptomatic patterns. For example, a patient experiencing an early relapse during follow-up (allegedly, a 'poor responder') could nevertheless continue, after that episode, with a stable pattern of full euthymia. On the other hand, another patient might experience a recurrence during follow-up period (a 'good responder'), but he could later develop an instable course of illness with subsyndromal symptoms, which would not be detected by the aforementioned standard assessment (Fig. 2). Most importantly, this standard assessment considers the course of illness

irrespectively of previous patterns of ciclicity, something which, once again, can fail detecting either positive or negative patterns of evolution. Because of this, it would be necessary to test treatments with designs that include a preexperimental treatment follow-up to be contrasted afterward to a postexperimental period that should not end after the first relapse/recurrence and that should include wider measures of mood stability, such as the ones proposed in this study.

The current MIF proposal inherits the spirit of pioneer trials on bipolar treatment. First studies on lithium in manic-depressive illness used 'mirror design', a methodology which takes into account the aforementioned variables in the clinical evolution of BD (47). In this paradigm outcomes are more complex, but offer a more realistic scenario of the course of illness.

Some limitations need to be stated. In this work, FAST examination was not carried out by a blind rater. However, FAST was rated previously to the assessment of clinical variables, and clinical variables during follow-up were documented by different researchers from those who assessed functioning. The small sample size limits our findings and may provide a type II error, failing to catch other clinical predictors. Some inclusion criteria of this work – namely euthymia and lack of drop-outs in the follow-up period – could have biased the selection toward patients with a less severe course of disease. On the other hand, our team is a reference center in our city to which patients seeking a second specialized opinion usually attend, so they represent, by definition, a subsample of difficult-to-treat patients. Moreover, we excluded patients with axis-I comorbidity, but we did not control for axis II comorbidities. This may potentially act as a confounding factor for the clinical parameters which were here investigated. Finally, as in similar, previous studies, we did not control factors that could affect functional outcome such as psychosocial interventions, familiar support, and housing and financial resources.

In conclusion, a significant amount of bipolar patients, despite receiving updated and guidelines-based treatments, do not succeed in returning to the full, previous functioning level, even after clinical remission. On the other hand, results of this proof-of-concept study show that new methodologies including subsyndromal symptoms and mood instability parameters should be used to test for new treatments for functional recovery. Finally, if the correlation between parameters of mood instability and functional recovery is confirmed, future studies should look for possible correlations with cognitive function and their implications in the construction of a model of staging of bipolar disorders.

Declaration of interest

Sergio A. Strejilevich has been speaker for Glaxo-Smith-Kline, Astra Zeneca, Janssen-Cilag, Novartis, and Elli Lilly. Diego J. Martinoa and Julia Teitelbauma declare no conflict of interest. Andrea Murru has received support from Bristol-Myers-Squibb and has been speaker for Astra Zeneca. Guillermo Fassia, Eliana Marengoa, and Ana Igoaa declare no conflict of interest. Francesc Colom has served as advisor or speaker for the following companies: Astra Zeneca, Bristol-Myers, Eli Lilly, Glaxo-Smith-Kline, MSD-Merck, Otsuka, Pfizer Inc, Sanofi-Aventis, Shire, Adamed, Lundbeck, and Tecnifar, and research funding from the Spanish Ministry of Science and Innovation — Instituto de Salud Carlos III.

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